Is Laparoscopic Surgery the Standard of Care for GI Luminal Cancer?

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Abstract As surgeons in India strive to keep pace with the technical advances in the field of laparoscopic surgery, we endeavor to evaluate the mounting global evidence regarding laparoscopic gastric and colorectal resections for cancer. We seem to be riding on the crest of excellence in traditional open surgery for gastrointestinal malignancies, opening avenues for research and for the establishment of practice guidelines in laparoscopic surgery. Results from available trials along with those from ongoing studies are paving the path toward the acceptance and standardization of these procedures. What must be ascertained is whether sound oncological principles, which are ultimately exhibited by long-term outcomes, are being preserved while garnering the established benefits of minimally invasive surgery.

Keywords Laparoscopic surgery · GI cancer · Gastric cancer · Colorectal cancer

Introduction

Minimal access surgery has firmly grown roots in almost every sphere of surgery, finding increasing application for

over three decades now. Gastrointestinal (GI) surgery is no exception. Series abound describing innovative laparoscopic techniques, which are feasible and reproducible, providing superior immediate postoperative outcomes with undoubted cosmetic supremacy. Arguably, the primary point of contention for laparoscopic surgery in GI cancers remains whether outcomes demonstrating oncological superiority can be ascertained, based primarily on long-term overall and disease-free survival. As substantial evidence accumulates validating oncological equivalence particularly in colon and early gastric cancers [1–6], we await results of other trials which may more convincingly demonstrate similar outcomes in rectal [7–9] and advanced gastric cancers [10].

Technical advancement in open surgery for GI cancers has plateaued, causing the unit comprising both the surgeon and the patient to focus on more alluring minimally invasive methodologies. But is this impetus justified in cancer patients in whom the goals following surgery are more farsighted? This, along with actualities such as the prolonged learning curve associated with advanced laparoscopic surgery together with early reports of port-site metastases following curative laparoscopic cancer surgery [11], has decelerated the hasty acceptance of these procedures. Many acclaimed surgeons remain content to offer first-rate open surgery, claiming to have achieved maximal stage-by-stage survival rates [12]. A few determined laparoscopic surgeons, after refining their skills coupled with the assistance of new stapling devices and vessel sealing systems, have come a long way in the arduous task of convincing experts of being able to produce results similar to contemporary open surgery [13].

In this article, we deliberate the growing evidence available and forthcoming trials regarding minimally invasive GI cancer surgery and whether its potential to become the standard of care is, or can ever be, realized. The discussion will be restricted to laparoscopic surgery for gastric and colorectal cancer.

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Laparoscopic Resection for Gastric Cancer

Since gastric cancer is the most common malignant GI tumor in Far East Asian countries, it is no surprise that the path of laparoscopic surgery for this cancer was trail-blazed by Japanese surgeons. Kitano et al. [14] first described laparoscopy-assisted distal gastrectomy (LADG) with lymph node dissection in 1994. As the detection of early gastric cancer increased in the 1990s, along with LADG, procedures such as laparoscopic gastric wedge resection [15] and laparoscopic intragastric mucosal resection [16] were also developed. The latter procedures which do not involve lymph node dissection have been increasingly replaced by endoscopic treatment procedures such as endoscopic mucosal resection and endoscopic submucosal dissection [17] in non-ulcerated, mucosal tumors <2 cm in diameter.

Laparoscopy-Assisted Distal Gastrectomy

Initial studies have focused on laparoscopic resection for distal early gastric cancers [18, 19]. Usually, these included mucosal cancers which were ulcerated, or ≥ 2 –4 cm in diameter, and submucosal cancers. A limited (D1) lymph node dissection was considered sufficient for such tumors [20]. For more advanced tumors, a D1 +, or D2 dissection was proposed to be more appropriate, although the extent of lymph node dissection in gastric cancer continues to remain an issue of international debate [21–23].

In Japan, LADG is performed in 25 % of patients with gastric cancer. With the standardization of LADG practices and the refinement of laparoscopic expertise among surgeons, the 10th Japanese National Survey reported a reduced intraoperative and postoperative complication rate of 1.1 and 7.5 %, respectively. The more frequent intraoperative complications were bleeding and injury to other organs, while anastomotic stenosis and leakage were the more common postoperative complications [24].

