Canadian Journal of Gastroenterology and Hepatology

Minimally Invasive Gastric Cancer Surgery in the Era of Precision Medicine

Lead Guest Editor: Xiaohua Jiang
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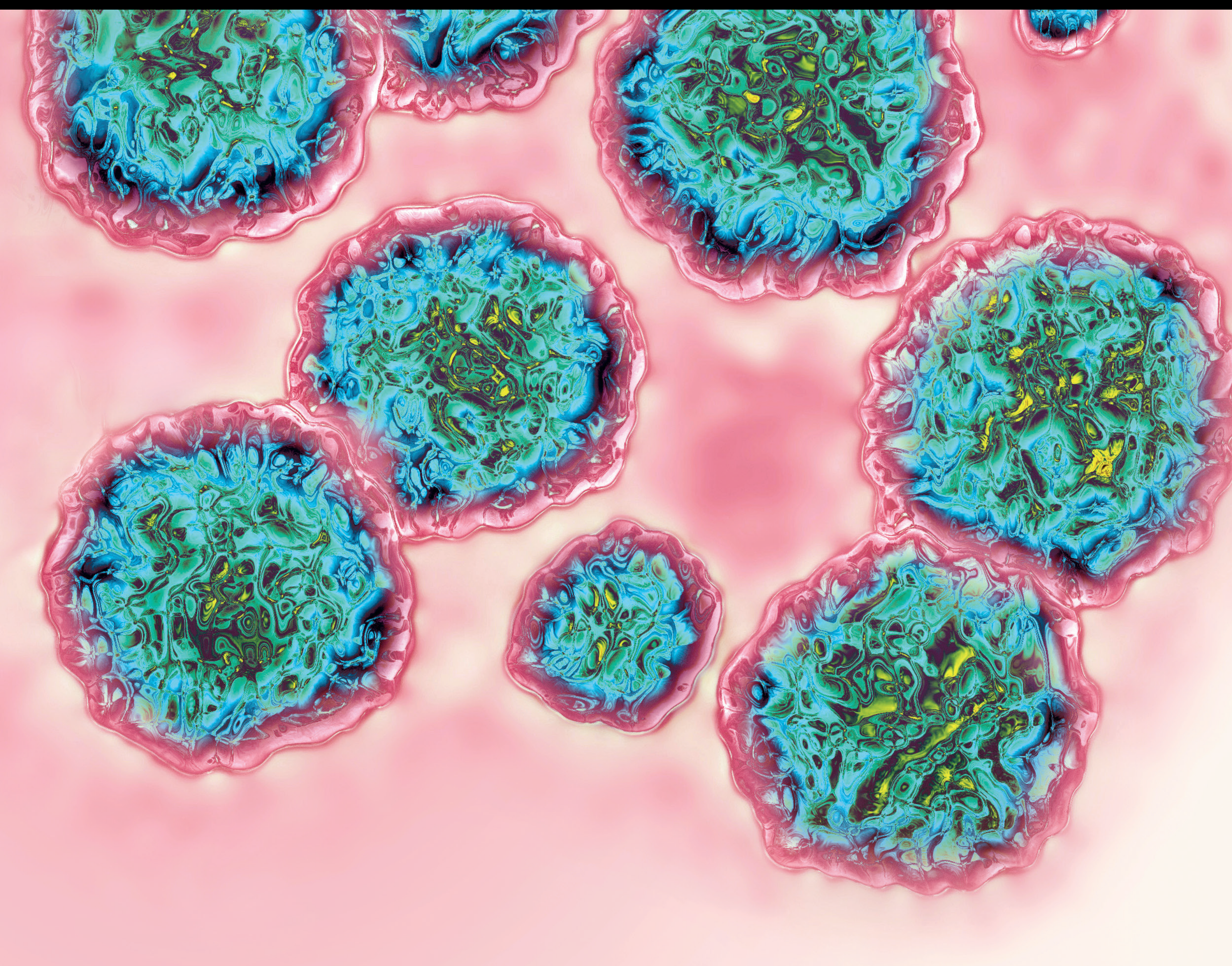

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Contents

Hindawi
Canadian Journal of Gastroenterology and Hepatology
Volume 2023, Article ID 6351330, 6 pages
https://doi.org/10.1155/2023/6351330

Research Article

Comparison of [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/MRI in the Preoperative Diagnosis of Gastric Cancer

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Received 26 May 2022; Revised 18 September 2022; Accepted 10 October 2022; Published 8 April 2023

Academic Editor: Alessandro Granito

Purpose. Our objective was to compare the value of positron emission tomography/magnetic resonance imaging (PET/MRI) with the new imaging agent [^{68}Ga]Ga-DOTA-FAPI-04 and the traditional imaging agent [^{18}F]FDG for the preoperative diagnosis of gastric cancer. *Methods*. Forty patients with gastric cancer diagnosed by gastroscopy in gastrointestinal surgery at our hospital from June 2020 to January 2021 were analyzed. All patients underwent simultaneous [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/MRI. The standard uptake value (SUV), fat removal standard uptake value (SUL), and diagnostic sensitivity, specificity, and accuracy for primary and metastatic lesions were compared, and their diagnostic value for different lymph node dissection stages was analyzed. *Results*. The median age of the patients in this cohort was 68 years. Twenty-nine patients underwent surgery, and 11 patients underwent gastroscopic biopsy. The SUV_{max} of primary lesions in the FDG group and the FAPI group was 5.74 ± 5.09 and 8.06 ± 4.88, respectively ($P < 0.01$); SUL_{max} values were 3.52 ± 2.80 and 5.64 ± 3.25, respectively ($P < 0.01$). The SUV_{max} of metastases in the two groups was 3.81 ± 3.08 and 5.17 ± 2.80, respectively ($P < 0.05$). The diagnostic sensitivities for primary lesions in the FDG group and the FAPI group were 0.72 and 0.94, respectively ($P < 0.05$). Combined with postoperative pathological staging, there was no difference in diagnostic sensitivity and specificity of lymph node staging between the FDG and FAPI groups ($P > 0.05$). *Conclusion*. Compared with the traditional imaging agent, [^{68}Ga]Ga-DOTA-FAPI-04 has better diagnostic efficiency but no substantial advantage for preoperative lymph node staging.

1. Introduction

Cancer-associated fibroblasts (CAFs) are the main components of the matrix around epithelial cancer cells and can selectively produce fibroblast activation protein (FAP). FAP is highly expressed in a variety of epithelial cancers, such as gastric cancer, colorectal cancer, esophageal cancer, and ovarian cancer, but it is almost not expressed in the matrix of normal tissues [1, 2]. Based on this characteristic, fibroblast activation protein inhibitor (FAPI) has been used as the imaging agent for positron emission tomography (PET) in the last few years, for which [^{68}Ga]Ga-FAPI-04 was developed [3]. Because stromal cells account for 90% of the total weight of tumors, cell matrix-based targeted PET may be more sensitive than glucose metabolism PET imaging. Studies have shown that [^{68}Ga]Ga-FAPI-04 has stable performance and can reflect some characteristics of different solid tumors [4, 5]. Other studies have shown that [^{68}Ga]Ga-FPAI-04 positron emission tomography/computed tomography (PET/CT) results in clearer contours and a higher target-to-background ratio than [^{18}F]FDG PET/CT for solid tumors [6]. In addition, [^{68}Ga]Ga-FAPI-04 PET/CT has a higher uptake value and diagnostic accuracy for some suspicious tumors that cannot be characterized by [^{18}F]FDG PET/CT [7].

Gastric cancer is a common disease, and its occurrence is related to many factors, such as HP and garlic [8, 9]. PET/MRI has been widely used in the evaluation of gastric cancer in the last few years. It has the advantages of better soft tissue contrast, functional imaging, and less ionizing radiation. Its disadvantage is also obvious: it is easily affected by respiration and gastric peristalsis during imaging, which results in artifacts. It was found that [^{18}F]FDG PET/MRI has better advantages in preoperative TNM staging than PET/CT [10]. Another study showed that multidetector CT (MDCT) combined with [^{18}F]FDG PET/MRI improves the diagnostic accuracy of a preoperative M-stage in recurrent gastric cancer and has advantages in evaluating the resectability of lesions [11]. At present, research on [^{68}Ga]Ga-FAPI-04 PET/MRI in the diagnosis of gastric cancer is very limited. This study sought to compare the value of [^{68}Ga]Ga-FAPI-04 and [^{18}F]FDG PET/MRI for the diagnosis of gastric cancer.

2. Materials and Methods

2.1. Patients. This study is a prospective cohort study that included 40 patients with gastric cancer diagnosed by gastroscopy in the Department of Gastrointestinal and Anorectal Surgery of our hospital from June 2020 to January 2021. The inclusion criteria were as follows: diagnosed with gastric cancer by gastroscopy, age between 18 and 80 years, and no contraindication for PET or MRI. The exclusion criteria were as follows: combined with other tumors, accompanied by pyloric obstruction or bleeding or other severe organ dysfunction. All patients underwent simultaneous [^{68}Ga]Ga-FAPI-04 and [^{18}F]FDG PET/MRI.

2.2. PET/MRI Imaging. All patients underwent [^{68}Ga]Ga-FAPI-04 (d1) and [^{18}F]FDG PET/MRI (d3) in turn, with an interval of more than 48 hours. All examinations were conducted in the nuclear medicine discipline of East Hospital affiliated with Tongji University according to the standard process. [^{18}F]FDG PET/MRI : the patient fasted for 12 h before the examination, with blood glucose < 11 mmol/L. After lying flat for 20 minutes, [^{18}F]FDG (5.5 MBq/kg) was intravenously injected, and the patient drank 1000 ml of water after resting for 40 minutes. The scanning range was whole-body from the head to the groin for approximately 30 minutes. [^{68}Ga]Ga-DOTA-FAPI-04 PET/MRI: [^{68}Ga]Ga-DOTA-FAPI-04 was injected at the same concentration, and the remaining steps were the same as those for [^{18}F]FDG PET/MRI.

2.3. Imaging Review. PET/MRI images were analyzed by two nuclear medicine physicians with experience in PET/MRI for more than 2 years. The standard uptake value (SUV), fat removal standard uptake value (SUL), diagnostic sensitivity, specificity, and accuracy of primary and metastatic lesions were measured, and their diagnostic value for different lymph node dissection stages was analyzed. The participants were not given information about the other PET/MRI scan. In case of disagreement in diagnosis, the two doctors discussed and reached a consensus.

The main function of PET is to detect a lesion, and MRI images are used to confirm whether the hypermetabolic area is the tumor. TNM staging of gastric cancer was determined by referring to the 8th edition of the AJCC gastric cancer staging system. The criteria for lymph node metastasis of gastric cancer were as follows: shortest diameter > 5 mm, necrotic signs in the center, high DWI signal and low ADC signal, and higher metabolism than the background.

2.4. Statistical Analysis. Data are expressed as the mean ± standard deviation, and statistical analyses were conducted using SPSS 22.0 software. *T* tests were used to compare measurement data between two groups, and the chi-square test was used to compare count data. Sensitivity, specificity, and accuracy were compared by the McNemar test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patients' Clinical Characteristics. A total of 40 patients with a median age of 68 years were enrolled in this study, including 32 males and 8 females, with an average BMI of 22.1 ± 2.61. A total of 29 patients underwent radical resection, and 11 underwent biopsy only. Thirty-six cases of gastric cancer and 4 cases of benign diseases were confirmed by pathology. Thirteen patients had CEA > 5 ng/ml, and 10 patients had CA199 > 37 ng/ml. There were 18 cases with HER2 expression (+~+++), 5 cases with dMMR, and 2 cases with PDL-1 percentage > 5% (Table 1).

3.2. Uptake of [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04. All patients underwent [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04 PET/MRI (Figures 1 and 2). The results showed that the maximum SUVs (SUV_{max}) of primary lesions in the [^{18}F]FDG group and [^{68}Ga]Ga-DOTA-FAPI-04 group were 5.74 ± 5.09 and 8.06 ± 4.88, respectively (Table 2, $P < 0.01$); maximum SUL (SUL_{max}) values were 3.52 ± 2.80 and 5.64 ± 3.25, respectively ($P < 0.01$). For metastatic lesions, SUV_{max} values were 3.81 ± 3.08 and 5.17 ± 2.80 in the [^{18}F]FDG group and [^{68}Ga]Ga-DOTA-FAPI-04 group, respectively ($P < 0.05$); SUL_{max} values were 2.65 ± 2.21 and 3.80 ± 1.74, respectively ($P > 0.05$). There was no substantial difference between SUV_{max} or SUL_{max} between the two groups ($P > 0.05$).

3.3. Diagnostic Efficiency of Primary and Metastatic Lesions. The sensitivity, specificity, and accuracy of [^{18}F]FDG for the diagnosis of primary lesions were 0.72, 0.25, and 0.78, respectively; those for [^{68}Ga]Ga-DOTA-FAPI-04 were 0.94, 0, and 0.85, respectively. There was a substantial difference in sensitivity ($P < 0.05$) but no difference in specificity and accuracy ($P > 0.05$). The sensitivity, specificity, and accuracy of [^{18}F]FDG for the diagnosis of metastatic lesions were 0.33, 0.82, and 0.62, respectively; those for [^{68}Ga]Ga-DOTA-FAPI-04 were 0.58, 0.71, and 0.66, respectively, with no substantial difference (Table 3, $P > 0.05$).

Table 1: Patient characteristics.

Total patients	40
Median age	68
BMI	22.1 ± 2.61
Sex	
Male	32
Female	8
Treatment	
Biopsy only	11
Resection	29
Histology	
Adenocarcinoma	23
Signet ring cell carcinoma	13
Benign	4
CEA > 5 ng/ml	13
CA199 > 37 ng/ml	10
Tumor diameter	3.6 ± 1.56
Her2	
++/+++	10
+	8
−	8
None	14
MMR	
dMMR	5
pMMR	35
PDL-1	
>= 5%	2
< 5%	38

3.4. Diagnostic Efficiency of Lymph Node Staging. The lymph node staging of all 40 patients in the two groups is shown in Tables 4 and 5. Based on the postoperative pathology of 29 patients who underwent surgical resection, the numbers of N0, N1, N2, and N3 cases were 17, 6, 1, and 5, respectively. Correspondingly, the numbers of N0, N1, N2, and N3 were 21, 3, 4, and 1 diagnosed in the [^{18}F]FDG group and 18, 3, 5, and 3 in the [^{68}Ga]Ga-DOTA-FAPI-04 group, respectively (Table 4). A total of 7 patients received preoperative neoadjuvant chemotherapy.

The sensitivity, specificity, and accuracy of [^{18}F]FDG were 0.33, 0.82, and 0.62, and that of [^{68}Ga]Ga-DOTA-FAPI-04 were 0.58, 0.71, and 0.66, respectively. The sensitivity, specificity, and accuracy of the two groups in the N1 phase were 0 and 0.33, 0.77 and 0.81, and 0.69 and 0.76, respectively, those of the N2 phase were 0 and 0, 0.96 and 0.96, and 0.83 and 0.79, and those of the N3 stage were 0 and 0, 0.82 and 0.81, and 0.79 and 0.72. However, there were no substantial differences between the two groups (Table 5, $P > 0.05$).

4. Discussion

The standard treatment of gastric cancer depends on accurate preoperative staging [12], which is also important for metastatic gastric cancer. The purpose of this prospective study was to compare the diagnostic value of the new imaging agent [^{68}Ga]Ga-DOTA-FAPI-04 and the traditional agent [^{18}F]FDG. Our results showed that the maximum uptake value of [^{68}Ga]Ga-DOTA-FAPI-04 was better than that of [^{18}F]FDG, with sensitivity in the diagnosis of primary lesions of gastric cancer being better than that of [^{18}F]FDG. Nonetheless, there was no substantial difference in the sensitivity and specificity of lymph node staging between the two groups.

The uptake values of SUV_{max} and SUL_{max} in the FAPI group were higher than those in the FDG group, which was consistent with the results of Chen et al. [13]. Some studies have shown that uptake of [^{18}F]FDG is lower in diffuse gastric cancer, gastric mucinous adenocarcinoma, and signet ring cell carcinoma, which affects the diagnosis of gastric cancer [14]. Therefore, our results suggest that [^{68}Ga]Ga-DOTA-FAPI-04 may be able to compensate for this deficiency, even though we did not conduct a subgroup analysis of gastric cancer histology type in this study. Further diagnostic analysis found that the sensitivity of [^{68}Ga]Ga-DOTA-FAPI-04 for primary lesions was 0.94, which was considerably higher than that of [^{18}F]FDG. This was consistent with the study of Guo et al. [15]. We speculate that this is related to the high uptake rate of [^{68}Ga]Ga-DOTA-FAPI-04. Because all patients were diagnosed with gastric cancer by gastroscopy, specificity could not be compared for the two groups. In the comparison of diagnostic efficacy for metastases, we found that the sensitivity of the FAPI group tended to increase (0.58 and 0.33, respectively), but there was no substantial difference in the P value. We speculate that this may have been due to the inconsistent judgment criteria for positive lymph nodes. In previous studies, the cutoff value of a lymph node's short diameter (usually 5 mm) was used as the criterion for determining positive lymph nodes [16, 17]. However, inflammation can also lead to lymph node enlargement, and even metastatic lymph nodes do not necessarily show a volume increase. These factors may affect the diagnostic efficacy of PET/CT or PET/MRI for lymph node metastasis. In addition, recent studies have shown that lymph node metastasis can be identified by DWI sequences and ADC images [18]. Therefore, the MRI signal combined with SUV_{max} was used to identify lymph node metastasis in this study. Although our data show that SUV_{max} of the FAPI group and FDG group was not significantly different, we speculate that this may have been due to the small number of cases or selection bias. However, the increasing trend of SUV_{max} in the FAPI group suggests that [^{68}Ga]Ga-DOTA-FAPI-04 had certain advantages in determining lymph node metastasis in gastric cancer.

We attempted to compare the diagnostic efficiency of the two imaging agents for different N stages of gastric cancer, though the results showed that the difference in diagnostic sensitivity and specificity between the two groups was not significant at N0 or N1-N3. We speculate the following reasons in addition to the factors of positive diagnostic criteria for lymph nodes. First, inflammation in lymph nodes may lead to increased uptake. Indeed, it has been reported that inflammation may lead to an abnormal increase in FDG metabolism in lymph nodes, thus increasing the false-negative rate [19]. Second, there may have been selection bias with regard to the patients enrolled. Only 41.4% (12/29) of the patients had lymph node metastasis confirmed by postoperative pathology. The small number of N1, N2, and N3 stage cases

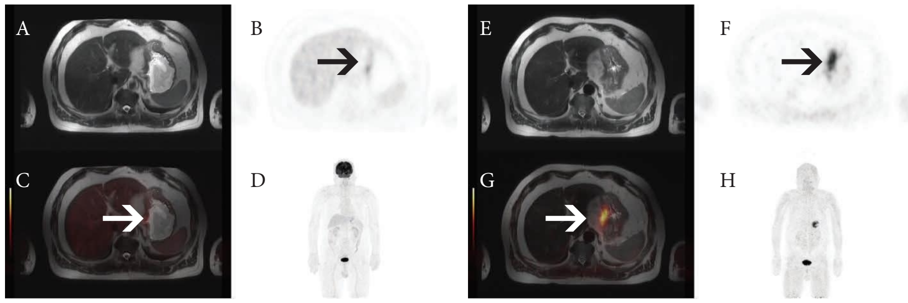

Figure 1: A 64-year-old male patient with gastric cancer diagnosed as gastric fundus tumor by gastroscopy. FDG-PET MRI showed a slight increase in FDG metabolism, with an SUVmax of 3.74 and no increase in metabolism in perigastric lymph nodes (A-D). FAPI-PET/MRI showed obvious thickening of the cardia, gastric fundus and lesser curvature of the gastric body, and an abnormal increase in FAPI uptake (arrow), with an SUV_{max} of 11.2 (E-H). Small lymph node shadows were detected behind the lesser curvature of the stomach and the pancreas, and there was no FAPI uptake.

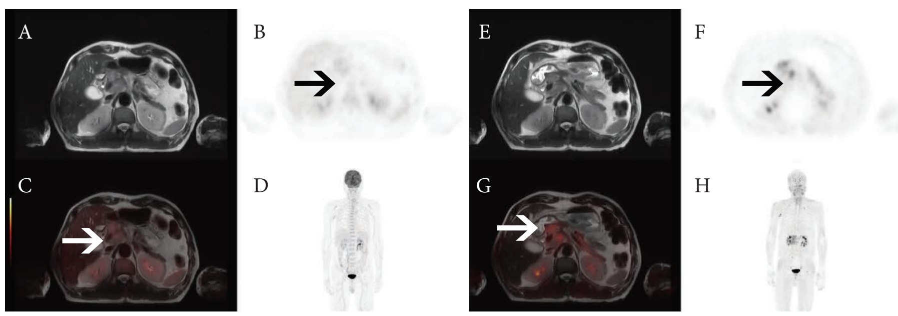

Figure 2: A 63-year-old male patient with gastric cancer, a gastroscopy showed that gastric cancer had invaded the lower esophagus, with perigastric infiltration. PET/MRI showed abnormal increases (arrow) in FDG metabolism (A-D) and FAPI uptake (E-H).

Table 2: Comparison of [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04 uptake in gastric cancer.

	Primary lesions		Metastatic lesions	
	SUV_{max}	SUL_{max}	SUV_{max}	SUL_{max}
FDG	5.74 ± 5.09	3.52 ± 2.80	3.81 ± 3.08	2.65 ± 2.21
FAPI	8.06 ± 4.88	5.64 ± 3.25	5.17 ± 2.80	3.80 ± 1.74
P value	0.004	0.005	0.018	0.08

Table 3: Diagnostic performances of [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/MRI in assessment of gastric tumor and lymph node involvement.

Basis of analysis and modality	Imaging diagnosis	Pathologic diagnosis		Sensitivity	Specificity	Accuracy
Primary lesions		+	−			
FDG	+	26	3	0.72	0.25	0.68
	−	10	1			
FAPI	+	34	3	0.94	0.25	0.88
	−	2	1			
P value				0.02	1.00	0.07
Metastatic lesions						
FDG	+	4	3	0.33	0.82	0.62
	−	8	14			
FAPI	+	7	5	0.58	0.71	0.66
	−	5	12			
P value				0.25	0.50	0.79

Table 4: Clinical stage and pathological stage of patient.

