A Single-centre Early Phase Randomised Controlled Three-arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (CORAL)

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Abstract

Background: Laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) are increasingly popular, but high-level evidence for these techniques remains lacking.

Objective: To compare the outcomes of patients undergoing open radical cystectomy (ORC), RARC, and LRC.

Design, setting, and participants: From March 2009 to July 2012, 164 patients requiring radical cystectomy for muscle-invasive bladder cancer or high-risk non–muscle-invasive bladder cancer were invited to participate, with an aim of recruiting 47 patients into each arm. Overall, 93 were suitable for trial inclusion; 60 (65%) agreed and 33 (35%) declined.

Intervention: ORC, RARC, or LRC with extracorporeal urinary diversion.

Outcome measurements and statistical analysis: Primary end points were 30- and 90-d complication rates. Secondary end points were perioperative clinical, pathologic, and oncologic outcomes, and quality of life (QoL). The Fisher exact test and analysis of variance were used for statistical analyses.

Results and limitations: The 30-d complication rates (classified by the Clavien-Dindo system) varied significantly between the three arms (ORC: 70%; RARC: 55%; LRC: 26%; \( p = 0.024 \)). ORC complication rates were significantly higher than LRC (\( p < 0.01 \)). The 90-d complication rates did not differ significantly between the three arms (ORC: 70%; RARC: 55%; LRC: 32%; \( p = 0.068 \)). Mean operative time was significantly longer in RARC compared with ORC or LRC. ORC resulted in a slower return to oral solids than RARC or LRC. There were no significant differences in QoL measures. Major limitations are the small sample size and potential surgeon bias.

Conclusions: The 30-d complication rates varied by type of surgery and were significantly higher in the ORC arm than the LRC arm. There was no significant difference in 90-d Clavien-graded complication rates between the three arms.

Patient summary: We compared patients having open, robotic, or laparoscopic bladder removal surgery for bladder cancer and found no difference in Clavien-graded complication rates at 90 d.

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1. Introduction

Until 1995, open radical cystectomy (ORC) was the only surgical approach available in the management of muscle-invasive bladder cancer (MIBC) or high-risk non–muscle-invasive bladder cancer (NMIBC) [1,2]. ORC is associated with high morbidity and significant mortality but remains the gold standard [3]. Two minimally invasive surgical approaches, laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC), have become available in recent years, with the perceived advantage of reduced morbidity and faster convalescence [4]. Although many institutions have purchased surgical robots, they are expensive, and in many parts of the world, laparoscopic surgery still prevails as an alternative to open surgery [5]. Although a few trials have compared ORC and RARC [6–8], currently none have compared all three modalities.

2. Patients and methods

2.1. Hypothesis, study design, and patients

The Cystectomy Open Robotic and Laparoscopic (CORAL) trial is a randomised controlled study comparing ORC, LRC, and RARC from March 2009 to July 2012, conducted at Guy’s Hospital, London, UK. Our hypothesis was that the greater precision offered by robotic technology would reduce complication rates for RARC compared with ORC and LRC. All patients aged between 18 and 80 yr requiring radical cystectomy (RC) for MIBC or high-risk NMIBC were invited to participate. Trial inclusion did not affect diversion type or eligibility for neoadjuvant chemotherapy. Patients were excluded from randomisation if deemed unsuitable for LRC or RARC due to severe cardiopulmonary comorbidities or extensive abdominopelvic surgery or radiation. Eligible patients were counselled by a trial nurse (J.W.) and gave informed consent.

The study was prospectively registered with the Guy’s and St. Thomas’s research and development office (RJ108/0375) after National Health Service Research Ethics Committee approval (08/H0804/135), and retrospectively registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN28499748; http://www.isrctn.com/ISRCTN28499748).

2.2. Randomisation

Randomisation was undertaken by the trial nurse (J.W.) using identical sealed opaque envelopes, each containing a piece of paper designating the surgical modality (ORC, LRC, or RARC). Simple randomisation was performed in two groups of 30. In each group, each modality was allocated 10 envelopes. These were shuffled and then numbered 1–30. Patients received the next envelope in numerical order. Envelopes were kept in a locked room, accessed only by the trial nurse to minimise opportunities for tampering, and they were opened by the patient in the presence of three members of the research team to ensure that no changes were made to allocation. This study was nonblinded because the different incisions would be difficult to camouflage.

