The impact of robotic surgery in bladder cancer patients

Francesco Greco\textsuperscript{1,2}, Nicola Pesenti\textsuperscript{1}, Alberto Vismara\textsuperscript{1}, Lorenzo Tessa\textsuperscript{1}, Rocca Lisanti\textsuperscript{1}, Luigi Domanico\textsuperscript{1,2}, Riccardo Farci\textsuperscript{1}, Emanuele Micheli\textsuperscript{1}, Vincenzo Maria Altieri\textsuperscript{1}

\textsuperscript{1}Department of Urology, Humanitas Gavazzeni, Bergamo, Italy; \textsuperscript{2}Humanitas University, Milan, Italy

Contributions: (I) Conception and design: F Greco; (II) Administrative support: N Pesenti, VM Altieri, E Micheli; (III) Provision of study materials or patients: F Greco, R Lisanti, L Tessa; (IV) Collection and assembly of data: A Vismara, L Domanico; (V) Data analysis and interpretation: F Greco; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Francesco Greco. Department of Urology, Humanitas Gavazzeni, Via M Gavazzeni 21, 24125 Bergamo, Italy.
Email: francesco_greco@ymail.com.

Abstract: To investigate the impact of robotic surgery in bladder cancer (BCa) patients, analysing surgical, functional, and oncologic outcomes of robot-assisted radical cystectomy (RARC) in comparing to open radical cystectomy (ORC). A systematic literature search of all randomized controlled trials (RCTs) comparing RARC with ORC was performed in November 2019. For each selected study, the following items were recorded in an Excel (Microsoft, Redmond, United States) sheet: surgical data (operative time, blood loss, transfusion rate, in-hospital stay, complication rates) and oncologic data (positive surgical margins, lymph node yields, disease-free survival, cancer-specific survival, overall survival). We consider 5 RCTs for the analysis including 548 cases (276 cases for RARC and 272 cases for ORC), which fulfilled the predefined inclusion criteria and were included in the final analysis. All selected studies presented a LoE 1b. One of the limits presented by RARC was the median operating time. All included studies reported longer OP time when compared to ORC. RARC resulted superior to ORC when considered estimated blood loss (EBL) and transfusion. No significant differences in overall complications (grades I–V) were identified between the treatment groups and the proportion of patients who had major complications (grades III–IV) was also similar between the groups. When considering progression-free survival, recurrence-free survival and BCa-specific survival, RARC demonstrated its non-inferiority to open cystectomy without any risk for port-site metastases. RARC robotic cystectomy is non-inferior to open cystectomy for surgical complications and oncological outcomes. Nevertheless, the supposed benefits of a mini-invasive approach concerning reduced hospital stay and improved postoperative QoL could be not demonstrated. Increased adoption of robotic surgery the therapy of muscle-invasive BCa should lead to future randomised trials to assess if RARC could become the new gold standard for RC.

Keywords: Bladder cancer (BCa); surgical therapy; robot-assisted cystectomy; outcomes

Received: 29 December 2019; Accepted: 10 March 2020; Published: 25 June 2021.
doi: 10.21037/amj.2020.03.14
View this article at: http://dx.doi.org/10.21037/amj.2020.03.14

Introduction

Bladder cancer (BCa) is the 11th most commonly diagnosed tumor in human with a worldwide age-standardised incidence rate (per 100,000 person/years) of 9.0 for men and 2.2 for women (1).

The gold standard therapy for muscle-invasive urinary bladder cancer (MIBC) is still represented by radical cystectomy (RC) which presents 66% recurrence-free survival at 10 years follow-up (2). Moreover, the overall survival (OS) rates can be improved of 5% by adding of neoadjuvant platinum-based chemotherapy (3).

Although RC remains the gold standard for treatment for MIBC and high-risk superficial tumors resistant to intravesical treatment, robot-assisted radical cystectomy (RARC) has been increasingly adopted for the treatment...
of MIBC and actually it represents the standard treatment in many high-volume tertiary centres (4-7). RARC was initially described by Menon et al. in 2003 (5). Since then, its diffusion has been worldwide increased as it is supposed to presents several benefits, including evidence of oncologic equivalence, faster recovery, shorter lengths of hospital stay and a quicker return to normal activities when compared with open RC (8-10).

Due to increasing evidence in the field of RARC, we investigated the impact of robotic surgery in BCa patients, analysing perioperative, functional, and oncologic outcomes of RARC in comparison with ORC.

Methods

The first author (FG) established, prior to conducting the systematic review, the selection criteria and research protocol. A systematic literature search was performed in November 2019. The searches included a free-text protocol using the terms “robot-assisted radical cystectomy or da Vinci radical cystectomy or mini-invasive radical cystectomy” in all fields of the records for PubMed and Scopus searches and in the title and topic fields for the Web of Science search.

