



Original research

The effects of neoadjuvant chemotherapy on resectability of locally-advanced gastric adenocarcinoma: A clinical trial



Shahriyar Hashemzadeh ^a, Ali Pourzand ^a, Mohammad Hossein Somi ^b, Sina Zarrintan ^{a,*},
Reza Javad-Rashid ^c, Ali Esfahani ^d

^a Department of General & Vascular Surgery, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

^b Division of Gastroenterology, Department of Internal Medicine, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

^c Department of Radiology, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

^d Division of Hematology & Oncology, Department of Internal Medicine, Ghazi Medical Center, Tabriz University of Medical Sciences, Tabriz, Iran

HIGHLIGHTS

- Neoadjuvant chemotherapy increases resectability in locally-advanced gastric cancer.
- CT can distinguish locally-advanced gastric adenocarcinomas preoperatively.
- Neoadjuvant chemotherapy can shrink the primary locally-advanced gastric tumor.

ARTICLE INFO

Article history:

Received 8 July 2014

Received in revised form

17 July 2014

Accepted 10 August 2014

Available online 23 August 2014

Keywords:

Adenocarcinoma

Stomach

Chemotherapy

Locally-advanced

ABSTRACT

Introduction: Surgical resection is the only curative treatment for gastric cancer. However, the overall prognosis of gastric adenocarcinoma is poor and advanced disease may even make surgical treatment impossible. It has been theoretically proposed that administration of chemotherapy before surgical resection may down-stage the disease state and facilitate resectability especially in locally-advanced tumors. **Aim:** We wanted to assess the effect of administration of neoadjuvant chemotherapy on tumor resectability in patients with locally-advanced gastric adenocarcinoma. **Materials and methods:** During a randomized-controlled trial, we divided 60 patients with locally-advanced gastric adenocarcinoma into two groups of neoadjuvant chemotherapy and surgery (case) versus surgery alone (control). Because of patient dropouts, we analyzed the results for 22 and 29 patients in case and control groups respectively. The study period was March 21, 2011 to March 20, 2014. A non-randomized set of 23 patients were also added to the control group (Multi-center analysis). The analysis was repeated for non-randomized patients (22 case patients versus 52 control patients). **Results:** The mean age of patients in case and control groups was 58.3 ± 9.1 and 59.7 ± 8.7 years of age respectively ($p > 0.05$). Male to female ratio was 15/7 and 41/11 in case and control groups respectively ($p > 0.05$). In Randomized patients, 19 patients (86.4%) were resectable in case group; while 16 patients (55.2%) were resectable in control group ($p < 0.05$). Multicenter analysis also revealed resectability in 19 patients (86.4%) and 31 patients (59.6%) of case and control groups respectively ($p < 0.05$). **Conclusion:** We conclude that neoadjuvant chemotherapy could increase tumor resectability rate in patients with locally-advanced gastric adenocarcinoma. However, further studies are necessary to confirm the effect of this modality on patients' overall survival.

© 2014 Surgical Associates Ltd. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Adenocarcinoma is the most common primary malignant gastric neoplasm which accounts for 95% of gastric cancers. In 1930,

gastric cancer was among the leading causes of cancer death in the United States of America but today, it is not even included among the top ten causes [1]. However, Iranian studies suggest that incidence of esophageal cancer shows a declining pattern while the incidence of gastric, colon and breast cancer have a growing pattern in recent decade [2]. Furthermore, a population-based study has estimated that esophageal and gastric cancers have high rates in

* Corresponding author. Golgasht St. Imam Reza Hospital, General Surgery, Tabriz University of Medical Sciences, Tabriz 51664, Iran.

E-mail address: s.zarrintan@yahoo.com (S. Zarrintan).

East Azerbaijan province, including 11.7% and 11.6% of cancers respectively [3].

Surgical resection is the only curative treatment for gastric cancer [1,4–7]. The aim of curative surgical resection is R0 resection. Thus, all proximal, distal and radial margins should be negative and an adequate lymphadenectomy performed [1,7]. The standard operation for gastric cancer is radical subtotal gastrectomy. However, total gastrectomy is performed when it is required for R0 resection [1,4,7–9].

In general, the survival of gastric adenocarcinoma is poor because most surgical patients have stage II disease or greater. Even after potentially curative surgery, overall survival at 5 years for patients with gastric adenocarcinoma remains as low as 20%–30% [1,7]. Advanced gastric cancer may even make surgical treatment impossible and lead to unnecessary laparotomy [1,7,10].

Theoretically, administration of chemotherapy before surgical resection can address micrometastatic lesions and down-stage the disease. It also allows for an assessment of chemotherapeutic efficacy in patients with measurable disease (primary or perigastric nodal disease) on imaging [7,11]. Some concerns regarding preoperative therapy are progression of disease before resection and the potential for surgery-preventing toxicity. In reality, the patients who progress on preoperative therapy may be spared unnecessary laparotomy, because their disease is likely beyond surgical therapy at presentation. Toxicity remains an issue, because the platinum-based regimens that are often used can be difficult to tolerate [7].

Because of poor prognosis of gastric adenocarcinoma, neoadjuvant chemotherapy was proposed to be administered to patients with locally-advanced disease [1,4]. A number of trials have been conducted to assess the effect of neoadjuvant chemotherapy on survival of patients with locally-advanced gastric adenocarcinoma but none of them is conclusive [7]. The role of neoadjuvant therapy for resectable disease was also examined in several recent prospective studies [12]. The main criticisms of literature studies are poor preoperative staging, limited statistical power and unpredictable efficacy of chemotherapy regimens.

In the present study, we wanted to assess the effectiveness of preoperative chemotherapy on tumor resectability in patients with locally-advanced gastric adenocarcinoma. It is still unclear whether neoadjuvant chemotherapy is beneficial in gastric adenocarcinoma or not. Moreover, the subgroups of patients who might have more survival benefits from neoadjuvant chemotherapy are not clearly identified. In the cases of resectable disease, survival benefit is the primary outcome of interest. However, in locally-advanced disease, resectability is a potential concern because surgical resection is the only curative treatment modality.

2. Methods

The aim of this study was to assess the effect of neoadjuvant chemotherapy on increasing the rate of resectability in patients with locally-advanced gastric adenocarcinoma. We designed a randomized-controlled trial to evaluate the outcome of preoperative chemotherapy on resectability of locally-advanced gastric tumors.

The state of locally-advanced gastric tumor was assessed by the preoperative abdominopelvic computed tomography (CT). We used 64-slice multi-detector CT for our preoperative assessment in all study patients. Presence of peri-gastric lymph node involvement in the preoperative CT scans was considered locally-advanced tumor. We studied only tumors with preoperative diagnosis of adenocarcinoma. The preoperative diagnosis was made by histopathological examination of endoscopic biopsies.

