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Systematic Review and Cumulative Analysis of Perioperative Outcomes and Complications After Robot-assisted Radical Cystectomy

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Abstract

Context: Although open radical cystectomy (ORC) is still the standard approach, laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) have gained popularity.

Objective: To report a systematic literature review and cumulative analysis of perioperative outcomes and complications of RARC in comparison with ORC and LRC.

Evidence acquisition: Medline, Scopus, and Web of Science databases were searched using a free-text protocol including the terms robot-assisted radical cystectomy or da Vinci radical cystectomy or robot* radical cystectomy. RARC case series and studies comparing RARC with either ORC or LRC were collected. Cumulative analysis was conducted.

Evidence synthesis: The searches retrieved 105 papers. According to the different diversion type, overall mean operative time ranged from 360 to 420 min. Similarly, mean blood loss ranged from 260 to 480 ml. Mean in-hospital stay was about 9 d for all diversion types, with consistently high readmission rates. In series reporting on RARC with either extracorporeal or intracorporeal conduit diversion, overall 90-d complication rates were 59% (high-grade complication: 15%). In series reporting RARC with intracorporeal continent diversion, the overall 30-d complication rate was 45.7% (high-grade complication: 28%). Reported mortality rates were ≤3% for all diversion types. Comparing RARC and ORC, cumulative analyses demonstrated shorter operative time for ORC, whereas blood loss and in-hospital stay were better with RARC (all p values <0.003). Moreover, 90-d complication rates of any-grade and 90-d grade 3 complication rates were lower for RARC (all p values <0.04), whereas high-grade complication and mortality rates were similar.

Conclusions: RARC can be performed safely with acceptable perioperative outcome, although complications are common. Cumulative analyses demonstrated that operative time was shorter with ORC, whereas RARC may provide some advantages in terms of blood loss and transfusion rates and, more limitedly, for postoperative complication rates over ORC and LRC.

Patient summary: Although open radical cystectomy (RC) is still regarded as a standard treatment for muscle-invasive bladder cancer, laparoscopic and robot-assisted RC are becoming more popular. Robotic RC can be safely performed with acceptably low risk of blood loss, transfusion, and intraoperative complications; however, as for open RC, the risk of postoperative complications is high, including a substantial risk of major complication and reoperation.

1. Introduction

Radical cystectomy (RC) with regional lymph node dissection is the standard surgical treatment for muscle-invasive and high-risk non–muscle-invasive urothelial carcinoma of the bladder [1]. Although open RC (ORC) is still the most commonly adopted surgical approach [2], minimally invasive techniques have gained popularity such that laparoscopic RC (LRC) and robot-assisted RC (RARC) are routinely performed with promising short- and intermediate-term results [3].

Due to increasing evidence in the field of RARC and in preparation for the Pasadena international consensus meeting on best practice in RARC and urinary diversion, we performed a systematic literature review of perioperative, functional, and oncologic outcomes of RARC in comparison with ORC and LRC. We report the findings of this review with a cumulative analysis of perioperative outcomes and postoperative complications.

2. Evidence acquisition

The systematic literature search was initially performed in September 2013 using the Medline, Scopus, and Web of Science databases. The searches included a free-text protocol using the terms robot-assisted radical cystectomy or da Vinci radical cystectomy or robot* radical cystectomy in all fields of the records for PubMed and Scopus searches and in the Title and Topic fields for the Web of Science search. No limits were applied. A full update of the searches was done April 28, 2014.

Two authors (G.N. and B.Y.) separately reviewed the records to select RARC case series as well as studies that compared RARC with ORC and RARC with LRC. Discrepancies were resolved by open discussion. Other significant studies cited in the reference lists of the selected papers were evaluated, as were studies published after the systematic search.

All noncomparative studies reporting intraoperative and perioperative data (operative time, blood loss, transfusion rate, in-hospital stay, readmission, complication rates), functional data (urinary continence, erectile function), and oncologic data (positive surgical margins, lymph node yield, disease-free survival, cancer-specific survival, overall survival) of RARC were collected. The present review included only studies reporting perioperative outcomes and complications.

Studies reporting partial cystectomy, prostate-sparing cystectomy, salvage cystectomy, cystectomy for urachal cancers or benign diseases, single-case reports, or pure laparoscopic (or mixed) series; those focusing on RC with laparoendoscopic single-site or natural orifice transluminal endoscopic surgery; experimental studies on animal models; congress abstracts; review papers; editorials; population-based studies; and book chapters were not included in the review. All data retrieved from the selected studies were recorded in an electronic database.

Papers were categorized according to the Oxford Level of Evidence Working Group 2011 levels of evidence (LOEs) for therapy studies: LOE 1, systematic review of randomized trials or n-of-1 trials; LOE 2, randomized trial or observational study with dramatic effect; LOE 3, nonrandomized controlled cohort or follow-up study; LOE 4, case series, case–control study, or historically controlled study; or LOE 5, mechanism-based reasoning [4]. Papers were categorized according to the IDEAL recommendations [5]. Methodological reporting of complications was evaluated according to the Martin criteria [6]. The systematic review was performed in agreement with the PRISMA statement [7].

2.1. Statistical analysis

Cumulative analysis was conducted using Review Manager v5.2 software designed for composing Cochrane Reviews (Cochrane Collaboration, Oxford, UK). Statistical heterogeneity was tested using the chi-square test. A p value <0.10 was used to indicate heterogeneity. If there was a lack of heterogeneity, fixed-effects models were used for the cumulative analysis. Random-effects models were used in cases of heterogeneity. For continuous outcomes, the results were expressed as weighted mean differences (WMDs) and standard deviations (SDs); for dichotomous variables, results were given as odds ratios (ORs) and 95% confidence intervals (CIs). Due to limitations in the Review Manager v5.2 software, cumulative analysis of continuous variables was possible only when rough data were presented as mean and SD. Authors of the papers were contacted to provide missing data whenever necessary. For all statistical analyses, two-sided $p < 0.05$ was considered statistically significant.

3. Evidence synthesis

3.1. Quality of the studies and level of evidence

The flow of this systematic review of the literature is shown in Figure 1. In total, 70 surgical series [8–77] and 23 comparative studies [78–100] reported perioperative outcomes and complications of RARC.

Most of the surgical series were retrospective, single-center studies, with the exception of some prospective studies [8,9,29,32,33,48,62,63,67,69,71,73,77] and some multi-institutional collaboration papers [19,24,26,30,38,39,43,45,72] (LOE 4). Only three of the comparative studies were randomized [78–80] (LOE 2b); all other comparative studies were nonrandomized, whether prospective or retrospective (LOE 4).

3.2. Perioperative outcomes after robot-assisted radical cystectomy

Table 1 summarizes mean operative time, blood loss, transfusion rate, intraoperative complication rate, time to flatus, time to bowel movement, in-hospital stay, and readmission rate in the RARC surgical series.

Once duplicate publications and collaborative studies were excluded, weighted mean operative time was 360 min (range: 230–618 min) for RARC with extracorporeal conduit, 420 min (range: 300–496 min) for RARC with extracorporeal neobladder, 340 min (range: 292–660 min) for RARC with intracorporeal conduit, and 420 min (range: 420–450 min) for

RARC with intracorporeal neobladder. Overall mean blood loss was 375 ml (range: 208–763 ml) for RARC with extracorporeal conduit, 390 ml (range: 167–400 ml) for RARC with extracorporeal neobladder, 270 ml (range: 200–1118 ml) for RARC with intracorporeal conduit, and 480 ml (range: 225–500 ml) for RARC with intracorporeal neobladder. Transfusion rates vary, at 12% for RARC with extracorporeal conduit, 44% for RARC with extracorporeal neobladder, 14.7% for RARC with intracorporeal conduit, and 7% for RARC with intracorporeal neobladder.

The intraoperative complication rate was 3% in the series reporting RARC with extracorporeal conduit, whereas no intraoperative complications were reported in papers evaluating either extracorporeal neobladder or intracorporeal diversions. Sufficient data on time to flatus and bowel movements were available only for the series analyzing RARC with extracorporeal conduit, demonstrating mean time to flatus of 2.5 d (range: 2.1–3.4 d) and mean time to bowel movement of 3.1 d (range: 2.8–4 d).

Length of stay was 8.7 d (range: 3.3–20.7 d) for RARC with extracorporeal conduit, 8.9 d (range: 6.7–9 d) for RARC with extracorporeal neobladder, 8.6 d (range: 4.5–9 d) for RARC with intracorporeal conduit, and 8.5 d (range: 8–9 d) for RARC with intracorporeal neobladder. Readmission rates were consistently high, ranging from 19% for RARC with extracorporeal conduit to 75% in one small study for RARC with intracorporeal neobladder.

3.3. Perioperative outcomes after robot-assisted radical cystectomy and patient characteristics

Two studies analyzed the impact of patient body mass index (BMI) on perioperative outcomes [64,70] (Table 2). Butt et al assessed a cohort of 49 patients receiving RARC and extracorporeal ileal conduit at Roswell Park Cancer Institute (Buffalo, NY, USA) and failed to demonstrate any major significant difference in perioperative outcomes in patients with BMI <25, 25–29, and ≥30 [70]. More recently, Poch et al reported on 56 consecutive patients treated at the same institution with RARC and intracorporeal conduit and demonstrated that only blood loss was significantly higher in obese patients [64].

3.4. Aspects of surgery influencing perioperative outcomes after robot-assisted radical cystectomy

Table 3 summarizes the studies assessing the effects of particular surgical aspects on perioperative outcomes. Five papers evaluated the effect of the number of cases previously performed on perioperative outcomes [18,35,65,68,71]. Whereas Pruthi et al failed to demonstrate any significant modification of the perioperative outcomes among the first 50 cases of RARC with extracorporeal diversion [18], Hayn et al found significant improvements in both mean time for RARC (from 180 min in the first 50 cases to 136 min in the last 64 cases; $p < 0.001$) and lymph node yield (from 16 nodes in the first 50 cases to 24 nodes in the last 64 cases; $p < 0.001$) among the first 164 RARC cases performed with extracorporeal urinary diversion [71]. Analyzing their first 60 cases of RARC with extracorporeal urinary diversion, Richards et al demonstrated reduction in overall complication rates from 70% in the first 20 cases to 30% in the second and third 20 cases ($p = 0.013$) [35].

With regard to reporting intracorporeal diversion, in a series of 100 cases receiving RARC with mainly conduit diversion, Azzouni et al found significant reduction in overall diversion time with experience (from 140 min in the first 25 cases to 103 min in the last 25 cases; $p = 0.002$) [65]. Finally, in a series of 45 patients treated with RARC and intracorporeal neobladder, Schumacher et al demonstrated significant improvement in many aspects, including increased adoption of lymph node dissection and reduction in operative time (from 523 min in the first 15 cases to 434 min in the last 15 cases; $p = 0.005$), in-hospital stay (from 22.5 d in the first 15 cases to 9.5 d in the last 15 cases; $p = 0.006$), and >30-d complication rates (from 54% in the first 15 cases to 20% in the last 15 cases; $p = 0.005$) [68].

Hayn et al evaluated the impact of previous experience with robot-assisted radical prostatectomy (RARP) on RARC outcome [72]. Specifically, RARP experience was stratified into four groups: <50, 51–100, 101–150, and >150 cases. RARC operative time, blood loss, and lymph node yield were all significantly associated with prior RARP experience (all p values <0.001), with the most experienced RARP surgeons experiencing lower blood loss but longer operative time and lower lymph node yield [72].

Finally, two studies compared perioperative outcomes in RARC with intracorporeal and extracorporeal diversion [73,74]. Specifically, Guru et al compared the outcomes of 13 patients receiving intracorporeal ileal conduit and 13 receiving extracorporeal ileal conduit at Roswell Park Cancer Institute and failed to demonstrate any significant difference between the two groups [73]. Similarly, Kang et al compared 38 patients receiving RARC with either extracorporeal conduit (n = 22) or neobladder (n = 14) and 4 patients receiving RARC with intracorporeal diversion (three conduits and one neobladder) and demonstrated shorter operative time for extracorporeal diversions [74]. Both studies had low power to draw definitive conclusions on the issue.

3.5. Postoperative complication rates after robot-assisted radical cystectomy

Table 4 summarizes complication rates in the RARC surgical series stratified by diversion type. In series reporting on RARC with extracorporeal conduit diversion, overall 30- and 90-d complication rates were 44% (range: 26–78%) and 59% (range: 30–77%), respectively. Low-grade complications were the most prevalent, at 29.4% (range: 8–62%) and 54% (range: 15–79%) at 30 d and 90 d, respectively. High-grade complications at 30 d and 90 d were present in 11.8% (range: 0–35%) and 15% (range: 4–19%), respectively, including high reoperation rates (9.7% at 30 d and 14% at 90 d) and relatively low mortality rates (1.6% at 30 d and 3% at 90 d).

