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UROONCOLOGY
Invited Review

Current evidence for robotic surgery in radical cystectomy

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ABSTRACT

Robotic-assisted radical cystectomy (RARC) has been gaining momentum as an alternative to its conventional open radical cystectomy (ORC) for the management of invasive bladder cancer. Although RARC, in general, demonstrated less blood loss and shorter hospital stay than ORC, whether there is any significant difference in the overall complication rate still requires further investigation. Thus, both RARC and ORC share a similar oncology outcome, with comparable positive surgical margin rates, disease-free survival, and overall survival. Techniques of intracorporeal urinary diversion (ICUD) have not yet been standardized. ICUD may result in a lower risk of ureteroileal anastomotic stricture than extracorporeal urinary diversion (ECUD). However, ECUD is still a valid and commonly practiced option according to the available data. In general, RARC has been demonstrated to provide promising results. Long-term data and functional outcome after RARC and ICUD are needed to further validate the role of RARC in the management of bladder cancer.

Keywords: Bladder cancer; cystectomy; robotic surgery; review.

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Introduction

Although age-standardized incidence rates of bladder cancer have declined across both sexes, the number of new bladder cancer cases have increased by 1.5-fold between 1990 and 2013 to more than 400,000 cases in a year.[1] The standard of care for muscle-invasive bladder cancer or high-grade bacillus Calmette–Guerin refractory bladder cancer is radical cystectomy with pelvic lymph node dissection (LND) and urinary reconstruction. Conventionally, radical cystectomy is performed by an open approach. Historical rates of open radical cystectomy (ORC) complications lie between 30% and 65% in a few larger series.[2-4] With the rising popularity and maturity in the laparoscopic technique, laparoscopic radical cystectomy (LRC) has become an alternative option with less blood loss and a shorter hospital stay.[5] However, LRC has not yet gained the momentum as its counterparts of other laparoscopic urological surgery, for example, laparoscopic nephrectomy and laparoscopic prostatectomy. The technical challenges of LRC have prohibited its wide adoption in different parts of the world.

The introduction of da Vinci® surgical system has changed the landscape of urological surgery. The incorporation of robotic assistance has decreased the hurdle of radical cystectomy to be performed in a minimally invasive manner. Menon et al.[6] and Beecken et al.[7] reported the first case series of robotic-assisted laparoscopic radical cystectomy in 2003. Since then, the growth of robotic-assisted radical cystectomy (RARC) has accompanied that of robotic surgery. There are multiple systematic reviews and meta-analyses for RARC (Table 1).[8-13] However, well-conducted studies comparing RARC with other modalities of radical cystectomy are still lacking. This review presents the available evidence in the literature to define the role of RARC in the contemporary context.

Technique of RARC

The surgical technique for RARC has evolved over the past 2 decades. Descriptions of RARC adopted port placement, which is similar to that of robot-assisted radical prostatectomy, except in general, the ports are placed more cephalad. Two common port configurations were described by the Karolinska group and the City of

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Table 1. Recent systematic reviews and meta-analyses for RARC

Author	Year	Operations reviewed	Studies included	Number of patients	Outcome assessment	Main results
Peng et al.[8]	2020	RARC LRC	1 RCT 3 Prospective 4 Retrospective	594	Perioperative	RARC and LRC have similar EBL, intraoperative blood transfusion, PSM, oral intake time, hospital stay, and complications.
Albisinni et al.[9]	2019	RARC ORC	5 RCT	543	Perioperative Pathological Oncological	ORC had shorter operative time (WMD: 95.14 minutes; 95% CI: 50.59–139.68; p<0.0001). RARC had lower EBL (WMD: –277.60 mL; 95% CI: –471.02 to –84.18; p=0.005) and lower risk of transfusions (OR: 0.52; 95% CI: 0.32–0.85; p=0.008). No difference was recorded in the pathological and oncological outcomes.
Satkunasivam et al.[10]	2019	RARC ORC	5 RCT	560	Perioperative Oncological	No difference between RARC and ORC in RFS/PFS (HR: 0.89; 95% CI: 0.64–1.24), PSM, and LND yield.
Rai et al.[11]	2019	RARC ORC	5 RCT	541	Oncological Perioperative	RARC and ORC may result in a similar time to recurrence (HR: 1.05; 95% CI: 0.77–1.43). RARC and ORC may result in similar rates of major complications (RR: 1.06; 95% CI: 0.76–1.48).
Iwata et al.[12]	2019	RARC ORC	5 RCT 28 series	501	Perioperative Oncological	No difference in the rate of PSM, lymph node yield, and recurrence rate between RARC and ORC in RCT. In non-RCT, only PSM rates were better for RARC.
Sathianathen et al.[13]	2019	RARC ORC	5 RCT	540	Oncological Perioperative Quality of life	No difference between RARC and ORC in disease progression (RR: 0.94; 95% CI: 0.69–1.29), major complications (RR: 1.06; 95% CI: 0.75–1.49), and quality of life (standardized mean difference: –0.03; 95% CI: –0.27 to 0.21). RARC has a reduced risk of perioperative blood transfusion (RR: 0.58; 95% CI: 0.43–0.80). Operative time was longer in RARC (mean difference: 68.51 min; 95% CI: 30.55–105.48).

