Robotic assisted radical cystectomy versus open radical cystectomy: a review of what we do and don't know

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Abstract: Radical cystectomy (RC) is the gold standard treatment for muscle-invasive and high-risk, noninvasive bladder cancer. Since 2003, robot-assisted radical cystectomy (RARC) has been gaining popularity. Metanalyses show that the primary advantage of RARC is less blood loss and the primary advantage of open radical cystectomy (ORC) is shorter operative times. There do not appear to be significant differences in complications, cancer-related outcomes or survival between the two approaches. Cost analyses comparing RARC and ORC are complicated by the often-ill-defined distinction between the cost to the hospital versus the cost to payors. However, it is likely that for both hospitals and payors, RARC is cost effective at high-volume centers. It is feasible that in the future, increased experience with RARC will lead to improved outcomes and justify the use of RARC over ORC.

Keywords: Cost analysis; cystectomy; randomized controlled trials (RCTs) as topic; robotics; treatment outcome

Introduction

Radical cystectomy (RC) is the gold standard treatment for muscle-invasive and high-risk, noninvasive bladder cancer. Owing to its technical complexity and the relative frailty of patients often being considered for surgery, RC confers significant risks for morbidity and mortality. Traditionally, open radical cystectomy (ORC) has been the most common surgical approach. As in other disease states, robotic surgery has gained popularity following the first report of the robot-assisted radical cystectomy (RARC) by Menon *et al.* in 2003 (1). Even in the absence of level I evidence to support its superiority, RARC continues to gain ground on ORC (*Figure 1*). Not surprisingly, the increased availability and widespread dissemination of RARC has bred debate as to the optimal surgical approach. The technical benefits of minimally invasive surgery—notably, robotic platforms—have been well described. However, whether these putative advantages translate to improved patient outcomes or alleviate the overall cost burden of treatment remains to be proven. Herein we provide a contemporary critical review of the available data comparing ORC and RARC.

Methods

We performed a search of the PubMed, Cochrane Library, and Google Scholar databases during April 2019 to identify all relevant studies using the following keywords: "radical cystectomy" and "open versus robotic radical cystectomy." Only comparative analyses between the open and robotic approaches were included in the review. Emphasis was placed on identifying prospective studies, including randomized controlled trials (RCTs), and meta-analyses that reported on perioperative, oncological, and functional outcomes. Cited references from the relevant studies were
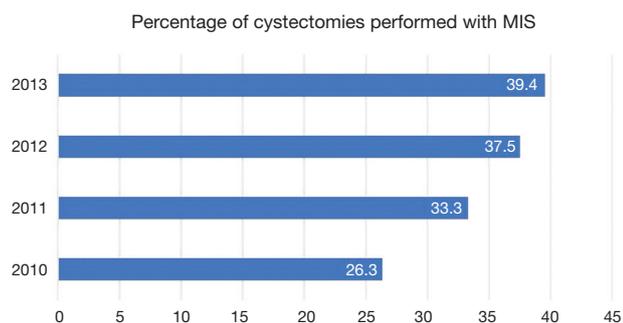
2210

Gul et al. Robot assisted RC vs. open RC

Percentage of cystectomies performed with MIS

Figure 1 Percentage of all cystectomies performed via MIS from 2010–2013, adapted from Bachman *et al*. (2). MIS, minimally invasive surgery.

also assessed for potential inclusion. Case reports, single-center retrospective series, comments, editorials, letters, and articles not published in English were excluded. Four authors (ZGG, ABK, JSW, RM) independently screened the search results to select those studies most relevant to this review.

RCTs of RARC

In 2010, the first RCT comparing ORC and RARC was published by Nix *et al*. (3). The authors compared 21 RARC patients to 20 ORC patients who were operated on between 2008 to 2009. There were no significant differences in the baseline characteristics between the two groups. The primary endpoint, lymph node (LN) yield, was not significantly different between the two groups. However, RARC was associated with a significantly longer operative time (4.2 *vs.* 3.5 h; P<0.0001), a lower estimated blood loss (EBL) (258 *vs.* 500 cc; P<0.0001), lower narcotic requirements (89 *vs.* 147 mg of morphine equivalents; P=0.004), and a faster return of bowel function (3.2 *vs.* 4.3 days to first bowel movement; P=0.0008) (3).

A second RCT of comparable size, the Cystectomy Open Robotic and Laparoscopic (CORAL) trial, was published by Kahn *et al.* in 2016. It compared 20 RARC to 20 ORC patients who underwent surgery between 2009 to 2012. The primary endpoints were 30- and 90-day complications rates. They found no significant difference between major complications, defined as Clavien grade 3 or higher, at 30 or 90 days. Again, RARC was associated with a longer operative time (389 *vs.* 293 min; P<0.001), but a shorter length of stay (LOS) (12 *vs.* 14 days; P=0.031) and a shorter time to tolerating solids (4 *vs.* 7.5 days; P=0.03). There were

no significant differences in EBL, time to flatus, or quality of life (QoL) (4).