All patients with gastric adenocarcinoma who had locally-advanced tumor confirmed by computed tomography were

chosen and assessed for eligibility. The study period was March 21, 2011 to March 20, 2014. The inclusion and exclusion criteria were considered to select the study patients. The inclusion criteria consisted of being younger than 70 years of age, confirmation of adenocarcinoma by histopathological examination of endoscopic gastric tissue biopsies, the presence of peri-gastric lymph node involvement in CT scan (i.e., locally-advanced tumor) and being resectable based on CT findings. The exclusion criteria consisted of being older than 70 years of age, pathologies other than adenocarcinoma, presence of distant metastasis on preoperative CT scans, any contraindication to chemotherapy and history of previous chemoradiation for any reason. Locally-advanced gastric tumors are defined by tumor size (T) and lymph node involvement (N). T3 and N positive tumors are considered locally-advanced. Defining locally-advanced gastric adenocarcinoma preoperatively necessitates endoscopic ultrasound (EUS) to assess the tumor size (T) and lymph node involvement (N), i.e., radiological staging. Lymph node involvement should be confirmed by EUS-FNA (Endoscopic Ultrasound-guided Fine Needle Aspiration). Stage II gastric tumors which are T3N0, T1N2 and T2N1 are considered locally-advanced. In addition, stages IIIA and IIIB tumors with TNMs of T2N2, T3N1 and T3N2 are considered locally-advanced. Because we do not have EUS at our institution, we considered per-gastric lymph node involvement in preoperative CT scan as N⁺ tumors that are locally-advanced [1,5].

After the enrollment of patients with locally-advanced gastric adenocarcinoma and consideration of inclusion and exclusion criteria, 60 patients were selected for the study. The study patients were randomly divided into two groups of case and control using the website www.randomizer.org. Each group consisted of 30 patients. All patients were studied at Imam Reza Hospital, the tertiary and referral center of East Azerbaijan, Iran. This institution is affiliated to Tabriz University of Medical Sciences and the main wards of the Department of General and Vascular Surgery are located there.

The patients of the case group delivered neoadjuvant chemotherapy while the patients in the control group did not. The case patients received a combined chemotherapy regimen consisted of docetaxel 75 mg/m², IV, 1 h infusion on first day, cisplatin 75 mg/m², IV, 2 h infusion on first day and 5-fluorouracil 750 mg/m²/day, IV continuous infusion, days 1–5. The regimen was repeated every 3 weeks for 6 courses. The control patients did not get any chemotherapy regimens preoperatively. They also did not get placebo treatment. The reason for not using placebo regimen for the control group was that the main therapy in gastric cancer is surgery. Delaying surgical treatment for placebo administration could be hazardous to patients and that is why this study could not be controlled by placebo. In addition, we could not perform a blinded study because the patients were aware whether they have received neoadjuvant chemotherapy or not.

We did surgical exploration for all patients in case and control groups to assess the resectability and then continued with possible gastric resection. We performed ROD1 or ROD2 sub-total or total gastrectomy as a curative treatment in patients with gastric cancer. Placement of jejunostomy tube was not mandatory and was considered based on the surgeons' judgment of the patient's nutritional and physiologic status. During the present study, the patients in case group received neoadjuvant chemotherapy and underwent surgery 4–6 weeks after their last course of chemotherapy. The patients in control group underwent surgery as soon as they entered the trial. The allocation of patients to case and control groups is illustrated in Fig. 1 as the follow diagram or CONSORT of the study (*Consolidated Standard of Reporting Trials*).

We conducted control CT scans for the patients in case group after completion of their neoadjuvant chemotherapy courses. The

control CT scans were assessed for shrinkage of the primary tumor by 30% or more and decline of peri-gastric lymph node involvement by 30% or more (cut-off points of 30%). The CTs before and after neoadjuvant chemotherapy was reviewed by a single radiologist who was expert in computed tomography.

The resectability of the tumor was compared between two groups of the study. The resectability was considered as the primary outcome of the study. The secondary outcomes were also compared between two groups. They consisted of total admission days, admission days in surgical intensive care unit (SICU), postoperative mechanical ventilatory support, days of nil per os (NPO), postoperative day of removal of nasogastric tube, duration of operation, need for intraoperative blood transfusion, need for postoperative blood transfusion, occurrence of postoperative metabolic acidosis, need for central venous catheter placement, postoperative day of ambulation and in-hospital morbidity and mortality. In-hospital morbidity consisted of wound dehiscence, wound infection, bleeding, need for reoperation etc.

The background variables were age, sex, primary symptoms, endoscopic findings, familial history of gastrointestinal cancer, preoperative hemoglobin concentration, preoperative anemia, history of dyspepsia, history of peptic ulcer disease, history of antiulcer treatment, history of *Helicobacter pylori* (*H. pylori*) infection, history of receiving *H. pylori* treatment regimens, past medical history, past surgical history, past drug history, history of cigarette smoking, history of hooka smoking and history of opiate use.

Intraoperative findings were recorded for all study patients. They included the type of operation, duration of operation (previously mentioned as a secondary outcome), extent of lymphadenectomy, resection of adjacent involved organs (such as spleen, transverse colon, and tail of pancreas), location of tumor and placement of feeding jejunostomy. The types of operation were

total, subtotal or proximal gastrectomy. The resections were R0 and lymphadenectomies were either D1 or D2.

In the cases of resectable gastric adenocarcinoma, the specimens were sent for histopathological analysis. The pathological staging was done by TNM system based on definitions of International Union against Cancer (IUAC) and American Joint Committee on Cancer (AJCC). The grading of the tumors was also reported for the specimens in three categories: well-differentiated, moderately differentiated and poorly-differentiated. The histological classification was also presented by Lauren classification system: intestinal type, diffuse type, and unclassified.

For the purpose of including patients from other institutions, we recruited patients of locally-advanced gastric adenocarcinoma from Sina Hospital which is also affiliated to Tabriz University of Medical Sciences, Tabriz, Iran. We considered the study inclusion and exclusion criteria for these patients and enrollment was done during the same time period but allocation was not randomized. The entire patient selection was a multi-center non-randomized clinical trial without placebo. Fig. 2 illustrates the follow diagram for the patients from Imam Reza and Sina hospitals.

We used descriptive statistics to explain the frequencies of background variables. We used mean \pm SD (Standard Deviation) and frequency (%). The comparison of background variables between two groups were done by independent sample *t*-test and chi-square test for scale and dichotomous variables respectively. The comparative analyses between primary and secondary outcomes were also done by independent sample *t*-test and chi-square test for scale and dichotomous variables respectively. All statistical analyses were done by SPSS software 19.0.

Informed consent was obtained from all study patients prior to their enrollment to the study. According to Helsinki declaration, all patients had the right to leave the study anytime they wished. We

