



Minimally invasive lymphadenectomy for gastric cancer: Could the robotic approach provide any benefits than laparoscopy?

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Abstract

Gastrectomy is the cornerstone of treatment for gastric cancer. Since the introduction of minimally invasive techniques, the main challenge for surgeons has been to achieve the same surgical radicality, adequate lymphadenectomy, and negative resection margins as with the open approach. Previous Eastern trials showed non-inferiority of laparoscopic gastrectomy, whereas Western trials reported a higher number of complications. This may depend on the different eligibility criteria to select patients and surgeons. Currently, the increased availability of robotic systems has led to renewed enthusiasm. We present a critical review of published randomized control trials (up to October 2024) to investigate the real benefits of robotic compared to open and laparoscopic approaches. Robotic gastrectomy has shown similar oncological outcomes in survival and lymph node retrieval, particularly in suprapancreatic stations, with the advantage of a more acceptable rate of pancreatic fistula and feasible anastomotic reconstruction. Some clinical situations, such as postchemotherapy interstitial fibrosis and distortion of anatomical planes, may increase the technical difficulty. Only four published trials assessed the implications of a pre-operative therapy, with no robotic surgery cases. Robotic systems may reduce intraoperative blood loss, the risk of conversion and allow more extensive lymphadenectomies in cancers with a high risk of extraperigastric metastases, or with clinically proven para-aortic node metastases, although clinical trials evaluating robotic gastrectomy after neoadjuvant therapy have not yet been published.

Key Words: Gastric cancer; Robotic gastrectomy; Laparoscopic gastrectomy; Lymphadenectomy; Neoadjuvant; Randomized control trial

Core Tip: Robotic gastrectomy is likely to become the way forward for treating gastric cancer. It offers technical advantages in terms of lower rate of intraoperative blood loss and postoperative complications, with comparable survival and lymph node retrieval to open surgery. Our systematic review of randomized control trials analyzes the potential benefits of robotic systems, sheds light on the remaining uncertainties, and outlines future lines of research. Further evidence is needed to confirm its advantages in postneoadjuvant cases.

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INTRODUCTION

The lymphatic route is the main manner by which gastric cancer (GC) spreads, and lymph node involvement strongly correlates with prognosis after potentially curative resection (R0)[1,2]. It is therefore unanimously acknowledged that lymphadenectomy is a critical step in gastric surgery. The extent of lymph node dissection has been a subject of considerable debate for some time. After years of intensive research, hundreds of studies and many clinical trials, the international scientific community has reached a consensus. Most guidelines recommend the D2 lymphadenectomy as the “gold standard” for non-early-stage disease in patients suitable for this procedure, with adequate physiological reserves and a life expectancy sufficient to justify an extensive surgical approach rather than a palliative intervention[3-5].

Indeed, D2 lymphadenectomy could provide at least a potential clinical benefit, if correctly performed: (1) By increasing the number of nodes removed, and achieving adequate disease staging (> 16 nodes) in most cases[6,7]; (2) Removing potentially metastatic nodes with consequent increase of surgical radicality[8-10]; (3) A reduction in GC recurrence during the follow-up; and (4) A possible improvement in long-term survival. It is noteworthy that the Dutch trial demonstrated the cancer-specific survival benefit of D2 in a 15-year follow-up analysis[11]. The D1 and D2 survival curves overlapped until 2.5 years, and then diverged significantly in favor of the D2 procedure in the later follow-up periods. This finding may be indicative of locoregional disease control achieved through adequate lymph node clearance. Similar to the Dutch trial, the recent results of the Italian trial showed the survival benefit of the D2 at 2 years after surgical treatment[12]. Its results confirmed the oncological role of lymph node dissection, as described and standardized by the Japanese authors, in Western patients and led to the inclusion of the D2 procedure in curative gastrectomy for non-metastatic GC[3,4].

REPRODUCIBILITY OF THE D2 LYMPHADENECTOMY IN MINIMALLY INVASIVE SURGERY

Assuming that D2 dissection is the basic principle in the surgical approach to GC, the main issue is its reproducibility with minimally invasive surgery (MIS). We critically evaluate the advantages and limitations of MIS gastrectomy, particularly in oncological outcomes, surgical complexity, and postoperative complications. By reviewing existing randomized controlled trials (RCTs), this article determined whether robotic gastrectomy offers significant benefits or if further randomization in clinical trials is still necessary.

Several trials conducted in East Asia compared laparoscopic *vs* open gastrectomy; the main surgical and oncological selection criteria of these trials were clinical tumor stage (early/advanced forms), extent of gastrectomy (distal/total gastrectomy), and expertise of the centers involved. Table 1 shows a list of Eastern RCTs (last access in PubMed [MEDLINE] in October 2024). The medical subject headings and keywords “Randomized Controlled Trial,” “Clinical Trial,” “Gastric surgery,” “Gastrectomy,” “Gastric Cancer,” “Laparoscopic,” “Robotic,” “Lymphadenectomy,” and “Minimally Invasive” were investigated and combined to obtain the maximal number of articles. The articles were then screened for the presence of the following defined eligibility criteria according to the PICO format: P - population: Patients enrolled in an RCT; I and C - intervention and comparator: Minimally invasive gastrectomy for GC compared to laparoscopic or open approaches; O - outcomes of interest: Morbidity, lymphadenectomy, survival. Only published RCTs with full text in English language were included. The reference lists of all selected publications were hand searched for additional relevant articles. The following data were recorded and detailed in tables: Mono- or multi-centricity, country of origin, year of publication, study period, sample size, approach, surgical procedure, pre- or peri-operative treatment, pathological tumor-node-metastasis (TNM). Studies were excluded if the rate of D2 lymphadenectomies could not be determined. Additionally, trials analyzing hand-assisted laparoscopic gastrectomy or those enrolling patients undergoing exclusively or predominantly gastrectomy with Billroth I reconstruction were not considered.

