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TOPIC HIGHLIGHT

2016 Laparoscopic Surgery: Global view

Laparoscopic gastric cancer surgery: Current evidence and future perspectives

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Abstract

Laparoscopic gastrectomy has been widely accepted as a standard alternative for the treatment of early-stage gastric adenocarcinoma because of its favorable short-term outcomes. Although controversies exist, such as establishing clear indications, proper preoperative staging, and oncologic safety, experienced surgeons and institutions have applied this approach, along with various types of function-preserving surgery, for the treatment of advanced gastric cancer. With technical advancement and the advent of state-of-the-art instruments, indications for laparoscopic gastrectomy are expected to expand as far as locally advanced gastric cancer. Laparoscopic gastrectomy appears to be promising; however, scientific evidence necessary to generalize this approach to a standard treatment for all relevant patients and care providers remains to be gathered. Several multicenter, prospective randomized trials in high-incidence countries are ongoing, and results from these trials will highlight the short- and long-term outcomes of the approach. In this review, we describe up-to-date findings and critical issues regarding laparoscopic gastrectomy for gastric cancer.

Key words: Gastrectomy; Laparoscopic resection; Early gastric cancer; Stomach neoplasms; Advanced gastric cancer; Minimally invasive surgery

Core tip: Laparoscopic gastrectomy has been widely accepted as a standard alternative to open gastrectomy for the treatment of early gastric cancer. Its clinical indications are expanding to include more

extensive surgeries along with more sophisticated conserving or function-preserving surgeries. Although some controversies limit extensive application of the procedure, including a lack of evidence of oncologic safety and discrepancy between high- and low-incidence countries, laparoscopic gastrectomy for gastric adenocarcinoma could become widespread as new technologies, improved surgical techniques, and evidence from ongoing multicenter trials emerge.

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INTRODUCTION

Surgical resection is the main curative modality to treat gastric adenocarcinoma. Although this multidisciplinary approach can also provide effective and individualized care for the gastric cancer patient, it has shown only incremental progress to improve survival. Meanwhile, over the last two decades, the surgical modality for gastric cancer has been dramatically altered and improved in various ways that limit surgical insult to the patient, subsequently facilitating recovery[1,2]. Using laparoscopic gastrectomy to treat early gastric cancer in Eastern countries, where detection is increasing, could expedite the development and propagation of this approach for the treatment of gastric cancer[3-5]. In this review, we describe the current evidence promoting laparoscopic gastrectomy for gastric adenocarcinoma and concerns regarding its use.

INDICATIONS OF LAPAROSCOPIC SURGERY

Early gastric cancer has a favorable long-term survival when treated with curative surgical resection and lymph node dissection. When the tumor is confined to the mucosal layer, long-term survival is almost 99%; survival is 96% when the tumor is limited to the submucosa[6,7]. Ideally, endoscopic mucosal resection or endoscopic submucosal dissection is the best way to preserve patient quality of life. However, this approach can only be applied to limited number of patients that meet strict criteria and can only prudently be performed at specialized centers in high-incidence countries[8]. The initial indication for laparoscopic surgery for gastric adenocarcinoma is a tumor limited to the submucosal layer of the mid-to-lower part of the stomach with no evidence of regional lymph node metastasis, which does not necessarily require extended lymph node dissection, except in those cases suitable for endoscopic treatment[9,10]. Laparoscopic total gastrectomy is indicated for a proximal lesion such as T1N0[10]. In Eastern Asian countries, the current indication for laparoscopic gastrectomy has been expanded to serosa-negative advanced cancers with or without limited involvement of perigastric lymph nodes[11]. However, experienced surgeons have explored the use of laparoscopic surgery for advanced gastric cancer beyond these indications[12-14], and the use of the laparoscopic approach for selected advanced cancers has no detrimental effects compared to open conventional surgery. Despite this early promise, data from well-designed studies are still too scarce to recommend the use of this approach in cases requiring extensive lymph node dissection for the treatment of advanced gastric cancer. Randomized clinical trials examining outcomes of laparoscopic gastrectomy *vs* open gastrectomy for gastric cancer are listed in Table 1[15-22].

