

Current Status of Robot-Assisted Radical Cystectomy and Intracorporeal Urinary Diversion

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Abstract Robot-assisted surgery has become a widely used surgical approach in the management of urologic malignancies. With its initial experience in the treatment of prostate cancer, the technology rapidly expanded to other urologic malignancies including bladder cancer. Since its introduction in 2003, robot-assisted radical cystectomy has seen refinement and increased penetration over the last decade. Furthermore, urologic surgeons have expanded its use to perform urinary diversions. The concept of intracorporeal urinary diversion is still in development but continues to see increased refinement among high volume academic centers.

Keywords Robot-assisted radical cystectomy · Intracorporeal urinary diversion · Robotic cystectomy

Introduction

Over 608,000 patients live with bladder cancer in the USA, and it is expected that 74,000 new patients will become

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diagnosed with bladder cancer in 2015 [1]. Unfortunately, bladder cancer continues to have a significant cancer-specific mortality with approximately 31,000 patients dying from their disease each year [1]. The majority of patients (70 %) who are newly diagnosed present with non-muscle-invasive disease involving either the bladder mucosa or into the lamina propria (Tis, Ta, or T1) [2]. A significant minority of patients (30 %) present with muscle invasive disease (T2). Due to the unfortunate aggressive nature of bladder cancer, a small number of patients unfortunately present with evidence of invasive carcinoma into perivesical fat (T3), surrounding organs (T4), or even distant metastases either into distant organs or into lymph nodes [2]. Despite the many advances that have benefitted modern medicine, bladder cancer continues to carry a heavy disease burden on those who become afflicted with the condition.

While non-muscle invasive bladder cancer (Tis–T1) can be managed with therapies aimed towards bladder preservation, the gold standard treatment for managing muscle-invasive bladder cancer is radical cystectomy, pelvic lymph node dissection, and urinary diversion. The past several decades have seen major advances in the management of muscle-invasive bladder cancer including the growing utilization of neoadjuvant chemotherapy, the advent of robot-assisted technology, and the refinement of standard and extended pelvic lymph node dissections. For the scope of this article, we will focus on robot-assisted technology and its role in the management of bladder cancer.

The evolution to robot-assisted surgery was a natural technological extension of laparoscopic surgery which entered into urology in 1990–1991 when Clayman, Kavoussi, and colleagues performed the first laparoscopic radical nephrectomy [3]. Soon after, the first laparoscopic radical prostatectomy and laparoscopic cystectomy were performed as retroperitoneal and pelvic spaces were easily developed with gaseous

insufflation [4, 5, 6]. Our field witnessed rapid implementation of minimally invasive surgery, and many of the laparoscopic techniques pioneered by early urologic laparoscopists are still utilized today.

While initially developed for application in cardiac surgery, robot-assisted technology entered urologic practice just after the turn of the millennium in 2000 when Menon and Tewari detailed their initial experience with robot-assisted laparoscopic prostatectomy (RALP) [7, 8]. The ease of developing pelvic spaces with insufflation as well as the benefits afforded by robotic technology includes reduction of tremor, ability for joint articulation of robotic instruments, and enhanced visualization provided by newer generation optics led to rapid penetration of robot-assisted technology into the management of urologic malignancies. Menon and colleagues extrapolated on their experience with robot-assisted laparoscopic prostatectomies to detail their initial experience utilizing robot-assisted technology in performing radical cystectomies [6, 9, 10]. In the following years, robot-assisted surgery became more widely used to treat invasive bladder cancer, and in 2007, Pruthi and Wallen published a formal guide to performing robot assisted radical cystoprostatectomy [11]. Shortly after the initial experiences of using robot-assisted technology to perform radical cystectomy, additional series detailed the utilization of robot-assisted technology to perform intracorporeal urinary diversions, which we will expound on later in this article.