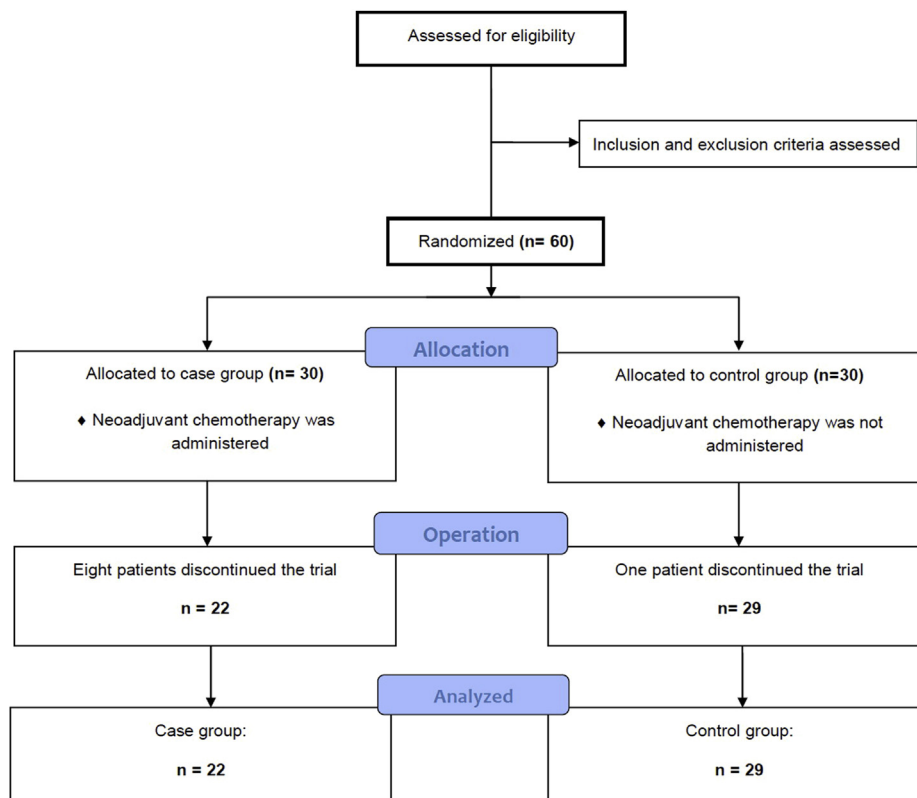


Fig. 1. Follow diagram for randomized allocations of patients at Tabriz Imam Reza hospital.

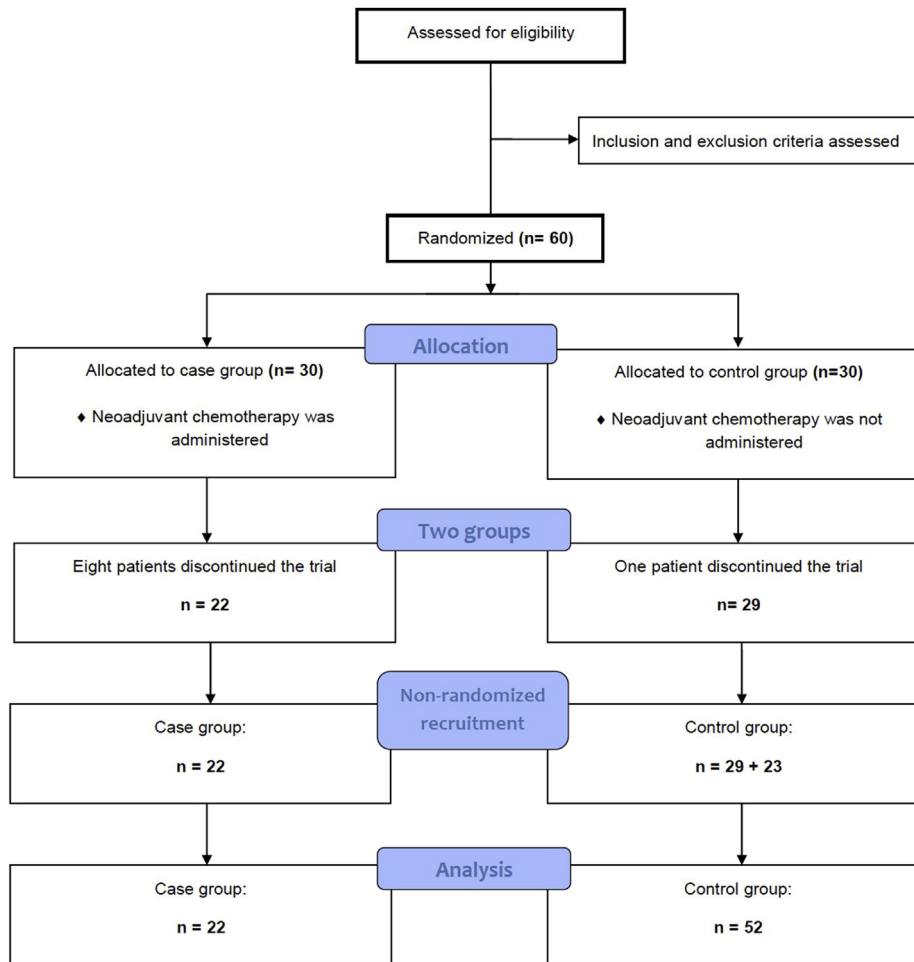


Fig. 2. Follow diagram of all study patients recruited from Tabriz Imam Reza and Sina hospitals (Multi-center recruitment).

explained that their participation in the trial is voluntarily and they will be allocated to case or control groups randomly. They were aware that participation in the trial would not expose them to increased risk and they would receive the standard treatment either they were allocated to case or control groups. The patients were assured that the study would not pose additional expenses to them.

The study of this protocol was reviewed by the research committee of the Tabriz Faculty of Medicine for dissertations and ethics committee of the Research Vice Chancellor Office, Tabriz University of Medical Sciences, Tabriz, Iran. The protocol of the trial was also registered to the Iranian Registry of Clinical Trials (IRCT) under the number *IRCT2014 053113736N1* at www.irct.ir. The study was supported by the research deputy of Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

3. Results

A total of 60 patients with locally-advanced gastric adenocarcinoma were allocated to case and control groups randomly during this study. Dropouts were one patient and eight patients in control and case groups respectively. The analysis for the randomized controlled trial was done for 22 patients and 29 patients in case and control groups respectively. The multicenter recruitment of patients from both Imam Reza and Sina hospital consisted of 22 patients and 52 patients in case and control groups respectively.

The mean age of all study participants were 59.2 ± 8.8 years of age. The mean age was 58.3 ± 9.1 and 59.7 ± 8.7 years of age for case and control groups respectively. The study patients consisted of 56 (75.7%) males and 18 (24.3%) females. The case group consisted of 15 (68.2%) males and 7 (31.8%) females; while the control group consisted of 41 (78.8%) males and 11 (21.2%) females. There was not any significant difference between age and sex distribution of patients in case and control groups ($p > 0.05$). Table 4.1 illustrates descriptive statistics and frequencies of background variables in the study patients. As it is seen in Table 1, there was not any significant difference between background characteristics of case and control groups.

The primary outcome of the study was the resectability of the gastric tumor. This outcome was analyzed twice. Once we did the comparison for the randomized patients and we did it again for all the patients of two studied centers (Imam Reza and Sina hospitals). The chi-square test illustrated that the resectability rate was significantly higher in patients who received neoadjuvant chemotherapy ($p < 0.05$). The analyses between the randomized patients and the multi-centrally recruited patients confirmed this finding. Fig. 3 illustrates the differences between case and control patients. In Randomized patients, 19 patients out of 22 (86.4%) were resectable in case group; while 16 patients out of 29 (55.2%) were resectable in control group ($p = 0.017$). Multicenter analysis also revealed resectability in 19 patients out of 22 (86.4%) and in 31 patients out of 52 (59.6%) in case and control groups respectively.

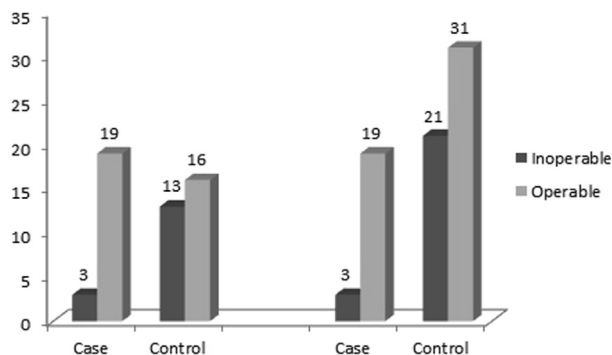
Table 1
Background characteristics of the study patients.