EVIDENCE FOR THE USE OF LAPAROSCOPIC SURGERY IN EARLY GASTRIC CANCER

Since the first published report regarding laparoscopic gastrectomy for early gastric cancer[2], many retrospective studies and small randomized clinical trials have shown the short-term benefits of laparoscopic gastrectomy over open conventional surgery and long-term outcomes that are comparable between the two[1,11,16,17,23,24]. Several meta-analyses also confirm that laparoscopic gastrectomy is an equivalent method to conventional open surgery[25-28]. However, these reports were conducted mainly with randomized clinical trials and with distal subtotal gastrectomy. Generally, laparoscopic distal gastrectomy causes less blood loss, shorter or similar hospital stays, lower complication rates, and comparable mortality rates compared to open conventional surgery[11,25]. However, a reduced number of retrieved lymph nodes, as well as longer operation time, is a weaknesses of the approach[25]. An interim analysis of 179 laparoscopic and 161 open gastrectomy patients from the largest randomized clinical trial for preoperatively diagnosed early gastric cancer (finished enrollment: 1416 patients; 705 laparoscopic *vs* 711 open distal gastrectomy) revealed similar complication and mortality rates between the groups[11].

Among all gastric cancer cases, the penetration rate of laparoscopic total gastrectomy is quite low because of its technical difficulties - even for experienced surgeons - compared to laparoscopic distal gastrectomy[27,29-33]; this low rate of use may be attributed especially to the difficulties of lymph node dissection and anastomosis[31,33-37]. Well-designed trials regarding this procedure are, therefore, scarce, and only some experienced surgeons report the safety and feasibility of laparoscopic lymph node dissection

