

## Neoadjuvant or adjuvant therapy for gastric cancer

Laurent Quéro, Sophie Guillerm, Christophe Hennequin

Laurent Quéro, Sophie Guillerm, Christophe Hennequin, Department of Radiation Oncology, Saint Louis Hospital, 75010 Paris, France

**Author contributions:** Quéro L designed, researched and analyzed the literature, and helped write the paper; Guillerm S and Hennequin C analyzed the literature, and helped write the paper.

**Conflict-of-interest statement:** The authors have no conflict of interest related to the manuscript.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Laurent Quéro, MD, PhD, Department of Radiation Oncology, Saint Louis Hospital, 1 Avenue Claude Vellefaux, 75010 Paris, France. [laurent.querro@sls.aphp.fr](mailto:laurent.querro@sls.aphp.fr)  
**Telephone:** +33-142-499034  
**Fax:** +33-142-494081

Received: March 10, 2015

Peer-review started: March 13, 2015

First decision: April 13, 2015

Revised: May 8, 2015

Accepted: July 11, 2015

Article in press: July 14, 2015

Published online: August 15, 2015

### Abstract

Currently, there is no international consensus on the best treatment regimen for patients with advanced resectable gastric carcinoma. In the United States, where a limited lymph-node dissection is frequently performed, adjuvant chemoradiotherapy after surgery

is the standard treatment. In Europe, intensified perioperative chemotherapy is commonly administered. In Japan and South Korea, postoperative S-1-based adjuvant chemotherapy after surgery with D2 lymph-node dissection is the standard treatment. Several ongoing trials are currently evaluating the optimal sequence of chemotherapy, radiotherapy, and surgery, as well as the place of targeted therapeutic agents in the treatment of advanced gastric carcinoma.

**Key words:** Radiotherapy; Chemotherapy; Review; Gastric cancer

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Gastric cancer (GC) treatment is controversy, particularly between Asia and Western countries. In this paper, we have performed a systematic and up-to-date review of resectable GC treatment strategies and discussed different treatment options. We have also described ongoing clinical randomized phase 3 trials and future directions in GC treatment.

Quéro L, Guillerm S, Hennequin C. Neoadjuvant or adjuvant therapy for gastric cancer. *World J Gastrointest Oncol* 2015; 7(8): 102-110 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v7/i8/102.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v7.i8.102>

### INTRODUCTION

Gastric cancer (GC) is one of the most common cancers worldwide, with a total of 989600 new cases diagnosed and 738000 deaths estimated for 2008, which accounted for 8% of total cancer cases and 10% of total deaths from cancer. Over 70% of new cases and deaths occur in developing countries, with the highest incidence rates in Eastern Asia, Eastern Europe, and South America<sup>[1]</sup>. In the United States, the incidence of GC is

**Table 1 Neoadjuvant chemotherapy in gastric carcinoma: Randomized meta-analysis**

Studies	Country	Years	Randomization	arms	Surgery	Protocol	Patients (n)	Overall survival	P value	Disease free survival	P value				
Xiong <i>et al</i> <sup>[16]</sup> meta-analysis	-	2014	Neoadjuvant chemotherapy			-	-	753	46.6% at 53 mo <sup>1</sup>	0.01	41.1% at 3 yr <sup>1</sup>	< 0.0001			
			Chemotherapy	-	-								813	43.7% at 53 mo	27.5% at 3 yr
			Surgery alone	-	-										

<sup>1</sup>Statistically significant result.

approximately 22000 per year and the mortality rate is nearly 11000 per year<sup>[2]</sup>. The worldwide incidence of GC has declined rapidly over the last three decades in Western countries.

Patients with resectable gastric carcinoma have a poor prognosis with a 5-year overall survival of approximately 20%-30% worldwide, but, in Japan, patients with gastric carcinoma have a better prognosis with a 70% 5-year overall survival rate. This difference is probably because of screening programs for GC in Japan, where the higher incidence of GC results in detection of disease at an earlier stage in approximately 50% of cases. In contrast, gastric carcinoma is usually diagnosed at a later stage in Western countries where there is no such screening program<sup>[3]</sup>. Moreover, patients with GC in Western countries have more frequently lesions in the upper third of the stomach, whereas patients from Asia have more frequently lesions in the middle or lower third of the stomach; a lesion in the upper third of the stomach has a worse prognosis than a lesion in the lower third<sup>[4,5]</sup>.

