Robot Assisted Radical Cystectomy with intracorporeal urinary diversion versus Open Radical Cystectomy: Results from the iROC prospective randomised controlled trial

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Keywords: Bladder cancer, Cystectomy, Robotic surgery, Radical Cystectomy, RARC, Activity trackers, Complications, Recovery, Enhanced Recovery

Abstract

BACKGROUND

There are few data to inform whether robot-assisted surgery delivers improved post-operative recovery over open surgery. Most prospective comparisons have compared longer term outcomes. Radical cystectomy (RC) with pelvic lymphadenectomy is the gold standard treatment for aggressive bladder cancer. We evaluated if reductions in morbidity from RC were achieved through complete robot-assisted surgery.

METHODS

We undertook the first prospective RCT comparing open RC (ORC) with complete intra-corporeal Robot Assisted RC (iRARC) across 9 British cancer centres. The primary outcome was number of days alive out of hospital within 90 days of surgery (DAOH90). Secondary outcomes included complications, physical activity, quality of life, disability, survival and cancer recurrence. Analyses were intention to treat and adjusted for type of diversion and centre.

RESULTS

We screened 1,095 patients, randomised 338 participants, of whom 306 (91%) received their allocated approach, 11 (3%) chose route and 21 (6%) did not undergo cystectomy. Most participants were male (79%), the mean age was 69 years, 34% of patients received neoadjuvant chemotherapy and ileal conduit was the most common reconstruction (89%). The two arms were similar for patient and disease features. Patients undergoing iRARC spent more time out of hospital (DAOH90: median 82 days (IQR 76 to 84)) than for ORC (80 (72 to 83); p=0.012), reflecting shorter inpatient stays (iRARC median 7 days (6-10) vs. ORC 8 (6-14) p=0.045) and fewer readmissions (21.8% vs. 32.2%, respectively, p=0.04). Thromboembolic (1.9% vs. 8.3% (difference -6.5 (95%CI: -11.4 to -1.4)) and wound complications (5.6% vs. 16.0% (difference -1.7 (-18.6 to -4.6)) were less common with iRARC than ORC. Patients recovering from iRARC reported higher quality of life and lower disability outcomes, walked more steps per day and had more stamina than those after ORC. Differences disappeared after 12 weeks. No significant differences were seen in cancer recurrence [15/161 (9.3%) and 11/156 (7.1%) participants after iRARC and ORC, respectively] and overall mortality [(23/161

(14.3%) vs.23/156 (14.7%)) after iRARC and ORC, respectively] rates at median follow-up 18.4 (IQR: 12.8 to 21.1) months.

CONCLUSIONS

Within this trial, participants undergoing iRARC spent less time in hospital, within 90 days of surgery, than those receiving ORC. Those undergoing iRARC had lower transfusion rates, appeared to have higher quality of life, less disability and more stamina than those receiving ORC. This was associated with fewer thromboembolic and wound related complications.

(Funded by The Urological Foundation, Champniss Foundation, the NIHR and others; ISRCTN13680280 and NCT03049410).

Introduction

Guidelines recommend Radical Cystectomy (RC) with pelvic lymphadenectomy as the standard treatment for aggressive bladder cancer (BC) [1]. Survival following RC reflects tumour stage and subtype [2], the use of multimodal treatment and patient fitness [3]. BC is more common in smokers and older persons [4], and so many affected individuals have prior co-existing illnesses [5]. Consequently, RC can be a morbid operation performed in individuals at high-risk of complications. High-volume centres report around 20% of patients require further intervention whilst recovering from RC and 20-30% are readmitted post-discharge [6]. Complications lead to prolonged hospital stay, are expensive to manage and rates vary considerably between providers [7].

Reductions in morbidity from major surgery have occurred through centralization of services [8], improvements in anaesthesia and surgery, and enhanced recovery pathways [9,10]. Further reductions may be obtained using robot assisted surgery to achieve smaller incisions and reduce blood loss. However, current trials do not suggest that robot assisted surgery is superior to comparisons. For example, Jayne et al. found robot-assisted rectal surgery had similar risks of open conversion as traditional laparoscopy [11], and Yaxley et al. reported similar oncological and functional outcomes from robot-assisted and open radical prostatectomy [12]. More worryingly, population-based and prospective trial data report lower disease-free rates with robot-assisted and laparoscopic hysterectomy for cervical cancer, when compared to open approaches [13,14].

The risk profile of patients undergoing RC suggests they may benefit more from robot assisted surgery than those undergoing other procedures [5]. Parekh et al. reported robot assisted RC was non-inferior to open RC with respect to cancer recurrence at 2 years [15]. Participants receiving robotic surgery had lower blood loss, fewer transfusions, longer operations and shorter length of hospital stays than for open surgery. Within this trial, reconstruction after robotic cystectomy was performed through an additional separate, open incision (so called extra-corporeal route). Extra-corporeal reconstruction may remove some of the benefits from robot-assisted surgery [16]. Intra-corporeal reconstruction avoids the need for a separate open incision, but is technically more challenging and may have a different risk/benefit profile. Given the lack of randomised evidence regarding its benefit and safety, we conducted the

first prospective randomised trial comparing total intracorporal robot assisted RC (iRARC) and Open RC (ORC) in patients with BC. We hypothesised that differences would be most apparent in the initial recovery phase after surgery.

Materials and methods

Trial design

iROC was an investigator initiated, phase 3, multicentre, unblinded, prospective randomised trial conducted at 9 NHS cancer centres in the United Kingdom. The primary objective was to test the hypothesis that iRARC is associated with faster recovery and fewer days in hospital than ORC. Design and pilot feasibility have been published previously [17,18]. The trial received ethical approval from Newcastle & North Tyneside Research Ethics Committee (REC reference 16/NE/0418), was sponsored by University College London, and registered (ISRCTN 13680280 and ClinicalTrials.gov NCT03049410) before commencement. The trial was overseen by external Trial Steering and Data Monitoring committees (see appendix 1).

Patients: Inclusion and exclusion

Briefly, participants undergoing RC were recruited through urological clinics from March 2017 to March 2020. Recruitment was closed one month early due to the COVID pandemic. Eligible patients were adults (18+ years), suitable for either approach, with non-metastatic urothelial, squamous, adenocarcinoma or variant bladder cancer (node status ≤ N1), fit for RC (ECOG grade 1, 2 or 3) and able to give informed written consent. Patients with prior abdominal/pelvic surgery, pelvic radiotherapy or concomitant diseases that rendered them unsuitable for either approach, with upper urinary tract tumours, who were pregnant or lactating, unable or unwilling to give consent were excluded.

