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Review

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Is laparoscopic rectal surgery really not non-inferior?

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Abstract

Laparoscopic rectal surgery has gained popularity over the last 20 years. Currently there are still questions surrounding the safety and efficacy of this technique as compared to the traditional open modalities. To date, despite the initial enthusiasm for laparoscopic rectal surgery this technique is yet to reach non-inferiority in trials when compared to open resection. This review article discusses the current evidence exploring the value of laparoscopic rectal surgery. It will discuss its evolution over the last 20 years, exploring all the major randomised control trials and their results. It is our belief that laparoscopic rectal surgery for malignancy is not non-inferior to conventional open surgery.

Keywords: Rectal cancer, laparoscopic, open surgery, non-inferior, survival rate

INTRODUCTION

In Western society, rectal cancer is the third most common cause of cancer related deaths[1]. It encompasses approximately 30% of all colorectal malignancies[2]. Surgical resection of the rectum remains pivotal to the successful management of rectal cancer, especially in stage II or III disease[3,4].

The treatment of rectal cancer has undergone significant change over the last 50 years. Prior to total mesorectal excision (TME) rectal cancer had a locoregional recurrence rate of 40% and 5-year survival of less than 50%[5,6]. It was revolutionised in the early 1980's by Heald, who demonstrated that TME significantly improved the outcomes and prognosis for patients being treated for rectal cancer[6]. TME is the precise surgical dissection technique which involves the complete removal of the rectum, together with its draining

lymph nodes, within an intact mesorectum[1]. TME, in addition to neoadjuvant and adjuvant treatments have led to a reduction in locoregional recurrence to less than 10% and 5-year survivals of more than 70%[7,8]. The removal of the rectum and its mesorectum allows for potentially curative resection, pathological staging, prognosis and aids in further treatment decisions[9]. The quality of this resection is associated with improved outcomes in terms of survival and locoregional recurrence, thus the push for standardised good quality surgery[10,11].

Over the last 30 years there has been a drive towards minimally invasive techniques. Advances in laparoscopic surgery was thought to further revolutionise the surgical treatment of rectal cancer. Current evidence supports the concept of laparoscopic colonic resection over the traditional open modalities with known improvements in short-term outcomes, in addition to equivalent long-term results, when compared to open surgery[12,13]. In the short-term patients were noted to have faster recoveries, earlier feeding, decreased overall morbidity, earlier return of bowel function and decreased amounts of intraoperative blood loss[14,15]. In the intermediate term there was an earlier return to work. More importantly though the long term oncological outcomes regarding local recurrence, disease free survival and overall survival were shown to be improved[16].

Unfortunately to date the promise of similar results in laparoscopic rectal surgery has not yet been delivered. Several studies have shown laparoscopic rectal surgery has failed to reach noninferiority when compared to open resection in terms of short term pathological outcomes[10,17]. However, early reports from some of the major trials are suggesting that laparoscopic rectal surgery and open resection are equivalent regarding long-term disease-free survival, overall survival and local recurrence[18-20].

This review article aims to answer the question "is laparoscopic rectal surgery really is non-inferior to open surgery?" Is there too much focus on the short term pathological outcomes or should we be more patient and wait for the long-term survival data before we answer this question?

This article will outline the evidence to date, discuss the evolution of laparoscopic colonic surgery and its applicability to rectal surgery and finally discuss the current evidence for long term oncological outcomes and the evidence that is yet to be published. It is our belief that laparoscopic rectal surgery is not non-inferior to open surgical techniques in experienced hands.

EVOLUTION OF LAPAROSCOPIC COLONIC SURGERY

Laparoscopic colonic surgery had a relatively slow progression into accepted surgical practise. It was noted to have a steep learning curve, there was limited evidence regarding randomised control trials (RCTs), concerns were raised regarding its lymph node harvests, oncological outcomes and reports of port site metastasis[21]. Eventually over time, these concerns were laid to rest with robust, quality evidence. Laparoscopic colectomies have proven to be not only cost effective but have shown to have improved short-term outcomes with equivalent long-term oncological outcomes[21].

In 1991, Jacobs *et al.*[22] published their first case series of 20 patients who had received laparoscopic assisted colectomies. Lacy[23] published the first RCT which was a single institution study comparing 219 patients. This study revealed significant short-term benefits for the laparoscopic patient group regarding reduced blood loss, early return of intestinal function and overall decreased morbidity[23]. However, concerns were raised over the low lymph node harvests in both groups (average yield of 13 lymph nodes) and the low number of patients receiving adjuvant chemotherapy[21,23]. Furthermore, there were initial concerns raised about port site metastasises with reported incidences of 1%-21%[24]. Ultimately this was disproven, with an accepted incidence of 1%[19]. The accepted incidence of cutaneous metastasis after open resection is 1%-1.5%[25].