N stage	Standard	N		Neoadjuvant chemotherapy
		FDG	FAPI	
N0	17	21	18	0
N1	6	3	3	2
N2	1	4	5	2
N3	5	1	3	3

Table 5: Diagnostic results of N stage between [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/MRI according to the gold standard.

		Sensitivity (%)	Specificity (%)	Accuracy (%)
N0	FDG	0.82	0.63	0.62
	FAPI	0.71	0.58	0.66
	P	1.00	0.50	0.56
N1	FDG	0.00	0.77	0.69
	FAPI	0.33	0.81	0.76
	P	None	1.00	0.27
N2	FDG	0.00	0.96	0.83
	FAPI	0.00	0.96	0.79
	P	None	1.00	0.47
N3	FDG	0.00	0.82	0.79
	FAPI	0.00	0.81	0.72
	P	None	0.50	0.25

precluded analysis. In addition, only 29 of 40 patients received surgical treatment, and the limited number of cases affected N-stage diagnostic efficiency. In addition, we believe that the use of FAPI is beneficial to improve the preoperative N stage of patients, as well as perioperative management including neoadjuvant chemotherapy and postoperative follow-up. The results of this study show that the uptake value of [^{68}Ga]Ga-DOTA-FAPI-04 in gastric cancer is higher than that of [^{18}F]FDG; its diagnostic efficiency for primary lesions is also higher, which indicates that [^{68}Ga]Ga-DOTA-FAPI-04 MRI may be a more effective method for the diagnosis of gastric cancer. Of course, this study also had some limitations, such as the small number of enrolled cases and the lack of data on tumor T staging. In addition, the number of patients with dMMR and PDL-1 positivity was relatively small, and there was a lack of subgroup analysis. Prospective studies with a larger number of patients in the future may provide more evidence.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

This study was supported by National Natural Science Foundation of China (No. 81871953) and Medical Discipline Construction Project of Pudong Health Committee of Shanghai (No. PWYgf2021-02).

References

[1] M. A. Mankoff Da Sellmyer, "PET of fibroblast-activation protein for breast cancer diagnosis and staging," *Radiology*, vol. 302, no. 1, pp. 48-49, 2022.

[2] R. Katsube, K. Noma, T. Ohara et al., "Fibroblast activation protein targeted near infrared photoimmunotherapy (NIR PIT) overcomes therapeutic resistance in human esophageal cancer," *Scientific Reports*, vol. 11, no. 1, p. 1693, 2021.

[3] M. Rohrich, D. Leitz, F. M. Glatting et al., "Fibroblast activation protein-specific PET/CT imaging in fibrotic interstitial lung diseases and lung cancer: a translational exploratory study," *Journal of Nuclear Medicine*, vol. 63, no. 1, pp. 127–133, 2022.

[4] T. Lindner, A. Loktev, A. Altmann et al., "Development of quinoline-based theranostic ligands for the targeting of fibroblast activation protein," *Journal of Nuclear Medicine*, vol. 59, no. 9, pp. 1415–1422, 2018.

[5] F. L. Giesel, C. Kratochwil, T. Lindner et al., "(68)Ga-FAPI PET/CT: biodistribution and preliminary dosimetry estimate of 2 DOTA-containingFAP-targeting agents in patients with various cancers," *Journal of Nuclear Medicine*, vol. 60, no. 3, pp. 386–392, 2019.

[6] C. Kratochwil, P. Flechsig, T. Lindner et al., "(68)Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer," *Journal of Nuclear Medicine*, vol. 60, no. 6, pp. 801–805, 2019.

[7] H. Chen, L. Zhao, D. Ruan et al., "Usefulness of [(68)Ga]Ga-DOTA-FAPI-04 PET/CT in patients presenting with inconclusive [(18)F]FDG PET/CT findings," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 48, no. 1, pp. 73–86, 2021.

[8] I. A. Charitos, D. D'Agostino, S. Topi, and L. Bottalico, "40 years of *Helicobacter pylori*: a revolution in biomedical thought," *Gastroenterology Insights*, vol. 12, no. 2, pp. 111–135, 2021.

[9] A. Forma, Z. Chilimoniuk, J. Januszewski, and R. SitarZ, "The potential application of allium extracts in the treatment of gastrointestinal cancers," *Gastroenterology Insights*, vol. 12, no. 12, 2021.

[10] Y Liu, J. J. Liu, J. X. Cui et al., "Comparing PET/MRI with PET/CT for pretreatment staging of gastric cancer," *Gastroenterology Research and Practice*, vol. 2019, Article ID 9564627, 11 pages, 2019.

[11] I. Yoon, J. S. Bae, J. Yoo, and S. H. Lee Dh Kim, "Added value of [(18)F]FDG PET/MRI over MDCT alone in the staging of recurrent gastric cancer," *European Radiology*, vol. 31, no. 10, pp. 7834–7844, 2021.

[12] K. Nagao, T. Shimura, T. Yamada et al., "The modified eCura system for identifying high-risk lymph node metastasis in patients with early gastric cancer resected by endoscopic submucosal dissection," *Gastroenterology Insights*, vol. 13, no. 1, pp. 60–67, 2022.

[13] H. P. Y. Chen, J. Wu, L. Zhao et al., "Comparison of [(68)Ga] Ga-DOTA-FAPI-04 and [(18)F] FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer," *European Journal of Nuclear*

Medicine and Molecular Imaging, vol. 47, no. 8, pp. 1820–1832, 2020.

[14] M. Yun, "Imaging of gastric cancer metabolism using 18 F-FDG PET/CT," *Journal of Gastric Cancer*, vol. 14, no. 1, pp. 1–6, 2014.

[15] W. Guo, L. Zhao, C. Fan et al., "Imaging fibroblast activation protein in liver cancer: a single-center post hoc retrospective analysis to compare [(68)Ga]Ga-FAPI-04 PET/CT versus MRI and [(18)F]-FDG PET/CT," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 48, no. 5, pp. 1604–1617, 2021.

[16] K. Paydary, S. M. Seraj, M. Z. Zadeh et al., "The evolving role of FDG-PET/CT in the diagnosis, staging, and treatment of breast cancer," *Molecular Imaging and Biology*, vol. 21, no. 1, pp. 1–10, 2019.

[17] E. C. Gertsen, A. S. Borggreve, H. J. F. Brenkman et al., "Evaluation of the implementation of FDG-PET/CT and staging laparoscopy for gastric cancer in The Netherlands," *Annals of Surgical Oncology*, vol. 28, no. 4, pp. 2384–2393, 2021.

[18] Y. X. Ge, S. D. Hu, Z. Wang et al., "Feasibility and reproducibility of T2 mapping and DWI for identifying malignant lymph nodes in rectal cancer," *European Radiology*, vol. 31, no. 5, pp. 3347–3354, 2021.

[19] P. Martineau, J. Gregoire, F. Harel, and M. Pelletier-Galarneau, "Assessing cardiovascular infection and inflammation with FDG-PET," *American Journal of Nuclear Medicine and Molecular Imaging*, vol. 11, no. 1, pp. 46–58, 2021.

Hindawi
Canadian Journal of Gastroenterology and Hepatology
Volume 2022, Article ID 9094934, 5 pages
https://doi.org/10.1155/2022/9094934

Research Article

Application of Overlap Gastroduodenostomy in Billroth I Anastomosis after Totally Laparoscopic Distal Gastrectomy for Gastric Cancer

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Received 11 February 2022; Revised 1 July 2022; Accepted 16 July 2022; Published 12 August 2022

Academic Editor: Shun Zhang

Delta-shaped gastroduodenostomy (DSGD) and overlap gastroduodenostomy (OGD) are the two most widely used intracorporeal Billroth I anastomosis methods after distal gastrectomy. In this study, we compared the short-term outcomes of DSGD and OGD in total laparoscopic distal gastrectomy (TLDG). In a retrospective cohort study, we examined 92 gastric cancer patients who underwent TLDG performed by the same surgeon between January 2014 and June 2018. All patients underwent Billroth I reconstruction (OGD, $n = 45$; DSGD, $n = 47$) and D2 lymph node dissection. We retrospectively reviewed the surgical outcomes, clinical pathological results, and endoscopy results. Laparoscopic surgery was successfully performed in both groups without conversion to open surgery. The demographic and clinical characteristics were similar between the two groups ($P > 0.05$). There were no significant differences between the two groups in operation time (158.9 ± 13.6 min vs. 158.8 ± 14.8 min, $P = 0.955$), anastomotic time (19.4 ± 3.0 min vs. 18.8 ± 2.9 min, $P = 0.354$), intraoperative blood loss (88.9 ± 25.4 mL vs. 83.7 ± 24.3 mL, $P = 0.321$), number of lymph node dissections (31.0 ± 7.1 vs. 29.2 ± 7.5, $P = 0.229$), length of hospital stay (8.8 ± 2.7 days vs. 9.1 ± 3.0 days, $P = 0.636$), fluid intake time (3.1 ± 0.7 days vs. 3.2 ± 0.7 days, $P = 0.914$), and morbidity of postoperative complications (6.7% [3/45] vs. 10.6% [5/47], $P = 0.499$). Endoscopy performed 6 months postoperatively showed that the residual food ($P = 0.033$), gastritis ($P = 0.029$), and bile ($P = 0.022$) classification score significantly decreased in the OGD group, and there were no significant differences 12 months postoperatively. OGD is a safe and effective reconstruction technique with comparable postoperative surgical outcomes and endoscopy results when compared with those of DSGD.

1. Introduction

Gastric cancer (GC) is one of the most common malignancies in China [1]. The incidence of the early detection of GC has increased significantly with an increase in the frequency of endoscopic screening. Surgical resection remains the only curative treatment. Laparoscopic gastrectomy has been widely used since it was first reported in 1994 by Kitano et al. [2]. In recent years, an increasing number of clinical studies have shown that laparoscopic gastrectomy has similar or better outcomes than open gastrectomy [3–6].

Owing to the narrow and restricted space, it is difficult to perform anastomosis in laparoscopic-assisted distal gastrectomy (LADG), especially in obese patients or in patients with a small remnant stomach. Therefore, many surgeons prefer total laparoscopic distal gastrectomy (TLDG), and several techniques for intracorporeal anastomosis have been developed [7].

Billroth I, Billroth II, and Roux-en-Y are the three most commonly used reconstruction methods after distal gastrectomy, and Billroth I gastroduodenostomy is the only method that retains the physiological digestive tract and poses no risk of internal hernia. Delta-shaped gastroduodenostomy (DSGD), which was first introduced by Kanaya et al. [8], is the most popular anastomosis method in Billroth I reconstruction after TLDG overlap gastroduodenostomy (OGD), first introduced by Song et al. [9] and modified by Byun et al. [10], appears to be another simple and convenient method for Billroth I reconstruction after TLDG. In this study, we assess the short-term results of OGD and compare them with those of DSGD.

2. Materials and Methods

2.1. Materials. This single-surgeon retrospective cohort study was performed between January 2014 and June 2018 at six different hospitals in Zhejiang Province, China. The inclusion criteria were as follows: (1) preoperative diagnosis of cT1N0M0~cT2N0M0-stage GC and (2) postoperative pathology confirming R0 resection. All perioperative management procedures were performed under the surgeon's guidance.

According to the above criteria, 92 patients were included in this retrospective study, including 47 with DSGD and 45 with OGD. As the surgeon changed the main reconstruction method when performing Billroth I anastomosis, DSGD was mainly completed between January 2014 and September 2016, and OGD was mainly completed between September 2016 and June 2018.

2.2. Surgical Procedure. Under general anesthesia, the patients were placed in the reverse Trendelenburg position at approximately 30°. Pneumoperitoneum was established with CO_2 at a pressure of 11–13 mmHg. We placed five ports in V-shape, and at the vertex position was a 10-mm camera port. The other four working ports were placed in the right upper quadrant (5 mm), right middle quadrant (5 mm), left middle quadrant (5 mm), and left upper quadrant (12 mm) of the abdomen.

Lymph node dissection and omentectomy were performed according to Japanese guidelines. The resection lines of the duodenum and stomach were determined according to the tumor site. We used a 60-mm endoscopic linear stapler to perform resection and reconstruction in the OGD group and a 45-mm endoscopic linear stapler in the DSGD group.

2.3. DSGD. We modified the DSGD to be similar to that reported by Huang et al. [11] We rotated the duodenum 90° clockwise when it was transected, and a small incision was made on the posterior side of the greater curvature of the remnant stomach and on the posterior side of the duodenum. Then, we inserted the linear stapler, closed and fired it, and created a V-shaped anastomosis on the posterior wall. After verifying the absence of bleeding from the anastomosis, we closed the common stab incision along the blind angle of the duodenum.

2.4. OGD. There is no need to perform a 90° rotation when the duodenum is transected. A small incision was made on the greater curvature of the remnant stomach, and another small incision was created on the superior edge of the duodenal transection line. The linear stapler was introduced into the remnant stomach and duodenum, where the two sides were put together, and the stapler was closed and fired. After verifying that there was no bleeding on the stapler line, a one-stay suture was added in the middle of the common stab incision. We then pulled the stay suture and two ends of the common stab incision and closed the incision using the linear stapler.

2.5. Postoperative Follow-Up Evaluation. All patients were managed in a similar manner, following the postoperative clinical path. The gastric tube was removed on postoperative day 1, and water intake was initiated on postoperative day 2.

Monitoring indicators included operation time, anastomotic time, intraoperative blood loss, number of lymph node dissections, length of hospital stay, fluid intake time, and complications. Regular follow-ups were conducted 3, 6, 9, and 12 months postoperatively, and endoscopic examinations were performed in the first 6 and 12 months postoperatively. Endoscopic findings were evaluated using the residual food, gastritis, and bile (RGB) classification [12].

2.6. Statistical Analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 20.0 for Windows (SPSS Inc., Chicago, United States). Data are expressed as mean ± standard deviation. Categorical variables were analyzed using the chi-square test or Fisher's exact test, while continuous variables were analyzed using Student's *t*-test. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Clinicopathological Characteristics. The clinicopathological characteristics of the two groups are summarized in Table 1; 45 patients received OGD, and 47 patients received DSGD. No significant differences in age, sex, body mass index, history of abdominal surgery, tumor size, and TNM stage were found between the two groups.

3.2. Operative and Postoperative Characteristics. Laparoscopic surgery was successfully completed in all patients without conversion to open surgery. As Table 2 shows, there were no significant differences between the two groups in operation time (158.9 ± 13.6 min vs. 158.8 ± 14.8 min, $P = 0.955$), anastomotic time (19.4 ± 3.0 min vs. 18.8 ± 2.9 min, $P = 0.354$), intraoperative blood loss (88.9 ± 25.4 mL vs. 83.7 ± 24.3 mL, $P = 0.321$), number of lymph node dissections (31.0 ± 7.1 vs. 29.2 ± 7.5, $P = 0.229$), length of hospital stay (8.8 ± 2.7 days vs. 9.1 ± 3.0 days, $P = 0.636$), fluid intake time (3.1 ± 0.7 days vs. 3.2 ± 0.7 days, $P = 0.914$), and morbidity of postoperative complication (6.7% [3/45] vs. 10.6% [5/47], $P = 0.499$).

The types of complications were comparable between the two groups. Two patients (4.4%) in the OGD group and one patient (2.1%) in the DSGD group developed delayed gastric

Table 1: Clinicopathological characteristics of patients.

Characteristics	OGD ($n = 45$)	LSGD ($n = 47$)	P value
Age (years, $\overline{x} \pm s$)	59.1 ± 9.3	60.79 ± 11.6	0.435
Gender (no. %)			0.666
Male	25 (55.6)	24 (51.1)	
Female	20 (44.4)	23 (48.9)	
BMI (kg/m^2, $\overline{x} \pm s$)	22.9 ± 2.8	23.2 ± 2.5	0.543
Previous abdominal surgery (no. %)	5 (11.1)	7 (14.9)	0.590
Tumor size (cm, $\overline{x} \pm s$)	2.4 ± 0.8	2.6 ± 0.8	0.301
T classification (no. %)			0.333
T1	25 (55.6)	19 (40.4)	
T2	19 (42.2)	26 (55.3)	
T3	1 (2.2)	2 (4.3)	
N classification (no. %)			0.516
N0	17 (37.8)	11 (23.4)	
N1	19 (42.2)	25 (53.2)	
N2	8 (17.8)	10 (21.3)	
N3	1 (2.2)	1 (2.1)	

Table 2: Operative and postoperative characteristics.

Characteristics	OGD ($n = 45$)	LSGD ($n = 47$)	P value
Operation time (min, $\overline{x} \pm s$)	158.9 ± 13.6	158.8 ± 14.8	0.955
Anastomotic time (min, $\overline{x} \pm s$)	19.4 ± 3.0	18.8 ± 2.9	0.354
Blood loss (ml, $\overline{x} \pm s$)	88.9 ± 25.4	83.7 ± 24.3	0.321
Retrieved lymph nodes (n, $\overline{x} \pm s$)	31.0 ± 7.1	29.2 ± 7.5	0.229
Length of stay (days, $\overline{x} \pm s$)	8.8 ± 2.7	9.1 ± 3.0	0.636
Liquid diet buildup (days, $\overline{x} \pm s$)	3.1 ± 0.7	3.2 ± 0.7	0.914
Any complication (no. %)	3 (6.7)	5 (10.6)	0.499
Wound infection	0 (0.0)	1 (2.1)	0.323
Leakage	0 (0.0)	2 (4.3)	0.160
Delayed gastric emptying	2 (4.4)	1 (2.1)	0.537
Pulmonary	1 (2.2)	1 (2.1)	0.976

emptying. All three of them were placed under conservative management. In the OGD group, the two patients were discharged on postoperative days 25 and 30, while, in the DSGD group, the patient was discharged on postoperative day 33. Two patients (4.3%) in the DSGD group had anastomotic leakage, whereas no patient had leakage in the OGD group. No in-hospital mortality was observed in either group.

3.3. Endoscopic Findings. Table 3 shows the endoscopic findings of the two groups 6 and 12 months postoperatively. Six months postoperatively, the RGB classification scores in the OGD group were significantly lower than those in the DSGD group ($P = 0.033$, $P = 0.029$, $P = 0.022$, respectively). Twelve months postoperatively, there were no significant RGB classification score differences.

4. Discussion

TLDG, in which all procedures including gastric resection and digestive tract reconstruction are performed intracorporeally without making an additional abdominal incision, has become much more acceptable to surgeons because of its advantages over LADG [13, 14].

Currently, DSGD is the most popular reconstruction approach for Billroth I following TLDG. Although it is reported that DSGD has a satisfactory result and a relatively short learning curve [15], the rate of anastomosis-related complications is still relatively high [16–20]. The most important reason for this is that in DSGD, the surgeon must rotate the duodenal stump and the remnant stomach. However, these actions are mandatory procedures, and insufficient rotation might leave ischemic tissue between the transection lines and the anastomosis line. The OGD method has no such problems because it is a side-to-side overlap anastomosis, and duodenal rotation is unnecessary, thus reducing the possibility of damage to the surrounding structures and anastomotic ischemia. In our study, we had two cases of leakage in the DSGD group, while there was no case of leakage in the OGD group, although the difference was not significant.

In the OGD procedure, attention should be paid to the complications of delayed gastric emptying. We had two cases (4.4%) that resulted in delayed gastric emptying, and although all of them were cured after conservative treatment, the hospital stays were prolonged and the costs increased. The reason for this is not well known, and it might be because more stomach is retained, especially at the greater curvature, to insert the linear stapler and perform the

Table 3: Endoscopic findings in postoperative 6 and 12 months.

Characteristics	6 months			12 months		
	OGD ($n = 45$)	LSGD ($n = 47$)	P value	OGD ($n = 45$)	LSGD ($n = 47$)	P value
Residual food (no. %)			0.033			0.194
Grade 0	28 (62.2)	15 (31.9)		25 (55.6)	16 (34.0)	
Grade 1	5 (11.1)	12 (25.5)		6 (13.3)	11 (23.4)	
Grade 2	5 (11.1)	4 (8.5)		5 (11.1)	4 (8.5)	
Grade 3	4 (8.9)	8 (17.0)		6 (13.3)	8 (17.0)	
Grade 4	3 (6.7)	8 (17.0)		3 (6.7)	8 (17.0)	
Gastritis (no. %)			0.029			0.072
Grade 0	5 (11.1)	3 (6.4)		5 (11.1)	3 (6.4)	
Grade 1	30 (66.7)	20 (42.6)		28 (62.2)	22 (46.8)	
Grade 2	8 (17.8)	22 (46.8)		8 (17.8)	20 (42.6)	
Grade 3	2 (4.4)	2 (4.3)		4 (8.9)	2 (4.3)	
Bile reflux (no. %)			0.022			0.168
Grade 0	28 (62.2)	18 (38.3)		26 (57.8)	19 (40.4)	
Grade 1	17 (37.8)	29 (61.7)		12 (26.7)	17 (36.2)	

anastomosis. All patients underwent D2 lymph node dissection, which may have influenced the blood supply to the remnant stomach, especially with a larger remnant stomach. This lack of blood supply might have caused delayed gastric emptying [21].

Regarding endoscopic findings based on the RGB classification, OGD was significantly lower 6 months postoperatively, but these differences disappeared 12 months postoperatively. This is probably owing to two reasons. First, the anastomosis in DSGD was posterior with rotation of the duodenum, which could then be twisted when food passed. Meanwhile, the anastomosis in OGD is a morphological "up and down" reconstruction where gastric content can pass easily. Second, in OGD, we used a 60-mm linear stapler (compared with the 45-mm stapler used in DSGD) that resulted in a larger anastomosis lumen and therefore faster passing of gastric content into the duodenum. OGD may thereby reduce the incidence of gastritis and bile reflux. In the DSGD group, these endoscopic findings improved from 6 to 12 months, which Lee et al. [22] have previously found, whereas, in the OGD group, they were almost the same.

Our study has some limitations. First, it was a retrospective cohort study, and the surgeon changed the main reconstruction method from DSGD to OGD. Although the surgeon had 12 years of experience in gastrectomy and 8 years of experience in laparoscopic gastrectomy, the surgical skill of reconstruction and D2 lymphadenectomy may have improved, which might have caused a bias. Second, our results came from only one surgeon without representing others; thus, a multicenter prospective study is needed. Finally, our study lacks long-term data. To evaluate postoperative outcomes, administering questionnaires would strengthen our findings.

