

Comparing robotic, laparoscopic and open cystectomy: A systematic review and meta-analysis

Thomas Fonseka¹, Kamran Ahmed², Saied Froghi², Shahid A Khan³, Prokar Dasgupta², Mohammad Shamim Khan²

¹ King's College London School of Medicine, London, UK;

² MRC Centre for Transplantation, King's College London, King's Health Partners, Department of Urology, Guy's Hospital, London, UK;

³ Surrey and Sussex Healthcare NHS Hospital, Redhill, UK.

Summary *Objective: To conduct a systematic review and meta-analysis comparing outcomes between Open Radical Cystectomy (ORC), Laparoscopic Radical Cystectomy (LRC) and Robot-assisted Radical Cystectomy (RARC). RARC is to be compared to LRC and ORC and LRC compared to ORC.*

Material and methods: A systematic review of the literature was conducted, collating studies comparing RARC, LRC and ORC. Surgical and oncological outcome data were extracted and a meta-analysis was performed.

Results: Twenty-four studies were selected with total of 2,104 cases analyzed. RARC had a longer operative time (OPT) compared to LRC with no statistical difference between length of stay (LOS) and estimated blood loss (EBL). RARC had a significantly shorter LOS, reduced EBL, lower complication rate and longer OPT compared to ORC. There were no significant differences regarding lymph node yield (LNY) and positive surgical margins (PSM.) LRC had a reduced EBL, shorter LOS and increased OPT compared to ORC. There was no significant difference regarding LNY.

Conclusion: RARC is comparable to LRC with better surgical results than ORC. LRC has better surgical outcomes than ORC. With the unique technological features of the robotic surgical system and increasing trend of intra-corporeal reconstruction it is likely that RARC will become the surgical option of choice.

KEY WORDS: Radical cystectomy; Robotic assisted radical cystectomy; Laparoscopic radical cystectomy; Open radical cystectomy; Bladder cancer.

Submitted 22 December 2014; Accepted 31 December 2014

INTRODUCTION

Open Radical Cystectomy (ORC) is currently regarded as the gold standard surgical treatment for muscle-invasive and non-muscle invasive high-grade recurrent bladder cancer (1). However, the procedure is associated with high morbidity including increased blood loss, prolonged hospital stay and slower recovery. Laparoscopic Radical Cystectomy (LRC) was developed around two decades but Robot-assisted Radical Cystecto-

my (RARC) has since emerged as a viable alternative. RARC has been reported to be associated with fewer complications compared to LRC (2) and the appeal of the robotic surgical system has led to the adoption of the procedure worldwide. However the production of high-quality evidence that measures the relative merits of ORC, LRC and RARC is lacking with surgeons having to rely on systematic review. This article aims to compare surgical and oncological outcomes of ORC, LRC and RARC.

METHODS

Eligibility criteria

Data were collected on all patients over the age of 60 with muscle-invasive bladder cancer undergoing RARC, LRC or ORC. Surgical outcomes were; operative time (OPT), estimated blood loss (EBL), length of stay (LOS) and complication rate 90 days post-operatively. Oncological outcomes were; lymph node yield (LNY) and positive surgical margins (PSM). Comparisons were made between RARC, LRC and ORC and the outcomes of interest measured included both surgical and oncological outcomes.

The studies forming the current meta-analysis include comparative studies, either retrospective or prospective, as well as randomized control trials.

For a study to be included in our analysis it had to fulfill the following criteria. The study had to:

- Compare outcome measures of two or all three surgical techniques (ORC, LRC and RARC).
- Use quantitative data for at least one outcome measure.
- Be a high quality study.

If it was one of two studies that were produced by the same institution, it was ensured the data were mutually exclusive.

Studies were excluded if they:

- Lacked reporting of the desired outcome measures listed above or presented the data in such a way that it was not possible to carry out an analysis for the study.
- Reported on only one of the techniques of ORC, LRC and RARC.
- Were written in non-English language.

Information sources

A systematic review of the literature was conducted using the following databases; *PubMed*, *Medline*, *the Cochrane Library* and *EMBASE*. The reference lists of reviews were also cross-referenced. The last search was conducted on 11/12/2014.

Search

The following search terms were used: “*Open cystectomy*”, “*Open radical cystectomy*”, “*Laparoscopic cystectomy*”, “*Laparoscopic assisted cystectomy*”, “*Laparoscopic radical cystectomy*”, “*Laparoscopic assisted radical cystectomy*”, “*Robotic cystectomy*”, “*Robot* assisted cystectomy*”, “*Robotic radical cystectomy*”, “*Robot* assisted radical cystectomy*”, “*Robot* assisted laparoscopic cystectomy*”, “*Robot* assisted laparoscopic radical cystectomy*”, “*Minimally invasive*”, “*Bladder cancer*”. The search terms were combined to ensure as many studies as possible that compared ORC, LRC and RARC, or any combination were included.

