Review Article

Minimally invasive gastrectomy after neoadjuvant chemotherapy: a literature review

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Objective: This review was conducted to assess the results of minimally invasive surgery for advanced gastric cancer after preoperative chemotherapy.

Background: Localized gastric cancer is treated mainly via surgery. Among recent advances in surgical treatments, minimally invasive gastrectomies have become standard treatment for early gastric cancer and are becoming a safe option for advanced gastric cancers. However, most studies on laparoscopic gastrectomies for locally advanced gastric cancer have been performed in patients undergoing primary surgery. In Western countries, most patients with locally advanced gastric cancer undergo preoperative chemotherapy. However, concerns remain regarding the indications for minimally invasive gastrectomies in patients with locally advanced gastric cancer, treated with preoperative chemotherapy.

Methods: We conducted a systematic search of the electronic medical databases to identify all relevant publications on minimally invasive gastrectomy. Eight papers were analyzed.

Conclusions: Neoadjuvant chemotherapy does not adversely influence the results of a minimally invasive gastrectomy, and minimally invasive surgery, even after neoadjuvant chemotherapy, may facilitate postoperative chemotherapy in terms of timing and number of completed chemotherapeutic cycles.

Keywords: Neoadjuvant chemotherapy, perioperative treatment, minimally invasive gastrectomy

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Introduction

Background

Gastric cancer is one of the most common malignant diseases and the third cause of cancer-related deaths worldwide (1). Its prevalence varies widely among countries. The highest incidence occurs in East Asia, whereas in Western countries, the incidence is <10 cases per 100,000 inhabitants (2).

In recent decades, much progress has been made in managing gastric cancer. While gastrectomies are the mainstay of treatment, perioperative chemotherapy has been shown to enhance oncologic outcomes in patients with locally advanced gastric cancer (LAGC) in Western countries compared with surgery alone (3,4). Minimally invasive (MI) surgical approaches for early cancers have been standardised.

In 1994, Kitano *et al.* performed the first reported laparoscopic distal gastrectomy (LDG) with a modified D1 lymph node dissection (5). Many studies followed this first experience, demonstrating the feasibility of MI gastrectomies and comparing their advantages and disadvantages to open surgery (6-9). The outcomes of these studies showed that laparoscopic gastrectomies (LGs) allow faster recovery, less pain, shorter hospital stays, an improved postoperative quality of life, and equal outcomes

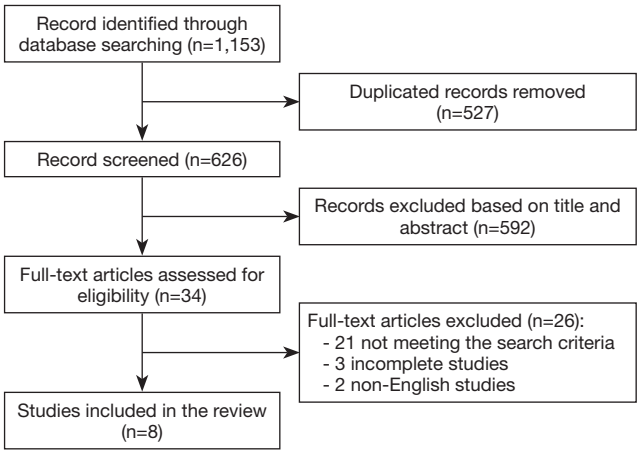


Figure 1 Flowchart of study inclusion.

of morbidity and mortality compared with those of open gastrectomies (OGs) (6-9). Therefore, laparoscopies are widely used, mainly in Eastern countries, to treat distal early gastric cancers. Several randomized studies have confirmed their safety and advantages, and LG has been introduced in the *Japanese Gastric Cancer Treatment Guidelines* (10) for treating stage I distal cancers.

Studies applying MI gastrectomies for advanced cancers have also been conducted. A multicentre randomized controlled trial (RCT) of stage II/III gastric cancer (JLSSG0901) from the Japanese Laparoscopic Surgery Study Group (JLSGG) was conducted to confirm the feasibility of LDG in terms of technical safety and short-term surgical outcomes (11). No statistical differences were found between LDG and traditional surgery.