Short-term outcomes after LADG are reported in numerous randomized and nonrandomized studies, which have been extensively analyzed in eight meta-analyses [5, 6, 25–30] in English literature. There are currently six randomized trials [31–36] of which results are available comparing LADG with open distal gastrectomy (ODG) (Table 1). The quality of these trials is rather mixed, the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) [32] being the only multicenter study with a large sample size. This data collectively demonstrates that LADG can be safely performed with less blood loss with a longer operating time. Although not statistically significant, the complication rate after LADG seems to be lower than ODG. The quality of lymphadenectomy in terms of lymph node yield appears to be inferior by the laparoscopic approach. This contradicts apparently biased nonrandomized reports [37–39]. Individual randomized reports also demonstrated advantages of LADG such as earlier

recovery of intestinal movement, lower analgesic requirement, shorter hospital stay, and lesser extent of impaired respiratory function [32, 34, 35].

Long-term outcomes are not as abundant. Four nonrandomized trials [40–43] and one randomized trial [31] report 5-year survival rates (Table 2). The largest retrospective study including 1,185 patients reported an estimated 5-year disease-free survival rate of 99.8 % for stage IA, 98.7 % for stage IB, and 85.7 % for stage II cancers. This results suggesting non-inferiority of the laparoscopic approach were reiterated by other three nonrandomized studies. The lone randomized study by Huscher et al. [31] also showed no difference in the 5-year disease-free survival rate between patients who underwent either procedure.

Future Perspectives

There is an obvious dearth in long-term oncological data, limiting the establishment of laparoscopic surgery as a standard for gastric cancer treatment, even for early-stage cancers. The revised 2010 version of the Japanese Gastric Cancer Treatment Guidelines also classifies LADG as an investigational procedure to be used for stage IA and IB cancers only [44]. This apparent void has, however, propelled ongoing randomized trials which are expected to provide more concrete evidence regarding long-term oncological outcomes. One such multi-institutional randomized phase III study has commenced in Japan (JCOG0912) [45] in March 2010, following a similar phase II study [46]. It is expected to accrue 920 patients in 5 years, with the primary end point being overall survival. Another ongoing randomized phase II trial (LANDSCOPE) [10] is incorporating neoadjuvant chemotherapy, which is widely practiced in the West.

Technical advancements in laparoscopic gastrectomy are developing in mainly two areas: proximal cancers and advanced gastric cancer, entailing expanded gastric resection and lymph node dissection. A review of three randomized and six nonrandomized trials comparing laparoscopy-assisted total gastrectomy with open total gastrectomy shows equivalent lymph node dissection between the two procedures, with less postoperative pain, faster recovery, and fewer complications experienced with the laparoscopic approach [47]. A recent Italian nonrandomized study involved laparoscopic resection of more advanced cancers and has shown equivalent results [48]. Less invasive techniques such as single-port surgery, natural orifice transabdominal endoscopic surgery (NOTES), and robotic surgery are also developing fast in this field.

Laparoscopic Gastrectomy: the Standard of Care?

No doubt, the overwhelming majority of gathered evidence is from East Asian countries with little contribution from the

Table 1 Short-term outcomes from randomized trials: laparoscopy-assisted distal gastrectomy (LADG) vs. open distal gastrectomy (ODG)

First author	Year	Country	Number of patients		Mean blood loss (ml)*		Mean operating time (min)*		Mean lymph node yield*		Morbidity (events)**		Mortality (events)***	
			LADG	ODG	LADG	ODG	LADG	ODG	LADG	ODG	LADG	ODG	LADG	ODG
Kitano [35]	2002	Japan	14	14	117	258	227	171	20.2	24.9	2 (14.3 %)	4 (28.6 %)	0	0
Lee [33]	2005	Korea	24	23	336	294	320	190	31.8	38.1	3 (12.5 %)	10 (43.5 %)	0	0
Hayashi [36]	2005	Japan	14	14	327	489	348	235	28	27	2 (14.3 %)	6 (42.9 %)	0	0
Huscher [31]	2005	Italy	30	29	229	391	196	168	30	33.4	8 (26.7 %)	9 (31 %)	1 (3.3 %)	2 (6.9 %)
Kim [34]	2008	Korea	82	82	112	258	253	171	39	45.1	0	4 (4.9 %)	0	0
Kim [32]	2010	Korea	179	161	109	200	NA	NA	NA	NA	17 (9.5 %)	24 (14.9 %)	2 (1.1 %)	0

