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Review

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Robotic total mesorectal excision: state of the art

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Abstract

Minimally-invasive conventional up-to-down laparoscopic approach is a widespread alternative for rectal cancer resection. Its potential benefits towards open surgery have been shown to rely, however, at secondary clinical outcomes, and its oncological non-inferiority compared with the traditional open approach has not been demonstrated yet. In this scenario, robotic-assisted minimally-invasive rectal resection has gained increasing popularity and promising expectancies. This narrative review aims to assemble the most updated evidence available and to discuss the future perspectives and challenges for this emergent surgical tool. The main benefit over conventional laparoscopy appears to be a reduction of conversion rates to open surgery, whereas the oncologic and functional outcomes seem similar than the other alternatives. Increased costs are the main limitation of the widespread of robotic technology. Low quality of the current evidence is remarkable.

Keywords: Rectal cancer, total mesorectal excision, robotic surgery, minimally-invasive surgery

INTRODUCTION

In 2018, colorectal cancer (CRC) was the third most commonly diagnosed cancer (10.2%), and the second leading cause of cancer death (9.2%). Nearby two million of new CRC cases and more than 800,000 deaths were estimated to occur worldwide in 2018[1]. Surgery remains as the mainstay treatment for rectal cancer, improvements on the outcomes have been observed since the introduction and widespread of the principles of total mesorectal excision (TME)[2]. Preoperative radiotherapy and chemotherapy have a major role in the treatment of locally advanced rectal tumors[3]. To perform an accurate mesorectal dissection achieving clean margins is mandatory for rectal resections. Obtaining both negative circumferential resection margin (CRM-) and a complete mesorectal excision is associated with lower recurrence rates an improved long-term survival[4-10].

Laparoscopic rectal surgery was introduced shortly after 1990. The earliest large randomized controlled trials (RCT) comparing conventional laparoscopic and open approaches for rectal cancer showed that the use of laparoscopy was associated with a lower blood loss, an earlier return of bowel movement, and a shorter length of hospital stay[11-14]. Further studies questioned the oncological safety of the approach, by means of obtaining a complete mesorectal quality or a composite pathologic outcome associating also free circumferential and distal margins[15-17]. Remarkably, the observed impairment should be reflected in the long-term oncologic prognosis in order to reach any clinical interest. The question remains still open after the publication of the mid-term (2-year) results of the latest trials[18-20]. Conventional laparoscopic instruments may not be appropriate for assuring the achievement of the best plane of dissection in all patients, especially in those with the narrow or irradiated pelvis[21]. Due to this, TME seems to be one of the procedures in which the robotic assistance will have a critical role[22-25].

At the time of the present review, the ROLARR study was the largest RCT comparing robotic-assisted *vs*. conventional laparoscopic surgery for patients with rectal cancer[26]. Two recent systematic reviews with meta-analyses summarized the outcomes from 7 and 5 RCTs with a similar design[27,28]. Other meta-analyses have been published including also non-randomized clinical trials[29,30]. No guidelines are now available suggesting the true role of robotics in colorectal surgery, high-quality clinical data is similarly lacking. In the present review, we dissected the current status of robotic TME, with special emphasis on surgical outcomes and near future perspectives.

BACKGROUND

A robot is a device that can be programmed to carry out a task, being controlled by mechanical and computing systems[31]. The concept of robotic surgery appeared in the 1970s as a military project of the Defense Advanced Research Project Administration endorsed by the National Aeronautics and Space Administration aiming to keep the surgeon from the battlefield[32]. In 1985, a robot was introduced into an operating theatre, an industrial robotic arm (PUMA 200) was modified to perform a preprogrammed intracranial biopsy. Shortly thereafter, the PROBOT® and ROBODOC® systems were developed, designed for transurethral prostatic resections and total hip arthroplasties, respectively[33,34]. The earliest systems required prior task programming, implying longer procedure duration and poor response to unexpected events. At the end of the 20th century, the way of conceiving abdominal surgery changed by the introduction of laparoscopy. The first laparoscopic colorectal surgery was performed in 1990 by Fowler[35]. In 1994, the automated endoscopic system for optimal positioning was the first real-time surgical manipulation system being commercialized. It consisted of an endoscope attached to a voice-controlled mechanical arm that modified its position following surgeon's orders. It allowed greater image stability and sometimes dispensed the need for an assistant but provided longer operative time compared with conventional laparoscopy[36,37].