RARC: robotic-assisted radical cystectomy; LRC: laparoscopic radical cystectomy; ORC: open radical cystectomy; RCT: randomized controlled trial; EBL: estimated blood loss; PSM: positive surgical margin; WMD: weighted mean difference; RR: relative risk; CI: confidence interval; HR: hazard ratio; RFS: recurrence-free survival; OR: odds ratio; PFS: Progression free surviva LND: lymph node dissection.

Main Points:

- RARC with ICUD is associated with less blood loss, a lower risk of gastrointestinal complication and a lower risk of uretero-ileal anastomotic complications when compared with its ECUD counterpart.
- RARC and ORC have a similar oncological outcome with respect to positive margin rate, cancer-specific survival and overall survival.
- RARC and ORC share a similar major complication rate. RARC was demonstrated to have a longer operative time but a shorter hospital stay.
- Day-time continence after RARC and intra-corporeal neobladder was reported to attain a day-time continence of more than 60%. A more standardized template for reporting functional outcomes after RARC is needed to make a proper assessment of RARC.

Hope group, which are based on anatomical landmark and measurements, respectively.[14] The fourth arm is used on the right or left depending on the surgeon's preference. The mainstay of RARC is performed with the da Vinci® Robotic Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). Before the era of the da Vinci® Xi system, the conventional RARC was performed by placing the patient cart between the patient's legs. This configuration allows the central column to be aligned with the long axis of the patient, resulting in readily available access to both sides of the abdominal structures. However, such a configuration restricts access to the perineal area, making concomitant urethrectomy impossible during the stage of robotic dissection. Chan et al.[15] reported their experience of a side-docking ap-

proach in RARC, which provides better perineal access without compromising the efficiency of the robotic surgical system. After da Vinci® Xi system has been introduced, the side-docking approach in RARC can be implemented in a more convenient manner.

The key steps of bladder excision in RARC were highlighted by Ahmed et al.[16] through the concept of "Technique of Spaces." Through the dissection of periureteral, lateral pelvic, anterior rectal, and retropubic spaces, surgical isolation of bladder in RARC can be standardized in a minimally invasive manner. A randomized trial by Gschwend et al.[17] did not show any statistically significant advantage of extended LND over standard LND in recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS). However, the OS rate increases with the number of dissected lymph nodes.[18] Contemporary RARC series reveals that the lymph node yield is comparable with ORC series.[19,20] Desai et al.[21] described the technique of LND in RARC, particularly demonstrating the feasibility of LND in the fossa of Marcille as well as the retrocolic technique for dissecting the left common iliac nodal packet posterior to the descending mesocolon. These provide the evidence that RARC can reliably replicate open surgery from a technical perspective (Figure 1).

The impact of urinary reconstruction is more significant than the removal of the bladder itself with respect to the postoperative course and complications.[22] Among the surgeons who perform RARC, both modalities of diversion techniques can be observed, namely, extracorporeal urinary diversion (ECUD) and intracorporeal urinary diversion (ICUD). The proponents of ECUD consider such an option to offer a shorter operative time, while taking the advantage of the pre-existing need of an incision for specimen removal.[23] In contrast, the proponents of ICUD believe that the procedure can even be faster than ECUD with the use of bowel staplers, and a true minimally invasive approach can be achieved especially when the specimen can be retrieved transvaginally after female cystectomy. An update from the International Robotic Cystectomy Consortium reported that the performance of ICUD increased from 0% cases in 2005 to 95% cases in 2015 in their group.[24] The Pasadena Consensus Panel on RARC proposed the potential benefits of ICUD to be decreased fluid loss, reduced estimated blood loss (EBL), less pain, quicker return of bowel function, and lower risk of anastomotic strictures.[25] A recent meta-analysis of 9 observational studies comprising 3,582 patients provided data to support such observation. Feng et al.[26] reported that compared with ECUD, ICUD was associated with lower EBL (mean difference: –90.50; 95% confidence interval [CI]: –131.26 to -49.74; p<0.0001), fewer gastrointestinal complications (relative risk [RR]: 0.65, 95% CI: 0.45–0.93; p=0.02), and lower risk of ureteroileal anastomotic stricture (RR: 0.36; 95% CI: 0.14–0.91; p=0.03).