Background variables	Case group ^a	Control ^a group	Total ^a	p-value ^a
Age	58.3 ± 9.1	59.7 ± 8.7	59.2 ± 8.8	0.550
Sex:				
- Male	15 (68.2%)	41 (78.8%)	56 (75.7%)	0.245
- Female	7 (31.8%)	11 (21.2%)	18 (24.3%)	
Primary symptom:				
- Dyspepsia	21 (95.5%)	46 (88.5%)	67 (90.5%)	0.323
- Others	1 (4.5%)	6 (11.5%)	7 (9.5%)	
Familial history of GI cancer	2 (9.1%)	10 (19.2%)	12 (16.2%)	0.236
Diabetes mellitus	0 (0.0%)	5 (9.6%)	5 (6.8%)	0.161
Hypertension	4 (18.2%)	5 (9.6%)	9 (12.2%)	0.223
Coronary artery disease	2 (9.1%)	5 (9.6%)	7 (9.5%)	0.534
Cigarette smoking	7 (31.7%)	14 (26.9%)	21 (28.4%)	0.436
Hooka smoking	0 (0.0%)	6 (11.5%)	6 (8.1%)	0.110
Pack-years of smoking ^b	26.6 ± 10.7	26.4 ± 10.3	26.7 ± 11.3	0.958
Opiate use	0 (0.0%)	5 (9.6%)	5 (6.8%)	0.161
Alcohol use	0 (0.0%)	7 (13.5%)	7 (9.5%)	0.074
Anemia	4 (18.2%)	12 (23.1%)	16 (21.6%)	0.447
Preoperative hemoglobin ^c	11.3 ± 1.3	11.4 ± 1.4	11.4 ± 1.4	0.861
History of ulcer treatment	7 (31.8%)	27 (51.9%)	34 (45.9%)	0.091
Duration of ulcer treatment ^d	25.2 ± 32.3	29.1 ± 40.3	24.2 ± 30.7	0.768
History of <i>H. pylori</i> infection	5 (22.7%)	18 (34.6%)	23 (31.1%)	0.234
History of <i>H. pylori</i> treatment	5 (22.7%)	18 (34.6%)	23 (31.1%)	0.234
Cardiovascular risk^e:				
- Low risk	20 (90.9%)	39 (75.0%)	59 (79.7%)	0.104
- Moderate risk	2 (9.1%)	13 (25.0%)	15 (20.3%)	
- High risk	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Total	22 (29.7%)	52 (70.3%)	74 (100%)	–

GI – Gastrointestinal; *H. pylori* – *Helicobacter pylori*.^a Scale and dichotomous variables are presented by mean ± SD and frequency (%) respectively.^b Mean ± SD is among smokers.^c Gram per deciliter.^d Mean ± SD is among patients with positive history of ulcer treatment.^e According to American Society of Anesthesiologists (ASA); Classes I and II were considered low risk; Class III was considered moderate risk; Classes IV and V were considered high risk.

($p = 0.021$). Among patients who received neoadjuvant chemotherapy (case group), 15 patients (68.2%) had 30% or more decline in lymph node involvement. In addition, 14 patients (63.6%) had 30% or more shrinkage of gastric involvement compared to the initial CT scans obtained prior to chemotherapy.

The intraoperative findings are presented in Table 2. As it is seen, the difference between duration of the operation was significant between case and control group ($p = 0.019$). However, the higher rate of inoperable patients in control group and subsequent termination of the operation may have led to this observation. Resecting adjacent organs was done in one case of control group

**Fig. 3.** Resectability of gastric tumors in case and control groups (Note that two comparisons are shown; left for the randomized patients and right for the multi-center recruitment).

and it was a T4 tumor with involvement of the tail of pancreas that necessitated splenectomy and distal pancreatectomy.

Postoperative findings have been considered as secondary outcomes. These findings are illustrated in Table 3 for case and control groups. There was not any significant difference between two study groups in respect to these outcomes ($p > 0.05$). Two patients in control group were dead during the hospitalization period. One of them was operable and another was inoperable. The operable patient was dead because of postoperative splenic bleeding and he underwent reoperation and splenectomy but he expired because of multi-organ failure (MOF). The inoperable patient was dead because of massive pulmonary embolus during the postoperative admission. The in-hospital mortality rate was then 3.8% for control group and 0.0% for case group. The difference was not statistically significant ($p = 0.491$).

Histopathological findings also did not reveal any significant difference between two groups. In case group, 12 (54.5%), 3 (13.6%) and 4 (18.2%) patients had well-differentiated, moderately-differentiated and poorly-differentiated histology respectively. In control group, 17 (33.3%), 5 (9.8%) and 8 (15.7%) patients had well-differentiated, moderately-differentiated and poorly-differentiated histology respectively ($p = 0.136$). There were 3 patients (13.6%) and 21 patients (41.2%) in case and control groups respectively who were inoperable and the grading was not applicable for them. According to the Lauren classification for histologic type, 12 (54.5%), 2 (9.1%) and 5 (22.7%) patients in case group had intestinal type, diffuse type and unclassified histology respectively. In control group, 17 (33.3%), 4 (7.8%) and 9 (17.6%) patients had intestinal type, diffuse type and unclassified histology respectively ($p = 0.137$).

TNM staging of the operable patients are presented in Table 4. The difference between tumor size (T) was not significant between two groups ($p = 0.596$). In addition, the difference between nodal involvement and staging (based on both T and N) did not show any significant difference between two study groups. The p -values were 0.376 and 0.568 respectively.

Table 2
Intraoperative findings in the study patients.

Intraoperative findings	Case group ^a	Control ^a group	Total ^a	p-value ^a
Operable	19 (86.4%)	31 (59.6%)	50 (67.6%)	0.021
Inoperable	3 (13.6%)	21 (40.4%)	24 (32.4%)	
Duration	145.5 ± 37.9	119.8 ± 48.9	127.4 ± 47.1	0.031
Location:				
- Cardia	6 (27.3%)	12 (23.1%)	18 (24.3%)	0.993
- Fundus	5 (22.7%)	15 (28.8%)	20 (27.0%)	
- Antrum	6 (27.3%)	15 (28.8%)	21 (28.4%)	
- Body	5 (22.7%)	10 (19.2%)	15 (20.3%)	
Type:				
- Total ^b	11 (50.0%)	15 (28.8%)	26 (35.1%)	0.052
- Subtotal ^b	7 (31.8%)	16 (30.8%)	23 (31.1%)	
- Proximal ^b	1 (4.5%)	0 (0.0%)	1 (1.4%)	
- Laparotomy & closure ^c	3 (13.6%)	21 (40.4%)	24 (32.4%)	
Lymphadenectomy:				
- D1	19 (86.4%)	0 (0.0%)	44 (59.5%)	0.065
- D2	25 (48.1%)	6 (11.5%)	6 (8.1%)	
Feeding tube placement			10 (13.5%)	
Total	22 (29.7%)	52 (70.3%)	74 (100%)	–

D – Lymphadenectomy; D1 includes lymphadenectomy of 3–6 levels (perigastric); D2 includes lymphadenectomy of 1, 2 (crural) and 7, 8, 11 (lymph nodes along left gastric, hepatic and splenic arteries respectively) in addition to levels 3–6.