In 2000, ZEUS® (Computer Motion, Goleta, California, USA), a three-armed robot mounted on the operating table; and the da Vinci® robot (Intuitive Surgical, Sunnyvale, California, USA) were developed. In 2003 Computer Motion was incorporated into Intuitive Surgical. The da Vinci® system provided a fourth arm and an independent console where the surgeon has a three-dimensional view of the field. Specifically designed devices with Endowrist® technology allow for 7º of freedom, 180º articulation and 540º rotation[38].

The latest release to date, the Xi version, appeared in 2014. It offers the possibility of adjusting the operating table without undocking the system, shortening the procedure length and allowing multi-quadrant single-docking procedures. Augmented-reality software allows the assessment of intestinal perfusion or real-time three-dimensional (3D) anatomical simulation of abdominal structures[39-41]. Senhance® Surgical Robotic System and the REVO-I® Robot Platform are the two other systems commercially available nowadays. Competitive industry players like Medtronic and Verb surgical (powered by GOOGLE® and Johnson & Johnson®) platforms are expected soon[42].

LEARNING CURVE OF ROBOTIC TME

The learning curve for robotic TME, from the beginning to the higher expertise, should include at least 20-23 cases, which is faster than for conventional laparoscopy[43,44]. Contrasting results have been reported regarding the impact of the previous proficiency on laparoscopy on the duration of the period[45,46]. Most of the publications evaluated the expertise with variables as "operative time", "bleeding" or "conversion" which may not be the most critical outcomes[47]. There is a wide agreement on the fact that operative times are longer during a learning curve, but a recent study on robotic rectal resection showed no relationship between extended operative time and morbidity[48]. The evaluation of the experience in oncologic surgery should also focus on the quality of the resected specimen, especially for rectal cancer resection. Only a recent meta-analysis showed no significant differences in CRM involvement between learning and competent surgeons. The authors did not found significant differences in the other clinic and pathologic variables, without evaluating the quality of the TME[49].

A learning curve is unavoidable, and robotic surgery requires special training and the development of new skills. The companies responsible for robotic systems are compelled by the Food and Drug Agency to develop technical training for the surgeons. The European Association of Endoscopic Surgeons (EAES) recommended a training officially-certified and based on a formal curriculum for skills and procedures[50]. The lack of standardization in robotic rectal surgery was specifically noted, this is critical to assure the safety and success of training surgeons in their future practice. Recent resources aim to provide an objective assessment of the acquired surgical skills to produce future standards for robotic surgeons on basic knowledge and procedural safety[50]. If any superiority favouring robotic TME is proven soon, the learning curve should not be an obstacle, but a necessary step for novel surgeons to reach the standards of quality. Noteworthy, there is an underlying and not despicable risk if surgeons abandon conventional laparoscopic surgery learning in favour of robotics. We may have soon a generation of surgeon incapable of performing laparoscopic surgery, with unclear but potentially serious consequences.

BENEFITS AND LIMITATIONS OF ROBOTIC RECTAL SURGERY

Technical advantages

Current robotic platforms display a 3D image, enhancing the visualization of the anatomical structures by improving the surgeon's depth perception and image quality. Compared to conventional laparoscopy, robotic surgery also allows to control a stable camera[47]. The system has recently incorporated the EndoWrist® technology, which improves dexterity and eliminates physiological tremor reducing the challenge of laparoscopic intra-corporeal suturing[51]. These technical advantages are expected to allow a better mesorectal dissection, preserving the integrity of the fascia and decreasing the odds of autonomic nerve injury resulting in sexual dysfunction, anterior resection syndrome, or urinary retention[38].

The use of robotic platforms is associated with better surgeon's ergonomics than those provided by conventional laparoscopy. Robotic assistance results in lesser activation of the upper-body mussels reducing musculoskeletal discomfort[52]. Berguer *et al.*[53] reported that robotic help makes less stressful performing complex tasks. Previous laparoscopic experience has a complex influence on the adaptation to the new approach[53]. Tele-surgery is the latest potential advantage of robotic surgery, allowing real-time international collaborations and mentoring[54].