NA not available

* $p < 0.00001$; ** $p < 0.003$; *** $p = 0.86$ (test for overall effect)

West. Differences in the management of this disease type between the East and the West will have to be taken into account, especially when the administration of neoadjuvant chemotherapy is in question. Also, the results from these trials involving mainly early gastric cancer may not be relevant in the West as well as in India, where more advanced cancers are more commonly encountered. The first large Indian series regarding open D2 gastrectomy [49] in the pre-neoadjuvant era from our institution has contributed to the better understanding of the surgical outcomes of this cancer type and has allowed for standardization of this procedure in our country. Later, outcomes in the neoadjuvant era were also evaluated to validate standard surgical practices for gastric cancer in our country [50]. LADG is at its infancy in our institution, and thus far, results from our laparoscopic series parallel those of our open surgery. We hope to generate and make available more data on this front in the coming year which will provide further insight regarding the feasibility of LADG in selected patients who are treated at a specialized center in India, with its unique disease spectrum and logistic constraints. Finally, all trials emphasize that surgeons performing these operations should be adequately trained and credentialed, preferably in high-volume centers. This fact should not be overlooked when efforts are made to implement these procedures locally, even if further evidence supports routine laparoscopic resection for gastric cancer. At present, we are still a fair distance away from incorporating laparoscopic gastric cancer resections as the standard of care, even more so in our part of the world.

Laparoscopic Resection for Colorectal Cancer

Just as evidence from stomach cancer has accumulated from the East, we depend predominantly on the Western

Hemisphere for substantiation of advances in colorectal surgery where colorectal cancer is one of the more common malignancies. Major advances in adjuvant and neoadjuvant therapy have not changed the fact that curative treatment is based on radical oncologic resection of the bowel segment bearing the tumor along with sufficient resection margins and regional lymph nodes. Laparoscopic colorectal surgery has been dramatically evolving since the first reported series of laparoscopic colonic resections by Jacobs et al. [51] in 1991. In order to gain universal acceptance, this novel surgical technology must be demonstrated to achieve superior, or at minimum, parallel survival outcomes when compared to that of time-tested open surgery.

Unlike those for gastric cancer, several large multicenter randomized controlled trials have been conducted regarding laparoscopic colorectal resections for cancer, many of which now have reported long-term outcomes. In a recent meta-analysis [13] regarding laparoscopic colorectal cancer surgery, 414 review articles and 39 trials were identified from the literature, 24 of which were randomized trials. Laparoscopy-assisted colon cancer surgery has been considered non-inferior to open surgery since 2004. Laparoscopic surgery for rectal cancer is more controversial, but has been increasingly accepted since 2006. Expectedly, minimally invasive surgery for colorectal cancer is being more commonly performed worldwide. We will primarily discuss evidence from major multicenter randomized trials and its implications.

Colon Cancer

Initial studies on laparoscopic colorectal surgery dealt exclusively with colonic surgery since surgical techniques for laparoscopic rectal surgery were developed later. Logically, long-term survival data for laparoscopic colonic surgery is more readily available, constantly demonstrating oncological non-inferiority to open surgery.

