Preoperative Chemoradiation With Image-guided IMRT in Patients With Locally Advanced Gastric Cancer

Jing SHEN
PUMCH  https://orcid.org/0000-0002-4566-5925

Xin LIAN
Peking Union Medical College Hospital

Qiu GUAN
Peking Union Medical College Hospital

Tingtian PANG
Peking Union Medical College Hospital

Lei HE
Peking Union Medical College Hospital

Tingting DONG
Peking Union Medical College Hospital

Jie SHEN (✉️ 13521039164@163.com)
Chinese Academy of Medical Sciences & Peking Union Medical College  https://orcid.org/0000-0002-3845-2040

Fuquan ZHANG
Peking Union Medical College Hospital

Research

**Keywords:** gastric cancer, preoperative chemoradiotherapy, pathological complete response, radiotherapy

**DOI:** https://doi.org/10.21203/rs.3.rs-774210/v1

**License:** © This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Purpose

To evaluate the efficacy and toxicity of preoperative chemoradiation with image-guided IMRT in locally advanced resectable gastric cancer patients.

Patients and methods

Patients with locally advanced (T3/T4 or N+) gastric cancer treated with neoadjuvant chemoradiotherapy followed by surgery between Jan 2013 and June 2019 in PUMCH were retrospectively analyzed. Radiotherapy(IMRT 45Gy/25#/5weeks) were delivered with megavolt computed tomography performed before every delivery to ensure the accuracy repeatability of gastric filling during treatment, with concurrent chemotherapy(Capecitabine alone or XELOX*2 cycles).

Results

A total of 95 patients were included in the study with 93 patients (97.9%) had stage cT3/T4, 85 patients (89.5%) had stage N+. The location of the tumors was in the upper 1/3 in 85 patients (89.5%). Alltogether 93/95(97.9%) patients finished the neoadjuvant chemoradiation, 80 patients (84.2%) underwent gastric resection(58 D2 and 22 D1 gastrectomy). Pathology downstaging was observed in 68 patients (85.0%), including 66 patients (82.5%) with T downstaging and 56 patients (70.0%) with N downstaging. 11 patients (13.75%) obtained pathological complete response (pCR). The median follow-up was 44.7 months (19-96 months). Compared with the clinical efficacy of neoadjuvant chemotherapy in the previous literature, the clinical efficacy of image-guided IMRT combined with concurrent chemotherapy in patients with locally advanced resectable gastric cancer was improved, the 5-year OS, LRFS, and DMFS rates of patients were 46.98% (95% CI: 38.60%-55.36%), 86.55% (95% CI: 79.11%-93.99%), and 60.71% (95% CI: 51.49%-69.93%), respectively. Grades 3-4 leukopenia, anemia, and thrombocytopenia were observed in 13 (13.68%) patients, 9 (9.47%) patients, and 5 (5.26%) patients, respectively. Multivariate analysis demonstrated that pCR was significant prognostic factor for OS (HR =11.211, 95% CI: 1.500–83.813, P = 0.024).

Conclusion

Compared with the previous literature results of preoperative neoadjuvant chemotherapy for patients with gastric cancer, the application of image-guided IMRT(45Gy/25#/5weeks) combined with chemotherapy in preoperative neoadjuvant therapy for patients with locally advanced gastric cancer can achieve improved clinical efficacy, with higher rates of OS, LRFS, and DMFS, good tolerance of concurrent chemoradiotherapy with acceptable side effects.

1. Introduction
Gastric cancer is the fifth most prevalent cancer and third leading cause of cancer death worldwide, near half of the global cases occur in China[1]. And more than 75% newly diagnosed patients are in an advanced stage (invaded the muscle layer or lymph node) because of the lack of the typical clinical premonitory symptoms, and the survival rates of advanced stage patients are only 20–50%[2], approximately 50% lost the chance of surgery. But due to the increasing adoption of chemotherapy and radiation approaches into treatment regimens, the overall incidence and mortality rate of gastric cancer has been declining [3].