Study selection

Studies were selected by two reviewers (T.F and S.F), independently. Where the decision was split and agreement could not be made, the study was included so as to include as many studies as possible.

Data items

After selection of the studies, the following data were extracted; primary author of the study, year of publication, country of study, study design, study exclusion criteria (if mentioned), total number of patients undergoing ORC, LRC and RARC, study population characteristics (mean age, mean BMI, mean American Society of Anesthesiologists (ASA) grade, Charlson’s Co-morbidity Index, gender, and pathological stage). For each technique (ORC, LRC and RARC), the following data were recorded: primary author of the study, year of publication, total number of patients undergoing each urinary diversion type (conduit or neo-bladder), total number of patients requiring blood transfusion, surgical outcomes (as previously listed) and oncological outcomes (as previously listed). Complications were assessed using the Clavien-Dindo grading system (3).

Risk of bias in individual studies

The Newcastle-Ottawa Quality Assessment Scale (4) was used to assess the quality of the studies. It was tailored to suit the analysis of the studies included in this evaluation. Areas analyzed for quality were patient selection, including representativeness of the exposed cohort, comparability of cohorts, and assessment of outcomes. Studies which were rated with five or more stars were deemed to be high-quality. The entire analysis was conducted using *Review Manager Version 5 (The Cochrane Collaboration, Software Update, Oxford)*.

Summary measures

To assess whether there was a statistically significant difference between data of a dichotomous nature, the odds ratio (OR) was calculated. The OR is a measure of the probability of an event occurring in an RARC patient group compared to either ORC or LRC patient groups or

LRC compared to ORC. When comparing adverse events, where an OR value was less than one it implied that RARC was favored. In order for the point estimate of the OR to be considered statistically significant at the P < 0.05 level, the 95% CI must not have included the value of one. When handling continuous data the mean weighted difference (MWD) was used instead of the OR. A negative MWD value indicated RARC was favored.

Synthesis of results

Guidance was sought from the Cochrane Collaboration as well as information from the QUORUM guidelines (5) to provide the framework of the statistical analysis. When studies reported of medians, ranges or confidence intervals for continuous variables, statistical algorithms were used to derive the appropriate means and standard deviations. The OR for continuous variables could be calculated using the Mantle-Haenszel Chi square method with the ‘random effects’ meta-analytical technique. The ‘random effects’ model is particularly useful when conducting surgical research. This is because it takes into account the almost inevitable natural variation inherent between studies. Subsequently a more conservative OR is produced. For both OR and MWD, corresponding 95% CI’s were calculated. Regarding the Forest plots produced, a square represents the point estimate of the treatment effect, that is the OR or MWD, with a horizontal bar going through the square showing the 95% CI. The summary measure of the pooled studies with 95% CI’s is represented by a diamond.

RESULTS

Study selection

The initial literature search identified 598 papers, which matched the search criteria. Of these, 486 papers were eliminated due to broad incoherency with the aims of this study. Of the 112 remaining, a further 83 papers were excluded based on the exclusion criteria as outlined above. On more in depth examination of the 29 remain-

Figure 1.

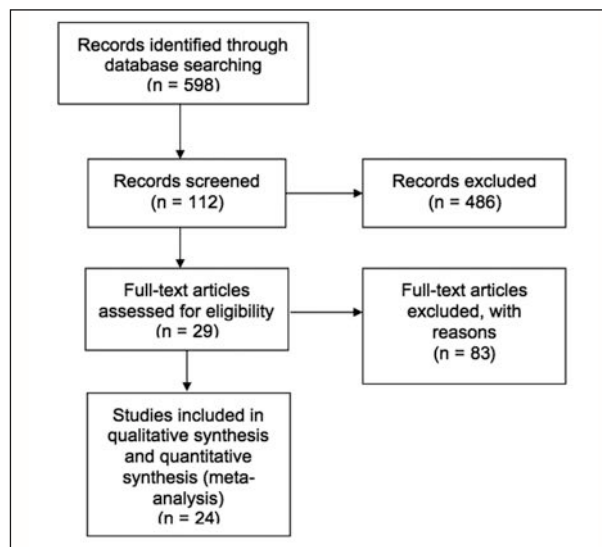


Table 1.

Study characteristics. Matching: 1 - Age; 2 - BMI; 3 - ASA; 4 - Charlson; 5 - Gender; 6 - Pathological stage; 7 - Urinary diversion type. Study type: RCT - Randomized control trial; R - Retrospective, P - Prospective.