5. Conclusion

Overlap gastroduodenostomy is a safe, simple, and feasible approach to intracorporeal anastomosis and has the same short-term results as delta-shaped gastroduodenostomy. However, long-term comparative studies are required for further assessment.

Data Availability

The data used to support the findings of this study were supplied by Linhua Zhu under license and so cannot be made freely available. Requests for access to these data should be made to Linhua Zhu, the e-mail address is zhulh@srrsh.com.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

[1] H. Sung, J. Ferlay, R. L. Siegel et al., "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *A Cancer Journal for Clinicians*, vol. 71, no. 3, pp. 209–249, 2021.

[2] S. Kitano, Y. Iso, M. Moriyama, and K. Sugimachi, "Laparoscopy-assisted billroth I gastrectomy," *Surgical Laparoscopy and Endoscopy*, vol. 4, no. 2, pp. 146–148, 1994.

[3] H. H. Kim, W. J. Hyung, G. S. Cho et al., "Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer," *Annals of Surgery*, vol. 251, no. 3, pp. 417–420, 2010.

[4] J. Cai, D. Wei, C. F. Gao, C. Zhang, H. Zhang, and T. Zhao, "A prospective randomized study comparing open versus laparoscopy-assisted D2 radical gastrectomy in advanced gastric cancer," *Digestive Surgery*, vol. 28, pp. 331–337, 2011.

[5] Y. K. Zeng, Z. L. Yang, J. S. Peng, H. S. Lin, and L. Cai, "Laparoscopy-assisted versus open distal gastrectomy for early gastric cancer," *Annals of Surgery*, vol. 256, no. 1, pp. 39–52, 2012.

[6] K. Misawa, M. Fujiwara, M. Ando et al., "Long-term quality of life after laparoscopic distal gastrectomy for early gastric cancer: results of a prospective multi-institutional comparative trial," *Gastric Cancer*, vol. 18, no. 2, pp. 417–425, 2015.

[7] H. Hosogi and S. Kanaya, "Intracorporeal anastomosis in laparoscopic gastric cancer surgery," *Journal of gastric cancer*, vol. 12, no. 3, pp. 133–139, 2012.

[8] S. Kanaya, T. Gomi, H. Momoi et al., "Delta-shaped anastomosis in totally laparoscopic Billroth I gastrectomy: new technique of intraabdominal gastroduodenostomy1," *Journal*

of the American College of Surgeons, vol. 195, no. 2, pp. 284–287, 2002.

[9] H. M. Song, S. L. Lee, H. Hur, Y. K. Cho, and S. U. Han, "Linear-shaped gastroduodenostomy in totally laparoscopic distal gastrectomy," *Journal of Gastric Cancer*, vol. 10, no. 2, p. 69, 2010.

[10] C. Byun, L. H. Cui, S. Y. Son, H. Hur, Y. K. Cho, and S. U. Han, "Linear-shaped gastroduodenostomy (LSGD): safe and feasible technique of intracorporeal billroth I anastomosis," *Surgical Endoscopy*, vol. 30, no. 10, 2016.

[11] C. M. Huang, M. Lin, J. X. Lin et al., "Comparision of modified and conventional delta-shaped gastroduodenostomy in totally laparoscopic surgery," *World Journal of Gastroenterology*, vol. 20, no. 30, 2014.

[12] M. Kubo, M. Sasako, T. Gotoda et al., "Endoscopic evaluation of the remnant stomach after gastrectomy: proposal for a new classification," *Gastric Cancer*, vol. 5, no. 2, pp. 83–89, 2002.

[13] J.-J. Kim, K. Y. Song, H. M. Chin et al., "Totally laparoscopic gastrectomy with various types of intracorporeal anastomosis using laparoscopic linear staplers: preliminary experience," *Surgical Endoscopy*, vol. 22, no. 2, pp. 436–442, 2008.

[14] O. Ikeda, Y. Sakaguchi, Y. Aoki et al., "Advantages of totally laparoscopic distal gastrectomy over laparoscopically assisted distal gastrectomy for gastric cancer," *Surgical Endoscopy*, vol. 23, no. 10, 2009.

[15] S. Kanaya, Y. Kawamura, H. Kawada et al., "The delta-shaped anastomosis in laparoscopic distal gastrectomy: analysis of the initial 100 consecutive procedures of intracorporeal gastroduodenostomy," *Gastric Cancer*, vol. 14, no. 4, pp. 365–371, 2011.

[16] S. W. Lee, N. Tanigawa, E. Nomura et al., "Benefits of intracorporeal gastrointestinal anastomosis following laparoscopic distal gastrectomy," *World Journal of Surgical Oncology*, vol. 10, no. 1, p. 267, 2012.

[17] H. Noshiro, H. Iwasaki, Y. Miyasaka et al., "An additional suture secures against pitfalls in delta-shaped gastroduodenostomy after laparoscopic distal gastrectomy," *Gastric Cancer*, vol. 14, no. 4, pp. 385–389, 2011.

[18] H. Okabe, K. Obama, S. Tsunoda, E. Tanaka, and Y. Sakai, "Advantage of completely laparoscopic gastrectomy with linear stapled reconstruction," *Annals of Surgery*, vol. 259, no. 1, pp. 109–116, 2014.

[19] N. Matsuhashi, K. Yamaguchi, N. Okumura et al., "The technical outcomes of delta-shaped anastomosis in laparoscopic distal gastrectomy: a single-center safety and feasibility study," *Surgical Endoscopy*, vol. 31, no. 3, 2017.

[20] T. Tokuhara, E. Nakata, T. Tenjo et al., "An option for delta-shaped gastroduodenostomy in totally laparoscopic distal gastrectomy for gastricï¿½cancer: a single-layer suturing technique for the stapler entry hole using knotless barbed sutures combined with the application of additional knotted sutures," *Oncology Letters*, vol. 15, no. 1, pp. 229–234, 2018.

[21] T. Pang, X.-Y. Yin, H.-T. Cui et al., "Analysis of risk factors and prevention strategies for functional delayed gastric emptying in 1243 patients with distal gastric cancer," *World Journal of Surgical Oncology*, vol. 18, no. 1, p. 302, 2020.

[22] H. H. Lee, K. Y. Song, J. S. Lee, S. M. Park, and J. J. Kim, "Delta-shaped anastomosis, a good substitute for conventional Billroth I technique with comparable long-term functional outcome in totally laparoscopic distal gastrectomy," *Surgical Endoscopy*, vol. 29, no. 9, 2015.

Hindawi
Canadian Journal of Gastroenterology and Hepatology
Volume 2022, Article ID 2349940, 7 pages
https://doi.org/10.1155/2022/2349940

Research Article

Comparison of Endoscopic Radiofrequency Ablation and Argon Plasma Coagulation in Patients with Gastric Low-Grade Intraepithelial Neoplasia: A Large-Scale Retrospective Study

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Received 11 February 2022; Revised 30 April 2022; Accepted 3 June 2022; Published 22 June 2022

Academic Editor: Xiaohua Jiang

Background. Gastric low-grade intraepithelial neoplasia (LGIN) is a precancerous lesion of gastric cancer. Endoscopic therapies represented by radiofrequency ablation (RFA) and argon plasma coagulation (APC) have been applied to treat gastric LGIN in recent years. However, no comparative study examining the effectiveness and safety profiles of RFA and APC has been reported. *Methods*. A single-center, large-scale, retrospective study, including 73 and 50 patients treated with RFA and APC, respectively, was conducted in the First Medical Center of Chinese PLA General Hospital from October 2015 to October 2020, with a two-year follow-up. Effectiveness, complications, operative factors, and other data were assessed. *Results*. At 2 years of follow-up, cure, relapse, recurrence, and progression rates were 90.4%, 9.6%, 9.6%, and 2.7% in the RFA group, respectively, versus 90%, 10%, 12%, and 4% in the APC group, respectively, with no statistically significant differences between the two groups (all $p > 0.05$). However, the mean lesion size was significantly larger in the RFA group (2.6 ± 1.0 cm) than in the APC group (1.5 ± 0.6 cm) ($p < 0.001$); there was also a significant difference in the composition ratio of large lesions between the two groups ($p < 0.001$). No serious postoperative complications showed in either group, and the abdominal pain was the most common symptom in the short term after surgery. *Conclusions*. RFA and APC are both safe and effective destructive therapies for gastric LGIN. RFA is more suitable for flat and large lesions, while APC is more suitable for small lesions, especially those with slight local uplift or depression. An intraoperative submucosal injection is expected to be an effective method for relieving postoperative abdominal pain.

1. Introduction

A few decades ago, the World Health Organization (WHO) introduced the notion of intraepithelial neoplasia in the recent classification of digestive system tumors, referring to the Vienna International Consensus [1–3]. In the latter classification, gastric mucosal intraepithelial neoplasia can be divided into high-grade intraepithelial neoplasia (HGIN) and low-grade intraepithelial neoplasia (LGIN), depending on the extent of cellular and structural atypia. It is well known that gastric mucosa intraepithelial neoplasia is a precancerous lesion of gastric cancer. If precancerous lesions can be eliminated, gastric cancer could be effectively prevented. With a deepened understanding of the disease progression and the improvement of therapeutic tools, a consensus has been formed on the clinical management of HGIN, namely; timely endoscopic treatment or surgery is the preferred option [4, 5]. Although no consensus has been reached on the principles of LGIN management, some guidelines [6, 7] have recommended aggressive endoscopic treatment for long-term gastric LGIN due to the potential progression to gastric cancer [8–11].

As LGIN is at an earlier stage than HGIN in precancerous lesions, endoscopic resection therapies are also feasible, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), as confirmed by previous reports [12, 13]. However, endoscopic resection is a high-level treatment endoscopic technique, with a long learning period, relatively difficult operation, complex postoperative management, high cost, and potential serious complications in the perioperative period [14]. The above disadvantages have limited the further application of endoscopic resection therapy in LGIN.

Correspondingly, radiofrequency ablation (RFA) and argon plasma coagulation (APC), the two most commonly used methods in damage therapy, have been preliminarily reported in clinical studies for the treatment of gastric LGIN in recent years [15–19]. They have the advantages of simple operation, low cost, low risk, and outpatient treatment, gradually showing good clinical application prospects.

No study has reported the differences in effectiveness and complication among damage therapies for gastric LGIN. For this purpose, we designed this retrospective study to compare RFA and APC in the treatment of gastric LGIN.

2. Methods

2.1. Patients. The records of 123 consecutive patients administered RFA or APC for gastric LGIN in The First Medical Center of Chinese PLA General Hospital between October 2015 and October 2020 and followed up for more than 2 years were reviewed in this single-center retrospective study. Among them, 73 and 50 patients received RFA and APC, respectively. All the patients provided written informed consent for the procedure, and the study was reviewed and approved by the Ethics Committee of Chinese PLA General Hospital.

2.2. Inclusion and Exclusion Criteria. The inclusion criteria were as follows: (a) treatment with RFA (macroscopic type 0-II lesions according to the Paris classification [20]) or APC (no specific limitation); (b) 18–85 years of age; and (c) according to the WHO standards [1], confirmed LGIN by preoperative biopsy and HGIN and early gastric cancer (EGC) ruled out. The exclusion criteria were as follows: (a) HGIN or EGC confirmed or not excluded by biopsy before the operation; (b) a history of gastric surgery; (c) patients with severe cardiopulmonary disease who could not undergo anesthesia; (d) patients with advanced chronic liver disease or other serious systemic diseases who could not tolerate the operation; and (e) patients with coagulation dysfunction or unable to complete follow-ups as required.

2.3. Instruments and Procedures for RFA and APC. The BARRX System (Covidien GI Solutions, Sunnyvale, CA, United States) was used for RFA, and the argon plasma coagulation unit (APC 300, ERBE Elektromedizin, Tübingen, Germany) was used for APC. A disposable injector (NM-200L-0425, Olympus, Tokyo, Japan) with normal saline solution was used for submucosal injections. An accessory of the BARRX System (Covidien TTS-1100, 60RFA Conduit 909300, Sunnyvale, CA, United States) was used for lesion ablation. Hemostatic forceps (FD-410 LR, Olympus Medical, Tokyo, Japan) were used to prevent hemorrhage and perforation. Other equipment and accessories included a high-frequency generator (ICC-200, ERBE Elektromedizin, Tübingen, Germany), gastroscopes (GIF-Q260 J, GIF-H260Z, GIF-HQ290, Olympus Medical, Tokyo, Japan), and carbon dioxide gas with a CO_2 insufflator (UCR, Olympus Medical, Tokyo, Japan).

The procedure applied for RFA has been reported previously [17]. After the lesions were found by routine gastroscopy, they were further examined by magnifying endoscopy (ME) combined with narrow-band imaging (NBI) to determine the size and range. Next, an RFA electrode was attached to the lesion surface with the assistance of endoscopy. The output power for RFA was set to 57 W, and the energy density was 15 J/cm^2. After ablation, the lesion surface showed white coagulation and necrosis. Before the next ablation, the coagulated necrotic tissue on the surface was removed with RFA electrodes. RFA was repeated three times for each lesion to ensure complete ablation. In addition, submucosal injection could be administered to lesions, which was beneficial for the procedure, especially in case of difficult lesions. Other details of the RFA procedure were described in our previous study [17].

The procedure applied for APC was simpler than that of RFA. First, it was also necessary to re-evaluate the lesions with ME combined with NBI. Next, with the help of endoscopy, an argon plasma catheter was placed close to the lesion surface and cauterized in a subcontact state. Unlike RFA, we set the output power for APC to 35 W. After APC, the lesion surface showed white, light yellow, or brown-black coagulation areas and necrosis. Finally, the procedure was considered to be completed after confirming that the treatment had completely covered the lesion area. It is important to note that APC does not require retreatment of the same lesion area except for a local omission. Similar to RFA, submucosal injection was used in APC during the procedure. Other details of the APC procedure were described in our previous study [21]. The procedures of RFA and APC, performed by three experienced gastrointestinal endoscopists (E. Q. Linghu, N. L. Chai, and N. J. Wang), are shown in Figure 1.

2.4. Additional Treatments and Follow-Up. Postoperative management and follow-up were performed according to the previous study [17].

Each patient fasted for 4–6 h after the procedure. Then, a liquid or semiliquid diet was provided, followed by gradual transition to a normal diet. At the same time, patients were administered a proton pump inhibitor (PPI) and a mucosal protectant for 1 month postsurgically. Moreover, we explained the Wong–Baker FACES Pain Rating Scale [22] to the patients who were each provided a form for self-recording the daily pain score in the first month after RFA or APC. The forms were returned 3 months after the patient returned to our hospital for the first review.

All patients were required to return to our hospital for follow-up at 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years after surgery. Patients were examined by gastroscopy, and biopsies were performed in the original treatment area and other suspected areas. Pathological

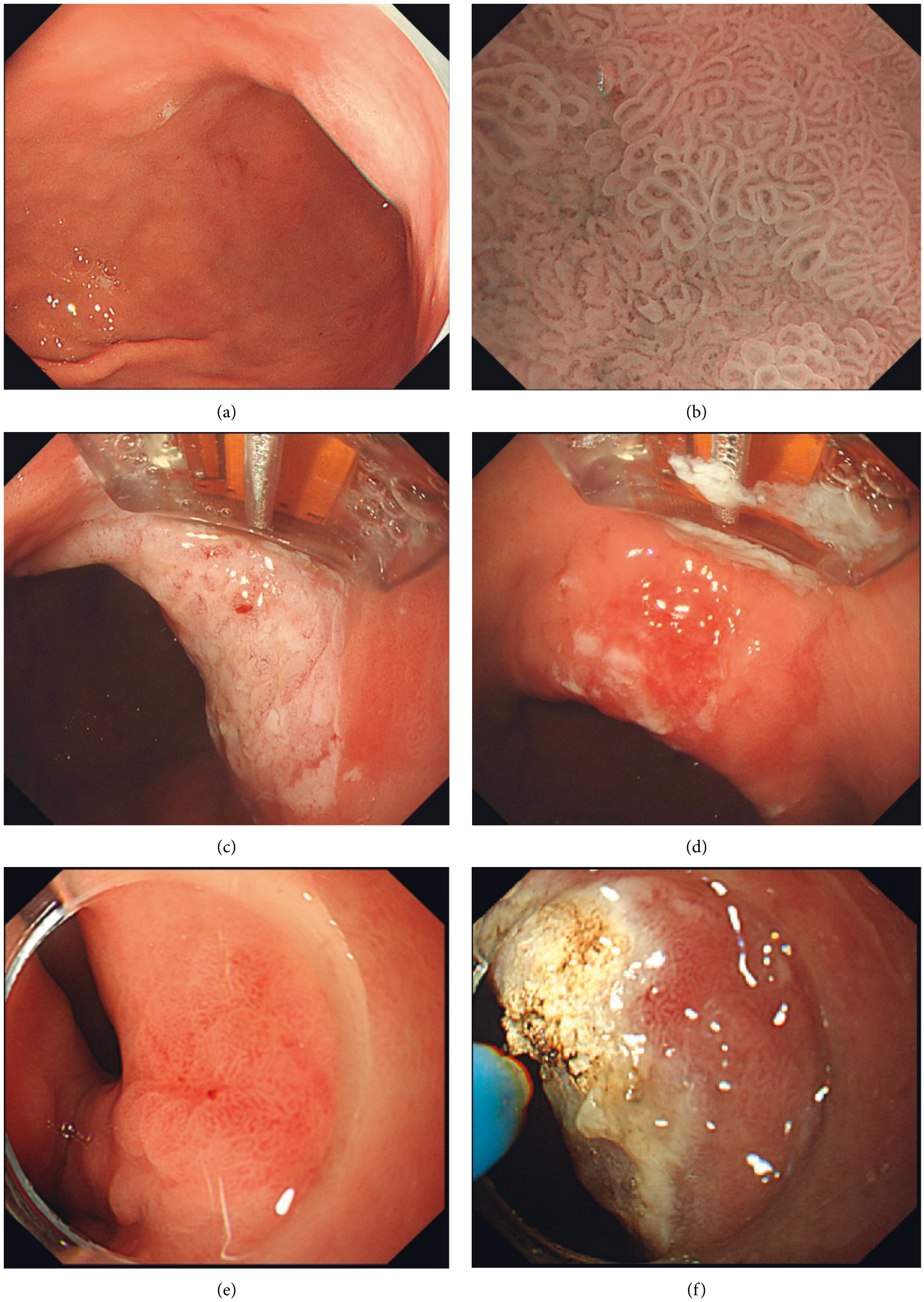

Figure 1: Radiofrequency ablation and argon plasma coagulation procedures for gastric low-grade intraepithelial neoplasia. (a) White-light imaging of the lesion. (b) Magnifying endoscopy with narrow-band imaging of the lesion (strong magnification). (c) After ablation, the surface of the lesion showed white coagulation and necrosis. (d) After scraping off the necrotic mucosal tissue on the surface. (e) White-light imaging of another lesion (reversed view). (f) After argon plasma coagulation, the surface of the lesion showed light yellow and brown-black coagulation and necrosis.

Table 1: Baseline characteristics, procedure-related parameters, and follow-ups.

	RFA group ($n = 73$)	APC group ($n = 50$)	p value
Sex, male/female (n)	45/28	32/18	0.791
Age, mean ± standard deviation (years)	57.1 ± 10.8	56.5 ± 11.2	0.759
A course of disease, n (%)			0.459
<1 year	40 (54.8)	24 (48.0)	
>1 year	33 (45.2)	26 (52.0)	
Macroscopic type, n (%)			<0.001
0-I	0 (0)	25 (50.0)	
0-II	73 (100)	23 (46.0)	
0-III	0 (0)	2 (4.0)	
Ulceration	0	0	
Location of lesions, n (%)			0.917
Gastric fundus	1 (1.4)	1 (2.0)	
Gastric body	4 (5.5)	3 (6.0)	
Angle of the stomach	29 (39.7)	17 (34.0)	
Gastric antrum	39 (53.4)	29 (58.0)	
Size of lesions, mean ± standard deviation (cm)	2.6 ± 1.0	1.5 ± 0.6	<0.001
Operating time, mean ± standard deviation (min)	15.2 ± 1.8	14.7 ± 1.8	0.133
Submucosal injection, n (%)	32 (43.8)	20 (40.0)	0.672
Helicobacter pylori infection, n (%)			0.525
Yes	15 (20.5)	8 (16.0)	
No	58 (79.5)	42 (84.0)	
Atrophy, n (%)			0.299
Yes	27 (37.0)	14 (28.0)	
No	46 (63.0)	36 (72.0)	
2-year follow-up, n (%)			
Curative	66 (90.4)	45 (90.0)	1.000
Relapse	7 (9.6)	5 (10.0)	1.000
Recurrence	7 (9.6)	6 (12.0)	0.669
Progression	2 (2.7)	2 (4.0)	1.000
Abdominal pain, n (%)	42 (57.5)	31 (62.0)	0.620

findings were used to determine whether the treatment was effective, as well as to assess relapse, recurrence, and progression. In this research, according to the study design, the data of patients followed up for 2 years after the operation were used as the evaluation criteria. The following definitions were used. (1) LGIN disappearance in the original treatment area indicated by pathological biopsy indicated a curative effect. (2) LGIN presence in the original treatment area indicated relapse. (3) LGIN presence in a nontreatment area was indicated recurrence. (4) HGIN or EGC presence in the original treatment area indicated disease progression.

On the other hand, perioperative complications and adverse events, including bleeding, perforation, infection, and postoperative abdominal pain, were used to assess the safety of each operation.