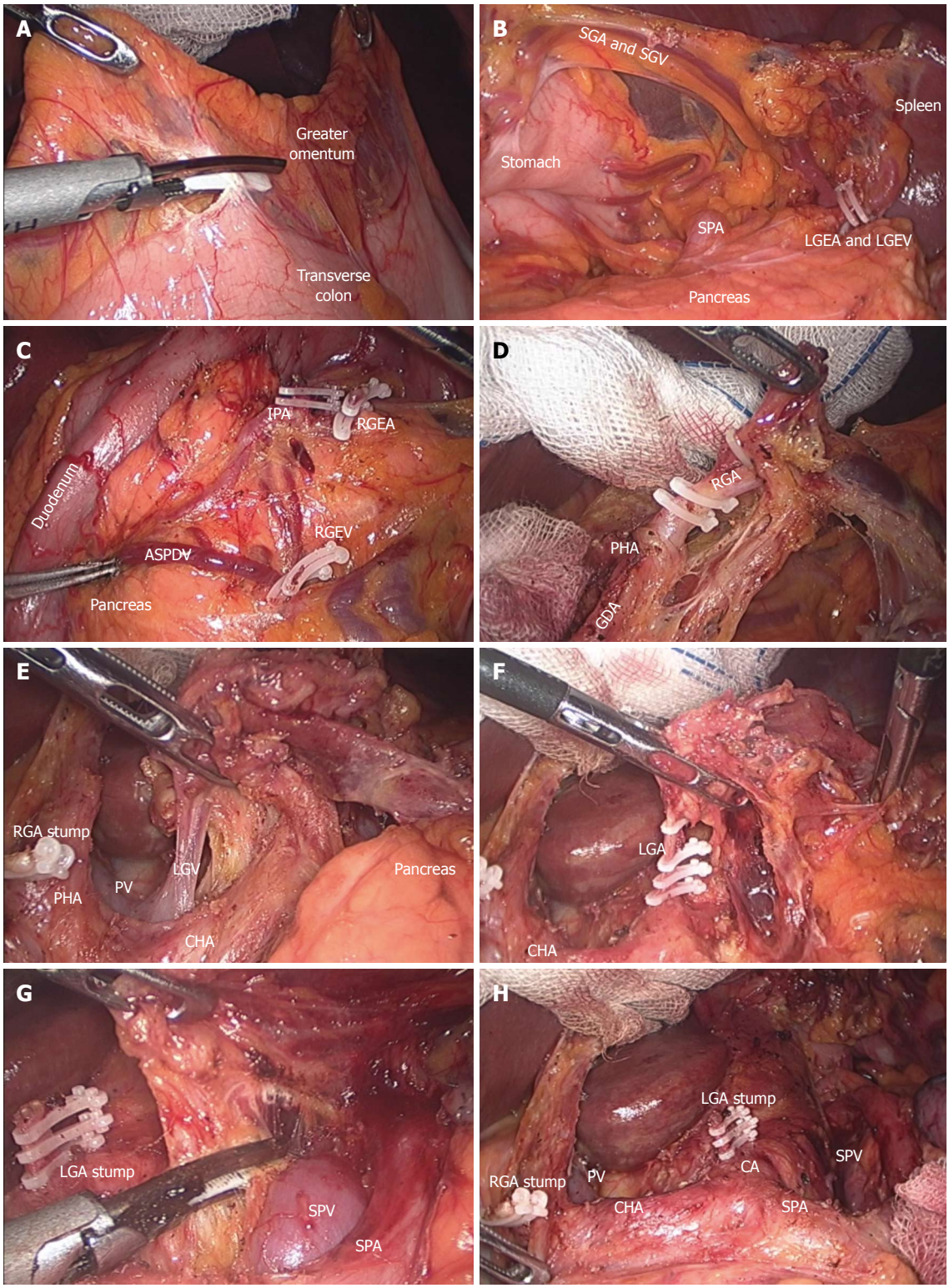

Figure 1 Intraoperative view during distal subtotal gastrectomy with D2 lymph node dissection. A: Division of the greater omentum; B: Isolation of the LGEA and LGEV; C: Exposure of the RGEA, RGEV, and ASPDV; D: Isolation of the RGA; E: Dissection of the hepatoduodenal ligament, exposure of the PV and isolation of the LGV; F: Isolation and ligation of the LGA; G: Dissection along the SPA and SPV; H: Suprapancreatic view after D2 lymph node dissection. RGEA: Right gastroepiploic artery; LGEA: Left gastroepiploic artery; LGEV: Left gastroepiploic vein; RGEV: Right gastroepiploic vein; ASPDV: Anterior superior pancreaticoduodenal vein; RGA: Right gastric artery; LGA: Left gastric artery; SPA: Splenic artery; SPV: Splenic vein; CHA: Common hepatic artery; GDA: Gastroduodenal artery; IPA: Infrapyloric artery; LGV: Left gastric vein; PHA: Proper hepatic artery; PV: Portal vein; SGA: Short gastric artery; SGV: Short gastric vein.

and their anastomosis methods in their retrospective analyses[34,38,39]. A multicenter, single-arm, phase Ⅱ clinical trial in Korea is expected to highlight long-term outcomes, as well as the feasibility and safety of laparoscopic total gastrectomy, for stage Ⅰ cancer [Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) 03 trial, NCT01584336].