Study	Study type	Cases			Matching	Mean age, yaers			Exclusion criteria	Study quality	Country
		ORC	LRC	RARC		ORC	LRC	RARC			
Abaza 2012	R	120	NR	35	1,2,6	69.8	NR	67.3	Undergoing lesser node dissection due to a history of radiation, aortoiliac grafting or significant comorbidity	***	USA
Abraham 2007	P	NR	20	14	1,2,3,5,7	NR	77.6	76.5	NR	****	USA
Gan 2013	P	20	19	20	NR	NR	NR	NR	NR	****	UK
Galich 2006	P	24	NR	13	1,2,3,6	63.03	NR	66.2	Morbid obesity (generally body mass index > 35), prior pelvic radiation, or significant medical comorbidities including pulmonary obstructive airway disease	****	USA
Gondo 2012	P	15	NR	11	1,2,4,5,6,7	69.7	NR	68.9	NR	****	Japan
Guillotreau 2009	P	30	38		1,2,3,5,6,7	64.9 (12.3)	67.9 (9.0)			*****	France
Ha 2010	R	34	36		1,2,5,6	55.9 (9.8)	67.5 (8.9)			****	Korea
Haber 2008	R	50	50		1,2	67	66			**	USA
Kader 2013	R	100	NR	103	1,2,3,5,6,7	66	NR	67	NR	****	USA
Khan 2012	P	52	58	48	1,2,3,5,6,7	65	69.8	66.5	NR	****	UK
Knox 2013	R	84	NR	58	1,2,3,5,6,7	67.07 (1.2)	NR	65.9 (1.2)	NR	****	USA
Lin 2014	RCT	35	35		1,2,3,5,6	63.6 (8.9)	63.2 (9.1)			*****	China
Martin 2010	P	14	NR	19	1,2,3,5,6	68	NR	74	NR	****	USA
Musch 2014	P	42		100	1,2,3,4,5,6,7	69.0 (11.5)		71.4 (9.4)		*****	Germany
Nepple 2013	R	29	NR	36	1,2,5,6,7	67	NR	72	Contraindication to robotic surgery	****	USA
Ng 2010	P	104	NR	83	1,2,3,5,6,7	67.2	NR	70.9	NR	****	USA
Nix 2010	RCT	20	NR	21	1,2,3,5,6,7	69.2	NR	67.4	1) not surgical candidates, 2) not allowing randomization 3) those with preference for specific surgical modality	****	USA
Parekh 2013	RCT	19	NR	20	1,2,3,5,6	69.5	NR	69.5	1) Inability to give informed consent, 2) unsafe for robotic approach, 3) clinical T4 bladder cancer, 4) clinical lymph node positive bladder cancer with grossly enlarged pelvic or retroperitoneal lymph nodes, 5) age younger than 30 or older than 90 years and 6) pregnancy.	*****	USA
Porpiglia 2007	P	22	20	NR	1,2,3,5,6,7	71	63.5	NR	NR	****	Italy
Pruthi 2007	R	24	NR	20	1,6,7	68.2	NR	62.3	NR	***	USA
Rhee 2006	P	23		7	1,2,3,5,6	67 (13)		60 (9)		*****	USA
Richards 2010	R	35	NR	35	1,2,3,5,6,7	66	NR	65	NR	****	USA
Styn 2012	P	100	NR	50	1,2,3,4,5,6,7	65.6	NR	66.6	NR	****	USA
Sung 2012	R	104	NR	35	1,2,3,5,6	65.9	NR	62.2	Had undergone radiotherapy before operation or for whom palliative treatment was the primary aim	****	Korea

ing papers, a subsequent 5 were removed for not meeting the requirements of the inclusion criteria. Thus 24 studies were included in the final quantitative and qualitative analysis (Figure 1) (6-29).

Study characteristics

Characteristics of all 24 studies included in the analysis are summarized in Table 1 (6-29). There were three randomized control trials with the remaining 21 made up of retrospective and prospective studies. Each study was either 2-arm or 3-arm. For the purposes of the statistics RARC was always regarded as experimental. LRC was also considered experimental except when being compared to RARC, in which case it was used as control. All of the stud-

ies included were fairly recent with the oldest published in 2006. The two reviewers who selected the studies were in complete agreement (100%) about data extraction. A total of 2,104 cases were analyzed, with 1,100 (52.3%) undergoing ORC, 276 (13.1%) LRC and 728 (34.6%) RARC. Approximately 65% of patients were male. With regards to the pathological stage of the tumors, the average percentage of tumors that were non-organ confined (pT3-4) was similar in both RARC and ORC groups. On average 30.1% of patients reported in the RARC studies had non-organ confined tumors compared with 29.5% in ORC group and 14.5% in the LRC group. On average 28% of patients undergoing RARC developed complications 90 days post-operatively. Major complications were defined as

Figure 2.

