The Efficacy of Minimally Invasive Total Gastrectomy and Side to Side Esophago- Jejunal Anastomosis in Proper Clinico-Pathological Assessment of Gastric Cancer After Neoadjuvant Chemotherapy

Mohamed Abdelmaaboud[1], Haitham Fekry Othman[2], Mohamed Aly Abdelhamed[3], Mina F. A. Fouad[4], Fouad Abdelshahid Fouad Saleep[5].

[1]*Assistant Lecturer of surgical oncology,*
[2]*Associate Professor of surgical oncology,*
[3]*Lecturer of surgical oncology,*
[4]*Professor of Surgical Oncology.*
[5]*Department of Surgical Oncology, National Cancer Institute, Cairo University.*

*Corresponding author: , E-mail: m.abdelmaaboud@cu.edu.eg

KEYWORDS

Minimally invasive total gastrectomy, gastric cancer, side-to-side esophagojejunostomy.

ABSTRACT

Background: Minimally invasive total gastrectomy (MITG) for gastric cancer (GC) has been shown to have many merits, such as smaller wounds, a larger workspace, and no limitation due to the patient's body size. More and more surgeons now prefer MITG as an appropriate method for upper body gastric cancer, or even adenocarcinoma of the esophagogastric junction (AEG), despite the high demand the procedure places on a surgeon's operating skills.

Esophagojejunostomy after MITG is technically challenging. Failure of the esophago-jejunal anastomosis can lead to significant morbidity, leading to short and long-term quality of life (QoL) impairment or mortality. The optimal reconstruction method following MITG remains controversial.

Neoadjuvant chemotherapy is an important part of the comprehensive treatment of advanced gastric cancer (GC). The effect of neoadjuvant chemotherapy plays a key role in the prognosis of GC patients. Pathological response can represent the effect of neoadjuvant chemotherapy.

Objectives: The aim of the present study was to assess the adequacy of minimally invasive total gastrectomy in achieving proper oncological resection and post-operative pathological data retrieval in patients with gastric adenocarcinoma who have received neoadjuvant chemotherapy.

Patients and methods: Twenty patients with gastric cancer who underwent minimally invasive total gastrectomy at the National Cancer Institute - Cairo University were involved in this study between January 2022 and January 2024.

All patients had side-to-side esophagojejunostomy (EJS) using linear stapler.

Results: Eighteen patients (90.0%) have undergone D2 Total gastrectomy, two with extended resection either Splenectomy + Distal Pancreatectomy or only Splenectomy. The mean operative time was 344.75 minutes, the average time of esophago-jejunal anastomosis was 51.50 minutes, and the
average hospital stay was 10.80 days. The average number of retrieved LNs (whether involved or not) in surgical specimens was 27.35 ± 11.92 ranging from 15.00 to 67.00 LNs. Importantly,
all cases demonstrated clear resection margins, emphasizing the oncological adequacy of MITG with proper
D2 LN dissection.

Conclusion: Our findings support MITG with intra-corporeal side-to-side esophagojejunostomy using linear stapler as a safe and effective surgical approach in gastric cancer management, offering favorable functional and
oncological outcomes and low complication rates

Introduction

Gastric adenocarcinoma is the 5th most frequent cancer worldwide, affecting more than one million patients, and it represents the 2nd most frequent cause of cancer-related death, with a predominance in male patients and Asian population.1,2

Surgery represents still the backbone of treatment despite potent chemotherapy and immunotherapy have been introduced during the last three decades.3,4 The first laparoscopic gastrectomy was already performed more than 30 years ago by Kitano et al.,5 but gastric cancer surgery is still performed by an open approach in many parts of the world. The recent European Society of Medical Oncology (ESMO) guidelines from 2022 still suggest that a laparoscopic approach should only be selectively offered for gastric cancer, when performed by expert surgeons.6

The shift towards minimal invasive surgery has been reluctant due to concerns about achieving complete tumor resection and adequate lymphadenectomy. Nevertheless, laparoscopic surgery for early gastric cancer (cT1/T2, N0) has proven its feasibility and safety, as well as favorable surgical and oncologic outcomes.7–14

More recent studies presented promising results also for the treatment of advanced tumor stages.15–21 To date, similar rates have been reported for postoperative complications between laparoscopic and open gastrectomy,18,19,22 with a shorter hospital stay after a laparoscopic approach,16,21–23 and conversion rates up to 10–15 % for complex gastric surgery.24,25

The aim of the present study was to assess the adequacy of minimally invasive total gastrectomy in achieving proper oncological resection and post-operative pathological data retrieval in patients with gastric adenocarcinoma who have received neoadjuvant chemotherapy.

Patients and methods:

This is a prospective cohort study that included twenty patients with gastric cancer who underwent minimally invasive total gastrectomy at National Cancer Institute between January 2022 and January 2024. Patients were followed for 6 months. The study protocol was approved by the ethics committee of the National Cancer Institute, Cairo University. Informed consent was obtained from all patients according to the local regulations.

Any patient with gastric cancer presenting at the National Cancer Institute was considered a candidate for radical surgical resection meeting the following criteria: all age groups, both sexes, all patients with histologically proven gastric cancer undergoing minimally invasive total gastrectomy, all patients with stage I-III tumors proved by CT scan, and patients who have received neoadjuvant chemotherapy. The following were excluded from our study: metastatic patients, and patients with comorbidities who were unfit for major surgical procedures, those with poor performance status (ECOG 3, 4).