Additional studies were evaluated in the reference lists of all retrieved articles. When multiple reports describing the same population were published, the most recent or complete report was used.

Literature research was restricted to articles published in the English language and only recent publication (published in the last 6 years) were considered.

All randomized controlled trials (RCTs) that compared RARC with ORC and had at least one of the quantitative outcomes were included.

For each selected study, the following items were recorded in an Excel (Microsoft, Redmond, United States) sheet: surgical data (operative time, blood loss, transfusion rate, in-hospital stay, complication rates) and oncologic data (positive surgical margins, lymph node yields, disease-free survival, cancer-specific survival, OS) of RARC were collected.

Postoperative complications were classified into 4 grades according to the Clavien-Dindo grading system (11), distinguishing major (grades 3–5) and minor (grades 1 and 2) complications.

Studies reporting partial cystectomy, prostate-sparing cystectomy, salvage cystectomy, cystectomy for urachal cancers or benign diseases, single-case reports, or pure laparoscopic (or mixed) series; those focusing on RC with laparoscopic single-site or natural orifice transluminal endoscopic surgery; experimental studies on animal models; congress abstracts; review papers; editorials; population-based studies; and book chapters were not included in the review.

Studies were rated for the level of evidence provided according to criteria by the Centre for Evidence-Based Medicine in Oxford, UK (12). The methodological quality of RCTs was assessed by the Cochrane risk of bias tool (13).

Results

We could identify 6 studies (6,7,14-17) which fulfilled the predefined inclusion criteria and were included in the final analysis. All selected studies presented a LoE 1b (12).

Two publications (7,14) had overlapping populations but with some different outcomes, whereas the data reported by Messer et al. (16) were excluded from the analysis because overlapping the outcomes reported by Parekh et al. (17).

Lastly, we consider only 5 RCTs (6,7,14,15,17) for the analysis including 548 cases (276 cases for RARC and 272 cases for ORC)

Perioperative outcomes (Table 1)

The RARC group included 212 male and 64 female while ORC included 204 male and 68 female.

One of the limits presented by RARC was represented by the median operating time. All included studies reported longer OP time when compared to ORC.

In the RAZOR study (15), RARC presented a statistically significant increased operating time than the open group [RARC 428 min (range, 322–509 min) vs. ORC 361 min (range, 281–450 min), P=0.0005], even if it was not distinguished the total op time form console time.

Bochner et al. (7) reported that ORC group presented reduced operative time by a mean time of 127 min (95% CI, 98–156; P<0.001) and this outcome was also confirmed by the CORAL study with a mean OP-time which was significantly longer for RARC compared with ORC (P<0.001) (6).

Surprisingly, Parekh et al. (17) could not find any differences for op time in both groups [RARC 300 min (range, 240–366 min) vs. ORC 285.5 min (range, 240–321.3 min), P=0.329].

We know from literature (5,18) that robotic surgery requires a significant learning curve and that, a gradual reduction in operative times can be perceived after
performing the first 20 cases; the Razor trial included only surgeons who had previously performed more than 100 ORCs and approximately 50 RARCs, thus reducing the bias induced by the learning curve for the robotic approach. This can explain the equivalence for the operating time between the RARC and ORC groups (15).

As expected, RARC resulted superior to ORC when considered estimated blood loss (EBL) and transfusions rate. The RAZOR trial (15) reported a median EBL of 300 mL (range, 200–500) after robot-assisted surgery and of 700 mL (range, 500–1,000) after open RC (P<0.0001). This difference was also confirmed by Bochner et al. (7). In the latter study, based on the intention-to-treat (ITT) analysis, intraoperative estimated blood loss was reduced in the RARC group by a mean of 159 mL (P=0.027).

Similar results were presented in the Parekh’s study (17) where RARC group had a significantly lower EBL than open group (P=0.003). Contrary to the other results, the CORAL study (6) could not evidence a statistically significant difference for EBL in favor of RARC (P=0.070).

In the last years, it has been investigated if blood transfusion (BT) could influence the surgical and oncologic outcomes after RC. Actually, there are controversies about this topic.

In fact, if several studies have suggested that intraoperative blood transfusion was associated with increased perioperative morbidity and worsened OS and CSS in patients undergoing RC (19-23), other studies could not demonstrate any significant correlation between BT and cancer recurrence and mortality after RC (24,25).

In a recent study, Moschini et al. (26) investigated the impact of perioperative blood transfusion (PBT) on RC patients for OS and after stratifying according to preoperative anemia status.