In 2015, Bochner *et al.* published "Comparing Open Radical Cystectomy and Robot-Assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial" (NCT01076387). From 2010 to 2013, 118 patients were enrolled 60 of whom underwent RARC and 58 of whom underwent ORC (5,6). Once again, operative time was longer (456 *vs.* 329 min; P<0.001) but EBL was lower (516 *vs.* 676 cc; P=0.027) in the RARC group (6). There were no significant differences in Clavien 2–5 complications, LN yield, positive surgical margin (PSM) rate, LOS, or QoL at 3 and 6 months. A recent update of this trial with longer follow-up was published in 2018 (7). In that study, Bochner and colleagues evaluated long-term outcomes including recurrence free, cancer specific, and overall survival. The median follow-up was 4.9 years. There were no statistically significant differences in recurrence rates or cancer specific/ overall survival. However, a large confidence interval made it difficult to render a definitive conclusion regarding recurrence rates. Interestingly, RARC patients had more peritoneal recurrences with abdominal wall involvement (n=5) compared to open cystectomy (n=2). It is important to note that comparing recurrence locations was not planned as part of the original analysis and that these values did not reach statistical significance.

The largest RCT to date is the RARC versus open radial cystectomy in patients with bladder cancer (RAZOR) trial (NCT01157676), which was a multi-institutional, non-inferiority trial that compared 176 RARC patients and 174 ORC patients who underwent surgery from 2011 to 2014 (8). With respect to the primary endpoint, which was disease progression, the authors found that RARC was non-inferior to ORC with a two-year follow up. Once again, operative time was significantly longer (428 *vs.* 361 min; P=0.0005) and EBL was significantly lower (300 *vs.* 700 cc; P<0.0001) in the RARC group. Likely secondary to a lower EBL, RARC was also associated with a lower incidence of intraoperative and postoperative transfusions (13% *vs.* 34%; P<0.0001 and 25% *vs.* 40%; P=0.0089, respectively). LOS was also significantly shorter in the RARC group (6 *vs.* 7 days; P=0.0216). There were no differences in the incidence of any or major complications at 90-days, LN yield, PSM rate, or 3- and 6-month QoL outcomes between the two groups. A comparison of the findings of these RCTs can be found in *Table 1*.

Recently, there have been two metanalyses of these RCTs, both of which also included an additional, 40-patient RCT (9). The first, by Satkunasivam *et al.*, found no

Table 1 Comparison of outcomes in RARC *vs.* ORC RCTs

	Survival Disease Specific	Recurrence	Minor complications	Major complications	OR time	Time to solids	Time to flatus	LOS	EBL	PSM	LN yield
Nix *et al.*, N=41	NR	NR	ND*		OC	NR	RARC	ND	RARC	ND	ND
CORAL, N=40	ND	ND	ND	ND	OC	RARC	ND	RARC	ND	ND	ND
Bochner *et al.*, N=118	ND	ND	ND	ND	OC	N/R	N/R	ND	RC	ND	ND
RAZOR, N=302	N/R	ND	ND	ND	OC	N/R	N/R	RC	RC	ND	ND

*, did not distinguish between major and minor complications, however the reported no difference in complication rates. RARC, robot-assisted radical cystectomy; ORC, open radical cystectomy; RCT, randomized controlled trial; ND, no difference; NR, not reported; OC, open cystectomy.

difference in recurrence free survival or progression free survival, PSM rate, or LN yield after RARC compared to ORC. Although recurrence rates were not significantly different between the two groups, patients who underwent RARC were more likely to have abdominal/distant recurrences as opposed to local recurrences. In addition, EBL was lower with RARC (difference –281 cc, 95% CI, –435 to –125) and mean operative time was shorter with ORC (difference 75 min, 95% CI, 26–123) (10). The second metanalysis, which did not include the Bochner 2018 data, found no difference in disease recurrence, 90-day incidence of major complications, and 90-day QoL among 458 patients. RARC was associated with a decreased incidence of perioperative transfusions (RR 0.58, 95% CI, 0.43–0.80) and shorter LOS (RR –0.63 days, 95% CI, –1.21 to –0.05 days). ORC was associated with shorter operative times (MD 68.51 min, 95% CI, 30.55–105.48 min). PSM rates were not significantly different between the two groups (11). These findings have been confirmed by another metanalysis performed on a subset of these RCTs (12).