Preoperative assessment:

All patients in the study had the following methods of evaluation:

1. **Thorough history taking:** for age, sex, special habits, weight loss, Diabetes,Hypertension, liver disease, other medical diseases and history of perviousabdominal surgeries.
2. **Clinical examination:** for anemia, ascites, abdominal mass, cachexia and . supraclavicular lymph node enlargement.

3**. Investigations:** A. Laboratory studies including: complete blood picture, liver and kidney functions tests, fasting and 2 hours postprandial blood sugar, coagulation profile, serum electrolytes level (Na, K). B. Medical assessment of the patient: electrocardiography, echocardiography and respiratory function tests were performed in accordance with the standard guidelines. C. Radiological studies and endoscopy: contrast enhanced computed tomography (CT) of chest, abdomen and pelvis for assessment of gastric mass, its site, its size, lymph node enlargement and distant metastases in lung or liver, upper gastrointestinal endoscopy for biopsy and histopathological examination.

Data collection:

All data has been collected and divided into Patients' factors, intraoperative and postoperative factors. Patients' factors have included patients' demographics, co-morbidities, neoadjuvant treatment, pathological data including tumor type and grade, number of lymph nodes retrieved, proximal and distal margins. and adjuvant therapy. Intra-operative factors have included principles of laparoscopic total gastrectomy and side to side esophago-jejunostomy.

The Pathological Staging was determined according to the 8th edition of AJCC TNM classification. Adequate lymph node staging (LNS), defined as the examination of at least 15 lymph nodes in the pathologic specimen, and margin status was classified as negative (R0) or positive (R1 or R2).

D2 lymph node dissection is defined as removal of peri-gastric nodes along greater and lesser curve (stations 1-6) + removal of lymph nodes along left gastric artery, common hepatic artery, celiac trunk, splenic artery and hilum (stations 7-12), according to Japanese Research Society for Gastric Cancer (JRSGS) (26).

Statistical analysis:

Data will be analyzed using SPSS win (statistical package of social science) version 26. Numerical data will be presented as means, standard deviation, median and ranges as appropriate. While categorical data will be presented as frequencies and percentages. Data will be explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Comparisons between the 2 groups for normally distributed numeric variables will be done using the Student t-test while for non-normally distributed numeric variables comparisons will be done by Mann-Whitney test. Comparison between groups of categorical data will be performed using Chi-Square test or Fisher's exact as appropriate. Probability (p-value) equal or less than 0.05 will be considered significant.

Source of funding:

No need for funding

Ethical committee approval:

This study will be started after approval of Institutional Review Board and Ethical Research Committee.

The study protocol will be presented to the Scientific Ethics Committee of the surgical Department at the National Cancer Institute – Cairo University.

Patients' data will be presented anonymously with protection of privacy and confidentiality.

The aim and nature of the study will be explained to each patient before their inclusion in the study. An informed written consent will be obtained from each patient, or a first degree relative before enrolment.

Cooperation with other departments:

Not applicable.

Results:

The mean age of our patients at the time of surgery is 53.90 ± 10.85,ranging from 34 to 74 years. The mean body mass index (BMI) of our patients is 23.50 ± 3.32, ranging from 17 to 29.Regarding gender distribution, 15 patients were males (75.0%) while 5 patients were females (25.0%).

Of our 20 cases, 12 patients have no medical comorbidities (60.0%), one patient is diabetic only, 2 patients are diabetic hypertensive, one patient is diabetic hypertensive having ischemic heart disease, 2 patients are diabetic having ischemic heart disease, and 2 patients are hypertensive.

Regarding American Society of Anesthesiologists (ASA) class, 6 patients are ASA class I (30.0%), 11 patients are ASA class II (55.0%) and 3 patient is ASA III (15.0%).

Three patients had previous abdominal surgery (15.0%) while 9 patients were smokers (45.0%).

		Mean	SD	Median	Minimum	Maximum
Age		53.90	10.85	54.50	34.00	74.00
BMI		23.50	3.32	23.00	17.00	29.00
				Count	%	
Gender	Male			15	75.0%	
	Female			5	25.0%	
Medical Comorbidities	DM			1	5.0%	
	DM, Hypertension			2	10.0%	
	DM, Hypertension, IHD			1	5.0%	
	DM, IHD			2	10.0%	
	Hypertension			2	10.0%	
	Medically free			12	60.0%	
ASA score	ASA I			6	30.0%	
	ASA II			11	55.0%	
	ASA III			3	15.0%	
Previous Abdominal Surgeries	Yes			3	15.0%	
	No			17	85.0%	
Smoke	Yes			9	45.0%	
	No			11	55.0%	

Table 1.Patient Characteristics.

Among our 20 cases, Thirteen cases was involving the gastric body (65.0%), while 7 cases was involving the gastric fundus (35.0%).

All patients received four cycles of neoadjuvant chemotherapy (FLOT) regimen (5-Flurouracil, Leucovorin, Oxaliplatin, and Taxotere) with 2 patients having complete clinical response (10.0%), 10 patients with partial tumor response (50.0%) and 8 of them (40.0%) showed no clinical response to treatment on preoperative imaging and clinical evaluation.