The CLASS-01 trial (12), a multicentre randomized clinical trial, examined the surgical and oncological safety of LDG for LAGC. The trial showed no statistically significant differences in the 3-year disease-free survival rates between OG and LG for advanced cancers (77.8% *vs.* 76.5%). The laparoscopic group had a similar complication rate and a faster postoperative recovery compared with that of OG. Additionally, the KLASS-02 (13) trial, a phase-III multicentre RCT in Korea, revealed no difference in terms of oncological radicality of the procedures (i.e., the number of lymph nodes retrieved and R0 resections). Patients' postoperative courses were significantly improved after LDG, with shorter postoperative hospital stays in this group.

Because of these findings, LDG is now considered noninferior to OG in terms of oncologic outcomes and beneficial in its postoperative course in patients with LAGC. However, most studies on this topic were conducted in Eastern countries, and patients included in these trials were typically not submitted to perioperative or neoadjuvant therapies because perioperative treatments are not standard in those countries. Therefore, uncertainty remains in recommending the optimal surgical approach for patients with LAGC after neoadjuvant or perioperative treatment (14-16). Preoperative chemotherapy could affect the normal tissue planes owing to profibrotic reactions induced by the oncologic agents and to cytotoxicity, which might complicate dissection during a laparoscopic lymphadenectomy (17,18). We present the following article in accordance with the Narrative Review reporting checklist (available at https://ales.amegroups.com/article/view/10.21037/ales-21-28/rc).

Objective

In Western countries, interest is increasing in determining the safety and efficacy of LG after perioperative chemotherapy. This review was conducted to assess the results of MI surgery for advanced gastric cancer after neoadjuvant perioperative treatment. We present the following article in accordance with the narrative review reporting checklist.

Methods

We conducted a systematic search of the electronic medical databases, including a comprehensive analysis of the PubMed, EMBASE and Cochrane databases, to identify all relevant publications on MI surgery for advanced gastric cancer. All articles published until January 2021 were eligible.

Search terms included "minimally invasive", "gastrectomy", "laparoscopic", "neoadjuvant therapy", and "perioperative treatment". The references of relevant articles were considered as additional articles. After rejecting nonrelevant papers, articles published in languages other than English, and incomplete articles, eight studies were included in this analysis (*Figure 1*). The search was conducted by three authors (S De Pascale, A d'Amore, F Ascari).

Results

Eight papers published on this topic fulfilled the search criteria (*Table 1*).

Table 1 Study characteristics

	Country	Publication date	Study design	Surgery type	Study aims
Z Li (19)	China	2016	Prospective	Distal gastrectomy	To evaluate the perioperative safety and efficacy of LDG following NAC in a prospective cohort study
Z Li (20)	China	2019	Randomized	Distal gastrectomy	To evaluate short-term outcomes of patients with LAGC who received either LDG or open distal gastrectomy
N Wang (21)	China	2019	Retrospective	Distal, proximal and total gastrectomies	To evaluate postoperative safety and long-time survival after LG compared with that of OG after NAC
N van der Wielen (22)	Europe	2020	Multicentre, international randomized	Total gastrectomy with D2	Non-inferiority of MITG compared to OTG after NAC with regard to oncological quality of the resection, postoperative outcomes and survival
K Yamamoto (23)	Japan	2020	Retrospective	Total and subtotal gastrectomies	To evaluate safety and clinical impact of MIS as conversion surgery after chemotherapy for stage IV GC
S Zhang (24)	China	2020	Retrospective	Total and distal gastrectomy	To evaluate the outcomes of LG after FLOT
Y Yan (25)	China, USA	2021	Multicentre retrospective	Total and distal gastrectomy	To evaluate the effect of NAC on postoperative outcomes in advanced GC treated with minimally invasive surgery
A van der Veen (26)	Netherlands (EU)	2021	Randomized	Total and distal gastrectomy	To verify whether laparoscopic gastrectomies lead to shorter hospital stays and fewer postoperative complications with comparable postoperative mortality, lymph node yields, and R0 resection rates

LDG, laparoscopic distal gastrectomy; NAC, neoadjuvant chemotherapy; LAGC, locally advanced gastric cancer; LG, laparoscopic gastrectomy; OG, open gastrectomy; MITG, minimally invasive total gastrectomy; OTG, open total gastrectomy; MIS, minimally invasive surgery.

Case-control studies

Five case-control trials, four prospective (19,20,22) and one retrospective (21), compared LG and OG after neoadjuvant therapy. Among the prospective studies, patients' distribution into groups was randomly established in three studies and guided by patient preference in one study. A total of 732 patients were enrolled in these trials: 276 underwent MI surgery; 456 underwent open surgery.