EVIDENCE FOR THE USE OF LAPAROSCOPIC SURGERY FOR ADVANCED GASTRIC CANCER

For the treatment of advanced gastric cancer, lymph nodes around the common hepatic artery (LN 8), celiac axis (LN 9), and splenic artery (LN 11p) should be completely removed, as should the lymph nodes around the proper hepatic artery (LN 12a) in cases of distal subtotal gastrectomy, and those around the distal part of the splenic artery (LN #11d) and splenic hilum (LN #10) in cases of total gastrectomy, according to Japanese guideline[40,41]. Figure 1 shows an intraoperative view during and after laparoscopic distal subtotal gastrectomy with D2 lymphadenectomy for advanced gastric cancer. Regardless of the discrepancy in what constitutes adequate lymph node dissection for advanced cancer between Eastern and Western countries, lymph node dissection using laparoscopy is irrefutably technically demanding[8,40,42]. The difficulties in laparoscopic lymph node dissection might explain recent meta-analyses' reports of fewer lymph nodes retrieved in laparoscopy than open surgery[25,27,28,43]. However, this finding could be clinically unimportant because there was no significant difference in the proportion within each group with 15 or more lymph nodes retrieved for proper staging[25]. Furthermore, studies evaluating laparoscopic gastrectomy for advanced cancer reported acceptable short-term outcomes when the procedure was performed by experienced surgeons[12,17,44-47]. Although evidence is still preliminary, laparoscopic gastrectomy with D2 lymph node dissection showed less blood loss and postoperative pain, shorter hospital stays, and similar complication and overall survival rates[48]. Ongoing, large-scale phase Ⅱ or Ⅲ multicenter trials are evaluating the feasibility and safety of laparoscopic surgery for advanced cancer in the Eastern countries: the KLASS 02 (NCT 01456598), the Japanese Laparoscopic Gastric Surgery Study group (JLSSG0901; UMIN-CTR 000003420), and the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS01; NCT01609309). The T-stage inclusion criteria are similar among studies (T2-T4a); however, regarding N-stage, more advanced disease is included in the JLSSG and CLASS trials. The primary outcome in the KLASS and CLASS trials is 3-year disease free survival, whereas the incidence of anastomosis leakage and pancreatic fistula (phase Ⅱ) and relapse-free survival (phase Ⅲ) is the primary outcome of the JLSSG trial. These well-designed clinical trials could give answers regarding the short- and long-term safety of laparoscopic distal gastrectomy for advanced gastric cancer. In terms of laparoscopic total gastrectomy for advanced gastric cancer, several experienced surgeons report similar short-term results to open conventional surgery in their retrospective analyses[49-53]. However, their data include selected cases in terms of depth of tumor invasion, extent of nodal involvement, tumor size, and status of adjacent organ invasion; thus, the results are biased. The feasibility and safety of more difficult laparoscopic total gastrectomy procedures, such as those requiring removal of bulky, hard, or fixed tumors or lymph nodes, multi-organ resection, and operations for remnant stomach should be elucidated for even the most experienced surgeons[34,54-57]. So far, there is no large-scale, multicenter randomized controlled trial for assessing the role of laparoscopic total gastrectomy for advanced proximal gastric cancer.

TECHNICAL CONSIDERATIONS

Laparoscopy-assisted gastrectomy requires mini-laparotomy for specimen removal and extracorporeal anastomoses. It is still widely performed and applied in most clinical trials. However, this method is troublesome, especially in obese patients[37,58,59]. Intracorporeal anastomosis, which made this procedure the so-called "totally laparoscopic surgery," enables more sophisticated reconstruction methods. It could reduce operation time, decrease length of the mini-laparotomy, and shift the incision for specimen retrieval below the umbilicus, which results in reduced incision-related pain[60,61]. After intracorporeal Billroth Ⅰ anastomosis was safely performed with delta-shaped anastomosis, totally laparoscopic distal subtotal gastrectomy gained popularity[62,63]. Many efforts have also been made to restore esophagojejunal anastomosis intracorporeally during total gastrectomy[36,37,64-68]. Recently, intracorporeal side-to-side esophagojejunostomy using linear staples was introduced, demonstrating its safety and feasibility[37,69]. Hand-sewn anastomosis is no longer an attractive choice for the procedure; however, reconstruction methods vary according to each surgeon's preference. The laparoscopic hand-sewn technique is still commonly performed to close the common entry hole of endolinear staplers during intracorporeal anastomosis.