Concomitantly with reports detailing robot-assisted radical cystectomies (RARC), there were also series detailing robot-assisted pelvic lymphadenectomies. The importance of lymphadenectomy in the management of invasive bladder cancer was widely established through the efforts of Stein and colleagues and Herr [12, 13]. Several reports further advocate that extended pelvic lymph node dissection has the potential of offering survival benefit to patients [14–16]. While the optimal extent of pelvic lymph node dissection remains debatable, robot-assisted pelvic lymphadenectomy is feasible with comparable yields and outcomes to the open approach [16]. The decision on performing a more extensive lymph node dissection is a clinically specific decision to be made jointly between the surgeon and patient.

We review recent series detailing the perioperative care, surgical techniques, and postoperative outcomes of RARC with pelvic lymph node dissection and intracorporeal urinary diversion (ICUD). A small number of randomized trials comparing the open and robot-assisted approach are also included; however, the majority of series are from either prospective or retrospective patient cohorts.

Perioperative Care

At our institution, we have adapted a strategy of not having our patients undergo routine formal preoperative bowel

preparations from the myriad of literature in general surgery repeatedly demonstrating no benefit with respect to infection rates or anastomotic breakdowns [17, 18]. All patients are medically optimized as much as possible, and when feasible, our patients undergo neoadjuvant chemotherapy under the direction of our medical oncologists. We adhere to the principals of antibiotic stewardship and provide our patients a single dose of ertapenem in concordance with the Surgical Care Improvement Project (SCIP) guidelines for clean-contaminated procedures [19]. When appropriate, alvimopan, an FDA-approved peripherally acting μ -opioid antagonist, is given to patients preoperatively and continued postoperatively to enhance bowel recovery. Its use is supported from recently published multi-institutional randomized controlled trials demonstrating its efficacy [20, 21]. A dose of subcutaneous heparin is also given to the patient preoperatively as recommended by the AUA best practice guidelines [22]. While an orogastric or nasogastric tube is placed during surgery, it is removed at the end of the procedure.

Postoperatively, barring extenuating circumstances, our patients typically go to a routine urology floor and continue on a general enhanced recovery program. Enhanced recovery protocols have become increasingly utilized in postoperative care in an effort to deliver higher quality care, reduce complications, and optimize healthcare costs [23, 24, 25]. With respect to the postoperative care after radical cystectomy and urinary diversion, all patients are kept NPO on postoperative 0 and are advanced to 8 oz of water every 8 h on postoperative day 1. If this is tolerated without any significant nausea or vomiting, patients are advanced to a formal clear liquid on postoperative day 2 and to a solid diet on postoperative day 3. Early refeeding plays a central role in the postoperative-enhanced recovery pathway after RARC as a well-established benefit in general surgical literature with respect to reductions in postoperative infection, decreased overall mortality, and improved wound healing has been demonstrated [23]. A similar benefit has been established for patients undergoing radical cystectomy and urinary diversion [24, 25–28]. Patients are considered for discharge on either postoperative day 4 depending on their overall clinical condition and comfort with home care [24, 25–28].

RARC and Pelvic Lymph Node Dissection

Patients with muscle-invasive stage bladder cancer are often seen in a multidisciplinary clinic to discuss options of radiation, chemotherapy, and surgery [29]. At our institution, the recommendation is made for all eligible patients to receive platinum-based neoadjuvant chemotherapy [30, 31–33]. Barring extenuating circumstances such as prior history of extensive radiation, abdominal or pelvic surgery, or inability for the patient to tolerate abdominal insufflation or Trendelenberg positioning, a robot-assisted approach is

routinely offered. Concomitantly, a pelvic lymph node dissection is also performed, and the decision to perform a standard versus an extended dissection is based on the clinical scenario as well as surgeon preference.

The safety and efficacy of RARC has been well noted from a number of single-institution and multi-institutional studies. While many are retrospective in nature, there are a number of prospective studies as well that not only report on the outcomes after RARC but also offer a contemporary comparison to the open approach. Three randomized control trials comparing open radical cystectomy (ORC) with the robot-assisted approach are also available for review and a more comprehensive randomized control trial (RAZOR) will have results forthcoming soon.