Three studies were conducted in Asia. In two of them (19,20), all patients underwent either laparoscopic or laparotomic distal gastrectomy; in the third trial (21), both distal and total gastrectomies were included. Two randomized trials in Europe (one in the Netherlands and one in several European countries) compared LG and OG. The STOMACH trial included only patients requiring total gastrectomies after neoadjuvant chemotherapy (NAC) (22). The LOGICA trial included patients with both early and advanced gastric cancers treated with either a distal or a total gastrectomy to reflect the daily practice in Western countries (26); 77% of patients had advanced gastric cancer in the laparoscopic group, and 75% had advanced gastric cancer in the open group. In the laparoscopic group, 67% of patients underwent NAC; in the open group, 78% of patients underwent NAC (*Table 2*).

Preoperative chemotherapy regimens differed among the studies and within some of the studies. Nonhomogeneous neoadjuvant treatments were not analysed. Patients' baseline demographic and clinical characteristics were similar in all studies. All trials analysed the surgical, postoperative and oncological results of each group; however, long-term oncological results were available only in some of the studies.

Operative results

Oncological radicality of the procedure was defined as complete resection of the primary tumour, achievement of cancer-free resection margins (R0), and an adequate lymphadenectomy (27). Appropriate lymphadenectomy

Table 2 LOGICA trial (26)

	MIG	OG
Patients n°	115	112
LAGC	88 (77%)	84 (75%)
Preoperative chemotherapy	77 (67%)	87 (78%)
Surgery with curative intent	109	107
Total gastrectomy	48 (41.7%)	43 (39.1%)
Distal gastrectomy	59 (51.3%)	64 (58.2%)
Other resection	1	0
Postoperative chemotherapy	41 (35.7%)	44 (40%)
Time to postoperative chemotherapy (day)	45	50

MIG, minimally invasive gastrectomy; OG, open gastrectomy.

was considered to be D2 dissection with at least 15 lymph nodes retrieved. All studies reported the number of lymph nodes harvested (*Table 3*). Both groups met the criteria for adequate lymphadenectomy in all studies. The numbers of harvested lymph nodes did not differ between the groups.

In the STOMACH trial, three of 47 patients in the laparoscopic group had positive margins compared with one of 49 in the open group (P=n.s.). Li *et al.* and the LOGICA trial both reported similar positive margin incidences in both groups (P=n.s.) (20,26). Wang *et al.* did not report the R0 resection rate (21). In one study, all patients had R0 resections (19) (*Figure 2*).

Estimated blood loss was lower in the laparoscopic groups, but the mean operative time was slightly longer. All studies reported longer operative times for the MI group; however, only four studies found statistically significant differences (20-22,26).

Postoperative results

One study reported that the overall complication rate within 30 postoperative days was significantly lower in the laparoscopic group than in the open group (20% *vs.* 46%; P=0.007) (20); however, severe complications (Clavien-Dindo grade III or higher) were similar in both groups. No differences were noted between the groups in the other studies, neither for overall complication rate nor for Clavien-Dindo grade III or higher. Postoperative recovery times were comparable between the two groups in four of the five studies. One of the five reported a significantly shorter postoperative stay for the laparoscopic group (P<0.05) (20) (*Table 4*, *Figure 3*).

Postoperative chemotherapy

Two studies considered the influence of the access route on postoperative chemotherapy. Li *et al.* (20) reported that patients who underwent laparoscopic surgery were more likely to complete more cycles of postoperative chemotherapy and less likely to discontinue it because of adverse effects.

The LOGICA trial (26) revealed no significant difference in postoperative chemotherapy rates between the groups. The laparoscopic group had a slightly shorter interval between surgery and adjuvant therapy than did the open-surgery group (P=n.s.).

Long-term results

Long-term follow-up is ongoing in two studies. The only available data on 3-year disease-free survival (DFS) and overall survival (OS) were from the retrospective study: 3- and 5-year OS rates were 75.6% and 65.8% in the laparoscopic group and 55.9% and 49.7% in the open group, respectively. These rates did not significantly differ (22). The LOGICA and STOMACH trials reported that the 1-year OS did not differ between the groups. Longer follow-up is ongoing in both trials.