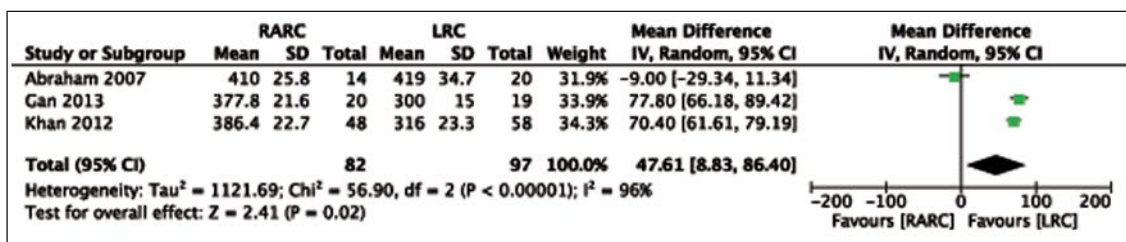


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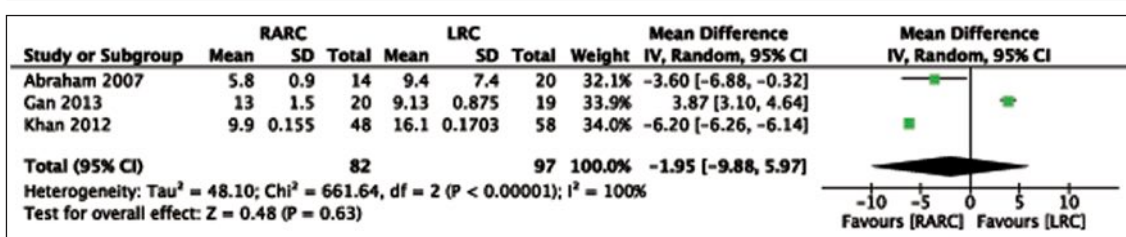


Figure 4.

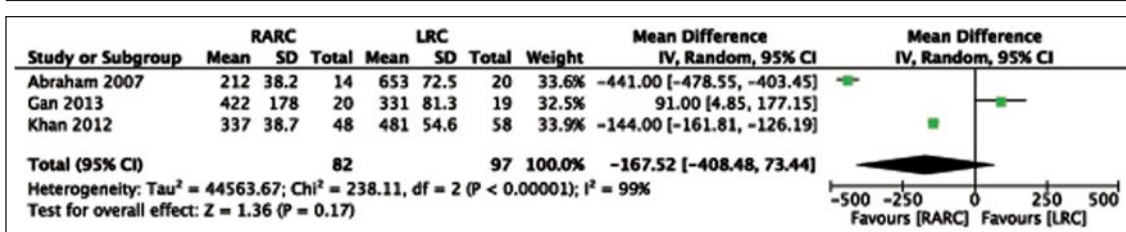
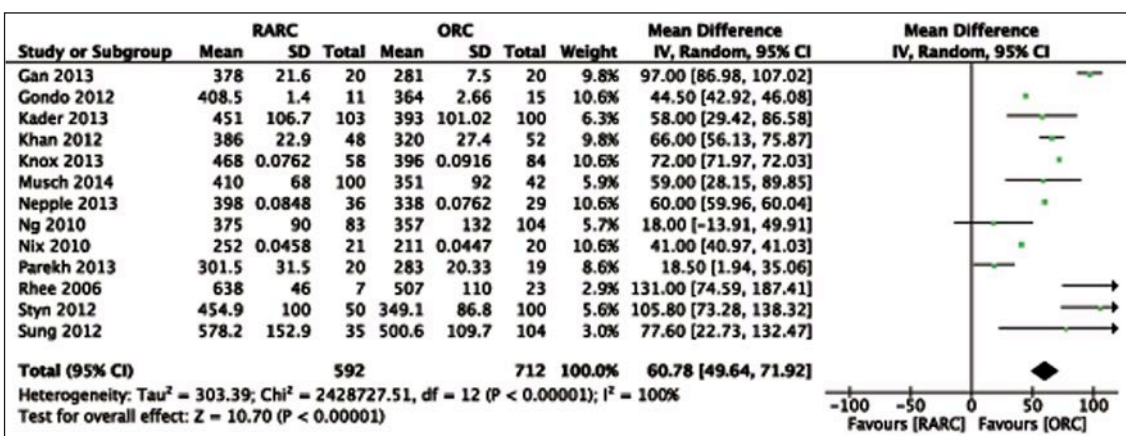


Figure 5.



complications above Clavien grade 3, including return to operating room (OR) within 30 days post-operatively and death within 90 days post-operatively. 8.51% of patients undergoing RARC had major complications with 3 deaths (0.412%) within 90 days post-operatively. In the LRC studies, 72.1% of patients developed complications with 3 deaths (1.087%) within 90 days post-operatively. The overall complication rate in ORC was 47.2% with an average of 8.5% of patients having major complication. There were 7 deaths (0.64%) within 90 days post-operatively. The type of urinary diversion created with each technique was broadly classified into either conduit or bladder substitution (neo-bladder). On average 17.4% of RARC patients had a bladder substitution compared to 13.04% in LRC and 12.4% in the ORC groups and the remaining had an ileal conduit urinary diversion.