Single Institution

Kauffman et al. detail their initial experience of 79 patients undergoing RARC. In their patient cohort, 58 % had a Charlson Index score of ≥ 3 . The overall 90-day complication rate was 49 % of which 16 % were high-grade complications [34]. A follow-up analysis performed by Kauffman et al. detailed the pathologic outcomes from 85 consecutive patients undergoing RARC, of which 98 % of patients underwent an extended pelvic lymph node dissection [35]. The overall 2-year survival from their series was 79 % with stage of disease being the most important predictor of survival [35]. In a series from Germany, Treiyer et al. outline the outcomes of 91 patients undergoing RARC [36]. In this cohort of patients, the authors report a 2.1 % positive surgical margin rate, 50 % postoperative complication rate with 11 % representing major (Clavien grade 3 or higher) complications, mean operative time of 412 min, mean intraoperative blood loss of 294 mL, and a mean length of stay of 18.8 days [36]. Another series by Khan et al. from the UK describes the outcomes of 50 patients undergoing RARC [37]. These patients had a postoperative complication rate of 34 % of which 10 % were Clavien grade 3 or higher [37]. In a follow-up study by Khan et al., the outcomes of 14 patients were analyzed and it was found that at a follow-up of at least 5 years, a 64 % overall survival rate, 75 % disease-specific survival rate, and a 50 % disease-free survival rate was reported [38]. Finally, in a series by Hayn et al. from Roswell Park, the outcomes of 156 consecutive patients undergoing RARC with a 90-day follow-up was reported [39]. The Clavien grade 2 or higher complication rate from this series was 46 %, and the 90-day mortality rate was reported at 5.8 % [39].

Multi-institution

In a series of 104 patients undergoing RARC across 7 Korean institutions, Kang et al. report a combined mean operative time of 554 min, mean blood loss of 526 mL, mean length

of stay of 18 days, and a mean complication rate of 27 % of which 7.7 % were major complications as defined by the Clavien system [40]. Smith et al. report on the combined experience from the University of North Carolina, the University of Alabama, Mayo-Scottsdale, and Tulane [41•]. In this series totaling 227 patients, the authors report a mean operative time of 390 min, mean blood loss of 256 mL, mean length of stay of 5.5 days, and a 30 % complication rate with 7 % representing a complication classified as Clavien 3 or higher [41•].

Prospective and Retrospective Studies Comparing RARC and ORC

Xia and colleagues recently published a meta-analysis compiling 19 observational studies as well as the RCTs available to date detailing the comparative outcomes of RARC vs ORC [42••]. In their combined analysis, the authors reported statistically significant odds ratios favoring RARC over ORC for blood loss, blood transfusions, hospitalizations, and lymph node yield, as well as 30- and 90-day postoperative complication rates [42••]. ORC was favorable to RARC with respect to shorter operative time [42••]. Preston et al. performed a combined analysis of notable single-institution series as well as the RCTs published to date. They reported no statistically significant differences between RARC and ORC with respect to positive margins, lymph node yields, and short-term survival [43]. The 90-day readmission rate after ORC is 27 % in open contemporary series and similar studies report a 25.5 % 90-day readmission rate after RARC [44–46].

Patients afflicted with muscle-invasive bladder cancer are being offered neoadjuvant chemotherapy more prevalently, and overall, the utilization of neoadjuvant chemotherapy in the management of advanced bladder cancer has seen dramatic rise across both community and academic centers. Outcomes for patients undergoing radical cystectomy after neoadjuvant chemotherapy are similar from either an open or robot-assisted approach with respect to positive surgical margins, lymph node involvement, perioperative results, and short-term recurrence rates [47, 48••].

Randomized Control Studies

With respect to establishing RARC as a safe option that has equivalent outcomes to ORC, a total of three randomized control studies have been conducted comparing the two approaches. The first is a study from the University of North Carolina investigating the safety and efficacy of RARC versus ORC with a primary endpoint of lymph node yield [49•]. Nix et al. randomized 41 patients, 21 to RARC and 20 to ORC, and reported a mean of 19 lymph nodes removed from the RARC group compared to 18 in the ORC group [49•]. Secondary endpoints were also examined, and the authors

reported statistically significant benefits to the robot-assisted approach with respect to, estimated blood loss, lower analgesic use (measured in morphine equivalents) and a non-statistically significant trend towards a shorter length of stay [49•]. The robot-assisted approach demonstrated a longer operative time, and no difference was appreciated between the two groups with respect to time to bowel movement [49•]. No positive surgical margins were seen in either group [49•].