Radical cystectomy: Open and iRARC

Surgeons required accreditation from the Trial Management Group (TMG), needed to use ERAS pathways [9,10] and to have submitted outcomes to the public BAUS Oncology database [19]. Robotic surgeons needed to have completed at least 30 iRARCs as sole surgeons. Radical cystectomy included removal of the prostate and seminal vesicles in men, and the uterus, fallopian tubes and vaginal wall (± one or both ovaries) in women, as detailed [17,20]. The female

urethra was preserved in those receiving neobladder reconstruction. Variations to this approach needed prior agreement from the TMG. The minimum pelvic lymphadenectomy template included the external iliac, obturator and internal iliac nodes, with a proximal extension to the level of the ureteric crossing of the common iliac vessels. Open surgery was performed through a lower midline incision [20]. iRARC was performed using a da Vinci surgical robot (various models used across the centres) and included robotic cystectomy and reconstruction [21]. Specimens were retrieved using appropriate extraction bags through the vagina in females (after exenteration) or extension of the peri-umbilical port in males (at the end of the procedure).

Outcomes

The primary outcome was days alive and out of hospital within 90 days of surgery (DAOH90) [22]. This accounts for post-operative length of stay (LOS) and readmissions within 90 days. Secondary outcomes were complications and adverse events up to 90 days, overall survival and oncological outcomes (BC recurrence free rates), and quality of life (HRQOL; including WHODAS 2.0 disability [23], EQ-5D-5L [24], EORTC-QLQC30 [25] and EORTC-BLM30 [26] questionnaires), physical activity (average and maximum number of steps taken per day over a 7 day period, and number of chair to stands in 30 seconds (CTS30 [27])) recorded at 5, 12 and 26 weeks. Steps were measured using a wrist worn tracker (Shine, Misfit, Fossil Group Inc.) returned by participants to the trial unit by mail. Steps were also recorded 5 days after surgery by research nurses. CTS30 were counted at clinic visits by independent research nurses. HRQOL questionnaires were self-completed and mailed back, or completed by independent research nurses(if participant was in hospital. Cancer recurrence was recorded by research nurses determined from hospital notes or CT scans performed for clinical suspicion or at routine follow up at 26 and 52 weeks, and annually thereafter.

Statistical analysis

It was anticipated that DAOH90 would have a skewed distribution, and thus the calculations of sample size were based on the number of days not alive or not at home, transformed to a log scale (i.e., ln(90-DOAH90 +1)). Based on the 2015 BAUS national dataset [19], the sample size calculation was determined to detect a difference between groups on the log scale of 0.22 units, assuming a standard deviation of 0.7 units. We calculated that with 160 patients

in each group and 5% significance level, the trial would have 80% power. A planned interim analysis of the first 30 recruited patients [18] highlighted a larger than expected SD, hence the sample size was inflated to 170 patients per group.

The primary outcome was compared between arms using a regression model for the same log-transformed values used for sample size calculation, to satisfy assumptions for linear regression, adjusting for site and reconstructive choice. The analysis was performed using the Intention to Treat (ITT) principle and excluded all patients that dropped out from the trial before 90 days. Descriptive statistics for the primary outcome and for its components are also calculated, by treatment arm. Secondary outcomes were summarised, by treatment arm and when relevant at different follow-up time points, using appropriate descriptive statistics according to the nature of the variables. Differences in percentages and their associated unadjusted 95% CIs were reported for surgical complications and their Clavien-Dindo classification. Analogously, 95% CIs for the differences between arms in quality of life and physical activity outcomes were obtained at several follow-up time points using appropriate regression models, adjusting for site, reconstructive choice and baseline measures for the outcome considered, when available. Proportions of cancer recurrence and all-cause mortality are reported by arm, and cause of mortality described. Furthermore, we obtained Kaplan-Meier survival plots, by arm, for both outcomes. Data were censored for patients without the events (death or cancer recurrence) at the last available follow up visit or date on record (e.g. for complications or other secondary outcomes), whichever occurred last. No confidence interval should be used to infer definitive treatment effects for secondary outcomes, instead results should be considered exploratory and hypotheses generating. Statistical analyses were performed with the use of R software, version 4.0.3 or higher, and Stata software, version 17. An independent data monitoring committee reviewed recruitment and outcomes during the running of this trial. The study was registered [ISRCTN13680280 and NCT03049410] prior to opening.

Role of the funding source

This work was funded by The Urological Foundation and The Champniss Foundation (#4300 BLADC/2016). Robotic consumables were supplied at no cost by Intuitive Surgical. JDK is funded by the UCL NIHR Biomedical Research Centre, PK is funded a Urology Foundation

fellowship and JWFC is funded by an NIHR Research Professorship. The funders had no role in the design, analysis or collection of the data, in writing the manuscript or interpretation of data, or in the decision to submit the manuscript for publication.

Results

Participants

In total, we screened 1,095 patients and randomised 338 participants (figure 1), of whom 306 (91%) received their allocated approach and 11 (3%) chose their route. Twenty-one (6%) randomised patients did not undergo cystectomy (3 received radiotherapy, 7 had disease progression prior to RC, 4 opted for another choice, 1 was judged unfit at the time of surgery and in 6 the reason was for unclear) and so were excluded from analysis. Participants undergoing ORC and iRARC were balanced for patient and disease factors. As typical for BC, most participants were male (79%), the average age was 69 years (st. dev. 8.2), 19 (6%) were over 80 yrs. old and most were current or ex-smokers (71%) (table 1). Prior to RC, 34% of patients received neoadjuvant chemotherapy. At surgery, most patients underwent ileal conduit reconstruction (89%). Cystectomy specimens confirmed muscle invasive BC in 140 (44%) patients, high grade non-muscle invasive disease in 96 (30%) and no residual cancer (pT0) in 14%. Most patients had urothelial carcinoma (295 (79%)). Lymph node yields were sufficient for an adequate lymphadenectomy [28]. Positive surgical margins were present in 20(6%) of cases (of which: 70% were urothelial and 30% circumferential soft-tissue or peritoneal).