Other studies

Three studies examined the relationship between NAC and

Table 3 Summary of the studies, including KLASS-02 RCT and CLASS 01: operative results

	Patients n°	Operative time (min)	Blood loss (mL)	No. of lymph nodes	R0 rate, n (%)
STOMACH trial (22)	MIG: 47 OG: 49	MIG: 244 (IQR 198-293); OG: 200 (IQR 164-245); p= 0.005	MIG: 171 (IQR 64–300); OG: 200 (IQR 100–400); P=0.45	MIG: 40.7 (SD 16.3); OG:44.3 (SD 16.7); P=0.20	MIG: 44 (93.6%); OG: 48 (98%); P=0.6
Z. Li (19)	MIG: 20 OG: 24	MIG: 214 (±42.2); OG: 200 (±52.5); P=0.34	MIG: 94 (±36); OG: 97.9 (±52.1); P=0.77	MIG: 24.7 (±8.3); OG:24.6 (±10.0); P=0.96	MIG: 20 (100%); OG: 24 (100%); P>0.05
Z. Li (20)	MIG: 45; OG: 50	MIG: 224.8 (SD 35.8); OG: 182.9 (SD 44.8); P<0.001	MIG: 87 (IQR, 60–150); OG: 100 (IQR, 58–200); P=0.22	MIG: 31 (IQR, 24–38); OG: 33 (IQR, 28–41); P=0.43	MIG: 44 (98%); OG: 46 (92%); P=0.37
N. Wang (21)	MIG: 49; OG: 221	MIG: 221.5 (SD 69.9); OG: 201.1 (SD 56.7); P=0.06	MIG: 260.2 (SD 232.1); OG: 241 (SD 186.3); P=0.59	MIG: 32.9 (±13.6); OG: 30 (±14); P=0.19	Not reported
LOGICA trial (26)	MIG: 115; OG: 112	MIG: 216 (SD 68.8); OG: 182 (SD 53.7); P<0.01	MIG: 150 (IQR, 50–250); OG: 300 (IQR, 150–508); P=0.001	MIG: 29 (IQR, 21–37); OG: 29 (IQR, 22–39); P=0.48	MIG: 103 (95.4%); OG: 102 (95.3%); P=1.0
K. Yamamoto (23)	MIG: 41; OG: 53	MIG: 339 (IQR, 155–607); OG: 266 (IQR, 154–470); P=0.039	MIG: 10 (IQR, 0–430); OG: 520 (IQR, 85–1,555); P<0.001	MIG: D2 dissection (87.8%); OG: D2 dissection (79.2%); P=0.12	MIG: 28 (68.3%); OG: 36 (67.9%); P=0.64
S. Zhang (24)	MIG: 23	MIG: 255 (IQR 195-310)	MIG: 105 (IQR, 50–350)	MIG: 25 (IQR 19-38)	MIG: 21 (91.3%)
KLASS 02 RCT (13)	MIG: 513; OG: 498	MIG: 227; OG: 165; P=0.001	MIG: 153; OG: 230; P<0.001	MIG: 46.6; OG:46.9; P=0.74	MIG: 503 (99.1%); OG: 491 (98.6%); P=0.3
CLASS 01 (12)	MIG: 519; OG: 520	MIG: 217; OG: 186; P=0.001	MIG: 105; OG: 117; P<0.001	MIG: 36.1 (SD 16.7); OG: 36.9 (SD 16.1); P=0.7	MIG:100%; OG: 100%

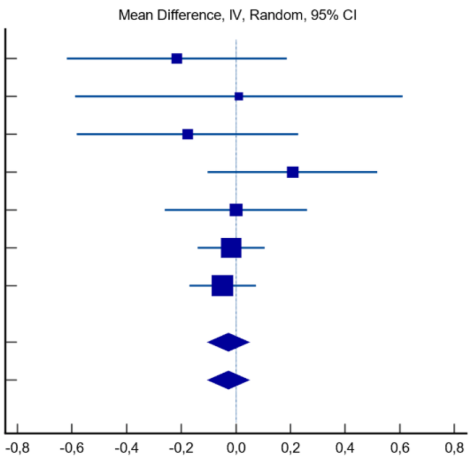
SD, standard deviation; IQR, interquartile range; MIG, minimally invasive gastrectomy; OG, open gastrectomy.