Neoadjuvant and adjuvant therapies are generally accepted to improve disease-free survival (DFS) and overall survival (OS) in other gastrointestinal cancers, including esophageal and rectal cancer[4][5]. However, there is relatively limited prospective data about preoperative treatment for locally advanced gastric carcinoma (LAGC) patients[6]. Several RCTs and meta-analyses have proven the survival benefits of neoadjuvant chemotherapy in addition to surgery alone[7]. However, previous studies failed to obtain a clear conclusion and the ideal neoadjuvant treatment strategy of LAGC patients. The aim of this study is to evaluate the efficacy and feasibility of preoperative chemoradiation in these patients.

2. Patients And Methods

2.1 Patients

It was a retrospective analysis, we collected data from Jan 2013 and June 2019. The eligibility criteria were as follows: histologically confirmed gastric with: (1) 18-70 years old; (2) performance status (PS) of 0-1 by Eastern Cooperative Oncology Group (ECOG) criteria; (3) local advanced stage (cT3-4N0-2M0 or cT1-4N1-2M0) by chest and abdomen computed tomography (CT), and trans-esophageal ultrasound. Some patients received positron emission tomography/computed tomography (PET/CT).

Exclusion criteria included M1, peritoneal carcinomatosis (gross or microscopic), distant lymph node metastasis (supravacuicular or retroperitoneal), or uncontrolled medical conditions.

The study protocol is listed below, see details in Figure 1.

2.2 Radiotherapy

All patients received a CT simulation (16-slice Philips Brilliance CT BigBore, Deventer, Netherlands) in the supine position with oral and intravenous contrast agents. Bowel preparation were conducted before the CT scan (200ml liquid to fill the stomach). The clinical target volume (CTV) were contoured on the axial CT slices. The CTV scans were delineated based on the endoscopy, and CT/MRI or ultrasound into consideration. Involved lymph nodes were defined as short diameter>1 cm or confirmed by diffusion weighted imaging or PET/CT. Gross tumour volumes (GTV) have to be delineated for the primary tumour (GTVtumour) as well as for the involved lymph nodes (GTVnodal). The global clinical target volume (CTV) will be obtained by the addition of the following structures (including the lymphatic spread ways in between these volumes): CTV tumour (which will be obtained by adding a margin of 1.5 cm to
GTV tumour), CTV nodal (which will be obtained by adding a margin of 0.5 cm to GTVnodal). The planning clinical target volume (PCTV) was the CTV plus 8 mm margin craniocaudal direction, and 6 mm in anteroposterior and left–right directions. The regime consists of a total dose to PCTV of 45 Gy in 25 daily fractions of 1.8 Gy on five days a week. Radiotherapy plans were generated on the Eclipse treatment planning system (Eclipse Inc., Madison, WI, USA). The planning goals were delivering at least 95% of the prescribed dose to 95% of the PCTV. Dose prescription and recording has to comply with the recommendations of the ICRU 50/62. Daily patient set-up was performed using laser alignment to reference marks on the skin of the patient. And CBCT was used for image guidance before every day treatment delivery. Using soft tissue registration, if the filling of the stomach does not meet the image requirements of positioning, it is necessary to suspend the current treatment and start the treatment after meeting the accuracy of the location. Patients were repositioned after co-registration of CBCT images with the planning CBCT images. (see Figure 2 as an example).

2.3 Chemotherapy

All patients received concurrent capecitabine alone (60 mg/m2 orally on days 1-5 during the radiation treatment) or XELOX (capecitabine (60 mg/m2 by oral on days 1-14 of a 3-week cycle and oxalipatin (100 mg/m2, intravenously, on day 1). The choice of chemotherapy was based on the patient’s age, physical condition and economic situation. Patients were assessed for acute chemotherapy-related toxicity during therapy. Postoperative chemotherapy was given capecitabine alone until one year after surgery.

2.4 Surgery

Before surgery, patients received a gastric CT/MRI/trans-esophageal ultrasound for reassessment of staging and resectability by surgeons. Gastroectomy surgery was performed for gastric carcinoma patients at least 6 weeks after neoadjuvant radiotherapy. Whether to perform D2 gastroectomy surgery or not was decided by the attending surgeon, based on the clinical response to neoadjuvant treatment, and the patient’s preference.