A number of ICUD techniques have been described for neobladder reconstruction. Florence robotic intracorporeal neobladder proposed a neobladder with a neotrigone without an afferent

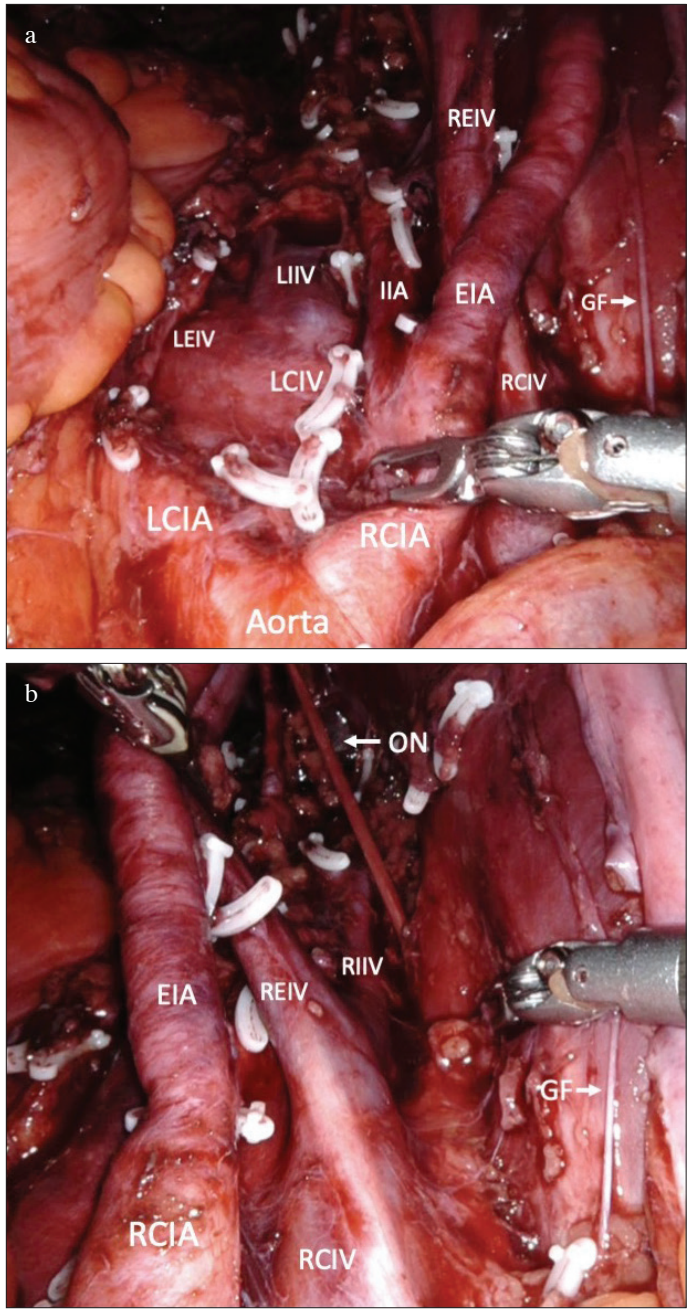

Figure 1. a, b. Feasibility of the robotic surgical approach to replicate the technique of conventional ORC. (a) Extended LND up to bifurcation of aorta. (b) Achieving lymph node clearance in the fossa of Marcille

RCIA: right common iliac artery; LCIA: left common iliac artery; RCIV: right common iliac vein; LCIV: left common iliac vein; EIA: right external iliac artery; IIA: right internal iliac artery; LEIV: left external iliac vein; LIIV: left internal iliac vein; REIV: right external iliac vein; RIIV: right internal iliac vein; GF: genitofemoral nerve; ON: obturator nerve; LND: lymph node dissection; ORC: open radical cystectomy

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limb.[27] The Karolinska group adopted a double-folding neobladder similar to the concept of Studer pouch.[28] With the University of Southern California (USC) technique, the posterior plate is created and rotated 90° before urethroileal anastomosis, which is followed by a double folding.[29] To what extent these different techniques of ICUD neobladder impact the long-term functional outcome is not yet clear. Furthermore, the long-term quality-of-life data comparing between ICUD and ECUD is scarce. A comprehensive assessment of ICUD is needed to ascertain the role of its individual component.