A

Study	MIG Mean	MIG SD	MIG Total	OG Mean	OG SD	OG Total	Weight (%)	Mean difference	95% CI
N. van der Wielen 2021	40,7	16,3	47	44,3	16,7	49	3,62	-0,216	-0,620 to 0,187
Z. Li 2016	24,7	8,3	20	24,6	10	24	1,69	0,0106	-0,589 to 0,611
Z. Li 2019	31	10,2	45	33	12,1	50	3,58	-0,176	-0,582 to 0,229
N. Wang 2020	32,9	13,6	49	30	14	221	6,00	0,208	-0,103 to 0,518
A. van der Wielen 2021	29	15	115	29	16,3	112	8,53	0,000	-0,261 to 0,261
HJ. Lee 2019	46,6	17,9	513	46,9	16,5	498	37,77	-0,0174	-0,141 to 0,106
J. Yu 2019	36,1		519	36,9	16,1	520	38,82	-0,0487	-0,170 to 0,0729
Total (fixed effects)			1308			1474	100,00	-0,0270	-0,103 to 0,0488
Total (random effects)			1308			1474	100,00	-0,0270	-0,103 to 0,0488

Heterogeneity:

Q	3,8215
DF	6
Significance level	P = 0,7008
I^2 (inconsistency)	0,00%
95% CI for I^2	0,00 to 54,93



B

Study	MIG Events/Total	OG Events/Total	Odds ratio	95% CI	Weight (%)
N. van der Wielen 2021	44/47	48/49	0,306	0,0306 to 3,047	4,69
Z. Li 2016	20/20	24/24	-		
Z. Li 2019	44/45	46/50	3,826	0,411 to 35,581	4,98
A. van der Wielen 2021	103/115	102/112	0,842	0,348 to 2,034	31,81
K. Yamamoto 2020	28/41	36/53	1,017	0,424 to 2,440	32,38
HJ. Lee 2019	503/513	491/498	0,717	0,271 to 1,899	26,14
J. Yu 2019	519/519	520/520	-		
Total (fixed effects)	1261/1300	1267/1306	0,894	0,550 to 1,454	100,00
Total (random effects)	1261/1300	1267/1306	0,883	0,536 to 1,452	100,00

Heterogeneity

Q	2,7687
DF	4
Significance level	P = 0,5972
I^2 (inconsistency)	0,00%
95% CI for I^2	0,00 to 71,72

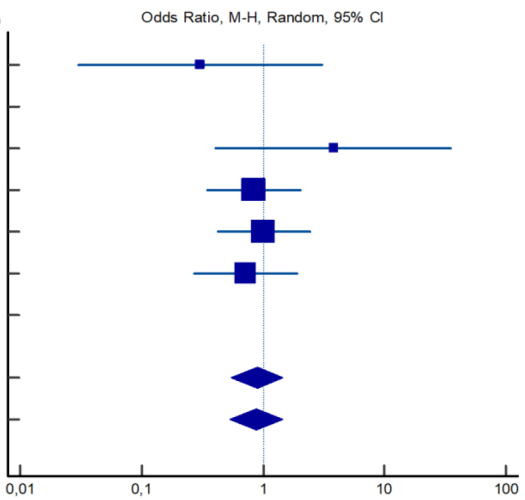


Figure 2 Forest plot of retrieved lymph nodes (A). Forest plot of R0 resections (B).

MI surgery for LAGC but lacked a straight comparison between laparoscopic and open surgery after NAC (23-25).

LG and conversion surgery

Yamamoto *et al.* (23) retrospectively analysed the outcomes of patients who underwent conversion surgery after chemotherapy for stage IV gastric cancer to determine the feasibility of an MI approach in this setting. Ninety-four patients were included; 41 underwent LG, and 53 underwent OG. Patients in the OG group had larger tumours with peritoneal metastasis or required

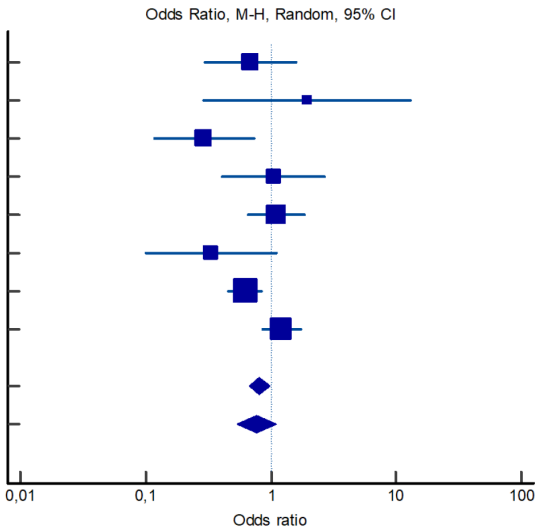
Table 4 Summary of the studies, including KLASS-02 RCT and CLASS 01: postoperative results