Synthesis of results

RARC versus LRC

As shown in Figure 2, OPT was significantly longer in RARC when compared to LRC (P = 0.02; mean weighted

difference (MWD) was 47.61 with 95% confidence interval (CI) of 8.83 to 86.40). There was no statistically significant difference concerning LOS (P = 0.63; MWD = -1.95, 95% CI = -9.88 to 5.97) (Figure 3). There was also no statistical significance observed when comparing EBL (P = 0.17; MWD = -167.52, 95% CI = -408.48 to 73.44) (Figure 4).

RARC versus ORC

OPT was significantly longer in RARC when compared to ORC (P = < 0.00001; MWD = 60.78, 95% CI = 49.64 to 71.92) (Figure 5). Comparing other parameters of EBL, LOS and complications the analysis showed that there was significant reduction in EBL (P = < 0.00001; MWD = -638.24, 95% CI = -850.26 to -426.21) (Figure 6), LOS after RARC (P = 0.004; MWD = -1.75, 95% CI = -2.94 to -0.56) (Figure 7) and complications in the RARC group (P = < 0.0001; MWD = 0.53, 95% CI = 0.40 to 0.71) (Figure 8). There was no statistical difference in LNY (P = 0.87; MWD = -0.22, 95% CI = -2.83 to 2.39) (Figure 9) or PSM (P = 0.42; MWD = 0.80, 95% CI = 0.47 to 1.37) (Figure 10).

LRC versus ORC

Comparing LRC to ORC operative time was significantly longer using LRC (P = 0.002; MWD = 34.93, 95% CI =

12.76 to 57.10) (Figure 11). EBL was significantly reduced in the LRC group (P = 0.0009; MWD = -480.96, 95% CI = -765.04 to -196.88) (Figure 12). Likewise LOS was signif-

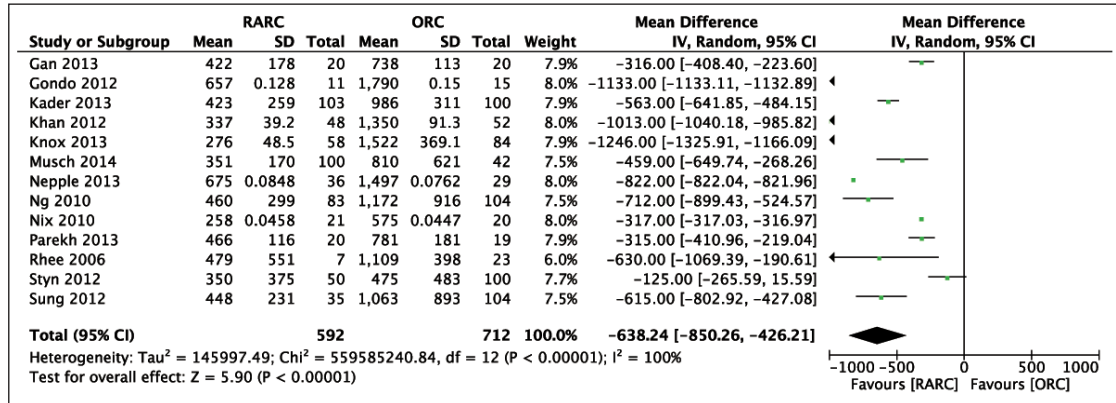


Figure 6.

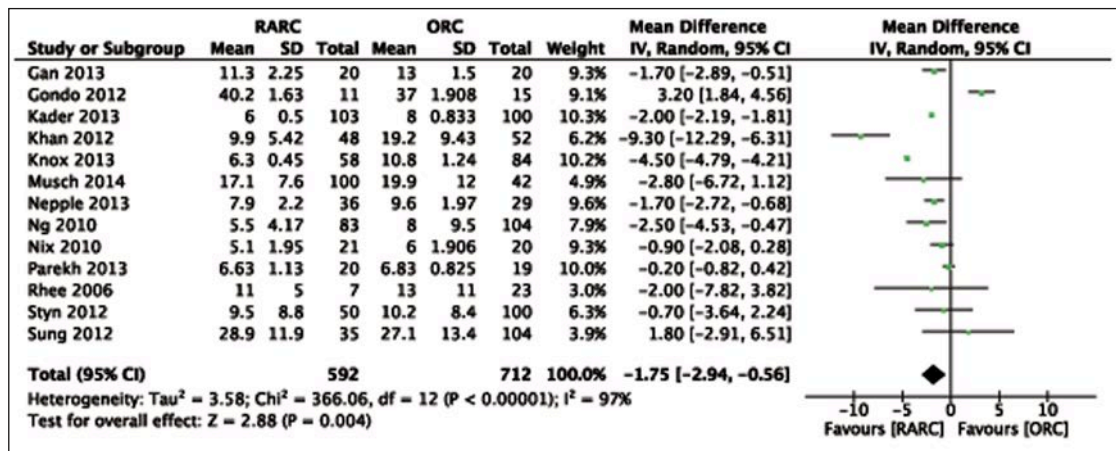


Figure 7.