Primary Outcome, Length of stay and Readmission

The primary outcome (DAOH90) was available in 305 (96%) participants. The median (IQR) DAOH90 was 82 days (76 to 84) for iRARC and 80 days (72 to 83) for ORC (p=0.012, Figure 2). The median (IQR) length of stay in hospital was 7 days (6 to 10) for iRARC and 8 days (6 to 14) for ORC (p=0.045), not including the day of cystectomy. Readmission after discharge occurred in 34/156 (22%) patients who received iRARC and 48/149 (32%) who received ORC (p=0.04). Length of readmission was similar between arms (mean (SD) 2.99 (9.93) for iRARC vs. 3.05 (7.61) days for ORC).

Procedures and complications

All surgeries were completed by NHS consultant urological surgeons. The mean (SD) operative duration from first incision to wound closure was 5.0(1.2) hours for iRARC and 4.3(2.1) hours for ORC. Intra-operative blood loss (mean (SD)) was measured as 281(262) mls for iRARC and 759(907) mls for ORC. Blood transfusion occurred in 2 (1%) and 1 (1%) patient prior to, and 4 (2.6%) and 10 (6.5%) cases during iRARC and ORC, respectively. Intra-operative injuries to viscera during iRARC and ORC were rare; major vessel 1 vs. 2, rectum 1 vs. 2, small intestine 1 vs. 1, respectively. Various other complications were reported; including an ischemic ileal conduit that needed revising, and unresectable lymph nodes (n=2) for iRARC; and hemostatic device failure, incidental cecal carcinoma requiring hemi-colectomy, urethral stricture needing urethrotomy, rectal repair and heavy DVC bleeding for ORC.

Following surgery, 208 (65.6%) participants had at least one complication within 12 weeks, including 102 (63.4%) in the iRARC and 106 (67.9%) in the ORC arms. Most complications were mild (Clavien-Dindo ≤2 table 2a) and the distribution of severity did not differ between the arms. When compared, participants receiving iRARC were less likely to have wound related (5.6% vs. 17.3%, difference -11.72% (95% CI of difference: -18.59 to -4.58)) and thromboembolic (1.9% vs 8.3%, difference: -6.47% (-11.43 to -1.38)) complications than those receiving ORC (table 2b and supplementary table 1). Rates of the other complications did not differ between arms.

Quality of life

Generic HRQOL, as measured by EQ-5D-5L, was broadly similar by arm at baseline (figure 2a supplementary table 2). At 5 weeks, the ORC cohort reported more problems compared to iRARC participants and comparisons of EQ-5D-5L scores revealed worse HRQOL for ORC (difference in means (95%CI): -0.08 (-0.11 to -0.03)). Differences disappeared by 12 weeks. Cancer specific HRQOL as measured by EORTC-QLQ-C30 summary scores were similar at baseline and 26 weeks (figure 2b supplementary table 3). Participants who received iRARC had superior HRQOL to those in the ORC arm at both 5 weeks (difference in mean scores (95%CI): -9.33 (-13.45 to -5.21) for ORC) and 12 weeks (-4.87 (-8.34 to -1.41) for ORC). Cystectomy specific HRQOL was determined using the EORTC-BML30 questionnaire

(supplementary table 4). No differences were seen in any domain by arm at baseline, 5, 12 and 26 weeks.

Disability

Self-reported disability after surgery was assessed using the WHODAS 2.0 questionnaire. At baseline no differences were seen between the arms (figure 2c, supplementary table 5). Disability scores more than doubled after surgery (2.2 fold for iRARC and 2.9 fold for ORC). More disability was reported in the ORC cohort compared to those receiving iRARC at 5 weeks (difference in scores (95%CI): 0.52 (0.21-0.83)) and 12 weeks (0.46 (0.14-0.78)) after surgery. Differences between the arms disappeared by 26 weeks.

Physical activity levels: Steps walked per day

Activity levels measured using the average or maximum number of steps taken per day (over a 7-day period) were similar between arms at recruitment (figures 2d and e, supplementary table 6). Average and maximum steps per day dropped dramatically 5 days after surgery to 30-31% of baseline for iRARC and 25-27% for ORC. Levels recovered to 72-74% and 61-66% at 5 weeks, and 87-89% and 90-93% at 12 weeks for iRARC and ORC, respectively. Comparisons revealed fewer average steps taken for participants receiving ORC than iRARC at 5 days after surgery (difference in mean (95%CI): -420 (-797 to -43)). Comparisons at other times and for maximum per day were not different.

Strength and stamina: Chair to stand test

Strength and stamina were measured using the CTS30 test (figure 2, supplementary table 7). At baseline both arms were similar (mean (SD) stands in 30 seconds: 14.0 (4.5) for iRARC and 13.8 (3.8) for ORC). However, by 5 weeks after surgery participants receiving iRARC (8.8 (5.0)) managed more stands than for ORC (6.4 (4.1))(mean difference (95%CI) in stands: 2.2 (0.67 to 3.73). Differences remained at 12 weeks (mean difference (95%CI) in stands: 1.18 (0.2 to 2.16), before disappearing by 26 weeks.

Oncological and survival outcomes

At reporting (median follow-up 18.4 (IQR: 12.8 to 21.1) months), there were 15/161 (9.3%) patients with cancer recurrence in the iRARC and 11/156 (7.1%) in the ORC, including 2 (1.2%)

and 4 (2.6%), respectively (figure 4), within 90 days from surgery. All cause mortality occurred in 23/161 (14.3%) patients in the iRARC and 23/156 (14.7%) in the ORC arms. Of these, 2 (1.2%; from cardiorespiratory failure and cancer progression) and 4 (2.6%; from intra-abdominal sepsis/laparotomy/organ failure (2), PE and cancer progression) from occurred within 90 days from iRARC and ORC, respectively.

Discussion

Last year there were more than 1.2 million robot-assisted surgeries performed worldwide using the da Vinci platform [https://isrg.intuitive.com/static-files/80b10bf5-c1da-4ad3-bb0e-8c595e2c712c]. This approach has become the most common choice for many cancer operations, surgeons are looking to expand into further procedures and new robot platforms are reaching clinical practice [29]. The promise of robot-assisted surgery is that smaller incisions, clearer vision and greater precision, combined with improved surgeon dexterity and ergonomics will translate into superior patient outcomes. However, to date, prospective comparative trials have not supported these assumptions. Whilst blood loss appears lower than with open surgery [30] and operative times may be faster for some procedures [12], trials have shown no difference in short or long term functional recovery [31], HRQOL [30] or the risks of conversion to open surgery [11], and have raised oncological concerns [13,14].