2.5 Tumor response and toxicity criteria

After chemoradiation, abdominal CT scan was performed to evaluate tumor response according to the Response Evaluation Criteria for Solid Tumors (RECIST) 1.1.14 Pathological complete response (path CR) was defined as an absence of carcinoma cells in the primary site and lymph nodes, and pathological partial response (path PR) was defined as less than 10% residual carcinoma cells in the lesion. Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC) 3.0.

2.6 Follow-up and evaluation of toxicities

Patients had follow-up examinations every 3 months during the first 2 years, every 6 months during the next 3–5 years, and then once each year. Carbohydrate antigen 19–9 and carcinoembryonic antigen levels were measured every 3 months together with imaging examination that included CT scan of the
thorax and abdomen. Chemoradiotherapy-related toxicities and postoperative complications were recorded.

Acute toxicities during chemoradiotherapy were evaluated every week. Toxicities were evaluated with Common Terminology Criteria for Adverse Events, version 3.0.

2.7 Statistics

The pCR rate, the clinical end points including resection rate, downstaging rate, acute and postoperative complications, pattern of failure, and survival, were also calculated. The 5-year OS, LRFS, and DMFS were estimated with the Kaplan–Meier methods, and the univariate log rank test was used to evaluate the significance of prognostic factors for survival. Multivariate analysis, using the Cox proportional regression method, was performed for the covariates selected in the univariate analysis. An equivalent dose in 2-Gy fractions (EQD2) was calculated with $\alpha/\beta=10$ for the tumor. A significance level of 0.05 was used. All the statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Patients characteristics

A total of 95 patients were enrolled. Patients’ and tumors’ characteristics are detailed in Table 1. Overall 54/95 (56.84%) patients were more than 60 years old. The male patients occupied the majority 81/95 (85.26%), all patients were diagnosed pathologically with locally advanced gastric carcinoma, 93 patients (97.89%) with stage cT3 or cT4; 85 patients (89.47%) had positive lymph nodes. The location of tumors was in the upper 1/3 in 85 patients (89.47%). poorly differentiated tumor were more than other types 64/95 (67.36%), CEA(carcinoembryonic antigen) was the most related bold tumor marker with the 35/95 (36.84%) abnormality. 71/95 (74.74%) patients received capecitabine alone while 24/95 (25.26%) with XELOX for chemotherapy, Postoperative chemotherapy was given to 41/95 (51.25%) patients with capecitabine alone until one year after surgery. see the details in Table 1.

3.2 Treatment and acute toxicities

A dose of 45 Gy in 25 fractions was delivered to all patients. The median interval to finish radiotherapy was 39 days (range, 34–49 days). Accompanied with concurrent chemotherapy, capecitabine alone was used in 74.74% (71/95) of patients and XELOX in 25.26% (24/95) of patients. Grades 3–4 leukopenia, anemia, and thrombocytopenia were observed in 13 (13.68%) patients, 9 (9.47%) patients, and 5 (5.26%) patients, respectively. Seven patients (7.37%) developed grade 3 nausea.

93 (97.89%) of 95 patients finished the chemoradiotherapy. Two patients did not finish the treatment (one presented with intestinal obstruction during treatment; one patient presented with intestinal hemorrhage). 80 (84.21%) of 95 patients underwent gastrectomy. 58 patients (72.5%) underwent a D2 gastrectomy, and 22 patients (27.5%) underwent an D1 gastrectomy. Gastrectomy was not performed in the remaining 13
patients due to late stage (4 with peritoneal carcinomatosis, 3 with liver metastasis, 3 with lung metastasis, and 3 with duodenal and pancreatic invasion).