Eventually large randomised trials such as COST (Clinical Outcomes of Surgical Therapy) Study group, COLOR (Colon cancer Laparoscopic or Open Resection) trial, ALCCaS (Australian laparoscopic colon cancer study) trial, and the MRC CLASICC (Conventional versus laparoscopic-assisted surgery in patients with colorectal cancer) have shown the safety and efficacy of laparoscopic colonic surgery[26-28]. This same journey seems to parallel that of for laparoscopic rectal surgery. Currently the main criticism is that the short term oncological outcome of the resected specimen is not reaching noninferiority of the same specimens resected via open surgery. However, the long-term survival data that is emerging, is supporting equivalent outcomes regarding long term disease free survival, overall survival and locoregional recurrence.

COMPLEXITIES OF LAPAROSCOPIC RECTAL SURGERY

Laparoscopic rectal surgery can be divided into an abdominal component and a pelvic component. For the operation to be considered laparoscopic both components need to be completed laparoscopically. Regarding the traditional open operations this could be achieved by either the conventional laparotomy or via a hybrid procedure where the abdominal component is accomplished by laparoscopy (therefore taking advantage of the known benefits of laparoscopic colonic surgery). The pelvic component is then completed via a pfannensteil incision which allows direct vision of the rectum and surrounding mesorectal envelope[17,29].

There are several theoretical advantages to completing the operation completely laparoscopically as compared to open. The first of which is an intensely magnified view of the pelvis, which could allow improved preservation of the autonomic nerves. Furthermore, this magnification could lead to better visualisation of the TME plane and theoretically allow a more precise dissection. In addition to this, there has been evidence to support less blood loss, earlier feeding, early return of bowel function and decreased length of stay in hospital following laparoscopic procedures[29].

However, the learning curve of laparoscopic TME dissection is significant and requires time to master; more so than that of the curve for laparoscopic colonic resections. It is particularly challenging working within the narrow, confined space of the bony pelvis which creates issues with tissue retraction and dissection of the mesorectum[29]. Furthermore, the technical issues with laparoscopic equipment, particularly with laparoscopic stapling devices and the linear energy devices can be quite difficult to use inside the rigid, narrow pelvis, therefore requiring a high level of surgical expertise[29].

EVIDENCE FROM MULTICENTRE RANDOMISED CONTROL TRIALS (SHORT TERM ONCOLOGICAL DATA)

To date there have been several studies comparing the short term oncological outcomes of laparoscopic rectal surgery to that of open surgery. The landmark multicentre RCTs include the early UK-based MRC CLASICC (Conventional *vs.* Laparoscopic-Assisted Surgery in Colorectal Cancer) trial[27], the North American COLOR (Colon Cancer Laparoscopic or Open Resection) II trial[18], the South Korean based COREAN (Comparison of Open Versus Laparoscopic Surgery for mid or low Rectal Cancer After Neoadjuvant Chemoradiotherapy) trial[20], the Australian based ALaCaRT (Australian Laparoscopic Cancer of the Rectum Trial) trial[17] and the US based ACOSOG Z6051[10].

Some of the earliest data published came from the MRC CLASICC trial which was published in the Lancet in 2005. This was a multicentre trial that compared laparoscopic colon and rectal surgery to the conventional open modalities. Overall, the trial recruited 794 patients of which 242 had rectal cancer between 1996 and 2002. The relatively concerning results reported, likely reflected the challenges of laparoscopic rectal surgery and its early utilization. Thirty-four percent of patients required conversion, there was a 5% mortality rate and there was a high positive circumferential resection margin (CRM) rate of 12% for the

laparoscopic group and 6% for the open group. As compared to the 2015 ALaCaRT trial which had a 6.7% positive CRM rate in the laparoscopic group[27].

COLOR II trial was a noninferiority trial that recruited 1044 patients from 30 centres across 8 countries between 2004 and 2010, with adenocarcinoma of the rectum, within 15 cm of the anal verge. The primary outcome measure was to compare the locoregional recurrence after 3 years. Secondary outcome measures was 3-year disease free and overall survival. Included in the analysis was a comparison of the pathological data of the resected rectums. On pathological analysis the authors did not find any significant difference in TME quality, CRM or distal resection margin (DRM)[18].