2.3. Interventions

Our technique of RARC was previously reported [9]; ORC and LRC techniques are detailed in Supplement 1. Urinary diversion was performed extracorporeally for all RARC and LRC cases, and all neobladders were fashioned using the Studer technique [10]. Lymph node dissection templates were standardised including obturator, external/internal/common iliac, and presacral nodes. Lymph nodes were not analysed in separate packets [11]. Three expert surgeons performed ORC (M.S.K.), LRC (P.R.), and RARC (P.D.). At trial initiation, M.S.K. had performed >150 ORCs, and P.R. and P.D. had performed about 110 LRCs and RARCs, respectively.

2.4. Postoperative management and follow-up

All patients underwent a standardised Enhanced Recovery Pathway for RC [12]. After discharge, patients were reviewed at 2 wk, 3, 6, and 12 mo, and then yearly. Following local protocol, loopogram studies were performed at 3 mo to assess for ureteroenteric anastomotic strictures. Chest, abdomen, and pelvis computed tomography scans were performed at 6 and 12 mo for recurrence and other complications.

2.5. Outcome measures

Primary end points were 30- and 90-d complication rates classified by Clavien-Dindo grades [13]. Secondary end points were perioperative parameters (operative time, estimated blood loss [EBL], delay in bowel function, and length of hospital stay [LOS]), pathologic outcomes (margin status and number of lymph nodes retrieved), 12-mo oncologic outcomes, and quality of life (QoL).

2.6. Quality of life

QoL was assessed by the Functional Assessment of Cancer Therapy-Bladder (FACT-B) scale v4 [14], covering physical well-being, functional well-being, emotional well-being, social/family well-being, and additional questions specific to bladder cancer (BCa; Bladder Cancer Subscale).

2.7. Power calculations and statistical analysis

Based on early experience, we estimated the RARC complication rate as 10–15% [15] and that for ORC as 25–60% [16]. Therefore, the number needed in each arm ranges from 43 to 58 so the 95% confidence interval (CI) for the estimated difference in rates is ±16%. Based on these considerations, we aimed to recruit 47 patients per arm (based on the range of complication rates). However, a 3-yr interim analysis suggested no significant difference in primary outcomes between arms, and coupled with recruitment difficulties, our institutional research project steering board recommended terminating the trial at this point.

Binary outcomes were compared using the Fisher exact test. Analysis of variance (ANOVA) including the baseline value where appropriate was used to compare means of continuous outcome measures. If the difference between groups was statistically significant, post hoc analysis was performed using the Fisher exact pairwise comparison, Mann-Whitney U, or the Tukey honest significant difference test. Where test assumptions for ANOVA were not justified, the Kruskal-Wallis test was used. Survival analysis using the log-rank test was conducted, and Kaplan-Meier survival curves were constructed. Additional QoL analysis included adjusting for age, sex, and urinary diversion [17].

Data analysis was performed using SPSS v.21 (IBM Corp, Armonk, NY, USA). A two-sided p value < 0.05 was considered significant. Results were analysed by intention to treat.

3. Results

A total of 164 patients with MIBC or high-risk NMIBC were assessed for trial inclusion between 2009 and 2012. Of 93 eligible patients, 60 (65%) agreed to participate, and 33 (35%) declined. The reason for declining was most commonly patient preference for a specific approach.
One patient assigned to LRC was withdrawn after further histologic review showed small cell BCA for which surgery was inappropriate, leaving 59 patients in the trial. All 20 patients assigned to ORC received the intended procedure. One patient assigned to RARC was converted to ORC due to equipment failure. Of the 19 patients allocated to LRC, 3 were converted to RARC because of laparoscopic surgeon unavailability at short notice. One patient was converted to ORC due to large tumour size. All patients completed 90-d follow-up, and 97% completed a 12-mo follow-up (Fig. 1).

3.1. Patient demographics

There were no important differences in baseline characteristics (Table 1), number receiving neoadjuvant chemotherapy, preoperative stage distribution (NMIBC or MIBC), diversion type, and final pathologic stage between the three arms (Table 2).