The average duration between the end of chemotherapy and surgical intervention was 4.79 ± 0.93 weeks ranging from 3.30 to 6.00 weeks.

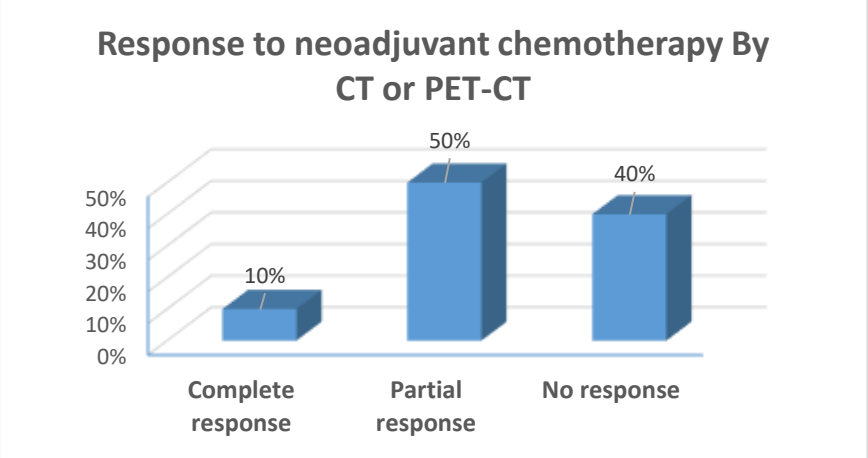

Figure 1. Clinical response to neoadjuvant chemotherapy.

All our patients had the procedure laparoscopically with only one case has been converted to open surgery as the tumor was locally advanced and seems to be infiltrating the spleen and while doing lymphadenectomy and assessing the true splenic infiltration, there was bleeding from the splenic vessels tributaries and associated with technical problem in the insufflator

• The specimen was extracted through Pfannenstiel incision in 14 cases (70.0%) and 6 cases (30.0%) through widening of a port.
• No adverse intraoperative major events occurred during Operations.

Pathological analysis of surgical specimens was performed and revealed the following data:

Of our 20 patients, 18 patients (90.0%) have undergone D2 Total gastrectomy, two patients have undergone extended resection either Splenectomy + Distal Pancreatectomy or only Splenectomy.

The pathology of all cases was invasive adenocarcinoma where four of them associated with signet ring differentiation (20.0%).

Most gastric adenocarcinomas in our study were moderately differentiated in 11 cases, grade II, (55.0%), while 7 cases were poorly differentiated, grade III, (35.0%). Two cases showed a complete pathological response.

Regarding T stage, 3 of our patients had no residual tumor as they had pathological complete response (15.0%), one patient had T1 tumor (5.0%), 7 patients had T2 tumor (35.0%), 7 patients had T3 tumor (35.0%), while 2 patients had T4a (10.0%).

Regarding N stage, majority of cases had no pathologically involved lymph nodes (8 cases representing 40.0%), 6 patients had one or two positive LNs (N1) representing 30.0%, while 5 patients had three to six positive LNs (N2) representing 25.0%. Only One patient had ten positive LNs (N3a) representing 5.0%.

The average number of retrieved LNs (whether involved or not) in surgical specimens was 27.35 ± 11.92 ranging from 15.00 to 67.00 LNs.

Of our 20 involved cases, 2 patients had pathological complete response to neoadjuvant treatment (10.0%), 4 patients had stage I disease (IB) (20.0%), 11 patients had stage II disease (55.0%), either stage IIA (30.0%), or stage IIB (25.0%) and 3 patients had stage III disease (15.0%), either stage IIIA (10.0%), or stage IIIB (5.0%).

		Count	%
Resection	D2 Total gastrectomy + Splenectomy + Distal Pancreatectomy	1	5.0%
	D2 Total gastrectomy + Splenectomy	1	5.0%
	D2 Total gastrectomy	18	90.0%
Pathology Type	Invasive Adenocarcinoma with Signet Ring Differentiation	4	20.0%
	Invasive Adenocarcinoma	16	80.0%
Tumor Grade	G0	2	10.0%
	G2	11	55.0%
	G3	7	35.0%
PT	T0	3	15.0%
	T1	1	5.0%
	T2	7	35.0%
	T3	7	35.0%
	T4a	2	10.0%
PN	N0	8	40.0%
	N1	6	30.0%
	N2	5	25.0%
	N3a	1	5.0%
AJCC stage	Stage 0	2	10.0%
	Stage IB	4	20.0%
	Stage IIA	6	30.0%
	Stage IIB	5	25.0%
	Stage IIIA	2	10.0%
	Stage IIIB	1	5.0%

Table 2. Pathological data.

	Mean	SD	Median	Minimum	Maximum
number of +ve LNs	2.10	2.67	1.00	0.00	10.00
total number of LNs	27.35	11.92	26.50	15.00	67.00

Table 3. N stage (pathological).

Surgical Safety Margin:

All cases had clear safety margins, either proximal or distal margin. The average proximal margin distance from the tumor edge 3.11 ± 1.07 cm. The least proximal margin was 2.00 cm, while the widest was 5.00 cm. The average distal margin distance from the tumor edge 9.55± 4.22 cm. The least distal margin was 4.00 cm, while the widest was 25.00 cm.