With regard to RARC with extracorporeal continent diversion, virtually all studies reported the experience of City of Hope Comprehensive Cancer Center (Duarte, CA, USA) with an overall 90-d complication rate of up to 77%, including 45% low- and 32% high-grade complications. The 90-d mortality rate was as high as 5% [25,55,56,58,59].

In series reporting on RARC with intracorporeal conduit diversion, the overall complication rates at 30, 30–90, and 90 d were 67% (range: 42–86%), 22% (range: 14–23%), and 59% (range: 30–77%), respectively. Low-grade complication rates were 45% (range: 32–50%), 2% (range: 0–14%), and 66% at 30, 30–90, and 90 d, respectively. High-grade complications were present in 24% (range: 0–54%), 20% (range: 0–23%), and 15% at 30, 30–90, and 90 d, respectively. Reoperation rates were 39% at 30 d, 19% at 30–90 d, and 25% at 90 d. Reported mortality rates were relatively low (0% at 30 d, 1.7% at 30–90 d, and 1.7% at 90 d).

In series reporting RARC with intracorporeal continent diversion, the overall complication rates at 30, 30–90, and 90 d were 45.7% (range: 43–62%), and 30% (range: 12–34%), respectively. Low-grade complications were reported in 19% (range: 12–33%) and 13.5% (range: 13–15%) at 30 d and 30–90 d, respectively. High-grade complications were present in 28% (range: 15–33%) and 18% (range: 12–21%) at 30 d and 30–90 d, respectively. Reoperation rates were 17% at 30 d, 16% at 30–90 d, and 33% at 90 d. Reported mortality rates were relatively low (1% at 30 d, 1.7% at 30–90 d, and 2.7% at 90 d).

3.6. Patient characteristics and aspects of surgery influencing postoperative complications after robot-assisted radical cystectomy

Table 5 summarizes the studies evaluating the impact of patient characteristics and surgical factors on complication rates in RARC series. Two studies analyzed the impact of patient BMI on complication rates [64,70]. Both papers failed to identify any significant difference in complication rates according to patient BMI. Five papers evaluated the effect of the number of cases performed on postoperative complications [18,35,65,68,71,77]. With regard to RARC with extracorporeal urinary diversion, Richards et al [35] demonstrated significant improvement in 90-d complication rates among the first 60 cases performed, with overall complication rates decreasing from 70% in the first 20 cases to 30% in the last 20 [35]. Conversely, Hayn et al reported stable 240-d complication rates in a larger series of 164 patients treated at Roswell Park Cancer Institute [71]. With regard to the series reporting intracorporeal conduit diversion, Azzouni et al demonstrated little change in 30- and 90-d complication rates among the first 100 cases performed [65]. Conversely, two series from the Karolinska Institute (Stockholm, Sweden), mainly reporting on RARC with intracorporeal neobladder, showed significant improvements in complication rates at 30 d and 30–90 d [68,77]. Finally, two studies compared postoperative complication rates for RARC with intracorporeal and extracorporeal diversion [73,74]. Both studies reported overlapping complication rates, but small sample size and other methodological limitations prevented any definitive conclusions from being drawn.

Few studies evaluated independent predictors of postoperative complications in a more formal way, including multivariable analyses (Table 6). Specifically, with regard to series reporting on RARC with mainly extracorporeal conduit diversion, three studies reported on predictors of complications [28,39,43] and one reported on predictors of readmission [48]. Specifically, Kauffman et al analyzed 79 patients treated at Weill Cornell Medical Center (New York, NY, USA) and demonstrated that preoperative creatinine level >1.4 mg/dl (OR: 4.2; $p = 0.038$) and intravenous fluids >5000 ml (OR: 4.1; $p = 0.025$) were predictors of any-grade complication, whereas patient age of >65 yr (OR: 12.7; $p = 0.04$), estimated blood loss >500 ml (OR: 9.7; $p = 0.015$), and intravenous fluids >5000 ml (OR: 42.1; $p = 0.003$) were predictors of high-grade complications [28]. In a multicenter series of 279 patients treated at four US institutions, Smith et al demonstrated that younger age of <65 yr (OR: 0.4; $p = 0.230$) and American Society of Anesthesiologists (ASA) score ($p = 0.025$) were associated with higher risk of complications [39]. In another, larger multi-institutional study involving >900 patients from >20 institutions, Johar et al performed sophisticated analyses evaluating preoperative and intraoperative predictors of any-grade and high-grade complications. Among preoperative variables, age at surgery (OR: 1.34; $p < 0.0001$); BMI (OR: 1.04; $p = 0.006$); and, notably, use of neoadjuvant chemotherapy (OR: 1.71; $p = 0.007$) were associated with any grade of complications, whereas age at surgery (OR: 1.39; $p = 0.02$), BMI (OR: 1.04; $p = 0.024$), use of neoadjuvant chemotherapy (OR: 1.88; $p = 0.006$), and current smoking status (OR: 1.68; $p = 0.018$) were predictive of high-grade complications. Among intraoperative variables, blood transfusion (OR: 1.84; $p = 0.006$) and conduit diversion (OR: 1.44; $p = 0.036$) were predictive of any grade of complications, whereas only blood transfusion (OR: 1.94; $p = 0.009$) was associated with high-grade complications [43]. In the same study, predictors of 90-d mortality were also assessed, with age (OR: 1.62; $p = 0.018$), among the preoperative variables, and blood transfusions (OR: 4.20; $p = 0.001$), among the intraoperative variables, as the only independent predictors [43]. Finally, Al-Daghmin et al reported on readmission rates and demonstrated 30- and 90-d readmission rates of 15% and 25%, respectively. Patient BMI (OR: 1.12; $p = 0.004$) and presence of any grade of complications (OR: 0.09; $p = 0.03$) were predictive of 30-d readmission, whereas male sex (OR: 0.41; $p = 0.014$) and BMI (OR: 1.1; $p = 0.004$) were predictive of 90-d readmission [48].

With regard to series reporting on RARC with mainly extracorporeal continent diversion, two papers reporting the experience of City of Hope Comprehensive Cancer Center assessed predictors [56,58]. In the largest series, reporting on 91 patients receiving orthotopic neobladder, 51 receiving Indiana pouch, and 67 receiving ileal conduit, Nazmy et al demonstrated that ASA score (OR: 7.39; $p = 0.01$), preoperative hematocrit (HCT; OR: 0.85; $p = 0.002$), and diversion type (Indiana pouch vs conduit: OR: 6.59; $p = 0.002$; neobladder vs conduit: OR: 4.0; p = 0.007) were associated with complications of any grade at 90 d, whereas Charlson comorbidity index (OR: 1.44; p = 0.003), preoperative HCT (OR: 0.88; p = 0.0009), and diversion type (neobladder vs conduit: OR: 4.9; p = 0.001) were predictive of high-grade complications at 90 d [58]. Yuh et al also included intraoperative variables and found that operative time (OR: 1.71; p = 0.006) and blood loss (OR: 1.0; p = 0.0003) were predictive of complications of any grade at 90 d [56].

3.7. Cumulative analysis of studies comparing robot-assisted radical cystectomy with open or laparoscopic radical cystectomy

Table 7 summarizes the comparative studies that report perioperative parameters and intraoperative complication rates after ORC, LRC, and RARC. With regard to the comparison of RARC and ORC, cumulative analyses showed statistically significant differences in terms of rates for operative time (WMD: 83.60; 95% CI, 57.1–110.1; p < 0.00001 in favor of ORC), blood loss (WMD: −521; 95% CI, −644 to −399; p < 0.00001 in favor of RARC), transfusion (OR: 0.16; 95% CI, 0.1–0.27; p < 0.00001 in favor of RARC), and in-hospital stay (WMD: −1.26; 95% CI, −2.08 to −0.43; p = 0.003 in favor of RARC), whereas rates for intraoperative complications (OR: 1.34; 95% CI, 0.37–4.77; p = 0.65) were similar for RARC and ORC (Fig. 2). Cumulative analysis of mean time to flatus and mean time to bowel movement was not possible. Notably, considering only the few available randomized controlled trials (RCTs), operative time (WMD: 74.7; 95% CI, −30.1 to 179.5; p = 0.16) and in-hospital stay (WMD: 0.03; 95% CI, −1.37 to 1.44; p = 0.96) were overlapping for the two procedures.

With regard to the comparison of RARC and LRC, cumulative analyses showed statistically significant differences in terms of rates for transfusion (OR: 0.19; 95% CI, 0.07–0.53; p = 0.001 in favor of RARC) (Fig.3). Cumulative analysis of the other variables was not possible.

Table 8 summarized the comparative studies that report postoperative complication rates after ORC, LRC, and RARC. With regard to the comparison of RARC and ORC, cumulative analyses showed that rates for any grade of complication at 90 d (OR: 0.44; 95% CI, 0.31–0.61; $p < 0.0001$) and for grade 3 complications at 90 d (OR: 0.55; 95% CI, 0.31–0.98; $p = 0.04$) were in favor of RARC. In contrast, rates at 30 d for any grade of complication (OR: 0.77; 95% CI, 0.56–1.4; $p = 0.09$), for grade 3 complications (OR: 0.70; 95% CI, 0.43–1.13; $p = 0.14$), and for high-grade complications (OR: 0.64; 95% CI, 0.32–1.29; $p = 0.21$); 30-d mortality rates (OR: 0.45; 95% CI, 0.14–1.44; $p = 0.18$); and rates at 90 d for high-grade complications (OR: 0.62; 95% CI, 0.37–1.03; $p = 0.06$) and mortality (OR: 0.45; 95% CI, 0.12–1.66; $p = 0.23$) were similar for RARC and ORC (Fig. 4).

With regard to the comparison of RARC and LRC, cumulative analyses showed that rates at 30 d for any grade of complication (OR: 0.18; 95% CI, 0.08–0.38; $p < 0.0001$) and for grade 3 complications (OR: 0.35; 95% CI, 0.15–0.82; $p = 0.02$) were significantly lower with RARC (Fig. 5).

3.8. Discussion

Following the success of RARP and other robotic procedures, da Vinci technology (Intuitive Surgical, Sunnyvale, CA USA) has been applied to RC, and the number of RARCs performed is increasing; however, according to the most current data available, <20% of RCs are performed robotically in the United States [2]. Our systematic review demonstrated that RARC can be performed safely, with acceptable operative time, relatively little blood loss, and relatively low transfusion rates. Although the risk of intraoperative complications is low, postoperative complications are common, and the rate of readmission is relatively high. Some preoperative patient characteristics, including age, BMI, renal function, and comorbidity, may be associated with the risk of complications. Our cumulative analyses demonstrated that operative time was shorter with ORC, whereas blood loss and transfusion rates were significantly lower with RARC than with ORC. Conversely, rates for any-grade and grade 3 complication at 90 d were slightly lower with RARC than with ORC. Similarly, transfusion rates were lower with RARC than with LRC, as were any-grade and grade 3 complication rates.

Perioperative outcomes and complication rates are critical issues for complex procedures such as RC. These outcomes have been reported extensively for ORC, including reports using standardized Martin criteria. In general, ORC is associated with a high risk of complications (>60%), including a considerable risk of high-grade complications (13–40% in large series) and mortality (up to 7% in some series) [101–105]. ORC outcomes appear to be associated with hospital and surgeon experience and volumes, with several studies demonstrating improved performance in high-volume centers by high-volume surgeons [106,107]. Our analysis suggests that RARC might provide benefit in terms of reduced blood loss and transfusion rates when compared with ORC, whereas operative time is shorter with ORC. Conversely, complication rates were mostly similar between RARC and ORC and slightly better for RARC in comparisons with LRC. However, many of the perioperative complications following RC may come from the reconstructive part of the procedure. Because most RARC cases reported had extracorporeal reconstruction, it can be hypothesized that this approach mitigated some potential benefit of a totally intracorporeal approach. However, intracorporeal diversion (especially orthotopic neobladder) is a very complex robotic procedure that is currently performed in very few centers and that has complication and readmission rates that appear quite high.

With regard to predictors of complications, in the most comprehensive report on ORC, Shabsigh et al demonstrated that sex, ASA score, and type of urinary diversion were associated with any grade of complications, whereas age at surgery, prior abdominal surgery, and estimated blood loss were associated with high-grade complications [101]. Moreover, Svatek et al suggested a role for BMI as a predictor of both any-grade and high-grade complications [104]. Very similar results were identified in our systematic review of the literature on RARC, with age, ASA score, Charlson comorbidity index, BMI, and blood transfusion among the most common predictors [28,39,43]. Notably, in a large multi-institutional study involving >900 patients from >20 institutions, Johar et al identified the use of neoadjuvant chemotherapy as a predictor for any-grade and major complication rates [43]. That finding is not in agreement with the literature on ORC [108] and needs to be reconfirmed in larger analyses.