Table 1 Summarized characteristics of Eastern published randomized control trials

Trial	Ref.	Country	Study period	Patients	Patients/center per year	Study design	Approach (n)			Surgery (n)		Neo adjuvant (%)	Pathological T (n)					D2 (%) ²	Primary outcomes	Main results
							Open	Laparoscopic	Robotic	Distal	Total ¹		1	2	3	4	x			
KLASS trial	Kim <i>et al</i> [77], 2010	South Korea	2006 to 2007	342 ⁴	24	cT1N0-1, cT2N0	161	179	0	342	0	0	/	/	/	/	/	68.7	30-day morbidity and mortality	No significant difference in postoperative complication rates (10.5% in the laparoscopic vs 14.7% in the open group; <i>P</i> = 0.137) and in mortality (1.1% vs 0; <i>P</i> = 0.497)
JLSSG0901	Inaki <i>et al</i> [78], 2015	Japan	2009 to 2013	174 ⁴	2	cT2-4a N0-2	89 (not analyzed)	86	0	174	0	0	32	18	19	17	0	86	Anastomotic leakage or pancreatic fistula in laparoscopic group	Single-arm: 4.7% patients underwent laparoscopic gastrectomy had anastomotic leakage or pancreatic fistula (4/86; 95%CI: 1.3-11.5; 1-sided <i>P</i> = 0.00024)
	Etoh <i>et al</i> [17], 2023		2009 to 2016	46	2	cT2-4a N0-2	233	227	0	460	0	0	128	122	123	87	0	100	5-year relapse-free survival	Relapse-free survival did not differ between groups: 73.9% in the open and 75.7% in the laparoscopic group (HR = 0.96; 95%CI: 0.72-1.26; <i>P</i> = 0.03)
Cui	Cui <i>et al</i> [79], 2015	Japan	2010 to 2012	270 ⁴	141	cT1-4a N0-3	142	128	0	148	122	0	/	/	/	/	/	100	Short-term surgical outcome	Laparoscopic group had similar number of harvested lymph nodes (29.3 vs 30.1; <i>P</i> = 0.574), less blood loss, longer operation time and faster recovery (<i>P</i> < 0.05) than open
KLASS-01	Kim <i>et al</i> [80], 2016	South Korea	2006 to 2010	1383 ⁴	24	cT1N0-1, cT2N0	657	726	0	1360	23	0	1102	224	41	1	10	60	30-day morbidity and mortality	The overall complication rate was significantly lower in the laparoscopic (13%) than open group (19.9%);

	Kim <i>et al</i> [14], 2019		2006 to 2010	1358 ⁴	24	cT1N0-1, cT2N0	645	714	0	1345	13	0	1097	/	/	/	/	60	5-year overall survival	<i>P</i> = 0.001. Mortality was similar (0.6% vs 0.3%; <i>P</i> = 0.687)
CLASS-01	Hu <i>et al</i> [81], 2016	China	2012 to 2014	1039 ⁴	33	cT1-4a N0-3	520	519	0	1015	24	39.4	248	/	/	/	/	99.7	30-day morbidity and mortality	Overall survival rates were 94.2% in the laparoscopic and 93.3% in the open group; <i>P</i> = 0.64
	Yu <i>et al</i> [82], 2019		2012 to 2014	1039 ⁴	33	cT2-4a N0-3	520	519	0	1015	24	39.4	248	/	/	/	/	99.7	3-year disease-free survival	Postoperative morbidity was 15.2% vs 12.9% (95%CI: -1.9 to 6.6; <i>P</i> = 0.285) and mortality rate was 0.4% vs zero (95%CI: -0.4 to 1.4; <i>P</i> = 0.249) in the laparoscopic and open group, respectively
	Huang <i>et al</i> [16], 2022		2012 to 2014	1039 ⁴	33	cT2-4a N0-3	520	519	0	1015	24	39.4	248	/	/	/	/	99.7	5-year overall survival	Disease-free survival did not differ between groups: 76.5% in the laparoscopic and 77.8% in the open group (log-rank <i>P</i> = 0.59; HR = 1.10; 95%CI: 0.84-1.43; <i>P</i> = 0.49)
JCOG 0912	Katai <i>et al</i> [13], 2017	Japan	2010 to 2013	912 ⁴	7.5	cT1N0-1, cT2N0	471	441	0	675	1 ⁴	0	788	83	31	9	1	24.9	Short-term surgical outcome	Overall survival did not differ between groups with each tumor stage: 72.6% in the laparoscopic and 76.3% in the open group (log-rank <i>P</i> = 0.19; HR = 1.17; 95%CI: 0.93-1.48; <i>P</i> = 0.19)
	Katai <i>et al</i> [18], 2019		2010 to 2013	912 ⁴	7.5	cT1N0-1, cT2N0	471	441	0	675	1	0	823	69	19	1	0	24.9	5-year relapse-free survival	Operative time was longer in laparoscopic than in open group (278 vs 194 minutes; <i>P</i> < 0.001), while blood loss was smaller (38 vs 115 mL, <i>P</i> < 0.001)
																			5-year relapse-free survival was 94.0% in the open and	

	Hikage <i>et al</i> [83], 2023		2010 to 2013	881 ⁴	7	cT1N0-1, cT2N0	447	434	0	653	0 ⁵	0	/	/	/	/	/	/	Associations between surgery-related factors and the development of late complications	95.1% in the laparoscopic group (HR = 0.84; 90%CI: 0.56-1.27; P = 0.0075) The surgical approach was not a risk factor for any late complications
	Akiyama <i>et al</i> [84], 2023		2010 to 2013	815 ⁴	7	cT1N0-1, cT2N0	/	/	0	578	1 ⁶	0	738	51	20	5	1	17.3	Frequency and location of lymph node metastases	10.9% had positive lymph node metastases. For cancer located in middle third of the stomach, metastases were widely located in each lymph node sites; for cancer located in lower third sites No. 4sb and 9 showed no metastasis
Shi	Shi <i>et al</i> [85], 2018	China	2010 to 2012	322 ³	133	cT2-4a N0-3	156	166	0	196	126	0	0	65	257	0	0	100	Short-term surgical outcomes	Laparoscopic group had longer operation time (P < 0.001), less estimated blood loss (P < 0.001), and less intraoperative transfusion (P = 0.048) than open. The average number of retrieved lymph nodes was 32 in both groups (P = 0.377)
	Shi <i>et al</i> [86], 2019		2010 to 2012	322 ³	133	cT2-4a N0-3	156	166	0	196	126	0	0	65	257	0	0	100	5-year overall survival	Overall survival rate was 49.0% in the laparoscopic and 50.7% in the open group; log-rank P = 0.59. No differences in each tumor stages
COACT 1001	Park <i>et al</i> [87], 2018	South Korea	2010 to 2011	195	21	cT2-4a N0-3	95	100	0	190	5	0	/	/	/	/	/	45.6	Noncompliance rate of the lymph node dissection	No significant differences between laparoscopic (47%) and open groups (43.2%); P = 0.648. For clinical stage III disease, the noncompliance rate was 52%