Oncological outcome of RARC

The systematic review by Yuh et al.[30] reported the oncological outcome of RARC. The overall positive surgical margin (PSM) rate was 5.6%. Cumulative analyses of the review did not show any significant difference in the rates of PSM between RARC and ORC. The 5-year RFS, CSS, and OS were 53%–74%, 66%–80%, and 39%–66%, respectively. A limitation of the systematic review is that among the 87 series in this study, only 6 series reported a mean follow-up time of more than 36 months.

A randomized, open-label, noninferiority, phase 3 trial was carried out to compare the progression-free survival of ORC with the progression-free survival of RARC. A total of 350 participants were recruited in the study, and in the final analysis, 152 patients were in the ORC group and 150 patients were in the RARC group. The 2-year progression-free survival was 72.3% and 71.6% for RARC and ORC, respectively ($p_{non\text{-}inferiority}$=0.001), ascertaining the noninferiority of RARC to ORC.[31] A Cochrane review of seven publications on five randomized controlled trials (RCTs) was published in 2019 to investigate the outcome of ORC and RARC.[11] The total number of participants under study in the ORC and RARC cohorts was 270 and 271, respectively. The authors concluded that RARC may have a similar time of recurrence as ORC (hazard ratio: 1.05; 95% CI: 0.77–1.43), and in absolute terms, RARC has 16 more recurrences per 1,000 participants (95% CI: 79 fewer to 123 more) than ORC. A similar observation applies to the PSM rate. This review indicated that RARC may result in a similar PSM rate compared with that of ORC (RR: 1.16; 95% CI: 0.56–2.40). This corresponds to eight more PSMs per 1,000 participants (95% CI: 21 fewer to 67 more).

Iwata et al.[12] performed a systematic review and meta-analysis, including the five RCTs in the Cochrane review as well as 28 nonrandomized studies. There was no significant difference in the PSM rates of patients with pathological T1–2 and T3–4 tumors between RARC and ORC in both RCTs (RR: 1.00; 95% CI: 0.14–6.97; p=1.00 and RR: 1.15;1.15, 95% CI: 0.50–2.66; p=0.75, respectively) and nonrandomized studies (RR: 1.11; 95% CI: 0.81–1.52; p=0.52 and RR: 0.90; 95% CI: 0.79–1.02; p=0.09, respectively). Lymph node yield was the same for both RARC and ORC. No significant difference was observed in RFS, CSS, and OS between RARC and ORC. Although RARC has proven itself to be sharing a similar oncological outcome as ORC, a longer follow-up period is needed to properly assess the long-term outcome.

Complications of RARC

A number of studies have demonstrated the advantage of RARC in terms of reduced perioperative morbidities. In a case series of 36 patients who underwent radical cystectomy, Matsumoto et al.[32] reported a mean EBL of 1,700 mL for ORC and 450 mL for RARC (p=0.0004). Blood transfusion rate was 56% for ORC and 0% for RARC.[32] A series of 368 patients who underwent RARC and ORC in Europe found that the RARC group had higher odds of prolonged operative time and low-grade complications (p<0.001), but at the same time, it also exhibited less blood loss and a shorter hospital stay (p<0.03).[33] Similarly, a systematic review of 105 articles by Novara et al.[34] indicated a shorter operative time for ORC, whereas better results in terms of EBL and hospital stay were observed for RARC (p<0.003). RARC with ICUD presented with an overall 30-day complication rate of 45.7% and a mortality rate of <3%. Data from the International Robotic Cystectomy Consortium reported that the incidence of complications and readmissions were more pronounced in the first 30 days after RARC (47% vs 28%, p<0.01).[18]

The recent Cochrane review of five randomized trials on RARC and ORC reported that RARC may result in similar rates of major complications (Clavien grades 3–5) as ORC (RR: 1.06; 95% CI: 0.761.48).[11] In contrast, whether RARC results in fewer minor complications (Clavien grades 1 and 2) than ORC is uncertain. A systematic review and meta-analysis by Tzelves et al.[35] investigated five randomized trials as well as 49 observational studies. A total of 29,697 patients were included in the analysis, showing that minor complications (Clavien grades 1 and 2) were fewer in the RARC group within both 30 and 90 days (OR: 0.54; 95% CI: 0.38–0.76; p<0.001). Major complications (Clavien grades 3–5) were fewer in the RARC group (OR: 0.78; 95% CI: 0.65–0.94; p=0.009) on the 90-day mark but not on the 30-day mark. The advantages of RARC with respect to reduced EBL and shorter hospital stay but with a longer operating time were again evident in the systematic review.