Technical disadvantages

The loss of haptic feedback is still the main technical limitation of the available robotic platforms. A multi-modal pneumatic feedback system offering tactile, kinesthetic, and vibrotactile feedback was incorporated in the da Vinci® Surgical System[55]. Other platforms, as Senhance® Surgical Robotic System and the REVO-I® Robot Platform, also incorporated haptic feedback assistance[56].

Costs

Increased costs attributed to robotic surgery are the most important current impediment for the widespread of this technology. The economic impact is an important point to assess in the setting of increasing demands on limited health resources. To accurately measure costs has a particular difficulty at economic evaluations. Total costs rely on direct, indirect and intangible costs. Direct costs can be divided into fixed costs (to buy and maintain the robotic system), and variable costs (consumable instruments). The cost of a robotic platform is $1-$2.3 million[47]. Cost-analysis studies determined that robotic is more expensive than open and laparoscopic surgeries[57,58]. Baek *et al.*[58] in 2012, reported that robotic rectal surgery charges were between $7,150-10,700, and $1,240 for laparoscopic surgery[58]. The ROLARR trial showed that health-care costs in the robotic-assisted laparoscopic group (£11 853 or $13 668) were higher than in the conventional laparoscopic group (£10 874 or $12 556). The higher costs were attributed to longer theater occupation and the use of specific instruments. Conversely, Ielpo *et al.*[59] found that the mean overall costs were similar between robotic and laparoscopic approach, excluding the initial purchase of the robotic system[59].

Few studies have assessed the cost-effectiveness of robotic rectal surgery, it is difficult to assign a monetary value to the measured outcomes in this particular scenario[60]. Morelli *et al.*[61] observed that excluding fixed costs and comparing experienced phase of robotic surgery with the laparoscopic approach, the variable operative costs were similar[61]. Therefore, robotic expertise has a critical role in the operative costs, similar to the procedures standardization, the surgical team's consistency, and the institution's volume[62]. Robotic surgery could mitigate increased expenditures whether provide lesser risk of conversion and shorter hospitalization[29,63]. Indirect costs have not been deeply evaluated for robotic rectal resections. Only Bertani *et al.*[57] found a faster physical recovery after 1 month in the robotic group compared with open surgery[57]. The ROLARR did not found differences between laparoscopic and robotic surgery in bladder and sexual dysfunction rates[26]. No cost-utility study aiming to determine indirect costs has been reported to date. Further research is needed to evaluate the quality of life; including sexual, stool, and urinary functions, using utility measures like the disability-adjusted life-year and the quality-adjusted life-year, to accurately compare the outcomes of the different surgical alternatives. For the latest 20 years, da Vinci® System has dominated robotic surgery, the lack of adversaries led to rising costs and maybe slowed the evolution of the technology[42]. In the near future, with the introduction of new robotic platforms, this situation is expected to change dramatically.

OUTCOMES OF ROBOTIC SURGERY FOR RECTAL CANCER

Intraoperative outcomes

Some authors suggested the potential advantage of robotic TME over conventional laparoscopy decreasing the conversion rates to open surgery: Prete *et al.*[28] [Risk Ratio (RR), 0.58; 95%CI: 0.35-0.97; $P = 0.04$], Jones *et al.*[29] [Odds Ratio (OR), 0.40; 95%CI: 0.29-0.55; $P < 0.00001$], Ohtani *et al.*[64] (OR, 0.30; 95%CI: 0.19-0.46; $P < 0.00001$), and Lee *et al.*[65] (RR, 0.28; 95%CI: 0.15-0.54; $P < 0.0001$)[28,29,64,65]. The benefit has been related to the use of three-dimensional vision and articulated instruments, facilitating the dissection during TME.

The ROLARR study, however, only found benefits in the men subgroup[26]. Although the study found no significant differences in the rest of the short-term outcomes being evaluated, trial's sample estimation, and the varying expertise on robotics of the participating surgeons assured the debate after its publication[26]. Existing research demonstrated longer operative time for robotics compared with open and laparoscopic rectal resections[28,65,66]. Ohtani *et al.*[64] reported an operative time 44 minutes greater than laparoscopy [weighted mean difference (MD), 44.80; 95%CI: 28.44-61.15; $P < 0.00001$][64]. Lee *et al.*[67] showed no differences in operative time between robotic and transanal-TME[67]. Other studies reported less blood loss for robotic TME, compared with the open and laparoscopic approaches[68,69]. Intraoperative complications were found similar for robotic surgery when compared with the open and laparoscopic approaches[26,66].