Wang	Wang <i>et al</i> [88], 2019	China	2014 to 2017	442 ⁴	26	cT2-4a N0-3	234	208	0	418	24	0	110	80	136	116	0	99.6	30-day morbidity and mortality	<i>vs</i> 25%; <i>P</i> = 0.043 No significant differences between laparoscopic (13.1%) and open groups (17.7%); <i>P</i> = 0.174. Independent risk factors were age (OR ≥ 60) and BMI (OR ≥ 25). No operation-related death occurred in both arms
Li	Li <i>et al</i> [89], 2019	China	2015 to 2017	95 ⁴	37	cT2-4a N0-3	47	48	0	92	3	100	18 ⁷	16	36	18	0	84.2	3-year recurrence-free survival (ongoing); short-term clinical outcomes	Laparoscopic group had lower postoperative complication rate (20% <i>vs</i> 46%; <i>P</i> = 0.007) after neoadjuvant, and better adjuvant chemotherapy completion (OR = 4.39; 95%CI: 1.63-11.80; <i>P</i> = 0.003)
KLASS-02	Lee <i>et al</i> [15], 2019	South Korea	2011 to 2015	1011 ⁴	23	cT2-4a N0-1	498	513	0	985	26	0	267	218	274	252	0	99.4	30-day morbidity and 90-day mortality	Morbidity was significantly lower after laparoscopic (16.6%) than after open gastrectomy (24.1%); <i>P</i> = 0.003. 90-day mortality was similar in both groups (laparoscopic 0.4% <i>vs</i> open 0.6%; <i>P</i> = 0.682)
	Son <i>et al</i> [90], 2022		2011 to 2015	974 ^{4,5}	22	cT2-4a N0-1	482	492	0	947	27	0	262	217	267	228	0	99.7	5-year overall survival and relapse-free survival	No significant difference in the 5-year overall survival (88.9% <i>vs</i> 88.7%; <i>P</i> = 0.30) and relapse-free survival (79.5% <i>vs</i> 81.1%; <i>P</i> = 0.658) between laparoscopic and open groups. Most common types of recurrence were peritoneal carcinomatosis (42.1%)

	Hyung <i>et al</i> [91], 2020		2011 to 2015	974 ^{4,5}	22	cT2-4a N0-1	482	492	0	947	27	0	262	217	267	228	0	99.7	3-year relapse-free survival	Relapse-free survival did not differ between groups: 81.3% in the laparoscopic and 80.3% in the open group (log-rank $P = 0.827$; HR = 1.035; 95%CI: 0.762-1.406; $P = 0.039$)
CLASS-02	Liu <i>et al</i> [92], 2020	China	2017 to 2018	214	10	cT1N0-1, cT2N0	109	105	0	0	214	0	144 ⁷	39	19	5	0	83.2	30-day morbidity and mortality	No significant difference in the overall postoperative complication rate (18.1% vs 17.4%) and in mortality (1% vs 0)
Lu	Lu <i>et al</i> [50], 2021	China	2017 to 2020	295 ³	121	cT1-4a N0-3	0	142	141	283	12	0	92	42	104	45	0	67.5	30-day postoperative outcomes, quality of lymphadenectomy	Surgical morbidity was comparable in the robotic and laparoscopic groups (3.5% vs 6.3%; $P = 0.279$). Higher extraperigastric lymph nodes were retrieved in the robotic group (17.6 vs 15.8; $P = 0.018$)
	Lu <i>et al</i> [93], 2024		2017 to 2020	283 ³	118	cT1-4a N0-3	0	142	141	283	0	0	92	42	104	45	0	67.5	3-year disease-free survival	3-year disease-free survival was 85.8% and 73.2% in the RDG and LDG groups ($P = 0.011$). Difference in local recurrence rate (2.1% vs 7.7%), while no difference in peritoneal and liver metastasis
Ojima	Ojima <i>et al</i> [54], 2021	Japan	2018 to 2020	236 ⁴	47	cT1-4a N0-3	0	119	113	160	76	0	131	24	51	30	0	47	Postoperative intra-abdominal infectious complications of C-D grade > 2	No significant difference in the incidence of intra-abdominal infectious complications (8.4% in the laparoscopic vs 6% in the robotic group; $P = 0.47$)

¹Proximal gastrectomies are included.

²D2 lymphadenectomy according to Japanese gastric cancer treatment guidelines.

³A fraction (< 10%) of patients underwent Billroth 1 reconstruction.

⁴A fraction (10%-70%) of patients underwent Billroth 1 reconstruction.

⁵Thirty-seven patients, including those who underwent R1/R2 resection, were lost to follow-up, or experienced operative mortality, were excluded to evaluate survival outcomes.

⁶Remnant patients underwent pylorus-preserving gastrectomy and gastro-gastro reconstruction.

⁷Remnant patients resulted ypT0 or ypTis.

C-D: Clavien-Dindo grade; CI: Confidence interval; CLASS: Chinese Laparoscopic Gastrointestinal Surgery Study Group; HR: Hazard ratio; JCOG: Japan Clinical Oncology Group; JLSSG: Japanese Laparoscopic Surgery Study Group; KCLASS: Korean Laparo-endoscopic Gastrointestinal Surgery Study Group; LDG: Laparoscopic distal gastrectomy; OR: Odds ratio; RDG: Robotic distal gastrectomy.

