Minimally invasive versus open surgery for rectal cancer: An overview and current status

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Abstract
Introduction
Although large multicenter randomized controlled trials have shown no difference in long term disease free or overall survival between open and laparoscopic approaches for colon cancer, the same has not been uniformly appreciated for rectal cancer. Some of the main questions regarding the safety and efficacy of minimally invasive surgery for rectal cancer is whether an equivalent total mesorectal excision, lymphadenectomy, circumferential resection margin involvement, local recurrence, disease free survival, and overall survival can be obtained in comparison to conventional open surgery. Our aim was to systematically review the current randomized controlled trials in the literature comparing minimally invasive and open rectal cancer surgery.

Discussion
Studies reviewed in this paper revealed comparative oncologic results and outcomes, though most are single institution studies with small sample sizes, and long term outcomes are scarce.

Conclusions
Larger multi-institutional studies such as ASCOG Z6051 and COLOR II will help us answer the question regarding long term oncologic results in regards to minimally invasive surgery for rectal cancer. Until then, it is recommended that minimally invasive surgery for rectal cancer be conducted within a randomized controlled trial.

Introduction
Minimally invasive surgery for colon cancer, initially described in the early 1990’s, was slowly adopted with the impression that laparoscopic surgery would decrease adherence to oncologic principles, aerosolize cancer cells, as well as increase the risk for port site implants and thus recurrence.¹²,²³ As a result, a near complete moratorium on laparoscopic surgery for colon and rectal cancer was advocated by large societies until prospective randomized controlled trials (RCT’s) could be conducted.⁴

In the early 2000’s, large multicenter RCT’s revealed no difference in disease free or overall survival between open and laparoscopic approaches for colon cancer.⁵,⁶,⁷ Although these trials, among others, have demonstrated non-inferiority for short and long term outcomes for colon cancer, the same has not been uniformly appreciated for rectal cancer.

There are several considerations unique to rectal cancer surgery, and specifically a minimally invasive approach. Limited by the bony confines of the pelvis, and a narrow working space, the rectum is in close proximity to multiple vital structures (arteries, veins, nerves, genitourinary structures) and minimally invasive approaches for rectal cancer are technically difficult with a significant learning curve.⁸

Some of the main questions regarding the safety and efficacy of minimally invasive surgery for rectal cancer is whether an equivalent total mesorectal excision (TME), lymphadenectomy, circumferential resection margin (CRM) involvement, local recurrence (LR), disease free survival (DFS), and overall survival (OS) can be obtained in comparison to conventional open surgery. We have systematically reviewed the current RCT’s in the literature comparing minimally invasive and open rectal cancer surgery (Table 1).

Discussion
Oncologic Resection (Table 2)
Total Mesorectal Excision
Macroscopic completeness of the TME specimen was only described in two studies, and although not statistically significant it slightly favoured an open approach. Completeness ranged from 74.4 - 92% in open, compared to 72.4 - 88% in the minimally invasive groups.⁹,¹⁰

Lymph Node Retrieval
Most studies revealed no statistically significant difference between the numbers of lymph nodes removed between approaches.⁷,⁹,¹⁰,¹¹,¹²,¹³ Araujo et al. revealed significantly more lymph nodes removed with open surgery (11.9 vs 5.5, p=0.04), while Lujan et al. showed significantly less (11.57 vs 13.63, p=0.026).¹⁴,¹⁵

Circumferential Resection Margin
No statistically significant differences were found between open and minimally invasive approaches regarding CRM positivity. The majority of trials defined positivity as a margin of 1mm or less, while the COLOR II trial used a definition of 2mm or less. The CLASSIC trial noted a high rate of positivity for laparoscopic versus open resections (12 vs 6%), though not statistically significant (p=0.19), and no difference was appreciated regarding local recurrence or survival with the 5 year follow up.⁷,¹⁶ The COLOR II trial noted that in the subset of patients with rectal cancer located within 5 cm of the anal verge the rate of CRM positivity was lower in the laparoscopic group (9 vs 22%, p=0.014), which they postulated was the result of improved visualization with the laproscope. They revealed the inverse with mid...
rectal cancers with 10% of laparoscopic procedures having a positive margin compared to 3% of open cases, though not statistically significant (p=0.068).10

