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The role of robotics in the invasive management of bladder cancer

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1 The role of robotics in the invasive management of bladder 2 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 pyocystitis 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].

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

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

83

84 Preoperative optimisation

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

93

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

99 Intra-operative measures

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

106
107 A nasogastric tube is inserted under anaesthetic to deflate the stomach, and a urinary catheter is inserted to drain the
108 urinary bladder. The Bair Hugger (3M, St Paul, MN, USA) device is used to maintain a temperature above 36
109 degrees Celsius.

110
111 Spinal analgesia with a dose of 1.5-2ml 0.5% heavy bupivacaine + 1mg diamorphine is used as standard in
112 conjunction with general anaesthesia. In addition to standard Association of Anaesthetists of Great Britain & Ireland
113 (AAGBI) invasive arterial and entropy monitoring is used to balance anaesthesia. Fluid replacement is optimised
114 using goal directed fluid therapy monitoring

115
116 The patient is positioned in a steep Trendelenburg position, with arms adducted to the sides and padding on all
117 possible pressure points. Intravenous paracetamol and lidocaine (2 mg/kg/hour for the duration of the operation) are
118 given for analgesia at the start of surgery, with the addition of diclofenac if the patient has good kidney function
119 (eGFR > 60). The use of IV lidocaine was first adopted for laparoscopic colectomy, and has been shown to reduce
120 the need for post-operative analgesia, opioid use and length of hospital stay, as well as to accelerate post-operative
121 bowel function[18].

122 Post-operative measures and the role of enhanced recovery after surgery 123 (ERAS)

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

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6 128 The nasogastric tube is removed prior to waking the patient up and all patients go to the high dependency unit for
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8 129 overnight optimisation postoperatively.
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12 131 Intermittent pneumatic compression in theatre, compression stockings and subcutaneous low molecular weight
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14 132 heparin are used as standard practice for all patients undergoing cystectomy as part of venous thromboembolism
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16 133 prophylaxis. The first dose is given within six hours post-operatively, and once daily thereafter for four weeks post-
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18 134 operatively.
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22 136 The implementation of enhanced recovery after surgery (ERAS) pathways including routine use of epidural or spinal
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24 137 analgesia, antimicrobial prophylaxis, standard anaesthetic protocols, preventing intraoperative hypothermia, early
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26 138 ambulation and early nasogastric tube removal has led to a reduction in time to tolerating oral diet without
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28 139 worsening morbidity[20]. The ERAS programme was first implemented in colorectal surgery, with a reduction in
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30 140 length of stay and complication rates, with no significant difference in readmission and mortality rates[21].
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32 141
33
34 142 ERAS pathways have been widely adopted, and have shown some success in improving outcomes for RARC, as
35
36 143 well as ORC. Julian et al., reported their experience in Southampton for ORC and found that the implementation of
37
38 144 an ERAS programme resulted in multiple marginal gains, which led to a significant decrease in median length of
39
40 145 stay from 14 days to 7 days[22]. The implementation of the ERAS programme for iRARC in our centre has also
41
42 146 significantly reduced the length of hospital stay and a reduction in morbidity[23]. The median length of stay in our
43
44 147 centre has reduced from 17 days with ORC to 10 days with iRARC, and a further reduction to 7 days with the
45
46 148 implementation of ERAS alongside iRARC. While this effect is largely attributed to the ERAS programme itself, it
47
48 149 must be recognised that the surgeons were further along their learning curve for these cases, and this could have
49
50 150 contributed to the faster recovery and discharge of patients.
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54 152 The EAU Robotic Urology Section Scientific Working Group Consensus review found that there is a lack of high-
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56 153 level evidence[24] for ERAS in patients undergoing RARC, but that it is difficult to assess the multimodal nature of
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154 such programmes through RCTs. The consensus recommends a standardised enhanced recovery programme specific
155 to patients undergoing RARC, and this has been used as a template for adoption by various centres including ours.
156
157 Our local set up process for ERAS involved an initial assessment of local data, implementing improvements and
158 analysing the marginal gains in various domain. Various tools are instrumental to the adoption of the ERAS
159 programme, such as stakeholder analysis, process compliance auditing, PDSA (Plan, Do, Study, Act) cycles etc.
160 Various resources such as *e-LfH* (eLearning for Healthcare)[25] and PRISM (perioperative improvement science
161 and management)[26] provide guidance for quality improvement methodology to use these tools optimally.

162 Outcomes

163 90-day complications

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

171
172 However, in a systematic review of only the randomized controlled trials comparing eRARC vs ORC[10], Tan et al.,
173 found that while RARC is associated with lower estimated blood loss, transfusion requirement and wound related
174 complications, there was no significant difference between groups in perioperative morbidity, length of stay,
175 positive surgical margin rate, lymph node yield and lymph node positive. There have been four RCTs comparing
176 eRARC vs ORC to date, and all of them did not show any significant difference in complications, but did establish
177 non-inferiority of eRARC to ORC.