Table 2 Long-term outcomes from large randomized trials: laparoscopy-assisted colonic resections vs. open colonic resections for cancer

Study	Year (follow-up)	Number of patients analyzed		Median follow-up period (months)	Number of patients disease-free at maximum follow-up		5-year disease-free survival		Number of patients surviving at maximum follow-up		5-year overall survival	
		Total	Open		Lap	Open	Lap	Open	Lap	Open	Lap	Open
COST [2]	2007	863	435	428	51	335/428	69.2 %	68.4 %	333/435	320/428	76.4 %	74.6 %
Barcelona [3]	2008	208	106	102	95	73/102	NA	NA	68/106	52/102	NA	NA
COLOR [53]	2009	1,076	534	542	53	429/534	66.5 %	67.9 %	406/534	417/542	73.8 %	74.2 %
CLASICC [1] (includes rectal cancer patients)	2013	794	526	268	62.9	160/212	(Median in months) 77.0; colon 86.6; rectum 70.8	(Median in months) 89.5; colon 106.6; rectum 67.1	242/526	124/268	(Median in months) 82.7; colon 81.9; rectum 82.7	(Median in months) 78.3; colon 105.7; rectum 65.8

No long-term survival differences between laparoscopic and open surgery attained statistical significance. The Barcelona study showed trends toward a survival benefit in the laparoscopic group
Lap laparoscopic, NA not available

COST Trial

The Clinical Outcomes of Surgical Therapy Study Group [4] in North America conducted a multicenter randomized non-inferiority trial. The primary end point was time to tumor recurrence. After exclusion, 863 patients who underwent surgery by credentialed surgeons were included in the final analysis who were divided in two groups: the laparoscopic arm ($n=435$) and the open arm ($n=428$). There was a conversion rate of 21 %.

The laparoscopic group experienced significantly longer operating times but had a faster postoperative recovery reflected by a shorter hospital stay, and decreased requirement of analgesics. The extent of resection including bowel margins and lymph node yield (median=12) was similar in both groups. The morbidity and mortality rates were also comparable.

With a median follow-up of 4.4 years, the 3-year recurrence rate was 16 % in the laparoscopic group and 18 % in the open surgery group. The 3-year overall survival rate was also very similar in both arms: 86 % in the laparoscopic group and 85 % in the open surgery group. There were therefore no significant differences between groups with regard to time to recurrence, disease-free survival, or overall survival for any stage of cancer.

The authors concluded that since recurrence rates are similar with no significant added morbidity, laparoscopy-assisted colectomy is a safe and acceptable alternative to open surgery for colon cancer.

COLOR Trial

The Colon Cancer Laparoscopic or Open Resection (COLOR) trial [52] was a European multicenter study. After randomization, 172 patients were excluded mainly due to the presence of distant metastasis or benign disease, leaving 1,076 patients with colon cancer eligible for analysis. The two arms were the laparoscopic group ($n=534$) and the open group ($n=542$); the study showed a conversion rate to open surgery of 17 %. The study was statistically designed for non-inferiority.

Short-term outcomes were predictable; the laparoscopic arm having lesser blood loss, earlier recovery of bowel function, fewer analgesic requirements, and shorter hospital stay while requiring longer operating times. The number of lymph nodes resected, the R-status, morbidity rates, and mortality rates were comparable. The study reported a median follow-up of 53 months. The 3-year disease-free survival and 3-year overall survival combined for all stages was 74.2 and 81.8 %, respectively, in the laparoscopic arm, and 76.2 and 84.2 %, respectively, in the open surgery arm which did not show a statistically significant difference [53].

Limitations of the study to be pointed out are the less-than-desirable average number of lymph nodes resected of 10 per

patient, a relatively high conversion rate, and the exclusion of obese patients with a BMI > 30 kg/m². Nevertheless, these results prompted the authors to conclude that laparoscopic surgery can be safely performed in patients with colon cancer.

MRC CLASICC Trial

The Medical Research Council Conventional vs Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trial [54] was a British multicenter trial which randomized 794 patients with colon and rectal cancer to undergo laparoscopic resection ($n=526$) or open resection ($n=268$) with a 2:1 ratio. The trial standardized pathological reporting, and all resected specimens were centrally reviewed. This included 421 patients with colon cancer. There was a 25 % conversion rate for laparoscopic colectomy. Converted patients experienced higher complication rates.