Surgical resection remains the cornerstone treatment for non-metastatic GC. In Asia, particularly in Japan and South Korea, gastrectomy with a D2 lymph-node dissection is the standard surgical treatment. In Europe, two randomized trials, performed in the United Kingdom and the Netherlands, have reported little initial benefit from gastrectomy with a D2 dissection compared to gastrectomy with a D1 dissection<sup>[6,7]</sup>. However, after a 15-year follow-up, the benefit of a gastrectomy with a D2 dissection was confirmed in the Dutch trial in terms of both locoregional recurrence and GC-related death<sup>[8]</sup>. Gastrectomy with a D2 dissection is now recommended by the National Comprehensive Cancer Network in the United States<sup>[9]</sup> and the European Society for Medical Oncology in Europe<sup>[10]</sup>.

Resected GC recurs in multiple patterns: locoregional, peritoneal, and distant sites are common modes of recurrence<sup>[11,12]</sup>.

To improve outcomes in patients with locally advanced GC, several strategies in association with surgical resection have been evaluated, such as neoadjuvant chemotherapy, perioperative chemotherapy, adjuvant chemotherapy, and adjuvant chemoradiotherapy.

## NEOADJUVANT CHEMOTHERAPY

Several randomized trials have evaluated neoadjuvant chemotherapy before surgery, but have reported conflic-

ting results. To date, four meta-analyses have been published on neoadjuvant chemotherapy for GC<sup>[13-16]</sup>. The first two meta-analyses were underpowered with only four and five randomized trials analyzed, respectively<sup>[13,15]</sup>. The third meta-analysis was biased because it included both neoadjuvant chemotherapy and chemoradiotherapy trials<sup>[14]</sup> (Table 1).

In 2014, Xiong *et al*<sup>[16]</sup> published a meta-analysis based on results extracted from published trial reports on 1820 patients from 12 different studies. Among these 12 studies, six were from Asia and six were from Western countries. The median follow-up period was 53 mo. The meta-analysis showed that patients treated with neoadjuvant chemotherapy plus surgery had only a marginally improved survival benefit over patients treated with surgery alone, with an odds ratio of 1.32 ( $P = 0.001$ ). However, the 3-year progression-free survival rate, the tumor down-staging rate, and the R0-resection rate were better in patients treated with neoadjuvant chemotherapy plus surgery, with odds ratios of 1.85 ( $P < 0.0001$ ), 1.71 ( $P = 0.0006$ ), and 1.38 ( $P = 0.01$ ), respectively. Subgroup analyses showed that patients treated with polychemotherapy or *via* an IV route had better survival, with odds ratios of 1.14 and 1.42, respectively. Subgroup analyses also showed that 5-year overall survival rates of patients treated with neoadjuvant chemotherapy plus surgery were statistically improved in studies conducted in Western countries, with an odds ratio of 1.39 ( $P < 0.01$ ), whereas similar trials in Asian countries found no significant differences ( $P = 0.32$ ).

## PERIOPERATIVE CHEMOTHERAPY

In locally advanced disease, preoperative chemotherapy may result in tumor downstaging and eradicate micrometastases. Two randomized trials in Western countries have evaluated perioperative chemotherapy in advanced gastroesophageal junction or GC. The United Kingdom Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) randomized trial compared surgery with or without perioperative ECF chemotherapy (epirubicin, cisplatin, infused fluorouracil). A total of 503 patients were enrolled in this trial; most patients had GC (74%), and approximately 50% of patients had a (y)pT3-T4 and 70% had a (y)pN+ tumor<sup>[17]</sup>. In this study, about 25% and 50% of patients were treated for GC, and received D1 or D2 surgery, respectively. Of the 86% of patients assigned

**Table 2 Perioperative chemotherapy in gastric carcinoma: Randomized trials**

Studies	Country	Years	Randomization arms	Surgery	Protocol	Patients (n)	Overall survival	P value	Disease free survival	P value
MRC MAGIC trial <sup>[17]</sup>	United Kingdom	2006	Chemotherapy and surgery	42.5% D2 surgery	ECF chemotherapy	250	36.3% at 5 yr <sup>1</sup>	0.009	34.8% at 5 yr <sup>1</sup>	< 0.001
			Surgery alone			253	23% at 5 yr		24.9% at 5 yr	
ACCORD07/FFCD 9703 trial <sup>[18]</sup>	France	2011	Chemotherapy and surgery	D2 recommended	5FU-CDDP chemotherapy	113	38% at 5 yr <sup>1</sup>	0.02	34% at 5 yr <sup>1</sup>	0.003
			Surgery alone			111	24% at 5 yr		19% at 5 yr	

<sup>1</sup>Statistically significant result. ECF: Epirubicin, cisplatin, and 5-fluorouracil; 5FU: 5-fluorouracil; RT: Radiotherapy; CDDP: Cisplatin.

to perioperative-chemotherapy and who received preoperative chemotherapy, only 55% also received postoperative chemotherapy. In this study, perioperative chemotherapy improved overall survival, and local + distant control, when compared with surgery alone. Five-year overall survival rates were 36% for patients treated with perioperative-chemotherapy vs 23% for those treated with surgery alone ( $P = 0.009$ ). In the perioperative-chemotherapy group, 14% had local recurrence vs 21% in the surgery group. Metastatic progression was also less frequent in the perioperative-chemotherapy group compared to the surgery-only group, at 24% and 37%, respectively (Table 2).