Postoperative outcomes

Anastomotic leak rate was not significantly different for robotics compared with open and laparoscopic operations[28,69]. Laparoscopic, transanal, and robotic TME also showed similar leak and reoperation rates[67,70]. Postoperative ileus, wound infection, and urinary retention were similar between open, laparoscopic, transanal procedures in comparison with robotic approach[30,65,69]. Length of hospital stay was shorter after robotic surgery compared with open (7.5 days *vs.* 13.24 days)[66,69], but no difference was found when comparing it with conventional laparoscopy[28,70]. Perioperative complications and mortality rates appear to be similar for all four approaches[28,30,69]. Mortality is low in elective rectal surgery, with only 2 cases in each arm among 466 patients (0.9%) in the ROLARR study[26].

Pathologic outcomes

As robotic assistance seems to facilitate mesorectal dissection, particularly in mid and low rectal tumours, a reduced rate of positive CRM+ was presupposed to be one of the major benefits conferred by the novel technology. However, different studies showed that CRM+ is similar when compared with the other techniques. Jayne *et al.*[26] reported no statistically significant differences in the odds of CRM+ between robotic and laparoscopic groups (OR, 0.78; 95%CI: 0.35-1.76; $P = 0.56$)[26]. Accordingly, a propensity adjusted analysis of 7616 patients support both for the resection of locally advanced rectal cancer, with equivalent CRM- rates (93% *vs.* 94%; 95%CI: 0.69-1.06)[71].

The completeness of the mesorectal resection became a valuable item to assess the oncologic safety of a rectal resection and predicts tumor recurrence in the pelvis[72]. Rausa *et al.*[30] showed no significant differences in complete, near-complete or incomplete mesorectal excision between laparoscopic and robotic approaches (complete RR, 0.8; 95%CI: 0.7-1.0; nearly-complete RR, 1.6; 95%CI: 0.9-2.7; incomplete RR, 1.5; 95%CI: 0.8-2.5)[30].

Liao *et al.*[27] associated the robotic approach with a longer distance to the distal margin in comparison with laparoscopy (MD, 0.83 cm, 95%CI: 0.29-1.37; $P = 0.003$)[27]. When comparing robotic and open surgeries, no differences were found (MD, 0.17; 95%CI: -0.14 to 0.48; $P = 0.27$)[69].

Truong *et al.*[73] analysed a retrospective cohort of patients looking at successful resections, defined as a circumferential and distal resection margins < 1 mm and complete mesorectal resection, which were similar between the robotic (75%) and open (76%) approaches[73]. There were no differences in the studies comparing all four approaches for rectal cancer regarding the number of lymph nodes retrieved[26,27,30,69].

Long-term oncologic outcomes

Local recurrence rates were similar between laparoscopic *vs.* robotic (RR, 1.4; 95%CI: 0.7-2.4) and transanal-TME *vs.* robotic (RR, 1.4; 95%CI: 0.5-3.4) in the meta-analysis performed by Rausa *et al.*[30]. Moreover, Ohtani *et al.*[64] also reported no differences in terms of local, metastatic, and overall recurrences, 3-year OS and 3-year DFS between robotic and laparoscopic approaches[64]. In their recent meta-analysis, Liao *et al.*[27]

described the OS and DFS after a mean follow-up of 29.2 months in the robotic group and 18.7 months in the laparoscopic group. The OS was 100% in the robotic group and 94.1% in the laparoscopic group. The DFS was 100% in the robotic group and 88.2% in the laparoscopic group. Studies comparing robotic and open resections also found non-significant long-term outcomes between them. Five-year DFS was 73.2% and 69.5% in the robotic and open groups, respectively. Five-year OS was 85.0% in the robotic and 76.1% in the open approach[69].