In another RCT conducted by Memorial Sloan Kettering by Bochner et al., a total of 118 patients were randomized with 60 patients in the RARC group and 58 in the ORC group [50•]. The primary endpoint in this study was the 90-day Clavien grade 2–5 complication rate [50•]. Of the 60 patients undergoing RARC, 37 (62 %) experienced a Clavien grade 2–5 complication within 90 days postoperatively compared to 38 (66 %) of patients undergoing an ORC [50•]. Bochner and colleagues also discussed secondary outcomes in their study. Patients undergoing RARC had less estimated blood loss but longer operative times [50•]. No statistically significant differences were seen with between the two groups with respect to positive margin rates, lymph node yields, and mean hospital length of stay, as well as 3- and 6-month quality of life outcomes [50•]. A cost analysis between the two approaches in this cohort of patients favored the open approach over the robot-assisted approach [50•].

The last RCT comparing RARC and ORC was published by Parekh et al. from the University of Texas San Antonio [51•]. The primary endpoints in this study were feasibility of randomization, lymph node yield, and positive margin rate [51•]. A total of 39 patients enrolled in the study with 20 patients undergoing RARC and 19 undergoing ORC [51•]. Feasibility of randomization was demonstrated, and no differences were seen in the lymph node yields and positive margin rates between the two groups [51•]. Additionally, secondary outcomes were also reported, and as seen with previous trials, lower blood loss and a trend towards shorter hospital stays were seen in the RARC group [51•].

Overall, the data from the available published studies demonstrate the feasibility, safety, and comparable efficacy of RARC compared to ORC. There are, however, several limitations. Most studies are either retrospective or observational in design. While a small number of RCTs demonstrate the viability of RARC as a surgical treatment for advanced stage bladder cancer, these RCTs are all single-institution experiences. Furthermore, none of the published RCTs were powered to examine outcomes or survival differences between RARC and ORC. Finally, the data is not large enough to delineate any significant subgroup analysis (i.e., differences between diversion type, use of neoadjuvant chemotherapy, etc). A more robust multi-institutional RCT (RAZOR) is set to release its initial round of data analysis detailing differences in oncologic outcomes as well as perioperative morbidity [52••].

Robot-Assisted Intracorporeal Urinary Diversion

There is debate on whether to perform an intracorporeal or extracorporeal urinary diversion (ECUD). Urologists preferring an extracorporeal approach to the urinary diversion justify the decision for reasons of shorter operative times and the existing need for an extraction incision [53]. A recent multi-institutional analysis published by Smith et al. estimates that over 95 % of urinary diversions are done extracorporeally during RARC [41•]. ICUD has inherent challenges including increased operative times and a steeper learning curve, as well as a number of technical challenges [54••]. Although the number to overcome the learning curve for ICUD has been suggested to be 30 cases, recent reports demonstrate that the approach is gaining traction among an increasing number of urologic surgeons [55, 56••]. While comparative studies between ICUD and ECUD are few in number, a systematic review performed by Yuh et al. concludes that no differences in surgical positive margins, lymph node yields, cancer specific survival, or overall survival exists between the two groups supporting the efforts of many centers to continue to refine the intracorporeal technique [57].

Though limited, several series from high volume centers demonstrate the feasibility of ICUD. In a study from the International Robotic Cystectomy Consortium (IRCC), outcomes from 49 patients undergoing RARC with extracorporeal diversion were compared to 41 patients undergoing RARC with ICUD. The patients who underwent ICUD had a significantly less likelihood of experiencing a complication within 90 days of their surgery (odds ratio 0.68) [58]. The authors estimate that approximately 18 % of patients undergoing RARC have ICUD performed, the majority (63.5 %) being ileal conduit urinary diversion [58].

