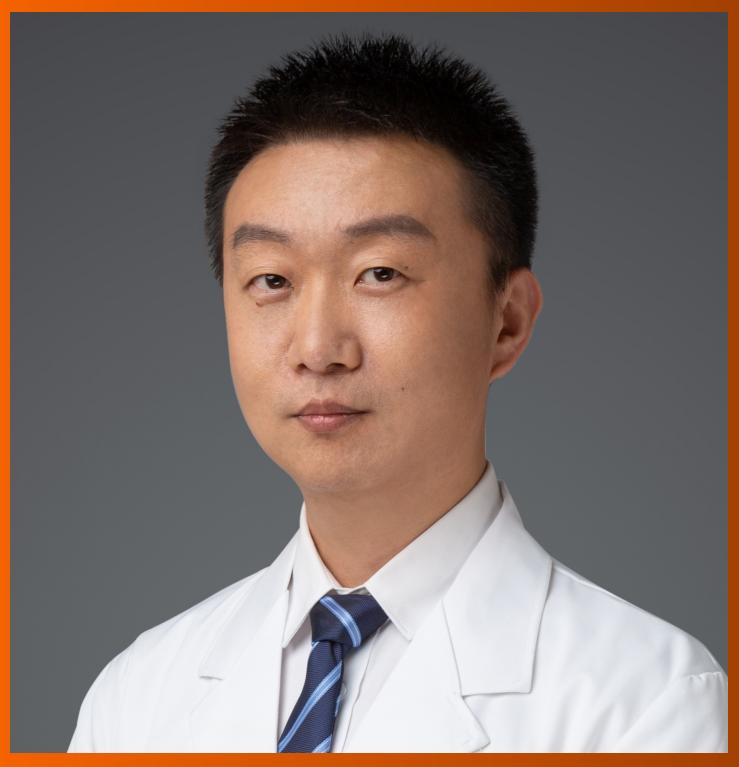
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Editorial Board Member of World Journal of Clinical Cases, Hong-Tao Xu, MD, PhD, Chief Physician, Professor, Department of Pathology, The First Affiliated Hospital and College of Basic Medical Sciences of China Medical University, Shenyang 110001, Liaoning Province, China. xuht@cmu.edu.cn

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CASE REPORT

Neoadjuvant chemoradiotherapy followed by laparoscopic distal gastrectomy in advanced gastric cancer: A case report and review of literature

Zi-Ning Liu, Yin-Kui Wang, Zi-Yu Li

ORCID number: Zi-Ning Liu 0000-0002-4355-6899; Yin-Kui Wang 0000-0002-5607-5138; Zi-Yu Li 0000-0001-5580-4979.

Author contributions: Li ZY, Wang YK, and Liu ZN determined the preoperative regimen and performed the operation; the postoperative follow-up was done by Wang YK; Liu ZN and Wang YK collected patient data, performed image processing, and composed the manuscript; and Liu ZN revised and provided recommendations for the manuscript; All authors read and approved the final manuscript. Liu ZN and Wang YK contributed equally to this work.

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Zi-Ning Liu, Yin-Kui Wang, Zi-Yu Li, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Gastrointestinal Cancer Center, Peking University Cancer Hospital & Institute, Beijing 100142, China

Corresponding author: Zi-Yu Li, MD, Professor, Department of Gastrointestinal Surgery, Peking University Cancer Hospital and Institute, No. 52 Fucheng Road, Haidian District, Beijing 100142, China. ziyu li@hsc.pku.edu.cn

Abstract

BACKGROUND

The laparoscopic technique has been widely applied for early gastric cancer, with the advantages of minimal invasion and quick recovery. However, there is no report about the safety and oncological outcome of laparoscopic gastrectomy with D2 lymph node dissection for patients after neoadjuvant chemoradiotherapy.