2.5. Statistical Analysis. Data analysis was performed using SPSS Statistics for Windows, version 26.0 (IBM, Armonk, NY, USA). The data were retrospectively collected, and the procedural parameters were compared. Measurement data were expressed as the mean ± standard deviation or the median with range, whereas numerical data were described as frequency and percentage and were compared by the $\chi 2$ test or Fisher's exact test. The Chi-square test was performed to compare categorical variables. The measurement data were analyzed by the t-test and one-way analysis of variance or the rank-sum test according to normality. $p < 0.05 p < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical Characteristics and Procedure-Related Parameters. A total of 123 patients with the mean age of 56.9 (range: 22–80) years were enrolled in the study (77 males and 46 females). Seventy-three patients received RFA and 50 underwent APC. Of all patients, 59 had a course of disease longer than 1 year, including 33 and 26 in the RFA and APC groups, respectively. In the RFA group, there were 1, 4, 29, and 39 lesions located in the gastric fundus, body, angle, and antrum, respectively, versus 1, 3, 17, and 29 cases in the APC group, respectively. The average operation time of the two procedures was about 15.2 minutes and 14.7 minutes, respectively. During the operation, 32 patients in the RFA group and 20 in the APC group received submucosal injection. In addition, there were 15 *Helicobacter pylori* (*H. pylori*) infection and 27 atrophic gastritis cases in the RFA group compared with that of 8 and 14 cases in the APC group, respectively. There were no statistically significant differences between the two groups in gender, age, disease course, lesion location, operation time, proportion of submucosal injection, *H. pylori* infection, and atrophic gastritis (all $p > 0.05$). However, the mean lesion size was significantly larger in the RFA group (2.6 ± 1.0 cm) than in the

Table 2: Submucosal injection for postoperative abdominal pain relief.

	Submucosal injection group	Non-submucosal injection group	p value
Abdominal pain relief ratio in the RFA group	22/32 (68.8)	9/41 (22.0)	<0.001
Abdominal pain relief ratio in the APC group	13/20 (65.0)	6/30 (20.0)	0.001
Total	35/52 (67.3)	15/71 (21.1)	<0.001

APC group (1.5 ± 0.6 cm) ($p < 0.001$). Moreover, there were also significant differences in the composition ratio of large lesions between the two groups ($p < 0.001$). All clinical characteristics and procedure-related parameters of both groups are shown in Table 1.

3.2. Therapeutic Effectiveness and Long-Term Outcomes. All patients in both groups completed 2 years of postoperative follow-up, including endoscopic and symptomatic examinations. At 2 years of follow-up, the cure, relapse, recurrence, and progression rates were 90.4%, 9.6%, 9.6%, and 2.7% in the RFA group, respectively, versus 90%, 10%, 12%, and 4% in the APC group, respectively. However, these differences were not statistically significant between the two groups (all $p > 0.05$). Some patients with relapse and recurrence were treated with RFA or APC again, while others were followed up for observation. The follow-up of these patients is still ongoing, and no case with further progression has been recorded yet. Additional ESD therapy was performed in all 4 patients with HGIN disease progression. The short-term follow-up results of all 4 patients indicated curative resection, and the long-term follow-up is still in progress. The specific data are also shown in Table 1.

3.3. Procedure-Related Adverse Events. As shown in Table 1, postoperative abdominal pain occurred in both groups, and the difference was not statistically significant (42, 57.5% vs. 31, 62.0%, $p = 0.620$). Most of the pain occurred within 14 days postoperatively. All these patients experienced gradual relief of symptoms after taking PPIs and mucosal protectants. Meanwhile, in the RFA group, abdominal pain was developed in 10 of the 32 patients administered submucosal injection, compared to 32 of the 41 who did not receive submucosal injection ($p < 0.001$). Similarly, in the APC group, 7 in 20 patients administered submucosal injection developed abdominal pain, while 6 in 30 individuals not administered submucosal injection had no obvious abdominal pain, showing a significant difference between the two groups ($p = 0.001$). Overall, only 17 of the 52 patients administered submucosal injection developed abdominal pain, while up to 56 of the 71 not administered submucosal injection developed abdominal pain, with a statistically significant difference ($p < 0.001$). These data are presented in detail in Table 2. In addition, no perioperative bleeding, perforation, infection, or other serious complications occurred in any of the 123 patients.

4. Discussion

Recently, endoscopic RFA and APC have been applied for the clinical treatment of gastric LGIN, with their working principles described in several previous reports [15–19, 21]. RFA causes the movement of charged particles in tissues to generate heat through the action of high-frequency alternating current to evaporate water inside and outside the cells, which dry, shrink, and fall off, resulting in aseptic necrosis. Furthermore, the output power and energy density of each RFA are controlled and do not increase with the operation time. Unlike RFA, APC is a noncontact damage treatment, which exerts effects by spraying ionized argon gas onto the target mucosal surface, thereby transferring high-frequency electrical energy to tissues and utilizing thermal effects to deactivate and dry the tissue and to cause coagulation and necrosis. In general, both procedures achieve the goal of treating lesions by inducing local damage.

As previously mentioned, a few studies have preliminarily explored the clinical treatment effectiveness of RFA and APC in gastric LGIN. However, no reports have compared large clinical samples between RFA and APC, and this study filled this gap.

First, we compared clinical characteristics and procedure-related parameters between the two groups. In this study, no statistically significant differences were found between the RFA and APC groups in terms of the gender, age, disease course, lesion location, operation time, proportion of submucosal injection, and mucosal background (*H. pylori* infection and atrophic gastritis). However, the overall lesions were larger in the RFA group than in the APC group, which may be related to divergent working principles of RFA and APC. For the former method, using an electrode patch for ablation can treat larger lesion areas, while the latter is more favorable for treating smaller lesions because of the point-like cauterization. Similarly, flat lesions were selected for RFA because the electrode patch used for ablation is flat, while the treatment method in APC is point-like cauterization so that APC is also suitable for swelling or sunken lesions. This caused a significant difference in the composition ratio of large lesions between the two groups. However, it should be noted that HGIN or EGC more likely occurs in nonflat lesions, especially in depressed ones. Therefore, special attention should be paid to preoperative evaluation and screening.

Secondly, both RFA and APC showed good clinical effectiveness for gastric LGIN, with effectiveness rates in both groups surpassing 90% in the 2-year follow-up period, which preliminarily suggests the damage therapy of gastric LGIN is simple and efficient. However, there were still some patients with postoperative relapse and recurrence. The results showed *H. pylori* infection and/or atrophic gastritis were present in 21 of all the 25 relapse or recurrence cases. Meanwhile, patients with a disease course longer than 1 year also accounted for a high proportion of relapse or recurrence cases (76%, 19/25). According to the results, *H. pylori* infection and atrophic gastritis might change the overall state and microenvironment of the gastric mucosa to some extent, and a longer disease course might further exacerbate these changes, which are all possible causes of LGIN relapse or recurrence. This finding corroborated previous studies [23, 24] because *H. pylori* predisposes the mucosa to intestinal metaplasia and the odds of intraepithelial neoplasia are higher in atrophic and intestinal metaplasia than in the normal mucosa. Meanwhile, we noted that more than half of lesions were concentrated in the gastric antrum, which might be associated with the early occurrence of mucosal atrophy in the gastric antrum and its susceptibility to *H. pylori*. This also supported our conclusions from another aspect.

In addition, during the follow-up period, 4 patients in both groups had disease progression, from LGIN to HGIN. A review of previous studies showed that lesion size >1 cm, erythema, erosion, ulceration, nodular changes on the lesion surface, and significant depression of the lesion are all risk factors for progression from LGIN to HGIN or EGC [25, 26]. Lesion sizes in our 4 cases were all over 1 cm; of these, 3 cases were accompanied by surface erythema and the remaining had mild erosion. At the same time, none of the 4 cases had ulceration or obvious depression. We reviewed the images obtained by preoperative magnification endoscopy again and found no significant loss of surface microstructures or microvessels, and these lesions were still included in patient screening. This also indicated that the existing endoscopic screening theory of EGC might still need to be further improved. We look forward to carrying out further research in this field in the future. On the other hand, although we carried out sufficient endoscopic assessment and localization, preoperative biopsy still could not fully reflect the overall situation of the lesion, and there is potential bias. This might allow some lesions already of the HGIN or EGC type to be included in the study. This is another possible cause of postoperative pathological escalation.

Thirdly, in terms of postoperative adverse events, more than half of patients in both groups experienced short-term abdominal pain after surgery. Further analysis indicated patients administered submucosal injection during surgery had a lower incidence of postoperative abdominal pain compared with those not administered submucosal injection in the RFA, APC, or whole cohort, corroborating a previous study [27]. The mechanism might involve the protection and thermal partition of the deep muscle tissue by using the liquid pad formed by submucosal injection. Therefore, the submucosal injection was recommended during the damage therapy. This needs to be clarified in subsequent, larger randomized controlled studies. Furthermore, no serious complications such as bleeding, perforation, and infection occurred in either group during the perioperative period, and the patients had satisfactory safety. However, the risk of perforation in APC was reported previously [28]. The main cause of perforation was deep burning during the operation. Therefore, it is very important to maintain the subcontact state between the argon plasma catheter and the lesion surface. For medical centers preparing to carry out this treatment, it is advisable for endoscopists with relatively long treatment experience to complete the procedure.

Last but not the least, operation times in both groups were very short, about 15 minutes. In general, RFA and APC can be performed by endoscopists as long as they are skilled in gastroscopy, which results in significantly reduced cost and the learning curve for surgical training in RFA and APC. Meanwhile, both procedures can be performed on an outpatient basis, which effectively saves medical resources. All these advantages constitute the basis for the clinical application and promotion of these techniques in the future.

This study had some limitations. Firstly, this was a single-center retrospective study with a certain inherent bias. In addition, improving the accuracy of preoperative evaluation remains a clinical difficulty that needs further investigation. Furthermore, it is also urgent to carry out large-sample randomized controlled clinical studies on submucosal injection for the relief of postoperative abdominal pain.

5. Conclusion

RFA and APC are both safe and effective damage therapies for gastric LGIN. RFA is more suitable for flat and large lesions, while APC is more suitable for small lesions, especially those with slight local uplift or depression. Intraoperative submucosal injection is expected to be an effective tool for relieving postoperative abdominal pain. As simple and efficient endoscopic treatment techniques for gastric LGIN, both tools are worthy of further clinical promotion.

Abbreviations

WHO:	World Health Organization
HGIN:	High-grade intraepithelial neoplasia
LGIN:	Low-grade intraepithelial neoplasia
RFA:	Radio frequency ablation
APC:	Argon plasma coagulation
EGC:	Early gastric cancer
ME:	Magnifying endoscopy
NBI:	Narrow-band imaging
PPI:	Proton pump inhibitor
H. pylori:	*Helicobacter pylori.*

Data Availability

All data obtained or analyzed during this work are included within the article.

Disclosure

Nanjun Wang and Ningli Chai are the co-first authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Nanjun Wang and Ningli Chai initiated the study design and drafted the manuscript. Longsong Li, Huikai Li, and Yaqi Zhai contributed to software and data curation. Xiuxue Feng, Shengzhen Liu, and Wengang Zhang contributed to supervision, review, and editing. Enqiang Linghu contributed to methodology, review, and editing. All authors read and approved the final manuscript.

Acknowledgments

This study was supported by the National Key R&D Program of China (2016YFC1303601) and grants or donations from the Beijing Municipal Science & Technology Commission (Grant no. Z181100001718177).

References

[1] J. D. Watterson, J. E. Mahoney, N. G. Futter, and J. Gaffield, "Iatrogenic ureteric injuries: approaches to etiology and management," *Canadian journal of surgery. Journal canadien de chirurgie*, vol. 41, no. 5, pp. 379–382, 1998.

[2] M. F. Dixon, "Gastrointestinal epithelial neoplasia: Vienna revisited," *Gut*, vol. 51, no. 1, pp. 130-131, 2002.

[3] R. J. Schlemper, R. H. Riddell, Y. Kato et al., "The Vienna classification of gastrointestinal epithelial neoplasia," *Gut*, vol. 47, no. 2, pp. 251–255, 2000.

[4] H. Ono, K. Yao, M. Fujishiro et al., "Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition)," *Digestive Endoscopy*, vol. 33, no. 1, pp. 4–20, 2021.

[5] Expert group of Beijing Municipal Science and Technology Commission Major Project, "Expert consensus on endoscopic standardized resection of early gastric cancer (2018, Beijing)," *Chinese Journal of Digestive Endoscopy*, vol. 36, no. 6, pp. 381–392, 2019.

[6] ASGE Standards of Practice Committee, J. A. Evans, V. Chandrasekhara et al., "The role of endoscopy in the management of premalignant and malignant conditions of the stomach," *Gastrointestinal Endoscopy*, vol. 82, no. 1, pp. 1–8, 2015.

[7] Division of Digestive Endoscopy of Beijing Medical Association, "Expert consensus on standardized diagnosis and treatment of gastric low-grade intraepithelial neoplasia (2019, Beijing)," *Chinese Journal of Gastrointestinal Endoscopy (Electronic Edition)*, vol. 6, no. 2, pp. 49–56, 2019.

[8] M. K. Kim, J. Y. Jang, J.-W. Kim et al., "Is lesion size an independent indication for endoscopic resection of biopsy-proven low-grade gastric dysplasia?" *Digestive Diseases and Sciences*, vol. 59, no. 2, pp. 428–435, 2014.

[9] A. Srivastava and G. Y. Lauwers, "Gastric epithelial dysplasia: the Western perspective," *Digestive and Liver Disease*, vol. 40, no. 8, pp. 641–649, 2008.

[10] S. C. Raftopoulos, P. Kumarasinghe, B. De Boer et al., "Gastric intraepithelial neoplasia in a Western population," *European Journal of Gastroenterology and Hepatology*, vol. 24, no. 1, pp. 48–54, 2012.

[11] C. D. Gregorio, P. Morandi, R. Fante, and C. De Gaetani, "Gastric dysplasia. A follow-up study," *American Journal of Gastroenterology*, vol. 88, no. 10, pp. 1714–1719, 1993.

[12] Y.-M. Park, E. Cho, H.-Y. Kang, and J.-M. Kim, "The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis," *Surgical Endoscopy*, vol. 25, no. 8, pp. 2666–2677, 2011.

[13] Y. Cao, C. Liao, A. Tan, Y Gao, Z Mo, and F Gao, "Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract," *Endoscopy*, vol. 41, no. 9, pp. 751–757, 2009.

[14] S. Y. Kim, J. K. Sung, H. S. Moon et al., "Is endoscopic mucosal resection a sufficient treatment for low-grade gastric epithelial dysplasia?" *Gut and Liver*, vol. 6, no. 4, pp. 446–451, 2012.

[15] F. Baldaque-Silva, H. Cardoso, J. Lopes, F. Carneiro, and G. Macedo, "Radiofrequency ablation for the treatment of gastric dysplasia," *European Journal of Gastroenterology and Hepatology*, vol. 25, no. 7, pp. 863–868, 2013.

[16] W. K. Leung, D. K. Tong, S. Y. Leung et al., "Treatment of gastric metaplasia or dysplasia by endoscopic radiofrequency ablation: a pilot study," *Hepato-Gastroenterology*, vol. 62, no. 139, pp. 748–751, 2015.

[17] N.-J. Wang, N.-L. Chai, X.-W. Tang, L.-S. Li, W.-G. Zhang, and E.-Q. Linghu, "Clinical efficacy and prognostic risk factors of endoscopic radiofrequency ablation for gastric low-grade intraepithelial neoplasia," *World Journal of Gastrointestinal Oncology*, vol. 14, no. 3, pp. 724–733, 2022.

[18] K. M. Lee, Y. B. Kim, S. J. Sin et al., "Argon plasma coagulation with submucosal saline injection for gastric adenoma on outpatient basis," *Digestive Diseases and Sciences*, vol. 54, no. 12, pp. 2623–2628, 2009.

[19] K. Y. Kim, S. W. Jeon, H. M. Yang et al., "Clinical outcomes of argon plasma coagulation therapy for early gastric neoplasms," *Clinical Endoscopy*, vol. 48, no. 2, pp. 147–151, 2015.

[20] "The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: november 30 to December 1, 2002," *Gastrointestinal Endoscopy*, vol. 58, no. 6, 2003.

[21] M. Meng, E. Q. Linghu, D. Wan et al., "Argon plasma coagulation for treatment of gastric low-grade intraepithelial neoplasia," *Chinese Journal of Gastrointestinal Endoscopy (Electronic Edition)*, vol. 1, no. 1, pp. 1–5, 2014.

[22] S. L. Lawson, M. M. Hogg, C. G. Moore et al., "Pediatric pain assessment in the emergency department," *Pediatric Emergency Care*, vol. 37, no. 12, pp. e950–e954, 2021.

[23] J. K. Sung, "Diagnosis and management of gastric dysplasia," *The Korean Journal of Internal Medicine*, vol. 31, no. 2, pp. 201–209, 2016.

[24] Y. L. Liu, Y. L. Cai, S. Chen et al., "Analysis of risk factors of gastric low-grade intraepithelial neoplasia in asymptomatic subjects undergoing physical examination," *Gastroenterol Res Pract*, vol. 2020, Article ID 7907195, 9 pages, 2020.

[25] J.-W. Kim and J. Y. Jang, "Optimal management of biopsy-proven low-grade gastric dysplasia," *World Journal of Gastrointestinal Endoscopy*, vol. 7, no. 4, pp. 396–402, 2015.

[26] D. H. Kang, C. W. Choi, H. W. Kim et al., "Predictors of upstage diagnosis after endoscopic resection of gastric low-grade dysplasia," *Surgical Endoscopy*, vol. 32, no. 6, pp. 2732–2738, 2018.

[27] X. T. Niu, *The Protective Effects of Submucosal Injection for Gastric Low-Grade Intraepithelial Neoplasia Treatment*, Nankai University, Tianjin, China, 2016.

[28] J. P. Watson, M. K. Bennett, S. M. Griffin, and K. Matthewson, "The tissue effect of argon plasma coagulation on esophageal and gastric mucosa," *Gastrointestinal Endoscopy*, vol. 52, no. 3, pp. 342–345, 2000.

Hindawi
Canadian Journal of Gastroenterology and Hepatology
Volume 2022, Article ID 3421078, 7 pages
https://doi.org/10.1155/2022/3421078

Research Article

Risk Factors and Timing of Additional Surgery after Noncurative ESD for Early Gastric Cancer

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Received 12 February 2022; Revised 18 May 2022; Accepted 30 May 2022; Published 21 June 2022

Academic Editor: Lu Zang

Background. Patients with early gastric cancer undergoing noncurative endoscopic submucosal dissection (ESD) have a risk of tumor recurrence and metastasis, and some patients need additional surgery. The purpose of this study was to explore the risk factors of cancer residue and lymph node (LN) metastasis after noncurative ESD for early gastric cancer and to compare the short outcome of early and delayed additional surgery. *Methods.* The clinicopathological characteristics of 30 early gastric cancer patients who received noncurative ESD and additional surgery were studied retrospectively. Multivariable regression was utilized to examine the independent risk factors for residual cancer and LN metastasis. Receiver operating characteristic curve was used to analyze the multivariable model's predictive performance. Furthermore, the perioperative safety and radical tumor performance of early surgery (≤30 days, $n = 11$), delayed surgery (>30 days, $n = 11$) after ESD, and upfront surgery ($n = 59$) were compared. *Results.* Multivariable regression showed that diffuse type of Lauren classification, submucosal invasion, and positive human epidermal growth factor receptor-2 (HER-2) were risk factors for residual cancer. Undifferentiated carcinoma, vascular invasion, and positive vertical margin were risk factors for LN metastasis. The area under the curve (AUC) of the multifactor model predicting cancer residue and LN metastasis was 0.761 and 0.792, respectively. The early surgery group experienced higher intraoperative blood loss and a longer operation time than the delayed surgery and upfront surgery groups. There was no significant difference in the number of LN dissections, LN metastasis rate, and postoperative complications among the three groups. *Conclusion.* Diffuse type of Lauren classification, submucosal invasion, and positive HER-2 are risk factors for residual cancer, while undifferentiated carcinoma, vascular invasion, and positive vertical margin are risk factors for LN metastasis. Delayed additional surgery after ESD (>30 days) has higher intraoperative safety, without affecting the radical resection in early gastric cancer patients.

1. Introduction

At present, gastric cancer is still one of the diseases seriously endangering human health. The treatment effect of advanced gastric cancer and early gastric cancer differs greatly, with the 5-year survival rate of the former being less than 30% while the latter exceeding 90% [1, 2]. Therefore, early detection and standardized treatment are the keys to improving the long-term outcome of gastric cancer patients.

Endoscopic submucosal dissection (ESD) is an important treatment for early gastric cancer. Japanese guidelines for the treatment of gastric cancer recommend ESD as the preferred treatment for early gastric cancer with a low risk of lymph node (LN) metastasis, and the eCura evaluation system is used to judge its radical performance [3]. The noncurative ESD mainly includes two types: one is nonwhole resection or positive horizontal resection margin (eCura-1) and the other is associated with high-risk factors for LN metastasis (eCura-2) [3–5]. For the former, individualized treatment can be adapted according to the specific situation, including re-ESD treatment [6], additional surgery [7], or close follow-up [8]. For the latter, additional surgery is recommended [9]. However, in practice, it was common that neither cancer residue nor LN metastasis was found in cases receiving additional surgery after noncurative ESD.

There is still some controversy on how to choose remedial measures for cases with noncurative ESD. Accurate evaluation of residual cancer and LN metastasis after ESD is the main basis for determining remedial measures. If corrective surgery is chosen, there is no agreement on the ideal time to perform it. Therefore, in the present study, we hypothesized that the clinicopathological features of the ESD tissue can be used to predict cancer residual and LN metastasis in patients with early gastric cancer. Meanwhile, the timing of additional surgery may affect the perioperative outcome.

2. Materials and Methods

The clinical and pathological data of 89 patients with early gastric cancer who received surgical treatment in the First Affiliated Hospital of Soochow University from July 2016 to June 2019 were collected.

Patients who have confirmed early gastric cancer by postoperative pathology, namely, the cancer invasion was limited to the mucosa and submucosa, and preoperative CT, MRI, and other examinations without signs of distant metastasis were included in the study. Patients who underwent emergency surgery due to bleeding or perforation caused by ESD treatment, or with a history of endoscopic gastric surgery or upper abdominal surgery, or with heart, lung, liver, kidney, and other organ dysfunction and abnormal coagulation function before surgery, or with other types of malignant tumors, or with incomplete clinical and pathological data were excluded from the study. This study was approved by the hospital ethical committee (20190511003).