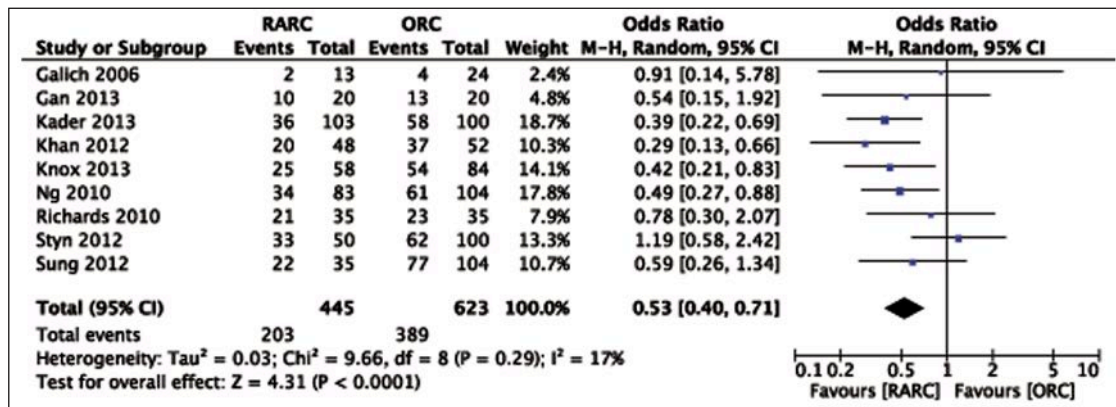


Figure 8.

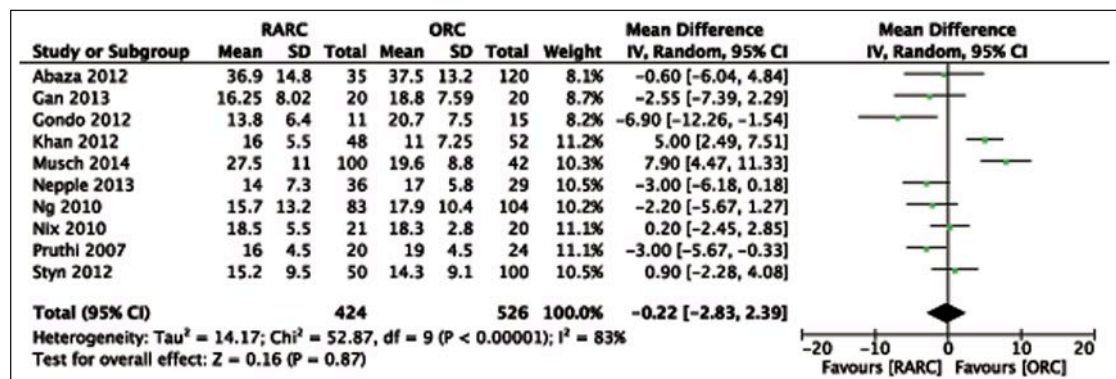


Figure 9.

Figure 10.

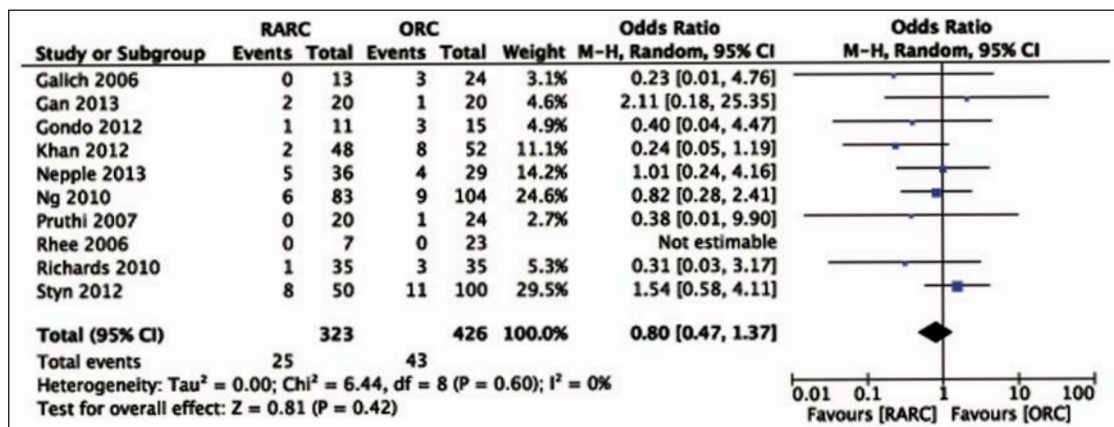


Figure 11.