With regard to the comparison of ORC and RARC, in a population-based analysis of the US Nationwide Inpatient Sample, Yu et al reported on >7000 patients receiving ORC and 1100 treated with RARC in 1050 hospitals from 44 states in the United States. Specifically, the authors found that RARC was associated with a lower rate of complications (49% vs 64%), reduced perioperative mortality (0% vs 2.5%), and lower parenteral nutrition use (6.4% vs 13.3%) compared with ORC, whereas blood transfusions and length of stay were similar in the two groups [109]. Conversely, in another population-based study evaluating almost 35 000 patients treated with ORC and 2100 with RARC at 279 hospitals across the United States between 2004 and 2010 and included in the Premier Perspective Database, Leow et al failed to demonstrate significant differences in 90-d postoperative mortality and major complication rates between RARC and ORC, whereas 46% decreased odds of minor complications, mainly due to reduced need for blood transfusion and total parenteral nutrition, were demonstrated [2]. On the whole, the data for our systematic review reconfirmed a lower risk of blood loss and transfusion for RARC compared with ORC and LRC and slightly lower risks of any-grade and high-grade complications at 90 d with RARC, whereas 30-d complication rates and 30- and 90-d mortality rates were similar for ORC and RARC. The reasons for such discrepancies are not clear but could include the well-known limited accuracy of population-based studies and differences in baseline characteristics of the patients treated with ORC and RARC both in population-based studies and in the comparative studies included in the present systematic review.

Although the conclusions of this systematic review represent the best evidence available in the literature, some drawbacks must be considered. The papers included in the present systematic review contained only three RCTs [78–80], and only one was adequately powered to assess a difference in complications [80]. Unfortunately, at the present time, that paper is published as a letter to the editor in the New England Journal of Medicine and reports a limited amount of data; a more detailed report of the study is awaited. Moreover, most of the other low-quality evidence did not adopt accurate methodology for reporting complications. It was almost impossible to evaluate the impact of surgeon ability on the reported results due to the fact that advanced analyses of the RARC learning curve are lacking, and most of the available studies stratifying patient outcomes according to prior experience with RARP or to the number of prior RARC cases performed were small and retrospective. However, two studies from the Karolinska Institute suggested a decrease in complication rates with increasing surgical experience [68,77]. Finally, our comparative analyses were not adjusted for the baseline differences in patient characteristics and surgical experience. Considering that most of the studies included were not RCTs, it is likely that major differences were present between study arms, and this might account for some of the observed findings.

4. Conclusions

RARC can be performed safely with acceptable operative time, little blood loss, and low transfusion rates. The risk of intraoperative complications is low, but postoperative complications and readmission after discharge are common. Cumulative analyses demonstrated that operative time was shorter with ORC, whereas blood loss and transfusion rates were significantly lower with RARC than with ORC. Conversely, rates for any-grade and grade 3 complications at 90 d were slightly lower with RARC than with ORC. Similarly, transfusion rates were lower with RARC than with LRC, as were any-grade and grade 3 complication rates. The lack of solid, high-quality evidence limits the strength of the data.

Author contributions: Giacomo Novara 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: Novara.

Acquisition of data: Novara, Yuh.

Analysis and interpretation of data: Novara.

Drafting of the manuscript: Novara.

Critical revision of the manuscript for important intellectual content: Novara, Catto, Wilson, Annerstedt, Chan, Declan G. Murphy, Motttrie, Peabody, Skinner, Wiklund, Guru, Yuh.

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Figure legends

Fig. 1 – Flowchart of the systematic review.

Fig. 2 – Comparison of (a) operative time, (b) blood loss, (c) transfusion rates, (d) intraoperative complication rates, and (e) in-hospital stay following robot-assisted radical cystectomy or open radical cystectomy.

CI = confidence interval; M-H = Mantel-Haenszel test; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy; SD = standard deviation; WMD = weighted mean difference.

Fig. 3 – Comparison of transfusion rates following robot-assisted radical cystectomy or laparoscopic radical cystectomy.

CI = confidence interval; LRC = laparoscopic radical cystectomy; M-H = Mantel-Haenszel test; RARC = robot-assisted radical cystectomy.

Fig. 4 – Comparison of rates for any grade of complication at (a) 30 d and (b) 90 d, (c) grade 3 complications at 30 and 90 d, (d) mortality at 30 and 90 d, and (e) major complication at 30 and 90 d following robot-assisted radical cystectomy or open radical cystectomy.

CI = confidence interval; M-H = Mantel-Haenszel test; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy.

Fig. 5 – Comparison of rates at 30 d for (a) any grade of complication and (b) grade 3 complications following robot-assisted radical cystectomy or laparoscopic radical cystectomy.

CI = confidence interval; LRC = laparoscopic radical cystectomy; M-H = Mantel-Haenszel test; RARC = robot-assisted radical cystectomy.

Table

Table 1 – Perioperative outcomes in robot-assisted radical cystectomy series stratified by urinary diversion type

Reference	Institution	IDEAL stage	Cases	Study design	Nerve-sparing surgery	Median/ mean operative time, min	Median/mean blood loss, ml	Transfusion rate, %	Intraoperative complications, %	Mean time to flatus, d	Mean time to bowel movement, d	In-hospital stay, d	Readmission rate
Mainly extracorporeal conduit diversion													
Guru et al, 2007 [8]	Roswell Park Cancer Institute, Buffalo, NY, USA	1	7	Prospective	–	–	335	–	0	–	–	8	–
Guru et al, 2007 [9]	Roswell Park Cancer Institute, Buffalo, NY, USA	1	20	Prospective	–	442	555	0	0	–	4	10	10%
Mottrie et al, 2007 [10]	O.L.V. Clinic, Aalst, Belgium	2a	27	Retrospective	29%	340	301	7	–	–	–	–	–
Hemal et al, 2008 [11]	All India Institute of Medical Sciences, New Delhi, India	1	6	Retrospective	–	330	200	17	0	–	–	9.2	0
Lowentritt et al, 2008 [12]	Tulane University Health Center, New Orleans, LA, USA	2a	4	Retrospective	–	375	338	0	0	–	–	5	–
Murphy et al, 2008 [13]	Guy's & St Thomas' NHS Foundation Trust, London, UK	2a	23	Retrospective	20%	397	278	4	–	–	–	11.6	–
Park et al, 2008 [14]	Yonsei University College of Medicine, Seoul, Korea	2a	4	Retrospective	–	355	550	–	–	–	–	12	–
Park et al, 2008 [15]	Yonsei University College of Medicine, Seoul, Korea	2a	11	Retrospective	–	309	615	–	–	–	–	–	–
Pruthi et al, 2008 [16]	University of North Carolina, Chapel Hill, NC, USA	2a	20	Retrospective	85%	366	313	–	5	2.1	2.8	4.4	–
Pruthi et al, 2008 [17]	University of North Carolina, Chapel Hill, NC, USA	2a	12 female	Retrospective	0	276	221	–	–	1.9	2.4	4.8	–
Pruthi et al, 2008 [18]	University of North Carolina, Chapel Hill, NC, USA	2b	50	Retrospective	–	306	271	–	–	2	2.6	4.5	–
Woods et al, 2008 [19]	Multicenter	2b	27	Retrospective	–	499	277	11	–	–	–	–	–
Yuh et al, 2008 [20]	Roswell Park Cancer Institute, Buffalo, NY, USA	2a	54	Retrospective	–	–	557	13	0	–	–	9.1	–
Gamboa et al, 2009 [21]	University of California, Irvine, CA, USA	2a	41	Retrospective	–	498	254	44	7	–	4	8	–
Pruthi et al, 2009 [22]	University of North Carolina, Chapel Hill, NC, USA	2b	50	Retrospective	–	302	268	–	–	1.9	2.6	4.5	–
Yuh et al, 2009 [23]	Roswell Park Cancer	2b	73	Retrospective	–	378	573	–	1	–	–	10	–

	Institute, Buffalo, NY, USA												
Hayn et al, 2010 [24]	Multicenter	2b	482	Retrospective	–	385	408	–	–	–	–	–	–
Josephson et al, 2010 [25]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	58	Retrospective	–	480	450	38	7	–	–	10	–
Kang et al, 2010 [26]	Multicenter	2b	104	Retrospective	–	554	526	–	4	3.4	–	18.4	–
Kasraeian et al, 2010 [27]	Montsouris Institute, Paris, France	2a	9	Retrospective	–	270	400	55	–	–	–	14	–
Kauffman et al, 2010 [28]	Weill Cornell Medical Center, New York, NY, USA	2b	79	Retrospective	–	360	400	3	0	–	–	5	–
Kwon et al, 2010 [29]	Kyungpook National University, Daegu, Korea	2a	17	Prospective	–	379	210	35	0	–	–	20.7	–
Martin et al, 2010 [30]	Multicenter	2b	59	Retrospective	–	–	–	–	–	–	–	–	–
Pruthi et al, 2010 [31]	University of North Carolina, Chapel Hill, NC, USA	2b	100	Retrospective	–	276	250/271	–	2	2.1	2.8	4.9	11% (30 d)
Hayn et al, 2011 [32]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	156	Prospective	–	577	400	16	–	–	–	8	21%)
Khan et al, 2011 [33]	Guy’s & St Thomas’ NHS Foundation Trust, London, UK	2a	50	Prospective	–	361	340	4	4	–	–	10	18%
Lavery et al, 2011 [34]	Ohio State University, Columbus, OH, USA	2a	15	Retrospective	–	423	160	–	–	–	–	3.4	13% (30 d)
Richards et al, 2011 [35]	Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA	2b	60	Retrospective	–	492	483	–	3	–	–	8.1	–
Shah et al, 2011 [36]	Ohio State University, Columbus, OH, USA	2b	30	Retrospective	–	411	170	3	–	–	–	3.3	20%
Lau et al, 2012 [37]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	23 aged >80 yr	Retrospective	–	384	300	61	4	–	–	13	–
Mmeje et al, 2013 [38]	Multicenter	2b	50	Retrospective	–	–	–	–	–	–	–	–	–
Smith et al, 2012 [39]	Multicenter	2b	227	Retrospective	–	291/327	200/256	–	–	–	–	5	–
Treiyer et al, 2012 [40]	University of Saarland, Homburg/Saar, Germany	2b	91	Retrospective	–	412	294	–	–	2.1	2.9	18.8	11% (30 d)
Tsui et al, 2012 [41]	Chang Gung University College of Medicine, Taoyuan, Taiwan	2a	8	Retrospective	–	430	763	63 (intraoperative)	–	–	–	10.8	–
Abbas et al, 2013 [42]	Cairo University, Cairo, Egypt	2a	25	Retrospective	–	618	700	40	–	–	–	–	–
Johar et al, 2013 [43]	Multicenter	2b	939	Retrospective	–	–	580	15	–	–	–	8	20%

Khan et al, 2013 [44]	Guy's & St Thomas Hospital, London, UK	1	14	Prospective	–	384	317	7	–	–	–	12.6	–
Marshall et al, 2013 [45]	Multicenter	2b	765	Retrospective	–	421	479	–	–	–	–	8	–
Saar et al, 2013 [46]	University of Saarland, Homburg/Saar, Germany	2b	62	Retrospective	–	410	404	–	–	2.2	2.9	17	13% (30 d)
Xylinas et al, 2013 [47]	Weill Cornell Medical Center, New York, NY, USA	2b	175	Retrospective	–	360	400	17	–	–	–	7	–
Al-Daghmin et al, 2014 [48]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	272	Prospective	–	373.9	487	14	–	–	–	–	25%
Lin et al, 2014 [49]	Taichung Veterans General Hospital, Taichung, Taiwan	2b	5	Retrospective	–	230	310	20	–	–	–	–	–
Phillips et al, 2014 [50]	Boston Medical Center, Boston, MA, USA	2b	23 (aged ≥80 yr)	Retrospective	–	253	208	30	–	–	–	8.2	–
Snow-Lisy et al, 2014 [51]	Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA	2b	17	Retrospective	–	–	–	–	–	–	–	–	–
Overall*						360 (range: 230–618)	375 (range: 208–763)	12% (range: 0–63%)	3% (range: 0–4%)	2.5 (range: 2.1-3.4)	3.1 (range: 2.8–4)	8.7 (range: 3.3–20.7)	19% (range: 0–25%)
Mainly extracorporeal continent diversion													
Menon et al, 2003 [52]	Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA	1	17	Retrospective	–	300	–	–	–	–	–	–	–
Menon et al, 2004 [53]	Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA	1	3 female	Retrospective	–	323	167	–	–	–	–	6.7	–
Manoharan et al, 2011 [54]	Miller School of Medicine, University of Miami, Miami, FL, USA	2a	14	Retrospective	–	360	310	–	0	–	–	8.5	–
Torrey et al, 2012 [55]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	34	Retrospective	–	510	504	53	–	–	–	12.9	39%
Yuh et al, 2012 [56]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	196	Retrospective	–	432	400	44	–	–	–	9	–
Pham et al, 2013 [57]	Medical College of Wisconsin, Milwaukee, WI, USA	2b	11	Retrospective	–	496	**315**	–	–	–	–	–	–
Nazmy et al, 2014 [58]	City of Hope Comprehensive	2b	209	Retrospective	–	–	–	–	–	–	–		