Among them, 30 patients received ESD treatment first and were pathologically assessed as noncurative ESD, followed by surgical treatment. The ESD indication was in line with the 5th edition of Japanese gastric cancer treatment guidelines [3]. The ESD noncurative resection was determined as long as the pathology meets one of the following criteria: positive horizontal or vertical margin, vascular infiltration, submucosal infiltration depth $\geq 500\,\mu$m (SM2), differentiated tumor with ulceration (cT1a stage) diameter >3 cm, and the depth of submucosal invasion was $<500\,\mu$m (SM1), but the diameter was >3 cm; the invasion of the undifferentiated tumor was deep submucosal or larger than 2 cm in diameter or accompanied by ulceration [3]. According to the time of additional surgery, the patients were divided into the early surgery group (≤30 days after ESD, 19 cases) and the delayed surgery group (>30 days after ESD, 11 cases). The other 59 patients underwent upfront surgical treatment.

General data, including age, gender, and body mass index (BMI), were collected. Pathological information consisting of lesion diameter, ulcer, Lauren classification, depth of invasion, vascular invasion, differentiation type, ESD margin, HER-2 expression, residual cancer, and LN metastasis were obtained. For the risk factors of cancer residue and LN metastasis after ESD surgery, the possible influencing factors were analyzed by univariable analysis, and then, the risk factors were obtained by multivariable logistic regressions. Furthermore, the receiver operating characteristic (ROC) curves of the independent factors and the multifactor model were used to judge their predictive capability. To investigate the best timing for additional surgery, intraoperative data including surgery approach, operation time, intraoperative blood loss, number of dissected LN, and postoperative data, containing flatus and defecation time, oral feeding time, postoperative complications, and postoperative hospital stay were compared among three groups (early surgery after ESD, delayed surgery after ESD, and direct surgery).

In this study, SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for data statistical analysis. Values with a normal distribution were reported as mean ± standard deviation (SD), and skewed data were expressed as median and 25–75% interquartile range (IQR). The difference between groups was compared using the chi-square test or Fisher's exact probability method. P was considered statistically significant.

3. Results

A total of 89 patients with early stage gastric cancer were included in this study, including 30 patients who underwent additional surgery after noncurative ESD and 59 patients who underwent upfront surgery. The effects of varied surgical time were compared in the overall patients after the noncurative ESD patients were examined.

3.1. Basic Characteristics of Patients with Noncurative ESD. Postoperative pathological analysis of 30 patients undergoing additional surgery showed residual cancer in 16 cases and LN metastasis in 5 cases. Patients were divided into two groups according to the presence of cancer residue and LN metastasis, and the differences in basic information and pathological features after ESD were compared between the two groups (Table 1). Between the two groups with and without cancer residue, significant difference in age, Lauren categorization, depth of cancer invasion, horizontal resection margin, vertical resection margin, and human epidermal growth factor receptor-2 (HER-2) expression were found. There were significant differences in tumor differentiation type, vascular invasion, vertical resection margin, and HER-2 expression between patients with and without LN metastasis. There were no significant differences in gender, BMI, ESD indication (absolute or enlarged), ulcer, and diameter between groups with or without cancer residue and with or without LN metastasis.

3.2. Risk Factor Analysis of Noncurative ESD Patients with Residual Cancer and LN Metastasis. First, univariable analysis was conducted for the risk factor of residual cancer and LN metastasis. Further multivariable regression analysis showed that diffuse type of Lauren classification (OR = 2.28, 95% CI: 1.81–2.45, $P = 0.014$), submucosal invasion

Table 1: Characteristics of patients with noncurative ESD.

	Residual cancer		P	LN metastasis		P
	Yes ($n = 16$)	No ($n = 14$)		Yes ($n = 5$)	No ($n = 25$)	
Gender						
Male	13	12	0.432	4	21	0.124
Female	3	2		1	4	
Age (years)						
≥65	2	7	0.025	1	8	0.592
<65	14	7		4	17	
BMI (kg/m^2)	23.1 ± 4.2	22.7 ± 3.6	0.032	24.3 ± 4.1	22.3 ± 3.9	0.104
ESD indication						
Absolute	6	4	0.521	2	8	0.221
Enlarged	10	10		3	17	
Lauren type						
Intestinal	2	11	0.001	1	12	0.191
Diffuse	14	3		4	13	
Ulcer						
Yes	5	4	0.523	2	7	0.592
No	9	12		3	18	
Lesion diameter						
≤3 cm	12	10	0.825	4	18	0.712
>3 cm	4	4		1	7	
Pathological type						
Differentiated	7	6	0.964	1	12	0.024
Undifferentiated	9	8		4	13	
Depth of invasion						
Mucosa	2	9	0.003	0	11	0.062
Submucosa (or deeper)	14	5		5	14	
Vascular invasion						
Positive	4	3	0.818	4	3	0.003
Negative	12	11		1	22	
Vertical margin						
Positive	12	0	0.001	4	6	0.015
Negative	4	14		1	19	
Horizontal margin						
Positive	9	0	0.001	2	9	0.864
Negative	7	14		3	16	
HER-2 expression						
Positive	11	1	0.001	4	8	0.045
Negative	5	13		1	17	

(OR = 1.87, 95% CI: 1.32–2.14, $P = 0.023$), and positive HER-2 (OR = 2.41, 95% CI: 2.03–2.71, $P = 0.008$) were independent risk factors for residual cancer (Table 2). Pathologically undifferentiated (OR = 2.76, 95% CI: 1.87–3.21, $P = 0.021$), vascular invasion (OR = 2.53, 95% CI: 2.21–2.98, $P = 0.013$), and positive vertical margin (OR = 1.81, 95% CI: 1.65–2.13, $P = 0.027$) were independent risk factors for LN metastasis (Table 3). Positive HER-2 was not an independent risk factor for LN metastasis, and age was not an independent risk factor for residual cancer.

3.3. The Single Independent Factor and Multifactor Model Predicting Residual Cancer and LN Metastasis. The above independent risk factor and multivariable models created ROC curves to assess the accuracy of residual cancer and LN metastatic prediction (Table 4). The results showed that the area under the curve (AUC) predicting cancer residue by the multifactor model was 0.761, the specificity was 0.714, and the sensitivity was 0.813 (Figure 1). The AUC, specificity, and sensitivity of the multifactor model for predicting LN metastasis were 0.792, 0.800, and 0.640 (Figure 2).

3.4. Comparison of Additional Surgery with Different Timing after ESD and Direct Surgery in Early Gastric Cancer Patients. In order to determine the optimal timing for additional surgery after noncurative ESD, patients undergoing additional surgery were divided into the early surgery group (≤30 days) and delayed surgery group (>30 days). Patients with early gastric cancer who underwent direct surgery were set as the control group. The safety and radical resection of the three groups were compared. The delayed surgery group had less intraoperative blood loss and a shorter operation time than the early surgery group, according to the findings. There were no significant differences in the number of LN

Table 2: Univariable analysis and multivariable logistic regression analysis for residual cancer.

	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
Age < 65	1.21	0.78–1.67	0.109			
Diffuse type of Lauren classification	3.67	2.53–3.78	0.007	2.28	1.81–2.45	0.014
Submucosal invasion	2.12	1.56–2.81	0.019	1.87	1.32–2.14	0.023
HER-2 positive	3.32	2.13–4.02	0.001	2.41	2.03–2.71	0.008

Table 3: Univariable analysis and multivariable logistic regression analysis for LN metastasis.

	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
Undifferentiated carcinoma	2.82	2.10–3.43	0.015	2.76	1.87–3.21	0.021
Vascular invasion	2.79	1.91–3.27	0.011	2.53	2.11–2.98	0.013
Vertical margin positive	1.97	1.72–2.34	0.021	1.81	1.65–2.13	0.027
HER-2 positive	1.19	0.91–1.44	0.213			

Table 4: The single independent factor and multifactor model predicting residual cancer and LN metastasis.

Factors	AUC	Specificity	Sensitivity
Predicting residual cancer			
Multifactor model	0.761	0.714	0.813
Diffuse type of Lauren classification	0.536	0.645	0.595
Submucosal invasion	0.673	0.589	0.829
HER-2 positive	0.553	0.512	0.614
Predicting LN metastasis			
Multifactor model	0.792	0.640	0.800
Undifferentiated carcinoma	0.581	0.504	0.631
Vascular invasion	0.629	0.577	0.812
Vertical margin positive	0.521	0.492	0.587

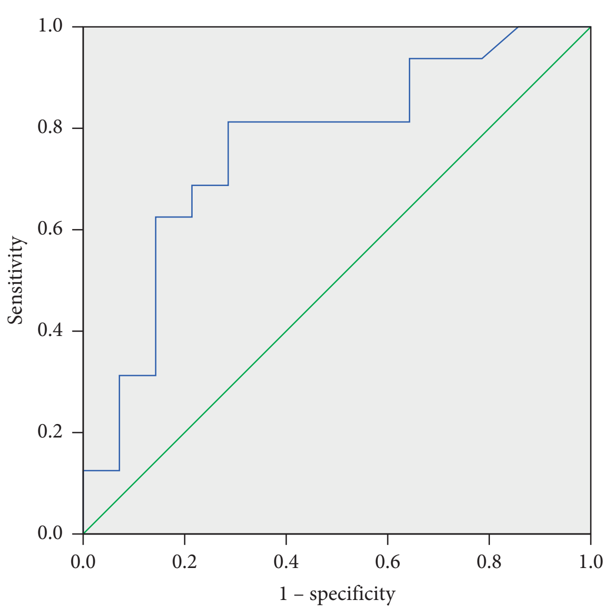

Figure 1: ROC curve for the selected logistic regression model in the diagnosis of residual cancer. Area under the curve = 0.761; sensitivity = 81.3%; specificity = 71.4%.

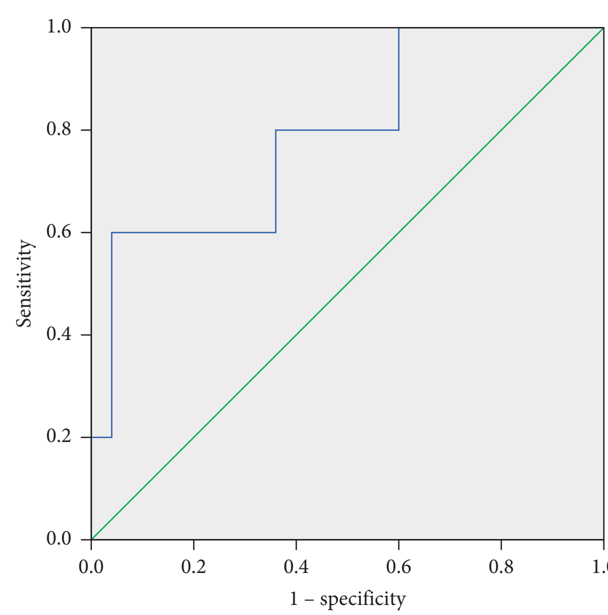

Figure 2: ROC curve for the selected logistic regression model in the diagnosis of LN metastasis. Area under the curve = 0.792; sensitivity = 80.0%; specificity = 64.0%.

dissections, LN metastatic rate, or postoperative complications between the two groups. The early surgery group also had more intraoperative blood loss and longer hospital stays than the direct surgery group. However, there was no significant difference in intraoperative and postoperative indicators between the delayed surgery group and the direct surgery group (Table 5).

4. Discussion

How to accurately predict residual cancer and LN metastasis after noncurative ESD is of great significance to guide clinical practice. There is no clear consensus on the timing of remedial surgery after ESD. Therefore, this study first analyzed the risk factors of cancer residue and LN metastasis in patients with noncurative ESD and then further compared the influence of early and delayed surgery on perioperative safety and radical resection. Postoperative pathologically confirmed tumor residue was found in 18 cases (accounting for 60.0%) of the 30 patients with early gastric cancer who underwent noncurative ESD and additional surgery, including 16 cases with primary tumor residue (accounting for 53.3%) and 5 cases with LN metastasis (accounting for 16.7%). Three of them (10%) had primary residual cancer with LN metastasis. This group of data shows that innocent surgical patients accounted for 40%.

Multivariable regression analysis showed that diffuse type of Lauren classification, submucosal invasion, and positive HER-2 were risk factors for residual cancer. The diffused invasive growth pattern of tumors may hinder endoscopists from accurately determining tumor tissue boundaries. The increased depth of vertical infiltration has the potential to exceed the excision layer of ESD operation. Sangjeong et al. found that the increase of positive margin length was an important risk factor for residual cancer. The sensitivity of positive margins with a total length of more than 6 mm to residual cancer diagnosis was 85.7% [10]. Sunagawa et al. found that positive horizontal and vertical margins were risk factors for residual cancer by analyzing 200 cases of noncurative ESD surgery [11]. Nie et al. observed that tumor diameter >3 cm, undifferentiated type, and positive horizontal margin enhanced the probability of residual cancer in a meta-analysis of 4870 cases [12]. A positive edge means that there are tumor cells within 2 mm of the boundary tissue [13], which is related to the burning of the edge and the fixation of the specimen. Proper surgery and specimen processing can help forecast the likelihood of residual cancer with more accuracy. In addition, endoscopic amplification and staining should be performed routinely before ESD to accurately determine the horizontal boundary of lesions. Endoscopic ultrasonography is useful for determining the depth of lesion invasion and identifying instances that are suited for ESD treatment. Numata et al. found that the overall positive rate of horizontal resection margin was 2% (21/1053) in 1053 cases of early gastric cancer undergoing ESD, and the follow-up found that the local recurrence rate was 0.3% (3/1053) in all patients, and the time of local recurrence ranged from 8 to 34 months [13]. Sekiguchi et al. analyzed 77 patients with positive horizontal resection margin after ESD and selected follow-up. They found that the local tumor recurrence rate within 5 years was 11.9%, and more than 6 mm was an effective indicator to predict recurrence [8]. Surgical operation is recommended for patients with positive vertical margin, but there is no unified opinion on whether to perform ESD again or additional surgery for follow-up treatment with positive horizontal margin (eCura-C1) [3], which needs to be determined by patients' specific conditions and hospital operation routine and needs to be confirmed by clinical studies with larger samples.

In this study, the proportion of LN metastasis in patients with noncurative ESD resection was 16.7% (5/30). This is slightly higher than the reported 9.8% incidence of LN metastasis in patients with additional surgery after endoscopic treatment [14]. This may be related to the fact that most of the patients with noncurative ESD in this study were with the extended ESD indications. Multivariable regression analysis showed that undifferentiated tumor, vascular invasion, and positive vertical margin were risk factors for LN metastasis. Undifferentiated gastric cancer includes poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma. Studies have shown that the LN metastasis rate of these three types of early gastric cancer can reach 6.0%–44.4% [15]. Undifferentiated intramucosal carcinoma above 2 cm is not an absolute indication for ESD because of the relatively high probability of LN metastasis [3]. LN metastasis was 6.7 times higher among patients with lymphovascular invasion than in those without, and LN positivity increased significantly with increasing depth of lesion invasion, according to a postoperative histopathological analysis of 3131 patients with early gastric cancer. Meta studies have found that the LN metastasis rate can reach 2.5% when the tumor infiltrates to the 300 μm submucosal layer, which is close to 2.8% when the tumor infiltrates to the 500 μm submucosal layer [16]. The submucosa contains a large number of lymphatic vessels, and tumor cells that infiltrate the submucosa are more likely to spread to LN via these vessels. Japanese guidelines also clearly indicate that additional surgery is imperative when submucosal invasion exceeds 500 μm, or there is undifferentiated carcinoma or vascular invasion (eCura-C2) [3]. This is consistent with our findings.

However, there is no consensus on when to perform surgery after noncurative ESD. Our study found that delayed surgery (>30 days) was associated with less intraoperative bleeding, operative time, and hospital stay than early surgery (≤30 days), and there were no significant differences in complications or radical outcomes. This is consistent with the results of other studies. By analyzing 154 patients undergoing additional surgery after ESD, Kim et al. found that compared with the delayed surgery group (>29 days), the early surgery group (<29 days) had longer operation time and more intraoperative blood loss [17]. There was no significant difference in the tumor recurrence rate between the two groups after additional follow-up [18]. By analyzing 107 cases of additional surgery after ESD, Lee et al. found that patients with an interval of fewer than 24 days and ESD-related ulcers over 4.6 cm had more intraoperative bleeding

Table 5: Comparison of safety and radical resection between different surgery timing for early gastric cancer.

	Early surgery after ESD ($n = 19$)	Delayed surgery after ESD ($n = 11$)	Direct surgery ($n = 59$)	P1 (early vs. delayed)	P2 (early vs. direct)	P3 (delayed vs. direct)
Age (year)	61.4 ± 10.3	63.5 ± 8.9	62.7 ± 11.4	0.532	0.312	0.571
Gender (male)	17	8	33	0.093	0.012	0.037
BMI (kg/m^2)	22.1 ± 4.2	24.5 ± 3.9	23.6 ± 4.7	0.211	0.421	0.542
Extent of gastric resection						
Distal gastrectomy	13	8	42			
Proximal gastrectomy	2	1	6	0.533	0.242	0.471
Total gastrectomy	4	2	11			
Surgery approach						
Laparoscopic	12	8	38	0.231	0.123	0.701
Open	7	3	21			
Operation time (min)	289 ± 74	230 ± 66	245 ± 102	0.046	0.072	0.144
Intraoperative blood loss (ml)	421 ± 218	252 ± 102	321 ± 138	0.012	0.025	0.059
No. of LN dissection	22 ± 7	19 ± 8	23 ± 7	0.634	0.453	0.323
LN metastasis rate	15.8% (3/19)	18.2% (2/11)	13.6% (8/59)	0.324	0.279	0.145
Postoperative flatus and defecation time (d)	6.1 ± 2.8	4.8 ± 2.2	4.9 ± 3.1	0.139	0.051	0.231
Postoperative oral feeding time (d)	5.3 ± 3.8	4.7 ± 3.5	4.7 ± 2.9	0.711	0.213	0.572
Postoperative hospital stay (d)	12.3 ± 5.8	10.5 ± 4.1	9.8 ± 2.9	0.062	0.031	0.342
Postoperative complications (n)	4	3	12	0.312	0.192	0.211

and longer operation time [19]. Within 4–8 weeks after ESD surgery, local edema, inflammation, and scar formation of gastric wall tissue exist [20]. This could be one of the reasons for the early surgical group's longer operative time and higher intraoperative blood loss. Tissue edema and inflammation may subside after more than a month, reducing the complexity of the surgery. Some studies have found that convergence of gastric mucosa due to scarring caused by ESD operation in the middle and upper stomach can affect the selection of additional surgical methods, and the proportion of distal gastrectomy is significantly reduced [21]. This is also a significant influence in increasing the duration of surgery and the amount of blood loss. But larger, higher-quality studies are needed to determine the best timing of additional surgery. The gender showed some difference between the direct surgery group and additional surgery group. We considered this was due to the small size of the ESD group which has a relatively high male proportion. Since the gastric surgery was performed in the upper abdomen and the BMI was comparable among the three groups, the gender difference theoretically should have little effect on the surgery process and recovery.

This study has some limitations. First, this was a single-center retrospective study, and some ESD cases were with expanded indications, which may have selection bias. Second, due to the small sample size, the power of test of the factor undifferentiated carcinoma was slightly weak. Thus, when we consider the effect of pathological type on LN metastasis in practice, we should take it with caution based on the present data. In addition, although the prediction ability of risk factors on cancer residue and LN metastasis was analyzed by the ROC curve in this study, it has not been verified in a large number of cases. Third, this study mainly observed the perioperative safety of patients, and the long-term prognosis has not been recorded, which needs to be further studied.

5. Conclusions

In conclusion, diffuse type of Lauren classification, submucosal invasion, and positive HER-2 were risk factors for residual cancer, while undifferentiated tumor, vascular invasion, and positive vertical margin were risk factors for LN metastasis. In early gastric cancer patients, delaying surgery after ESD (>30 days) improves intraoperative safety without compromising radical resection.

Data Availability

The datasets collected and analyzed in this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Kaipeng Duan, Dongbao Li, and Dongtao Shi contributed equally to this study.

Acknowledgments

This research was supported by the National Natural Science Foundation of China (81871952 and 81700788), Jiangsu Provincial Key Research and Development Program

(BE2020657), and Gusu Health Talents Cultivation Program (GSWS2019008).

References

[1] L. H. Eusebi, A. Telese, G. Marasco, F. Bazzoli, and R. M. Zagari, "Gastric cancer prevention strategies: a global perspective," *Journal of Gastroenterology and Hepatology*, vol. 35, no. 9, pp. 1495–1502, 2020.

[2] W. Chen, R. Zheng, P. D. Baade et al., "Cancer statistics in China, 2015," *CA: A Cancer Journal for Clinicians*, vol. 66, no. 2, pp. 115–132, 2016.

[3] A. Japanese, "Gastric cancer, Japanese gastric cancer treatment guidelines 2018 (5th edition)," *Gastric Cancer: Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association*, vol. 24, no. 1, pp. 1–21, 2021.

[4] S.-H. Lee, C. W. Choi, S. J. Kim et al., "Risk factors for lymph node metastasis in mucosal gastric cancer and re-evaluation of endoscopic submucosal dissection," *Annals of Surgical Treatment and Research*, vol. 91, no. 3, pp. 118–126, 2016.

[5] W. Hatta, T. Gotoda, T. Oyama et al., "A scoring system to stratify curability after endoscopic submucosal dissection for early gastric cancer: ecura system," *American Journal of Gastroenterology*, vol. 112, no. 6, pp. 874–881, 2017.

[6] M. Y. Jeon, J. C. Park, K. Y. Hahn, S. K. Shin, S. K. Lee, and Y. C. Lee, "Long-term outcomes after noncurative endoscopic resection of early gastric cancer: the optimal time for additional endoscopic treatment," *Gastrointestinal Endoscopy*, vol. 87, no. 4, pp. 1003–1013, 2018.

[7] B. W. Eom, Y.-I. Kim, K. H. Kim et al., "Survival benefit of additional surgery after noncurative endoscopic resection in patients with early gastric cancer," *Gastrointestinal Endoscopy*, vol. 85, no. 1, pp. 155–163, 2017.

[8] M. Sekiguchi, H. Suzuki, I. Oda et al., "Risk of recurrent gastric cancer after endoscopic resection with a positive lateral margin," *Endoscopy*, vol. 46, no. 4, pp. 273–278, 2014.

[9] K. Yamanouchi, S. Ogata, Y. Sakata et al., "Effect of additional surgery after noncurative endoscopic submucosal dissection for early gastric cancer," *Endoscopy International Open*, vol. 4, no. 1, pp. 24–29, 2016.