	Mean	SD	Median	Minimum	Maximum
Proximal margin from tumor edge (cm)	3.11	1.07	3.00	2.00	5.00
Distal margin from tumor edge (cm)	9.55	4.22	9.00	4.00	25.00
				Count	%
Proximal Margin status	Negative			20	100.0%
Distal Margin status	Negative			20	100.0%

Table 4. Surgical Safety Margin.

Response to preoperative treatment

Three patients had complete response to treatment (15.0%), 2 patients had near complete response (10.0%), 8 patients had partial therapy response (40.0%), while 7 patients had no response to treatment (35.0%).

Tumor Regression Grade (TRG) to neoadjuvant treatment According to modified Ryan Scheme	Count	%
0 (Complete response) = No viable cancer cells	3	15.0%
1 (Near complete response) = single cells or rare small groups of cancer cells < 10%	2	10.0%
2 (Partial response) = Residual cancer (10- 50%) with evident tumor regression	8	40.0%
3 (No response) = Extensive residual cancer > 50% with no tumor regression	7	35.0%

Table 5. Response to preoperative chemotherapy.

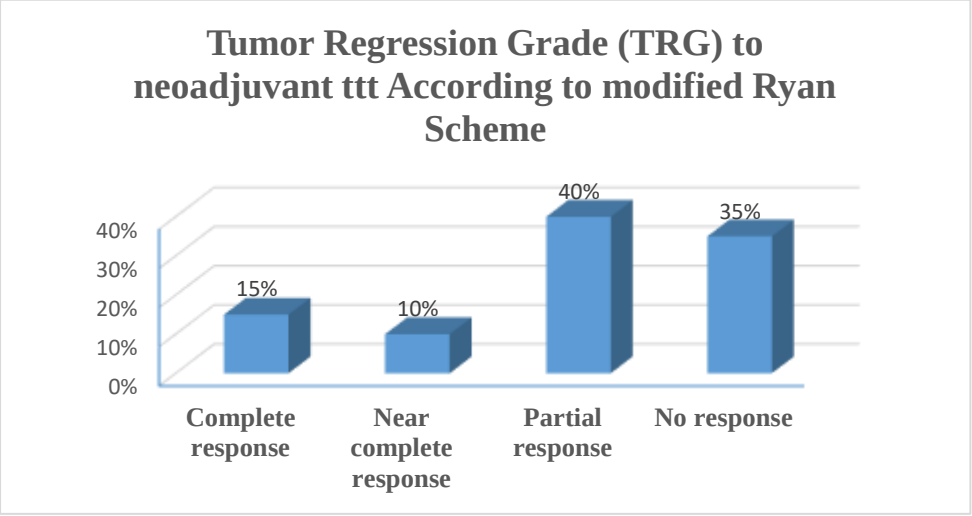

Figure 2. Pathological Response to neoadjuvant treatment.

Discussion:

The mean age of our patients was 53.90 years, with a considerable standard deviation of 10.85 years, reflecting a wide age range within our cohort. This distribution highlights the relevance of MITG across various age groups, from younger individuals to elderly patients, with gastric cancer necessitating surgical intervention. The inclusion of all age patients as young as 34 and as old as 74 underscores the importance of considering age-related factors in surgical decision-making and postoperative management. This is a quite similar to a study reported a mean age of 59 years (range: 27–86) for patients undergoing gastric cancer surgery, indicating that our cohort's age distribution, together with other studies, could not be a risk factor for developing gastric cancer (27).

Assessment of medical comorbidities, as reflected by the American Society of Anesthesiologists (ASA) classification, revealed that most of our patients were classified as ASA class I-II (85.0%), indicating minimal systemic disease and excellent overall health status. Although these risk factors are not a contraindication to performing MITG, they are identified as risk factors for postoperative complications in gastric cancer surgery in general. This underscores the importance of thorough preoperative assessment and risk stratification to identify potential factors that increase the risk of perioperative complications (28).

The tumor characteristics and preoperative data of patients undergoing minimally invasive total gastrectomy (MITG) and side to side esophago-jejunal anastomosis for gastric cancer provide critical insights into the disease stage, response to neoadjuvant treatment, and surgical timing within our patient cohort. Neoadjuvant chemotherapy plays a pivotal role in the management of locally advanced gastric cancer, aiming to downstage tumors, and improve oncological outcomes. In our study, all patients received four cycles of neoadjuvant chemotherapy (FLOT) regimen (5- Flurouracil, Leucovorin, Oxaliplatin, and Taxotere), with clinical response rate (RR) was 60.0% with complete clinical response in 2 patients (10.0%), and partial tumor response in 10 patients (50.0%). Eight patients had stable disease (40.0%). Koizumi et al., and Zhao et al., have found that the effective rate of neoadjuvant CTH in their clinical trials was 53%-59% and 47.9%- 49.8% respectively which is consistent with our cohort study (29), (30). A phase II clinical study in Japan showed that neoadjuvant CTH has demonstrated favorable clinical safety, as it resulted in high clinical and pathological responses without compromising surgical treatment in GC. Clinical RR was 88.2% with complete responses in 3 patients (8.8%) and partial responses in 27 patients (79.4%). Four patients had stable disease (11.8%) (31).