The concept of pentafecta was first introduced by Aziz et al.[36] in 2015, who proposed five criteria for radical cystectomy outcome assessment. Cacciamani et al.[37] from the USC later adopted the first four criteria, namely, (1) negative soft tissue surgical margin, (2) ≥16 lymph nodes removed, (3) absence of major complications (Clavien grades 3–5) within 90 days, and (4) absence of clinical recurrence before 12 months. Furthermore, they modified the fifth criterion from treatment-free time to sequelae of urinary diversion, specifically ureteroenteric stricture. Oh et

al.[38] recently reported the pentafecta outcome of 730 patients who have undergone RARC from the Korean Robot Assisted Radical Cystectomy database. Total complications rate was 57.8%, and major complications rate was 21.1%, with gastrointestinal complication being the most common (26.2%). Ureteroenteric stricture rate was 8.1%. In the entire cohort, 28.5% attained the RARC pentafecta. Compared with the group that could not attain pentafecta, the pentafecta attainment group had significantly higher OS and CSS rates [10-year OS: 70.4% vs 58.1% (p=0.016); 10-year CSS: 87.8% vs 70.0% (p=0.036)].

Functional outcome of RARC

Agility and magnification that come with the robotic surgical system allow meticulous dissection to be feasible. Different techniques have been endeavored in the hope to improve the functional outcome of RARC, for example, vagina-sparing RARC (Figure 2) and nerve-sparing RARC (Figure 3). However, functional outcomes of RARC were relatively less studied than its oncological counterpart. It can be attributed to the fact that functional outcomes encompass a wide spectrum, including continence, sexual function, and gastrointestinal function. Furthermore, standardization in functional outcome assessment is lacking. A retrospective 70-patient series of RARC with ICUD and neobladder reported a rate of 70%–90% daytime continence and satisfactory sexual function or potency at 12 months for both men and women.[39] Balbay et al.[40] reported their experience of 22 cases of RARC and ICUD with Studer pouch. Daytime full continence rate was 58.8% at 12 months. A modified posterior Rocco's repair, involving the Denovillier's fascia, the rhabdosphincter, and the posterior side of the ileal neobladder neck, was performed at Karolinska University Hospital. Rocco et al.[41] reported their experience of 11 patients with posterior reconstruction; the daytime and night-time continence rates were 100% and 44% at 12 months, respectively. A Y-shaped orthotopic neobladder was proposed by Clinique Saint-Augustin, and Asimakopoulos et al.[42] reported their experience of this form of ICUD together with the nerve-sparing technique. Daytime continence was 75% at postoperative 1 month, and nocturnal continence was 72.5% at 12 months. Erectile function returned to normal (International index of erectile function [IIEF]-6 score >17) in 77.5% patients at 3 months, and 72.5% patients attained their preoperative IIEF-6 score within 12 months. A retrospec-

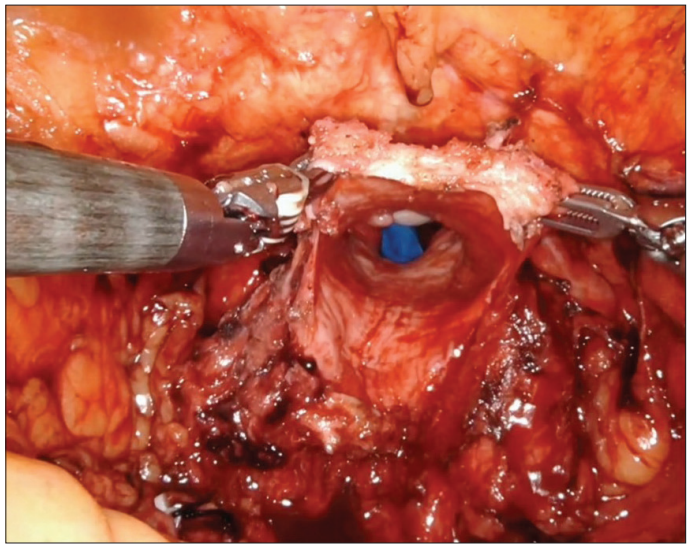

Figure 2. Vagina-sparing RARC with the vaginal vault preserved after dissection (cystectomy specimen was removed via the vaginal opening).
RARC: robotic-assisted radical cystectomy