For early-stage disease treated with distal gastrectomy, two large RCT - MIS *vs* open - have been completed: The Japanese JCOG0912 [laparoscopic assisted distal gastrectomy (LADG) *vs* open distal gastrectomy (ODG)][13] and the Korean KCLASS-01 (similar selection criteria)[14]. In JCOG0912, less than 30% of cases underwent D2 lymphadenectomy compared to approximately 60% of cases in KCLASS-01. Both trials demonstrated non-inferiority of laparoscopic approach compared to open in both early and late outcomes. The surgical volume of involved centers was 7.5 and 24 patients/center per year, respectively.

For advanced forms (clinical stage II-III) treated with distal gastrectomy, three large trials from East have been concluded: The Korean trial KCLASS-02 (distal gastrectomy with D2 lymphadenectomy and total omentectomy)[15], and the Chinese trial CLASS-01 (distal gastrectomy with D2 lymphadenectomy for GC without bulky nodes) demonstrated the non-inferiority of MIS *vs* D2 ODG for the established primary end-points (3-year recurrence-free survival and 3-year disease-free survival, respectively)[16]. The trial from the (JLSSG0901) randomized 502 patients from 37 institutions[17]. Five-year recurrence-free survival of LADG *vs* ODG were overlapping, with 73.9% (68.7%-79.5%) and 75.7% (70.5%-81.2%), respectively. There were also no significant differences in postoperative complications, overall survival and recurrence patterns between the two groups. The authors concluded that LADG with D2 lymph node dissection, when performed by qualified surgeons, could become a standard treatment for locally advanced GC.

Regarding total gastrectomy, some prospective studies are available for both early and advanced disease, but the quality of evidence is still inferior to that for LADG. JCOG1401 is a prospective, non-randomized, single-arm trial that confirmed the safety and efficacy of laparoscopy-assisted total gastrectomy (LATG) or laparoscopy-assisted proximal gastrectomy for clinical stage I proximal GC. The percentage of D2 dissection was 6.1%[18]. A similar trial has been conducted in 170 patients with clinical stage I GC of the upper third (19 institutions from South Korea, KCLASS-03). Morbidity and mortality rates were “acceptable”: 20.6% and 0.6% respectively, with 9.4% of grade \geq III complications, and 1.9% reoperation rate. However, a control group was lacking, and the rate of D2 dissection was 38.2%[19].

Some trials are still ongoing: The CLASS 02-01 and the KCLASS-06. The CLASS02-01 is a multicenter randomized, controlled non-inferiority trial, with primary end-point morbidity/mortality rates. Two hundred patients with clinical stage I GC will be randomized to LATG (100) or open total gastrectomy (OTG) group (100)[20]. The KCLASS-06 trial is a Phase 3 randomized trial comparing OTG and LATG for advanced GC located in the upper body of the stomach.

One issue with the Eastern RCT is that locally advanced GC was managed with upfront surgery. By contrast, the standard approach in the West for fit patients with locally advanced disease now involves surgery following neoadjuvant or perioperative chemotherapy (NAC)[21]. In this context, several RCTs have been performed and recently published in Europe. Table 2 shows a list of Western RCTs (last access in PubMed [MEDLINE] in October 2024).

The LOGICA trial randomized a total of 227 patients with resectable GC to laparoscopic (115) or open gastrectomy (112). Of note, more than 70% of included patients were previously submitted to NAC, and a D2 procedure was declared in almost all patients[22]. The main oncological results (R0 resection rate > 95%, median number of removed nodes of 29) were comparable in the two groups. However, survival results are still limited to 1-year follow-up; although no

Table 2 Summarized characteristics of Western published randomized control trials

Trial	Ref.	Country	Study period	Patients	Patients/center per year	Study design	Approach (n)			Surgery (n)		Neo adjuvant (%)	Pathological T (n)					D2 (%) ¹	Primary outcomes	Main results
							Open	Laparoscopic	Robotic	Distal	Total		1	2	3	4	x			
Huscher	Huscher <i>et al</i> [94], 2005	Italy	1998 to 2001	59	24.5	cT1-4 N0-2	29	30	0	59	0	0	13	15	21	10	0	69.5	Short-term surgical outcome, 5-year overall and disease-free survival	Laparoscopic group had similar mean number of harvested lymph nodes (33.4 vs 30; $P > 0.05$) and operative mortality (27.6% vs 26.7%; $P > 0.05$) than open. Five-year overall and disease-free survival rates were similar between groups; $P > 0.05$
STOMACH	van der Wielen <i>et al</i> [23], 2021	European Union	2015 to 2018	96	2	cT1-4a N0-3	49	47	0	0	96	100	14 ²	9	36	27	0	42.7	Oncological safety, measured as the number of resected lymph nodes and radicality	Mean number of resected lymph nodes was 43.4 ± 17.3 in open and 41.7 ± 16.1 in minimally invasive group ($P = 0.612$) after neoadjuvant. No significant differences in R0 resection between laparoscopic (98%) and open groups (93.6%); $P = 0.617$
LOGICA	van der Veen <i>et al</i> [22], 2021	Netherlands	2015 to 2018	215	6.5	cT1-4a N0-3	105	110	0	123	92	72.2	29 ²	26	89	55	0	99.5	Hospital stay	Median hospital stay was 7 days (interquartile range, 5-9) in both groups; $P = 5.34$
Ribeiro	Ribeiro <i>et al</i> [72], 2022	Brazil	2015 to 2020	60	12.5	cT1-4a N0-1	31	0	29	51	9	0	26	12	11	11	0	100	Short-term surgical outcome	Robotic group had similar mean number of harvested lymph nodes (41.3 vs 42.4; $P = 0.805$), longer surgical time (354 vs 215 minutes; $P < 0.001$), and less bleeding (124 vs 276 mL; $P < 0.001$) compared to open

¹D2 lymphadenectomy according to Japanese gastric cancer treatment guidelines.

