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The role of robotics in the invasive management of bladder cancer

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Abstract

Robotic assisted radical cystectomy (RARC) has been adopted widely in many centres, owed largely to the success of robotic assisted laparoscopic prostatectomy (RALP). It aims to replicate the oncological outcomes of open radical cystectomy (ORC), while providing a shorter recovery period. Despite this, previous RCTs have failed to show a benefit for RARC over ORC. These trials have compared extracorporeal RARC (eRARC) to ORC, which requires a further incision to mobilise the bowel for urinary reconstruction with an open technique. For intracorporeal RARC (iRARC), this urinary reconstruction is performed robotically without further incisions. There are theoretical benefits to this approach such as reduced recovery time for the bowel and reduced ileus rates, but no level 1 evidence currently exists to support this. While there has been an improvement in patient outcomes since the adoption of RARC, various other factors, such as enhanced recovery programmes and surgical learning curve, have made it difficult to attribute this solely to the robotic approach as many centres performing ORC have also shown similar improvements. In this review, we will discuss implementation of RARC as well as peri-operative measures that have helped improve outcomes, offer a comparison of outcomes between ORC and RARC, and highlight upcoming RCTs that may offer new evidence for or against a paradigm shift in the future of bladder cancer surgery.

Keywords: Robotic cystectomy; intracorporeal; extracorporeal; bladder cancer; enhanced recovery

Introduction

With the increased use of robotics in the operating theatre, robot-assisted radical cystectomy (RARC) has been adopted by many high volume tertiary centres as standard treatment. This has been supported by evidence of oncologic equivalence[1,2], and possible benefits of faster recovery, shorter lengths of hospital stay and a quicker return to normal activities when compared with its open counterpart. Open radical cystectomy (ORC) has traditionally been considered the gold standard treatment for muscle-invasive bladder cancer, but as with other surgical procedures, laparoscopic adaptations of the procedure such as laparoscopic radical cystectomy (LRC) and RARC have gained traction. Radical cystectomy has a high attrition rate from the disease process. Nearly 50% of patients have a metastatic recurrence within five years of surgery[3], and most of these patients subsequently die from the disease. Open cystectomy has a 5.1%[4] risk of mortality, and 90-day complication rates of up to 64.4%[5]. With increased costs of surgery due to adoption of RARC, health economics of adopting this approach will require an improvement in the outcomes compared to ORC[6] and LRC[7].

The first laparoscopic cystectomy was performed in 1992[8], although this was a simple cystectomy without lymphadenectomy for pyocystis and not bladder cancer. Sánchez de Badajoz et al.,[9] then described an LRC on a patient with muscle-invasive bladder cancer. With the arrival of the da Vinci system in 2001, there has been a lot of interest to replicate the principles and successes of LRC in RARC.
This has been a largely successful endeavour, with multiple randomized controlled trials and meta-analyses reporting equivalence in both oncologic and 90-day outcomes[10,11].

There are two main techniques used for urinary diversion during RARC, 1) extracorporeal urinary diversion (eRARC) and 2) intracorporeal urinary diversion (iRARC). Extracorporeal diversion involves an extra 5 to 7 cm skin incision[12] (muscle splitting incision in the right iliac fossa for an ileal conduit and lower midline incision for an orthotopic neobladder) to bring out the intestine following completion of the cystectomy. Intracorporeal diversion has additional potential benefits including less incisional pain, decreased bowel exposure and desiccation, and the potential for decreased fluid imbalances[13].

In the evolution of practice in our centre, we have moved from ORC to iRARC. One surgeon did perform 3 extracorporeal robotic assisted cystectomies (eRARC) before adopting iRARC, whereas the other switched directly from ORC to iRARC. Enhanced recovery has only been introduced in our centre in the last 16 months, but has provided significant additional improvement in various outcomes.

In this review, we will explore the role of robotics in the management of bladder cancer, with an emphasis on optimisation of the patient pathway, complications, outcomes and the future of robotics in the management of bladder cancer.

Preoperative optimisation

In our centre, the clinical pathway is set up to have a one-stop multidisciplinary team (MDT) assessment clinic, where patients have appointments with their urologist, anaesthetist, enhanced recovery team, urinary diversion team, pre-assessment and cardiopulmonary exercise testing (CPET). CPET is part of our local pre-operative investigations, as it can provide an objective measure of physiological reserve under stress, and can be used to stratify perioperative risk, identify the need for pre-operative optimisation and pre-empt post-operative complications. Our local experience suggests that patients with poor cardio-pulmonary reserve and patients with pre-operative anaemia undergoing iRARC have better outcomes and recovery in comparison with ORC[14,15].