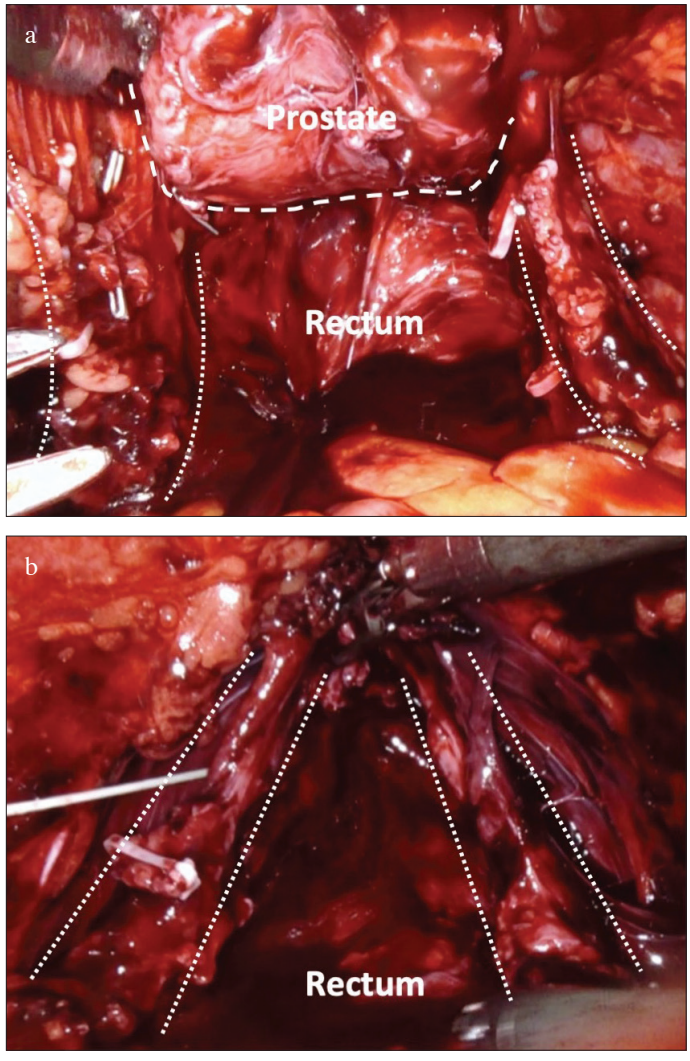

Figure 3. a, b. Nerve-sparing RARC. (a) Preservation of bilateral neurovascular bundles by dissection of the nerve away from the prostate in a posterior approach. (b) Preserved bilateral neurovascular bundles after cystectomy completion. Dashed line represents prostate contour, whereas dotted line represents neurovascular bundle outline
RARC: robotic-assisted radical cystectomy.

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tive review of 254 patients who have undergone RARC by Haberman et al.[43] reported that 66% of the patients could perform successful penetration in a cohort with a median follow-up of 32.9 months. Current evidence shows acceptable functional outcomes after RARC. More standardized templates for reporting functional outcomes as well as randomized studies to better compare ICUD techniques are required.[44]

Ongoing development of RARC

With the progress in robotic surgical techniques, RARC has also taken a few steps in different directions. Kaouk et al. [45] and Zhang et al.[46] described their preliminary experience of RARC and ICUD with the da Vinci® Single Port Surgical System. Both the groups have demonstrated the feasibility of such a technique through a transperitoneal approach. A transperineal approach by the same surgical system in a male cadaver was reported in a step-by-step manner.[47] However, the result of such a technique in the clinical setting is still awaited.

Conclusion

Adoption of RARC and ICUD for bladder cancer has grown in recent years, and progress has been made in the technical aspect of these techniques. The robotic approach has shown promising results with respect to oncological, functional, and perioperative outcomes. Increasing expertise is expected with increasing engagement of RARC. Further investigation by well-designed studies with long-term follow-up are needed for RARC to replace ORC as the standard of care.

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