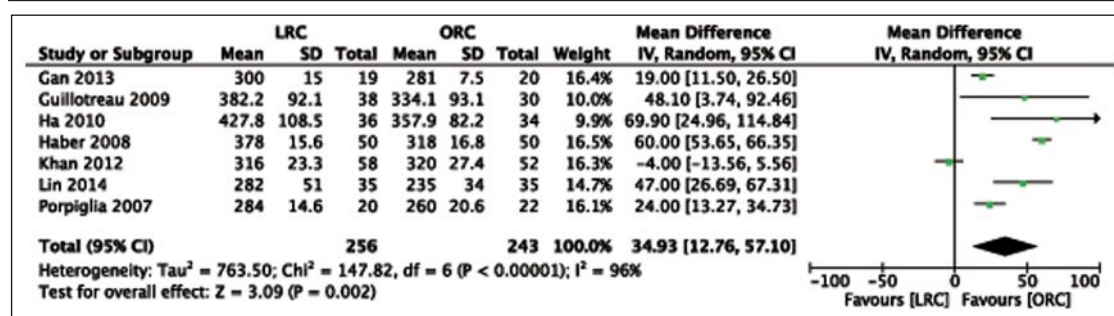


Figure 12.

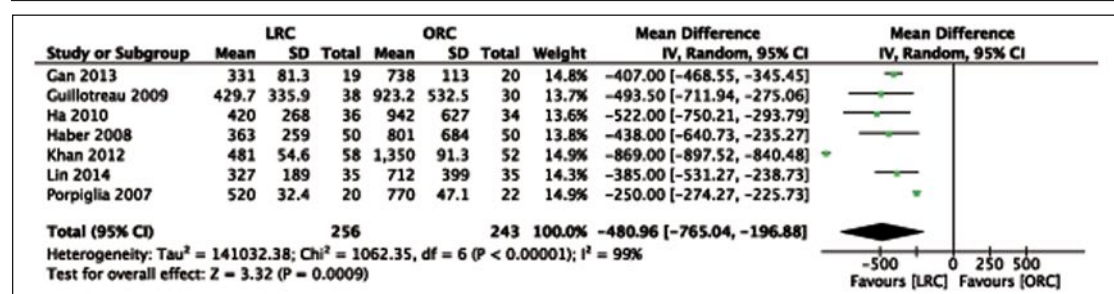


Figure 13.

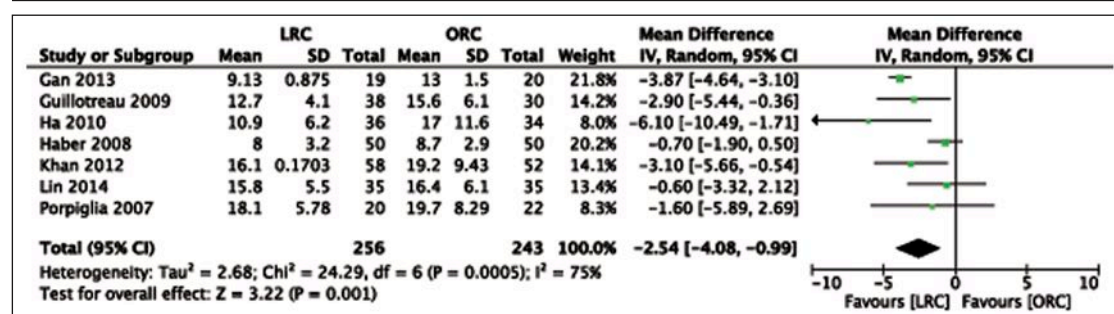
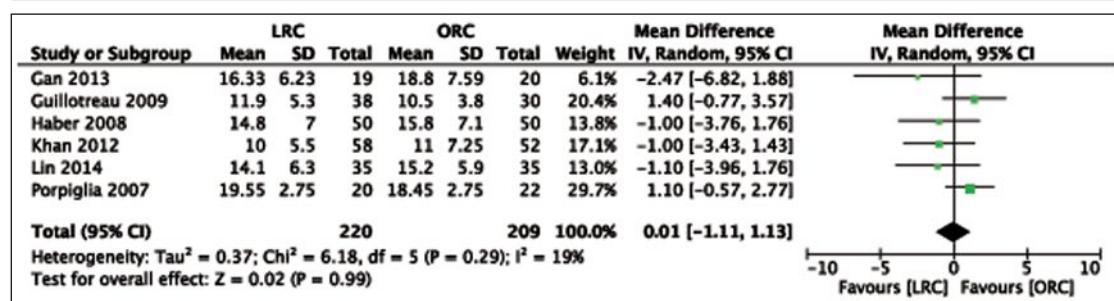


Figure 14.



icantly shorter in the LRC group (P = 0.001; MWD = -2.54, 95% CI = -4.08 to -0.99) (Figure 13). There was no statistical difference in LNY (P = 0.99; MWD = 0.01, 95% CI = -1.11 to 1.13) (Figure 14).

DISCUSSION

Comparing RARC to LRC, the results show that there is no statistical difference in LOS or EBL but the operating time is significantly longer. More data is needed to see

whether complication rate is significantly reduced when comparing RARC to LRC.

RARC takes longer to do than ORC but produces better surgical outcomes with reduced EBL, shorter LOS and fewer complications. There are equivalent oncological outcomes (LNY and PSM.)