	First aerofluxus time (days)	Complications	Clavien-Dindo grade III–V	Length of stay (days)	Time to postoperative chemotherapy (days)	Cycles of completed adjuvant therapy	12-month survival (%)	3-year survival (%)
STOMACH trial (22)	Unreported	MIG: 16 (34%); OG: 21 (42.9%); P=0.4	MIG: 8 (17%); OG: 6 (12.2%); P>0.05	MIG: 8 (IQR, 7–9); OG: 8 (IQR, 7–11); P=0.33	Unreported	Unreported	MIG: 86%; OG: 90.4%; P=0.7	Unreported
Z. Li (19)	MIG: 3.2 (±0.9); OG: 3.9 (±0.9); P=0.012	MIG: 3 (15%); OG: 2 (8.3%); P=0.39	MIG: 2 (10%); OG: 0 (0%)	MIG: 11 (IQR, 9–12.5); OG: 10 (IQR, 10–12.5); P=0.914	Unreported	Unreported	Unreported	Unreported
Z. Li (20)	MIG: 3.3; OG: 3.2; P=0.62	MIG: 9 (20%); OG: 23 (46%); P=0.007	MIG: 6 (13%); OG: 2 (4%); P=0.47	MIG: 9 (IQR, 8–10); OG: 9 (IQR, 8–13); P=0.10	MIG: 37 [34–50]; OG: 39 [34–44]; P=0.67	MIG: 5 cycles; OG: 4 cycles; P=0.06	unreported	Unreported
N. Wang (21)	Unreported	MIG: 6 (12.2%); OG: 26 (11.8%); P=0.75	MIG: 3 (6%); OG: 8 (4%); P>0.05	MIG: 11.1 (SD 4.4); OG: 13 (SD 7.3); P=0.02	Unreported	Unreported	MIG: 89.6%; OG: 81.6%; P>0.05	MIG: 75.6%; OG: 55.9%; P>0.05
LOGICA trial (26)	MIG: 4; OG: 4; P=0.74 (first defecation)	MIG: 50 (43.5%); OG: 46 (41.8%); P=0.907	MIG: 19 (16.4%); OG: 25 (22.8%); P=0.33	MIG: 7; OG: 7; P=0.30	MIG: 45 (IQR 38-60.75); OG: 50 (IQR 41-57); P=0.415	MIG: 41 (35%); OG: 44 (40%); P=0.49	MIG: 76%; OG: 78%; P=0.74	unreported
K. Yamamoto (23)	Unreported	MIG: 4 (9.8%) (CD >2); OG:13 (24.5%) (CD>2); P=0.058	MIG: 0; OG: 4 (7.6%); P=0.072	MIG: 8 (IQR, 6–15); OG: 12 (IQR, 6–100); P<0.0001	MIG: 25 [16–60]; OG: 39 [15–123]; P=0.0008	MIG: 95.1%; OG: 90.6%; P=0.39	MIG: 95%; OG: 75%; P=0.028	MIG: 75%; OG: 35%; P=0.028
S. Zhang (24)	MIG: 2.7 [1–6]	MIG: 7 (30.4%)	MIG: 1 (4.3%)	MIG: 13.2 (IQR, 8–31)	Unreported	Unreported	Unreported	Unreported
KLASS 02 RCT (13)	MIG: 3.5; OG: 3.7; P=0.025	MIG:85 (16.3%); OG: 120 (24.9%); P=0.003	MIG: 45 (8.8%); OG: 56 (11.2%); P>0.05	MIG: 8.1; OG: 9.3; P=0.003	Unreported	Unreported	Unreported	Unreported
CLASS 01(12)	MIG: 3.5; OG: 3.6; P=0.11	MIG: 79 (15.5%); OG: 67 (12.9%); P=0.28	MIG: 18 (3.5%); OG: 14 (2.8%); P>0.05	MIG: 10.8; OG: 11.3; P=0.001	Not reported	Not reported	Not reported	MIG: 83%; OG: 85%; P>0.05

SD, standard deviation; IQR, interquartile range; MIG, minimally invasive gastrectomy; OG, open gastrectomy.