3.3 Surgery and postoperative complications

In the 80 patients who underwent gastrectomy, pathologic CR was found in eleven patients. The primary tumor after surgery was T1 in three patients (3.75%), T2 in fifteen patients (18.75%), T3 in thirty-nine patients (48.75%), and T4a in twelve patients (1%). Additionally, thirty-nine patients (48.75%) had N0, twenty-nine patients (36.25%) had N1, eight patients (10.0%) had N2, and four patients (5.0%) had N3. The median number of dissected nodes was 19 (range 6-40). The median number of positive nodes was 5 (range 0-9).

Eight of 80 patients (10%) experienced postoperative complications, including 3 patients with anastomotic fistula, 2 patient with abdominal infection, 2 patients with bowel obstruction, 1 patients with anastomotic stenosis.

3.4 Pathologic response

Downstaging was observed in 68 patients (85.0%), including 66 patients (82.5%) with T downstaging and 56 patients (70%) with N downstaging. A pCR was observed in 11 patients (13.75%).

Compared with capecitabine alone, XELOX presented no significant difference in pCR (62.73% vs 79.10%, p=0.385). Pathologic T0 was also found in 14 patients (17.5%). Of the 80 patients with positive lymph nodes before treatment, negative lymph node involvement was observed in 39 patients (48.75%).

3.5 Pattern of failure and survival

The median follow-up was 44.7 months (range, 19-96 months). 37 patients (46.25%) experienced treatment failure, including local failure in 7 patients (8.75%), implant metastasis in 12 patients (15.0%) and distant metastasis in 33 patients (41.25%). The most common metastases were liver, followed by lung and bone. See details of failure patterns in Table 2.

The estimated 5-year OS, LRFS, and DMFS rates of patients were 46.98% (95% CI: 38.60%-55.36%), 86.55% (95% CI: 79.11%-93.99%), and 60.71% (95% CI: 51.49%-69.93%), respectively.

Univariate analysis showed that chemotherapy of XELOX (comparing with capecitabine alone) (p=0.002), D2 surgery(p=0.001), pCR (P=0.003), down T stage(p=0.001) and down N stage(p=0.005) were significant prognostic factors of OS. Meanwhile chemotherapy of XELOX(p=0.031), was significant prognostic factors of LC, D2 surgery(p=0.001), pCR (P=0.025),down T stage(p=0.001) and down N stage(p=0.003) were significant prognostic factors of DFS.

Multivariate analysis demonstrated that pCR was significant prognostic factor for OS (HR =11.211, 95% CI: 1.500–83.813, P = 0.024).See details in Table 3 and Figure 3.
4. Discussion

Gastric cancer is the most common tumor of the digestive system, accounting for the third most and the 5th of mortality in the total number of global tumors[8], and LAGC patients account for higher in China. More than half of patients with gastric cancer are II-III, how to improve the efficacy and survival rate of patients with LAGC is the main problem facing research scholars[9].

New-adjuvant radiation therapy in LAGC, mainly used to reduce tumor burden, control micrometastasis, and more likely to receive surgery. And the pathological response after the new adjuvant treatment is an important prognostic factor related to the survival of patients. Several major III clinical studies have also confirmed that preoperative new adjuvant radiotherapy has achieved better therapeutic effects in patients with gastric cancer[10][11][12][13]. (Table 4). Currently, III clinical TopGear Research[14], Preact Study[15] is also further comparing the effect of new-adjuvant chemo-radiotherapy and chemotherapy, but the results failed to show a clear conclusion. In our study, the patients received new-adjuvant chemo-radiotherapy showed well tolerance, 93/95 patients have completed the new-adjuvant chemo-radiotherapy treatment procedure, with no severe toxicity. Moreover the expected 5 years of OS, LRFS and DMFS were 46.98% (95% CI: 38.60% -55.36%), 86.55% (95% CI: 79.11 %-93.99%), 60.71% (95% CI: 51.49% -69.93%), comparing with the literature reports of new-adjuvant chemo-radiotherapy in LAGC, the survival advantage of new-adjuvant chemo-radiotherapy is shown.