We hypothesised that much of the benefit from robotic surgery occurs within the first few weeks and that prior prospective studies have focused on longer term outcomes that missed these aspects. The etiology of BC [4,32] means most affected individuals have co-existing medical conditions (with cardiovascular and pulmonary disease being most common [5]) that place them at high-risk for post-operative complications. This population seems one that would particularly benefit from reduced surgical morbidity and earlier post-operative mobilization. Several authors have conducted prospective trials comparing open and robot-assisted RC [30,33,34,35], although the RAZOR study is the only multi-centered trial large enough to detect differences. The authors focused on oncological safety given the aggressive nature of most BCs, the risks of dissemination from the pneumoperitoneum and reports of changing patterns of local or peritoneal recurrence with robotic cystectomy [36]. This was a prudent choice given subsequent reports in gynaecology [13,14]. The RAZOR trial concluded robotic surgery was non-

inferior to open RC in terms of cancer outcomes but did not focus on short term post-operative recovery. Surgeons within the trial used an extra-corporeal approach to urinary reconstruction, which potentially negated the benefits of robotic surgery. A similar limitation was seen in other single centre studies [33] [35].

To overcome prior limitations and to test our hypothesis, we conducted the first multicentred prospective randomised comparison of complete iRARC and open RC, to our knowledge. Intracorporeal reconstruction avoids the need for a separate incision and so may mean faster surgery (there is no need undock/drape/create new incision) which is more efficient (fewer consumables), but does require specialised training, may have different complications to other modes of RC and may compromise oncological safety as the bladder remains within the abdomen for longer. Our primary endpoint measured length of stay and readmission. These events objectively capture both patient recovery (including pain control, mobilization, return to diet and stoma management) and the incidence of significant complications. Most patients after RC have one or more complication and those of severity usually lead to delayed discharge or readmission [6]. As such, length of stay and readmission have been suggested as metrics for determining surgical quality [37] and are included in patient facing surgeon outcomes data [19]. By focusing upon post-operative recovery, iROC is the first prospective RCT to show superiority of robotic surgery over open comparisons. The two day difference in DAOH90 represents a 20% relative reduction in hospital bed usage and is equivalent to improvements seen from advances such as laparoscopy for colorectal cancer [38], maintaining normothermia during surgery [39] and using dexamethasone for hospitalized patients with Covid-19 [40].

To further test our hypothesis, we collected a range of secondary endpoints that measured qualitative recovery from different dimensions. Whilst one should caution in-depth analyses of secondary endpoints, especially given compliance rates, for each measure we observed differences favouring IRARC over ORC in the short term that disappeared by 3 or 6 months after surgery (suggesting that studies using 3-months as the first HRQOL time point [30] might miss these). For example, generic HRQOL appeared greater for iRARC over ORC at 5 weeks, whilst cancer specific HRQOL appeared superior at 5 and 12 weeks. The greatest differences between arms were seen in disability scores and CTS30 tests at 5 and 12 weeks. The mean

WHODAS 2.0 score at 5 weeks was 5.6 points higher for ORC than for iRARC, which is equivalent to the difference in disability scores seen for a 65 vs. 50 yrs. old participant in the WHO-SAGE collaboration [41]. Mean CTS30 test performance at the same time point was 37% greater in the iRARC (mean 8.8) than ORC (mean 6.4) cohort. This test is a component of the Fullerton Functional Fitness Test Battery and measures stamina, balance and muscle strength. A difference of 37% is similar to that seen with having COPD versus healthy controls [42] or an increase in age from 60 to 85 yrs. old [43]. To a lesser extent we also observed greater mobility (measured as average number of steps walked per day) in the iRARC cohort compared to ORC at 5 days after surgery. This difference was less than we anticipated, was not seen for maximum number of steps per day and might reflect that most participants were still in hospital (i.e., bed based and not self-caring), that most immediate post-operative mobility is directed by pain, nursing staff and recovery, rather than mode of RC, or that reduced compliance prevented meaningful comparisons. Regardless, it is intriguing to see measures suggesting less disability, greater stamina and more mobility with iRARC are associated with a four-fold reduction in rates of thrombo-embolism (1.9% vs 8.3%) compared to ORC. Participants in both arms received thromboprophylaxis as per NHS care (including low molecular weight heparin and compression stockings). This observation builds on findings in the RAZOR trial (in which the rate of thromboembolism was 8% for ORC and 5% for robotic surgery) and might be greater due to total intra-corporeal surgery.

There are various limitations that require discussion. Firstly, the trial was closed early and compliance with endpoints that required face to face contact or research nurse time was compromised due to the COVID pandemic. Whilst we reached statistical significance for our primary outcome, the missing results for some secondary outcomes limited the robustness of our findings. Secondly, DAOH90 was chosen as the primary outcome to capture surgical quality, healthcare design and patient recovery. The relevance of this measure might be questioned by patients primarily concerned with cancer cure or those working in other healthcare environments. However, the RAZOR trial confirmed oncological non-inferiority for robotic RC, and we believe the improved quality of recovery should be valued by patients, clinical staff and purchasers given the frequency and impact of complications and re-admissions on patient experience and healthcare costs [7]. Thirdly, compliance with the wearable activity trackers and exercise tests was lower than we anticipated. Studies of

wearables or pervasive phone applications in healthcare are emerging and authors report compliance can be a problem [44]. Future work is needed to understand how to improve this and to define how wearables can aid recovery. Interestingly, compliance with exercise tests and HRQOL questionnaires was lower in the ORC arm than in the iRARC cohort, perhaps a further measure of increased fatigue with open surgery. Finally, oncological outcomes are still immature and so we will continue to follow and report outcomes per arm as planned.

Conclusions

Within this trial, participants undergoing iRARC spent less time in hospital, within 90 days of surgery, than those receiving ORC. Those undergoing iRARC had lower transfusion rates, appeared to have higher quality of life, less disability and more stamina than those receiving ORC. This was associated with fewer thromboembolic and wound related complications. There was no difference in overall or cancer specific survival.