On the day of cystectomy, patients are permitted solid food until six hours prior to surgery, and clear fluids up to two hours prior to surgery. Patients are also provided high-calorie carbohydrate drinks to have the night before surgery and the morning of surgery to minimise insulin resistance and catabolism of non-carbohydrate products due to surgical stress[16]. Carbohydrate loading has been proven to reduce length of stay and early return to normal bowel function in an RCT setting for colorectal surgical patients[17].

Intra-operative measures

The patient is placed on a green foam non-slip mattress upon arrival in theatre. The skin around the incision sites is shaved and cleaned with chlorhexidine. Intravenous broad spectrum antibiotics (cefuroxime, metronidazole and gentamicin) are given intra-operatively, and continued for a further 24 hours post-operatively to reduce the risk of post-operative infections of the wounds as well as any potential bowel content spillage. If bowel content spillage is identified intra-operatively, the antibiotic regimen is continued for five days.

A nasogastric tube is inserted under anaesthetic to deflate the stomach, and a urinary catheter is inserted to drain the urinary bladder. The Bair Hugger (*3M*, St Paul, MN, USA) device is used to maintain a temperature above 36 degrees Celsius.

Spinal analgesia with a dose of 1.5-2ml 0.5% heavy bupivacaine + 1mg diamorphine is used as standard in conjunction with general anaesthesia. In addition to standard Association of Anaesthetists of Great Britain & Ireland (AAGBI) invasive arterial and entropy monitoring is used to balance anaesthesia. Fluid replacement is optimised using goal directed fluid therapy monitoring

The patient is positioned in a steep Trendelenburg position, with arms adducted to the sides and padding on all possible pressure points. Intravenous paracetamol and lidocaine (2 mg/kg/hour for the duration of the operation) are given for analgesia at the start of surgery, with the addition of diclofenac if the patient has good kidney function (eGFR > 60). The use of IV lidocaine was first adopted for laparoscopic colectomy, and has been shown to reduce the need for post-operative analgesia, opioid use and length of hospital stay, as well as to accelerate post-operative bowel function[18].

Post-operative measures and the role of enhanced recovery after surgery (ERAS)

Using a neuraxial block allows for some advantages over epidural anaesthesia as side effects such as hypotension and motor block are not encountered. It also enables early mobilisation as the patient is not continuously connected to an infusion pump[19].

The nasogastric tube is removed prior to waking the patient up and all patients go to the high dependency unit for overnight optimisation postoperatively.

Intermittent pneumatic compression in theatre, compression stockings and subcutaneous low molecular weight heparin are used as standard practice for all patients undergoing cystectomy as part of venous thromboembolism prophylaxis. The first dose is given within six hours post-operatively, and once daily thereafter for four weeks post-operatively.

The implementation of enhanced recovery after surgery (ERAS) pathways including routine use of epidural or spinal analgesia, antimicrobial prophylaxis, standard anaesthetic protocols, preventing intraoperative hypothermia, early ambulation and early nasogastric tube removal has led to a reduction in time to tolerating oral diet without worsening morbidity[20]. The ERAS programme was first implemented in colorectal surgery, with a reduction in length of stay and complication rates, with no significant difference in readmission and mortality rates[21].

ERAS pathways have been widely adopted, and have shown some success in improving outcomes for RARC, as well as ORC. Julian et al., reported their experience in Southampton for ORC and found that the implementation of an ERAS programme resulted in multiple marginal gains, which led to a significant decrease in median length of stay from 14 days to 7 days[22]. The implementation of the ERAS programme for iRARC in our centre has also significantly reduced the length of hospital stay and a reduction in morbidity[23]. The median length of stay in our centre has reduced from 17 days with ORC to 10 days with iRARC, and a further reduction to 7 days with the implementation of ERAS alongside iRARC. While this effect is largely attributed to the ERAS programme itself, it must be recognised that the surgeons were further along their learning curve for these cases, and this could have contributed to the faster recovery and discharge of patients.

The EAU Robotic Urology Section Scientific Working Group Consensus review found that there is a lack of high-level evidence[24] for ERAS in patients undergoing RARC, but that it is difficult to assess the multimodal nature of

such programmes through RCTs. The consensus recommends a standardised enhanced recovery programme specific to patients undergoing RARC, and this has been used as a template for adoption by various centres including ours.

Our local set up process for ERAS involved an initial assessment of local data, implementing improvements and analysing the marginal gains in various domain. Various tools are instrumental to the adoption of the ERAS programme, such as stakeholder analysis, process compliance auditing, PDSA (Plan, Do, Study, Act) cycles etc. Various resources such as *e*-L*f*H (eLearning for Healthcare)[25] and PRISM (perioperative improvement science and management)[26] provide guidance for quality improvement methodology to use these tools optimally.