[10] S. Ahn, I.-G. Do, J. H. Sohn, H.-J. Yang, C. H. Yoo, and K. Kim, "Total length of positive resection margins can predict remnant gastric cancer following endoscopic submucosal dissection," *Pathology, Research & Practice*, vol. 216, no. 11, p. 153183, 2020.

[11] H. Sunagawa, T. Kinoshita, A. Kaito et al., "Additional surgery for non-curative resection after endoscopic submucosal dissection for gastric cancer: a retrospective analysis of 200 cases," *Surgery Today*, vol. 47, no. 2, pp. 202–209, 2017.

[12] R.-C. Nie, S.-Q. Yuan, Y.-F. Li et al., "Additional gastrectomy in early-stage gastric cancer after non-curative endoscopic resection: a meta-analysis," *Gastroenterology Report*, vol. 7, no. 2, pp. 91–97, 2019.

[13] N. Numata, S. Oka, S. Tanaka et al., "Risk factors and management of positive horizontal margin in early gastric cancer resected by en bloc endoscopic submucosal dissection," *Gastric Cancer*, vol. 18, no. 2, pp. 332–338, 2015.

[14] S. Hoteya, T. Iizuka, D. Kikuchi et al., "Clinicopathological outcomes of patients with early gastric cancer after non-curative endoscopic submucosal dissection," *Digestion*, vol. 93, no. 1, pp. 53–58, 2016.

[15] B. D. Ye, S. G. Kim, J. Y. Lee et al., "Predictive factors for lymph node metastasis and endoscopic treatment strategies for undifferentiated early gastric cancer," *Journal of Gastroenterology and Hepatology*, vol. 23, no. 1, pp. 46–50, 2008.

[16] M. Sekiguchi, I. Oda, H. Taniguchi et al., "Risk stratification and predictive risk-scoring model for lymph node metastasis in early gastric cancer," *Journal of Gastroenterology*, vol. 51, no. 10, pp. 961–970, 2016.

[17] M. J. Kim, J.-H. Kim, Y. C. Lee et al., "Is there an optimal surgery time after endoscopic resection in early gastric cancer?" *Annals of Surgical Oncology*, vol. 21, no. 1, pp. 232–239, 2014.

[18] J. H. Cha, J.-H. Kim, H.-I. Kim et al., "The optimal timing of additional surgery after non-curative endoscopic resection to treat early gastric cancer: long-term follow-up study," *Scientific Reports*, vol. 9, no. 1, p. 18331, 2019.

[19] H. Lee, H. H. Lee, K. Y. Song, C. H. Park, and J. Lee, "Negative impact of endoscopic submucosal dissection on short-term surgical outcomes of subsequent laparoscopic distal gastrectomy for gastric cancer," *Annals of Surgical Oncology*, vol. 27, no. 1, pp. 313–320, 2020.

[20] O. Goto, M. Fujishiro, S. Kodashima et al., "Short-term healing process of artificial ulcers after gastric endoscopic submucosal dissection," *Gut and liver*, vol. 5, no. 3, pp. 293–297, 2011.

[21] J. Aoyama, S. Sakuramoto, Y. Miyawaki et al., "Impact of endoscopic resection on the choice of surgical procedure in patients with additional laparoscopic gastrectomy," *Gastric Cancer*, vol. 23, no. 5, pp. 913–921, 2020.

Hindawi
Canadian Journal of Gastroenterology and Hepatology
Volume 2022, Article ID 2422274, 8 pages
https://doi.org/10.1155/2022/2422274

Research Article

Application of Half-Transected and Self-Pulling Esophagojejunostomy in Total Laparoscopic Gastrectomy for Gastric Cancer: A Safe and Feasible Technique

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Received 7 February 2022; Revised 6 April 2022; Accepted 25 April 2022; Published 13 June 2022

Academic Editor: Xiaohua Jiang

Objective. This study introduces a technique for esophagojejunostomy with half transected and self-pulling (HTSP) and evaluates the safety, feasibility, and clinical results of this technique in totally laparoscopic total gastrectomy (TLTG). *Materials and Methods*. From May 2019 to March 2021, 42 patients (HTSP group) who underwent HTSP-TLTG surgery in the Department of Abdominal Tumor Surgery of Jiangxi Cancer Hospital were included in this study. The control group consisted of 50 patients undergoing conventional TLTG surgery (conventional anastomosis group) performed by the same surgical team from March 2018 to March 2020. The clinical data of the two groups were retrospectively analyzed and compared. *Results*. The mean operation time of the HTSP-TLTG surgery was 166.7 ± 13.1 minutes and the anastomosis time was 20.8 ± 2.0 minutes, which were significantly shorter than those of traditional TLTG ($P < 0.05$). There were no significant differences between the two groups in blood loss, time to first exhaust, postoperative hospital stay, and incidence of surgery-related complications. *Conclusion*. HTSP is a safe and feasible way of endoscopic esophagojejunal anastomosis, which requires a relatively low suture technique under endoscopy, and is suitable for promotion.

1. Introduction

Laparoscopic treatment of gastric cancer has been widely carried out in many countries around the world [1–3]. With the continuous maturity and improvement of laparoscopic technology, it is not limited to be the treatment for early gastric cancer, and its efficacy in advanced gastric cancer has gradually been recognized [4–8]. Compared with laparoscopic-assisted radical gastrectomy (LAG), total laparoscopic gastrectomy (TLG) has the advantages of better visualization, shorter operation time, less postoperative pain, and smaller incision, so it is widely accepted and respected by surgeons [9–11]. In view of the difficulty and high technical requirements of total esophagojejunostomy, TLTG is not as widely used as total laparoscopic distal gastrectomy (TLDG) [12–15].

Currently, esophagojejunostomy is mainly performed with circular and linear staplers. The former mainly includes the peroral stapler anvil device (OrVil™) method, reverse puncture placement (RPD) method, purse-string stapler method, and manual suture method; the latter mainly includes functional end-to-end anastomosis (FETE), partially overlapping side-to-side anastomosis (overlap group), and "π-type" anastomosis [16–20]. Anastomosis techniques are continuously improving and innovating but still face many problems, such as difficulty in laparoscopic anvil implantation, difficulty in common opening suturing, and high price.

To address these issues, our team created the half-transected self-pulling (HTSP) esophagojejunostomy technique in May 2019, based on a summary of traditional surgical experience, combined with the advantages of linear staplers. In this report, we will describe the novel stapling technique in detail and analyze its feasibility and short-term safety by comparing its clinical results with conventional TLTG (overlap or functional end-to-end anastomosis (FETE)). Our preliminary experiments have shown that HTSP is a simple and safe way for endoluminal esophagojejunostomy. Without the need to add any surgical steps, this technique makes the manual suture link of the common opening simpler and faster, further reduces the difficulties, and shortens the anastomosis time; therefore, it is more easily accepted and popularized by surgeons.

2. Material and Methods

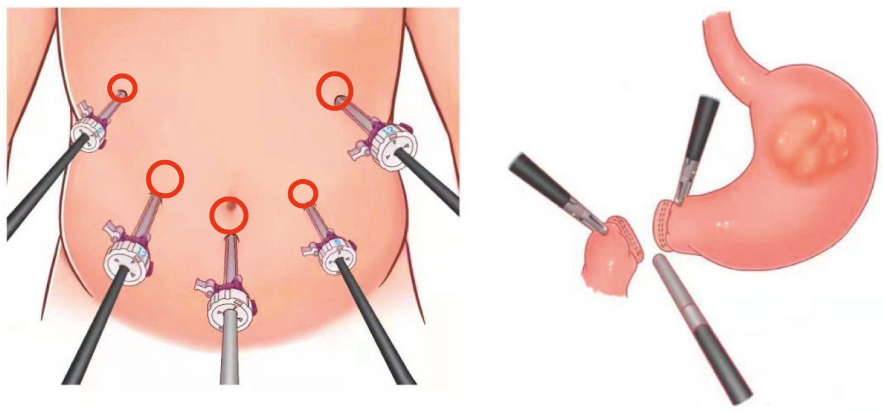
Between May 2019 and March 2021, 42 patients (HTSP group) who underwent HTSP-TLTG surgery in the Department of Abdominal Tumor Surgery of Jiangxi Cancer Hospital were included in this study. The control group consisted of 50 patients (conventional anastomosis group) undergoing conventional TLTG surgery performed by the same surgical team from March 2018 to March 2020. Preoperative evaluation methods mainly include endoscopy, ultrasonography, and enhanced CT.

Inclusion criteria of this study were as follows: (1) preoperative pathological confirmation of gastric adenocarcinoma; (2) endoscopy confirmed that the tumor is located in the gastric body, fundus, or cardia; (3) preoperative CT staging is cT1-4aN0-2M0; (4) patients signed an informed consent form; (5) approval by the Ethics Committee of Jiangxi Cancer Hospital. Patient information was collected, including age, gender, body mass index (BMI), operation and anastomosis time, blood loss, pathological stage, and postoperative complications.

2.1. Surgical Approach for HTSP-TLTG. Gastric tubes and urinary catheters were routinely placed in all patients before surgery. Under general anesthesia with endotracheal intubation, the patient was placed in the reverse Trendelenburg position with legs apart and the head elevated to about 15°. The chief surgeon was on the left side of the patient, the assistant was on the right side, and the camera holder was between the legs. The five-hole method was used in the operation. A longitudinal incision of 10 mm with trocar was made 1 cm below the umbilicus as the observation hole, and it was also used to establish pneumoperitoneum and maintain CO_2 pressure at 12–14 mmHg (1 mmHg = 0.133 kPa). A 12 mm trocar was placed 2 cm below the costal margin of the left anterior axillary line and 2 cm above the umbilicus of the right midclavicular line as the main operating hole for the chief surgeon and the right-hand operating hole for the assistant, respectively. A 5 mm trocar was placed 2 cm below the costal margin of the right anterior axillary line and 2 cm above the umbilicus of the left midclavicular line as the left-hand operating hole for the chief surgeon and assistant, respectively (Figure 1(a)). The abdomen and pelvis were explored to rule out peritoneal implants and distant metastasis. Routine D2 dissection was completed according to the standardized requirements for radical gastrectomy for gastric cancer. The need to transect part of the diaphragmatic crus was decided by judging the level of tumor location, and the duodenum was transected with a linear stapler (Figure 1(b))

2.2. Reconstruction of the Alimentary Canal with HTSP-TLTG. The lower esophagus is partially dissected (the gastric corpus tumor was cut off from the cardia and the esophagogastric junction tumor was cut off from the upper edge of the tumor) by using a linear stapler (Figures 2(a) and 2(b)), a small longitudinal hole perpendicular to the tangential line of the esophagus was made with an ultrasonic knife; then, the stomach and the greater omentum are all sent to the right abdomen of the patient, and the traction force to the right and downward of the esophagus is formed under the action of gravity, which is called "half-transected self-pulling" (Figures 2(c) and 2(d)). The jejunum was dissected with a linear stapler at 15-20 cm from the Treitz ligament, and a hole was made in the distal jejunum wall opposite to the mesentery at a distance of 8 cm from the cut end (Figures 3(a) and 3(b)). After that, the chief surgeon and the assistant switched positions, with the chief surgeon on the right side of the patient. The jejunum was lifted up, and the linear stapler was used to tilt 45° to complete the lateral-lateral anastomosis between the posterior esophageal wall and the jejunum wall opposite to the mesentery (if the tumor is low, the anastomosis is completed outside the crus of the diaphragm, and if the tumor is high, the anastomosis is completed inside the crus of the diaphragm) (Figures 3(c) and 3(d)). The common opening was closed with 3-0 barbed sutures from left to right in a continuous manner (Figures 4(a) and 4(b)). After the sutures were closed to about 3/4, the assistant cut off the remaining part of the esophagus with an ultrasonic knife (Figures 4(c) and 4(d)). After the common opening was completely closed, the jejunal seromuscular-diaphragmatic suture was continued from right to left to reinforce the common opening (Figure 5(a)). The proximal jejunum was perforated at 8 cm from the break, and the proximal jejunum was laterally anastomosed with the jejunum at about 40 cm from the esophagojejunostomy (Figure 5(b)), 3-0 barbed line full-thickness suture from left to right to close the common opening, followed by reinforcement of the seromuscular layer from right to left (Figures 5(c) and 5(d)). The specimen was placed in a specimen bag and removed through an extended umbilical incision and placed on a negative pressure drainage tube in the splenic fossa.

2.3. Evaluation Criteria. The surgical indicators, the occurrence of postoperative complications, and the postoperative recovery between the two groups were compared. The surgical indexes included operative time, anastomosis time, and intraoperative blood loss. The postoperative recovery indexes included the time to the first postoperative exhaust and the postoperative hospital stay. Postoperative complications included abdominal or anastomotic bleeding, anastomotic leakage, anastomotic stricture, pancreatic leak,



(a) (b)

Figure 1: (a) Trocar hole position distribution, 1 cm below the umbilical disposal into the 10 mm trocar as the observation hole. (b) The duodenum after transection.

lymphatic leak, abdominal infection, pulmonary infection, and reflux esophagitis.

2.4. Postoperative Management. The gastric tube was removed on the first day after surgery, and the patient was allowed to ingest a small amount of liquid food several times after the first postoperative exhaust. After operation, the abdominal cavity or anastomotic bleeding, lymphatic leakage, and pancreatic leakage were determined by the drainage of the abdominal cavity drainage tube. An upper gastrointestinal X-ray was performed on postoperative day 5 to evaluate for anastomotic leakage (Figure 6(a)). On the 6th day after operation, CT examination was performed to check for the presence of lung and abdominal infection. The patient was discharged 8–10 days postoperatively. Electronic gastroscopy was performed 6 months after discharge to check for the presence of anastomotic stenosis (Figures 6(b) and 6(c)).

2.5. Statistical Methods. SPSS 22.0 was used to analyze the data. Normally distributed measures were expressed as mean ± standard deviation and the *t*-test was used for the two samples; non-normally distributed measures were expressed as median (range) and the Mann-Whitney *U* test was used. $P < 0.05$ was considered a statistically significant difference.

3. Results

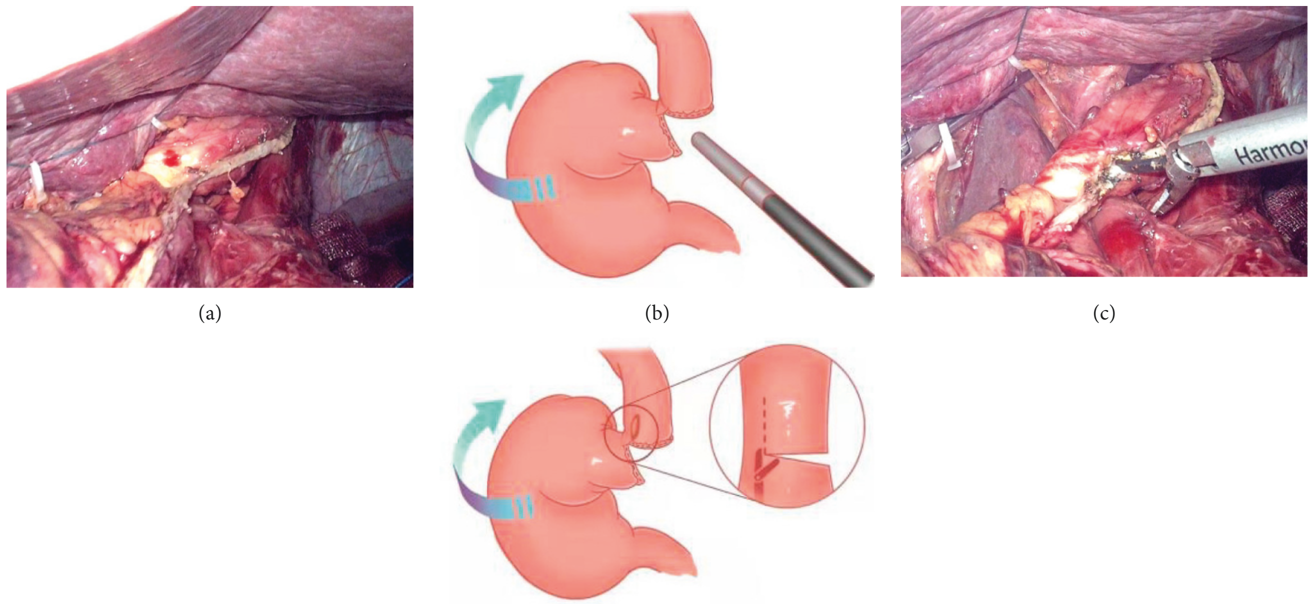
3.1. Comparison of Patient Characteristics. The general information of the patients in the two groups was compared (Table 1). There were 42 patients in the HTSP group, including 33 men and 9 women, with a median age of 63.0 years (17–80 years) and a mean BMI of $21.4 \pm 2.3\ \mathrm{kg/m^2}$. The average diameter of the tumor was 21.4 ± 2.3 cm, and 19 of them were located in the fundus or upper stomach, while 23 were located in the middle of the stomach. There were 50 patients in the overlap or FETE group, including 40 men and 10 women, with a median age of 61.5 years (38–83 years) and a mean BMI of $21.2 \pm 2.2\ \mathrm{kg/m^2}$. The average diameter of the tumor was 3.02 ± 1.8 cm, and 21 of them were located in the fundus or upper stomach, while 29 were located in the middle of the stomach.

3.2. Comparison of Intraoperative and Postoperative Conditions. The operation was successfully completed in both groups. There was no conversion to laparotomy due to anastomotic problems and no positive margin in both groups. There was no significant difference in blood loss, first exhaust time, and postoperative hospital stay between the two groups. However, the operation time and anastomosis time of the HTSP group were shorter than those of the traditional anastomosis group, and the differences were statistically significant (all $P < 0.05$) (Table 2).

3.3. Comparison of Surgery-Related Complications. Intraoperative complications, including spleen injury and vascular bleeding, were not present in this study in either group. The incidence of postoperative complications in the HTSP group was 4.7% (2/42), including 1 case of lymphatic leakage (3 days after surgery) and 1 case of pulmonary infection (4 days after surgery). All the patients were cured after conservative treatment, and there was no significant difference compared with the conventional TLTG group. Other common complications such as anastomotic or duodenal stump leakage, anastomotic bleeding, and intestinal obstruction or internal hernia were not found in this study. During the follow-up period, no HTSP patient complained of reflux symptoms or anastomotic stenosis, and only one patient had liver metastasis 9 months after operation (Table 3).

4. Discussion

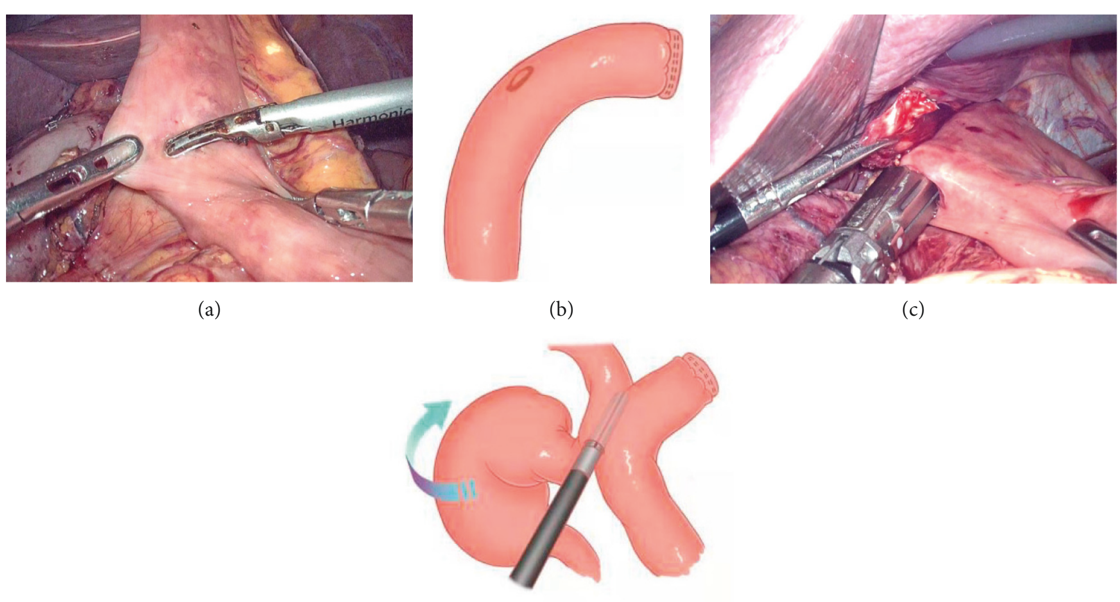
In recent years, although many studies have confirmed the safety and feasibility of TLTG with different anastomosis methods, TLTG has not been carried out as widely as TLDG [12–15]. The main reason is that the esophageal-



(a) (b) (c)

(d)

Figure 2: (a, b) The linear stapler transected the lower esophagus segment. (c, d) Ultrasonic knife perpendicular to the esophageal tangent to take a longitudinal hole, with the position under the action of gravity to produce downward-to-right traction.



(a) (b) (c)

(d)

Figure 3: (a, b) The intestinal wall was drilled 8 cm away from the stump. (c, d) Jejunum was lifted and a linear stapler was used to perform side-to-side anastomosis between the posterior wall of the esophagus and the opposite limbus of the jejunum.

jejunal anastomosis is difficult, with high technical requirements and high surgical risks. Compared with the circular stapler, the linear stapler is easier to operate, which is less likely to cause anastomotic stenosis, and is suitable for the esophagus with the small lumen. Therefore, it is widely recognized as an anastomosis method in many current methods [20–25]. However, the current mainstream linear anastomosis methods overlap and FETE have some shortcomings [14, 26]as follows: (1) In terms of closing common openings, overlap and FETE cannot provide a stable suture field of view, resulting in manual suture difficulties and high technical requirements for the surgeon. (2) Both the two methods will retract into the posterior mediastinum after esophageal transection, resulting in difficult operation and is unsuitable for cases requiring high esophageal transection.