²Remnant patients resulted ypT0 or ypTis.

significant differences in postoperative complications and mortality were observed, the 90-day mortality (10.4% and 9.1%, respectively) was not negligible, when considering that most cases were curatively resected. The European STOMACH trial compared OTG and LATG after NAC[23]. The number of randomized patients was rather small, 96 in total. The oncological and surgical results were not significantly different, with a very high number of lymph nodes removed (median > 40) and a leak rate of 10.2% vs 8.5% in OTG and LATG, respectively. Although this rate is not particularly low (given that gastroesophageal junction tumors were excluded), it is noteworthy that the anastomotic technique in open gastrectomy was circular in 49% of cases and linear in 51%. Overall, the results of the LOGICA and STOMACH trials may indicate that D2 gastrectomy after NAC may be a more complex operation than upfront surgery, even with an open

approach, supporting previous studies[24-26].

POTENTIAL DRAWBACKS OF LAPAROSCOPIC APPROACH

In general, the current literature suggests that laparoscopic gastrectomy for GC is a feasible and safe procedure in experienced hands. However, several specific issues need to be addressed, and definitive and robust long-term data are required before it can become standard practice, particularly in the West. These include considerations of patient, gastric tumor, and surgeon characteristics.

First, the typology of patients should be considered. Even when considering RCTs for advanced forms, the median age was much lower in Eastern (KLASS-02: 59 years, CLASS01: 57 years) than European patients (LOGICA: 67 years), with a low comorbidity rate. Similarly, the median body mass index (BMI) was 22-23 in the former, and the JLSSG0901 included only patients with BMI < 30. The laparoscopic approach in overweight patients is considered a more complex procedure. In the JCO0912, the incidence of grade III/IV complications in BMI > 25 group was almost doubled in the LADG (8.4%) than ODG (4.4%)[18]. Pancreatic fistula also seems to be more common in obese patients after laparoscopic approach. Regarding lymphadenectomy, a BMI > 25 may also partly influence oncological radicality, as it has been reported as an independent factor for non-compliance after LATG[27].

Second, the different tumor characteristics may play a role when translating the results of trials in clinical practice. In Eastern RCTs, more locally advanced forms (bulky nodes, Bormann type IV) were excluded. In fact, in KLASS-02, the mean number of metastatic nodes was 3.5, 45% of cases were N0 and only 33% of cases were stage III, similar to the JLSSG0901 trial[15,17]. These data differ significantly from what would be considered “locally advanced” in the West[2, 21]. The survival results of KLASS-02 (5-year overall survival > 80% in pathological stage III treated with upfront surgery) and JLSSG0901 are hardly achievable in Western patients at the same stage[1]. Despite the generally good prognosis of the RCTs, it should be noted that in clinically serosa exposed cases (approximately 15% of cases in JLSSG0901), the recurrence rate in the LADG was 46% compared to 35% in the ODG. Although not statistically significant, this trend merits further investigation in dedicated studies. Another important difference between the East and West is the use of NAC in locally advanced disease. As mentioned above, clinical stages II/III are treated with upfront surgery in the East and with NAC in the West. In the former, NAC is only indicated in patients with bulky lymph nodes[5]. Both LOGICA and STOMACH showed no oncological or surgical differences between open and laparoscopic approaches. However, long-term results are lacking and a trend towards a higher risk of postoperative complications after NAC has been suggested. Indeed, recent real-world experience suggests that conversion rates and morbidity are increased after laparoscopic gastrectomy in patients undergoing NAC[28]. Regardless of tumor characteristics in Western patients, a significant proportion of cases involve posterior (stations 8p, 12p/b, 13) and para-aortic lymph nodes[10,29]. These patients may benefit from a more extended (D2plus/D3) lymphadenectomy[30]. The latest JGCA guidelines also indicate that in cases with bulky lymph nodes, NAC and para-aortic dissection should be considered. These procedures generally require an open approach and are difficult to perform laparoscopically[31].

Third is the surgeon. In the Eastern trials, a rigorous selection was required before entering the trials. In KLASS-02, only surgeons who had performed 50 cases each of laparoscopic distal gastrectomy and ODG in high-volume centers (> 80 cases/year) were included in the study. Following validation in a separate clinical trial (KLASS-02-QC), a steering committee reviewed videos of the surgical fields for every 10 cases. The JLSSG0901 required the Endoscopic Surgical Skill Qualification System certification[32]. Indeed, data from literature indicate that the learning curve for a laparoscopic gastrectomy is 44 to 36 based on anastomotic leakage rate[33,34]. A rapid overview of published studies highlights that 79/83 studies on laparoscopic/robotic learning curve come from East. It is well known that the surgical volume of gastrectomy is much lower in the West than in the East. For example, more than 50% of patients with GC in Italy are operated on in centers with a volume of < 10 cases/year[35]. In addition, the changing epidemiology of GC, with a relative increase in diffuse, proximal tumors and synchronous peritoneal dissemination, has led to a further reduction in early-stage cases in the West, which now represent a minority of total GC cases (less than 30%)[2,36]. Therefore, an adequate learning curve for laparoscopic gastrectomy is hardly achievable for Western surgeons during their training program.

POTENTIAL ADVANTAGES OF ROBOTIC APPROACH

The use of robotic gastrectomy has increased worldwide, as has the amount of published case series[37]. These numbers are expected to grow exponentially in the future as patents expire and costs come down. With the entry of new competitors, increased market competition is expected to drive down prices for robotic platforms, consumables, and maintenance. Additionally, the impending expiration of key patents will likely allow for the adaptation and integration of third-party instruments and drapes, reducing dependency on proprietary robotic tools and further lowering costs. Moreover, a recent cost analysis reported that the overall cost increase for robotic surgery was primarily due to indirect costs, such as capital equipment, supplies, and maintenance costs. Direct costs, like medical and nursing costs, were lower for robotic surgery than for laparoscopy[38]. Robotic systems are claimed to facilitate complex reconstruction after gastrectomy, reduce the technical difficulties with their magnified vision and stable movements, and avoid early conversion even in patients with advanced GC[39-41]. Enhanced precision, particularly in complex procedures such as extended lymphadenectomies and anastomosis, may further help prevent costly complications. However, numerous large-scale studies have not demonstrated a clear superiority compared to laparoscopy[42,43]. This could be due to the

large differences in the selected cohorts between the studies. Eastern trials enrolled patients with lower BMI (mean 23 kg/m² vs 28 kg/m² in the West), clinical stage I-II, and tumors located in the lower third of the stomach. On the other hand, 55%-75% of cancers in the West were locally advanced and located in the upper or middle third of the stomach, resulting in a higher rate of total gastrectomy[44,45].