The interval between completion of neoadjuvant therapy and surgical intervention is a subject of ongoing debate, with optimal timing influenced by factors such as treatment response, tumor regression kinetics, and patient fitness. Surgery was usually performed within 4–6 weeks after the last dose of preoperative chemotherapy. However, the optimal timing of surgery is not clearly defined (32). In our study, the average duration between the end of chemotherapy and surgical procedure was 4.79 ± 0.93 weeks ranging from 3.30 to 6.00 weeks, falling within the commonly recommended timeframe for surgical resection following neoadjuvant treatment. This interval allows for adequate recovery from acute treatment-related toxicities while minimizing the risk of disease progression and facilitating optimal surgical outcomes.

The pathological data from our study provide critical insights into tumor characteristics, response to neoadjuvant treatment, and surgical adequacy in patients undergoing MITG with side-to-side intra-corporeal esophagojejunostomy for gastric cancer. Perioperative chemotherapy has been widely recommended as a standard treatment for LAGC in both Western and Eastern countries. This concept is based on the positive results of 2 benchmark phase 3 trials: the MAGIC7 and the Fédération Nationale des Centres de Lutte contre le Cancer/Fédération Francophone de Cancérologie Digestive (FNCLCC/FFCD) trials. (33- 37).

According to the previous studies, pathological data assessment of gastric cancer post neoadjuvant chemotherapy revealed that 48.9% were moderately differentiated adenocarcinomas, while the poorly differentiated ones were 51.1%. Regarding pathological (T) staging, the rate of T0, T1, T2, T3, T4 was (2.8, 5.1, 18.5, 28.7, 44.9 %) respectively and pathological (N) staging, the rate of N0, N1, N2, N3 was (33.2, 16.2, 22.7, 27.8 %), respectively. Regarding the group staging, the rate of stages I, II, III, IV was (4.4, 17.8, 71.1, 6.7 %), respectively (38- 40).

Most gastric adenocarcinomas in our study were moderately differentiated in 11 cases, grade II, (55.0%), while 7 cases were poorly differentiated, grade III, (35.0%). Two cases showed a complete pathological response. Regarding T stage, 3 of our patients had no residual tumor as they had pathological complete response (15.0%), while the rate of T1, T2, T3, T4 was (5, 35, 35, 10 %), respectively. Regarding N stage, majority of cases had no pathologically involved lymph nodes (N0 representing 40.0%), while the rate of N1, N2, N3a was (30, 25, 5 %), respectively.

Regarding the group staging, the rate of stages 0, I, II, III was (10, 20, 55, 15 %), respectively, where of our 20 involved cases, 2 patients had pathological complete response to neoadjuvant treatment (10.0%). For patients with localized resectable gastric cancer, the NCCN Guidelines recommend gastrectomy with a D1 or a modified D2 lymph node dissection, with a goal of examining 16 or more lymph nodes. The guidelines emphasize that D2 lymph node dissections should be performed by experienced surgeons in high-volume centers. Routine or prophylactic pancreatectomy is not recommended with D2 lymph node dissection, and splenectomy is acceptable only when the spleen is involved or extensive hilar adenopathy is noted (34).

Of our 20 patients, 18 patients (90.0%) have undergone D2 Total gastrectomy, two patients have undergone extended resection either Splenectomy + Distal Pancreatectomy or only Splenectomy. According to ("Japanese Gastric Cancer Treatment Guidelines (JGCTG) 2021 (6th Edition)," 2022), D2 lymphadenectomy is indicated for $cN+ or \geq cT2$ tumors and a D1 or D1 + for cT1N0 tumors. Since preand intraoperative diagnoses regarding the depth of tumor invasion and nodal involvement remain unreliable, D2 lymphadenectomy should be performed whenever the possibility of nodal involvement cannot be dismissed.

In terms of the adequacy of lymph node yield, in the previous studies, the number of harvested lymph nodes ranged from 15–84 LN (41) with an average number of retrieved LNs in these studies; (42), (27), and (43) of 47.89±9.54, 35.51 ± 10.44, and 46.1±16.5 LN, respectively.

In our study, the average number of retrieved LNs (whether involved or not) in surgical specimens was 27.35 ± 11.92 ranging from 15.00 to 67.00 LNs. All cases had clear safety margins, with the average proximal margin distance from the tumor edge was 3.11 ± 1.07 cm, while the average distal margin distance from the tumor edge was 9.55± 4.22 cm. These results match with the previous studies and also with NCCN and JGCTG guidelines indicating the efficacy of minimally invasive total gastrectomy with D2 lymphadenectomy allowing proper lymph nodes
retrieval in our study.

It's important to acknowledge the limitations of our study, including its non-comparative, single-center design, and relatively small sample size. Future studies with larger cohorts and longer follow-up periods are warranted to further elucidate the oncological outcomes, functional outcomes, and long-term survival benefits associated with MITG with side-to-side esophagojejunostomy in gastric cancer surgery. Additionally, prospective randomized trials comparing different techniques of intracorporeal esophagojejunostomy with traditional surgical approaches are needed to validate the safety, efficacy, and oncological equivalence of this technique in the multimodal management of gastric cancer.