3.2. Primary clinical end point

3.2.1. 30-d complications

Overall, 14 of 20 ORC patients (70%), 11 of 20 RARC patients (55%), and 5 of 19 LRC patients (26%) had at least one 30-d complication (any Clavien grade). The overall variability between groups was statistically significant. In addition, ORC versus LRC arms were significantly different (95% CI for difference, 44% [15–72%]; p = 0.01). There were no statistically significant differences between surgical arm and 30-d major complications (Clavien ≥3) (Table 3).

3.2.2. 90-d complications

No statistically significant differences were found between surgical arm and rates of all or major 90-d complications. Complications are further classified by Clavien grade and system (Tables 4 and 5). Clavien grade 1 was significantly different at 30 d (ORC: 8; RARC: 3; LRC: 1; p = 0.030). There were no statistically significant differences between other Clavien grades at 30 or 90 d.

Table 1 – Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>ORC (n = 20)</th>
<th>RARC (n = 20)</th>
<th>LRC (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean (SD)</td>
<td>66.6 (8.8)</td>
<td>68.6 (6.8)</td>
<td>68.6 (9.9)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>27.4 (3.9)</td>
<td>27.5 (4.2)</td>
<td>26.2 (3.6)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (90)</td>
<td>17 (85)</td>
<td>15 (79)</td>
</tr>
<tr>
<td>ASA grade, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA 1</td>
<td>4 (20)</td>
<td>4 (20)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>ASA 2</td>
<td>15 (75)</td>
<td>15 (75)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>ASA 3</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>3 (16)</td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiologists; BMI = body mass index; LRC = laparoscopic radical cystectomy; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy; SD = standard deviation.
3.3. Secondary end points

3.3.1. Perioperative outcomes
Mean operative time was significantly longer for RARC compared with ORC (p < 0.001) and LRC (p < 0.001). Time to solids was significantly longer for ORC compared with RARC (p = 0.049) and LRC (p = 0.01). LOS was significantly longer after ORC compared with LRC only (p = 0.005). There were no statistically significant differences between surgical arms and time to flatus or EBL (Table 6).

3.3.2. Pathologic outcomes
Overall, 2 of 20 ORC patients (10%), 3 of 20 RARC patients (15%), and 1 of 19 LRC patients (5%) had positive surgical margins (PSMs). Of these, three had carcinoma in situ (CIS) at the proximal urethral margin, and the other three had bladder PSMs. There was no significant relationship between surgical arm and PSMs.

Mean lymph node yield was 18.8 in the ORC group, 16.3 in the RARC group, and 15.5 in the LRC group. The differences in lymph node yield between ORC and LRC were statistically significant (p = 0.01).

3.4. Oncologic outcomes
At 12 mo, 10 patients had disease recurrence (ORC: 2 of 19, RARC: 5 of 19, LRC: 3 of 18; p = 0.5) and 4 had died (ORC: 0 of 19, RARC: 1 of 20, LRC: 3 of 18; p = 0.1) including two from BCa (ORC: 0 of 19, RARC: 0 of 20, LRC: 2 of 18; p = 0.1). One ORC patient and one LRC patient were lost to follow-up. Table 7 shows the details of recurrences. There were no port-site metastases. There was no statistically significant relationship between surgical arm and 12-mo oncologic outcomes (recurrence, overall mortality, or disease-specific mortality).

Figure 2 shows Kaplan-Meier survival estimates from surgery to death or last follow-up. Figure 3 breaks this down by surgical modality. The differences in survival were not statistically significant (p = 0.7). Longer-term follow-up is currently underway.

3.5. Quality-of-life measures
Overall, 53 patients completed the QoL questionnaire. One questionnaire was analysed per patient (average 8 mo postoperatively). Incomplete questionnaires were excluded. There were no statistically significant relationships in QoL according to surgical arm (Table 8).

4. Discussion
The CORAL trial is the first randomised controlled trial comparing ORC, RARC, and LRC. Although randomisation was feasible, single-centre recruitment was slow. The best means of recruitment is to contact patients directly while maintaining clinical equipoise. Follow-up was achievable with minimal attrition: 100% and 97% completed 90-d and 12-mo follow-up, respectively.

The 30-d complication rates (at least one complication) were significantly different between the groups overall; specifically, ORC patients had significantly more 30-d complications compared with LRC. There was no difference in 30-d major complications and all or major 90-d complications. Although RARC was associated with longer operative times compared with ORC and LRC, patients
undergoing ORC had a longer time to return to solids and longer LOS compared with the minimally invasive approaches. Significantly more lymph nodes were retrieved in the ORC group compared with LRC but not RARC.