	Cancer Center, Duarte, CA, USA												
Yuh et al, 2014 [59]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	162	Retrospective	–	438	400	–	–	–	–	–	–
Overall*						420 (range: 300–496)	390 (range: 167–400)	44	0	–	–	8.9 (range: 6.7–9)	39%
Mainly intracorporeal conduit diversion													
Yohannes et al, 2003 [60]	Creighton University, Omaha, NE, USA	1	2	Retrospective	0	660	1118	–	–	–	–	6	–
Pruthi et al, 2010 [61]	University of North Carolina, Chapel Hill, NC, USA	2a	12	Retrospective	–	318	221	–	0	2.2	3.2	4.5	17%
Jonsson et al, 2011 [62]	Karolinska Institute, Stockholm, Sweden	2b	9	Prospective	–	460	350	–	–	–	–	17	–
Goh et al, 2012 [63]	Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	2a	7	Prospective	–	450	200	71	0	–	–	9	43%
Poch et al, 2012 [64]	Roswell Park Cancer Institute, Buffalo, NY	2b	56	Retrospective	–	356	338	–	–	–	–	7.9	29% (30 d)
Azzouni et al, 2013 [65]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	100	Retrospective	–	352	300	10	–	–	–	9	16% (30 d) /20% (90 d)
Bishop et al, 2013 [66]	Hertfordshire and South Bedfordshire Urological Cancer Centre, Lister Hospital, Stevenage, UK	2a	8	Not reported	–	360	225	25	–	–	–	9	0
Collins et al, 2013 [67]	Karolinska Institute, Stockholm, Sweden	2b	43	Prospective	16%	292	200	–	–	–	–	9	–
Overall*						340 (range: 292–660)	270 (range: 200–1118)	14.7% (range: 10–71%)	0	2.2	3.2	8.6 (range: 4.5–9)	19.7% (range: 0–43%)
Mainly intracorporeal continent diversion													
Jonsson et al, 2011 [62]	Karolinska Institute, Stockholm, Sweden	2b	36	Prospective	–	480	625	–	–	–	–	9	–
Schumacher et al, 2011 [68]	Karolinska Institute, Stockholm, Sweden	2b	45	Retrospective	–	476	669	–	–	–	–	9	–
Goh et al, 2012 [63]	Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	2a	8	Prospective	–	450	225	37	0	–	–	8	75%
Collins et al, 2013 [67]	Karolinska Institute, Stockholm, Sweden	2b	70	Prospective	70%	420	500	–	–	–	–	9	–

Tyritzis et al, 2013 [69]	Karolinska Institute, Stockholm, Sweden	2b	70	Prospective	58% BNS 8% UNS	420	500	4	–	–	–	9	–
Overall*						420 (range: 420–450)	480 (range: 225–500)	7% (range: 4–37%)	0	–	–	8.5 (range: 8–9)	75%

BNS = bilateral nerve sparing; UNS = unilateral nerve sparing.

* Once duplicate publications from the same centers and multicenter papers were excluded.

Table 2 – Impact of patient characteristics on perioperative outcomes in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases	Study design	Intracorporeal urinary diversion %	Conduit diversion, %	Median/ mean operative time, min	Median/mean blood loss, ml	Transfusion rate, %	Intraoperative complications, %	Mean time to flatus, d	Mean time to bowel movement, d	In-hospital stay, d	Readmission rate
Patient BMI														
Butt et al, 2008 [70]	Roswell Park Cancer Institute, Buffalo, NY, USA	2a	BMI <25: 14	Retrospective	0	100	359	630	–	0	–	–	11.8	–
			BMI 25–29: 18			89	366	496					7.7	
			BMI ≥30: 17			94	371	532					9.1	
Poch et al, 2012 [64]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	56	Retrospective	100	100	356	338	–	–	–	–	7.9	29% (30 d)
			BMI <25 : 14				349	150					7	23% (30 d)
			BMI 25 to <30: 21				380	300					8	33% (30 d)
			BMI ≥30: 21				349	500					8.5	32% (30 d)

BMI = body mass index.

Table 3 – Impact of surgical factors on perioperative outcomes in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases	Study design	Intracorporeal urinary diversion, %	Conduit diversion, %	Median/mean operative time, min	Median/mean blood loss, ml	Transfusion rate, %	Intraoperative complications	Mean time to flatus, d	Mean time to bowel movement, d	In-hospital stay, d	Readmission rate
Case volume														
Pruthi et al, 2008 [18]	University of North Carolina, Chapel Hill, NC, USA	2b	50	Retrospective	0	58	306	271	–	–	2	2.6	4.5	–
			Cases 1–10			70	378	335			2.1	2.8	4.2	
			Cases 11–20			60	342	330			2.2	3	4.6	
			Cases 21–30			50	276	245			1.9	2.4	4.6	
			Cases 31–40			40	270	233			1.7	2.1	4.2	
			Cases 41–50			70	264	210			1.9	2.6	4.9	
Hayn et al, 2011 [71]	Roswell Park Cancer Institute, Buffalo, NY, USA	2a	Cases 1 – 50	Prospective	–	93	–	566	–	–	–	–	–	–
			Cases 51 – 100					631						
			Case 101–164					521						
Richards et al, 2011 [35]	Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA	2b	60	Retrospective	0	92	492	483	–	3%	–	–	8.1	–
			Cases 1–20			80	524	511					9.2	
			Cases 21–40			95	503	459					7.8	
			Cases 41–60			100	449	479					7.4	
Schumacher et al, 2011 [68]	Karolinska Institute, Stockholm, Sweden	2b	45	Retrospective	100	20	476	669	–	–	–	–	9	–
			Cases 1–15			33	532	627					12	
			Cases 16–30			20	462	728					8	
			Cases 31–45			7	434	654					8	
Azzouni et al, 2013 [65]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	100	Retrospective	100	100	352	300	10	–	–	–	9	16% (30 d), 20% (90 d)
			Cases 1–25				366	400	0				7	12% (30 d), 12% (90 d)
			Cases 26–50				349	350	12				9	20% (30 d), 28% (90 d)
			Cases 51–				373	300	4				10	20% (30

			75											d), 24% (90 d)
			Cases 76–100				344	200	24				9	16% (30 d), 20% (90 d)
Prior RARP experience														
Hayn et al, 2010 [72]	Multicenter	2b	482	Retrospective	–	75	385	408	–	–	–	–	–	–
			≤50 previous RARP: 83				421	418						
			51–100 previous RARP: 173				338	286						
			101–150 previous RARP: 168				401	575						
			>150 previous RARP: 48				444*	188*						
Intracorporeal vs extracorporeal diversion														
Guru et al, 2010 [73]	Roswell Park Cancer Institute, Buffalo, NY, USA	2a	13 extracorporeal ileal conduit	Prospective	0	100	387	454	–	0	–	–	8.5	23%
			13 intracorporeal ileal conduit		100		391	315		8			8.8	8%
Kang et al, 2012 [74]	Korea University School of Medicine, Seoul	2a	22 extracorporeal ileal conduit	Retrospective	0	100	420	370	–	–	2.5	–	14.5	–
			3 intracorporeal ileal conduit		100		510	400					14.2	
Kang et al, 2012 [74]	Korea University School of Medicine, Seoul	2a	14 extracorporeal neobladder	Retrospective	0	0	496	390	–	–	2.3	–	16.8	–
			1 intracorporeal neobladder		100		545	500			2.5		14	

RARP = robot-assisted radical prostatectomy.

Table 4 – Complication rates in robot-assisted radical cystectomy series

<table>
<tr><th rowspan="2">Reference</th><th rowspan="2">Institution</th><th rowspan="2">IDEAL stage</th><th rowspan="2">Cases</th><th rowspan="2">Study design</th><th rowspan="2">Martin criteria</th><th rowspan="2">Follow-up duration</th><th rowspan="2">Overall complication rate, %</th><th colspan="5">Complication rate, %</th></tr>
<tr><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th><th>Grade 5</th></tr>
<tr><td colspan="13">Mainly extracorporeal conduit diversion</td></tr>
<tr><td>Guru et al, 2007 [8]</td><td>Roswell Park Cancer Institute, Buffalo, NY, USA</td><td>1</td><td>7</td><td>Prospective</td><td>4</td><td>–</td><td>14</td><td>0</td><td>14</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Guru et al, 2007 [9]</td><td>Roswell Park Cancer Institute, Buffalo, NY, USA</td><td>1</td><td>20</td><td>Prospective</td><td>4</td><td>–</td><td>–</td><td>–</td><td>–</td><td>10</td><td>0</td><td>5</td></tr>
<tr><td>Hemal et al, 2008 [11]</td><td>All India Institute of Medical Sciences, New Delhi, India</td><td>1</td><td>6</td><td>Retrospective</td><td>3</td><td>–</td><td>–</td><td>–</td><td>–</td><td colspan="3">0</td></tr>
<tr><td>Murphy et al, 2008 [13]</td><td>Guy's & St Thomas' NHS Foundation Trust, London, UK</td><td>2a</td><td>23</td><td>Retrospective</td><td>3</td><td>–</td><td>26</td><td>4</td><td>4</td><td>18</td><td>–</td><td>–</td></tr>
<tr><td>Park et al, 2008 [14]</td><td>Yonsei University College of Medicine, Seoul, Korea</td><td>2a</td><td>4</td><td>Retrospective</td><td>–</td><td>–</td><td>–</td><td colspan="2">–</td><td colspan="3">0</td></tr>
<tr><td>Pruthi et al, 2008 [16]</td><td>University of North Carolina, Chapel Hill, NC, USA</td><td>2a</td><td>20</td><td>Retrospective</td><td>5</td><td>90 d</td><td>30</td><td colspan="2">15</td><td>15</td><td>–</td><td>–</td></tr>
<tr><td>Woods et al, 2008 [19]</td><td>Multi-institutional</td><td>2b</td><td>27</td><td>Retrospective</td><td>3</td><td>–</td><td>33</td><td colspan="2">–</td><td colspan="3">–</td></tr>
<tr><td>Gamboa et al, 2009 [21]</td><td>University of California, Irvine, CA, USA</td><td>2a</td><td>41</td><td>Retrospective</td><td>4</td><td>–</td><td>29</td><td colspan="2">17</td><td colspan="2">12</td><td>0</td></tr>
<tr><td rowspan="2">Kauffman et al, 2010 [28]</td><td rowspan="2">Weill Cornell Medical Center, New York, NY, USA</td><td rowspan="2">2b</td><td rowspan="2">79</td><td rowspan="2">Retrospective</td><td rowspan="2">9</td><td>30 d</td><td>69</td><td colspan="2">58</td><td>8</td><td>3</td><td rowspan="2">0</td></tr>
<tr><td>90 d</td><td>100</td><td>37</td><td>42</td><td>17</td><td>4</td></tr>
<tr><td>Kang et al, 2010 [26]</td><td>Multicenter</td><td>2b</td><td>104</td><td>Retrospective</td><td>8</td><td>–</td><td>27</td><td colspan="2">19</td><td>6</td><td>0</td><td>2</td></tr>
<tr><td>Kwon et al, 2010 [29]</td><td>Kyungpook National University, Daegu, Korea</td><td>2a</td><td>17</td><td>Prospective</td><td>7</td><td>–</td><td>29</td><td colspan="2">29</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Pruthi et al, 2010 [31]</td><td>University of North Carolina, Chapel Hill, NC</td><td>2b</td><td>100</td><td>Retrospective</td><td>7</td><td>30 d</td><td>36</td><td colspan="2">28</td><td colspan="3">8</td></tr>
<tr><td rowspan="2">Hayn et al, 2011 [32]</td><td rowspan="2">Roswell Park Cancer Institute, Buffalo, NY, USA</td><td rowspan="2">2b</td><td rowspan="2">156</td><td rowspan="2">Prospective</td><td rowspan="2">10</td><td>30 d</td><td>40</td><td>10</td><td>17</td><td>11</td><td>0</td><td>2</td></tr>
<tr><td>90 d</td><td>48</td><td>14</td><td>21</td><td>15</td><td>0</td><td>2</td></tr>
<tr><td>Khan et al, 2011 [33]</td><td>Guy's & St Thomas' NHS Foundation Trust, London, UK</td><td>2a</td><td>50</td><td>Prospective</td><td>8</td><td>90 d</td><td>34</td><td>6</td><td>18</td><td>10</td><td>0</td><td>0</td></tr>
<tr><td>Lau et al, 2012 [37]</td><td>City of Hope Comprehensive</td><td>2b</td><td>23 (aged >80 yr)</td><td>Retrospective</td><td>8</td><td>30 d</td><td>78</td><td>4</td><td>58</td><td>31</td><td>0</td><td>4</td></tr>
</table>