Most surgeons use at least five trocars for laparoscopic gastrectomy. However, with advanced techniques and improved technology, reduced port or even single-port (incision) laparoscopic gastrectomy has been safely performed[70-73]. However, because these procedures were reported from experienced surgeons or exceptionally high-volume institutions, technical feasibility, safety, and standardization of the procedure have not yet been fully elucidated[72,73]. So far, it is difficult to assess whether reduced port or single

Table 1 Recent randomized clinical trials of laparoscopic *vs* open gastrectomy for the treatment of gastric cancer

Study	Year	Eligibility	Procedure	LND extent	No. of patient (LAG/OG)	Operative time	Blood loss	No. of retrieved LN	Hospital stay	Morbidity	Mortality
Kitano *et al*[1]	2002	cT1	LADG/ODG	Not mentioned	14/14	ODG	LADG	Equivalent	Equivalent	Equivalent	Equivalent
Fujii *et al*[15]	2003	cT1	LADG/ODG	Not mentioned	10/10	ODG	Equivalent	NE	NE	Equivalent	Equivalent
Hayashi *et al*[16]	2005	cT1	LADG/ODG	Not mentioned	14/14	ODG	Equivalent	Equivalent	LADG	NE	Equivalent
Huscher *et al*[17]	2005	cT1-4N0-2	TLDG/ODG	D1, D2	30/29	Equivalent	TLDG	Equivalent	TLDG	Equivalent	Equivalent
Lee *et al*[18]	2005	cT1	LADG/ODG	D2	24/23	ODG	Equivalent	Equivalent	Equivalent	LADG	NE
Kim *et al*[19]	2008	cT1N0-1	LADG/ODG	D1, D2	82/82	ODG	LADG	ODG	LADG	NE	NE
Kim *et al*[11]	2010	cT1-2N0-1	LADG/ODG	D1 + beta, D2	179/163	ODG	LADG	NE	NE	Equivalent	Equivalent
Cai *et al*[14]	2011	cT2-3	LAG/OG (DG, TG, PG)	D2	49/47	OG	Equivalent	Equivalent	Equivalent	Equivalent	NE
Sakuramoto *et al*[20]	2013	cT1	LADG/ODG	D1+beta	31/32	ODG	LADG	Equivalent	Equivalent	Equivalent	NE
Takiguchi *et al*[21]	2013	cTNMI	LADG/ODG	D1, D2	20/20	ODG	LADG	Equivalent	LADG	NE	NE
Aoyama *et al*[22]	2014	cTNMI	LADG/ODG	D1 + beta, D2	13/13	ODG	LADG	Equivalent	NE	Equivalent	Equivalent

LND: Lymph node dissection; LADG: Laparoscopy-assisted distal gastrectomy; TLDG: Totally laparoscopic distal gastrectomy; ODG: Open distal gastrectomy; LAG; Laparoscopy-assisted gastrectomy; OG: Open gastrectomy; DG: Distal gastrectomy; TG: Total gastrectomy; PG: Proximal gastrectomy; LN: Lymph node; NE: Not evaluated. Favored group in each value were shown.

incision gastrectomy is less invasive than conventional laparoscopic surgery in terms of postoperative clinical outcomes[74]. However, a recent comparison of 50 cases of single-port laparoscopic distal gastrectomy with 50 multi-port surgery demonstrated better short-term results for single-port procedures, including reduced blood loss, lower maximum pain score on the operative day and postoperative day 1, less use of parenteral analgesics, and lower C-reactive protein levels on postoperative day 5, although the reduction of operative insult in single-port surgery did not extend to reducing length of hospital stays[73].

LIMITED EXTENT SURGERY USING LAPAROSCOPY

Limiting the extent of surgery is a goal of minimally invasive gastrectomy because of its ability to preserve patient function. Thus, laparoscopic techniques have potential to ease patients' recovery and have been investigated for feasibility and efficacy in sentinel lymph node navigation surgery, pylorus-preserving gastrectomy, and proximal gastrectomy.