Functional outcomes

Two trials evaluated the urinary function of using the International Prostate Symptom Score (I-PSS) comparing robotic and laparoscopy TME. Lee *et al.*[65] showed improved urinary continence for robotic surgery at 3 months, but there was no statistical difference on I-PSS at 6 or 12 months after surgery[65]. Erectile dysfunction rates did not differ between robotic and laparoscopic groups (OR, 0.54; 95%CI: 0.19-1.58; P = 0.26)[64]. Somashekhar *et al.*[66] analyzed erectile dysfunction and retrograde ejaculation using the European Organization for Research and Treatment of Cancer questionnaire QLQ-C38. A total of 18 % of male patients in the robotic group and 26% in the open group had sexual dysfunction[66]. Li *et al.*[70] published a meta-analysis reporting lesser incidence of urinary retention using robotic TME[70]. The ROLARR trial evaluated bladder function, male sexual function and female sexual function separately by using I-PSS, International Index of Erectile Function and Female Sexual Function Index, respectively. This study did not find any differences between laparoscopic and robotic surgery after 6-months follow-up[26].

FUTURE PERSPECTIVES

Fluorescence-guided robotic rectal resection

Near-infrared (NIR) light (650-900 nm) has optimum characteristics for *in vivo* imaging[74], resulting in higher penetration depth and minimum background auto-fluorescence[75]. Indocyanine green (ICG) is the only available fluorophore in the NIR window, it is confined into the vascular compartment through binding plasmatic proteins presenting low toxicity[76]. The applications of ICG are increasing, especially at colorectal cancer surgery. NIR has been used for assessing tissue perfusion and to detect sentinel nodes, peritoneal carcinomatosis, or liver metastases[77-80]. Anastomotic leak remains as the main complication in colorectal surgery, ischemia of intestinal stumps constitutes a major risk factor[81,82]. To determine the viability of the intestinal stumps when performing the anastomosis may decrease the odds of leak development. The earliest RCT on the subject just showed a reduction (9% *vs*. 5%), but non-significant, of the anastomotic leak rate in the fluorescence arm after colorectal resection[83]. Only two retrospective studies have been conducted using robotic technology[84,85].

The "enhanced permeability and retention" effect is the mechanism involved. It reflects the affinity of ICG towards tumoral and near-tumoral tissue due to neovascularization. Few studies are trying to elucidate the role of ICG in carcinomatosis, with contrasting results[79,86]. Neoadjuvant therapy with bevacizumab decreases the sensitivity of ICG to detect peritoneal metastases of colorectal cancer[87]. Mucinous metastases cannot be identified with ICG. A recent RCT comparing the use of white light versus NIR and ICG showed increasing sensitivity from 80% to 96%[88]. ICG can be alternatively used to improve surgical safety when marking important structures, as the ureters or the hepatic ducts, and even for tattooing colonic neoplasms instead of ink[89].

Robotic-assisted transanal TME

Over the last few years, the transanal approach gained popularity as seemed to facilitate complex pelvic dissections. Several studies reported that Ta-TME achieved similar technical success and perioperative outcomes than laparoscopic TME, with a lower conversion rate[90]. Recent studies also showed that serious complications secondary to wrong down-to-up dissection planes were not despicable, same for anastomotic leaks[91]. To improve the accuracy of the transanal dissection, robotic technology could also be helpful[92]. Two surgical teams (abdominal and perineal) can work together with the new platforms[93]. At present, however, further investigations are still needed to assure the long-term functional, and more critically, the oncological outcomes of the transanal approach for resecting rectal tumors[94].

CONCLUSION

The use of robotic assistance provides interesting improvements that may overcome some of the technical limitations of conventional laparoscopic instruments. Acceptable oncologic outcomes have been similarly reported. Increased costs, poor availability, and special training requirements are still important barriers to be overcome. Surgeons and health-care providers should notice that no important benefits have been yet demonstrated for robotic TME compared with the other available surgical alternatives. The combination of emerging technology, technical refinements, and an optimal trainee learning system may allow robotic surgery to be a gold standard for rectal cancer in the near future.

DECLARATIONS

Authors' contributions

Concept and design: Sebastián-Tomás JC, García-Granero E, Martínez-Pérez A

Collection and assembly of data: Sebastián-Tomás JC, Santarrufina-Martínez S, Navarro-Martínez S, Gonzálvez-Guardiola P, Martínez-López E, Payá-Llorente C

Provision of study materials or patients, data analysis and interpretation, manuscript writing and final approval: All authors

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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