	Cancer Center, Duarte, CA, USA											
Saar et al, 2013 [46]	University of Saarland, Homburg/Saar, Germany	2b	62	Retrospective	9	30 d	44	11	23	8	0	2
Smith et al, 2012 [39]	Multicenter	2b	227	Retrospective	5	30 d	30	23		7		0
Treiyer et al, 2012 [40]	University of Saarland, Homburg/Saar, Germany	2b	91	Retrospective	6	30 d	49	15	23	7	3	1
Johar et al, 2013 [43]	Multicenter	2b	939	Retrospective	9	30 d	41	–		–	–	1.3
						90 d	48	29		14.8		4.2
Xylinas et al, 2013 [47]	Weill Cornell Medical Center, New York, NY, USA	2b	175	Retrospective	10	30 d	42	8	22	7	3	2
						90 d	45	–	–	–	–	4
Al-Daghmin et al, 2014 [48]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	272	Prospective	8	30 d	–	–		–		1
						90 d	77	58		14		5
Phillips et al, 2014 [50]	Boston Medical Center, Boston, MA, USA	2b	23 (aged ≥80 yr)	Retrospective	7	90 d	35	0	31	4	0	0
Snow-Lisy et al, 2014 [51]	Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA	2b	17	Retrospective	5	–	53	12	12	17	12	0
Overall*						30 d	Any-grade complication: 44% (range: 26–78%)	Low–grade complication: 29.4% (range: 8–62%)		High–grade complication: 11.8% (range: 0–35%) Reoperation: 9.7% (range: 0–31%) Mortality: 1.6% (range: 0–4%)		
						90 d	Any-grade complication: 59% (range: 30–77%)	Low–grade complication: 54% (range: 15–79%)		High–grade complication: 15% (range: 4–19%) Reoperation: 14% (range: 4–17%) Mortality: 3% (range: 0–5%)		
Mainly extracorporeal continent diversion												
Josephson et al, 2010 [25]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	58	Retrospective	4	90 d	69	64		3		2
Kasraeian et al, 2010 [27]	Montsouris Institute, Paris, France	2a	9	Retrospective	5	–	33	0	11	22	0	0
Torrey et al, 2012 [55]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	34	Retrospective	9	90 d	91	16	69	14	0	1
Yuh et al, 2012 [56]	City of Hope Comprehensive Cancer Center,	2b	196	Retrospective	10	90 d	80	45		31		4

	Duarte, CA, USA											
Nazmy et al, 2014 [58]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	209	Retrospective	10	90 d	77	45		27		5
Yuh et al, 2014 [59]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	162	Retrospective	8	52 mo	82	45		37		
Mainly intracorporeal conduit diversion												
Pruthi et al, 2010 [61]	University of North Carolina, Chapel Hill, NC, USA	2a	12	Retrospective	5	30 d	42	–	–	–	–	–
						90 d	58					
Jonsson et al, 2011 [62]	Karolinska Institute, Stockholm, Sweden	2b	9	Prospective	8	30 d	44	11	0	22	11	0
						After first 30 d	33	22	0	22	0	0
Goh et al, 2012 [63]	Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	2a	7	Prospective	8	30 d	45	45		0		
						After first 30 d	14	14				
Azzouni et al, 2013 [65]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	100	Retrospective	8	30 d	63	50		13		
						90 d	81	66		15		
Bishop et al, 2013 [66]	Hertfordshire and South Bedfordshire Urological Cancer Centre, Lister Hospital, Stevenage, UK	2a	8	Not reported	6	30 d	75	25	25	25	0	0
Collins et al, 2013 [67]	Karolinska Institute, Stockholm, Sweden	2b	43	Prospective	8	30 d	86	9	23	42	12	0
						After first 30 d	23	0	0	19	2	2
Overall*						30 d	Any-grade complication: 67% (range: 42–86%)	Low–grade complication: 45% (range: 32–50%)		High–grade complication: 24% (range: 0–54%) Reoperation: 39% (range: 25–42%) Mortality: 0%		
						30–90 d	Any-grade complication: 22% (range: 14–23%)	Low–grade complication: 2% (range: 0–14%)		High–grade complication: 20% (range: 0–23%) Reoperation: 19% Mortality: 1.7% (range: 0–2%)		
						90 d	Any-grade complication: 59% (range: 30–77%)	Low–grade complication: 66%		High–grade complication: 15% Reoperation: 25% (range: 14–51%) Mortality: 1.7% (range: 0–2%)		
Mainly intracorporeal continent diversion												
Akbulut et al, 2011 [75]	Ankara Ataturk training and research hospital	2a	12	Not reported	7	30 d	67	25	25	17	0	0
						After first 30 d	41	8	17	8	0	8
Jonsson et al, 2011 [62]	Karolinska Institute, Stockholm, Sweden	2b	36	Prospective	8	30 d	39	14	6	19	0	0
						After first 30 d	33	14	3	16	0	0
Schumacher et al, 2011 [68]	Karolinska Institute, Stockholm, Sweden	2b	45	Retrospective	10	30 d	40	13	4	20	2	0
						After first 30 d	31	11	2	18	0	0

Canda et al, 2012 [76]	Ankara Ataturk training and research hospital	2a	27	Not reported	6	30 d	48	11	22	11	0	4
						After first 30 d	27	4	11	8	0	4
Goh et al, 2012 [63]	Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	2a	8	Prospective	8	30 d	62	37		25		0
						After first 30 d	12	–		12		0
Collins et al, 2013 [67]	Karolinska Institute, Stockholm, Sweden	2b	70	Prospective	8	30 d	43	4	8	20	11	0
						After first 30 d	34	0	13	19	1	1
Overall*						30 d	Any-grade complication: 45.7% (range: 43–62%)	Low–grade complication: 19% (range: 12–33%)		High–grade complication: 28% (range: 15–33%) Reoperation: 17% (range: 11–20%) Mortality: 1% (range: 0–4%)		
						30–90 d	Any-grade complication: 30% (range: 12–34%)	Low–grade complication: 13.5% (range: 13–15%)		High–grade complication: 18% (range: 12–21%) Reoperation :16% (range: 8–19%) Mortality: 1.7% (range: 0–4%)		
						90 d	–	–		Reoperation: 33% (range: 19–39%) Mortality: 2.7% (range: 0–8%)		

* Once duplicate publications from the same centers and multicenter papers were excluded.

Table 5 – Impact of patients characteristics and surgical factors on complication rates in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases	Study design	Intracorporeal urinary diversion, %	Conduit diversion, %	Martin criteria	Follow-up duration	Overall complication rate, %	Complication rate, %				
										Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Patients BMI														
Butt et al, 2008 [70]	Roswell Park Cancer Institute, Buffalo, NY, USA	2a	BMI <25: 14	Retrospective	0	100	5	–	21	–	–	–	–	0
			BMI 25–29: 18			89			33					0
			BMI ≥30: 17			94			24					6
Poch et al, 2012 [64]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	56	Retrospective	100	100	5	90 d	57	–	–	–	–	–
			BMI <25 : 14						43					
			BMI 25 to <30: 21						67					
			BMI ≥30: 21						57					
Case volume														
Hayn et al, 2011 [71]	Roswell Park Cancer Institute, Buffalo, NY, USA	2a	Cases 1–50	Prospective	–	93	9	240 d	68	26	18	18	0	6
			Cases 51–100						62	14	22	24	0	2
			Case 101–164						62	17	23	21	0	0
Richards et al, 2011 [35]	Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA	2b	60	Retrospective	0	92	6	90 d	43	3	53	33	10	3
			Cases 1–20			80			70*	5	45	5	10	5
			Cases 21–40			95			30*	0	20	10	0	0
			Cases 41–60			100			30*	0	15	10	5	0
Schumacher et al, 2011 [68]	Karolinska Institute, Stockholm, Sweden	2b	45	Retrospective	100	20	10	30 d (>30 d)	40 (31) *	13 (11)	4 (2)	20 (18)	2 (0)	0
			Cases 1–15			33			66 (53) *	27 (7)	7 (7)	27 (40)	7 (0)	
			Cases 16–30			20			27 (20) *	13 (7)	7 (0)	7 (14)	0 (0)	
			Cases 31–45			7			27 (20) *	0 (20)	0 (0)	27 (0)	0 (0)	
Azzouni et al, 2013 [65]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	100	Retrospective	100	100	8	30 d (90 d)	63 (81)	50 (66)		13 (15)		
			Cases 1–25						52 (72)	32 (48)		20 (24)		
			Cases 26–50						56 (76)	36 (56)		20 (20)		
			Cases 51–75						76 (88)	68 (80)		8 (8)		
			Cases 76–100						68 (88)	64 (80)		4 (8)		
Collins et al, 2014 [77]	Karolinska	2b	Cases 1–10	Prospective	100	0	6	30 d (>30 d)	70 * (60)*	10 (0)	30 (10)	20 (50)	10 (0)	0
			Cases 11–20						20 * (40)*	10 (0)	0 (10)	0 (20%)	10%	

	Institute, Stockholm, Sweden												(10%)	
			Cases 21–30						20 * (20)*	0 (0)	0 (20)	20 (0)	0 (0)	
			Cases 31–40						30 * (10)*	0 (0)	0	30 (10)	0 (0)	
			Cases 41–47						29 * (29)*	0 (0)	0 (29)	0 (0)	29 (0)	
Intracorporeal vs extracorporeal diversion														
Guru et al, 2010 [73]	Roswell Park Cancer Institute, Buffalo, NY, USA	2a	13 intracorporeal ileal conduit	Prospective	100	100	7	90 d	30	0	15	15	0	0
			13 extracorporeal ileal conduit		0				38		23	15		
Kang et al, 2012 [74]	Korea University School of Medicine, Seoul, Korea	2a	38 extracorporeal diversion	Retrospective	0	58	5	90 d	42	21		21		
			4 intracorporeal diversion		100	75			25	25		0		

BMI = body mass index.

* Statistically significant.

Table 6 – Predictors of complication rates in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases	Study design	Martin criteria	Follow-up duration	Overall complication rate, %	Predictors of complications
Mainly extracorporeal conduit diversion								
Kauffman et al, 2010 [28]	Weill Cornell Medical Center, New York, NY, USA	2b	79	Retrospective	9	30 d	69	Any-grade complications: creatinine level >1.4 mg/dl, i.v. fluids >5000 ml High-grade complications: patients aged >65 yr, EBL >500 ml, and i.v. fluids >5000 ml
						90 d	100	
Smith et al, 2012 [39]	Multicenter	2b	227	Retrospective	5	30 d	30	High-grade complications: aged <65 yr, higher ASA score
Johar et al, 2013 [43]	Multicenter	2b	939	Retrospective	9	30 d	41	Any-grade complications: age, BMI, neoadjuvant chemotherapy, receipt of blood transfusion, conduit diversion High-grade complications: age, BMI, neoadjuvant chemotherapy, current smoking, receipt of blood transfusion
						90 d	48	
Al-Daghmin et al, 2014 [48]	Roswell Park Cancer Institute, Buffalo, NY, USA	2b	272	Prospective	8	30 d	–	30-d readmission: BMI 90-d readmission: sex and BMI
						90 d	77	
Mainly extracorporeal continent diversion								
Yuh et al, 2012 [56]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	196	Retrospective	10	90 d	80	90-d any-grade complications: age, ASA, preop HCT, OR time, EBL, diversion type 90-d high-grade complications: CCI, preop. HCT, orthotopic diversion
Nazmy et al, 2014 [58]	City of Hope Comprehensive Cancer Center, Duarte, CA, USA	2b	209	Retrospective	10	90 d	77	90-d any-grade complications: ASA, preop HCT, diversion type 90-d high-grade complications: CCI, HCT, diversion type

ASA = American Society of Anesthesiologists; BMI = body mass index; CCI = Charlson comorbidity index; EBL = estimated blood loss; HCT = hematocrit; i.v. = intravenous; OR = operating room; preop = preoperative.