CASE SUMMARY

A 60-year-old man was diagnosed with advanced distal gastric cancer, cT4aN1M0 stage III. The neoadjuvant chemoradiotherapy was performed based on the regimen of gross tumor volume 50G y/25 f and clinical target volume 45 Gy/25 f, as well as concurrent S-1 60 mg Bid. Then laparoscopic distal gastrectomy with D2 lymph node dissection was undertaken successfully for him after achieving partial response evaluated by radiological examination. The patient recovered smoothly without moderate or severe postoperative complications. The postoperative pathological stage was ypT3N0M0 with American Joint Committee on Cancer tumor regression grade 1. He was still in good condition after 5 years of follow-up.

CONCLUSION

Neoadjuvant chemoradiotherapy followed by laparoscopic technique could be applicable and may achieve satisfactory oncological outcomes. Our finding requires further validation by cohort studies.

Key Words: Gastric cancer; Neoadjuvant chemoradiotherapy; Laparoscopic; Distal gastrectomy; S-1; Case report

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Core Tip: The radicalness for locally advanced gastric cancer depends on the completed R0 resection. Although perioperative treatment strategies have been widely used for patients to reinforce the treatment effect, the use of neoadjuvant chemoradiation is controversial, let alone whether the patients can benefit from minimally invasive surgery. We presented the first case treated by laparoscopic distal gastrectomy following neoadjuvant chemoradiation. The perioperative safety and short-term and long-term oncological outcomes in this patient are described in detail.

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INTRODUCTION

Since the first case of laparoscopic distal gastrectomy was reported by Kitano in 1994[1], the laparoscopic technique has been widely applied in early gastric cancer, with the advantages of minimal invasion and quick recovery [2-4]. Laparoscopic gastric surgery is the preferred option for early gastric cancer. The promising outcome from such surgery has promoted the application of laparoscopy in advanced gastric cancer. Although it is not known whether laparoscopic gastrectomy was suitable for locally advanced gastric cancer, the safety and feasibility of laparoscopic gastrectomy have been explored in several clinical trials[5-9]. Inspiring results have been achieved by these studies, proving that laparoscopic gastrectomy for locally advanced gastric cancer is not inferior to that of open surgery.

Although surgery is the only curative option for gastric cancer, the mortality of patients after radical surgery remains high because of a significant number of local regional or systemic recurrences[10]. Chemoradiotherapy has been recommended as a supplement to radical surgery by the National Comprehensive Cancer Network[11]. Postoperative therapy administration is restricted in some patients due to surgical complications because the recovery time may exceed the prescribed time period for treatment[12]. However, perioperative treatment modality can avoid the shortcomings. Neoadjuvant chemoradiotherapy (NACRT) has the advantages of avoiding unnecessary surgery by shrinking the tumor size and facilitating a high rate of R0 resection, with acceptable rates of acute and late toxicities[13-15].

To the best of our knowledge, this is the first report to date regarding the safety and short-term oncological outcome of NACRT followed by laparoscopic D2 gastrectomy.

CASE PRESENTATION

Chief complaints

A 60-year-old man presented with abdominal distension and weight loss of over 10 kg for approximately 6-mo duration.

History of present illness

He was an otherwise healthy man with no remarkable medical history.

History of past illness

There was no obvious abnormality in any past illness.

Personal and family history

There was no special history and personal history. The patient had no known family history of cancer.

Physical examination

Physical examinations revealed a thin, emaciated male with normal vital signs. The



abdomen was tender, and there was no palpable mass. Superficial lymphadenopathy was not detected.

Laboratory examinations

Routine blood test revealed small cell hypochromic anemia: The hemoglobin was 85 g/L; the mean corpuscular volume was 65 fL; the mean corpuscular hemoglobin was 18.60 pg; the mean corpuscular hemoglobin concentration was 286 g/L. His white blood cell (6.24 × 10⁹/L) and platelet (333 × 10⁹/L) were within the normal range. Neutrophil-to-lymphocyte ratio was 2.25. The blood biochemistry was normal except for albumin, which was 30.0g/L. All tumor markers in gastrointestinal cancer were within the normal range: Carcinoma embryonic antigen was 3.44 ng/mL, cancer antigen 19-9 was 12.69 U/mL, cancer antigen 72-4 was 3.78 U/mL, and cancer antigen 242 was 10.76 U/mL.