Lymphadenectomy

Previous reports have shown improved 3-year survival with robotic gastrectomy in patients with stage I/II GC[46]. It is generally accepted that the robotic approach can provide accurate lymphadenectomy, allowing better staging of the disease[47,48]. A recent update of the Italian Research Group for Gastric Cancer database shows a strong correlation between removed and positive lymph nodes, with this relationship reaching a plateau when 40-50 lymph nodes are examined. It suggests that survival for patients with the same number of metastatic nodes is significantly influenced by the total number of nodes removed: 12% for less than 10 nodes, 26% for 11 to 15 nodes, and 60% for more than 25 nodes [31]. As the number of lymph nodes harvested can be a predictor of survival, more extensive lymphadenectomy (*i.e.*, removal of para-aortic and/or posterior nodes) may be indicated in GC with a high risk of extraperigastric metastases, such as located in the upper third of the stomach, with serosa involvement or exhibiting bulky nodes in the second level perigastric nodal stations[10]. No statistical differences in morbidity, mortality rates and mean hospital stay were observed compared to D2 lymphadenectomy[49]. The robotic system allows to mimic open surgical principles to perform more extended lymphadenectomy, including para-aortic nodes. In a Chinese RCT (283 patients in one high-volume hospital), more extraperigastric lymph nodes were retrieved in the robotic assisted distal gastrectomy group (RADG) (17.6 ± 5.8) than LADG (15.8 ± 6.6), particularly in the para-aortic stations (Figure 1). The noncompliance rate, defined as the absence of nodes from more than one station that should have been excised, was lower (7.7% vs 16.9%)[50]. Interestingly, the RADG group showed less intense inflammatory responses and fewer postoperative complications (9.2% vs 17.6%), resulting in faster postoperative recovery and earlier initiation of adjuvant chemotherapy.

Pancreatic fistula

A known problem with MIS is pancreatic fistula caused by blunt trauma from compressing the pancreas and thermal injury from continuous use of energy devices[51]. A higher incidence of pancreatic fistula was described for laparoscopic approach when compared with robotic assisted (22.5% vs 10%)[52]. Assuming that this is probably related to the higher rate of pancreatic injury during lymph node dissection at stations 6, 8a, 9, 12, and 13, the highly articulated instruments and the possibility of retroversion facilitate the access to these stations better than the retraction of the human first assistant can guarantee (Figure 2)[53]. Similarly, a Japanese trial (236 patients in two institutions) reported fewer overall (8.8% vs 19.7%) and major (5.3% vs 16.2%) complications with the robotic approach, with no cases of pancreatic fistula and a similar rate of intra-abdominal infectious complications[54].

Obesity

The number of patients with high BMI is increasing in Western countries[55]. As a result, less experienced surgeons tend to favor open over minimally invasive techniques to achieve adequate lymphadenectomy and negative resection margins. Recent series have shown an advantage of robotic gastrectomy in the incidence of grade > II postoperative complications in the obese cohort (11.5% vs 22.0%)[56]. Near-infrared fluorescence imaging (NIR) is an emerging technique. It may help surgeons locate tumors, follow lymph nodes and map critical anatomical structures also in the presence of elevated levels of visceral fat. Eastern series reported a higher number of lymph nodes retrieved with NIR in whole population (48.9 vs 35.2) and patients with high BMI (48.4 vs 39.8), without increasing the operative time[57,58]. However, some clinical situations, such as postchemotherapy interstitial fibrosis or cytotoxicity, may limit the use of NIR during surgery, especially in Western countries that emphasize the use of neoadjuvant therapy.

Neoadjuvant therapy

Several clinical trials have reported the efficacy of NAC in downstaging the primary tumor and increasing R0 resection rates, albeit with increased operative time and risk of intraoperative complications. Indeed, distortion of anatomical planes of dissection, interstitial fibrosis, and sclerotic tissue changes, may increase surgical difficulty[31]. It is intuitive that a greater number of lymph nodes to be excised, along with the side effects of chemotherapy, contribute to a steeper learning curve. Nonetheless, preoperative treatment does not eliminate the need for a complete radical resection when oncological resectability is to be pursued. RADG showed to be a potential therapeutic option for patients with advanced GC who underwent preoperative chemo/radio-chemotherapy[59]. In an Asian propensity score-matched analysis of 67 patients per group, RADG showed lower intraoperative blood loss and higher lymph node retrieval (50.7 vs 39.5, more extraperigastric and suprapancreatic), with similar operative time and postoperative complication rates to LADG. It suggests a clear technical advantage after NAC (SOX 2 cycles)[60]. Similar results have been confirmed in the Western context, where a low prevalence of disease favors the technical proficiency required for more advanced clinical stages. A series of 32 patients who underwent robotic surgery were less likely to have R+ (6.3% vs 20%) or inadequate lymphadenectomy (25% vs 43.6%) compared to open surgery[61]. These data suggest that robotic gastrectomy can be performed by lower-volume surgeons in Western centers serving older populations with higher BMI and comorbidities. However, these are analyses of retrospectively collected patients. So far, only four trials have investigated the outcomes after NAC, two from Eastern countries (NAC: 39.4% of 1039 cases and 100% of 95 cases) and two from Western countries (STOMACH: 100% of 96 cases, LOGICA: 72.2% of 215 cases). However, all of these studies included patients who underwent laparoscopic surgery. More RCT focused on robotic surgery are expected to be conducted soon.