Short Term Outcomes (Table 3)

Operative Time
Laparoscopy was statistically significantly longer in all but one study and ranged from 120 - 262 minutes compared to 106 - 284 minutes in the open groups.7,9,10,11,12,13,15,17 Araujo et al. reported a statistically significant shorter operative time in the laparoscopic group (228 min vs 284 min, p=0.04), and attributed the difference to numerous teams performing open surgery, while only one team performed minimally invasive resections.14

Conversion Rate
Conversion rates ranged from 0% to 34%, although the definition of conversion is not standardized, which makes comparisons amongst trials difficult.7,9,10,11,12,13,14,15 The CLASICC trial was the first multicenter RCT comparing open and laparoscopic resection for rectal cancer, with the highest documented conversion rate of 34%. Converted patients had trends towards higher morbidity (37%, 32%, 59% for open, laparoscopic, converted, p=0.78) and mortality (5%, 1%, 9% for open, laparoscopic, converted, p=0.34).7

Even with higher morbidity and mortality, DFS was not significantly different. More recent multicenter RCT's reported fewer conversions. The COLOR II and COREAN trials showed conversion rates of 16% and 1.2%, respectively, which may be the result of improved techniques and experience, surgical volume, preoperative evaluation, and more modern equipment.9,10

Unlike the CLASICC trial, the COLOR II and COREAN trials utilized preoperative imaging to evaluate depth of invasion. The most common reason for conversion in the CLASICC trial was tumour extension. The conversion rate in the CLASICC trial decreased from 38% in year one to 16% by year 6, suggesting a learning curve.7

The CLASICC study required surgeons to perform 20 laparoscopic cases prior to participation, while the COLOR II and COREAN trials had more stringent requirements. In the COLOR II trial, surgeons wishing to participate were required to submit 5 unedited videos of laparoscopic total mesorectal excisions for review, or were observed by one of the 5 “governors.”

The COREAN trial required video recordings, which were reviewed by the study’s committee. Seven surgeons at three high volume hospitals performed the rectal resections in the COREAN study, with a median experience of 75 laparoscopic colorectal resections among the surgeons before the trial.7,9,10

Blood Loss
Blood loss ranged from 20 - 321mL with the laparoscopic approach, compared to 92 - 555.6mL with open surgery.7,9,10,11,12,13,14,15,17 Blood loss was statistically significantly less for the laparoscopic approach in all studies except for one.7,9,10,11,12,14,15,17 Ng et al. showed no difference with a loss of 280mL in the laparoscopic group and 337.3mL in the open group (p=0.338).13

Leak Rate
Leak rates were comparable between open and minimally invasive approaches and ranged from 1.2 - 13% in the laparoscopic groups and 0 - 12% in the open groups.7,9,10,11,13,15,17

Morbidity and Mortality
Morbidity and mortality were similar between surgical approaches, although trials did not use uniform criteria to define morbidity. Morbidity ranged from 12.4 - 52.1% for open, and 6.1 - 69% in the minimally invasive groups.7,9,10,11,12,13,14,15,17

One study reported a statistically significant lower morbidity in the laparoscopic group (6.1% vs. 12.4%, p<0.05).17 Mortality ranged from 0 - 5% with open surgery compared to 0 - 4% for minimally invasive approaches.

Length of Stay
As a result of earlier return of bowel function, ambulation, tolerability of diet, and better pain control, most studies revealed a statistically significant shorter length of stay for the minimally invasive (8 - 10.8 days) compared to the open (9 - 13.6 days) groups.7,10,11,13,17 Araujo et al. reported an average length of stay of 10.5 days in the laparoscopic group and <10.5 days in the open group.14 Three studies showed no difference.9,12,15

Long Term Outcomes (Table 4)

Local Recurrence
Three studies looked at LR in abdominoperineal resections (APR). Araujo et al. reported a LR of 13.3% with open APR, and 0% laparoscopically, after an average follow up of 47.2 months.14 Ng et al. revealed LR was 5% in the minimally invasive and 11.1% in the open group, over an average follow up of 87.2 and 90.1 months, respectively.15 The 3-year data from the CLASICC trial showed a LR of 21.1% with open APR and 15.1% with laparoscopic APR, though LR was not presented in the 5-year follow up study.16,18 Local recurrence with open low anterior resections (LAR) ranged from 4.9 - 7.6% and 2.9 - 9.4% for laparoscopic approaches.11,13,15,16,18,19 No study reported a statistically significant difference.