The COREAN trial recruited 340 (170 patients in each group) patients with mid to low rectal cancer from 3 tertiary hospitals in South Korea between 2006 and 2009. It differs from the other trials in that all their patients received neoadjuvant chemoradiotherapy, whereas not all patients received neoadjuvant treatment in ALaCaRT or ACOSOG Z6051. Short term outcome measures such as CRM, TME quality, DRM and number of harvested lymph nodes were collected. Other measures such as post-operative quality of life, morbidity and return of bowel function were also investigated. Secondary outcomes included longer term outcomes (disease free and overall survival) at 3 years. Pathological assessment of the resected specimen in this study showed no statistical difference between the groups. The authors in this study supported the use laparoscopic rectal surgery after neoadjuvant chemoradiotherapy as it had an improved short-term benefit regarding post-operative outcomes and its pathological assessment was equivalent between the two groups[20].

ALaCaRT was a multicentre, randomised, noninferiority trial which aimed to investigate the safety and outcomes of laparoscopic rectal surgery as compared to open surgery. It recruited 475 patients (237 open resection group and 238 laparoscopic resection group) from 24 institutions from across Australia and New Zealand between 2010 and 2014 with T1-T3 rectal cancers within 15 cm of the anal verge. The primary aim of the study was to compare pathological outcome of the resected specimen. Secondary outcome measures compared were disease free survival, local pelvic recurrence at 2 years and overall survival at 5 years. The oncological quality of the specimen was a composite measure of completeness of TME, CRM and DRM. A successful resection needed to fulfil all the requirements of the composite outcome. The major distinction of this trial compared to the other landmark trials was the incorporation of the hybrid technique into the open group. The results failed to show that laparoscopic rectal surgery is non-inferior to open rectal surgery with only 82% of laparoscopic resected specimens being considered successful in contrast to 89% of the open group. However, the quality of the surgery was high, with 87% of laparoscopic TME's being complete, 93% of CRM negative and a clear DRM in 99%. The conversion from laparoscopic to open was only 9%. The authors concluded that there wasn't sufficient evidence for the routine incorporation of laparoscopic rectal surgery. The longer-term outcome measures are still awaited[17].

ACOSOG Z6051 was a similar study to ALaCaRT as it also evaluated the short term pathological outcomes using the composite outcome measures defined previously. It was a multicentre, randomised control trial that recruited 462 patients with clinical stage II or III rectal cancer (laparoscopic resection n = 240, open resection n = 222) from 35 institutions across the United States and Canada between October 2008 to September 2013. The only difference is that the ACOSOG Z6051 defined an acceptable TME as either complete or nearly complete (TME Grades 2 and 3) whereas the ALaCaRT trial only considered a complete TME (TME Grade 3) as successful. As with the ALaCaRT trial this multicentre trial failed to prove that laparoscopic rectal cancer was non-inferior to open rectal surgery. The results revealed 81.7% of laparoscopically resected specimens as compared to 86.9% of the open group were successful resections with respect to the composite pathological outcome measure. The conversion rate was only 11.3% which suggested the quality of surgical experience was high. The authors concluded that their findings did not support the use laparoscopic rectal resection[10].

The evidence from these landmark trials has highlighted the improvement in oncological outcomes as experience and expertise with laparoscopic rectal surgery increases.

LONGER TERM ONCOLOGICAL OUTCOMES FOR RECTAL SURGERY

At present, there is only limited published data available for the longer term oncological data that compares laparoscopic and open approaches to rectal cancer. Currently, available datasets include the 10-year data from the MRC CLASICC trial, the 3-year data from the COREAN and COLOR II trials. The initial 2-year longer term oncological outcomes are still awaited from ALaCaRT and ACOSOG Z6051 trials.

The MRC CLASICC trial has revealed quite promising outcomes in terms of locoregional recurrence, disease free survival and overall survival after 10 years. There was no difference in the overall survival, disease free survival or local recurrence on subgroup analysis. The median disease-free survival was 70.6 months (open 67.1 months, laparoscopic 70.8 months; $P = 0.925$) with the median overall survival being 73.6 months (65.8 months open group, 82.7 months laparoscopic group; $P = 0.147$)[19].

In the COREAN trial the 3-year disease free survival was 79.2% for laparoscopic surgery and 72.5% for the open resection group[20], which was not statistically significant. There was also no significant difference in the rates of local recurrence or overall survival (disease free survival $P = 0.34$). These results were similar to the results of the COLOR II trial in which 3-year disease free survival was 74.8% in the laparoscopic surgery group and 70.8% in the open group, which did not result in a statistically significant difference[18]. The 3-year overall survival of the laparoscopic and open TME groups was 86.7% and 83.6% respectively. This was not statistically significant. Both groups in the COLOR II trial had a 5% locoregional recurrence rate[18]. In both studies, the authors concluded that laparoscopic rectal surgery was comparable to that of the open resection group.