This study adds to the existing literature as the only study with LRC as a separate arm in addition to ORC and RARC. Inclusion of LRC was deemed logical at trial initiation because RARC was not yet widely performed in the United Kingdom, and it was believed that LRC could be a valuable tool for institutions lacking the means to set up a robotic program.

Three randomised trials have been published comparing ORC with RARC, with strikingly similar results. RARC has been shown to improve some perioperative parameters such as EBL and LOS, but in all three studies no significant differences were found in complication rates [6–8]. A recent systematic review comparing RARC with ORC similarly concluded that although RARC can be performed safely, complication rates remain significant [18].

In terms of primary outcomes, although the only statistically significant difference was in 30-d complications between ORC and LRC, we found an unexpected overall trend toward reduced complication rates for LRC. Although a surgeon bias could have influenced the results, we have minimised this by ensuring that all surgeons in the trial were well over their learning curve for cystectomy. In addition, study arms were well matched (Tables 1 and 2). Compared with previously published LRC outcomes, LRC complication rates reported in this study were particularly good, which could have resulted from the small numbers in each arm because the target sample size could not be met due to early trial termination. For example, a recent multicentre study including data from the LRC surgeon in this trial reported an LRC complication rate of 54% [19] that is considerably higher than our findings (26% and 32% at 30 and 90 d, respectively). Ultimately, LRC remains a technically challenging procedure, and it also lacks the ergonomic advantage offered by RARC [20]. Our findings are insufficient to recommend LRC over RARC, but they do suggest that in expert hands, LRC could achieve good results.

We reported PSM rates of 10%, 15%, and 5%, respectively, for ORC, RARC, and LRC. The rate for RARC seems high, especially considering the Pasadena Consensus Panel recommendation of <7% PSM rate for RARC [21]. However, we believe our findings reflect our practice of not routinely performing simultaneous urethrectomy unless there is tumour in the urethra because this increases morbidity.

### Table 4 – Complications classified by Clavien grade

<table>
<thead>
<tr>
<th>Clavien grade</th>
<th>ORC 30 d</th>
<th>RARC 30 d</th>
<th>LRC 30 d</th>
<th>p value ORC 30 d</th>
<th>p value RARC 30 d</th>
<th>p value LRC 30 d</th>
<th>ORC 90 d</th>
<th>RARC 90 d</th>
<th>LRC 90 d</th>
<th>p value ORC 90 d</th>
<th>p value RARC 90 d</th>
<th>p value LRC 90 d</th>
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<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>10</td>
<td>3</td>
<td>0.030</td>
<td>0.001</td>
<td>0.087</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0.001</td>
<td>0.001</td>
<td>0.079</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0.013</td>
<td>0.027</td>
<td>0.013</td>
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<td>1</td>
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<td>0.001</td>
<td>0.001</td>
<td>0.013</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<td>0.001</td>
<td>0.001</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<td>5</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0.001</td>
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</tr>
</tbody>
</table>

LRC = laparoscopic radical cystectomy; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy.

Note: Some patients had more than one complication.

### Table 5 – Complications classified by system

<table>
<thead>
<tr>
<th>System</th>
<th>ORC 0–30 d</th>
<th>ORC 30–90 d</th>
<th>RARC 0–30 d</th>
<th>RARC 30–90 d</th>
<th>LRC 0–30 d</th>
<th>LRC 30–90 d</th>
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<tbody>
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<td>Infectious (n = 27)</td>
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<tr>
<td>Intra-abdominal collection</td>
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<tr>
<td>Urosepsis</td>
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<td>5</td>
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<td>4</td>
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<td>Ileus</td>
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<tr>
<td>Anastomotic bowel leak</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Ureteric stricture/hydroureteronephrosis requiring drainage</td>
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<td>0</td>
<td>1</td>
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<tr>
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<td>0</td>
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<td>1</td>
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<tr>
<td>Thromboembolic (n = 1)</td>
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<tr>
<td>Cardiac (n = 1)</td>
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<td>Myocardial infarction</td>
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<tr>
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<tr>
<td>Postoperative bleeding</td>
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<td>0</td>
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<tr>
<td>Neurologic (n = 1)</td>
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<tr>
<td>Acute confusional state</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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Instead, patients with positive urethral margins undergo interval urethrectomy, and this practice has not affected our long-term oncologic outcomes. The three patients in this series who only had CIS at the urethral margin underwent interval urethrectomy, and this practice has not affected our long-term oncologic outcomes. The three patients in this series who only had CIS at the urethral margin underwent interval urethrectomy, and this practice has not affected our long-term oncologic outcomes. The three patients in this series who only had CIS at the urethral margin underwent interval urethrectomy, and this practice has not affected our long-term oncologic outcomes. The three patients in this series who only had CIS at the urethral margin underwent interval urethrectomy, and this practice has not affected our long-term oncologic outcomes. 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can confound trials running over many years [27]. This consideration, coupled with our interim analysis suggesting no significant difference in primary outcomes between the arms, informed our decision to terminate the trial after 3 yr. One problem with recruitment was that a significant number of patients declined randomisation because they preferred the robotic approach. Despite this, 65% of eligible patients did participate, showing that randomisation into surgical trials is feasible provided that patients are well counselled.