Table 7 – Perioperative parameters and intraoperative complication rates after open, laparoscopic, and robot-assisted radical cystectomy

Comparison	LOE	Reference	No. of cases	Median/ mean operative time, min	Median/mean blood loss, ml	Transfusion rate, %	Intraoperative complications, %	Mean time to flatus, d	Mean time to bowel movement, d	In-hospital stay, d
RARC vs ORC	2b									
		Nix et al, 2010 [78]	21 RARC 20 ORC	252 211	258 575	–	–	2.3 3.2	3.2 4.3	5.1 6.0
		Parekh et al, 2013 [79]	20 RARC 20 ORC	308 ± 77 288 ± 60	627 ± 554 1113 ± 935	40 50	–	–	–	9.2 ± 7.8 8.9 ± 5.6
		Bochner et al, 2014 [80]	60 RARC 58 ORC	456 ± 82 329 ± 77	–	–	–	–	–	8 ± 3 8 ± 5
	4									
		Rhee et al, 2006 [81]	7 RARC 23 ORC	638 ± 46 507 ± 110	479 ± 551 1109 ± 398	57 87	–	–	–	11 ± 2 13 ± 3
		Galich et al, 2006 [82]	13 RARC 24 ORC	697 395	500 1250	54 75	–	–	–	–
		Pruthi et al, 2007 [83]	20 RARC 24 ORC	366 222	313 588	–	5 0	2.1 2.9	2.8 3.8	4.4 5.3
		Ng et al, 2010 [84]	83 RARC 104 ORC	375 ± 90 357 ± 132	460 ± 299 1172 ± 916	–	–	–	–	5.5 8
		Richards et al, 2010 [85]	35 RARC 35 ORC	530 240	350 1000	17 71	–	–	–	7 8
		Martin et al, 2011 [86]	19 RARC 14 ORC	280 320	255 696	–	–	–	–	5 10
		Gondo et al, 2012 [87]	11 RARC 15 ORC	408.5 ± 55.886 363 ± 111.255	656.9 ± 452.02 1788.7 ± 972.13	0 40	9 0	–	–	40.2 ± 9.282 37 ± 9.921
		Khan et al, 2012 [88]	48 RARC 52 ORC	386 320	337 1351	4 58	–	–	–	9.9 19.2

		Styn et al, 2012 [89]	50 RARC 100 ORC	455 ± 100 349 ± 87	350 475	4 24	–	–	–	9.5 ± 8.8 10.2 ± 8.4
		Sung et al, 2012 [90]	35 RARC 104 ORC	578 ± 153 501 ± 110	448.0 ± 231.6 1063.4 ± 892.7	11 57	1 0	–	–	28.9 ± 11.9 27.1 ± 13.4
		Anderson et al, 2013 [91]	103 RARC 375 ORC	403 ± 93 281 ± 77	411 ± 271 806 ± 660	–	–	–	–	–
		Kader et al, 2013 [92]	100 RARC 100 ORC	451 393	420 983	15 47	–	–	–	7.8 12.2
		Knox et al, 2013 [93]	58 RARC 84 ORC	468 396	276 1522	5 80	–	4.3 5.9	–	6.3 10.8
		Maes et al, 2013 [94]	14 RARC 14 ORC	383 268	470 942	7 29	–	–	–	11.2 11.4
		Musch et al, 2014 [95]	100 RARC 42 ORC	410 ± 68 351± 92	351 ± 170 810 ± 621	27 60	3 5	–	2.3 ± 1.5 2.3 ± 1.1	17.1 ± 7.6 19.9 ± 12
		Nepple et al, 2013 [96]	36 RARC 29 ORC	410 345	675 1497	39 83	–	–	–	7.9 9.6
		Trentman et al, 2013 [97]	96 RARC 102 ORC	372 ± 73 259 ± 70	257.7 ± 164.3 601.8 ± 491.4	31 60	–	–	–	7.1 ± 5.8 9.8 ± 5
		Ahdoot et al,2014 [98]	51 RARC 51 ORC	346 369	300 900	22 33	–	–	–	7 7
RARC vs LRC	4									
		Abraham et al, 2007 [100]	14 RARC 20 LRC	410 419	212 653	42 70	7 15	–	–	5.8 ± 0.9 9.4 ± 7.4
		Khan et al, 2012 [88]	48 RARC 58 LRC	386 316	337 480	4 26	–	–	–	9.9 16

LOE = level of evidence; LRC = laparoscopic radical cystectomy; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy.

Table 8 – Comparative studies evaluating complication rates after open, laparoscopic, and robot-assisted radical cystectomy

Comparison	LOE	Reference	No. of cases	Intracorporeal urinary diversion, %	Conduit diversion, %	Martin criteria	Follow-up	Overall complication rate, %	Complications rate, %				
									Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
RARC vs ORC	2b	Nix et al, 2010 [78]	21 RARC 20 ORC	0	66 70	3	–	33 50	–	–	–	–	–
		Parekh et al, 2013 [79]	20 RARC 20 ORC	0	–	4	–	–	–	25 25			
		Bochner et al, 2014 [80]	60 RARC 58 ORC	0				–	–	–	22 21		
	4												
		Galich et al, 2006 [82]	13 RARC 24 ORC	0	100	6	–	15 17	–	–	–	–	0 4
		Wang et al, 2008 [99]	33 RARC 21 ORC	0	53 52	5	–	21 24	–	–	–		
		Pruthi et al, 2007 [83]	20 RARC 24 ORC	0	50	5	90 d	30 33	–	–	–	–	–
		Ng et al, 2010 [84]	83 RARC 104 ORC	0	57 49	10	30 d	41 59	12 7	19 22	8 19	1 6	0 5
							90 d	48 61	13 8	17 23	16 20	1 6	0 6
		Richards et al, 2010 [85]	35 RARC 35 ORC	0	86	6	30 d	60 66	3 11	37 29	11 14	6 11	3 0
		Gondo et al, 2012 [87]	11 RARC 15 ORC	0	63 60	5	30 d	54 73	18 40	36 27	0 7	0 0	0 0
		Khan et al, 2012 [88]	48 RARC 52 ORC	0	87 90	7	–	42 71	25 40		17 27	0 2	0 2
		Styn et al, U2012 [89]	50 RARC 100 ORC	0	72 72	8	30 d	66 62	72 79		28 21		
		Sung et al, 2012 [90]	35 RARC 104 ORC	0	37 82	8	90 d	63 74	26 5	29 45	6 16	0 4	3 3
		Kader et al, 2013	100	0	97	6	90 d	35	1	25	6	3	1

		[92]	RARC 100 ORC		83			57	7	30	11	11	0
		Knox et al, 2013 [93]	58 RARC 84 ORC	0	91 89	8	30 d	24 58	5 4	12 38	21 14	3 6	2 2
							90 d	45 78	–		–		
							>90 d	73 88					
		Maes et al, 2013 [94]	14 RARC 14 ORC	0	100 –	4	–	57 78	36 64		21 14		
		Musch et al, 2014 [95]	100 RARC 42 ORC	0	76 –	10	90 d (60 d for ORC)	59 93	35 51		24 43		
RARC vs LRC	4												
		Abraham et al, 2007 [100]	14 RARC 20 LRC	0 0	100 100	5	–	21 55	– –	14 35	7 20	– –	– –
		Khan et al, 2012 [88]	48 RARC 58 ORC	0	87 96	7	–	42 81	25 41		17 36	0 0	0 3

LOE = level of evidence; LRC = laparoscopic radical cystectomy; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy.

Illustration

Figure 1

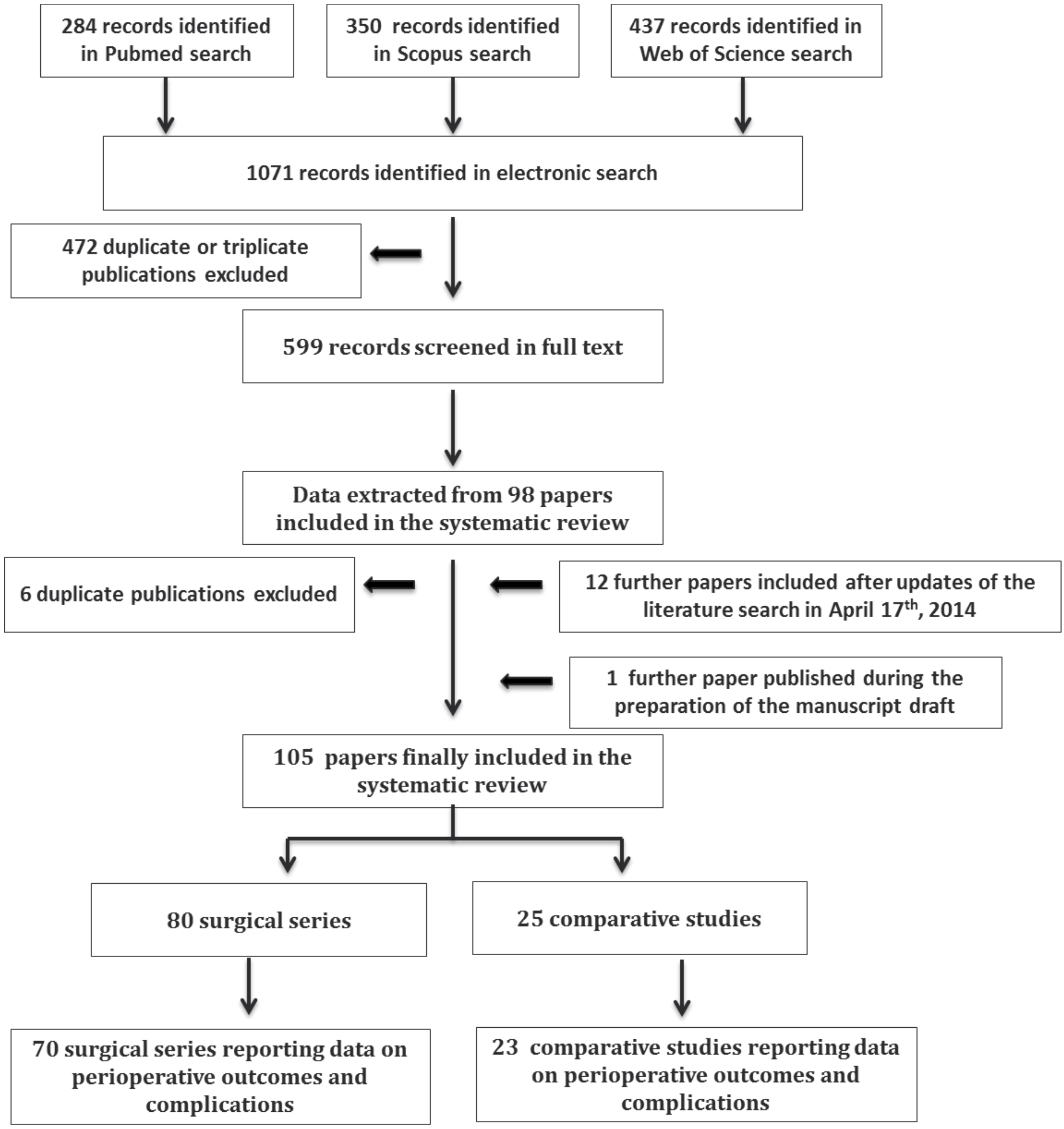
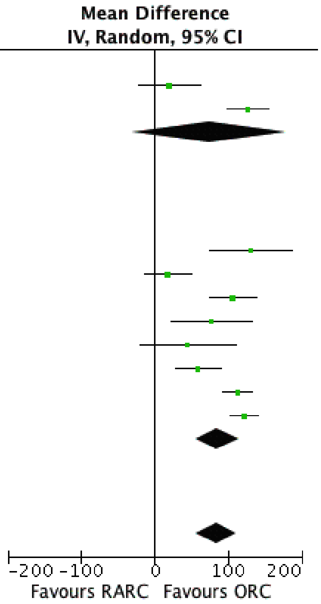


Figure 2

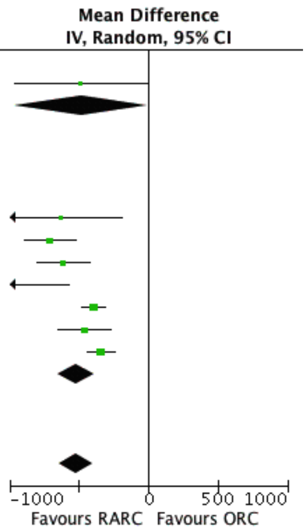
(A)