Disease Free Survival
DFS at five years in the CLASICC trial for open LAR was 57.6%, and 57.7% for laparoscopic. DFS for APR was 36.2% with open cases, and 41.4% laparoscopically.16 These are lower rates compared to other studies as shown in table 4. Lujan et al. reported a DFS of 81% with an open approach and 84.8% laparoscopically, over an average follow up of 34.1 and 32.8 months, respectively.15 These were similar to the 10-year data presented by Ng et al., which showed open and laparoscopic DFS of 80.4% and 82.9%, respectively.13

Overall Survival
The COREAN study reported high overall survival at three years for both open and laparoscopic surgery.

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The open approach had an OS of 90.4%, and 91.7% laparoscopically. This study was conducted between seven surgeons experienced in laparoscopic surgery for rectal cancer at three high volume centres. All patients received neoadjuvant chemoradiotherapy (CRT) and underwent CT, MRI, and endorectal ultrasound, which may explain the improved survival.\textsuperscript{19} The use of neoadjuvant CRT was variable between studies. In studies that utilized neoadjuvant CRT there was no statistically significant difference between laparoscopic and open approaches.\textsuperscript{9,10,11,12,14,15} The 5-year OS from the CLASICC study was 56.7% for open resection and 62.8% laparoscopically. There was a significantly worse outcome for patients who were converted from a laparoscopic to an open approach. The overall survival for those converted was 49.6 %, compared to 58.5% and 62.4% for the open and laparoscopic groups, respectively (p=0.005).\textsuperscript{16} The 10-year OS data from Ng et al. was comparable to the CLASICC trial. The 5-year data presented by Lujan et al. was

### Table 1: Study and Patient Demographic Information.

<table>
<thead>
<tr>
<th>Author / Trial</th>
<th>Year</th>
<th>Country</th>
<th>Study Type</th>
<th>Neoadjuvant CRT (%)</th>
<th>Surgical Approach</th>
<th>Gender (# male and % total)</th>
<th>Age (mean)</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Araujo et al.</td>
<td>2003</td>
<td>Brazil</td>
<td>RCT Single Center</td>
<td>Open – 100 Lap – 100</td>
<td>Open – 15 Lap – 13</td>
<td>Open (10, 67%) Lap (9, 69%)</td>
<td>Open – 56.4 Lap – 59.1</td>
<td>Open – 25.6 Lap – 23.5</td>
</tr>
<tr>
<td>Guilhou et al.</td>
<td>2005</td>
<td>United Kingdom (Multi-institutional)</td>
<td>RCT Multi-center</td>
<td>Open – 268 Lap – 526</td>
<td>Open (145, 54%) Lap (296, 56%)</td>
<td>Open – 69 Lap – 69</td>
<td>Open – 26 Lap – 25</td>
<td></td>
</tr>
<tr>
<td>Braga et al.</td>
<td>2007</td>
<td>Italy</td>
<td>RCT Single Center</td>
<td>Open – 14.1 Lap – 16.9</td>
<td>Open – 85 Lap – 83</td>
<td>Open (64, 75%) Lap (55, 66%)</td>
<td>Open – 62.8 Lap – 65.3</td>
<td>Open – NR Lap – NR</td>
</tr>
<tr>
<td>Jayne et al.</td>
<td>2007</td>
<td></td>
<td>RCT Single Center</td>
<td>Open – 0 Lap - 0</td>
<td>Open – 48 Lap – 51</td>
<td>Open (30, 63%) Lap (31, 61%)</td>
<td>Open – 63.5 Lap – 63.7</td>
<td>Open – NR Lap – NR</td>
</tr>
<tr>
<td>Ng et al.</td>
<td>2008</td>
<td>China</td>
<td>RCT Single Center</td>
<td>Open – 74.8 Lap – 72.3</td>
<td>Open – 103 Lap – 101</td>
<td>Open (64, 62%) Lap (62, 61%)</td>
<td>Open – 66 Lap – 67.8</td>
<td>Open – NR Lap – NR</td>
</tr>
<tr>
<td>Lujan et al.</td>
<td>2009</td>
<td>Spain</td>
<td>RCT Single Center</td>
<td>Open – 57 Lap – 76</td>
<td>Open (48, 62%) Lap (37, 48%)</td>
<td>Open – 65.7 Lap – 66.5</td>
<td>Open – NR Lap – NR</td>
<td></td>
</tr>
<tr>
<td>Ng et al.</td>
<td>2009</td>
<td>China</td>
<td>RCT Single Center</td>
<td>Open – 77 Lap – 76</td>
<td>Open (48, 62%) Lap (37, 48%)</td>
<td>Open – 65.7 Lap – 66.5</td>
<td>Open – NR Lap – NR</td>
<td></td>
</tr>
<tr>
<td>Kang et al.</td>
<td>2010</td>
<td>South Korea</td>
<td>RCT Multi-center</td>
<td>Open – 100 Lap – 100</td>
<td>Open – 170 Lap – 170</td>
<td>Open (110, 65%) Lap (110, 65%)</td>
<td>Open – 59.1 Lap – 57.8</td>
<td>Open – 24.1 Lap – 24.1</td>
</tr>
<tr>
<td>Van der Pas et al. COLOR II</td>
<td>2013</td>
<td>Europe (Multi-institutional)</td>
<td>RCT Multi-center</td>
<td>Open – 34, 58&quot; Lap – 32,59</td>
<td>Open – 345 Lap – 699</td>
<td>Open (211, 61%) Lap (448, 64%)</td>
<td>Open – 65.8 Lap – 66.8</td>
<td>Open – 26.5 Lap – 26.1</td>
</tr>
</tbody>
</table>