Another systematic review and metanalysis that included RARC case series and prospective or retrospective comparisons of RARC to ORC found similar results (13). RARC was associated with less blood loss (WMD: –521; 95% CI, –644 to –399), lower incidence of transfusion (OR: 0.16; 95% CI, 0.1–0.27), shorter hospital stays (WMD: –1.26; 95% CI, –2.08 to –0.43), and longer operative times (WMD: 83.60; 95% CI, 57.1–110.1). RARC was also associated with a lower risk of complications at 90-days. There were no differences in complication rates at 30 days or 30- and 90-day mortality rates (13). Several other metanalyses, also found that RARC was associated

with a lower EBL and transfusion rate, shorter hospital stays, longer operative times, greater LN yields, and similar incidences of PSMs (14-16). One of these studies found that RARC was associated with a significantly shorter time to flatus and lower 90-day complication rates (16).

Extracorporeal urinary diversion (ECUD) *vs.* intracorporeal urinary diversion (ICUD)

A criticism of the aforementioned RCTs is that all patients underwent ECUD, thereby nullifying some of the benefits of minimally invasive surgery. Potential advantages of ICUD include decreased fluid losses, reduced EBL, smaller incisions, reduced pain, and faster return of bowel function (17,18). Notably, the utilization of ICUD has risen dramatically in the last decade. Among members of the International Robotic Cystectomy Consortium (IRCC), from 2005 to 2016 the percentage of all diversions that were intracorporeal increased from 9% to 91% (18). Therefore, the generalizability of these studies is unknown.

Currently, there are only a few studies comparing outcomes after ECUD and ICUD. One recent retrospective analysis of ECUD (all of which were ileal conduits) and ICUD, found that total operative time (375 *vs.* 330 min; P=0.019), EBL (425 *vs.* 300 cc; P=0.035), and 30-day complications rates (71.4% *vs.* 48.4%; P=0.008) were lower with ICUD. However, there were no statistically significant differences in LOS, mortality rates, or anastomotic stricture rates between the groups. Although selection bias is an important concern when interpreting these findings, there were no differences in baseline characteristics between the groups (19).

Another similar, multi-institutional analysis found that

2212

Gul et al. Robot assisted RC vs. open RC

patients undergoing ICUD experienced a lower EBL (500 *vs*. 400 cc; P=0.01) and a lower incidence of blood transfusions (23% *vs*. 5.4%; P=0.006). This study included patients who received ileal conduits and neobladders. However, on subgroup analysis including only patients who received an ileal conduit, EBL was lower in the ICUD group. There were no differences in operative time, LOS, or the need for transfusions (20).

A single-institution propensity matched analysis of ORC and RARC, with intracorporal or extracorporeal neobladders, found no significant differences in disease free survival, overall survival, or cancer specific survival at two years. However, ECUD patients experienced a higher incidence of perioperative complications (91.3% *vs*. 42.2%; P<0.001), most of which were due to the increased need for blood transfusions (21).

A review from the IRCC database compared patients who underwent ECUD and ICUD. The study found that patients who underwent ICUD had shorter operative times (357 *vs*. 400 min; P<0.001), lower EBL (300 *vs.* 350 cc; P<0.001), and received fewer transfusions (5% *vs*. 13%; P<0.001). Unlike the previously mentioned studies, ICUD patients experienced more complications, especially in the first 30-days post-operatively (31% *vs*. 19%; P<0.001). The discrepancy in complication rates is likely explained by the fact that this analysis included patients from the early RARC experience, when the incidence of complications was significantly higher. There were no differences between the two groups in terms of LN yield and PSM. Interestingly, ICUD patients were more likely to experience peritoneal carcinomatosis (1.3% *vs*. 0.3%; P=0.01) and extra-pelvic LN metastasis (3% *vs*. 1%; P=0.01). Patients treated with ECUD experienced greater overall survival at 3- and 5-years, but the diversion approach was not significantly associated with recurrence free or disease specific survival. The observed overall survival advantage may be explained by the higher incidence of complications with ICUD, especially in the earlier stages of the ICUD experience (18).

Healthcare costs

Early hypotheses postulated that costs associated with RARC would be lower than ORC due to fewer complications and shorter LOS. However, the data have been conflicting. Using Surveillance, Epidemiology, and End Results Program (SEER) data from 2002 to 2012, Hu *et al*. found that RARC was associated with higher costs both during the inpatient hospital stay and at 30 days

following surgery. The median inpatient cost for RARC was $24,051 compared to $21,637 for ORC, however this difference was not statistically significant. Furthermore, RARC patients had a greater likelihood of requiring home health care after hospitalization (RR 1.14) significantly raising costs at 30- and 90-day follow up (22).