Partial resection of the stomach with sentinel basin lymph node dissection for small, T1N0M0 cancer is currently indicated for sentinel lymph node navigation surgery for gastric cancer[75,76]. A randomized clinical trial (JCOG 0302) using an intraoperative dye injection method showed a higher false-negative rate (46%), and accordingly stopped patient accrual[77]. Several meta-analyses have also pointed out the unsatisfactorily higher false-negative rate of sentinel lymph node navigation surgery[78-80]. However, a recent clinical trial by Kitagawa *et al*[75] highlighted acceptable results, with 93% accuracy of detecting lymph node metastasis and only a 7% false-negative rate. The learning curve effect is likely to reduce false-negative rates. Standardization of the procedure and relevant resources are required to widely adopt sentinel lymph node navigation surgery for gastric cancer. A multicenter phase Ⅲ trial [Sentinel Node Oriented Tailored Approach (SENORITA) trial, NCT01804998] of laparoscopic sentinel node biopsy and stomach-preserving surgery has been launched to examine the benefits of sentinel lymph node navigation surgery compared to conventional laparoscopic gastrectomy. Indications for this trial include pre-operatively-diagnosed T1N0 tumors less than 3 cm and receipt of laparoscopic segmental or wedge resection with sentinel basin lymph node dissection. The primary endpoint is 3-year disease free survival.

Another method capable of preserving function is pylorus-preserving gastrectomy. This procedure has been cautiously developed based on our understanding of patterns of lymph node metastasis around the pylorus. The likelihood of lymph node metastasis in the suprapyloric (LN 5) and the infrapyloric (LN 6) area is quite insignificant in the selected patients on whom the procedure has been performed[81-85]. Pylorus-preserving gastrectomy is indicated for middle third, stage cT1N0 cancer located more than 4 cm from the pylorus[81-83]. Advantages compared to conventional distal subtotal gastrectomy include decreased incidences of dumping syndrome, bile reflux, and gallstone formation[81,82,86]. Long-term oncologic results showed acceptable survival rates[87,88] if the procedure was performed by experienced surgeons on carefully selected patients; thus, the advantages for nutritional profiles and long-term consequences for quality of life of the patients should be elucidated by well-designed multicenter trials.

Proximal gastrectomy is a suitable option for proximal early gastric cancer that preserves gastric function after operation; higher rates of postoperative complication and long-term nutritional deterioration can occur in patients after total gastrectomy[89-91]. However,

laparoscopic proximal gastrectomy - especially its reconstruction methods - is yet to be standardized and has not shown significant benefits over conventional total gastrectomy[92]. Its major drawbacks include complications involving esophagojejunostomy (*i.e.*, stenosis), reflux esophagitis, and trivial improvement of nutritional profiles. A recent multicenter retrospective comparison study of nutritional profiles and some aspects associated with dumping syndrome revealed that proximal gastrectomy was superior to those of total gastrectomy[93]. However, there were no significant changes in body weight during the study period. The aforementioned function-preserving surgery should, therefore, be first standardized technically and conceptually and evaluated by multicenter clinical trials.

FUTURE PERSPECTIVES ON LAPAROSCOPIC GASTRECTOMY FOR GASTRIC CANCER

As surgical techniques and state-of-the-art technology improve, numerous innovative procedures will be developed and refined to increase quality of life for patients receiving gastrectomy for gastric cancer. Experienced surgeons in high-volume centers already apply laparoscopic approaches to complicated cases that were once contraindicated because of safety issues and a lack of robust evidence. Several important multicenter randomized clinical trials in Eastern Asian countries are expected to give answers regarding the issues related to laparoscopic gastrectomy. It will be very interesting to see how far this approach will grow and expand. On the other hand, there are few high-level evidences advocating laparoscopic gastrectomy for gastric cancer. Until now, laparoscopic distal subtotal gastrectomy for early gastric cancer was the sole standard alternative to conventional open surgery. There are abundant issues to be solved in terms of technical feasibility, oncologic safety, proper selection of indicated patients, cost, education, and credentialing. Therefore, the above-mentioned, newly developed operative techniques should be practiced in carefully selected patients, ensuring that patients understand the procedures.

CONCLUSION

Laparoscopic gastrectomy for gastric adenocarcinoma has evolved due to the advent of new technologies and improved surgical techniques. Clinical indications are expanding to more extensive surgeries in conjunction with more sophisticated, conserving surgeries. Although discrepancies in what constitutes a proper environment for laparoscopic treatment of gastric cancer between the high- and low-incidence countries hinders the implementation of non-biased, large-scale clinical trials and massive application of the procedure, strict validation should be followed before adopting the use of laparoscopy for the treatment of gastric cancer.

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