Tables

Table 1. Participants and tumours within the iROC randomised trial.

	iRARC		Open RC	
	n	%	n	%
Total				
	161		156	
Gender				
Male	128	80%	122	78%
Female	33	20%	34	22%
ECOG Performance Status				
0. Fully active.	113	70%	118	76%
1. Restricted in strenuous activity.	21	13%	25	16%
2. Self-caring but unable to work.	3	2%	1	1%
3. Limited self-care.	2	1%	1	1%
Missing	22	14%	11	7%
Age at surgery				
Years (mean (st. dev.))	69.3 (8.0)		68.7 (8.4)	
BMI (kg/m^2)	27.6 (5.5)		28.5 (11.6)	
Missing	2		0	
Patient received neoadjuvant chemotherapy				
No	107	66%	103	66%
Yes	54	34%	53	34%
Patient received immunotherapy				
No	128	80%	124	79%
Yes	21	13%	16	10%
Missing	12	7%	16	10%
Histology				
Urothelial cell carcinoma	149	81%	146	77%
Squamous carcinoma	18	10%	20	11%
Adenocarcinoma	4	2%	3	2%
Other	13	7%	20	11%
Grade of Tumor				
Grade 1	0	0%	3	2%
Grade 2	6	4%	4	3%
Grade 3	106	66%	102	65%
Missing	49	30%	47	30%
Flat CIS				
Absent	90	56%	79	51%
Present	54	34%	57	37%
Missing	17	11%	20	13%

Cystectomy histology pT stage				
pT0	25	16%	20	13%
pTis/pTa/pT1	46	29%	50	32%
pT2	30	19%	34	22%
pT3-4	42	26%	34	22%
pTx	2	1%	0	0%
Missing	16	10%	18	12%
Surgical Margins				
Positive	10	6%	10	6%
Clear	126	78%	115	74%
Missing	25	16%	31	20%
Lymph nodes (mean (SD))	16.1 (8.0)		15.1 (9.3)	
Missing	15	9%	16	10%
Urinary diversion				
Continent/Neobladder	19	12%	16	10%
Ileal conduit	142	88%	140	90%
Smoking status				
Current	18	11%	17	11%
Ex smoker	95	59%	93	60%
Never smoker	47	29%	46	29%
Missing	1	1%	0	0%
Haemoglobin (g/dL) (mean (SD))	13.2 (1.8)		13.3 (1.9)	
Missing	4	2%	1	1%
Creatinine (mmol/L) (mean (SD))	91.6 (30.7)		85.2 (21.5)	
Missing	3	2%	2	1%
Recruiting hospital site				
#1	60	37%	58	37%
#2	26	16%	27	17%
#3	25	16%	23	15%
#4	3	2%	2	1%
#5	13	8%	12	8%
#6	10	6%	11	7%
#7	9	6%	10	6%
#8	10	6%	9	6%
#9	5	3%	4	3%

Table 2. Complications recorded within 12 weeks of surgery stratified by arm and grouped according to a. Clavien-Dindo severity and b. system affected/type.

a. Clavien-Dindo severity

Clavien-Dindo	iRARC (n=161)	ORC (n=156)	% Difference (95%CI)
1. Grade I	22 (13.7%)	20 (12.8%)	0.8 (-6.7, 8.3)
2. Grade II	36 (22.4%)	40 (25.6%)	-3.3 (-12.6, 6.1)
3. Grade III	0 (0%)	1 (0.6%)	-0.6 (-2.8, 1.5)
4. Grade IIIa	8 (5%)	13 (8.3%)	-3.4 (-9, 2.3)
5. Grade IIIb	8 (5%)	10 (6.4%)	-1.4 (-6.7, 3.9)
6. Grade IV	0 (0%)	0 (0%)	0 (-1.7, 1.7)
7. Grade IVa	5 (3.1%)	4 (2.6%)	0.5 (-3.5, 4.5)
8. Grade IVb	0 (0%)	0 (0%)	0 (-1.7, 1.7)
9. Grade V	3 (1.9%)	3 (1.9%)	-0.1 (-3.5, 3.3)

b. Type

Surgical complications	iRARC (n=161)	ORC (n=156)	% Difference (95%CI)
Bleeding	1 (0.62%)	1 (0.64%)	-0.02 (-2.47; 2.39)
Cardiac	7 (4.35%)	6 (3.85%)	0.5 (-4.14; 5.09)
Gastrointestinal	46 (28.57%)	44 (28.21%)	0.37 (-9.54; 10.25)
Infection	38 (23.6%)	52 (33.33%)	-9.73 (-19.47; 0.24)
Genitourinary	19 (11.8%)	17 (10.9%)	0.9 (-6.19; 7.94)
Neurological	7 (4.35%)	10 (6.41%)	-2.06 (-7.23; 3.12)
Miscellaneous	4 (2.48%)	9 (5.77%)	-3.28 (-7.89; 1.37)
Pulmonary	7 (4.35%)	4 (2.56%)	1.78 (-2.55; 6.04)
Surgical	6 (3.73%)	3 (1.92%)	1.8 (-2.2; 5.72)
Thromboembolic	3 (1.86%)	13 (8.33%)	-6.47 (-11.43; -1.38)
Wound	9 (5.59%)	27 (17.31%)	-11.72 (-18.59; -4.58)
Other	22 (13.66%)	23 (14.74%)	-1.08 (-8.82; 6.66)

Figures

Figure 1. Consort diagram of recruitment and follow up in iROC RCT.