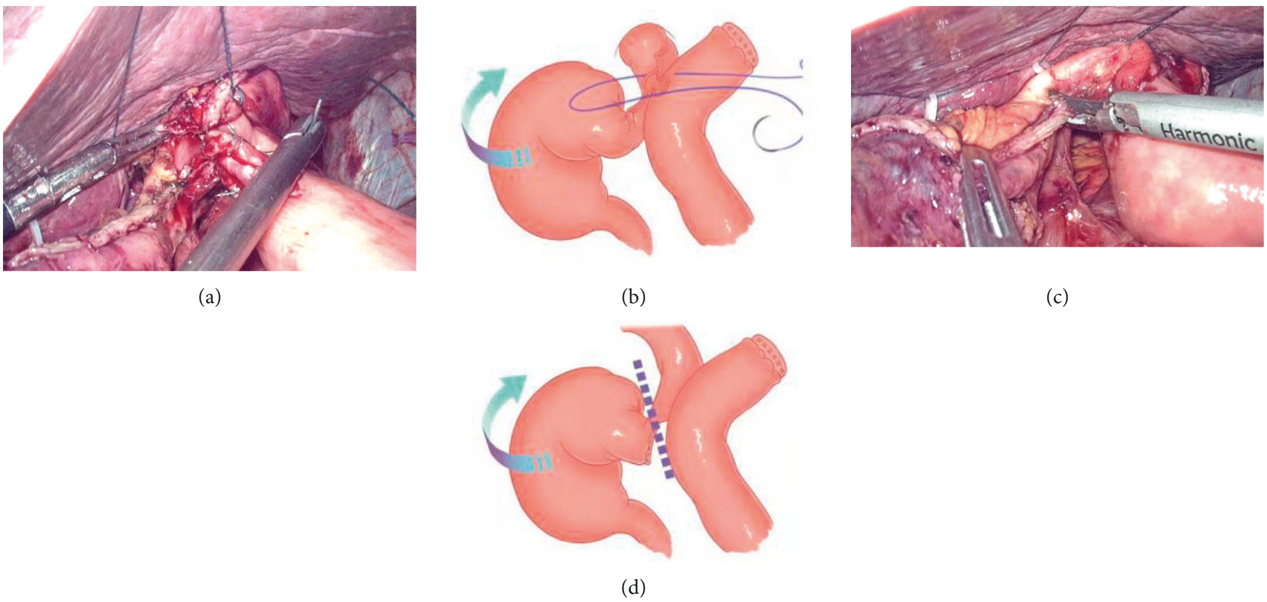


Figure 4: (a, b) A 3-0 barbed wire from left to right continuous sutured closure common opening. (c, d) Ultrasound knife transected the remaining part of the esophagus.

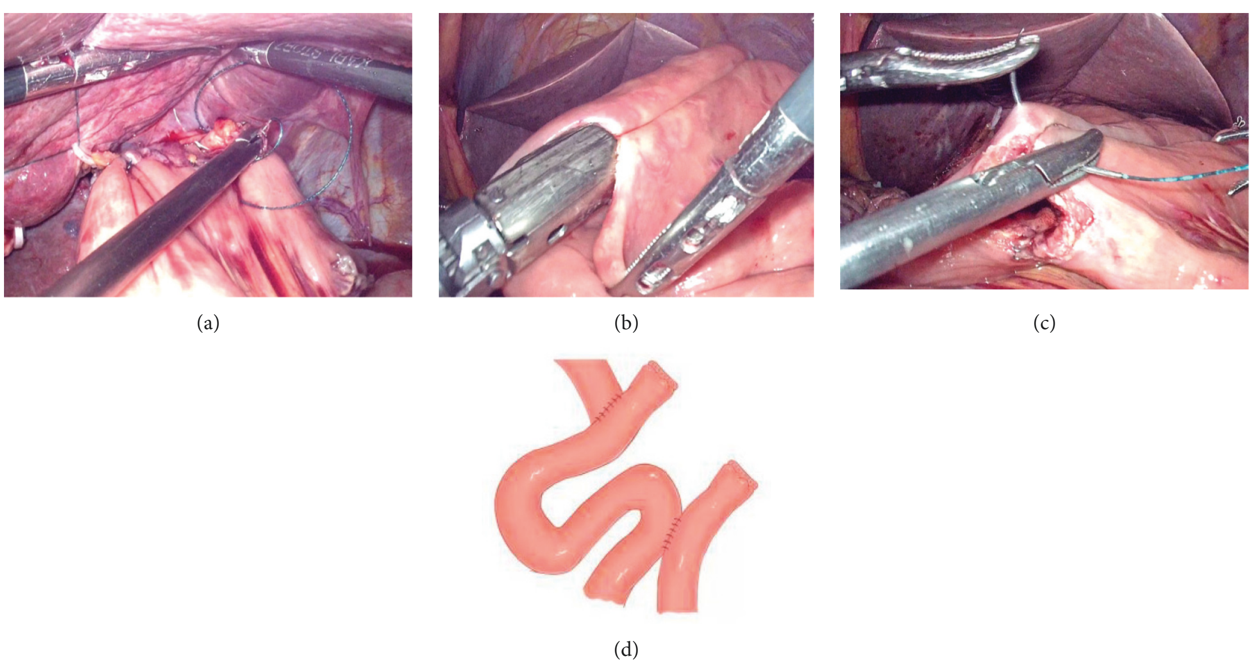


Figure 5: (a) 3-0 barbed wire from right to left for jejunal seromuscular-diaphragmatic suture. (b) The proximal jejunum was anastomosed to the jejunum side at 40 cm away from the esophagojejunostomy. (c, d) 3-0 barbed wire sutured to close the common opening.

Our team has tried and improved various TLTG methods since February 2018 and found that "half-transect" of the esophagus can avoid esophageal retraction into the posterior mediastinum and reduce the difficulty of surgery. Then, the other method was with the change of posture and full use of the gravity of the stomach and the greater omentum to produce downward and right traction on the esophagus, so as to close the common opening to provide a stable suture vision, called "self-pulling." Combining these two methods to form a "half-transected self-pulling modified overlap anastomosis" makes up for the above-mentioned deficiencies of linear anastomosis without adding any surgical steps and financial burden on the patient. Based on these technical features, we name it "half-transected self-pulling, HTSP."

The operation skills of HTSP are as follows: (1) The lower segment of the half-transected esophagus should be dismembered about 3/4. Excessive dismemberment is not

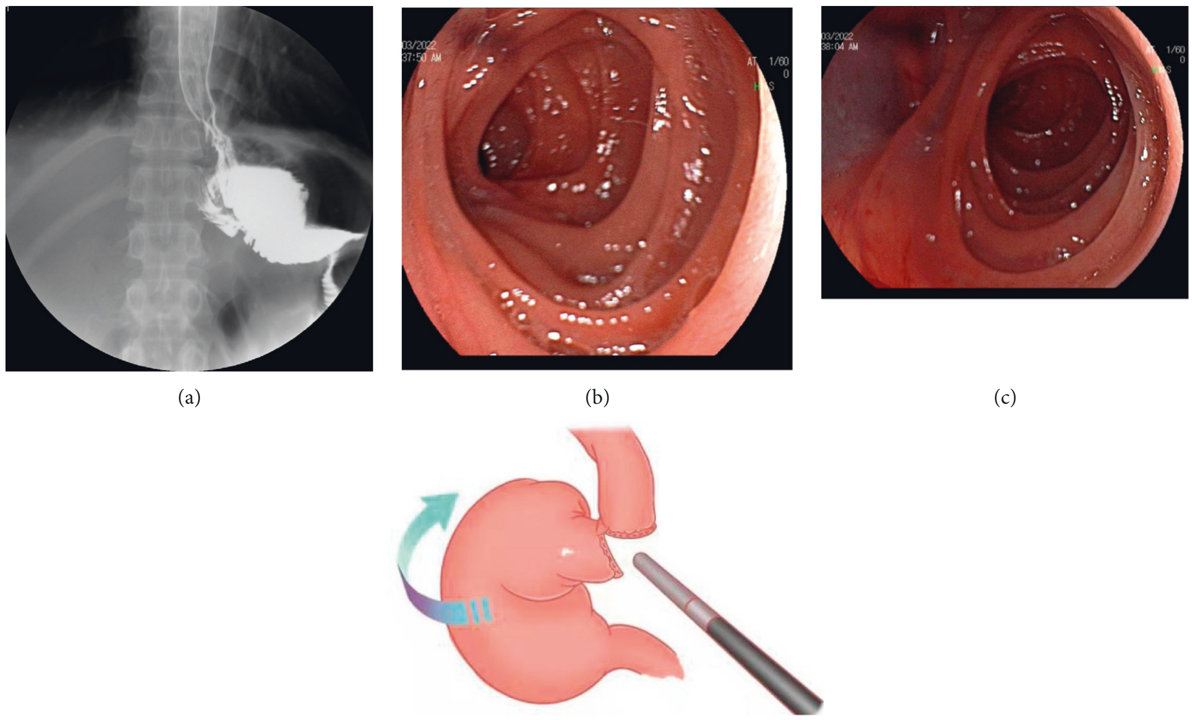


Figure 6: (a) Angiography on day five after surgery showing no anastomotic leakage. (b) Electronic gastroscopy 6 months after surgery showing no anastomotic stenosis. (c) Inside the dotted circle is the upper margin requiring a pathological examination.

conducive to revealing the true esophageal cavity, which may lead to entry into the submucous tract during anastomosis. However, too little dismemberment will lead to a huge common opening and increase the suture time. During operation, the chief surgeon is located on the left side of the patient, and the termination line of the linear stapler just falls on the right edge of the esophagus. (2) Before closing the common opening, the patient's head is lifted and the foot is lowered and tilted to the right. Through the adjustment of posture, the appropriate self-pulling force of the esophagus can be given, so as to provide a clear and stable suture vision for the surgeon. After different attempts on the position of the surgeon during suture, we believe that the suture with the chief surgeon on the right side of the patient and common openings is an ideal position. (3) To close the common opening by a continuous full-thickness suture from left to right with 3-0 barbed wire, the traditional control group was reinforced with the esophageal-jejunal seromuscular layer from right to left, while the team was reinforced with the diaphragmatic-jejunal seromuscular layer from right to left. This reinforcement method does not increase the risk of intraoperative complications and can reduce the risk of anastomotic leakage by reducing the tension of the anastomotic stoma.

The results of this study showed that without any increase in surgical steps, surgery-related complications, and economic burdens, the operation time was shortened to about 158 minutes on average, and the reconstruction time was shortened to 21 minutes on average. No serious complications occurred, which were attributed to the stable suture vision provided by this anastomosis method, thereby reducing the technical difficulty of the suture. The HTSP method has the following advantages: (1) HTSP can not only provide a stable and clear suture vision, but also provide better surgical field exposure and reduce the secondary tissue damage caused by a repeated grasp of the esophagus and jejunum during operation. (2) The downward-to-right traction of the esophagus by the HTSP method can be suitable for cases requiring higher level (gastroesophageal junction tumor) and improves the resection rate of R0. (3) The HTSP methods for laparoscopic suture technology requirements are relatively low, the learning curve is relatively short, and is more suitable for promotion. HTSP also has some shortcomings, that is, the specimens cannot be completely severed before anastomosis, so it is impossible to perform a rapid frozen pathological examination of the esophageal margin, and there is a potential risk of positive margin. For this reason, our team has also made different attempts to determine the upper incision margin. At present, for patients who need a rapid frozen pathological examination to determine the upper margin, our primary approach is to laparoscopically clip the partial proximal esophageal margin after half-transection and perform a rapid frozen pathological examination (Figure 6(d)). Of course, we will continue to explore a simpler and more effective method for determining the upper margin.

In summary, the HTSP method is a simple, safe, and feasible laparoscopic esophagojejunostomy technique, which can reduce the technical requirements for surgeons

Table 1: Comparison of general data of gastric cancer patients in the half-transected and self-pulling group (HTSP group) and the traditional anastomosis group (overlap or FETE group).

Groups	Number	Age (years, medain (range))	Male (number (%))	BMI (kg/ m^2,±s)	Tumor location (%)	
					Upper part	Middle part
HTSP	42	63.0 (17~80)	33 (78.5)	21.4 ± 2.3	19 (45.2)	23 (54.7)
Overlap or FETE	50	61.5 (38~83)	40 (80.0)	21.2 ± 2.2	21 (42.0)	29 (58.0)
Statistic value		$U = 930.0$	$X^2 = 0.168$	$t = 0.478$	$X^2 = 0.097$	
P value		0.349	0.866	0.643	0.755	

Groups	Tumor size (cm)	Clinical staging (number (%))			T staging (number (%))				
		I	II	IIIA-B	IIIA-B	T1	T2	T3	T4
HTSP	2.74 ± 1.6	8 (19.0)	12 (28.6)	19 (45.2)	3 (7.1)	4 (9.5)	6 (14.2)	5 (11.9)	27 (64.3)
Overlap or FETE	3.02 ± 1.8	9 (18.0)	14 (28.0)	22 (44.0)	5 (10.0)	7 (14.0)	4 (8.0)	2 (4.0)	37 (74.0)
P value	0.428		0.971				0.334		

Groups	N staging (number (%))				Pathological staging (number (%))			
	N0	N1	N2	N3	I	II	IIIA-B	IIIC
HTSP	18 (42.9)	6 (14.3)	9 (21.4)	9 (21.4)	10 (23.8)	8 (19.0)	16 (38.1)	8 (19.0)
Overlap or FETE	17 (34.0)	6 (12.0)	6 (12.0)	21 (42.0)	8 (16.0)	9(18.0)	13 (26.0)	20 (40.0)
P value		0.190					0.166	

Table 2: Comparison of intraoperative and postoperative conditions between half-transected and self-pulling group and the traditional anastomosis group.

Groups	Number	Operation	Anastomosis duration (min)	Blood loss	Time to first exhaust	Postoperative
HTSP overlap or FETE	42	166.7 ± 13.1	20.8 ± 2.0	72.1 ± 23.6	64.7 ± 18.7	7.4 ± 1.6
	50	181.9 ± 13.2	29.9 ± 1.7	73.5 ± 28.1	65.4 ± 17.9	7.5 ± 1.9
T value	5.520	24.02	0.257	0.191	0.148	0.148
P value	0.000	0.000	0.798	0.798	0.849	0.882

Table 3: Comparison of postoperative complications between half-transected and self-pulling group and traditional anastomosis group in patients with gastric cancer [number (%)]

Characteristic	HTSP ($n = 42$)	Overlap or FETE ($n = 50$)	P value
Postoperative complication (%)	4.7	4.0	0.858
Intra-peritoneal or digestive tract hemorrhage (n)	0	0	
Anastomotic leakage(n)	0	0	
Anastomotic stenosis (n)	0	0	
Pancreatic leakage(n)	0	1	
Lymphatic leakage (n)	1	0	
Intra-abdominal infection or abscess (n)	0	0	
Pulmonary infection (n)	1	1	
Reflux esophagitis (n)	0	0	

and has an important reference value for the extensive development of TLTG in the future. However, this study is only a single-center small-sample study, and comparative studies with multiple sample sizes, prospective randomized controlled trials, and long-term follow-up results are needed to further confirm the efficacy of this method.

Data Availability

The research data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Hongtao Wan and Jianyong Xiong contributed equally to this work.

Acknowledgments

This article was funded by the Natural Science Foundation of the Jiangxi Province (No. 20202BABL206093)

References

[1] N. Wada, Y. Kurokawa, S. Takiguchi et al., "Feasibility of laparoscopy-assisted total gastrectomy in patients with clinical stage I gastric cancer," *Gastric Cancer*, vol. 17, no. 1, pp. 137–140, 2014.

[2] H. Katai, M. Sasako, H. Fukuda et al., "Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703)," *Gastric Cancer*, vol. 13, no. 4, pp. 238–244, 2010.

[3] H. H. Kim, S. U. Han, M. C. Kim et al., "Long-term results of laparoscopic gastrectomy for gastric cancer: a large-scale case control and case-matched korean multicenter study," *Journal of Clinical Oncology*, vol. 32, no. 7, pp. 627–633, 2014.

[4] Y. Hu, C. Huang, Y. Sun et al., "Morbidity and mortality of laparoscopic versus open D2 distal gastrectomy for advanced gastric cancer: a randomized controlled trial," *Journal of Clinical Oncology*, vol. 34, no. 12, pp. 1350–1357, 2016.

[5] Y. Hu, M. Ying, C. Huang et al., "Oncologic outcomes of laparoscopy-assisted gastrectomy for advanced gastric cancer: a large-scale multicenter retrospective cohort study from China," *Surgical Endoscopy*, vol. 28, 2014.

[6] T. Shinohara, S. Satoh, S. Kanaya et al., "Laparoscopic versus open D2 gastrectomy for advanced gastric cancer: a retrospective cohort study," *Surgical Endoscopy*, vol. 27, no. 1, pp. 286–294, 2013.

[7] I. Uyama, K. Suda, and S. Satoh, "Laparoscopic surgery for advanced gastric cancer: current status and future perspectives," *Journal of Gastric Cancer*, vol. 13, no. 1, p. 19, 2013.

[8] J. H. Lee, S. Y. Son, C. M. Lee, S. H. Ahn, D. J. Park, and H. H. Kim, "Morbidity and mortality after laparoscopic gastrectomy for advanced gastric cancer: results of a phase II clinical trial," *Surgical Endoscopy*, vol. 27, no. 8, pp. 2877–2885, 2013.

[9] G. Liao, Z. Wang, W. Zhang et al., "Comparison of the short-term outcomes between totally laparoscopic total gastrectomy and laparoscopic-assisted total gastrectomy for gastric cancer: a meta-analysis," *Medicine (Baltimore)*, vol. 99, no. 7, Article ID e19225, 2020.

[10] S. Kanaya, Y. Kawamura, H. Kawada et al., "The delta-shaped anastomosis in laparoscopic distal gastrectomy: analysis of the initial 100 consecutive procedures of intracorporeal gastroduodenostomy," *Gastric Cancer*, vol. 14, no. 4, pp. 365–371, 2011.

[11] H. E. Jin, M. S. Kim, C. M. Lee et al., "Meta-analysis and systematic review on laparoscopic-assisted distal gastrectomy (LADG) and totally laparoscopic distal gastrectomy (TLDG) for gastric cancer: preliminary study for a multicenter prospective KLASS07 trial," *European Journal of Surgical Oncology*, vol. 45, no. 12, pp. 2231–2240, 2019.

[12] M. Nakauchi, K. Suda, S. Kadoya, K. Inaba, Y. Ishida, and I. Uyama, "Technical aspects and short- and long-term outcomes of totally laparoscopic total gastrectomy for advanced gastric cancer: a single-institution retrospective study," *Journal of the American College of Surgeons*, vol. 223, no. 4, p. e74, 2016.

[13] Y. Hiyoshi, E. Oki, K. Ando et al., "Outcome of esophagojejunostomy during totally laparoscopic total gastrectomy: a single-center retrospective study," *Anticancer Research*, vol. 34, no. 12, pp. 7227–7232, 2014.

[14] H. Okabe, K. Obama, E. Tanaka et al., "Intracorporeal esophagojejunal anastomosis after laparoscopic total gastrectomy for patients with gastric cancer," *Surgical Endoscopy*, vol. 23, no. 9, pp. 2167–2171, 2009.

[15] A. Umemura, K. Koeda, A. Sasaki et al., "Totally laparoscopic total gastrectomy for gastric cancer: literature review and comparison of the procedure of esophagojejunostomy," *Asian Journal of Surgery*, vol. 38, no. 2, pp. 102–112, 2015.

[16] O. Jeong and Y. K. Park, "Intracorporeal circular stapling esophagojejunostomy using the transorally inserted anvil (OrVil™) after laparoscopic total gastrectomy," *Surgical Endoscopy*, vol. 23, pp. 2624–2630, 2009.

[17] H.-I. Kim, I. Cho, D.-S. Jang, and W. J. Hyung, "Intracorporeal esophagojejunostomy using a circular stapler with a new purse-string suture technique during laparoscopic total gastrectomy," *Journal of the American College of Surgeons*, vol. 216, pp. e11–6, 2013.

[18] I. G. Kwon, Y.-G. Son, and S. W. Ryu, "Novel intracorporeal esophagojejunostomy using linear staplers during laparoscopic total gastrectomy: π-shaped esophagojejunostomy, 3-in-1 technique," *Journal of the American College of Surgeons*, vol. 223, pp. e25–9, 2016.

[19] W. Duan, K. Liu, X. Fu et al., "Semi-end-to-end esophagojejunostomy after laparoscopy-assisted total gastrectomy better reduces stricture and leakage than the conventional end-to-side procedure: a retrospective study," *Journal of Surgical Oncology*, vol. 116, pp. 177–183, 2017.

[20] J. Du, H. Xue, L. Zhao, J. Hua, J. Hu, and Z. Zhang, "Intracorporeal circular-stapled anastomosis after totally laparoscopic gastrectomy: a novel, simplest u-shaped parallel purse-string suture technique," *Journal of Surgical Oncology*, vol. 120, pp. 501–507, 2019.

[21] K. Inaba, S. Satoh, Y. Ishida et al., "Overlap method: novel intracorporeal esophagojejunostomy after laparoscopic total gastrectomy," *Journal of the American College of Surgeons*, vol. 211, no. 6, pp. 25–29, 2010.

[22] Y. Ebihara, S. Okushiba, Y. Kawarada, S. Kitashiro, and H. Katoh, "Outcome of functional end-to-end esophagojejunostomy in totally laparoscopic total gastrectomy," *Langenbeck's Archives of Surgery*, vol. 398, no. 3, pp. 475–479, 2013.

[23] H. Okabe, K. Obama, S. Tsunoda, E. Tanaka, and Y. Sakai, "Advantage of completely laparoscopic gastrectomy with linear stapled reconstruction: a long-term follow-up study," *Annals of Surgery*, vol. 259, no. 1, pp. 109–116, 2014.

[24] U. Bracale, E. Marzano, P. Nastro et al., "Side-to-side esophagojejunostomy during totally laparoscopic total gastrectomy for malignant disease: a multicenter study," *Surgical Endoscopy*, vol. 24, no. 10, pp. 2475–2479, 2010.

[25] E. Nagai, K. Ohuchida, K. Nakata et al., "Feasibility and safety of intracorporeal esophagojejunostomy after laparoscopic total gastrectomy: inverted T-shaped anastomosis using linear staplers," *Surgery*, vol. 153, no. 5, pp. 732–738, 2013.