Conclusion:

In summary, the pathological data from our study provide valuable insights into tumor characteristics, treatment response, and surgical outcomes in patients undergoing MITG with side-to-side esophagojejunostomy for gastric cancer. These findings contribute to the growing body of evidence supporting the role of MITG as a safe and effective surgical approach in the multidisciplinary management of gastric cancer, while also highlighting the need for further research to optimize patient selection, refine surgical techniques, and enhance long-term functional and oncological outcomes.

References

1. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 68(6), 394-424. https://doi.org/10.3322/caac.21492.

2. Etemadi, A., Safiri, S., Sepanlou, S. G., Ikuta, K., Bisignano, C., Shakeri, R., ... & Sekerija, M. (2020). The global, regional, and national burden of stomach cancer in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. The lancet Gastroenterology &

hepatology, 5(1), 42-54. doi:10.1016/S2468-1253(20)30020-0].

3. Choi, Y. Y., Noh, S. H., & Cheong, J. H. (2015). Evolution of gastric cancer treatment: from the golden age of surgery to an era of precision medicine. Yonsei medical journal, 56(5), 1177-1185. https://doi.org/10.3349/ymj.2015.56.5.1177.

4. Mantziari, S., St Amour, P., Abboretti, F., Teixeira-Farinha, H., Gaspar Figueiredo, S., Gronnier, C., ... & Schäfer, M. (2023). A comprehensive review of prognostic factors in patients with gastric adenocarcinoma. Cancers, 15(5), 1628.

5. Kitano, S., Iso, Y., Moriyama, M., & Sugimachi, K. (1994). Laparoscopy-assisted Billroth I gastrectomy. Surgical Laparoscopy Endoscopy & Percutaneous Techniques, 4(2), 146-148.

6. Lordick, F., Carneiro, F., Cascinu, S., Fleitas, T., Haustermans, K., Piessen, G., ... & Smyth, E. C. (2022). Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆. Annals of Oncology, 33(10), 1005-1020.https://doi.org/10.1016/j.annonc.2022.07.004.

7. Hayashi, H., Ochiai, T., Shimada, H., & Gunji, Y. (2005). Prospective randomized study of open versus laparoscopy-assisted distal gastrectomy with extraperigastric lymph node dissection for early gastric cancer. Surgical Endoscopy And Other Interventional Techniques, 19, 1172-1176.

8. Huscher, C. G., Mingoli, A., Sgarzini, G., Sansonetti, A., Di Paola, M., Recher, A., & Ponzano, C. (2005). Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. Annals of surgery, 241(2), 232-237. https://doi.org/10.1097/01.sla.0000151892.35922.f2.

9. Lee, J. H., Han, H. S., & Lee, J. H. (2005). A prospective randomized study comparing open vs laparoscopy-assisted distal gastrectomy in early gastric cancer: early results. Surgical Endoscopy And Other Interventional Techniques, 19, 168-173.

10. Kim, Y. W., Baik, Y. H., Yun, Y. H., Nam, B. H., Kim, D. H., Choi, I. J., & Bae, J. M. (2008). Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial.

11. Kim, H. H., Hyung, W. J., Cho, G. S., Kim, M. C., Han, S. U., Kim, W., ... & Song, K. Y. (2010). Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report—a phase III multicenter, prospective, randomized Trial (KLASS Trial).

12. Sakuramoto, S., Yamashita, K., Kikuchi, S., Futawatari, N., Katada, N., Watanabe, M., ... & Bax, L. (2013). Laparoscopy versus open distal gastrectomy by expert surgeons for early gastric cancer in Japanese patients: short-term clinical outcomes of a randomized clinical trial. Surgical endoscopy, 27, 1695-1705.

13. Katai, H., Mizusawa, J., Katayama, H., Takagi, M., Yoshikawa, T., Fukagawa, T., ... & Sasako, M. (2017). Short-term surgical outcomes from a phase III study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric cancer: Japan Clinical Oncology Group Study JCOG0912. Gastric Cancer, 20, 699-708.

14. Zhang, C. D., Yamashita, H., Zhang, S., & Seto, Y. (2018). Reevaluation of laparoscopic versus open distal gastrectomy for early gastric cancer in Asia: A meta-analysis of randomized controlled trials. International Journal of Surgery, 56, 31-43.

15. Kinoshita, T., Uyama, I., Terashima, M., Noshiro, H., Nagai, E., Obama, K., ... & Abe, T. (2019).

Long-term outcomes of laparoscopic versus open surgery for clinical stage II/III gastric cancer: a multicenter cohort study in Japan (LOC-A Study). Annals of surgery, 269(5), 887-894.

16. Lee, H. J., Hyung, W. J., Yang, H. K., Han, S. U., Park, Y. K., An, J. Y., ... & Kim, M. C. (2019). Short-term outcomes of a multicenter randomized controlled trial comparing laparoscopic distal gastrectomy with D2 lymphadenectomy to open distal gastrectomy for locally advanced gastric cancer (KLASS-02-RCT).

17. Yu, J., Huang, C., Sun, Y., Su, X., Cao, H., Hu, J., ... & Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. (2019). Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer: the CLASS-01 randomized clinical trial. Jama, 321(20), 1983-1992.