Imaging examinations

An endoscopy was undertaken and revealed an ulcerative lesion adjacent to the gastric antrum, with a dike-like bulge around the edge. Pylorus was invaded by the lesion, resulting in an incomplete obstruction (Figure 1). Enhanced abdominal computed tomography (CT) indicated that the wall of the antrum was thickened with significant enhancement, with a maximum thickness of 21 mm. The surface of the serosa was fuzzy; however, the border near the pancreas remained clear (Figure 2). Multiple enlarged lymph nodes were found in the lesser gastric curvature; the diameter of the largest one was 7mm. No distant metastasis was detected from the pelvis or chest CT.

HISTOPATHOLOGICAL EXAMINATIONS

The pathology obtained from the endoscopic biopsy confirmed a moderate to poor differentiated adenocarcinoma, with a Lauren type of intestine.

FINAL DIAGNOSIS

The patient was diagnosed as having a gastric antrum carcinoma, Borrmann type III, with lymph nodes metastases. The clinical stage was confirmed as being cT4aN1M0 stage III.

TREATMENT

NACRT and evaluation

The patient and his family had a very strong desire for radicalness of surgery. However, because of the wide infiltration of the primary foci with suspicion of lymph nodes metastasis, which were majorly localized on the lesser curvature, a direct surgery may not be capable of radical cure. A tumor downstaging by chemoradiation was strongly recommended for the preparation of surgical radicalness. Moreover, the patient was 60-years-old. Despite his stable physical status before cancer diagnosis, with 172 cm height and 45 kg weight, his body mass index was only 15.2 kg/m² with nutritional deficiency anemia at the moment. Even if the patient received a completed D2 lymphadenectomy with R0 resection, his nutritional status required a long period of recovery. The chance that he could benefit from, or be able to receive, the adjuvant treatment was bleak, as adjuvant chemotherapy is often assumed to have little benefit for delayed initiation. With the concerns above, a preoperative concurrent radiochemo therapy was designed by the multidisciplinary team.

The NACRT was given at a total dose of gross tumor volume 50 Gy and clinical target volume 45 Gy, in 25 fractions, five times a week, with concurrent S-1 60 mg twice daily. The NACRT was well tolerated with no severe adverse events according to the Common Terminology Criteria for Adverse Events v5.0[16]. The most serious problems among the mild-to-moderate adverse events was the grade 2 white blood cell decrease (white blood cells count $2.92 \times 10^{\circ}/L$) 3 wk after radiotherapy (RT) completion. The white blood cell count went back to normal $(8.69 \times 10^9/L)$ after oral leucocyte increasing drugs treatment (Diyu Shengbai tablets) for 3 wk. For the incomplete obstruction, enteral nutrition was recommended for the patient. The

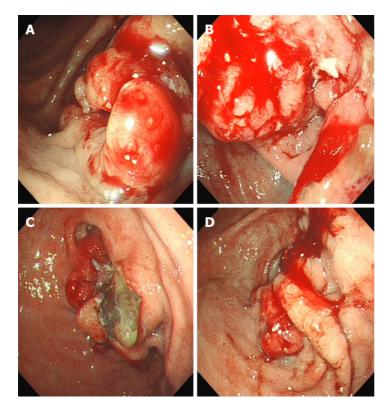


Figure 1 Gastrointestinal fiberscope before chemoradiotherapy showed an ulcerative lesion located surrounding the gastric antrum with ulceration causing stenosis. A-D: Tumor surface identified from different angles and distances.

nutrition status of the patient gradually improved during the NACRT and waiting period. With a 15 kg increase in weight, his albumin rose to 41.4 g/L, and the hemoglobin returned to 101 g/L. His neutrophil-to-lymphocyte ratio, on the other hand, dropped to 1.87 before surgery.