[26] J. Hong, Y. P. Wang, J. Wang, Y. B. Bei, L. C. Hua, and H. K. Hao, "A novel method of self-pulling and latter transected reconstruction in totally laparoscopic total gastrectomy: feasibility and short-term safety," *Surgical Endoscopy*, vol. 31, no. 7, pp. 2968–2976, 2017.

Hindawi
Canadian Journal of Gastroenterology and Hepatology
Volume 2022, Article ID 8324242, 5 pages
https://doi.org/10.1155/2022/8324242

Review Article

How to Decide Approaches and Procedures for Early and Advanced Gastric Cancer?

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Received 8 February 2022; Revised 12 March 2022; Accepted 21 March 2022; Published 4 April 2022

Academic Editor: Shun Zhang

In the 6th edition of the Japanese Gastric Cancer Treatment Guidelines, laparoscopic surgery is recommended as one of the standard treatments for cStage I. On the other hand, the recommendation of robot-assisted surgery for gastric cancer was also added, albeit not conclusively, to perform it for cStage I gastric cancer. Conversely, laparoscopic surgery for cStage II/III is not recommended, and several randomized controlled trials (RCTs) are being conducted in East Asia to expand the indication for advanced gastric cancer. Although laparoscopic surgery and robot-assisted surgery are now recommended in the Guidelines for Early-Stage Gastric Cancer, each institution should set its own criteria for indications according to its level of proficiency and try to provide high-quality treatment. For advanced gastric cancer, although there is no solid evidence for laparoscopic or robot-assisted surgery, the reality is that it is already being performed in facilities with ample experience. New evidence is expected to be reported in the future, based on which the recommendations may change.

1. Introduction

In the 6th edition of the Japanese Gastric Cancer Treatment Guidelines, laparoscopic surgery is recommended as one of the standard treatments for cStage I. On the other hand, the recommendation of robot-assisted surgery for gastric cancer was also added, albeit not conclusively, to perform it for cStage I gastric cancer [1]. Conversely, laparoscopic surgery for cStage II/III is not recommended, and several randomized controlled trials (RCTs) are being conducted in East Asia to expand the indication for advanced gastric cancer.

In this paper, we discuss the choice of approach for early and advanced gastric cancers based on the results of previous and ongoing clinical trials.

2. Laparoscopic Gastrectomy

Laparoscopic surgery for gastric cancer was first reported in 1994 [2], and almost 30 years have already passed since then (Figure 1). The development of techniques and the development and advancement of devices have greatly improved the safety and quality of surgery. Several large-scale prospective clinical trials and studies using big data have already proven its safety and oncological validity.

In the 5th edition of the Japanese Guidelines for the Treatment of Gastric Cancer, it was stated that "laparoscopic gastrectomy may be an option for routine practice in cStage I patients who are eligible for distal gastrectomy." [3] However, in a subsequent preliminary guideline based on the results of a study by the Japan Clinical Oncology Group

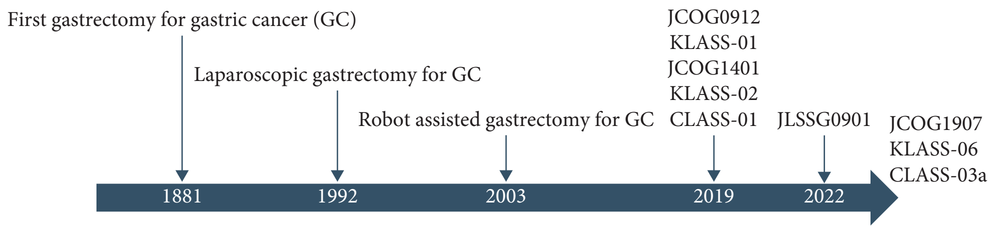


Figure 1: The historical timeline of gastrectomy.

(JCOG), "laparoscopic distal gastrectomy (LADG), laparoscopic total gastrectomy (LATG), and laparoscopic proximal gastrectomy (LAPG) are recommended as one of the standard treatments for patients with cStage I gastric cancer." However, the evidence for advanced gastric cancer is not sufficient, and the 6th edition of the same guideline states that "there is insufficient evidence to recommend LADG for gastric cancer of cStage II or higher [1].

2.1. cStage I. LADG was shown to be safe in JCOG0703, a phase II single-arm study with the primary endpoint of incidence of anastomotic leakage and pancreatic fistula [4]. In addition, JCOG0912 demonstrated noninferiority to open distal gastrectomy (ODG) in the primary endpoint of a 5-year recurrence-free survival (LADG 95.1% vs. ODG 94.0%) [5]. The same results were reported in an RCT (KLASS-01) conducted in Korea [6]. Based on these results, the 6th edition of the Japanese Gastric Cancer Treatment Guidelines states that "LADG is strongly recommended as one of the standard treatment options for cStage I gastric cancer." [1] On the other hand, JCOG0912 states that LADG surgeons or leading assistants should be surgeons certified by the Japan Society for Endoscopic Surgery or surgeons certified by the group as having equivalent skills with experience of at least 30 cases of LADG. The safety of the procedure has been proven, and each institution should set its own criteria for indication according to the level of proficiency.

LATG and LAPG were shown to be safe in JCOG1401, a nonrandomized, single-arm study with the primary endpoint of the incidence of suture failure of esophageal jejunal anastomosis (grade 2–4 esophageal jejunal anastomotic suture failure: 2.5%) [7]. As for long-term results, it was considered to be acceptable to extrapolate the results of JCOG0912, but since no clear data were presented, the guideline only stated a weak recommendation to do so. Also in this study, the primary surgeon or leading assistant was strictly defined by the same criteria as in the JCOG0912 study.

To compare and validate the safety of LADG with ODG, a study using big data from the National Clinical Database (NCD) has also been conducted. In both the retrospective and prospective studies, the incidence of postoperative complications and mortality were similar to ODG; however, grade B pancreatic fistulas or higher were significantly more common in LADG [8]. NCDs have been studied in LATG/LAPG as well as in LADG, but a predominantly higher incidence of suture failure has been reported in LATG, especially in retrospective studies.

In addition to its safety and oncological relevance, laparoscopic gastrectomy should be actively performed for cStage I patients if the educating system is in place and based on proficiency of the surgeons, considering its less invasive nature and better esthetic appearance compared with open surgery.

2.2. cStage II/III. RCTs on LADG for advanced cancer have been conducted in East Asian countries. In Japan, JLSSG0901 by the Japan Laparoscopic Gastrectomy Study Group (JLSSG) is underway to investigate the safety and long-term results (follow-up completed in August, 2021). As for short-term results, they were reported in 2018 and showed that laparoscopic gastrectomy is safe [9]. Results on long-term outcomes will be reported in 2022. KLASS-02 in Korea and CLASS-01 in China demonstrated the non-inferiority of LADG to ODG in terms of short-term results and 3-year recurrence-free survival [10, 11]. However, it has been emphasized that none of the trials proved the non-inferiority of LADG from a statistical point of view, including the method of analysis and stability of results. Subcategory analysis also showed a trend toward poorer results in the LADG group in patients with serous invasion. In addition, the operative time and blood loss differed significantly from the results of JLSSG0901, suggesting that the details of the procedure may have differed; therefore, the final conclusion should await the results of JLSSG0901 performed in Japan.

As for RCTs on LATG for advanced cancer, KLASS-06 is ongoing in Korea, and JCOG1809, a single-arm study to evaluate the safety of laparoscopic spleen-sparing splenectomy, is ongoing in Japan. There was no significant difference in recurrence-free survival or overall survival between laparoscopic surgery and laparotomy in reports including total gastrectomy. However, only small-scale RCTs have been conducted, and further evidence is needed.

A multicenter study using big data in Japan also showed that the long-term outcome of laparoscopic surgery was not different from that of open surgery, but in an observational study of total gastrectomy using NCD, LATG resulted in significantly more anastomotic leakage than open gastrectomy [12].

Presently, laparoscopic surgery is indicated for cStage II/III patients only at centers with a lot of experience, and it is not yet the standard of care in Japan. In addition, the indications for serous invasion and cases requiring total resection should be considered carefully.

2.3. Postchemotherapy. Several prospective and retrospective studies on gastric cancer after chemotherapy have been conducted in Japan and China, but the sample size was not sufficient in any of them. A prospective RCT of 95 patients with advanced gastric cancer in a single center in China was conducted with 3-year recurrence-free survival as the primary endpoint. The short-term results showed that laparoscopic surgery was associated with fewer complications and a higher completion rate of postoperative adjuvant chemotherapy compared to laparotomies [13]. The long-term results are anticipated. In China, they are conducting a multicenter prospective RCT of laparoscopic surgery versus laparotomy after chemotherapy (CLASS-03a) and are currently recruiting patients.

The results so far are insufficient as evidence, and since surgery after chemotherapy has a high risk of complications, it is necessary to carefully select the approach method according to the indications of each institution and the proficiency of surgeons.

3. Robot-Assisted Gastrectomy

Robot-assisted gastrectomy for gastric cancer was first reported in 2003 (Figure 1) [14]; since then, many institutions have introduced robot-assisted gastrectomy.

Although laparoscopic gastrectomy for gastric cancer has already been widely spread, pancreas-related complications such as pancreatic fistula and intra-abdominal abscess are not uncommon problems. While various efforts have been made to prevent pancreatic fistula in laparoscopic surgery through preoperative image evaluation [15] and surgical manipulation [16], robot-assisted surgery is expected to enable the use of forceps with a three-dimensional field of view and a high degree of freedom with an antishake function, making it possible to safely and accurately perform procedures that are difficult to perform with conventional laparoscopic surgery.

3.1. cStage I. In a single-center phase II trial for cStage I gastric cancer, the primary endpoint was the incidence of intra-abdominal infectious complications of Clavien–Dindo classification (CD) grade II or higher, with an expected value of 4%, a threshold of 12%, and a one-sided confidence interval of 5%. The complication rate was 3.3% (4 cases), indicating the safety of robot-assisted gastrectomy [17]. In a multicenter prospective clinical trial, 330 patients with cStage I/II gastric cancer were enrolled, and the results showed that postoperative complications of CD grade IIIa or higher were reduced to 2.45%, less than half that seen in conventional laparoscopic surgery [18]. Conversely, an RCT conducted in Korea reported that there was no difference between robot-assisted and laparoscopic surgeries, with the respective values being 1.3% and 1.4% [19]. In Japan, an RCT (JCOG1907) is currently enrolling patients to evaluate the safety and superiority of robot-assisted gastrectomy over laparoscopic gastrectomy in cT1-2N0-2 gastric cancer with the primary endpoint of CD grade II or higher intra-abdominal infectious complications. As for long-term results, such as recurrence rate and survival, they are presumed to be similar to those of laparoscopic surgery, but evidence is insufficient.

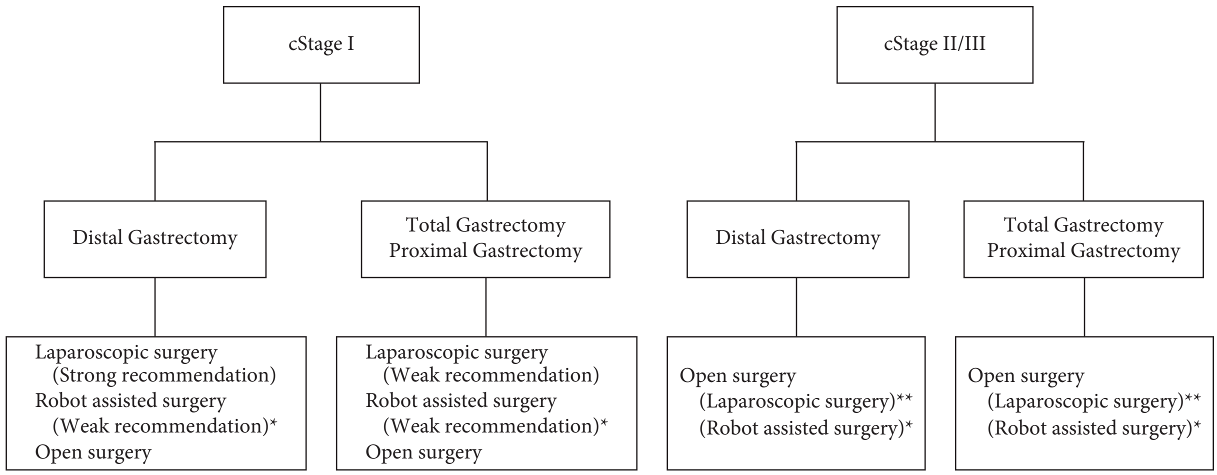
The 6th edition of the Japanese Guidelines for the Treatment of Gastric Cancer states that although robot-assisted gastrectomy is as safe as laparoscopic gastrectomy and has the potential to reduce complications, the long-term results are unknown. The report weakly recommends the use of robot-assisted gastrectomy for cStage I patients, provided that it is performed by a certified physician who is proficient in this procedure, or under the guidance of a certified proctor [1].

3.2. cStage II/III. The safety of robot-assisted gastrectomy in cStage II has been demonstrated in a prospective multicenter clinical trial as described earlier. With regard to cStage III, the results of a multicenter prospective RCT in patients with cStage I–III disease showed that there was no difference in the incidence of intra-abdominal infectious complications, which was the primary endpoint. However, the incidence of all complications above CD grade II was significantly lower in the robot-assisted surgery. We are awaiting the results of the JLSSG0901 study, which examined the safety and long-term results of laparoscopic gastrectomy in advanced gastric cancer, and the results of JCOG1907, a randomized controlled study on robot-assisted gastrectomy versus laparoscopic gastrectomy in cT1-2N0-2 gastric cancer.

Until the evidence is established, robot-assisted gastrectomy for advanced cancer should be performed as a clinical trial by surgeons skilled in gastrectomy after considering the indications at each institution and fully explaining to patients the uncertainties of long-term and short-term outcomes.

4. Esophagogastric Junction Cancer

In the case of esophagogastric junction cancer, there is no consensus on the choice of surgical technique or approach in the Guidelines for Gastric Cancer Treatment, and the choice is currently left to the discretion of the surgeon or institution. The Japanese Gastric Cancer Society and the Japanese Esophageal Association conducted a prospective study on cT2-4 esophagogastric junction cancer and investigated the frequency of lymph node metastasis [20]. Although long-term results are not yet available, based on the results, it is considered reasonable to perform surgery using the trans-right thoracic approach for patients with esophageal invasion of more than 4 cm, the trans-esophageal hiatus approach for patients with esophageal invasion of 2 cm or less, and the appropriate approach in each institution for patients with invasion values that are within this range. There is no solid evidence on the choice of laparotomy, laparoscopic surgery, or robot-assisted surgery, and we await the publication of evidence in the future.



* Recommendations may change according to JCOG1907

** Recommendations may change according to JLSSG0901

Figure 2: The selection of the current evidence-based surgical approach for gastrectomy for gastric cancer.

Table 1: Multicenter prospective trials for minimal-invasive gastric cancer surgery.

Trials	Main outcomes	Authors	Year
JCOG0703	Safety of LADG.	Kurokawa et al.	2008
JCOG0912	Noninferiority of LADG to ODG regarding survival outcomes for early gastric cancer.	Katai et al.	2019
KLASS-01	Noninferiority of LADG to ODG regarding survival outcomes for early gastric cancer.	Kim et al.	2019
JCOG1401	Safety of LATG and LAPG.	Katai et al.	2019
KLASS-02	Noninferiority of LADG to ODG regarding safety and survival outcomes for advanced gastric cancer.	Lee and hyung et al.	2019 and 2020
CLASS-01	Noninferiority of LADG to ODG regarding safety and survival outcomes for advanced gastric cancer.	Yu and huang et al.	2019 and 2022
JLSSG0901	Noninferiority of LADG to ODG regarding safety and survival outcomes for advanced gastric cancer.	Ongoing	
KLASS-06	Noninferiority of LATG to OTG regarding safety and survival outcomes for advanced gastric cancer		
JCOG1907	Superiority of RAG to LAG regarding safety and survival outcomes for T1-2N0-2 gastric cancer.	Ongoing	
CLASS-03a	Safety of LAG after neoadjuvant chemotherapy.	Ongoing	

LADG, laparoscopic distal gastrectomy. ODG, open distal gastrectomy. LATG, laparoscopic total gastrectomy. LAPG, laparoscopic proximal gastrectomy. OTG, open total gastrectomy. RAG, robot-assisted gastrectomy. LAG, laparoscopic gastrectomy.

5. Conclusion

The selection of the current evidence-based surgical approach for gastrectomy for gastric cancer was described (Figure 2). Significant advancement of medical technologies and robust clinical trials lead to dramatic change in choosing approach for gastrectomy in the last decade (Table 1). Although laparoscopic surgery and robot-assisted surgery are now recommended in the Guidelines for the Treatment of Gastric Cancer for early-stage gastric cancer, each institution should set its own criteria for indications according to its level of proficiency and try to provide high-quality treatment. As considering the criteria of operator, an objective and evidence-based criteria should be needed. For advanced gastric cancer, although there is no solid evidence for laparoscopic or robot-assisted surgery, the reality is that it is already being performed in facilities with ample experience. New evidence is expected to be reported in the future, based on which the recommendations may change.

Data Availability

The data supporting this REVIEW are from previously reported studies and datasets, which have been cited.

Conflicts of Interest

The authors declare no conflicts of interest for this article.

Authors' Contributions

DI and SN conceptualized and designed the manuscript.

Acknowledgments

The authors would like to thank Editage (https://www.editage.com) for English language editing.

References

[1] A. Japanese Gastric Cancer, *Japanese Gastric Cancer Treatment Guidelines*, Springer, Berlin, Germany, 6th edition, 2021.

[2] S. Kitano, Y. Iso, M. Moriyama, and K Sugimachi, "Laparoscopy-assisted billroth I gastrectomy," *Surgical Laparoscopy & Endoscopy*, vol. 4, no. 2, pp. 146–148, 1994.

[3] A. Japanese Gastric Cancer, "Japanese gastric cancer treatment guidelines 2018 (5th edition)," *Gastric Cancer*, vol. 24, no. 1, pp. 1–21, 2021.

[4] N. Hiki, H. Katai, H. Katai et al., "Long-term outcomes of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG0703)," *Gastric Cancer*, vol. 21, no. 1, pp. 155–161, 2018.

[5] H. Katai, J. Mizusawa, H. Katayama et al., "Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial," *The Lancet Gastroenterology & Hepatology*, vol. 5, no. 2, pp. 142–151, 2020.

[6] H.-H. Kim, S.-U. Han, M.-C. Kim et al., "Effect of laparoscopic distal gastrectomy vs. open distal gastrectomy on long-term survival among patients with stage I gastric cancer," *JAMA Oncology*, vol. 5, no. 4, pp. 506–513, 2019.

[7] H. Katai, J. Mizusawa, J. Mizusawa et al., "Single-arm confirmatory trial of laparoscopy-assisted total or proximal gastrectomy with nodal dissection for clinical stage I gastric cancer: Japan Clinical Oncology Group study JCOG1401," *Gastric Cancer*, vol. 22, no. 5, pp. 999–1008, 2019.

[8] M. Honda, N. Hiki, T. Kinoshita et al., "Long-term outcomes of laparoscopic versus open surgery for clinical stage I gastric cancer," *Annals of Surgery*, vol. 264, no. 2, pp. 214–222, 2016.

[9] N. Inaki, T. Etoh, T. Ohyama et al., "A multi-institutional, prospective, phase II feasibility study of laparoscopy-assisted distal gastrectomy with D2 lymph node dissection for locally advanced gastric cancer (JLSSG0901)," *World Journal of Surgery*, vol. 39, no. 11, pp. 2734–2741, 2015.

[10] W. J. Hyung, H.-K. Yang, Y.-K. Park et al., "Long-term outcomes of laparoscopic distal gastrectomy for locally advanced gastric cancer: the KLASS-02-RCT randomized clinical trial," *Journal of Clinical Oncology*, vol. 38, no. 28, pp. 3304–3313, 2020.

[11] J. Yu, C. Huang, Y. Sun et al., "Effect of laparoscopic vs. open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer," *JAMA*, vol. 321, no. 20, pp. 1983–1992, 2019.

[12] T. Kinoshita, I. Uyama, M. Terashima et al., "Long-term outcomes of laparoscopic versus open surgery for clinical stage II/III gastric cancer," *Annals of Surgery*, vol. 269, no. 5, pp. 887–894, 2019.

[13] Z. Li, F. Shan, X. Ying et al., "Assessment of laparoscopic distal gastrectomy after neoadjuvant chemotherapy for locally advanced gastric cancer," *JAMA Surgery*, vol. 154, no. 12, pp. 1093–1101, 2019.

[14] M. Hashizume and K. Sugimachi, "Robot-assisted gastric surgery," *Surgical Clinics of North America*, vol. 83, no. 6, pp. 1429–1444, 2003.

[15] K. Kumagai, N. Hiki, S. Nunobe et al., "Impact of anatomical position of the pancreas on postoperative complications and drain amylase concentrations after laparoscopic distal gastrectomy for gastric cancer," *Surgical Endoscopy*, vol. 32, no. 9, pp. 3846–3854, 2018.

[16] M. Tsujiura, N. Hiki, M. Ohashi et al., ""Pancreas-Compressionless gastrectomy": a novel laparoscopic approach for suprapancreatic lymph node dissection," *Annals of Surgical Oncology*, vol. 24, no. 11, pp. 3331–3337, 2017.

[17] M. Tokunaga, R. Makuuchi, Y. Miki et al., "Late phase II study of robot-assisted gastrectomy with nodal dissection for clinical stage I gastric cancer," *Surgical Endoscopy*, vol. 30, no. 8, pp. 3362–3367, 2016.

[18] I. Uyama, K. Suda, M. Nakauchi et al., "Clinical advantages of robotic gastrectomy for clinical stage I/II gastric cancer: a multi-institutional prospective single-arm study," *Gastric Cancer*, vol. 22, no. 2, pp. 377–385, 2019.

[19] H.-I. Kim, S.-U. Han, H.-K. Yang et al., "Multicenter prospective comparative study of robotic versus laparoscopic gastrectomy for gastric adenocarcinoma," *Annals of Surgery*, vol. 263, no. 1, pp. 103–109, 2016.

[20] Y. Kurokawa, H. Takeuchi, Y. Doki et al., "Mapping of lymph node metastasis from esophagogastric junction tumors," *Annals of Surgery*, vol. 274, no. 1, pp. 120–127, 2021.