A

Study	MIG Events/Total	OG Events/Total	Odds ratio	95% CI	Weight (%)
N. van der Wielen 2021	16/47	21/49	0,688	0,301 to 1,574	11,13
Z. Li 2016	3/20	2/24	1,941	0,291 to 12,951	3,24
Z. Li 2019	9/45	23/50	0,293	0,117 to 0,735	9,83
N. Wang 2020	6/49	26/221	1,047	0,406 to 2,698	9,45
A. van der Wielen 2021	50/115	46/112	1,104	0,652 to 1,869	16,84
K. Yamamoto 2020	4/41	13/53	0,333	0,0995 to 1,112	6,77
HJ. Lee 2019	85/513	120/498	0,626	0,459 to 0,853	21,83
J. Yu 2019	79/519	67/520	1,214	0,855 to 1,724	20,92
Total (fixed effects)	252/1349	318/1527	0,810	0,670 to 0,981	100,00
Total (random effects)	252/1349	318/1527	0,774	0,537 to 1,115	100,00



B

Study	MIG Events/total	OG Events/total	Odds ratio	95% CI	Weight (%)
N. van der Wielen 2021	8/47	6/49	1,470	0,468 to 4,614	10,11
Z. Li 2016	2/20	0/24	6,622	0,300 to 146,378	1,68
Z. Li 2019	6/45	2/50	3,692	0,705 to 19,326	5,42
N. Wang 2020	3/49	8/221	1,736	0,444 to 6,797	7,58
A. van der Wielen 2021	19/115	25/112	0,689	0,355 to 1,337	21,28
K. Yamamoto 2020	0/41	4/53	0,133	0,00693 to 2,534	1,85
HJ. Lee 2019	45/513	56/498	0,759	0,502 to 1,147	32,37
J. Yu 2019	18/519	14/520	1,299	0,639 to 2,639	19,70
Total (fixed effects)	101/1349	115/1527	0,926	0,698 to 1,228	100,00
Total (random effects)	101/1349	115/1527	1,029	0,684 to 1,550	100,00

Heterogeneity

Q	9,8719
DF	7
Significance level	P = 0,1959
I^2 (inconsistency)	29,09%
95% CI for I^2	0,00 to 68,27

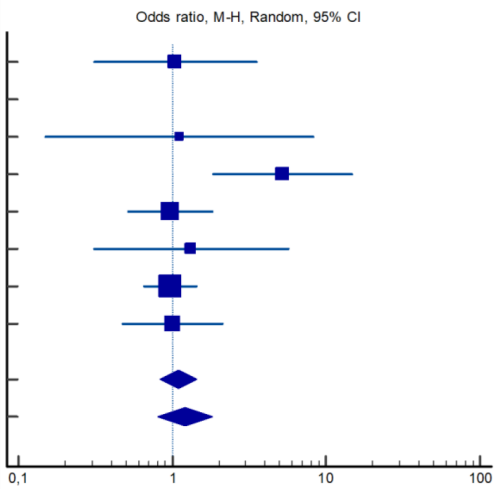


Figure 3 Forest plot of overall complications (A) and Clavien-Dindo III or higher complications (B).

splenectomies. The other background characteristics were comparable between the groups. Data regarding operative factors and postoperative outcomes were collected, and few significant differences were observed. Operative times were longer in the laparoscopic group, but operative blood loss was consistently lower. Hospital stays were significantly shorter in the laparoscopic group.

OS and DFS were calculated over an 18-month observational period. The most relevant prognostic factor was R0 resection, which was achieved in nearly 70% of patients and equally distributed between the groups. However, patients in the laparoscopic group had higher DFS and OS rates than did the OG group. Although the baseline disease stages were not comparable, MI surgery was not detrimental in terms of OS after conversion surgery. Moreover, the interval from surgery to postoperative

Table 5 Summary of the study by Yan *et al.* (27)

	Neoadjuvant chemotherapy + surgery	Upfront surgery	P value
Patients n°	97	97	
Mean number of lymph nodes	35.7 (±12.6)	31.9 (±13.8)	0.037
R0 rate, number (%)	Unreported	Unreported	
Mean operative time (min)	358.7 (±101.9)	324.3 (±93.4)	0.04
Mean blood loss (mL)	93.6 (±99.7)	115.4 (±116.5)	0.2
First aerofluxus time	4.2	4.4	0.39
Complications	29 (30%)	26 (26.8%)	0.34
Clavien-Dindo grade III/IV	5 (5.1%)	5 (5.1%)	–
Length of stay (days)	7.5 (± 4.6)	7.7 (±6.2)	0.13

chemotherapy was significantly shorter in the MI group than in the open group.

Effect of preoperative chemotherapy on LG

Zhang *et al.* (24) designed a study to clarify the effects of the FLOT regimen in patients with LAGC and determine its effect on subsequent LG. Twenty-three patients were enrolled; all received four cycles of FLOT completed at least 4 weeks before surgery. According to tumour site, 12 patients underwent total gastrectomies, and 11 underwent distal gastrectomies. The median number of lymph nodes retrieved was 25, and the R0 rate was 91.4%. Six patients reported overall complications (26%), with one severe (grade III) (4.3 %). Data on the operative time, intraoperative bleeding, first flatus and hospital stay were similar to those reported in the case-control trials.