The PCR rate after new-adjuvant chemotherapy/ chemo-radiotherapy is a clear indicator of survival prognosis [16][17][18]. In this study, the PCR of patient with new-adjuvant chemo-radiotherapy was 13.75%, which was similar to the PCR rate reported by the relevant literature(13.0% to 17.0%)[11][12][19].The literature reported with new-adjuvant chemo-radiotherapy, the PCR ratio was increased by 2.8 times (95% CI 2.27-3.47; P <0.001) relative to the new-adjuvant chemotherapy[19]. In our study, comparing with the patients who did not receive PCR, those prompting patients with PCR showed survival advantage with 5 year OS 72.67% vs 40.99% P = 0.003, which is similar to those related to the relevant literature.

In this study, 13 patients who completed the new-adjuvant chemo-radiotherapy were found with new M1 in the preoperative evaluation, with peritoneal carcinomatosis(4) ,lung metastases(3), unresectable liver metastasis(3), and unresectable pancreatic invasion(3), so they did not undergo surgery for the limited possibility of surgical treatment and the small benefits[3][20]. The median time of PFS has been obtained for 13 months. and the median survival time(MST) is 21 months. The patient did not appear more than grade 3 or more toxic side reactions. For those noncurable metastasis category stage IV gastric cancer patients, the reported MST of conversion therapy was 6 months[21][22]. At present, the digestive system tumor recommends a positive treatment model of multidisciplinary collaboration, such as rectum, pancreatic cancer and other tumors, radiotherapy has played a good perioperative treatment[5][23], the radiotherapy might be one of the main roles of treatment stragergy in stage IV GC patients.

This study has some limitations. First, as a retrospective, single-center study, there may be selection bias. Second, the results were comparing with the previous literature reports, so the effects of CCRT may have
been overestimated. Despite these limitations, this is a large-scale population study exploring the efficacy of CCRT and its effects on LAGC patients; it has high value as a reference and offers guidance in selecting treatment for LAGC patients.

**Conclusion**

Compared with the previous literature results of preoperative neoadjuvant chemotherapy for patients with gastric cancer, the application of image-guided IMRT (45 Gy/25#/5 weeks) combined with chemotherapy in preoperative neoadjuvant therapy for patients with locally advanced gastric cancer can achieve improved clinical efficacy, with higher rates of OS, LRFS, and DMFS, good tolerance of concurrent chemoradiotherapy with acceptable side effects.

**Abbreviations**

LAGC: locally advanced gastric carcinoma  
CRT: chemo-radiotherapy  
CT: chemotherapy  
IMRT: intensity modulated radiation therapy;  
PCR: pathological complete response  
OS: overall survival

**Declarations**

**Ethical approval and Consent to participate**

The Institutional Review Board (IRB) of Peking Union Medical College Hospital (PUMCH) reviewed the protocol. This is retrospective study. The protocol is rational and scientific. The study accords with principle of ethics. The IRB thus approve the protocol. This is a retrospective study and written human subject consent was unnecessary.

**Consent for publication**

Not applicable

**Availability of data and materials:**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
Competing interests

The authors declare that they have no conflict of interest.

Funding

This work was supported by the 13th Five-Year Research Fund of China (Grant No. 2016YFC0105207).

Authors’ contributions

SJ and LX were responsible for data collection and drafted the manuscript;
GQ, PTT, DTT, HL participated in the design of the study;
SJ performed statistic analysis and data interpretation;
SJ designed the study and revised the manuscript;
All authors read and approved the manuscript.

Acknowledgment

No

References

1. Collaborators, G.B.D.S.C., The global, regional, and national burden of stomach cancer in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet Gastroenterol Hepatol, 2020. 5(1): p. 42-54.

2. Edge, S.B. and C.C. Compton, The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol, 2010. 17(6): p. 1471-4.

3. Machlowska, J., et al., Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. Int J Mol Sci, 2020. 21(11).

4. Triantafyllou, T. and B. Wijnhoven, Multidisciplinary treatment of esophageal cancer: The role of active surveillance after neoadjuvant chemoradiation. Ann Gastroenterol Surg, 2020. 4(4): p. 352-359.

5. Recio-Boiles, A., et al., Rectal Cancer, in StatPearls. 2020: Treasure Island (FL).
6. Van Cutsem, E., et al., Gastric cancer. Lancet, 2016. 388(10060): p. 2654-2664.