Outcomes

90-day complications

In a systematic review of the literature, Novara et al.[11], identified 105 articles describing outcomes of RARC (both iRARC and eRARC) vs ORC. In the meta-analysis of this data, they concluded that RARC, both intracorporeal and extracorporeal, can be performed safely within acceptable operative time, lower blood loss and transfusion rates. The risk of intraoperative complications is low, but post-operative complications are similarly high to ORC, with high grade complications of 33% at 90 days. Overall, they concluded that blood loss and hospital stay was better with RARC, and low-grade complications were lower for RARC but high grade complications were similar to ORC.

However, in a systematic review of only the randomized controlled trials comparing eRARC vs ORC[10], Tan et al., found that while RARC is associated with lower estimated blood loss, transfusion requirement and wound related complications, there was no significant difference between groups in perioperative morbidity, length of stay, positive surgical margin rate, lymph node yield and lymph node positive. There have been four RCTs comparing eRARC vs ORC to date, and all of them did not show any significant difference in complications, but did establish non-inferiority of eRARC to ORC.

Most 90-day major complications are related to surgical technical complications such as urinary leak, anastomotic stricture, significant bleeding, herniation and wound dehiscence[27]. For experienced surgeons, risk of urinary leak

is similar to ORC, and these leaks can be managed conservatively. The International Robotic Cystectomy Consortium reported the 30-day and 90-day outcomes of 939 patients undergoing RARC, and 53 patients from this group returned to the operating theatre. The common reasons for re-operating were fascial dehiscence (n = 12), small bowel obstruction (SBO) or partial SBO (n = 8), urine leak (n = 7), and bleeding (n = 5).

Furthermore, a volume-outcome relationship has been identified with radical cystectomy and other high-risk operations, where higher surgical volume can reduce mortality by up to 37%[28]. Combined with the high cost of robotic surgery, this has resulted in a shift towards centralization and consolidation of cancer services[29] in an effort to improve outcomes.

Late complications

Late complications can include some early complications such as urinary leak and strictures. Other complications that can occur after 90 days include incisional hernias, uretero-ileal stenosis, small bowel obstruction, febrile UTIs, sub-neovesical obstruction, metabolic complications, incontinence and retention[23].

Due to RARC being a relatively new procedure, long term complication data is not well-described in the literature as most studies describe complications up to 90 days. In a survey of 406 patients with a median of 27 months follow-up, 23% (92) patients required surgical intervention after eRARC[30]. Re-operation rate was 5%, 2% and 16% at 31, 31-90 and greater than 90 days respectively. Of these, uretero-ileal complications were the most common (48 cases), followed by interventions for bowel obstruction, fistulas and abdominal wall related complications. For comparison, a large series of 923 patients undergoing ORC by Hautmann et al., long-term complication rate was 40.8%[31].

Functional outcomes

Functional measures such as urinary continence and quality of life are greatly relevant to patients undergoing cystectomy with neobladder formation. Continence rates tend to improve as time from surgery increases, and continence can continue to improve over a period of a few years. For instance, daytime continence increased from 59% at less than 3 months postoperatively to 92% by 12 to 18 months[32], and night-time continence rates of 75%

at 12 months improved to 94% at 3 years in ORC[33]. A systematic review of the literature found that in RARC, 12-month continence rates with continent diversion were 83–100% in men for daytime continence and 66–76% for night-time continence, but they commented that very limited data was available for functional outcomes. This variance is likely to be related to surgeons being on their learning curve. A similar trend was observed initially for robotically-assisted radical prostatectomy (RALP) when compared to open prostatectomy, but continence rates are now similar for both procedures among experienced surgeons[34].

Post-operative quality of life is being recognised as an important outcomes measure following major surgery, and the health-related quality of life (HRQoL) measures have gained traction. Messer et al., performed an RCT evaluating HRQoL for ORC vs eRARC using the Functional Assessment of Cancer Therapy-Vanderbilt Cystectomy Index questionnaire[35]. They found that there were no significant differences between HRQoL outcomes between ORC and eRARC, with a return of quality of life scores to baseline 3 months after surgery in both cohorts, with a slightly higher physical well-being score in the RARC group at 6 months. This was a relatively small study of 47 patients, but HRQoL is being measured in an ongoing trial in a randomised setting[36].