Third, as previously mentioned, each surgical modality was carried out by a different surgeon, which can potentially introduce surgeon bias. We are confident that this bias was minimised to the best of our ability because, as stated earlier, all three surgeons were well over their learning curves for their respective operative modality, but this point does lend caution to our outcomes, and we would recommend further trials of this nature be carried out in multiple centres with multiple surgeons.

Fourth, there was significant crossover between arms, especially between LRC and RARC due to the LRC surgeon being unavailable due to emergencies at his base hospital at short notice. However, it was thought inappropriate to delay the operation for this reason, and therefore patients proceeded with their operation but using a different modality than their original assignment. To reduce bias, analysis was performed by intention to treat.

Lastly, the proportion of patients within our cohort who had an orthotopic neobladder may be considered low at 10%. However, this figure is representative of our practice and also of UK patients in general [28]. Also, all urinary diversions were performed extracorporeally, which was standard of care when the trial was conceived. RARC is increasingly performed intracorporeally, and future studies should take this into consideration.

Professor Studer commented at the 2015 European Association of Urology congress that while RARC is feasible, there is yet insufficient evidence to consider it the gold standard [29]. The findings of the CORAL trial support this statement, and we recommend a multicentre trial such as the ongoing RAZOR trial [30] in the United States to further evaluate this technique.

5. Conclusions

This is the first randomised controlled trial comparing ORC, RARC, and LRC. The 30-d complication rates varied significantly by surgical modality and were significantly greater for ORC compared with LRC. There were no significant differences in 30-d complication rates between RARC and either ORC or LRC. There were no significant differences in 90-d complication rates.

**Author contributions:** Muhammad Shamim Khan 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:** Khan, Rimington, Dasgupta.  
**Acquisition of data:** Khan, Gan, Ismail, Watkins, Rimington, Dasgupta.

### Table 8 – Quality-of-life analysis

<table>
<thead>
<tr>
<th>QoL variable</th>
<th>ORC, n = 16 (mean (SD))</th>
<th>RARC, n = 15 (mean (SD))</th>
<th>LRC, n = 15 (mean (SD))</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-BI ***</td>
<td>124.9 (12.7)</td>
<td>122.3 (17.1)</td>
<td>127.4 (13.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>FACT-G **</td>
<td>90.0 (9.9)</td>
<td>87.9 (14.6)</td>
<td>92.9 (12.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>TOI, 0–104</td>
<td>80.3 (11.7)</td>
<td>78.8 (12.2)</td>
<td>81.7 (9.0)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**FACT-BI** total score, 0–152  
**FACT-G** total score, 0–108  
**TOI** score = PWB, FWB, and BICS.  
**FACT-G** score = PWB, SWB, EWB, FWB, and BICS.  
**TOI** score = PWB, FWB, and BICS.
Analysis and interpretation of data: Khan, Gan, Ahmed, Ismail, Summers, Peacock, Dasgupta.

Drafting of the manuscript: Khan, Gan, Summers.

Critical revision of the manuscript for important intellectual content: Khan, Gan, Ahmed, Summers, Peacock, Dasgupta.

Statistical analysis: Summers, Peacock.

Obtaining funding: Khan, Dasgupta.

Administrative, technical, or material support: Watkins.

Supervision: Khan, Dasgupta.

Other (specify): None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2015.07.038.

References