EVIDENCE FROM META-ANALYSES FOR RECTAL CANCER

The most recent meta-analysis was published by Arezzo *et al.*[30] in 2015. This included all RCTs and non-randomised control trials published between 2000 and 2013 (therefore not including the ALaCaRT and ACOSOG Z6051 trials). Their ultimate primary end point was CRM positivity, but they also analysed DRM, quality of TME and local recurrence at 5 years. Essentially this revealed no significant difference in any of these outcome measures. The authors concluded that there was some evidence to support laparoscopic rectal resection in terms of short term outcomes, pathological outcomes and longer-term outcomes[30].

Moreover, there was a Cochrane review article published in 2014 that evaluated the short and longer-term outcomes of laparoscopic and open rectal surgery. This review only reviewed RCTs. The conclusion was that there was moderate strength evidence to support laparoscopic resection. It revealed similar outcomes for disease free survival, overall survival and local recurrence. In addition, it also noted that there was a decrease in hospital length of stay and time to first defection in the laparoscopic resection group[1].

Even though the evidence is not considered to be as strong, the general impression is that laparoscopic rectal surgery is not non-inferior to open rectal resection.

SHIFTING OF FOCUS

Should the focus of these noninferiority studies shift focus from immediate oncologic analysis and focus more upon the long-term survival data? In an experienced surgeon's hands there appears to be a definite short-term benefit regarding reduced post-operative morbidity and hospital length of stay[29]. This cannot be accepted if the long-term survival data is not equivalent to that of the open surgical group.

Of note, there is overwhelming data supporting that there are improved outcomes with the increasing quality of TME excision. However, this evidence was collected in the open operation era. Is quality of the TME the only predictor in overall survival? Bouvy *et al.*[31] published an article in 1997 which suggested that laparoscopic surgery was associated with less tumour growth when compared to conventional open surgery because of the reduced operative trauma. They believed that reduced operative stress lead to decreased production of growth factors and therefore decreased stimulation of tumour cell growth[31]. More recently, endocrine and metabolic markers have been studied in attempt to quantify this operative stress. Human leukocyte antigen (HLA) and the pro-inflammatory marker interleukin 6 (IL-6) have been proposed potential surrogates to measure the surgical stress response. The evidence suggests that there is preserved immune function and less inflammation in laparoscopy as compared to the conventional open resections[32].

Could this be the reason that despite current trials being unable to show non-inferiority, early survival data appears equivalent? To answer this, we await the survival data from the more recent trials with great interest.

Should the next focus be more on the quality of the TME using minimally invasive techniques (robotics or trans-anal TME)? If we are currently obtaining equivalence in survival outcomes with lower grade TME quality, surely survival will improve with the development of higher quality minimally invasive TME.

Kim *et al.*[33] have recently published their experience with robotic TME. They retrospectively compared 732 patients (robotic n = 272; laparoscopic n = 460) aiming to evaluate the long term oncological outcomes between the robotic and laparoscopic TME. Ultimately, they were able to show that the overall 5-year survival for robotic TME and laparoscopic TME was 90.5% and 78% respectively, with the 5-year disease free survival being 72.6% and 68% respectively. Despite the limitations of this study, it does reveal that robotic TME may have a meaningful impact on long term outcomes (in regard to overall survival and disease free survival)[33]. Long-term oncological outcomes from the prospective trials Robotic versus Laparoscopic Resection for Rectal Cancer (ROLARR) and Comparison of Laparoscopic versus Robotic-Assisted Surgery for Rectal Cancer (COLRAR) trials are awaited.

CONCLUSION

Currently there is conflicting evidence for the role of laparoscopic TME for rectal cancer patients. The evidence from recent well executed RCTs would suggest that the short term oncological outcome of the laparoscopic TME has failed to reach noninferiority. The long-term survival data from the limited literature is promising and is showing equivalence between the 2 groups. However more evidence from recent trials needs to publish to further evaluate this.

It is our belief that in experienced hands laparoscopic rectal resection is not non-inferior but is equivalent to open resection. In saying this, it is important that whichever modality is chosen, that the surgeon is comfortable and well trained in that technique. Ultimately the quality of the surgery will facilitate the outcomes for the patient and hopefully the desired long-term outcome.

DECLARATIONS

Authors' contributions

Design, manuscript editing, manuscript revision: O'Donohue PF, Warren CD, Chow CFK
Literature research, data analysis, manuscript writing: O'Donohue PF, Warren CD

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