An enhanced abdominal CT was performed to evaluate the response of NACRT at the time of completion and 6 wk after NACRT (Figure 3). The tumor thickness showed sustained shrinkage from 21-12 mm to 12-10 mm during the NACRT period. With shrinkage rate by 52%, a partial response was considered by the multidisciplinary team[17]. Endoscopic ultrasound was performed using a radial scanning ultrasound endoscope to evaluate the response of NACRT at the same time (Figure 4), which indicated an ulcerative lesion adjacent to the gastric antrum with pyloric stenosis. The lesion was reflected as a hypoechoic signal under the endoscopic ultrasound, invading the entire layer, partly to the serosa with the maximum thickness 1.09 cm. A hypoechoic nodule beside the antrum, measuring approximately 2.05 cm × 1.3 cm in size, was also detected. Therefore, an uT4aN1M0 tumor after NACRT was considered and restaged.

Surgery and postoperative recovery

Open distal gastrectomy with D2 lymph node dissection was planned for the patient. However, the patient was very eager to receive only minimally invasive surgery, and thus refused open surgery. The patient received laparoscopy-assisted distal gastrectomy with D2 lymph node dissection and Billroth II anastomosis successfully 4 wk after the last evaluation. The entire surgical procedure was recorded on video. The operation lasted for 240 min. The blood loss was 100 mL. The first flatus time was 3 d after the operation. Upper gastrointestinal radiography was performed 7 d after the operation, indicating that gastric peristalsis was good with no anastomosis leakage. The patient was allowed to intake a liquid diet and was then discharged on day 12 without grade II or more Clavien-Dindo complications[18].

OUTCOME AND FOLLOW-UP

Postoperative pathological evaluation was completed 7 d after surgery. Small groups of cancer cells were detected outside of the muscularis propria, accompanied by the



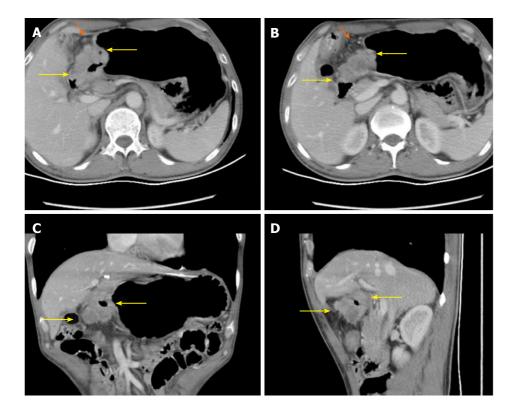


Figure 2 Enhanced abdominal computerized tomography indicated that the wall of the antrum was thickened with significant enhancement. The surface of serosa was fuzzy, but the border near the pancreas was still clear (yellow arrowheads). Multiple enlarged lymph nodes were found in the lesser gastric curvature (orange arrowheads). A-B: Transverse views of the primary lesion in different layers; C: Coronal view of the primary lesion; D: Sagittal view of the primary lesion.

formation of extracellular mucus pools, which were surrounded by fibrosis and chronic inflammatory cells (Figure 5). The necrosis rate was > 90% (residual tumor/tumor bed < 10%). Thus, the patient was evaluated as tumor regression grade 1 based on American Joint Committee on Cancer/College of Pathology criteria and as tumor regression grade 2 for Japanese Gastric Cancer Association system, both belonging to a subtotal regression. No vascular embolus or perineuronal invasion was detected. No metastases were found in lymph nodes (0/31). Fibrosis was detected in some lymph nodes, which was considered as change post NACRT. No cancer cell was detected in the gastric stump or duodenal stump. Therefore, the pathological stage was ypT3N0M0.

One month after the operation, the patient returned to the clinic for a follow-up. The enhanced abdominal CT and all the laboratory tests showed that the patient was generally in good condition. Adjuvant chemotherapy was conducted with three cycles of S-1 plus oxaliplatin. Five years after the surgery, the patient was still in good condition, with no recurrence or metastasis.