When comparing LRC to ORC, LNY is equivalent but there is an increase in OPT, reduction in EBL and shorter LOS using the laparoscopic approach. The results therefore are in favor of using LRC in preference to ORC. It may be that it is when the robotic technique is used with intracorporeal urinary diversion, as opposed to extracorporeal, that it is superior to LRC. Most studies included used extracorporeal urinary diversion.

Intracorporeal urinary diversion has been demonstrated to be technically feasible with good oncological outcomes (13,30). More data is needed to assess long-term outcomes.

The difficulty in obtaining data on complications results from a lack of consistency in reporting complications. In this paper the Clavien-Dindo system was used and it is broadly accepted as the better current standard for reporting of surgical complications. All future trials assessing the complications in radical cystectomy should use this system to facilitate universal comparison (31).

One outcome in which data was lacking was PSM. A study using data from the International Robotic Cystectomy Consortium (IRCC) (32) found that the rate of PSM was similar between RARC and ORC, consistent with the results of this meta-analysis. Variables associated with increased probability of PSM using RARC included older age, higher pathological T stage and lymph node positivity.

A similar study by the IRCC reviewed the outcomes of extended lymph node dissection, an essential part of radical cystectomy (33). Similar lymph node yields were obtained in RARC and ORC, which were found to be the case in this study. The study also identified that high volume institutions (≥ 100 cases) had 3.46-times increased probability of carrying out extended lymph node dissection (LND).

It is crucial that survival data is reported in the studies of different surgical techniques to see if technology is having an influence on the survival of these patients.

This would only be possible with longer follow up after surgical procedures. Kaplan-Meier plots to compare survival rates between the three operative techniques would prove valuable in assessing the evidence for RARC.

Guru et al. (34) have shown that surgical and oncological outcomes constantly improve with each RARC case the surgeon performs. The learning curve for RARC was defined by results from the IRCC. Using proxy measurements for RARC quality such as OPT, EBL, LNY and margin positivity it was found that acceptable proficiency in the procedure was attained by the 30th case.

The cost of RARC is estimated to be about \$20,000 per case and is an important factor to consider when evaluating the use of RARC. *Lee et al.* (35) have found that RARC is less expensive than ORC when ileal conduit or continent cutaneous diversion is performed. The main driver of cost was LOS and though material cost was higher with RARC, in high-volume centres RARC can be more cost-

effective particularly with ileal conduit urinary diversion. The true benefit of RARC may lie in the improved ergonomics of the robotic system. The more comfortable operating system may cause less fatigue to the surgeon as compared to laparoscopic methods, thereby leading to fewer errors. This was shown by *Elhage et al.* (36) where time taken to perform a suturing task was not only shorter compared to laparoscopic and open, but there were also fewer errors made when compared to the laparoscopic method. The major limitation of this study is the possibility of bias. When evaluating surgical procedures there is always a lack of blinding and natural variation in both the skill of the surgeon pathology of different cases. This is reflected in the significant heterogeneity found in the forest plots of this study. Inclusion criteria varied among studies as well as there being different systems of follow-up with differing outcome definitions. Publication bias is also a possibility that was not factored into this study.

CONCLUSIONS

The results of this meta-analysis shows that LRC provides better outcomes than ORC but that RARC provides similar outcomes to LRC, only with longer OPT. More randomised control trials are required to provide conclusive evidence to show whether or not RARC is in fact a better alternative to ORC or LRC. These studies must use a unified system for the classification of complications and assess both surgical and oncological outcomes. More data is also needed on the ergonomics, learning curve, cost-effectiveness and patient-perspectives of RARC.

ACKNOWLEDGEMENTS

P.D. acknowledges financial support from the *National Institute for Health Research (NIHR) Biomedical Research Centre* based at *Guy's and St Thomas' NHS Foundation Trust* and *King's College London*. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the *Department of Health*. P.D. also acknowledges the support of the *MRC Centre for Transplantation, London Deanery, London School of Surgery and Olympus*. P.D., S.K. and K.A. acknowledge funding for the *SIMULATE* project from the *Urology Foundation (TUF)* and the *BAUS*. KA and PD acknowledge educational funding from the *Royal College of Surgeons of England*.

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Correspondence

Thomas Fonseka (BSc)
King's College London School of Medicine, London, UK

Kamran Ahmed, MRCS, PhD (Correspondent Author)

kamran.ahmed@kcl.ac.uk

Saied Froggi, MBBS

Prokar Dasgupta, MSC, MD, FEBU, FRCS Urol

Mohammad Shamim Khan, OBE, FEBU, FRCS Urol

NIHR Academic Clinical Lecturer /Specialist Registrar in Urology

MRC Centre for Transplantation, Guys Hospital

St Thomas Street, London SE1 9RT, UK

Shahid A Khan, FRCS Urol

Surrey and Sussex Healthcare NHS Hospital, Redhill, UK