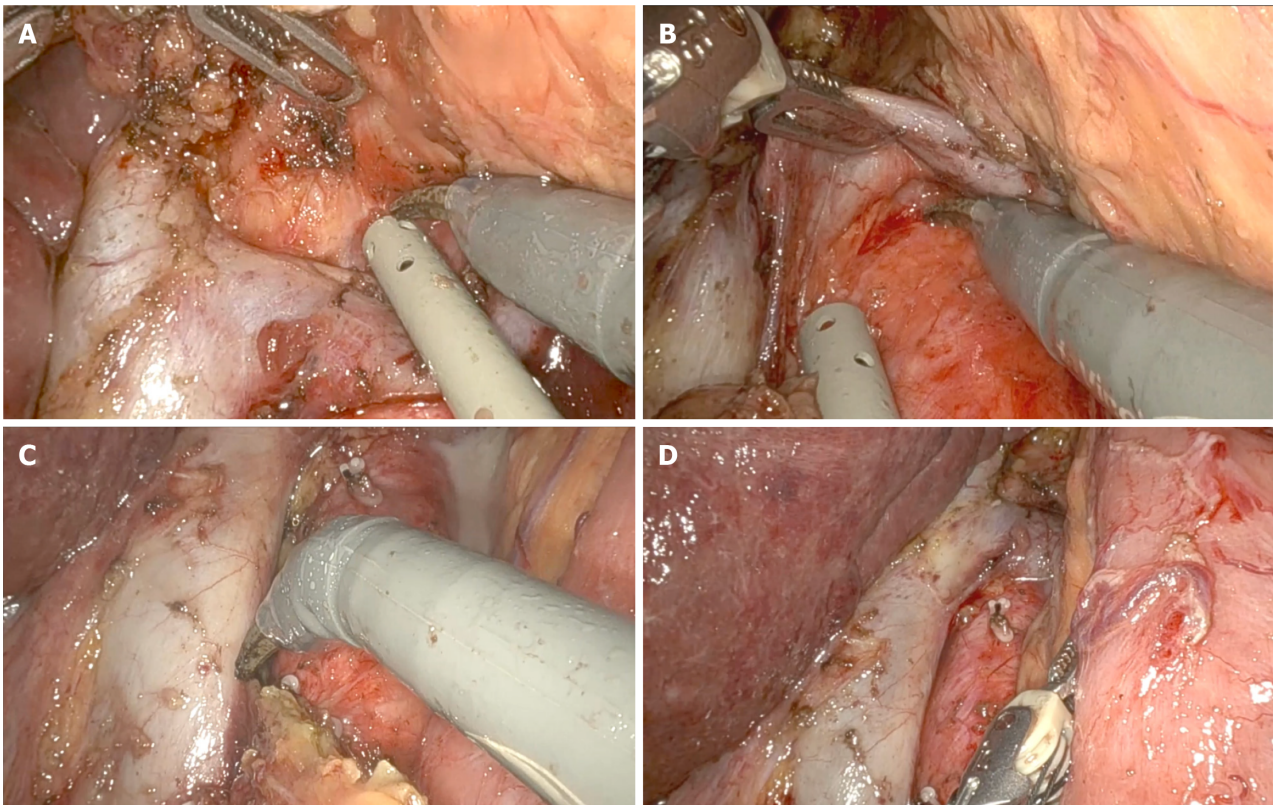


Figure 1 Robotic dissection of para-aortic nodes No. 16. A: Station 16a2; B: Under the left renal vein; C: Station 16b1; D: Complete dissection.

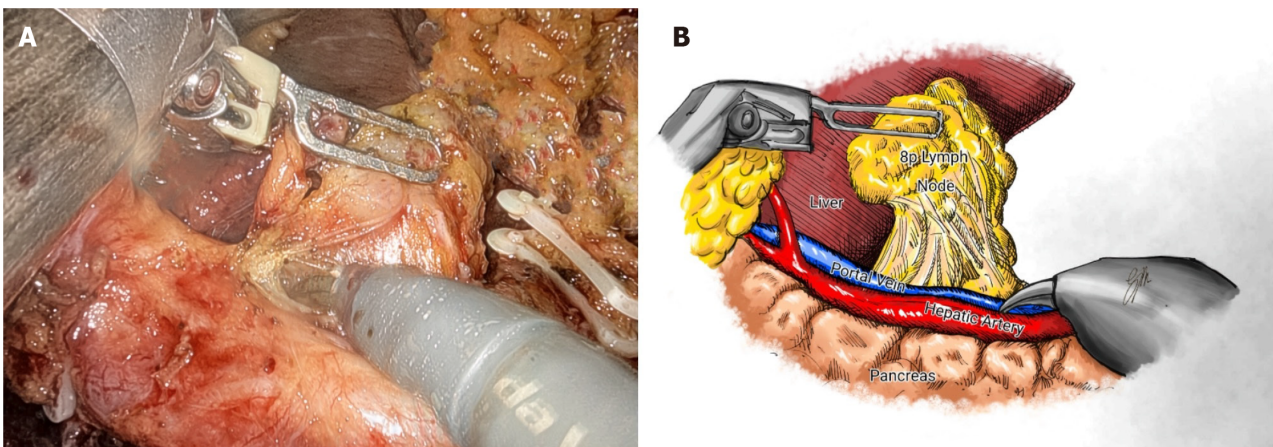


Figure 2 Robotic dissection of common hepatic artery and lymph node station No. 8. A: Intraoperative frame; B: Design.