^a Scale and dichotomous variables are presented by mean ± SD and frequency (%) respectively.^b Total, subtotal and proximal gastrectomy.^c In the cases of inoperable gastric tumor.

Table 3
Postoperative findings in the study patients.

Postoperative findings	Case group ^a	Control ^a group	Total ^a	p-value ^a
Postoperative MVS	5 (22.7%)	10 (19.2%)	15 (20.3%)	0.479
POD of extubation ^b	0.27 ± 0.55	0.46 ± 1.8	0.41 ± 1.6	0.504
Post-op metabolic acidosis	2 (9.1%)	4 (7.7%)	6 (8.1%)	0.794
CV-line placement	11 (50.0%)	15 (28.8%)	26 (35.1%)	0.071
NPO days	4.6 ± 1.1	3.9 ± 2.3	4.1 ± 2.0	0.053
NGT removal day	3.5 ± 1.1	3.0 ± 2.1	3.2 ± 1.9	0.268
POD of Ambulation	2.8 ± 1.1	2.7 ± 2.0	2.7 ± 1.8	0.769
Intra-op PC infusion	2 (9.1%)	10 (19.2%)	12 (16.2%)	0.236
Post-op PC infusion	2 (9.1%)	3 (5.7%)	5 (6.8%)	0.541
Reoperation	0 (0.0%)	1 (1.9%)	1 (1.4%)	0.703
In-hospital mortality	0 (0.0%)	2 (3.8%)	2 (2.8%)	0.685
Morbidity:				
- Wound dehiscence	0 (0.0%)	1 (1.9%)	1 (1.4%)	0.520
- Wound infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	
- Bleeding	2 (9.1%)	2 (3.8%)	4 (5.6%)	
- Pneumothorax	0 (0.0%)	1 (1.9%)	1 (1.4%)	
Total	22 (29.7%)	52 (70.3%)	74 (100%)	–

MVS – Mechanical Ventilatory Support; POD – Postoperative Day; post-op – postoperative; CV-line – Central Venous Line; NPO – Nil per os; NGT – Nasogastric Tube; intra-op – intraoperative.

^a Scale and dichotomous variables are presented by mean ± SD and frequency (%) respectively.

^b Mean ± SD is among patients who transferred intubated to SICU after the operation.

4. Discussion

Neoadjuvant chemotherapy for gastric adenocarcinoma has two different aspects in respect to the disease state. Administration of chemotherapy regimens before surgery to patients with locally-advanced disease may increase the possibility of a curative resection [7,13,14]. However, in resectable gastric cancers, the administration of neoadjuvant chemotherapy focuses on survival benefits rather than resectability [7,12]. In advanced disease, the effects of preoperative chemotherapy can be followed by computed tomography (CT) to ensure response of primary tumor and perigastric lymph nodes to the administered regimens [11,14]. However, in the cases of resectable gastric cancer, potential concern exists because delaying definite surgical resection may lead to disease progression and unresectability [7,15,16].

In a recent study, Oki et al. evaluated the efficacy and safety of preoperative chemotherapy with docetaxel plus S-1 for resectable advanced gastric cancer. They used pathological response rate as the primary end point. The response rate to preoperative chemotherapy was 34%. The authors concluded that the combination of docetaxel and S-1 is promising as a preoperative chemotherapy regimen for patients with potentially resectable advanced gastric cancer [17].

In a retrospective analysis by Del Rio et al., nine patients out of 93 with advanced gastric cancer received chemotherapy before surgical resection. The authors' experience showed that the neoadjuvant therapy can reduce staging and increase the R0 resection. They suggested that it should be proposed in young patients with low comorbidity [18].

In a randomized double-blinded controlled trial performed at the Firoozgar hospital in Tehran, Basi et al. compared efficacy of preoperative neoadjuvant chemotherapy and surgery versus surgery alone in patients with resectable gastroesophageal cancer. They showed that combination of chemotherapy and surgery compared to surgery alone improved R0 resection status, but mid-term survival rate was similar in the two groups. They concluded that R0 resection status can effectively predict appropriate mid-term survival in undertreated patients [19].

Nagahama et al. evaluated the outcome of preoperative treatment with S-1 and cisplatin for the treatment of advanced gastric cancer. Preoperative treatment with S-1 and cisplatin was not only an effective initial treatment; it potentially accentuated tumor regression [20]. Advanced gastric cancers which respond to initial preoperative chemotherapy, can safely undergo curative resection [21,22]. Some studies indicate promising results for stage IV tumor. Although surgical resection may compromise to R1 in these cases, survival benefits in 2-year follow-up have been evident [23].

A number of other trials have also indicated the effectiveness of neoadjuvant chemotherapy in the management of locally-advanced gastric cancer. Kosaka et al. showed the effectiveness of docetaxel and S-1 in locally-advanced cases in a recent clinical trial [24]. Isobe et al. [25], Park et al. [26], Chen et al. [27], Zhang et al. [28], Molina et al. [29] and Tsuburaya et al. [30] also reported similar results indicating effectiveness of neoadjuvant chemotherapy in advanced gastric adenocarcinoma.

Promising efficacies of neoadjuvant chemotherapy in gastric cancer has been demonstrated in several clinical trials with the safe use of radical curative surgery followed by lymphadenectomy. However, the choice between D1 or D2 gastrectomy depends on the institutional policies. D2 surgery is performed by experienced surgeons and is usually conducted in Asian studies mainly from Japan [1,20,23,30,31]. Because neoadjuvant chemotherapy is used

Table 4
TNM staging of operable study patients in case and control group based on International Union against Cancer (IUAC) and American Joint Committee on Cancer (AJCC).

TNM	Case group ^a	Control ^a group	Total ^a	p-value ^a
T1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.596
T2	3 (15.8%)	7 (22.6%)	10 (20.0%)	
T3	16 (84.2%)	23 (74.2%)	39 (78.0%)	
T4	0 (0.0%)	1 (3.2%)	1 (2.0%)	
N0	5 (26.3%)	3 (9.7%)	8 (16.0%)	0.376
N1	10 (52.6%)	21 (67.7%)	31 (62.0%)	
N2	4 (21.1%)	6 (19.4%)	10 (20.0%)	
N3	0 (0.0%)	1 (3.2%)	1 (2%)	
Stage IB	1 (5.3%)	0 (0.0%)	1 (2.0%)	0.568
Stage II	5 (26.3%)	8 (25.8%)	13 (26.0%)	
Stage IIIA	10 (52.6%)	17 (54.8%)	27 (54.0%)	
Stage IIIB	3 (15.8%)	4 (12.9%)	7 (14.0%)	
Stage IV	0 (0.0%)	2 (6.5%)	2 (4.0%)	
Total	19 (38.0%)	31 (62.0%)	50 (100%)	–

TNM – Tumor, Node, Metastasis.