DISCUSSION

The results of ARTIST and ARTIST-2 have put chemoradiotherapy (CRT) into an uncertain situation in patients undergoing D2 lymphadenectomy [19,20]. In ARTIST, although the postoperative chemotherapy plus CRT revealed a superior benefit in disease-free survival (DFS) compared to chemotherapy alone in patients with positive lymph node metastasis, the survival benefit was not retained in all patients[20]. In the subsequent ARTIST-II trial interim result, no difference in DFS between S-1 and oxaliplatin (SOX) and SOX plus CRT was found (P = 0.667)[19]. However, as gastric adenocarcinoma is theoretically radio-sensitive, the futility of CRT may be credited to more ways than one: Does the minimal peritoneal metastasis already exist before treatment; is the delineation of gastric lymph node stations under the same treating protocol? On the other hand, rather than being a role of supplementary or salvage after surgery, NACRT brings more than what postoperative RT/CRT can offer. Not only do patients have better performance status and are often more tolerant to

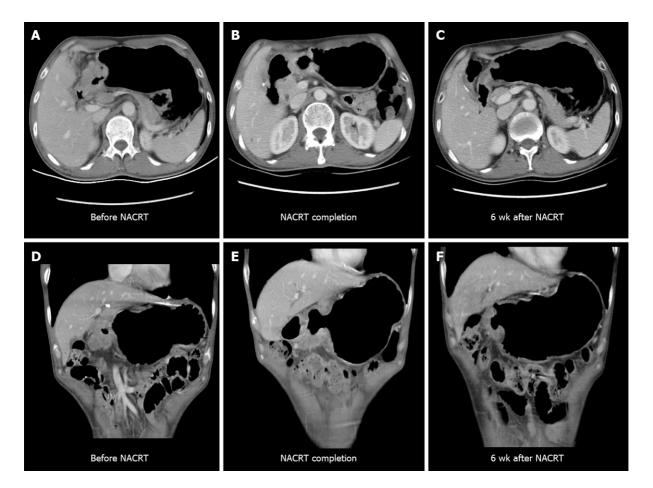


Figure 3 Enhanced abdominal computerized tomography performed before, immediately after, and 6 wk after neoadjuvant chemoradiotherapy to evaluate the response to neoadjuvant chemoradiotherapy. Imaging after neoadjuvant chemoradiotherapy (NACRT) imaging revealed maximum thickness change from 21 mm to 12 mm (shrinking 42.9%) with lymph nodes (diameter 7 mm) in the great curvature shrinking so obviously that they could not be clearly detected in the computed tomography, but the surface of serosa was still fuzzy. The computed tomography 6 wk after neoadjuvant chemotherapy indicated a change from 12 mm to 10 mm (shrinking 16.7%) with no obviously enlarged lymph nodes around the stomach, retroperitoneal area, or pelvis. A-C: Transverse views of the lesion's change from pre-NACRT to post-NACRT; D-E: Coronal views of the lesion's change from pre-NACRT to post-NACRT.

radiation predated to surgery, but it could minimize the primary site, enhance the R0 resection rate (especially for those with borderline resectable tumor), reduce the extent of surgery (conserving stomach), benefit form minimal invasion, etc.

The depiction of NACRT is restricted by the scant number of clinical trials with high levels of evidence. As we reviewed the phase II/III studies of NACRT (not for esophagogastric junction or esophagus) on gastric cancer following curative gastrectomy from the past 20 years through a search of the PubMed, MEDLINE and EMBASE (language was limited to English, Table 1 and 2)[21-34], to date only Skoropad et al[32] reported a complete phase III trial result with no significant findings in 10-year overall survival (NACRT + Surgery vs Surgery, 32% vs 18%). However, neither the dose nor the technique in target delineation met the current standard. Patients in their study received RT rather than CRT modalities that are commonly accepted today. While the rest of the phase III trials are worth watching (Table 2), many phase II trials can shed light on the patterns of NACRT. The higher rate of pCR (mean pCR rate 16.4% in initially resected cases) can be found in most of them (Table 1), when compared with neoadjuvant chemotherapy, usually no more than 10% [35].