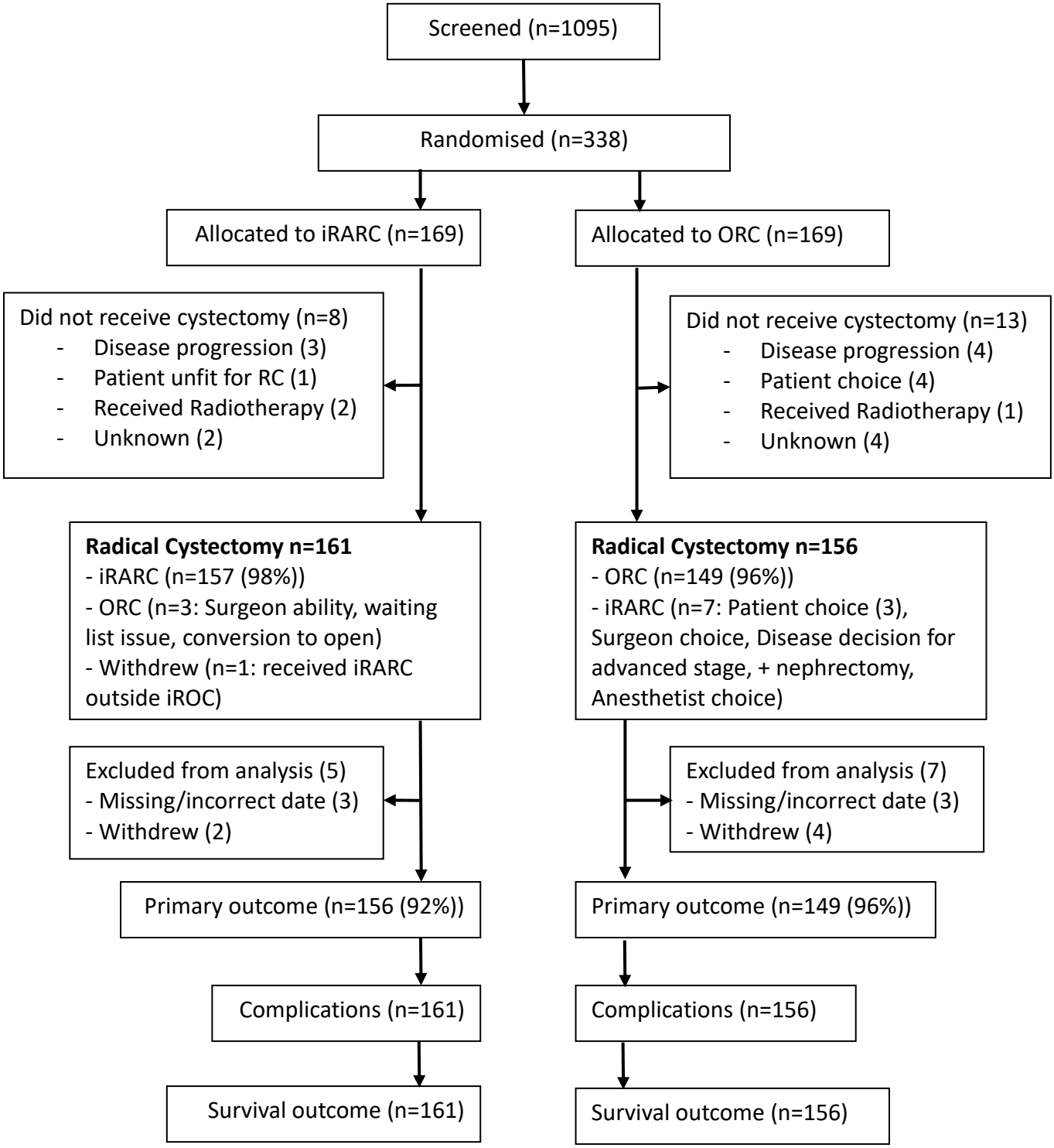


Figure 2. Histogram plots of days alive and out of hospital within 90 days of surgery (DAOH90) according to randomised arm. As shown, the median (IQR) DAOH90 was 82 days (76 to 84) for iRARC and 80 days (72 to 83) for ORC (p=0.012 (linear regression, adjusted for site and reconstruction)).

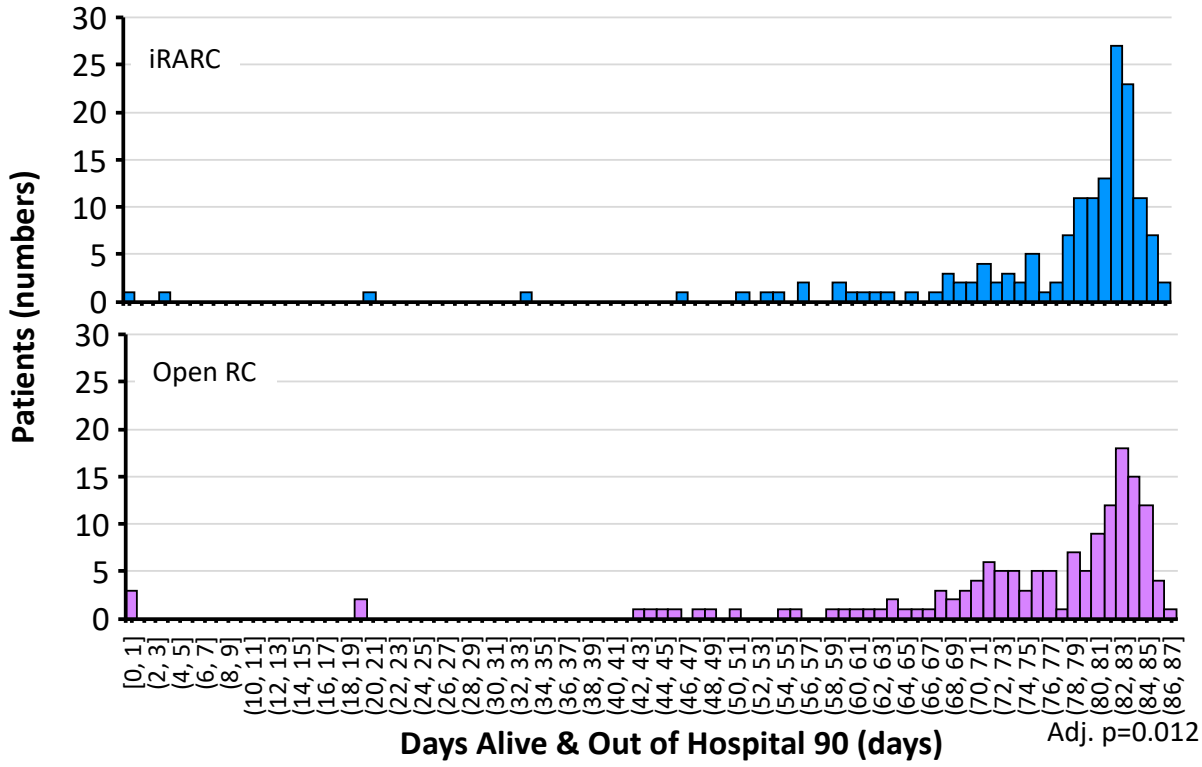


Figure 3. Comparative outcomes for quality of recovery after radical cystectomy. Self reported quality of life as (mean (SD)) measured using a. EQ-5D-5L and b. EORTC QLC30 tools, and extent of disability measured using c. WHODAS 2.0 questionnaire, reveal superior recovery at 5 weeks (and 12 weeks for b. and c.) for participants receiving iRARC compared to ORC. Activity levels measured using wrist appplied exercise trackers show patients receiving iRARC averaged more steps per day in week 5 (d.), but no difference in maximal values or at other time points (e). f. Strength and stamina measurement using the Chair to Stand test revealed patients undergoing iRARC could achieve more stands in 30 seconds than those receiving ORC at week 5 and 12. For each time point the number of completed outcomes/participants is shown for each arm.