^a Presented by frequency (%).

mostly for advanced gastric cancers, it has been proposed that D2 resection may provide some survival benefits [31]. Postoperative chemotherapy is administered for almost all patients with gastric cancers stage II or higher. However, postoperative chemoradiation, which is a standard treatment in North America, is only regarded as a treatment option for patients after inadequate surgery (i.e. <D2 dissection) in many European countries [32]. According to Asian strategies, surgery is still considered to be the mainstay for the treatment of localized gastric cancer with negative margins (R0-resection) and an adequate lymph-node-dissection (D2-lymphadenectomy). The extent of surgical resection is a more favorable strategy than postoperative adjunct modalities [33,34].

It should be declared that chemotherapy as an adjuvant therapy may be administered postoperatively for all patients with gastric cancers of locally-advanced or advanced stages regardless of curative resection [1,4]. The efficacy of adjuvant chemotherapy in R0 or R1 gastric resections is not clearly established [5]. However,

the theory behind neoadjuvant chemotherapy is to improve cure. This possibly results from down-staging, primary tumor shrinkage, attenuation of lymph node involvement and differentiating surgical planes by tumor regression and regeneration of fat pads [7,11,32–34]. For this reason, resectability should be considered a potential primary output when neoadjuvant chemotherapy is administered. However, survival analysis should prospectively prove beneficial effects of chemotherapy regimens [31].

Although a number of trials suggest that neoadjuvant chemotherapy affords beneficial effects in locally-advanced cases of gastric adenocarcinoma, the standard treatment of gastric cancer in any stage is surgical resection unless preoperative CT suggests distant metastasis [1,4,7]. Considering conclusive clinical trials and evidence-based studies, preoperative staging and subsequent neoadjuvant therapies are becoming standard approaches for locally-advanced gastric cancers in some centers [7,27,29].

In the present study, we wanted to assess the effect of neoadjuvant chemotherapy with docetaxel, cisplatin and 5-fluorouracil on patients with locally-advanced gastric adenocarcinoma. During a preliminary clinical trial, we aimed to evaluate the effects of this neoadjuvant chemotherapy regimen on (a) local regression of tumor and involved lymph nodes and (b) the rate of resectability of locally-advanced gastric tumors (R0 gastrectomy).

The results of this study revealed that neoadjuvant chemotherapy by combined docetaxel, cisplatin and 5-fluorouracil regimen potentially increases the rate of resectability in patients with locally-advanced gastric adenocarcinoma. In addition, attenuation of primary tumor spread and perigastric lymph node involvement after neoadjuvant chemotherapy was considerable.

All the resections in our series in case and control groups were R0. Thus, it is evident that neoadjuvant chemotherapy has potentially increased the rate of curative resection. Del Rio et al. also reported an increase in the rate of R0 resection in their retrospective analysis of advanced gastric cancer patients who received neoadjuvant chemotherapy [18]. Patel & Kooby assessed 12 studies on neoadjuvant chemotherapy in gastric cancer. According to their analysis, patients who received neoadjuvant chemotherapy had a marginal improvement in overall survival compared to the control group. Three studies out of twelve found 3-year progression-free survival to be higher in the neoadjuvant compared with the control group. A significant down-staging effect was also seen in the neoadjuvant group compared with controls, and complete resection (R0) was found to be higher in the neoadjuvant group [7]. Another study by Lowy et al. reported higher survival rates for patients who received neoadjuvant chemotherapy [35].

In a subgroup analysis by Li et al., it was revealed that patients who had gastric cancer with later stages of disease (pT3–4) benefited more from neoadjuvant therapy than those at earlier stages (pT1–2) when overall survival rate was the end point and monotherapy was inferior to combination therapy regimens [36]. Thus, it is of potential importance that patients with locally-advanced disease are likely to benefit more from neoadjuvant chemotherapy. We have included only patients with locally-advanced disease because we hypothesized that neoadjuvant intervention may diminish tumor extent and increase the possibility of curative resection. Administration of neoadjuvant chemotherapy to patients with advanced disease is safe. The primary indication of trial enrollment for neoadjuvant therapy is T3 and N positive tumors [1]. Even with T4 tumors, the delay of surgical resection for administration of neoadjuvant chemotherapy is acceptable because unresectable gastric tumors may have likely been beyond surgical therapy at presentation [7].

It has been accepted that surgery is the only curative treatment in gastric cancer. It is also accepted that the surgeon should avoid surgical nihilism and do not deprive the patient from surgery [1].

Thus, increasing the rate of resectable cases in gastric locally-advanced adenocarcinoma is of potential clinical interest. However, survival analyses show marginal benefits in favor of neoadjuvant chemotherapy and prospective analysis of locally-advanced gastric cancer patients is strongly warranted. Moreover, the endpoint should be outlined. Three-year disease free survival seems to improve more than overall survival by administration of neoadjuvant chemotherapy [7]. Because surgery is the only curative modality in gastric cancer, we considered resectability as the primary endpoint in this preliminary clinical trial. Future prospective follow-up of patients is of potential interest and will be conducted by principal investigator of this study in the following years.

Preoperative staging is necessary for precise decision making especially when preoperative chemotherapy is planned. Endoscopic Ultrasound (EUS) is the modality of choice for preoperative radiological staging. EUS can determine tumor size (T) and assess perigastric lymph node involvement (N) [4]. Preoperative abdominal CT scan is done for all gastric cancer patients [1,4,5]. Preoperative CT has been recently used successfully for detection of perigastric lymph node involvement. In addition, control CT scans after courses of neoadjuvant chemotherapy may illustrate primary tumor shrinkage and perigastric attenuation of positive lymph nodes [6,14,16]. In the present study, we used preoperative CT to detect perigastric involvement. Control CTs had promising results in illustrating tumor regression by neoadjuvant chemotherapy.

Adjuvant chemotherapy is administered for gastric cancer patients with stage II or higher [1]. The therapeutic benefits of this strategy is not understood completely yet [6]. However, a number of studies suggest that adjuvant chemotherapy should be administered to patients with positive lymph nodes on histopathological analysis, i.e., pN positive tumors. In addition, the extent of lymphadenectomy is another issue. Some experienced surgeons conduct D2 gastrectomy. It seems that adjuvant chemotherapy may not be necessary in patients who undergo D2 resection [7]. Adjuvant therapy is essential in patients who undergo R1 or R2 resection or in inoperable cases [5]. In our study, we did gastrectomy in 50 patients in case and control groups. Forty-four patients (88%) underwent D1 gastrectomy while six patients (12%) underwent D2 gastrectomy.

In the mentioned study from Iran, Basi et al. studied neoadjuvant chemotherapy with docetaxel, cisplatin and 5-fluorouracil in patients with resectable gastric cancer. According to their results, neoadjuvant chemotherapy could increase R0 resection. They also reported significant down-staging in T and N states after preoperative chemotherapy [19]. We studied effectiveness of neoadjuvant chemotherapy by the same regimen on locally-advanced gastric cancers. Advanced gastric adenocarcinomas are inoperable in some cases and patients undergo unnecessary laparotomy [5,6]. It is not possible to determine the resectability precisely to avoid surgical exploration. However, by considering this possibility, curative treatment in probable inoperable gastric tumors may be provided by preoperative neoadjuvant modalities. Thus, we assessed the effects of neoadjuvant chemotherapy on resectability of gastric locally-advanced tumors while Basi et al. [19] aimed to increase R0 resection to improve survival. The distinction between resectability during laparotomy and R0 resection should be considered because different patient subgroups are treated in each category.