It is now been recognized that mature laparoscopic technique did not greatly influence patients survival as well as postoperative complications [36,37]. Also, the number of retrieved lymph nodes in the laparoscopic procedure was not inferior to open surgery. Zhao et al[38] reported a retrospective study of 659 patients who were treated by laparoscopic or open gastrectomy and found that the average number of lymph node dissections in the laparoscopic gastrectomy and open gastrectomy group were 33.2 and 32.8, respectively, with no significant difference. The average time for the laparoscopic gastrectomy and open gastrectomy procedures did not differ significantly ($211 \pm 56 \min vs \ 204 \pm 41 \min$); however, bleeding during the operation in



Table 1 Phase II published studies of neoadjuvant/preoperative radiation/chemoradiation following curative gastrectomy in gastric cancer (with or without esophagogastric junction)

Author	Year of published	N (RT + Surgery /RT)	Eligibility	Preoperative treatment arms	Surgery	Response rate	Survival	Adverse outcomes
Roth <i>et al</i> [<mark>21</mark>]	2003	18/18	Stomach, LAGC	CF × 2 + RT (3 titers)	D2	6% pCR, 50% ORR	2-yr OS 71%, 3- yr OS 59%	No TRM; no postoperative death; 17% minimal peritoneal carcinomatosis; 44% grade 3-4 AE
Skoropad <i>et</i> al[22]	2003	67/91	Stomach (43% distal), cM0	45 Gy/25 fractions + metronidazole	D1	NA	5-yr OS 46%, 10- yr OS 36%, MST 46 mo	No TRM; 26% metastasis/inoperable; 6% postoperative death; 4% grade 4 AE
Ajani et al[23]	2004	29/33	Stomach/EGJ (24% distal), cT2-3NxM0 or cT1N1M0	45 Gy/25 fractions + 5- Fu	D2	30% pCR, 55% ORR	2-yr OS 54%, MST 34 mo	3% TRM; 3% postoperative death; 12% metastasis/inoperable; no grade 4 AE
Ajani <i>et al</i> [24]	2006	36/43	Stomach/EGJ (23% antrum), cT2-3NxM0 or cT1N1M0	$CF \times 2 \rightarrow 45Gy/25$ fractions + 5-Fu	D2 recommended	26% pCR.	1-yr OS 72%, MST 23 mo	No TRM; no postoperative death; 17% progression; 5% grade 3 AE; 58% site failure
Wydmanski et al[25]	2007	32/40	Stomach, LAGC (31% middle/distal)	45 Gy/25 fractions + 5- Fu	D2 recommended	18% pCR, 38% ORR	1-yr OS 75%, 2- yr OS 63%, MST not reach	5% TRM; no postoperative death; 12.5% metastasis/inoperable; no grade 4 AE
Rivera <i>et al</i> [26]	2011	8/13	Stomach/EGJ (41% distal), initially unresectable cM0	$IC \times 2 \rightarrow 45 \text{ Gy}/25$ fractions + IC	D1 and beyond	No pCR, 8% PR	2-yr OS 27%, MST 10.5 mo (in 17 patients)	15% TRM, 12.5% postoperative death; 23% metastasis/inoperable; 46% grade 3-4 neutropenia
Pera <i>et al</i> [27]	2012	31/41	Stomach/EGJ/Esophagus (29% stomach), locally advanced (M0)	Oxaliplatin/cisplatin/5- FU + 45 Gy/25 fractions		22% pCR, 44% ORR	2-yr OS 58%, MST 28 mo	2% TRM; 13% postoperative death; 24% progression/inoperable; 14% grade 3-4 neutropenia
Michel <i>et al</i> [28]	2014	31/42	Stomach/EGJ (45% lower), cT > 2 or cN > 1 (M0)	FOLFIRI × $4 \rightarrow 50$ Gy/25 fractions + 5-Fu	D2 recommended	7% pCR	2-yr OS 27%, MST 26 mo	No TRM; 17% postoperative death; 6% metastasis; 41% grade 3- 4 AE
Trip et al[<mark>29</mark>]	2014	24/25	Stomach, cTNM IB-IV (M0)	45 Gy/25 fractions + TC	D1+, D2	16% pCR, 77% ORR	MST 15 mo	No TRM; 4% postoperative death; 4% progression; no grade 4 AE
Liu <i>et al</i> [<mark>30</mark>]	2018	33/36	Stomach/EGJ, cTNM III (53% lower)	SOX × 1 \rightarrow 45 Gy/25 fractions + S-1 \rightarrow SOX×1	D2 recommended	8% pCR, ORR 42%	1-yr OS 92%, 2- yr OS 56%, MST 30 mo	No TRM, no postoperative death; 3% metastasis; no grade 4 AE
Kim et al[<mark>31</mark>]	2019	31/39	Stomach/EGJ (33% antrum), high-risk	TPS × 2 \rightarrow 45 Gy/25 fractions + CS	D2	10% pCR, 33% ORR	3-yr OS 76%, MST not reach	No TRM; no postoperative death; 15% metastasis/inoperable; no grade 4 AE during CRT