Yan *et al.* (25) compared the postoperative outcomes of patients undergoing MI surgery alone or combined with NAC for LAGC. They enrolled 673 patients: 112 in the NAC + surgery cohort and 561 in the surgery upfront cohort. After 1:1 propensity score-matching, 97 patients were included in each cohort. The two groups did not significantly differ in terms of intra- and postoperative data. Significantly more lymph nodes were retrieved in the NAC + surgery group (*Table 5*).

Discussion

Although an MI approach to early gastric cancer is considered a safe surgical procedure and extensively accepted, the role of laparoscopy in LAGC is controversial. Technical issues related to tumour size, possible infiltration of other organs, demanding extensive resections, and the requirement of a D2 dissection make the MI approach challenging. In recent years, relevant data have emerged from high-quality trials conducted in Eastern countries (11-13). These trials assessed the feasibility of LDG, even in LAGC, showing comparable oncological outcomes and better postoperative outcomes for LG than for open surgery relative to postoperative pain and recovery time. However, patients included in these trials were treated with primary surgery, whereas in Western countries, most LAGC is treated with NAC (14-17). Neoadjuvant therapies are aimed at improving localized disease control and long-term survival. The effects of neoadjuvant therapies on subsequent surgeries conducted via MI approaches are unclear.

Only eight studies were analysed in this review. Only a few were randomized, and most were not homogeneous in the type of preoperative chemotherapy used. In this review, the R1 and R2 rates were comparable between the open and laparoscopic groups and in the percentages reported in the CLASS01 and KLASS02 trials. Only the STOMACH trial reported slightly but non-significantly higher R1 resection rates in the MI group than in the open group (6% *vs.* 2%). Notably, this was the only trial that analysed total gastrectomies for proximal tumours.

Preoperative chemotherapy does not seem to directly affect lymphadenectomies during LG; the number of retrieved lymph nodes in these studies did not differ between open and laparoscopic resections. Moreover, postoperative complication rates, mainly CD ≥3 were similar in both groups.

Pretreated patients lost less blood during LG, but this

was counterbalanced by a significantly longer operative time. These results are consistent with those reported in the CLASS-01 and KLASS-02 trials. Thus, NAC does not appear to directly affect the surgical difficulty of the intervention. These studies demonstrated no clear superiority of the MI approach in terms of postoperative morbidity.

The authors of the LOGICA trial determined the health-related quality of life (HRQoL) at different time points after surgery, testing their patients with standardized questionnaires. The groups did not significantly differ at any scheduled time points.

Notably, the STOMACH trial evaluated the results of MI and open gastrectomies in terms of HRQoL [paper submitted]. Here too, no differences were noted in HRQoL scores between the two groups. Importantly, in this trial, the number of patients who were fit enough after surgery to receive adjuvant chemotherapy was higher in the MI group than in the open group. Two other studies reported similar results in that patient who underwent MI gastrectomies were more likely to complete postoperative chemotherapy in terms of number of cycles and time between surgery and adjuvant therapy (20,23). Conversely, the LOGICA trial found no difference in the number of completed cycles but reported a slightly shorter interval between surgery and the beginning of adjuvant therapy (2). A study of colon cancer reported similar benefits in the laparoscopic cohort (28). Whether these results can be translated to advanced gastric cancer remains uncertain.

As stated, the overall and severe complications rates appeared comparable between both groups. It remains to be determined whether laparoscopy, owing to visual magnification, better exposure, and more delicate manipulation, can mitigate the increased risk of surgical complications induced by the chemotherapy-associated tissue fibrosis and disrupted anatomical planes (17,18,29-32). These studies reported no difference in the overall rate, type, or severity of postoperative complications among patients who either received or did not receive NAC.

The effect of MI surgery after NAC on long-term oncological outcomes remains uncertain. Four studies reported a long-term follow-up (21,22,23,26). In these studies, DFS and OS after MI gastrectomies were comparable to those of open surgery.

Conclusions

Few studies have addressed the issue of laparoscopic surgery after NAC. The results of these studies indicate that NAC does not adversely influence MI gastrectomy results. The MI approach, even after NAC, may facilitate postoperative chemotherapy in terms of timing and number of cycles.

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Footnote

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