In another study, Brenner et al. administered neoadjuvant cisplatin–fluorouracil followed by postoperative intraperitoneal floxuridine–leucovorin to patients with locally advanced gastric cancer. They stated that these regimens were safely delivered to patients undergoing radical gastrectomy and D2 lymphadenectomy. According to their results, the R0 resection and the survival rates were encouraging [37]. Basi et al. also indicated an increase in R0 resection by neoadjuvant chemotherapy [19] but Brenner and

colleagues have also utilized intraperitoneal chemotherapy [37]. We studied the outcome of patients with locally-advanced disease similar to the study of Brenner and colleagues. They treated thirty-eight patients and both preoperative and postoperative chemotherapy were administered and all the patients had resectable tumors. However, three patients (13.6%) who delivered preoperative chemotherapy had unresectable tumors in our study. It may be due to unavailability of EUS to exclude stage IV tumors by T4 size. Advanced gastric tumors with extensive adjacent invasion may constitute a different subgroup of patients that should undergo appropriate preoperative strategies different from locally-advanced cases.

This study suggests that neoadjuvant chemotherapy can increase resectability rate in patients with locally-advanced adenocarcinoma. To distinguish locally-advanced gastric tumors, CT scan may offer useful diagnostic benefits. Preoperative CT may detect perigastric lymph node involvement and mural involvement. Neoadjuvant chemotherapy can attenuate primary tumor size and lymph node involvement in patients with locally-advanced gastric adenocarcinoma. It can be detected radiologically by follow-up CT scans. However, benefits of neoadjuvant chemotherapy are of potential clinical interest and precise determination of locally-advanced cases with exact preoperative techniques such as EUS is warranted.

The present study illustrates that neoadjuvant chemotherapy increases curability of locally-advanced gastric cancer patients because surgical resection is the only curative treatment for gastric cancer. However, it should be addressed that beneficial effects of neoadjuvant chemotherapy in this setting should be confirmed by prospective trials to evaluate disease free and overall survival rates of patients treated by neoadjuvant chemotherapy and surgery versus surgery alone. In addition, preoperative staging should be done precisely by the use of EUS to allocate subgroups of locally-advanced gastric adenocarcinomas to chemotherapy regimens of different combinations and durations. Then, prospective follow-up of subgroups may determine patients who get more survival benefits from neoadjuvant chemotherapy. Moreover, precise preoperative staging may distinguish patients who benefit more from early surgical resection rather than neoadjuvant chemotherapy.

Ethical approval

Iranian Registry of Clinical Trials.
IRCT2014 053113736N1.

Funding

Tabriz University of Medical Sciences, Tabriz, Iran.

Author contribution

SH, AP, MHS and SZ contributed to the study design. SH, SZ, RJR and AE did data collection. SH and SZ drafted the manuscript. SZ did the statistical analysis and designed the tables. All authors approved the final version of the manuscript.

Conflicts of interests

The authors declare that they have do not have any conflicts of interest.

Acknowledgments

The authors acknowledge research deputy of Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran for their

kind support. The authors also thank Prof. Mohammad Hossein Zarrintan from the Department of Pharmaceutics, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran for reading and revising this article.

References

- [1] D.T. Dempsey, Stomach, in: F.C. Brunicaardi, D.K. Andersen, T.R. Billiar, D.L. Dunn, J.G. Hunter, J.B. Matthews, et al. (Eds.), *Schwartz's Principles of Surgery*, McGraw-Hill, New York, 2010, pp. 931–935.
- [2] G. Roshandel, A. Sadjadi, M. Aarabi, A. Keshtkar, S.M. Sedaghat, S.M. Nouraei, et al., Cancer incidence in Golestan Province: report of an ongoing population-based cancer registry in Iran between 2004 and 2008, *Arch. Iran. Med.* 15 (4) (2012) 196–200.
- [3] M.H. Somi, S. Farhang, S.K. Mirinezhad, S. Naghashi, M. Seif-Farshad, M. Golzari, Cancer in East Azerbaijan, Iran: results of a population-based cancer registry, *Asian Pac. J. Cancer Prev.* 9 (2) (2008) 327–330.
- [4] D.M. Mahvi, S.B. Krantz, Stomach, in: C.M. Townsend, R.D. Beauchamp, M. Evers, K.L. Mattox (Eds.), *Sabiston Textbook of Surgery*, Elsevier Saunders, New York, 2012, pp. 1198–1217.
- [5] J.T. Langell, S.J. Mulvihill, Gastric adenocarcinoma and other gastric neoplasms (except gastrointestinal stromal tumors), in: M.J. Zinner, Ashley (Eds.), *Maingot's Abdominal Operations*, McGraw-Hill, China, 2013, pp. 463–488.
- [6] D.W. McFadden, J.G. Schneider, Gastric adenocarcinoma, in: J.L. Cameron, A.M. Cameron (Eds.), *Current Surgical Therapy*, Elsevier Saunders, Philadelphia, 2011, pp. 80–84.
- [7] S.H. Patel, D.A. Kooby, Gastric adenocarcinoma surgery and adjuvant therapy, *Surg. Clin. N. Am.* 91 (5) (2011) 1039–1077.
- [8] M.F. Brennan, Total gastrectomy for carcinoma, in: J.E. Fischer, D.B. Jones, F.B. Pomposelli, G.R. Upchurch, V.S. Klimberg, S.D. Schwaizberg, et al. (Eds.), *Fischer's Mastery of Surgery*, Wolters Kluwer; Lippincott Williams & Wilkins, Philadelphia, 2012, pp. 1058–1066.
- [9] J.T. Mullen, Subtotal gastrectomy for gastric cancer, in: J.E. Fischer, D.B. Jones, F.B. Pomposelli, G.R. Upchurch, V.S. Klimberg, S.D. Schwaizberg, et al. (Eds.), *Fischer's Mastery of Surgery*, Wolters Kluwer; Lippincott Williams & Wilkins, Philadelphia, 2012, pp. 1067–1079.
- [10] I. Proserpio, S. Rausei, S. Barzaghi, F. Frattini, F. Galli, D. Iovino, et al., Multimodal treatment of gastric cancer, *World J. Gastrointest. Surg.* 6 (4) (2014) 27 55–58.
- [11] M.L. Hansen, E. Fallentin, C. Lauridsen, I. Law, B. Federspiel, L. Bæksgaard, et al., Computed tomography (CT) perfusion as an early predictive marker for treatment response to neoadjuvant chemotherapy in gastroesophageal junction cancer and gastric cancer – a prospective study, *PLoS One* 9 (5) (2014) e97605.
- [12] H.H. Hartgrink, C.J. van de Velde, H. Putter, I. Songun, M.E. Tesselar, E.K. Kranenbarg, et al., Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial, *Eur. J. Surg. Oncol.* 30 (6) (2004) 643–649.
- [13] A.M. Mongan, R. Kalachand, S. King, N.J. O'Farrell, D. Power, N. Ravi, et al., Outcomes in gastric and junctional cancer using neoadjuvant and adjuvant chemotherapy (epirubicin, oxaliplatin, and capecitabine) and radical surgery, *Ir. J. Med. Sci.* (2014), <http://dx.doi.org/10.1007/s11845-014-1135-y>.
- [14] M.G. Guo, Q. Zheng, J. Zhong Di, Z. Yang, Histological complete response to a combined docetaxel/cisplatin/fluorouracil neoadjuvant chemotherapy for T4 stage gastric adenocarcinoma, *World J. Surg. Oncol.* 12 (1) (2014) 150.
- [15] S. Jack, M.A. West, D. Raw, S. Marwood, G. Ambler, T.M. Cope, et al., The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery, *Eur. J. Surg. Oncol.* (2014), <http://dx.doi.org/10.1016/j.ejso.2014.03.010>. S0748-7983(14) 00364-373.
- [16] S. Blank, F. Lordick, F. Bader, M. Burian, M. Dobritz, L. Grenacher, et al., Post-therapeutic response evaluation by a combination of endoscopy and CT scan in esophagogastric adenocarcinoma after chemotherapy: better than its reputation, *Gastric Cancer* (2014), <http://dx.doi.org/10.1007/s10120-014-0367-x>.
- [17] E. Oki, Y. Emi, T. Kusumoto, Y. Sakaguchi, M. Yamamoto, N. Sadanaga, et al., Phase II study of docetaxel and S-1 (DS) as neoadjuvant chemotherapy for clinical stage III resectable gastric cancer, *Ann. Surg. Oncol.* 21 (7) (2014) 2340–2346.
- [18] P. Del Rio, M. Rocchi, P. Dell'Abate, F. Pucci, C. Mazzetti, M. Sianesi, Advanced stage gastric cancer and neoadjuvant chemotherapy: our experience in surgical resectability, *Ann. Ital. Chir.* 84 (6) (2013) 623–629.
- [19] A. Basi, S. Sohrabkhani, F. Zamani, M. Baghai-Wadji, N. Rabiei, S.M. Razavi, et al., Comparing efficacy of preoperative neo-adjuvant chemotherapy and surgery versus surgery alone in patients with resectable gastroesophageal cancer, *Int. J. Hematol. Oncol. Stem Cell Res.* 7 (4) (2013) 24–28.
- [20] T. Nagahama, M. Ando, R. Seki, K. Fujiya, H. Amagasa, J. Takasaki, et al., Pre-operative chemotherapy for advanced gastric cancer, *Gan To Kagaku Ryoho* 40 (12) (2013) 2217–2219.
- [21] T. Aoyama, T. Hayashi, H. Fujikawa, T. Ogata, H. Cho, H. Wada, et al., Safety and feasibility of gastrectomy after neoadjuvant chemotherapy for gastric cancer, *Gan To Kagaku Ryoho* 40 (12) (2013) 1621–1622.
- [22] Q. Zhao, Y. Li, B.B. Tan, Y. Tian, Z.K. Jiao, X.F. Zhao, et al., Effects of XELOX regimen as neoadjuvant chemotherapy on radical resection rate and