Study or Subgroup	RARC Mean	RARC SD	RARC Total	ORC Mean	ORC SD	ORC Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.1.1 Randomized studies									
Parekh 2013	308	77	20	288	60	20	9.5%	20.00 [-22.78, 62.78]	2013
Bochner 2014	456	82	60	329	77	58	11.1%	127.00 [98.31, 155.69]	2014
Subtotal (95% CI)			**80**			**78**	**20.6%**	**74.73 [-30.11, 179.56]**	
Heterogeneity: Tau² = 5379.13; Chi² = 16.57, df = 1 (P < 0.0001); I² = 94%									
Test for overall effect: Z = 1.40 (P = 0.16)									
1.1.2 Non-randomized studies									
Rhee 2006	638	46	7	507	110	23	8.1%	131.00 [74.59, 187.41]	2006
Ng 2010	375	90	83	357	132	104	10.7%	18.00 [-13.91, 49.91]	2010
Styn 2012	455	100	50	349	87	100	10.7%	106.00 [73.46, 138.54]	2012
Sung 2012	578	153	35	501	110	104	8.2%	77.00 [22.08, 131.92]	2012
Gondo 2012	408.5	55.8	11	363	111.2	15	7.2%	45.50 [-19.72, 110.72]	2012
Musch 2013	410	68	100	351	92	42	10.8%	59.00 [28.15, 89.85]	2013
Trentman 2013	372	73	96	259	70	102	11.8%	113.00 [93.06, 132.94]	2013
Anderson 2013	403	93	103	281	77	375	11.9%	122.00 [102.42, 141.58]	2013
Subtotal (95% CI)			**485**			**865**	**79.4%**	**85.32 [56.80, 113.83]**	
Heterogeneity: Tau² = 1295.79; Chi² = 42.64, df = 7 (P < 0.00001); I² = 84%									
Test for overall effect: Z = 5.86 (P < 0.00001)									
Total (95% CI)			**565**			**943**	**100.0%**	**83.60 [57.06, 110.14]**	
Heterogeneity: Tau² = 1444.29; Chi² = 59.24, df = 9 (P < 0.00001); I² = 85%									
Test for overall effect: Z = 6.17 (P < 0.00001)									
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%									



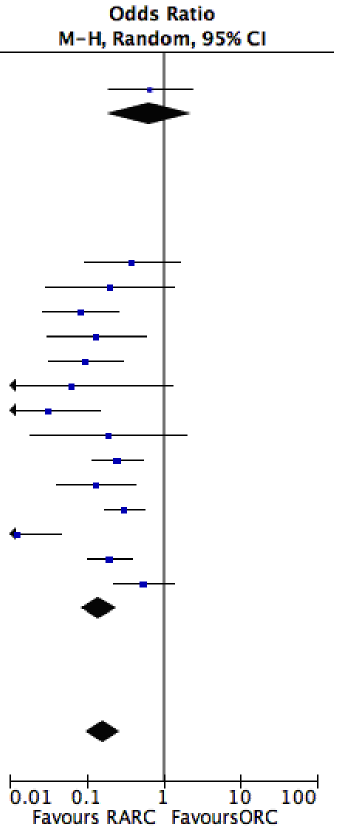
(B)

Study or Subgroup	RARC Mean	RARC SD	RARC Total	ORC Mean	ORC SD	ORC Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.2.1 Randomized studies									
Parekh 2013	627	554	20	1,113	935	20	5.1%	-486.00 [-962.30, -9.70]	2013
Subtotal (95% CI)			**20**			**20**	**5.1%**	**-486.00 [-962.30, -9.70]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.00 (P = 0.05)									
1.2.2 Non-randomized studie									
Rhee 2006	479	551	7	1,109	398	23	5.8%	-630.00 [-1069.39, -190.61]	2006
Ng 2010	460	299	83	1,172	916	104	14.9%	-712.00 [-899.43, -524.57]	2010
Sung 2012	448	232	35	1,063	892	104	14.9%	-615.00 [-802.88, -427.12]	2012
Gondo 2012	656.9	452	11	1,788.7	972.1	15	4.0%	-1131.80 [-1691.58, -572.02]	2012
Anderson 2013	411	271	103	806	660	375	20.7%	-395.00 [-479.86, -310.14]	2013
Musch 2013	351	170	100	810	621	42	14.7%	-459.00 [-649.74, -268.26]	2013
Trentman 2013	257	164	96	601	491	102	19.9%	-344.00 [-444.78, -243.22]	2013
Subtotal (95% CI)			**435**			**765**	**94.9%**	**-526.18 [-655.47, -396.88]**	
Heterogeneity: Tau² = 18405.79; Chi² = 22.61, df = 6 (P = 0.0009); I² = 73%									
Test for overall effect: Z = 7.98 (P < 0.00001)									
Total (95% CI)			**455**			**785**	**100.0%**	**-521.76 [-644.02, -399.50]**	
Heterogeneity: Tau² = 16929.17; Chi² = 22.64, df = 7 (P = 0.002); I² = 69%									
Test for overall effect: Z = 8.36 (P < 0.00001)									
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%									



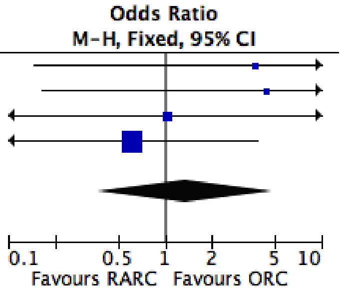
(C)

Study or Subgroup	RARC Events	RARC Total	ORC Events	ORC Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.3.1 Randomized studies							
Parekh 2013	8	20	10	20	6.8%	0.67 [0.19, 2.33]	2013
Subtotal (95% CI)		**20**		**20**	**6.8%**	**0.67 [0.19, 2.33]**	
Total events	8		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.63 (P = 0.53)							
1.3.2 Non-randomized studies							
Galich 2006	7	13	18	24	6.0%	0.39 [0.09, 1.62]	2006
Rhee 2006	4	7	20	23	4.3%	0.20 [0.03, 1.37]	2006
Richards 2010	6	35	25	35	7.3%	0.08 [0.03, 0.26]	2010
Styn 2012	2	50	24	100	5.8%	0.13 [0.03, 0.58]	2012
Sung 2012	4	35	59	104	7.4%	0.10 [0.03, 0.30]	2012
Gondo 2012	0	11	6	15	2.3%	0.06 [0.00, 1.28]	2012
Khan 2012	2	48	30	52	5.7%	0.03 [0.01, 0.15]	2012
Maes 2013	1	14	4	14	3.3%	0.19 [0.02, 2.00]	2013
Musch 2013	27	100	25	42	9.2%	0.25 [0.12, 0.54]	2013
Nepple 2013	14	36	24	29	7.1%	0.13 [0.04, 0.43]	2013
Trentman 2013	30	96	61	102	10.0%	0.31 [0.17, 0.55]	2013
Knox 2013	3	58	68	84	6.6%	0.01 [0.00, 0.05]	2013
Kader 2013	15	100	47	100	9.6%	0.20 [0.10, 0.39]	2013
Ahdoot 2014	11	51	17	51	8.5%	0.55 [0.23, 1.33]	2014
Subtotal (95% CI)		**654**		**775**	**93.2%**	**0.15 [0.09, 0.25]**	
Total events	126		428				
Heterogeneity: Tau² = 0.55; Chi² = 37.00, df = 13 (P = 0.0004); I² = 65%							
Test for overall effect: Z = 7.30 (P < 0.00001)							
Total (95% CI)		**674**		**795**	**100.0%**	**0.16 [0.10, 0.27]**	
Total events	134		438				
Heterogeneity: Tau² = 0.58; Chi² = 40.92, df = 14 (P = 0.0002); I² = 66%							
Test for overall effect: Z = 7.04 (P < 0.00001)							
Test for subgroup differences: Chi² = 4.82, df = 1 (P = 0.03), I² = 79.2%							



(D)

Study or Subgroup	RARC Events	RARC Total	ORC Events	ORC Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Pruthi 2007	1	20	0	24	9.9%	3.77 [0.15, 97.74]	2007
Gondo 2012	1	11	0	15	8.8%	4.43 [0.16, 119.48]	2012
Sung 2012	1	104	0	35	17.2%	1.03 [0.04, 25.84]	2012
Musch 2013	3	100	2	42	64.1%	0.62 [0.10, 3.84]	2013
Total (95% CI)		**235**		**116**	**100.0%**	**1.34 [0.37, 4.77]**	
Total events	6		2				
Heterogeneity: Chi² = 1.61, df = 3 (P = 0.66); I² = 0%							
Test for overall effect: Z = 0.45 (P = 0.65)							



(E)

Study or Subgroup	RARC Mean	RARC SD	RARC Total	ORC Mean	ORC SD	ORC Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.5.1 Randomized studies									
Parekh 2013	9.2	7.8	20	8.9	5.6	20	3.9%	0.30 [-3.91, 4.51]	2013
Bochner 2014	8	3	60	8	5	58	30.8%	0.00 [-1.49, 1.49]	2014
Subtotal (95% CI)			**80**			**78**	**34.7%**	**0.03 [-1.37, 1.44]**	
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.90); I^2 = 0%									
Test for overall effect: Z = 0.05 (P = 0.96)									
1.5.2 Non-randomized studies									
Rhee 2006	11	2	7	13	3	23	18.6%	-2.00 [-3.92, -0.08]	2006
Gondo 2012	40.2	9.2	11	37	9.9	15	1.3%	3.20 [-4.19, 10.59]	2012
Sung 2012	28.9	11.9	35	27.1	13.4	104	3.1%	1.80 [-2.91, 6.51]	2012
Styn 2012	9.5	8.8	50	10.2	8.4	100	7.9%	-0.70 [-3.64, 2.24]	2012
Trentman 2013	7.1	5.8	96	9.8	5	102	30.0%	-2.70 [-4.21, -1.19]	2013
Musch 2013	17.1	7.6	100	19.9	12	42	4.5%	-2.80 [-6.72, 1.12]	2013
Subtotal (95% CI)			**299**			**386**	**65.3%**	**-1.94 [-2.96, -0.91]**	
Heterogeneity: Chi^2 = 6.12, df = 5 (P = 0.29); I^2 = 18%									
Test for overall effect: Z = 3.71 (P = 0.0002)									
Total (95% CI)			**379**			**464**	**100.0%**	**-1.26 [-2.08, -0.43]**	
Heterogeneity: Chi^2 = 11.06, df = 7 (P = 0.14); I^2 = 37%									
Test for overall effect: Z = 2.97 (P = 0.003)									
Test for subgroup differences: Chi^2 = 4.92, df = 1 (P = 0.03), I^2 = 79.7%									

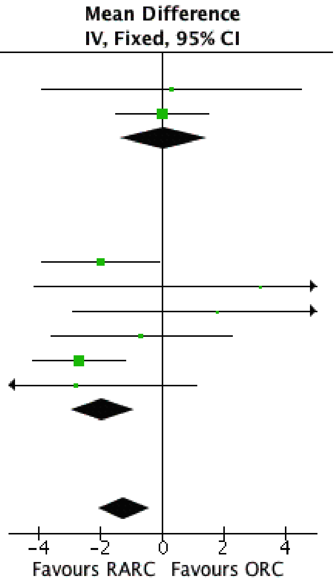


Figure 3

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Abraham 2007	6	14	14	20	33.6%	0.32 [0.08, 1.34]	2007
Khan 2012	2	48	15	58	66.4%	0.12 [0.03, 0.58]	2012
Total (95% CI)		**62**		**78**	**100.0%**	**0.19 [0.07, 0.53]**	
Total events	8		29				

Heterogeneity: $Chi^2 = 0.81$, df = 1 (P = 0.37); $I^2 = 0\%$

Test for overall effect: Z = 3.18 (P = 0.001)

Odds Ratio
M-H, Fixed, 95% CI

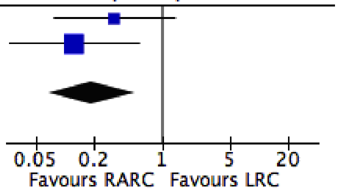
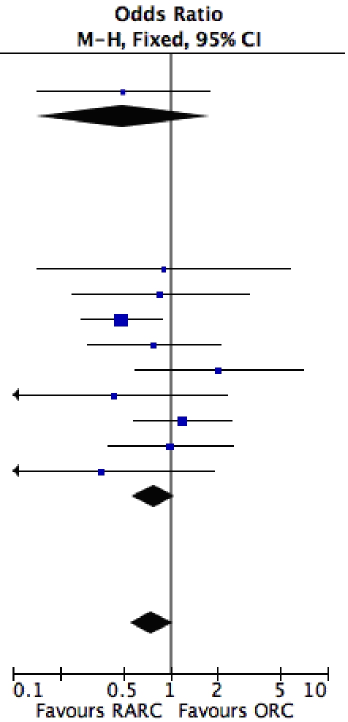