18. van der Wielen, N., Straatman, J., Daams, F., Rosati, R., Parise, P., Weitz, J., ... & van der Peet, D. L. (2021). Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. Gastric Cancer, 24, 258-271.

19. van der Veen, A., Brenkman, H. J., Seesing, M. F., Haverkamp, L., Luyer, M. D., Nieuwenhuijzen, G. A., ... & LOGICA Study Group. (2021). Laparoscopic versus open gastrectomy for gastric cancer (LOGICA): a multicenter randomized clinical trial. Journal of Clinical Oncology, 39(9), 978-989.

20. Hu, H. T., Ma, F. H., Xiong, J. P., Li, Y., Jin, P., Liu, H., ... & Tian, Y. T. (2022). Laparoscopic vs open total gastrectomy for advanced gastric cancer following neoadjuvant therapy: a propensity score matching analysis. World Journal of Gastrointestinal Surgery, 14(2), 161.

21. Trastulli, S., Desiderio, J., Lin, J. X., Reim, D., Zheng, C. H., Borghi, F., ... & Parisi, A. (2021). Laparoscopic compared with open D2 gastrectomy on perioperative and long-term, stage-stratified oncological outcomes for gastric cancer: a propensity score-matched analysis of the IMIGASTRIC database. Cancers, 13(18), 4526.

22. Caruso, S., Giudicissi, R., Mariatti, M., Cantafio, S., Paroli, G. M., & Scatizzi, M. (2022). Laparoscopic vs. open gastrectomy for locally advanced gastric cancer: a propensity score-matched retrospective case-control study. Current Oncology, 29(3), 1840-1865.

23. Shinohara, T., Satoh, S., Kanaya, S., Ishida, Y., Taniguchi, K., Isogaki, J., ... & Uyama, I. (2013). Laparoscopic versus open D2 gastrectomy for advanced gastric cancer: a retrospective cohort study. Surgical endoscopy, 27, 286-294.

24. Lombardi, P. M., Bernasconi, D., Baiocchi, G. L., Berselli, M., Biondi, A., Castoro, C., ... & Ferrari, G. (2022). Open versus laparoscopic gastrectomy for advanced gastric cancer: a propensity score matching analysis of survival in a western population—on behalf of the Italian Research Group for Gastric Cancer. Gastric Cancer, 25(6), 1105-1116.

25. Holguin, R. A. P., Stahl, K. A., Hendriksen, B. S., Wong, W. G., Olecki, E. J., Vining, C. C., ... & Shen, C. (2022). Predictors of Conversion During Minimally Invasive Gastrectomy for Malignancy. Journal of Surgical Research, 279, 275-284.

26. Sano, T., & Aiko, T. (2011). New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. Gastric Cancer, 14(2), 97–100. https://doi.org/10.1007/s10120-011-0040-6.

27. Wang, Y., Liu, Z., Shan, F., Ying, X., Zhang, Y., Li, S., Jia, Y., Jiang, Z., Yang, X., Li, B., Li, Z., & Ji, J. (2021). Short-term outcomes after totally laparoscopic total gastrectomy with

esophagojejunostomy constructed by π-shaped method versus overlap method. Journal of Surgical Oncology, 124(8), 1329–1337. https://doi.org/10.1002/jso.26642.

28. Roh, C. K., Lee, S., Son, S., Hur, H., & Han, S. (2021). Risk Factors for the Severity of Complications in Minimally Invasive Total Gastrectomy for Gastric Cancer: a Retrospective Cohort Study. Journal of the Korean Gastric Cancer Association, 21(4), 352. https://doi.org/10.5230/jgc.2021.21.e34.

29. Koizumi, W., Takiuchi, H., Yamada, Y., Boku, N., Fuse, N., Muro, K.,Komatsu, Y., & Tsuburaya, A. (2009). Phase II study of oxaliplatin plusS-1 as first-line treatment fo r advanced gastric cancer (G-SOX study).Annals of Oncology, 21(5), 1001–1005. https://doi.org/10.1093/annonc/mdp464.

30. Zhao, Q., Lian, C., Huo, Z., Li, M., Liu, Y., Fan, L., Tan, B., Zhao, X.,Zhang, Z., Wang, D., Liu, Y., Guo, H., Yang, P., Tian, Y., & Li, Y. (2020). The efficacy and safety of neoadjuvant chemotherapy on patients with advanced gastric cancer: A multicenter randomized clinical trial. Cancer Medicine, 9(16), 5731–5745. https://doi.org/10.1002/cam4.3224.

31. Konishi, S., Manaka, D., Ikeda, Y., Ota, T., Kudo, R., Ann, H.,Kawaguchi, K., Sasaki, N., Hamasu, S., & Nishitai, R. (2019). Phase II study of neoadjuvant chemotherapy with S-1 plus oxaliplatin at a dose of 130mg/m2 (nacG-SOX130) in clinical(c)Stage III gastric cancer.Annals of Oncology, 30, iv27–iv28.
https://doi.org/10.1093/annonc/mdz155.101.

32. Wu, C., Zhou, H., Wang, T., Zhang, X., Chen, Y., & Zhao, D. (2019). Impact of the time from the completion of neoadjuvant chemotherapy to surgery on the outcomes of patients with gastric cancer. Translational Cancer Research, 8(5), 1853–1862. https://doi.org/10.21037/tcr.2019.08.42.

33. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). (2022). Gastric Cancer, 26(1), 1–25. https://doi.org/10.1007/s10120-022-01331-8.

34. Ajani, J. A., D'Amico, T. A., Bentrem, D. J., Chao, J., Cooke, D.,Corvera, C., Das, P., Enzinger, P. C., Enzler, T., Fanta, P., Farjah, F.,Gerdes, H., Gibson, M. K., Hochwald, S., Hofstetter, W. L., Ilson, D.
H., Keswani, R. N., Kim, S., Kleinberg, L. R., . . . Pluchino, L. A. (2022).Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network,
20(2), 167–192. https://doi.org/10.6004/jnccn.2022.0008.

35. Lutz, M. P., Zalcberg, J. R., Ducreux, M., Adenis, A., Allum, W., Aust,D., Carneiro, F., Grabsch, H. I., Laurent-Puig, P., Lordick, F., Möhler,M., Mönig, S., Obermannova, R., Piessen, G., Riddell, A., Röcken, C.,
Roviello, F., Schneider, P. M., Seewald, S., . . . Otto, F. (2019). The 4th St. Gallen EORTC Gastrointestinal Cancer Conference: Controversial issues in the multimodal primary treatment of gastric, junctional and
oesophageal adenocarcinoma. European Journal of Cancer, 112, 1–8. https://doi.org/10.1016/j.ejca.2019.01.106.

36. Prc, N. H. C. O. (2019). Chinese guidelines for diagnosis and treatment of gastric cancer 2018 (English version). Chinese Journal of Cancer Research, 31(5), 707–737. https://doi.org/10.21147/j.issn.1000-

9604.2019.05.01.

37. Ychou, M., Boige, V., Pignon, J., Conroy, T., Bouché, O., Lebreton, G.,Ducourtieux, M., Bedenne, L., Fabre, J., Saint-Aubert, B., Genève, J.,Lasser, P., & Rougier, P. (2011). Perioperative Chemotherapy
Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial.Journal of Clinical Oncology, 29(13), 1715–1721. https://doi.org/10.1200/jco.2010.33.0597.

38. Lin, J., Tang, Y., Lin, G., Ma, Y., Desiderio, J., Li, P., Xie, J., Wang, J.,Lu, J., Chen, Q., Cao, L., Lin, M., Tu, R., Zheng, C., Parisi, A., Truty,M. J., & Huang, C. (2022). Association of Adjuvant Chemotherapy With
Overall Survival Among Patients With Locally Advanced Gastric Cancer After Neoadjuvant Chemotherapy. JAMA Network Open, 5(4),e225557. https://doi.org/10.1001/jamanetworkopen.2022.5557.

39. Charruf, A. Z., Ramos, M. F. K. P., Pereira, M. A., Dias, A. R., De Castria, T. B., Zilberstein, B., Cecconelo, I., & Ribeiro, U. (2020).Impact of neoadjuvant chemotherapy on surgical and pathological
results of gastric cancer patients: A case-control study. Journal of Surgical Oncology, 121(5), 833–839. https://doi.org/10.1002/jso.25839.

40. Achilli, P., De Martini, P., Ceresoli, M., Mari, G. M., Costanzi, A.,Maggioni, D., Pugliese, R., & Ferrari, G. (2017). Tumor response evaluation after neoadjuvant chemotherapy in locally advanced gastric
adenocarcinoma: a prospective, multi-center cohort study. Journal of Gastrointestinal Oncology, 8(6), 1018–1025.https://doi.org/10.21037/jgo.2017.08.13.

41. Yan, Y., Wang, D., Mahuron, K., Wang, X., Lu, L., Zhao, Z., Melstrom,L., Li, C., Paz, I. B., Liu, J., Fong, Y., Li, W., Fu, W., & Woo, Y. (2023).Different Methods of Minimally Invasive Esophagojejunostomy After
Total Gastrectomy for Gastric Cancer: Outcomes from Two Experienced Centers. Annals of Surgical Oncology, 30(11), 6718–6727.https://doi.org/10.1245/s10434-023-13771-2.

42. Chen, C., Wei, M., Feng, X., Han, H., Wang, C., He, Q., & Yu, W.(2020). Comparison of reverse puncture device and overlap in laparoscopic total gastrectomy for gastric cancer. Journal of Minimal Access Surgery, 18(1), 31. https://doi.org/10.4103/jmas.jmas_276_19.

43. Yang, H., Hyung, W. J., Han, S., Lee, Y., Park, J., Cho, G. S., Kwon, O.K., Kong, S., Kim, H., Lee, H., Kim, W., Ryu, S. W., Jin, S., Oh, S. J.,Ryu, K. W., Kim, M., Ahn, H. S., Park, Y. K., Kim, Y. H., . . . Kim, J. (2020). Comparison of surgical outcomes among different methods of esophagojejunostomy in laparoscopic total gastrectomy for clinical stage I proximal gastric cancer: results of a single-arm multicenter phase II clinical trial in Korea, KLASS 03. Surgical Endoscopy, 35(3), 1156–1163. https://doi.org/10.1007/s00464-020-07480-0.