BMI – Body Mass Index, CRT – Chemoradiotherapy, Lap – Laparoscopic, NR – Not Recorded, RCT – Randomized Controlled Trial
**++* denotes both colon and rectal cases**
slightly higher at 75.3% for open, and 72.1% laparoscopically. There was no difference in OS between approaches.

**Costs**
In comparison to open, laparoscopic surgery is more expensive. Braga et al. revealed a decrease in length of stay and fewer postoperative complications, which resulted in a savings of $1,396 per laparoscopic surgery. However, operating room charges were $1,748 more, which resulted in an added expense of $351 per patient for a minimally invasive approach. Ng et al. also published similar results showing the cost of laparoscopic surgery was significantly greater than open ($9,588 vs $7,517, p<0.001).

**Future Studies**
To date randomized controlled trials have shown equivalent short-term outcomes with minimally invasive surgery for rectal cancer. Sample sizes in these studies are small and lack long term outcomes. Minimally invasive surgery for rectal cancer is still considered investigational and larger randomized trials with long term outcomes are needed to confirm oncologic safety. Trials in progress include COLOR II and The American College of Surgeons Oncology Group (ACOSOG) Z6051.

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The COLOR II trial is a multi-institutional European RCT evaluating outcomes for resectable rectal cancer located within 15cm of the anal verge. Short term outcomes have been reported revealing no significant difference, but three-year survival data is still pending.

ACOSOG Z6051 is an American multi-institutional prospective RCT comparing laparoscopic and open resection for rectal cancer located within 12cm of the anal verge. Pilot study results revealed equivalent oncologic and perioperative outcomes, though long term results have not been published.20

### Conclusion

The aim of our study was to systematically review all RCT's in the literature comparing minimally invasive and open surgery for rectal cancer in regards to short and long term outcomes.

Although studies reviewed in this paper show comparative oncologic results and outcomes, most are single institution studies with small sample sizes, and long term outcomes are scarce. Larger multi-institutional studies such as ASCOG Z6051 and COLOR II will help us answer the question regarding long term oncologic results. Until then it is recommended that minimally invasive surgery for rectal cancer be conducted within a randomized controlled trial.

### References

10. Van der Pas MHGM, Haglind E, Cuesta MA, et al. Laparoscopic versus