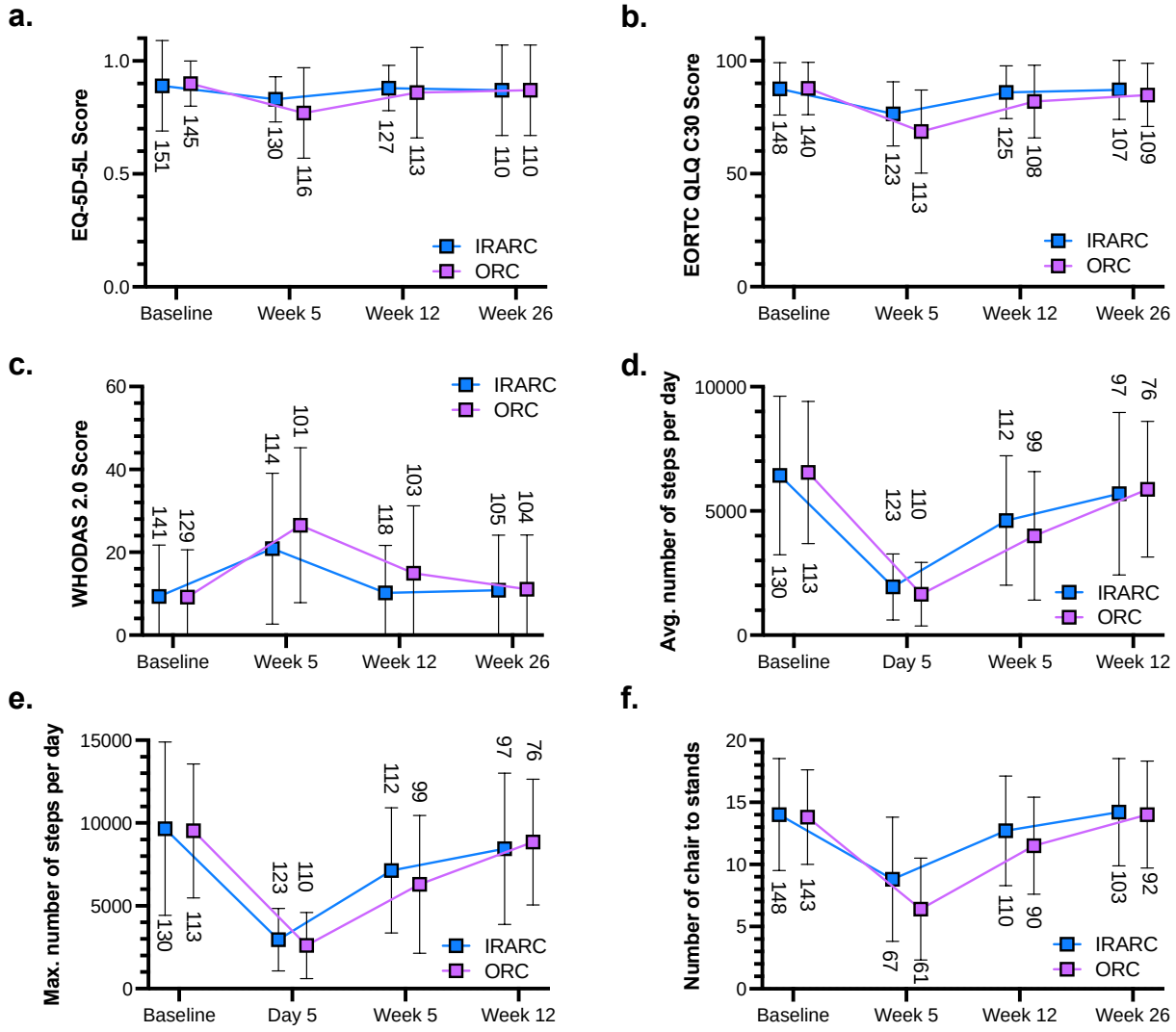
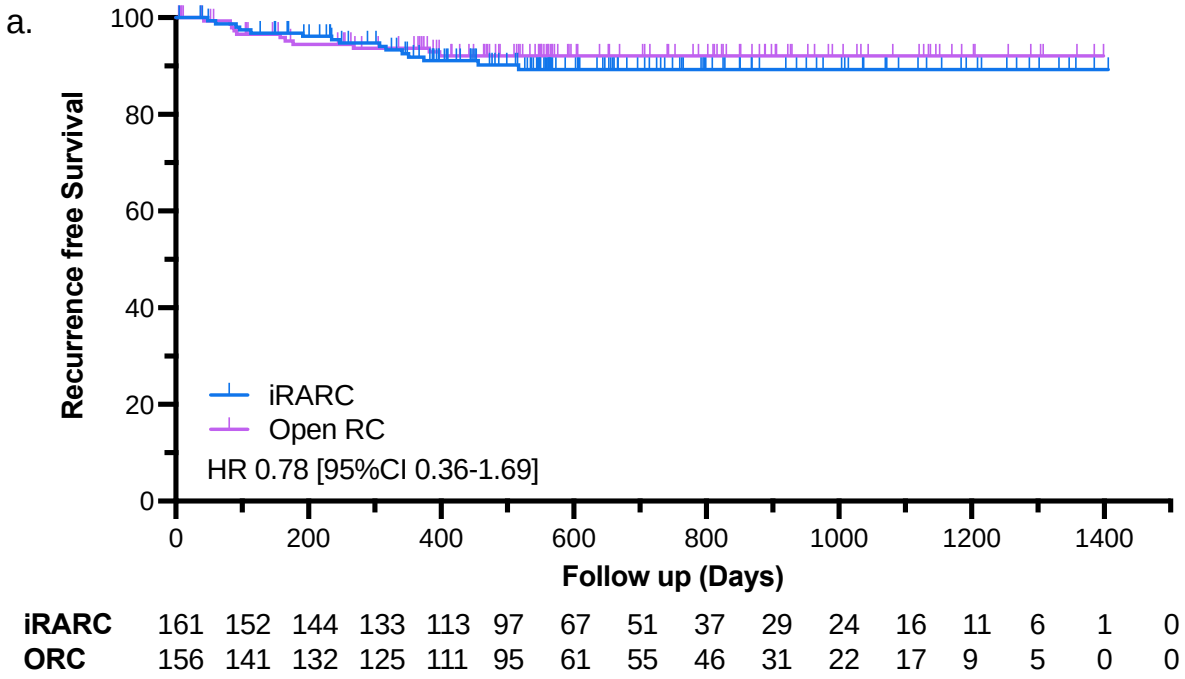
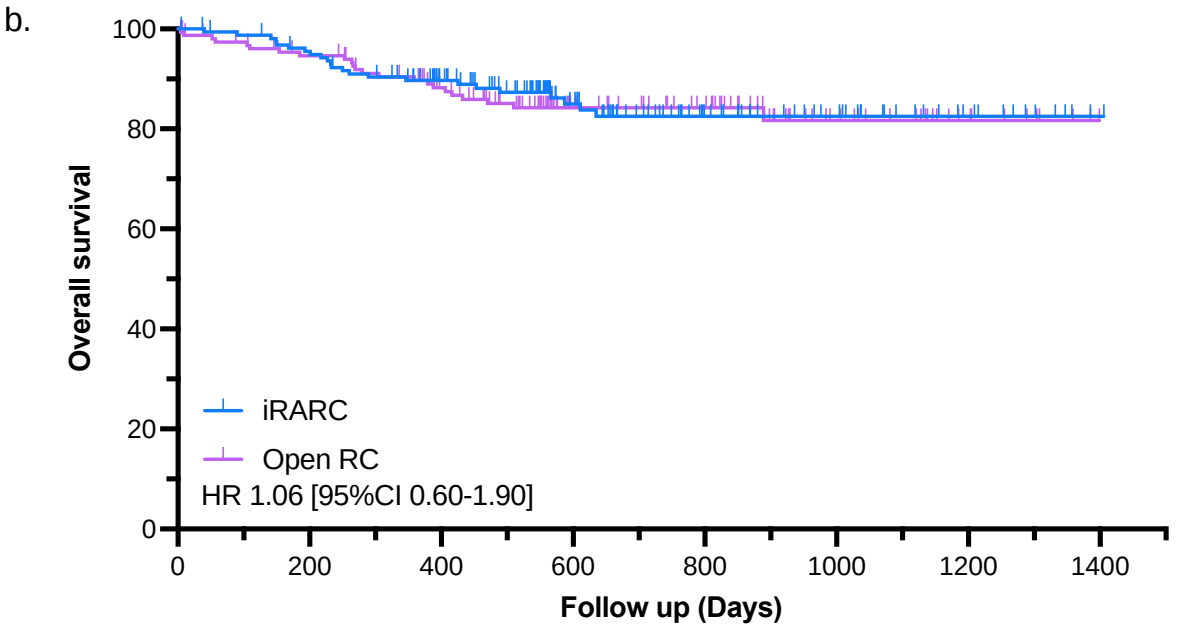