AE: Adverse events; CF: Cisplatin/5-Fu; CRT: Chemoradiotherapy; CS: Cisplatin/S-1; DCF: Docetaxel/Cisplatin/5-Fu; EGJ: Esophagogastric junction; FOLFIRI: Fluorouracil/Leucovorin/Irinotecan; Gy: Grey; IC: Irinotecan/Cisplatin; LAGC: Locally advanced gastric cancer; MST: Median survival time; NA:

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Not available; ORR: Objective response rate; OS: Overall survival; pCR, Pathological complete response; PR: Partial response; RT: Radiotherapy; SOX: S-1/Oxaliplatin; TC: Paclitaxel/Carboplatin; TPS: Docetaxel/Cisplatin/S-1; TRM: Treatment-related mortality.

> the laparoscopic group was significantly less than that in the open group $(128 \pm 85 \text{ mL})$ vs 301 ± 156 mL, P < 0.001). Similar results were confirmed by Pugliese et al[39] and Hwang et al[40]. Additionally, although with limited cases, several studies revealed laparoscopic and open gastrectomy had comparable long-term and short-term outcomes[41-43].

> Our previous experience has proved neoadjuvant chemotherapy does not increase the complications of radical gastrectomy [44]. In this case, the number of lymph node dissection was 31 and the blood loss was 100 mL without complications, which may indicate that the laparoscopic technique is applicable to patients with advanced gastric cancer after NACRT. However, in this case, the severe fibrosis around the stomach make the surgery more difficult and delicate, resulting in a relatively longer operation time (240 min) in the patient treated by NACRT compared to those who were not. Yet with the amplification effect of laparoscopy, laparoscopic gastrectomy was safe and feasible for advanced gastric patients who were treated by an experienced department.

> Although the patient in our department recovered smoothly with no postoperative complications, it remains debatable whether NACRT followed by laparoscopic gastrectomy increases postoperative complications. The most frequent complications for gastric cancer patients after NACRT have been reported as nonspecific surgical complications^[45].

CONCLUSION

NACRT followed by laparoscopic distal gastrectomy with D2 lymph node dissection was safe and achieved satisfactory oncological outcomes for the present patient. However, well-designed prospective trials are still required to prove whether laparoscopic gastrectomy can be recommended as an initial treatment for advanced distal gastric cancer after NACRT.