The technique of ICUD is adapting to allow for more adaptation of across a greater number of medical centers. Expanding on the technique developed by Gill and colleagues from the University of Southern California, Desai et al. describe the technical aspects utilized to improve operative times from the initial experience at that institution [59•]. For those patients undergoing an intracorporeal ileal conduit urinary diversion, the last 10 patients had statistically significant lower operative times and time to complete ureteroileal anastomoses compared to the first nine patients ($p=0.0412$, 269 vs 330 min) [59•]. The operative times comparing the last nine patients to the first eight patients undergoing an intracorporeal neobladder approached statistical significance ($p=0.0513$, 60 vs 77 min) [59•]. In another study from the University of Southern California, Abreu and colleagues detail their experience from 103 patients undergoing RARC and intracorporeal urinary diversion [60]. In this cohort, 57 patients had an ileal conduit performed and the remaining 46 had an orthotopic neobladder reconstruction. Pathologic and perioperative outcomes mimic prior series and previous open experiences [60].

The authors report a mean OR time of 420 min, EBL of 200 mL, average LOS of 7 days, a 42 % 30-day Clavien 1–2 complication rate, and a 17 % 30-day Clavien 3–5 complication rate [60].

The largest series detailing outcomes after intracorporeal orthotopic neobladder diversion comes from the Karolinska Institute where Tyritzis and colleagues report their experience from 70 patients who had RARC with intracorporeal urinary diversion performed by one of two experienced robotic surgeons [60] (Table 1). The authors describe a U-shaped neobladder technique and report 80–90 % daytime continence rates among men and 70 % among women at 12 months [61]. Nighttime continence rates were expectedly worse with 8–15 % experiencing nighttime continence by 6–12 months [61]. Stricture rates from this series was reported to be <3 % compared to 7–12 % in comparable open series [61, 62, 63]. Perioperative outcomes, preliminary oncologic results, 90-day complication rates, and short-term cancer-specific and overall survival are similar to open series [61].

In 2013, Azzouni et al. from Roswell Park describe the 90-day outcomes from their series of 100 patients undergoing RARC with intracorporeal ileal conduit urinary diversion

[64]. They report an overall 66 % 90-day Clavien 1–2 complication rate and a 15 % 90-day Clavien 3–5 complication rate [64]. Mean operative time was reported to be 352 min and mean estimated blood loss was 300 mL with a 10 % intraoperative transfusion rate noted [64].

Intracorporeal continent urinary diversion has also been recently reported in literature, but the technique is still in its nascent phase. Goh and colleagues describe an initial case report demonstrating the feasibility of performing a modified intracorporeal Indiana pouch continent urinary diversion which took 180 min in diversion operative time [65]. No significant complications were reported, and the patient was doing well at 1 year postoperatively [65]. A limited experience is also detailed by Chopra and colleagues from the University of Southern California [56]. Their initial experience of nine cases did not require significantly longer operative time and incur any intraoperative complications, and no blood transfusions were needed [56]. The use of continent urinary diversion has always been undertaken cautiously given a higher complication rate and need for careful patient selection. This continues to be true when the procedure is performed intracorporeally.

Table 1 Summary of recent notable series detailing outcomes after RARC with intracorporeal urinary diversion