Oncological outcomes

There is no level one evidence comparing oncological outcomes between RARC and ORC. However, various observational studies have reported similar outcomes[2,37,38] for RARC when compared to ORC. Lymph node yield is considered a surrogate for quality of surgery, and in RARC it has been comparable to ORC[2,39], with some studies reporting higher lymph node yield[40] in RARC compared to ORC. Following RARC, port-site metastases have been reported[41], but this is similar to surgical site metastases following ORC[42]. From the results of the International Robotic Cystectomy Consortium, 5-year disease-free survival, cancer-specific survival and overall survival rates following RARC are 67%, 75% and 50% respectively[43].

iRARC vs eRARC

While the extirpative component (radical cystectomy and lymphadenectomy) is performed robotically in both eRARC and iRARC, the difference is in the reconstructive component (urinary diversion). This is performed by open surgery in eRARC while being done completely intracorporeally in iRARC. An interesting hypothesis is that

physiological stress response associated with minimally invasive cystectomy and intracorporeal reconstruction would be less than that of extracorporeal reconstruction or open surgery.

The four RCTs comparing RARC vs ORC have all used eRARC for their reconstruction of the bladder, and as previously mentioned, these RCTs failed to show any significant difference. It has been established that iRARC is feasible with good complication rates, comparable early oncological outcomes[44] and similar recurrence patterns to ORC. To our knowledge, there have been no RCTs comparing intracorporeal reconstruction (iRARC) with either ORC or eRARC. Observational data has been used to compare outcomes of iRARC, and 90-day outcomes were found to be similar to that of eRARC, with a non-significant trend in 90-day complication rate favouring iRARC (41% vs 49%, p = 0.05)[45]. However, it is difficult to draw conclusions from retrospective observational data, and high quality level 1 and level 2 evidence is required to compare the two techniques.

Learning curve

There is no accepted definition of what constitutes an experienced surgeon for RARC. For comparison, the definition of proficient surgeon for RALP varies from having performed between 20 to 250 cases[46–48]. Relatively few publications in the literature have explored the nature of the learning curve and its effect on outcomes. Hayn et al., used operative time, estimated blood loss, lymph node yield and positive surgical models, and estimated that 21 patients were required for operative time to reach 6.5h and 8, 20, and 30 patients were required to reach an LNY of 12, 16, and 20, respectively[49]. Richards et al., found that complications decreased as the learning curve progressed from 14 (70%) in the 1st tertile to 6 (30%) in each of the 2nd and 3rd tertiles, mean total operative time trended down from the 1st to 3rd tertile from 525 minutes to 449 minutes but the blood loss was unchanged[50].

The Pasadena Consensus Panel recommends that a surgeon's initial learning curve is the first 20-30 cases, and they should be supervised by an experienced mentor with a reduced focus on operative time, and avoiding complex patients (bulky tumours, obese patients, patients with previous radiotherapy, surgery or adhesions). For the next approximately 70 cases, the surgeon should focus on reducing operative time, blood loss and starting building on intracorporeal reconstruction experience. After a total of 100 cases, the surgeon is considered very experienced and

should take on more challenging cases. Particularly at the early stages of the learning curve, surgeons should have a low threshold for converting to ORC[51].

Ongoing trials

As discussed previously, observational data suggests that oncological outcomes of RARC are non-inferior to ORC, but this has not been reported in a trial setting. The randomized open vs open cystectomy (RAZOR) is a multi-centre RCT to compare oncological outcomes of eRARC vs ORC at 15 centres, with a primary endpoint 2-year progression free survival[36]. As of February 2015, 306 patients had been recruited (total expected recruitment of 320 patients), and results of the study are expected in 2017.

No previous RCTs have compared iRARC to either techniques in a trial setting. The intracorporeal Robotic vs Open Cystectomy (iROC) trial[52] is a multi-centre RCT in the UK to compare 90-day outcomes between iRARC and ORC. It has started recruitment in March 2017 and aims to recruit 320 patients, with a primary endpoint of days alive and out of hospital at 90 days[53]. Where previous trials have shown non-inferiority of eRARC to ORC, the iROC trial will be the first trial to attempt to compare iRARC performed by experienced surgeons (>30 cases) versus ORC performed by similarly experienced surgeons.

Conclusions

Over the last 15 years, there have been various improvements in the instruments, techniques and surgeon expertise in robotic uro-oncology. While complications are common after RARC, current data suggests that complication rates are similar to ORC. With expert consensus on peri-operative care, it is important to understand the impact of enhanced recovery programmes on patient care. The constant evolution of methods and improvements in peri-operative tools such as enhanced recovery programmes have confounded the assessment of the true advantages of robotics in the context of bladder cancer.

As surgeons become experienced or even expert at RARC, we eagerly await the results of ongoing trials in the modern setting to answer a very important question: is there going to be a new gold standard in radical treatment of bladder cancer?

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