- prognosis in patients with advanced gastric cancer, *Zhonghua Zhong Liu Za Zhi* 35 (10) (2013) 773–777.
- [23] K. Miyamoto, T. Koyama, T. Ohishi, O. Takahashi, H. Sakahira, Y. Ueda, et al., Strategy for the treatment of stage IV gastric cancer with preoperative chemotherapy, *Gan To Kagaku Ryoho* 40 (12) (2013) 1618–1620.
- [24] T. Kosaka, H. Akiyama, H. Makino, R. Takagawa, J. Kimura, H. Ono, et al., Preoperative S-1 and docetaxel combination chemotherapy in patients with locally advanced gastric cancer, *Cancer Chemother. Pharmacol.* 73 (2) (2014) 281–285.
- [25] T. Isobe, K. Hashimoto, J. Kizaki, M. Miyagi, K. Aoyagi, K. Koufuji, et al., Neoadjuvant chemotherapy with combined S-1 plus weekly low-dose cisplatin followed by surgical resection for advanced gastric cancer, *Gan To Kagaku Ryoho* 40 (10) (2013) 1331–1335.
- [26] I. Park, M.H. Ryu, Y.H. Choi, H.J. Kang, J.H. Yook, Y.S. Park, et al., A phase II study of neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) chemotherapy followed by surgery and adjuvant S-1 chemotherapy in potentially resectable gastric or gastroesophageal junction adenocarcinoma, *Cancer Chemother. Pharmacol.* 72 (4) (2013) 815–823.
- [27] S.S. Chen, X.C. Yang, F. Chi, W.Z. Yu, Z.B. Wang, F.L. Ning, et al., A phase II study of preoperative chemotherapy with modified FOLFOX6 followed by surgery and postoperative chemoradiation in patients with localized gastric adenocarcinoma, *Oncol. Res.* 20 (7) (2013) 327–332.
- [28] C.D. Zhang, Y.J. Zeng, H.W. Li, Z.M. Zhao, J.K. Zhang, D.Q. Dai, Neoadjuvant chemotherapy for nonmetastatic esophago-gastric adenocarcinomas: a systematic review and meta-analysis, *Cancer Investig.* 31 (6) (2013) 421–431.
- [29] R. Molina, A. Lamarca, B. Martínez-Amores, A. Gutiérrez, A. Blázquez, A. López, et al., Perioperative chemotherapy for resectable gastroesophageal cancer: a single-center experience, *Eur. J. Surg. Oncol.* 39 (8) (2013) 814–822.
- [30] A. Tsuburaya, N. Nagata, H. Cho, N. Hirabayashi, M. Kobayashi, H. Kojima, et al., Phase II trial of paclitaxel and cisplatin as neoadjuvant chemotherapy for locally advanced gastric cancer, *Cancer Chemother. Pharmacol.* 71 (5) (2013) 1309–1314.
- [31] K. Fujitani, Overview of adjuvant and neoadjuvant therapy for resectable gastric cancer in the East, *Dig. Surg.* 30 (2) (2013) 119–129.
- [32] H. Wilke, F. Lordick, H.J. Meyer, M. Stahl, (Neo)-adjuvant chemo(-radio) therapy for adenocarcinomas of the gastroesophageal junction and the stomach in the West, *Dig. Surg.* 30 (2) (2013) 112–118.
- [33] C. Schuhmacher, D. Reim, A. Novotny, Neoadjuvant treatment for gastric cancer, *J. Gastric Cancer* 13 (2) (2013) 73–78.
- [34] T. Yoshikawa, Y. Rino, N. Yukawa, T. Oshima, A. Tsuburaya, M. Masuda, Neoadjuvant chemotherapy for gastric cancer in Japan: a standing position by comparing with adjuvant chemotherapy, *Surg. Today* 44 (1) (2014) 11–21.
- [35] A.M. Lowy, P.F. Mansfield, S.D. Leach, R. Pazdur, P. Dumas, J.A. Ajani, Response to neoadjuvant chemotherapy best predicts survival after curative resection of gastric cancer, *Ann. Surg.* 229 (3) (1999) 303–308.
- [36] W. Li, J. Qin, Y.H. Sun, T.S. Liu, Neoadjuvant chemotherapy for advanced gastric cancer: a meta-analysis, *World J. Gastroenterol.* 16 (44) (2010) 5621–5628.
- [37] B. Brenner, M.A. Shah, M.S. Karpeh, M. Gonen, M.F. Brennan, D.G. Coit, et al., A phase II trial of neoadjuvant cisplatin-fluorouracil followed by postoperative intraperitoneal floxuridine-leucovorin in patients with locally advanced gastric cancer, *Ann. Oncol.* 17 (9) (2006) 1404–1411.