Table 2 Phase III published and ongoing studies of neoadjuvant/preoperative radiation/chemoradiation following curative gastrectomy in gastric cancer (with or without esophagogastric junction)

Ref.	Trial (accrual period)	No pts	Eligibility	Treatment/Design	Surgery	Response rate	Survival	Adverse outcomes
Skoropad <i>et a</i> l[32]	(1974-1978)	102	Stomach/EGJ, cM0	20 Gy/5 fractions \rightarrow S vs S	D1 and beyond	NA	5-yr OS 30% <i>vs</i> 39%, NS; 10-yr OS 32% <i>vs</i> 18%, NS	Complications 57% <i>vs</i> 49%, NS; postoperative death 9.8% <i>vs</i> 11.8%, NS
Leong <i>et al</i> [33]	TOPGEAR (2009-2014)	75	Stomach/EGJ, cTNM IB-IIIC	ECF×2 \rightarrow 45 Gy/25 fractions + 5- Fu \rightarrow S \rightarrow ECF × 3 vs ECF × 3 \rightarrow S \rightarrow ECF × 3	D2, D1+	NA	In progress	No/noncurative surgery, 15% vs 10%, NS; Grade 3-4 AE 52% vs 50%, NS; surgical complications 22% vs 22% NS
https://clinicaltrials.gov/ct2/show/study/NCT01815853	Neo-CRAG (2013-)	620 (estimated)	LAGC, cT3N2/N3M0, cT4aN+M0, cT4bNanyM0	$\begin{array}{l} 45 \text{ Gy}/25 \text{ fractions} \rightarrow \text{XELOX} \times 3 \\ \rightarrow \text{S} \rightarrow \text{XELOX} \times 3 \textit{ vs} \text{ XELOX} \times 3 \\ \rightarrow \text{S} \rightarrow \text{XELOX} \times 3 \end{array}$	D2	In progress	In progress	In progress
Liu et al[<mark>34</mark>]	PREACT (2016-)	682 (estimated)	Stomach/EGJ, LAGC	$\begin{array}{l} \text{SOX} \times 1 \rightarrow 45 \text{ Gy}/25 \text{ fractions} + \text{S-} \\ 1 \rightarrow \text{SOX} \times 1 \rightarrow \text{S} \rightarrow \text{SOX} \times 3 vs \\ \text{SOX} \times 3 \rightarrow \text{S} \rightarrow \text{SOX} \times 3 \end{array}$	D2 recommended	In progress	In progress	In progress

AE: Adverse events; ECF: Epirubicin/cisplatin/5-Fu; EGJ: Esophagogastric junction; Gy: Grey; LAGC: Locally advanced gastric cancer; NA: Not available; NS: Not significant; OS: Overall survival; S: Surgery; SOX: S-1/Oxaliplatin; XELOX: Capecitabine/Oxaliplatin.

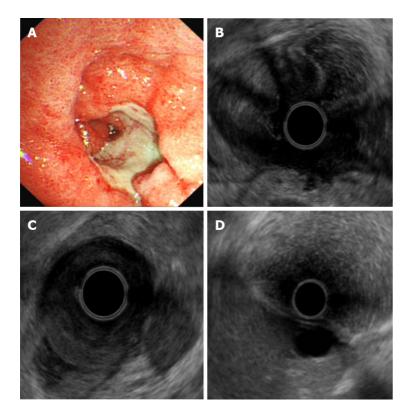


Figure 4 Endoscopic ultrasound was also applied to evaluate the response to neoadjuvant chemoradiotherapy, indicating that the ulcerative lesion location surrounded the gastric antrum with pyloric stenosis. A: Endoscopic view of the posttreatment lesion; B-D: Endoscopic ultrasound image of post-treatment lesion.

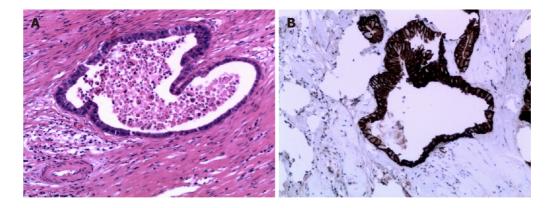


Figure 5 Postoperative pathological evaluation showed that the pathological stage after neoadjuvant chemoradiotherapy was T3N0M0, with necrosis rate > 90%. A: Hematoxylin and eosin stain; B: Human epidermal growth factor receptor 2 immunohistochemical stain highlights carcinoma cells (stained brown).

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