By contrast, after reviewing National Medicare claims to evaluate 90-day costs following RARC, Modi *et al*. found that RARC was associated with significantly lower costs ($38,071 *vs*. $34,369) (23). The authors hypothesized that their findings differed from those of Hu *et al*. because the latter evaluated outcomes from the early RARC experience. It is important to note that this study was analyzing Medicare payor cost as opposed to hospital costs (23). Some studies have found higher hospital costs with RARC (24,25). One analysis estimated that for RARC to be more cost effective than ORC, it had to either prevent complications 74% of the time or prevention transfusion 70% of the time (25).

Acknowledging that there is limited data comparing cost-effectiveness of RARC versus ORC, Michels *et al*. constructed a model to identify current evidence gaps and the main drivers of cost-effectiveness. In this model, monetary value was assigned to various aspects of perioperative and post-operative care. For example, the cost of the OR per minute was valued at $11, and complication costs ranged from $3,160 for a Clavien 1 to $23,606 for a Clavien 5. These values were derived from a metanalysis and guidelines. Using a 90-day model with 1,000 simulations, there was a 23% probability that RARC would have lower costs and result in fewer complications. The primary drivers of cost were LOS, OR time, and equipment cost. In this study, RARC was found to me cost effective if LOS were 4 days or less, operating time were less than 175 min, and robot equipment costs were less than $317. The associated savings from a lower complication rate did not outweigh the increase in cost for RARC cases (26).

Discussion

After a review of the literature, it is our understanding that the primary benefit of RARC compared to ORC is a reduction in blood loss and blood transfusions, and the primary disadvantage is longer operative times. On multivariable analysis, perioperative blood transfusions have been associated with cancer specific and all-cause mortality, with the risk being dose-dependent (27). However, results among multiple analyses have been inconsistent (28,29). The reduced incidence of perioperative transfusions alone is

likely insufficient to favor RARC over ORC. With respect to the advantages of ORC, although longer operative times correlate with an increased incidence of complications (30,31) the aforementioned metanalyses did not find any difference in the rates of complications after RARC or ORC (10,11), and so the shorter duration of ORC is of questionable clinical benefit.

In order to contextualize the debate over the potential benefits of RARC and ORC, we reviewed research comparing robot assisted radical prostatectomy (RALP) and open radical prostatectomy (ORP). Currently, RALP is the preferred approach and about 85% of all prostatectomies are performed robotically. Most studies have shown that the benefits of RALP, like RARC, include lower EBL, lower transfusion rate, and shorter hospital stay (32-34). Although other studies report equally short LOS with ORP (34), there have been no observed differences in QoL following RALP or ORC (35-37), and most studies, including an RCT, have demonstrated no difference in PSM (32,34,36,38). Costs are higher with RALP (39,40), except among surgeons who perform at least 104 procedures a year (33). Regarding complications, there is a preponderance of data supporting that RALP is associated with fewer complications than ORP. This is in stark contrast to the inconsistencies in the available outcomes data for RARC versus ORC. Overall, the advantages of RALP compared to ORP and RARC compared to ORC are similar, although the evidence that the robotic approach reduces complications is stronger for radical prostatectomy than RC.

One factor that may make complications more likely with RARC is the technical complexity. Research shows that among surgeons with previous robotic experience, there is a learning curve with a threshold of 30 procedures before PSM rates fall below 5% and a LN yield exceeds 20 nodes (41). However, in a review of the NCDB, Nielsen *et al.* found that the majority of radical cystectomies are performed at hospitals that average fewer than 10 cases per year and only 32% of hospitals performed 20 or more cystectomies annually. As such, it would take several years for most surgeons performing radical cystectomy to become proficient in RARC (42). Therefore, RARC is best left to experienced surgeons at high-volume centers.

Conclusions

In conclusion, we believe that both ORC and RARC are oncologically sound and feasible procedures. While there are benefits with RARC, primarily lower EBL, these benefits must be balanced against longer operative times. These findings are based on RCTs that performed only ECUD. It is unclear if performing ICUD will change these results. Finally, it is difficult to compare the costs of the two procedures and the results are muddied by the often-ill-defined distinction between costs to the hospital versus the cost to payors. However, it is likely that for both hospitals and payors, currently RARC is cost effective at high-volume centers. It is feasible that in the future, increased experience with RARC will lead to improved outcomes and justify the use of RARC over ORC. Until then, the decision to perform a robotic or open RC is best made on a patient-by-patient basis.

Footnote

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2214

Gul et al. Robot assisted RC vs. open RC

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