Reconstruction in total gastrectomy

Anastomotic leakage is the Achilles’s heel of the surgeon. Many predictive factors have been identified: Patient-related (preoperative nutritional status, smoking, respiratory and cardiological pathologies), tumor-related (mixed-type histology), and operative variables, D2 or more lymphadenectomy, laparoscopic approach (15.1% *vs* 7.7% in open gastrectomy), multivisceral resection and reconstruction technique, with circular anastomosis at high risk of developing leakage[62,63]. The impact of surgeon experience has also been documented as an independent risk factor for leakage, ranging from 12% for less experienced surgeons (< 30 gastrectomies) to 2.2% for highly experienced surgeons[64]. Although the introduction of laparoscopy initially limited the use of hand sewing due to its technical requirements, the greater flexibility of robotic systems has made hand sewn esophagojejunostomy easier and more feasible (leakage in 1 out of 54 cases)[65]. The incidence of postoperative leakage tends to decrease after the first 15 cases, reflecting the robotic learning curve for gastrectomy[66]. Similar advantages have been described with the Albert-Lembert with knotless barbed sutures method for esophagojejunostomy during robotic assisted total gastrectomy (1 of 31 cases), with no occurrence of anastomotic stenosis, and the intracorporeal phi-shaped esophagojejunostomy (1 of 11 cases)[67,68]. The Upper Gastrointestinal International Robotic Association registry reported anastomotic leak rates of 10% (4.5% circular stapled, 3.4% hand sewn, 2.1% linear stapled) and 2% (all linear stapled) after robotic assisted total gastrectomy and

RADG, respectively. Robotic linear staplers also appear to be associated with fewer anastomotic strictures than circular staplers due to easier calibration of the anastomotic angle and more precise reinforcement of the anastomosis[69]. With the aim of overcoming surgeon-related bias in demonstrating non-inferiority of robotic gastrectomy, completed trials have defined precise inclusion criteria for participants (Figure 3).

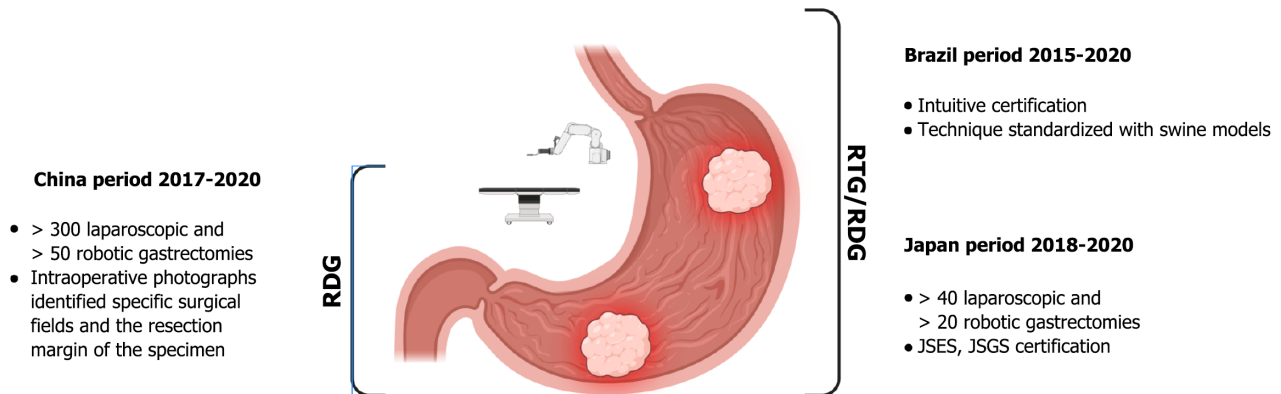


Figure 3 Surgical experience required to have been a participant in published trials on robotic gastric surgery. JSES: Japan Society for Endoscopic Surgery; JSGS: Japanese Society of Gastroenterological Surgery; RDG: Robotic distal gastrectomy; RTG: Robotic total gastrectomy.

Complications and postoperative course

Longer operative time is usually associated with robotic approach. The increase in operating times is generally attributed to the docking time, so defined “junk time”, which can take up to half an hour[70]. An interesting analysis of the first 32 robotic cases showed a gain in operating time of 90 minutes per day of reduced hospital stay[61]. Indeed, the large heterogeneity in published meta-analyses makes it difficult to interpret the evidence. A 2021 umbrella review (a review of meta-analyses) concluded that robotic gastrectomy is associated with less intraoperative bleeding, faster oral intake and shorter hospital stay, with an acceptable level of evidence rather than laparoscopic gastrectomy[71]. Similar results were found when compared with the open approach. The Brazilian trial (60 patients in a single center) showed a halving of bleeding and no difference in postoperative complication and mortality rates[72]. The simplicity of technical gesture may reduce the number of surgeries required to achieve an acceptable rate of postoperative complications, making robotic approach an advantageous option for Western centers with lower case volumes. Cumulative sum analyses of operative time ranged from 65 cases in Eastern countries[73] to 25-27 cases in the West[74].

CONCLUSION

Robotic surgery has been considered a safe and effective option for the treatment of GC since its introduction in 2003[75]. Prospective studies from the late 2010s were primarily conducted in East Asia, where early-stage GC is more common, and laparoscopy has long been the standard surgical approach for treating the disease. On the other hand, emerging evidence comes from the West, where the low incidence of disease implies limited study cohorts. Significant changes in the market dynamics may lead to substantial cost reductions soon and a higher number of patients enrolled.

Given the heterogeneity of published studies, this comprehensive review highlights its potential key advantages: (1) Comparable amount of lymph nodes retrieved as guaranteed by highly experienced laparoscopic surgeons, and consequent accurate staging; (2) More acceptable rates of pancreatic fistula and other postoperative complications; (3) Easier dissection in patients with high BMI or in case of delayed surgery; and (4) Feasible anastomotic reconstruction after total gastrectomy. To date, published randomized trials comparing open/laparoscopic and robotic gastrectomy have not yet shown a clear oncological advantage in terms of survival or recurrence rates[76].

Is it time to stop randomization? Certainly, optimizing operating times and reducing operating costs as competition grows may expand robotic surgery’s accessibility, encourage larger trials, and potentially establish it as the standard of care for GC. To support what has been argued above, artificial intelligence-driven image interpretation and computer vision further support robotic surgery by enhancing decision-making and automation. It may have many practical clinical implications such as safe dissection and lymph node mapping. Furthermore, the real-time data transmission enables procedures to be performed from anywhere, overcoming geographical barriers, addressing medical resource imbalances, and facilitating remote collaboration.

FOOTNOTES

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and data collection; Marrelli D, Carbone L, and Fusario D wrote the first draft of the manuscript; Gjoka M designed the figure; All authors provided comments on previous versions of the manuscript and read and approved the final manuscript.

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