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

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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 (supraclavicular 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

GTVtumour), 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 patients with abdominal infection, 2 patients with bowel obstruction, 1 patient 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 strategy 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(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.

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.

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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.

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No

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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 satge		
T2	2	2.1
T3	20	21.06
T4	73	76.84
Pretreatment node status		

N0	10	10.53
N1	34	35.79
N2	49	51.57
N3	2	2.11
Chemotherapy regiment		
Capectiabine	71	74.74
XELOX	24	25.26
Postoperate chemotherapy		
Yes	41	51.25
No	39	48.75

Table 2. Patterns of recurrence

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	
	0.001	2.808	1.352-5.832	0.151
Down T stage	52.9%			
Yes	12.0%			
no				
Down N stage	0.005	4.505	1.777-11.419	0.250
Yes	50.8%			
no	26.5%			

Table 3. Univariate and multivariate analysis of prognostic factors in 5-year OS

Factor	Univariate analysis	Multivariate analysis		
		HR	95% CI	p value
Chemotherapy	0.002	0.286	0.149-0.549	0.148
capecitabine	20.8%			
XELOX	49.3%			
Surgery	0.001	3.530	1.866-6.679	0.338
D1	13.6%			
D2	56.9%			
PCR	0.003	11.211	1.500-83.813	0.024*
Yes	90.9%			
no	35.7%			

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

Figures

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)

(A)

(B)

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 recommended 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