Authors	Institution	Demographics	Diversion	Pathology	Postoperative outcomes
Azzouni et al. 2013 [64]	Roswell Park	100 patients Mean age, 71 Mean BMI, 28.5 Male, 73 (73 %)	Ileal conduit, 100	NMIBC, 35 (35 %) MIBC, 65 (65 %) LNI, 17 (17 %)	OR time, 352 min EBL, 300 mL Intraoperative transfusions, 10 (10 %) PSM, 4 (4 %) LOS, 9 days 90-day Clavien 1–2 complications, 66 (66 %) 90-day Clavien 3–5 complications, 15 (15 %)
Tyritzis et al. 2013 [61]	Karolinska	70 patients Mean age, 60 Mean BMI, 26.8 NAC, 17 (24.3 %)	Neobladder, 70	pT0, 17 (25 %) pTa–pT1, 20 (29.4 %) pT2, 20 (29.4 %) pT3, 8 (11.8 %) pT4, 2 (2.9 %) LNI, 10 (14.3 %)	OR time, 420 min EBL, 500 mL Conversions, 4 (5.7 %) >30-day Clavien 1–2 complications, 8 (11.3 %) >30-day Clavien 3–5 complications, 13 (18.3 %)
Ahmed et al. 2014 [58]	IRCC (18 private and academic institutions)	148 patients Mean age, 66 Male, 118 (80 %) Mean BMI, 28 NAC, 10 (11 %)	Ileal conduit, 87 Neobladder, 61	pT0, 22 (15 %) pTa–pT1, 34 (23 %) pT2, 35 (24 %) pT3, 47 (32 %) pT4, 8 (6 %) LNI, 26 (20 %)	LOS, 9 (7–13) 90-day Clavien 1–2 complications, 43 (23 %) 90-day Clavien 3–5 complications, 34 (18 %) 90-day mortality, 3 (1.6 %)
Abreu et al. 2014 [60]	University of Southern California	103 patients Mean age, 66.9 Male, 84 (82 %) NAC, 18 (17.5 %)	Ileal conduit, 57 Neobladder, 46	OCD, 61 (59 %) EVD, 16 (16 %) LNI, 26 (25 %)	OR time 420 min EBL, 200 mL LOS, 7 days 30-day Clavien 1–2 complications, 43 (42 %) 30-day Clavien 3–5 complications, 18 (17 %)
Kouppais et al. 2015 [66]	Bristol	102 patients Mean age, 68 Male, 71 (70 %) NAC, 43 (42.2 %)	Ileal conduit, 91 Neobladder, 11	Not reported	Intraoperative transfusions, 20 (19 %) 90-day mortality, 1 90-day Clavien 1–2 complications, 23 (26 %) 90-day Clavien 3–5 complications, 9 (9 %)

BMI body mass index, *NAC* neoadjuvant chemotherapy, *NMIBC* non-muscle-invasive bladder cancer, *MIBC* muscle invasive bladder cancer, *LNI* lymph node involvement, *OCD* organ-confined disease, *EVD* extravesical disease, *OR* operative, *EBL* estimated blood loss, *PSM* positive surgical margins, *LOS* length of stay

Finally, Koupparis and colleagues conclude that ICUD may play a role in increasing the beneficial impact of enhanced recovery protocols following radical cystectomy [66]. In their experience of 56 consecutive patients undergoing RARC with ICUD, when compared to their open cohort of 56 patients, they found a statistically significant shorter length of stay in the hospital (8 vs 13 days) as well as a lower complication rate (31 vs 48 %) [66]. A summary table summarizing the outcomes from notable series of patients undergoing RARC with intracorporeal urinary diversion is provided below.

Conclusion

Robot-assisted technology has undergone significant transformation since its initial inception. Its utilization has been quickly adapted and expanded on by the urologic community, and today, robot-assisted surgeries account for a significant portion of urologic procedures, particularly within the scope of urologic oncology. Its use in the management of advanced bladder cancer has been well described, particularly in the extirpative removal of the bladder and surrounding organs. Since 2004 to 2010, the utilization of RARC has grown from 0.4 to 12.8 % [67]. While its use in performing a urinary diversion has seen less penetrance, this continues to be a growing area of interest for urologists. Randomized control studies have repeatedly demonstrated non-inferiority across many domains in comparing RARC to the open approach, and a more robust trial (RAZOR) is underway to more definitively describe the potential benefits of RARC over ORC. As the overall experience with robot-assisted technology continues to grow and RARC is more readily adopted, we expect to see continued refinement of operative outcomes resulting in more adaption of ICUD.

Compliance with Ethical Standards

Conflict of Interest Raj Kurpad, Michael Woods, and Raj Pruthi each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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