Figure 4

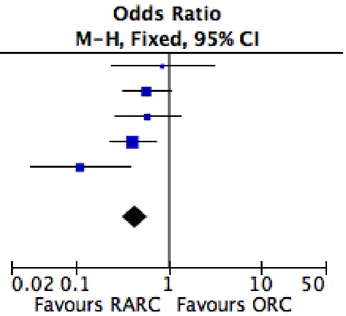
(A)

Study or Subgroup	RARC Events	RARC Total	ORC Events	ORC Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
1.6.1 Randomized studies							
Nix 2010	7	21	10	20	7.5%	0.50 [0.14, 1.77]	2010
Subtotal (95% CI)		**21**		**20**	**7.5%**	**0.50 [0.14, 1.77]**	
Total events	7		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.08 (P = 0.28)							
1.6.2 Non-randomized studies							
Galich 2006	2	13	4	24	2.6%	0.91 [0.14, 5.78]	2006
Wang 2008	7	33	5	21	5.3%	0.86 [0.23, 3.18]	2008
Ng 2010	34	83	61	104	35.1%	0.49 [0.27, 0.88]	2010
Richards 2010	21	35	23	35	10.1%	0.78 [0.30, 2.07]	2010
Khan 2012	20	24	37	52	4.3%	2.03 [0.59, 6.93]	2012
Gondo 2012	6	11	11	15	4.6%	0.44 [0.08, 2.27]	2012
Styn 2012	33	50	62	100	15.4%	1.19 [0.58, 2.42]	2012
Knox 2013	14	24	49	84	10.0%	1.00 [0.40, 2.51]	2013
Maes 2013	8	14	11	14	5.2%	0.36 [0.07, 1.91]	2013
Subtotal (95% CI)		**287**		**449**	**92.5%**	**0.79 [0.57, 1.08]**	
Total events	145		263				
Heterogeneity: $Chi^2 = 7.73$, df = 8 (P = 0.46); $I^2 = 0\%$							
Test for overall effect: Z = 1.47 (P = 0.14)							
Total (95% CI)		**308**		**469**	**100.0%**	**0.77 [0.56, 1.04]**	
Total events	152		273				
Heterogeneity: $Chi^2 = 8.18$, df = 9 (P = 0.52); $I^2 = 0\%$							
Test for overall effect: Z = 1.69 (P = 0.09)							
Test for subgroup differences: $Chi^2 = 0.47$, df = 1 (P = 0.49), $I^2 = 0\%$							



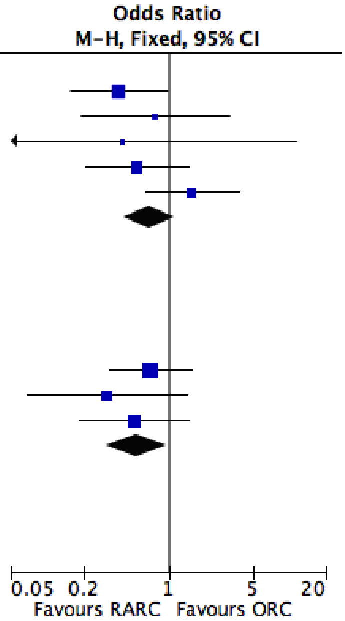
(B)

Study or Subgroup	RARC Events	RARC Total	ORC Events	ORC Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Pruthi 2007	6	20	8	24	4.7%	0.86 [0.24, 3.08]	2007
Ng 2010	37	77	64	104	26.3%	0.58 [0.32, 1.05]	2010
Sung 2012	22	35	77	104	13.4%	0.59 [0.26, 1.34]	2012
Kader 2013	36	100	58	100	34.6%	0.41 [0.23, 0.72]	2013
Musch 2013	59	100	39	42	21.0%	0.11 [0.03, 0.38]	2013
Total (95% CI)		**332**		**374**	**100.0%**	**0.44 [0.31, 0.61]**	
Total events	160		246				
Heterogeneity: $Chi^2 = 7.23$, df = 4 (P = 0.12); $I^2 = 45\%$							
Test for overall effect: Z = 4.92 (P < 0.00001)							



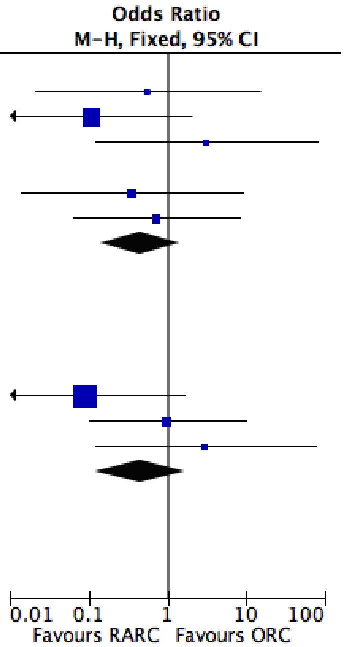
(C)

Study or Subgroup	RARC Events	RARC Total	ORC Events	ORC Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
1.8.1 30-day							
Ng 2010	7	83	20	104	39.8%	0.39 [0.15, 0.97]	2010
Richards 2010	4	35	5	35	10.8%	0.77 [0.19, 3.16]	2010
Gondo 2012	0	11	1	15	3.0%	0.42 [0.02, 11.31]	2012
Khan 2012	8	48	14	52	27.4%	0.54 [0.20, 1.44]	2012
Knox 2013	12	58	12	84	19.0%	1.57 [0.65, 3.78]	2013
Subtotal (95% CI)		**235**		**290**	**100.0%**	**0.70 [0.43, 1.13]**	
Total events	31		52				
Heterogeneity: Chi² = 5.19, df = 4 (P = 0.27); I² = 23%							
Test for overall effect: Z = 1.48 (P = 0.14)							
1.8.2 90-day							
Ng 2010	12	83	20	104	45.2%	0.71 [0.32, 1.55]	2010
Sung 2012	2	35	17	104	24.0%	0.31 [0.07, 1.42]	2012
Kader 2013	6	100	11	100	30.8%	0.52 [0.18, 1.46]	2013
Subtotal (95% CI)		**218**		**308**	**100.0%**	**0.55 [0.31, 0.98]**	
Total events	20		48				
Heterogeneity: Chi² = 0.96, df = 2 (P = 0.62); I² = 0%							
Test for overall effect: Z = 2.03 (P = 0.04)							



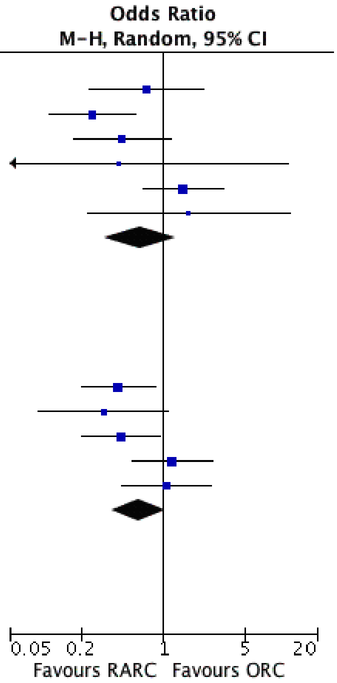
(D)

Study or Subgroup	RARC Events	RARC Total	ORC Events	ORC Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
1.9.1 30-day							
Galich 2006	0	13	1	23	11.3%	0.56 [0.02, 14.63]	2006
Ng 2010	0	83	5	104	51.5%	0.11 [0.01, 1.99]	2010
Richards 2010	1	35	0	35	5.1%	3.09 [0.12, 78.41]	2010
Gondo 2012	0	11	0	15		Not estimable	2012
Khan 2012	0	48	1	52	15.1%	0.35 [0.01, 8.90]	2012
Knox 2013	1	58	2	84	17.0%	0.72 [0.06, 8.12]	2013
Subtotal (95% CI)		**248**		**313**	**100.0%**	**0.45 [0.14, 1.44]**	
Total events	2		9				
Heterogeneity: Chi² = 2.46, df = 4 (P = 0.65); I² = 0%							
Test for overall effect: Z = 1.34 (P = 0.18)							
1.9.2 90-day							
Ng 2010	0	83	6	104	74.6%	0.09 [0.01, 1.63]	2010
Sung 2012	1	35	3	104	19.1%	0.99 [0.10, 9.84]	2012
Kader 2013	1	100	0	100	6.4%	3.03 [0.12, 75.28]	2013
Subtotal (95% CI)		**218**		**308**	**100.0%**	**0.45 [0.12, 1.66]**	
Total events	2		9				
Heterogeneity: Chi² = 2.99, df = 2 (P = 0.22); I² = 33%							
Test for overall effect: Z = 1.20 (P = 0.23)							



(E)

Study or Subgroup	RARC Events	RARC Total	ORC Events	ORC Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.10.1 30-day							
Richards 2010	7	35	9	35	18.3%	0.72 [0.24, 2.22]	2010
Ng 2010	8	83	31	104	23.2%	0.25 [0.11, 0.58]	2010
Khan 2012	8	48	16	52	21.0%	0.45 [0.17, 1.18]	2012
Gondo 2012	0	11	1	15	4.0%	0.42 [0.02, 11.31]	2012
Styn 2012	14	50	21	100	24.3%	1.46 [0.67, 3.20]	2012
Maes 2013	3	14	2	14	9.2%	1.64 [0.23, 11.70]	2013
Subtotal (95% CI)		**241**		**320**	**100.0%**	**0.64 [0.32, 1.29]**	
Total events	40		80				
Heterogeneity: Tau² = 0.36; Chi² = 10.57, df = 5 (P = 0.06); I² = 53%							
Test for overall effect: Z = 1.25 (P = 0.21)							
1.10.2 90-day							
Ng 2010	13	83	32	104	23.8%	0.42 [0.20, 0.86]	2010
Sung 2012	3	35	24	104	12.0%	0.31 [0.09, 1.11]	2012
Musch 2013	24	100	18	43	22.7%	0.44 [0.21, 0.94]	2013
Kader 2013	15	58	19	84	22.2%	1.19 [0.55, 2.60]	2013
Bochner 2014	13	60	12	58	19.3%	1.06 [0.44, 2.57]	2014
Subtotal (95% CI)		**336**		**393**	**100.0%**	**0.62 [0.37, 1.03]**	
Total events	68		105				
Heterogeneity: Tau² = 0.15; Chi² = 7.20, df = 4 (P = 0.13); I² = 44%							
Test for overall effect: Z = 1.86 (P = 0.06)							



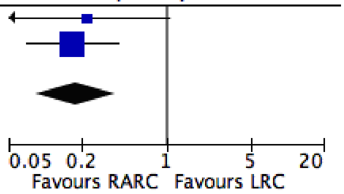
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

Figure 5

(A)

Study or Subgroup	RARC Events	RARC Total	LRC Events	LRC Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year	Odds Ratio M-H, Fixed, 95% CI
Abraham 2007	3	14	11	20	22.3%	0.22 [0.05, 1.05]	2007	
Khan 2012	20	48	47	58	77.7%	0.17 [0.07, 0.40]	2012	
Total (95% CI)		**62**		**78**	**100.0%**	**0.18 [0.08, 0.38]**		
Total events	23		58					

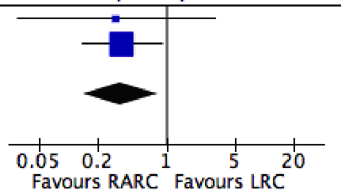
Heterogeneity: $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0\%$
Test for overall effect: Z = 4.42 (P < 0.00001)



(B)

Study or Subgroup	RARC Events	RARC Total	LRC Events	LRC Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year	Odds Ratio M-H, Fixed, 95% CI
Abraham 2007	1	14	4	20	16.2%	0.31 [0.03, 3.10]	2007	
Khan 2012	8	48	21	58	83.8%	0.35 [0.14, 0.89]	2012	
Total (95% CI)		**62**		**78**	**100.0%**	**0.35 [0.15, 0.82]**		
Total events	9		25					

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0\%$
Test for overall effect: Z = 2.42 (P = 0.02)



Illustration

Typesetter instructions re EURUROL-D-14-01778

Figure 1
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Figure 2a–2e
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--Format p values as: $p < 0.00001$, $p = 0.002$
--Change Chi^2 to: χ^2

Figure 3
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--Change Chi^2 to: χ^2

Figure 4a–4e
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