7. van Hagen, P., et al., Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med, 2012. 366(22): p. 2074-84.

8. Bray, F., et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018. 68(6): p. 394-424.

10. Zhang, Z.X., et al., Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)–report on 370 patients. Int J Radiat Oncol Biol Phys, 1998. 42(5): p. 929-34.

11. Stahl, M., et al., Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. Eur J Cancer, 2017. 81: p. 183-190.

12. Stahl, M., et al., Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol, 2009. 27(6): p. 851-6.

13. van Hagen, P., et al., Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med, 2012. 366(22): p. 2074-84.

14. Leong, T., et al., TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. Ann Surg Oncol, 2017. 24(8): p. 2252-2258.

15. Liu, X., et al., Study protocol of a randomized phase III trial of comparing preoperative chemoradiation with preoperative chemotherapy in patients with locally advanced gastric cancer or esophagogastric junction adenocarcinoma: PREACT. BMC Cancer, 2019. 19(1): p. 606.

16. Xu, X., et al., Is pathologic tumor regression grade after neo-adjuvant chemotherapy a promising
prognostic indicator for patients with locally advanced gastric cancer? A cohort study evaluating tumor regression response. Cancer Chemother Pharmacol, 2019. 84(3): p. 635-646.

17. Wang, T., et al., The Effect of Neoadjuvant Therapies for Patients with Locally Advanced Gastric Cancer: A Propensity Score Matching Study. J Cancer, 2021. 12(2): p. 379-386.

18. Martin-Romano, P., et al., Role of histological regression grade after two neoadjuvant approaches with or without radiotherapy in locally advanced gastric cancer. Br J Cancer, 2016. 115(6): p. 655-63.

19. Petrelli, F., et al., Neoadjuvant chemoradiotherapy or chemotherapy for gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis. Gastric Cancer, 2019. 22(2): p. 245-254.

20. Ajani, J.A., et al., Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw, 2016. 14(10): p. 1286-1312.

21. Yoshida, K., et al., Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. Gastric Cancer, 2016. 19(2): p. 329-338.

22. Yamaguchi, K., et al., The long-term survival of stage IV gastric cancer patients with conversion therapy. Gastric Cancer, 2018. 21(2): p. 315-323.

23. Mizrahi, J.D., et al., Pancreatic cancer. Lancet, 2020. 395(10242): p. 2008-2020.

**Tables**

**Table 1. Patients’ and tumors’ characteristics**
| Characteristics                        | n  | Percentage (%) |
|---------------------------------------|----|----------------|
| **Age**                               |    |                |
| <60                                   | 41 | 43.16          |
| ≥60                                   | 54 | 56.84          |
| **Gender**                            |    |                |
| Male                                  | 81 | 85.26          |
| Female                                | 14 | 14.74          |
| **ECOG performance status**           |    |                |
| 0                                     | 77 | 81.06          |
| 1                                     | 18 | 18.94          |
| **Tumor location**                    |    |                |
| Upper 1/3                             | 85 | 89.47          |
| other                                 | 10 | 10.53          |
| **Tumor differentiation**             |    |                |
| Well differentiated                    | 3  | 3.16           |
| Moderately differentiated             | 21 | 22.11          |
| Poorly differentiated                 | 64 | 67.36          |
| others                                | 7  | 7.37           |
| **Blood tumor markers**               |    |                |
| Carcinoembryonic antigen              | 35 | 36.84          |
| CA199                                 | 29 | 30.53          |
| CA242                                 | 29 | 30.53          |
| CA724                                 | 19 | 20.00          |
| CA125                                 | 14 | 14.74          |
| CA153                                 | 4  | 4.21           |
| **Pretreatment tumor stage**          |    |                |
| T2                                    | 2  | 2.1            |
| T3                                    | 20 | 21.06          |
| T4                                    | 73 | 76.84          |
| **Pretreatment node status**          |    |                |
Table 2. Patterns of recurrence

|        |       |       |
|--------|-------|-------|
| N0     | 10    | 10.53 |
| N1     | 34    | 35.79 |
| N2     | 49    | 51.57 |
| N3     | 2     | 2.11  |