In the French ACCORD07/FFCD 9703 multicenter phase-III trial<sup>[18]</sup>, 224 patients with resectable adenocarcinoma of the lower esophagus, the gastroesophageal junction, or the stomach were randomly assigned to receive surgery with or without infused fluorouracil-cisplatin perioperative chemotherapy. In this study, only approximately 25% of the patients had gastric carcinoma; most patients had lower esophageal or gastroesophageal-junction carcinoma (75%). Patients treated with surgery alone had a more advanced tumor than patients treated with surgery plus perioperative chemotherapy. Sixty-eight percent and 80% of patients treated with surgery alone had a (y)pT3-T4 or a (y)pN+ tumor, respectively, compared with 58% and 67% of patients treated with perioperative chemotherapy. Moreover, fewer patients had a R0 resection in the surgery arm compared to the perioperative-chemotherapy arm (74% vs 87%,  $P = 0.004$ ). Of the total, 87% of patients received preoperative chemotherapy as planned but only approximately 50% of patients were able to receive postoperative chemotherapy. Patients treated with surgery and perioperative chemotherapy had significantly better 5-year overall survival and disease-free survival rates than patients treated with surgery alone (38% vs 24%,  $P = 0.02$ ; 34% vs 19%,  $P = 0.003$ ), respectively. In both groups, of the approximately 80% of patients that had a relapse, this was a distant relapse. In multivariable analyses, perioperative chemotherapy was only significantly effective in patients with cancer within the esophagogastric junction, but not for those with GC; however, the gastric subgroup was too small (*i.e.*, 25% of the population) to distinguish between no effect or a small effect.

## ADJUVANT CHEMOTHERAPY

Several studies have evaluated adjuvant chemotherapy in GC, but the results are conflicting. Over the past two decades, six meta-analyses have been published regarding the role of adjuvant chemotherapy in GC<sup>[19-24]</sup>. Five of these six meta-analyses observed improved survival after adjuvant chemotherapy compared to surgery alone<sup>[20-24]</sup> (Table 3).

In 2010, the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration group published the largest meta-analysis to date, based on individual data from 3838 patients in 17 different studies. Among these studies, four were conducted in Asia and 13 in Western countries. The median follow-up period was approximately 7 years. This meta-analysis reported a small but significant absolute 5.8% benefit to 5-year overall survival (49.6% vs 55.3%,  $P < 0.001$ ) and a 7.4% benefit to 10-year overall survival (37.5% vs 44.9%). Adjuvant chemotherapy also improved disease-free survival compared with surgery alone, with an absolute 5.3% benefit at 5 years (48.7% vs 54.0%,  $P < 0.001$ )<sup>[24]</sup>.

The greatest benefit from adjuvant chemotherapy occurred in the Asian studies. Indeed, the Japanese Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer trial compared surgery with a D2 dissection and either with or without S-1 oral adjuvant chemotherapy in patients with stage-II or -III gastric carcinoma. This trial enrolled 1059 patients between October 2001 and December 2004<sup>[25]</sup>. Patients treated with surgery plus adjuvant S-1 chemotherapy had significantly better 5-year overall and disease-free survival rates than those treated with surgery alone (71.7% vs 61.1% and 65.4% vs 53.1%, respectively). Peritoneum and hematogenous metastases represented approximately 80% of the relapses. All tumor subgroups benefited from adjuvant chemotherapy. However, poor outcomes were observed in patients with stage-III B gastric carcinoma, with a 5-year overall-survival rate of 50.2% in the S-1 group and 44.1% in the surgery-alone group<sup>[26]</sup>. This observation suggests the need for therapeutic improvement in advanced gastric carcinoma. Because of these results, adjuvant chemotherapy without radiation for GC has now become the standard-of-care in Japan.