A total of 580 patients (38.9%) received PBT. At multivariable Cox regression analyses, PBT could not be associated with an increased risk of either CSM or OM (all P>0.3). Conversely, preoperative Hb levels were significantly associated with OM [hazard ratio (HR): 0.88; 95% CI, 0.83–0.95] and CSM (HR: 0.84; 95% CI, 0.77–0.95) (all P<0.001). A significant detrimental effect of PBT on OM (HR: 1.65; 95% CI, 1.08–2.52) and CSM (HR: 1.68; 95% CI, 1.04–2.70) (all P<0.03) was found in patients without preoperative anemia status.

When we consider that PBT should be really associated with worsened OS and CSS, then it could be postulated that RARC should improve CSM and OM by reducing the risk of anemia and PBT. Nevertheless, this is only a daring hypothesis which should be investigated and confirmed in future RCTs.

If hospital stay was inferior in the RARC group in the Razor trial (15) and in the CORAL study (6), Parekh’s (17) and Bochner’s (7) studies did not report significant differences in the two groups for length of stay (LOS).

Even if RARC resulted in early feeding, mobilization, and discharge by day 4 or 5 regardless of diversion type, no significant benefit in hospital stay was observed in the latter two studies for RARC. However, the authors did not consider postoperative clinical indicators for minor surgical trauma, such as time to return of bowel function or postoperative pain (7).

Parekh et al. (17) reported that the RARC cohort presented fewer prolonged hospitalizations (LOS greater than 5 days) and a faster return to a regular diet compared to the ORC group, although this was not significant.

This was confirmed also in other elderly studies. For example, Nix et al. demonstrated that RARC was associated with a shorter median time to return of flatus (2.3 vs. 3.2 days, P=0.0013) but a similar LOS (5.1 vs. 6.0 days,
No significant differences in overall complications (grades I–V) were identified between the treatment groups and the proportion of patients who had major complications (grades III–IV) was also similar between the groups (6,7,15,17).

In the Razor trial (15), the most common complications were urinary tract infection [53 (35%) in the robotic cystectomy group vs. 39 (26%) in the open cystectomy group] and postoperative ileus [33 (22%) in the robotic cystectomy group vs. 31 (20%) in the open cystectomy group].

In the Parekh’s study (17), the postoperative complications were represented in the robotic group by cardiac arrhythmia, cerebrovascular stroke, pneumonia, renal failure, evisceration and ileus. For the open group, the reported complications were cardiac arrhythmia, wound infection (n=2), fistula formation (n=1) and ileus.

**Oncologic outcomes (Table 2)**

When we consider oncologic outcomes after RC, we should firstly evaluate the incidence of positive surgical margins (PSM) and lymph node yields, both of which represent an independent prognostic factor for survival. The presence of PSM after RC increases the risk for local recurrence and the metastatic progression risk, as well as it adversely affects cancer-specific survival (28,29).

Single-centre RCTs could not evidence any statistically significant increased risk for PSM after RARC (7,17,27). This could be explained by the smaller cohort of patients included in these randomised studies. Even the RAZOR trial could not report statistically significant differences for PSMs between robotic surgery and open radical cystectomy (ORC), thus strengthening the concept that the absence of tactile feedback and excessive manipulation of the cystectomy specimen during RARC is not responsible for worse PSM rates (30).

Considering lymph node yields, the extent of lymph node dissection and lymph node counts were similar between the two groups in all included studies.

In the Razor trial, 2-year progression-free survival in the robotic cystectomy group (72%) was non-inferior to that of the open cystectomy group (72%; difference 0.7%, 95% CI, −9.6 to 10.9), suggesting that robotic cystectomy was not oncological inferior to open cystectomy (15).

The rate of local recurrences was similar between the RARC and ORC [6 (4%) of 150 patients in the robotic cystectomy group vs. 4 (3%) of 152 patients in the open cystectomy group; P=0.54] and local recurrence in the cystectomy bed was also similar [6 (4%) patients in the robotic cystectomy group vs. 2 (1%) patients in the open cystectomy group; P=0.17].

Bochner et al. (14) also found that recurrence-free survival and BCa-specific survival were similar between the robot and open surgery arms (P=0.4 and P=0.4, respectively), with a risk of recurrence at 5 years of 36% and 41% for RARC and ORC, respectively (difference: −5.2%; 95% CI: −25 to 14).