In-hospital mortality and quality of life were similar in both groups. There were no significant differences in 3-year [55] and 5-year [56] disease-free and overall survival between both groups. In 2006, the National Institute for Health and Clinical Excellence modified its guidelines to state “laparoscopic resection is recommended as an alternative to open resection in individuals with colorectal cancer in whom both laparoscopic and open surgeries are considered suitable.”

A recent update [1] of the long-term follow-up (median follow-up 62.9 months) revealed no statistically significant difference in disease-free and overall survival between the laparoscopic group (77 and 82.7 months, respectively) and the open group (89.5 and 78.3 months, respectively). These results continue to support the use of laparoscopic surgery for both colonic and rectal cancers.

Other Randomized Trials and Meta-Analyses

The LAPKON II trial [57] was a German multicenter randomized study including patients with colonic and upper rectal cancers. The long-term results of this study are awaited. The only statistically significant difference between the laparoscopic group and the open surgery group was the higher reoperation rate for postoperative adhesive bowel obstruction in the laparoscopic group.

One randomized trial has shown trends toward an oncological advantage with laparoscopic colon cancer surgery [58]. Although not statistically significant, there was a superior disease-free survival in the laparoscopic arm at a median follow-up of 95 months [3]. The study, however, reported an unacceptably high overall local recurrence rate.

Several meta-analyses [59–61] and a Cochrane review [62] on laparoscopic colonic resections almost unanimously conclude that under traditional perioperative treatment, laparoscopic colonic resection shows clinically relevant advantages

in selected patients. Another Cochrane review [63] analyzing long-term results from 12 trials involving laparoscopic colorectal cancer resections concluded that there was no difference in short-term and oncological long-term outcomes when laparoscopic surgery was compared to the open method. Thus, recent studies have consistently maintained the oncological equivalence of laparoscopic colonic surgery.

Rectal Cancer

Laparoscopic rectal surgery is steeped with pitfalls such as difficult, deep pelvic dissection and the precarious application of staples at the distal rectum. Reassuringly, potential benefits include improved optics and magnification along with the pneumoperitoneum aiding in the planar dissection. The most important concern is whether laparoscopic rectal surgery can render a proper total mesorectal excision (TME) which forms the basis for well-done rectal surgery and, therefore, acceptable oncological outcomes. The first randomized trial [64], although criticized to be underpowered, demonstrated equivalent short-term outcomes after laparoscopic rectal surgery when compared to open rectal resection. Laparoscopy for rectal cancer experienced a relatively delayed commencement, with results from high-quality studies only recently being realized.

MRC CLASICC Trial

This previously mentioned study included 373 patients with rectal cancer [54]. A high conversion rate of 34 % was observed among these patients who, once converted, experience a significantly higher postoperative complication rate. In patients who underwent anterior resection, the circumferential resection margin involvement was non-significantly increased in the laparoscopy arm when compared to the open arm (12.4 vs 6.3 %). The local recurrence rate was 9.4 % in the laparoscopic arm and 7.6 % in the open resection arm which was not significant different. The 5-year overall survival was 62.8 % after laparoscopic anterior resection compared to 56.7 % after open surgery. After abdominoperineal resection, the 5-year overall survival was 53.2 % in the laparoscopic group and 41.8 % in the open group.

For all rectal cancers, the 5-year disease-free survival was comparable between the laparoscopic and the open arms (53.2 vs 52.1 %) and between the extent of resection (anterior resection or abdominoperineal resection). The 5-year overall survival for rectal cancers as a whole was 60.3 % in the laparoscopic arm and 52.9 % in the open arm, which is encouraging. The recently published long-term results also confirm the oncological safety of laparoscopic surgery for rectal cancer in addition to colon cancer.

COREAN Trial

The Comparison of Open vs Laparoscopic Surgery for Mid and Low Rectal Cancer after Neoadjuvant Chemoradiotherapy (COREAN) trial [8] was the first multicenter randomized trial to incorporate preoperative chemoradiation. Three hundred forty patients with tumors <9 cm from the anal verge were randomized to undergo either laparoscopic or open surgery by experience colorectal surgeons. There was an exceptionally low conversion rate of 1.2 %.