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

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

185
186 Furthermore, a volume-outcome relationship has been identified with radical cystectomy and other high-risk
187 operations, where higher surgical volume can reduce mortality by up to 37%[28]. Combined with the high cost of
188 robotic surgery, this has resulted in a shift towards centralization and consolidation of cancer services[29] in an
189 effort to improve outcomes.

191 Late complications

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

195
196 Due to RARC being a relatively new procedure, long term complication data is not well-described in the literature as
197 most studies describe complications up to 90 days. In a survey of 406 patients with a median of 27 months follow-
198 up, 23% (92) patients required surgical intervention after eRARC[30]. Re-operation rate was 5%, 2% and 16% at 31,
199 31-90 and greater than 90 days respectively. Of these, uretero-ileal complications were the most common (48 cases),
200 followed by interventions for bowel obstruction, fistulas and abdominal wall related complications. For comparison,
201 a large series of 923 patients undergoing ORC by Hautmann et al., long-term complication rate was 40.8%[31].

203 Functional outcomes

204 Functional measures such as urinary continence and quality of life are greatly relevant to patients undergoing
205 cystectomy with neobladder formation. Continence rates tend to improve as time from surgery increases, and
206 continence can continue to improve over a period of a few years. For instance, daytime continence increased from
207 59% at less than 3 months postoperatively to 92% by 12 to 18 months[32], and night-time continence rates of 75%

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

214
215 Post-operative quality of life is being recognised as an important outcomes measure following major surgery, and
216 the health-related quality of life (HRQoL) measures have gained traction. Messer et al., performed an RCT
217 evaluating HRQoL for ORC vs eRARC using the Functional Assessment of Cancer Therapy-Vanderbilt Cystectomy
218 Index questionnaire[35]. They found that there were no significant differences between HRQoL outcomes between
219 ORC and eRARC, with a return of quality of life scores to baseline 3 months after surgery in both cohorts, with a
220 slightly higher physical well-being score in the RARC group at 6 months. This was a relatively small study of 47
221 patients, but HRQoL is being measured in an ongoing trial in a randomised setting[36].

223 Oncological outcomes

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

231 iRARC vs eRARC

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

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

237
238 The four RCTs comparing RARC vs ORC have all used eRARC for their reconstruction of the bladder, and as
239 previously mentioned, these RCTs failed to show any significant difference. It has been established that iRARC is
240 feasible with good complication rates, comparable early oncological outcomes[44] and similar recurrence patterns to
241 ORC. To our knowledge, there have been no RCTs comparing intracorporeal reconstruction (iRARC) with either
242 ORC or eRARC. Observational data has been used to compare outcomes of iRARC, and 90-day outcomes were
243 found to be similar to that of eRARC, with a non-significant trend in 90-day complication rate favouring iRARC
244 (41% vs 49%, $p = 0.05$)[45]. However, it is difficult to draw conclusions from retrospective observational data, and
245 high quality level 1 and level 2 evidence is required to compare the two techniques.

Learning curve

247 There is no accepted definition of what constitutes an experienced surgeon for RARC. For comparison, the
248 definition of proficient surgeon for RALP varies from having performed between 20 to 250 cases[46–48]. Relatively
249 few publications in the literature have explored the nature of the learning curve and its effect on outcomes. Hayn et
250 al., used operative time, estimated blood loss, lymph node yield and positive surgical margins, and estimated that 21
251 patients were required for operative time to reach 6.5h and 8, 20, and 30 patients were required to reach an LNY of
252 12, 16, and 20, respectively[49]. Richards et al., found that complications decreased as the learning curve progressed
253 from 14 (70%) in the 1st tertile to 6 (30%) in each of the 2nd and 3rd tertiles, mean total operative time trended
254 down from the 1st to 3rd tertile from 525 minutes to 449 minutes but the blood loss was unchanged[50].

255
256 The Pasadena Consensus Panel recommends that a surgeon's initial learning curve is the first 20-30 cases, and they
257 should be supervised by an experienced mentor with a reduced focus on operative time, and avoiding complex
258 patients (bulky tumours, obese patients, patients with previous radiotherapy, surgery or adhesions). For the next
259 approximately 70 cases, the surgeon should focus on reducing operative time, blood loss and starting building on
260 intracorporeal reconstruction experience. After a total of 100 cases, the surgeon is considered very experienced and

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

263 Ongoing trials

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

269
270 No previous RCTs have compared iRARC to either techniques in a trial setting. The intracorporeal Robotic vs Open
271 Cystectomy (iROC) trial[52] is a multi-centre RCT in the UK to compare 90-day outcomes between iRARC and
272 ORC. It has started recruitment in March 2017 and aims to recruit 320 patients, with a primary endpoint of days
273 alive and out of hospital at 90 days[53]. Where previous trials have shown non-inferiority of eRARC to ORC, the
274 iROC trial will be the first trial to attempt to compare iRARC performed by experienced surgeons (>30 cases)
275 versus ORC performed by similarly experienced surgeons.

276 Conclusions

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

283
284 As surgeons become experienced or even expert at RARC, we eagerly await the results of ongoing trials in the
285 modern setting to answer a very important question: is there going to be a new gold standard in radical treatment of
286 bladder cancer?

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