The CORAL study reported PSM rates of 10% for ORC and 15% for RARC respectively (6). If we consider the

### Table 2 Oncologic outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>LoE</th>
<th>PSM</th>
<th>Progression-free survival</th>
<th>Local recurrences, n (%)</th>
<th>Perioperative chemotherapy, n (%)</th>
<th>Lymph node yield, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORAL (6)</td>
<td>1B</td>
<td>RARC 3/20 (15%), ORC 2/20 (10%), P=0.09</td>
<td>Reported as not significant between RARC and ORC</td>
<td>RARC 5/19 (26%), ORC 2/19 (11%), P=0.5</td>
<td>RARC 2 (10%), ORC 3 (15%), P=NS</td>
<td>RARC 16.3, ORC 18.8, P=NS</td>
</tr>
<tr>
<td>Bochner et al. (7,14)</td>
<td>1B</td>
<td>RARC 2 (3.6%), ORC 3 (4.8%), P=0.7</td>
<td>Reported as not significant between RARC and ORC</td>
<td>RARC 10, ORC 4, P=0.077</td>
<td>RARC 19 (32%), ORC 26 (45%), P=NA</td>
<td>RARC 31.9, ORC 30, P=0.5</td>
</tr>
<tr>
<td>RAZOR (15)</td>
<td>1B</td>
<td>RARC 9 (6%), ORC 7 (5%), P=0.59</td>
<td>RARC 72.3%, ORC 71.8%, P&lt;0.001</td>
<td>RARC 6/150 (4.0%), ORC 4/152 (3.0%), P=0.5</td>
<td>RARC 41 (27%), ORC 55 (36%), P=NA</td>
<td>RARC 23.3, ORC 25.7, P=0.13</td>
</tr>
<tr>
<td>Parekh et al. (17)</td>
<td>1B</td>
<td>RARC 1/20 (5%), ORC 1/20 (5%), P=0.500</td>
<td>–</td>
<td>–</td>
<td>RARC 8/20 (40%), ORC 8/20 (40%), P=0.500</td>
<td>RARC 11, ORC 23, P=0.135</td>
</tr>
</tbody>
</table>

NS, not significant; NA, not available.
Pasadena Consensus Panel recommendation to avoid PSM rate >7% after RARC (9), then the rate of positive surgical margins after robotic surgery reported by the CORAL study should be considered to be high and this aspect could be critically discussed. Nevertheless, this worse result for RARC can be explained by the fact that the authors did not routinely perform simultaneous urethrectomy when urethra was not infiltrated, thus avoiding to increase morbidity for the patients.

An interval urethrectomy was subsequently planned only in presence of positive urethral margins, without influencing long-term oncologic outcomes. For these reasons, the 12-month disease recurrence and disease-specific mortality in the CORAL study were equivalent between ORC and RARC.

It has been postulated that robotic cystectomy could increase risk of peritoneal carcinomatosis, port site recurrences, and extra pelvic lymph node metastases, because of a risk of tumor seeding associated with pneumoperitoneum and excessive manipulation of the cystectomy specimen (31). In the Razor trial, no differences for local and distant recurrences were found between the RARC and ORC groups, confirming the safety of the robotic approach (15).

Quality of life and costs

Radical cystectomy with urinary diversion is a surgical procedure which affect patient QoL.

We found only few studies analyzing the impact of the surgical approach on QoL after RC. Messer et al. measured QoL using the Functional Assessment of Cancer Therapy-Vanderbilt Cystectomy Index questionnaire and no differences were reported between ORC and RARC (16).

In the CORAL study, the validated FACT-BI questionnaire was used but RARC and ORC presented with similar results (6).

Even the Razor trial (15) showed no difference between the open cystectomy and robotic cystectomy groups with regard to QoL and in the Bochner’s study (7), there were no clinical or statistical differences in QOL change from baseline to 3 months or from 3 to 6 months between RARC and ORC.

Cost analyses have previously suggested a benefit in favor of RARC over ORC (32), whereas others have not (4). Bochner et al. (7) suggested increased total costs (operating room and inpatient) for RARC procedures regardless the urinary diversion, although neobladder patients reported lower costs. The lack of difference in hospital LOS, the added equipment costs, and longer operating room times were responsible for increased costs associated with robotic procedures.

Moreover, when considering the costs, we should also consider the effect of the learning curve on them. A recent study could identify in 10 cases which are required by robotically trained new faculty to reach a steady-state level of performance, thus reducing the costs (33).

Conclusions

RARC is not inferior to ORC regarding surgical complications and oncological outcomes. Nevertheless, the supposed benefits of a mini-invasive approach and less surgical trauma basing on reduced hospital stay and improved postoperative QoL could be not demonstrated.

Increased adoption of robotic surgery for the therapy of muscle-invasive BCa should lead to future randomised trials to assess if RARC could become the new gold standard for RC.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2020.03.14). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2020.03.14