Chemotherapy regimen

|        |       |       |
|--------|-------|-------|
| Capectiabine | 71    | 74.74 |
| XELOX   | 24    | 25.26 |

Postoperate chemotherapy

|        |       |       |
|--------|-------|-------|
| Yes    | 41    | 51.25 |
| No     | 39    | 48.75 |
| Recurrence sites   | No. Of patients | % of recurrence patients (n=37) |
|--------------------|-----------------|-------------------------------|
| Single site        |                 |                               |
| Local recurrence   | 3               | 6.81                          |
| implant metastasis | 4               | 9.12                          |
| distant metastasis | 27              | 61.42                         |
| Two sites          |                 |                               |
| LR+IM              | 0               | 0                             |
| LR+DM              | 2               | 4.51                          |
| IM+DM              | 6               | 13.63                         |
| Three sites        | 2               | 4.51                          |
| Down T stage       | 0.001           | 2.808                         |
| Yes                | 52.9%           | 1.352-5.832                   |
| no                 | 12.0%           | 0.151                         |
| Down N stage       | 0.005           | 4.505                         |
| Yes                | 50.8%           | 1.777-11.419                  |
| no                 | 26.5%           | 0.250                         |

Table 3. Univariate and multivariate analysis of prognostic factors in 5-year OS
Table 4. Literature review of the effect of new-adjuvant radiotherapy

| study                  | Year/country              | phase | Sample size | Tumor site | groups          | Local control | survival       |
|------------------------|---------------------------|-------|-------------|------------|-----------------|---------------|----------------|
| Zhang et al. [10]      | 1998/china                | III   | 370         | EGJ        | RT+S vs S       | 61.4% vs 51.7% | 10-year OS 20.3% vs 13.3% |
| Stahl et al. [11][12]  | 2009/Germany              | III   | 119         | EGJ        | CRT+S vs C+S    | pCR 15.6% vs 2.0% | 3-year OS 47.4% vs 27.7% |
| Van Hagen et al.[13]   | 2012/England              | III   | 366         | EGJ or EC  | CRT+S vs S      | LRR 14% vs 34%  | 5-year OS 47% vs 34% |
| Trevor Leong et al. [14]| 2019/australia, Europa, Canada | III   | 752         | EGJ or EC  | CRT+S vs C+S    | On going       | On going       |
| Liu, X et al. [15]     | 2019/China                | III   | 682         | EGJ or EC  | CRT+S vs C+S    | On going       | On going       |
2013.1.1-2019.6.30
Neoadjuvant chemo-radiotherapy in LAGC
(n = 95)

Finish neoadjuvant chemo-radiotherapy LAGC patients

Chemotherapy:
- Capecitabine/
- XELOX*2 cycles

Radiotherapy:
- IMRT
- 45 Gy/25#/5 weeks

Finish the operations
(n = 80)

Did not finish the operations

Did not finish the neoadjuvant chemo-radiotherapy
(n = 21)

---

Figure 1

Flow diagram of study. *capecitabine: 60 mg/m2 orally on days 1-5 during the radiation treatment
*XELOX: capecitabine (60 mg/m2 by oral on days 1-14 of a 3-week cycle) and oxalipatin (100 mg/m2, intravenously, on day 1)
Figure 2

Example of image-guided radiotherapy. A 45 year old female presented with upper abdominal discomfort for one month. Gastroscopy revealed a 4*2cm ulcerative lesion on the lesser curvature of the cardia. Biopsy showed adenocarcinoma. CT showed thickening and uneven enhancement of the gastric cardia mucosa. No clear distant metastasis was found in the lung and liver. She was recomended to receive neoadjuvant chemoradiotherapy, figure A was the cross-section of GTV and the lesion of CTV was extent of GTVtumor+1.5cm, and the coronal map was shown in Figure B, showing the extent of GTVtumor and CTV.
Figure 3

Kaplan-Meier estimate of OS