Figure 4. Cancer recurrence and overall survival following Radical Cystectomy startifed by arm within the iROC trial. No difference was seen in rates of a. cancer recurrence (log rank p=0.5) and b. all cause mortality (log rank p=0.8) plotted using the Kaplan Meier method. Hazard ratios from Cox regression model shown.



iRARC	161	152	144	133	113	97	67	51	37	29	24	16	11	6	1	0
ORC	156	141	132	125	111	95	61	55	46	31	22	17	9	5	0	0



iRARC	161	155	148	139	122	105	72	54	39	30	25	16	11	6	1	0
ORC	156	145	138	129	116	98	62	56	47	31	22	17	9	5	0	0

Author contributions:

Conception and design of the iROC trial: JWFC, JDK, JMcG, PK, GA, NW and CBG

Funding: JWFC, CBG and JDK cobtained funding.

Protocol/Patient Information Sheet: JWFC, JDK, PK, JMcG, ER, AK, SK, RS, LG, GA, NW, MT, SD, AF and CBG

Statistcial analysis: FR and GA performed all statistcial analysis.

Writing of manuscript: JWFC, JDK, CBG, PK, FR, GA and NW. All authors have read and approved the final manuscript.

The trial will comply with the authorship criteria recommended by the International Committee of Medical Journal Editors.

Conflicts of interest/Disclaimers: JWFC has received reimbursement for consultancy from Astra Zeneca, Ferring, Roche, and Janssen; speaker fees from BMS, MSD, Janssen, Atellas, Nucleix and Roche; honoraria for membership of advisory boards for Ferring, Roche, Gilead, Photocure, BMS, QED therapeutics and Janssen; and research funding from Roche. SAH has received reimbursement for consultancy from Pierre Fabre, Bayer, Janssen Oncology, Roche, Merck, Bristol-Myers Squibb, AstraZeneca, Pfizer, Astellas, GSK; research funding from CRUK, MRC/NIHR, Boehringer Ingelheim, Roche, Janssen-Cilag, Pierre Fabre; support for attending meetings and/or travel from Janssen-Cilag, Bayer, Boehringer Ingelheim, Pierre Fabre, Pfizer, Roche, Bristol-Myers Squibb, AstraZeneca, MSD Oncology. JMcG has received educational funding from Intuitive Surgical. The remaining authors declare no conflicts of interest with this work.

Funding: This work was funded by The Urological Foundation and The Champniss Foundation (#4300 BLADC/2016). Robotic consumables were supplied at no cost by Intuitive Surgical within the iROC trial. JDK is funded by the UCL NIHR Biomedical Research Centre, PK is funded by The Urology Foundation and JWFC is funded by an NIHR Research Professorship. The funders had no role in the design, analysis or collection of the data, in writing the manuscript or interpretation of data, or in the decision to submit the manuscript for publication. The iROC RCT is sponsored by University College London, UK.

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

Appendix 1: The iROC study team

- Collaborators
- Lead Surgeon
- Other surgeons
- Lead nurses
- Other research nurses
- Pathology
- Radiology

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