Short-term results were comparable between the laparoscopic and open groups. This included circumferential resection margin involvement, quality of TME, lymph node yield, morbidity rates, and mortality rates. This trial also described a better quality of life and micturition function in the laparoscopic arm 3 months after surgery.

The authors concluded that laparoscopic surgery for mid and low rectal tumors following neoadjuvant chemoradiotherapy is feasible and does not increase short-term oncological risk. They did not, however, advocate routine laparoscopic rectal resection.

The limitations of this study were pointed out by the senior author of this paper [65], who noted that the key to the success of this trial was meticulous case selection with a low body mass index (BMI). Laparoscopic surgery, on the other hand, claims to greater benefit obese patients. Further progress in this avenue is due.

Other Important Trials

A recently published randomized trial involving 80 patients from Hong Kong compared laparoscopically assisted rectal surgery with open surgery for mid and low rectal cancers which underwent sphincter preservation surgery [9]. Postoperative recovery was significantly better in the laparoscopic arm. There were similar short-term outcomes in both arms. The projected 5-year disease-free and overall survivals were not significantly different after laparoscopic and open surgery.

The recent non-inferiority multicenter phase III trial (COLOR II) [7] analyzed 1,044 patients after exclusion. Short-term results demonstrate that laparoscopic surgery for rectal cancer within 15 cm from the anal verge, when performed by skilled surgeons, can result in similar safety, resection margins, and completeness of resection as open surgery, with improved postoperative recovery. Results for the primary end point (locoregional recurrence) are expected shortly.

We published our early series of 59 laparoscopic abdominoperineal resections from India [66]. Laparoscopic colorectal work has progressed since then with 81 elective colorectal resections over the last two and a half years. Rectal

resections comprise the majority of our work (80 %) with nearly 80 % of these presenting with locally advanced disease requiring neoadjuvant chemoradiation. Our mean operative times (colon, 140 min; rectum, 220 min), though longer than open surgery, compare well with operative times from published randomized trials [4, 8, 52, 54]. Oncological outcomes in terms of margin positivity (CRM positivity 4.7 %—all margins threatened on preoperative imaging) and lymph node yield (colon, 20.8; rectum, 11.3) are also favorable. This is comparable with results from our own series of open colorectal resections [67]. The conversion rate, though 36.4 % in 2010, has shown a steady decline to 14.3 % in 2013. We have had no mortality in this case series, and morbidity has been minor and largely self-limiting. With the recent acquisition of additional instrumentation, it is expected that laparoscopy will soon be at par with open surgery for colorectal cancer at our institution.

Future Perspectives

Studies incorporating enhanced recovery programs and fast-track surgery with laparoscopic surgery for colorectal cancers are underway [68, 69] and promise to further improve short-term results. Long-term results from trials, which have reported short-term results, are soon going to be available to strengthen the evidence regarding laparoscopic colorectal surgery. More multicenter randomized trials with convincing long-term oncological outcomes possibly designed for superiority of laparoscopic surgery are in order, especially for laparoscopic rectal cancer surgery.

Laparoscopic Colorectal Surgery: the Standard of Care?

Most important trials regarding laparoscopic colorectal surgery have been designed for non-inferiority. Therefore, proving that laparoscopic surgery is superior in the setting of cancer is difficult. On the contrary, with the high conversion rate described in trials, particularly for rectal cancer, the outcomes of these converted patients may be even worse than that of patients who undergo open surgery initially. Also, studies have recruited selected patients with colorectal cancer with favorable characteristics while implementing extensive exclusion criteria. Results, therefore, cannot be interpreted in the broader perspective of looking at laparoscopic colorectal surgery as a universal standard. We can therefore conclude that currently, with the available evidence, laparoscopic surgery for colorectal cancers can be considered only a reasonable alternative surgical technique for a selected group of patients in the hands of experienced surgeons. It is not hard to imagine that laparoscopic colorectal surgery might yet prove to be the standard in the not-so-distant future; therefore, further trials toward this end should, by no means, be discouraged.

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Conflict of Interest None

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