The Asian CLASSIC trial compared surgery with a

**Table 3 Adjuvant chemotherapy in gastric carcinoma: Randomized trials/meta-analysis**

Studies	Country	Years	Randomization arms	Surgery	Protocol	Patients (n)	Overall survival	P value	Disease free survival	P value
ACTS-GC trial <sup>[25,26]</sup>	Japan	2007	Chemotherapy and surgery	D2 surgery	Oral S1 chemotherapy	529	71.7% at 5 yr <sup>1</sup>	-	65.4% at 5 yr <sup>1</sup>	-
			Surgery alone	-	-	530	61.1% at 5 yr	-	53.1% at 5 yr	-
GASTRIC metaanalysis <sup>[24]</sup>	-	2010	Chemotherapy	-	-	1924	55.3% at 5 yr <sup>1</sup>	< 0.001	54% at 5 yr <sup>1</sup>	< 0.001
			Surgery alone	-	-	1857	49.6% at 5 yr	-	48.7% at 5 yr	-
CLASSIC trial <sup>[27]</sup>	South Korea	2012	Chemotherapy and surgery	D2 surgery	XELOX chemotherapy	520	83% at 3 yr <sup>1</sup>	0.049	74% at 3 yr <sup>1</sup>	< 0.0001
			Surgery alone	-	-	515	78% at 3 yr	-	59% at 3 yr	-

<sup>1</sup>Statistically significant result. XELOX: Xeloda and oxaliplatin.

D2 dissection either with or without adjuvant combined capecitabine/oxaliplatin (XELOX) chemotherapy in 1035 patients with stage II–III B gastric carcinoma<sup>[27]</sup>. After a median follow-up of 34 mo, 3-year disease-free and overall-survival rates were significantly better in the XELOX plus surgery group than with surgery alone (74% vs 59%,  $P < 0.0001$ ; 83% vs 78%,  $P = 0.0493$ , respectively). The most common sites of disease progression were the peritoneum and distant sites (*i.e.*, > 80%).

### ADJUVANT CHEMORADIOTHERAPY

In the United States, the SWOG 9008/ Intergroup 0116 trial reported a benefit after postoperative chemoradiotherapy. In this trial, 556 patients with locally advanced gastric adenocarcinoma or cancer within the gastroesophageal junction were randomized to receive surgery alone or surgery plus postoperative radiotherapy associated with 5-fluorouracil/leucovorin chemotherapy<sup>[28]</sup>. Three-year overall survival was 50% in the chemoradiotherapy group vs 41% in the surgery-only group ( $P = 0.005$ ). The 3-year relapse-free survival rate was 48% in the chemoradiotherapy group vs 31% in the surgery-only group ( $P < 0.001$ ). This benefit from postoperative chemoradiotherapy was confirmed in an update, published by Smalley *et al.*<sup>[29]</sup> in 2012, with 10-year overall survival of 25.9% vs 17.3% for surgery only ( $P = 0.0046$ ) and a 10-year relapse-free survival rate of 21.6% vs 14.4% ( $P < 0.001$ ).

Local and regional relapses were significantly less frequent in the chemoradiotherapy group, at 2% and 22% vs 5% and 31% in the surgery-alone group, respectively ( $P = 0.012$ ). There were no differences in terms of distant relapses between the two groups (16% and 17%, respectively) (Table 4).

However, several criticisms have been raised regarding this study. Most patients had limited lymph-node dissection and only 10% of patients received a formal D2 dissection (36% had a D1 and 54% had a D0 dissection) and many patients experienced high rates of acute toxicity (54% and 33% of patients had  $\geq$  grade 3 hematological and gastrointestinal toxicities, respectively). Only 64% of patients completed the protocol treatment in the chemoradiotherapy group:

17% of patients interrupted treatment because of its toxic side-effects and 8% declined further treatment. These high rates of toxicity may be explained by the use of the older 2D radiotherapy technique associated with the 5-fluorouracil Mayo Clinic chemotherapy regimen.

The United States CALGB80101 phase-III trial compared 546 patients with resected gastric or gastroesophageal-junction adenocarcinoma who had adjuvant chemoradiotherapy with the 5-fluorouracil Mayo Clinic chemotherapy regimen (SWOG 9008/Intergroup 0116 protocol) vs adjuvant chemotherapy with ECF (epirubicin, cisplatin, 5-fluorouracil) followed by chemoradiotherapy with fluorouracil<sup>[30]</sup>. Seventy-five percent and 69% of patients completed the planned treatments in the ECF and Mayo 5-fluorouracil arms, respectively. Patients receiving adjuvant ECF chemotherapy had lower rates of grade  $\geq 3$  diarrhea/mucositis (15% vs 7%) and also less grade-4 neutropenia compared to patients receiving the adjuvant fluorouracil Mayo-Clinic chemotherapy regimen (33% vs 19%). However, the 3- and 5-year overall survival rates were not significantly improved with ECF compared to fluorouracil (52% vs 50% and 44% vs 41%, respectively;  $P = 0.8$ ). These results suggest that the intensified chemotherapy in association with adjuvant radiotherapy was better tolerated but was not associated with better outcomes compared to the fluorouracil-based chemoradiotherapy used in the SWOG 9008/Intergroup 0116 protocol. However, a longer follow-up period is needed to confirm these results.

The Korean phase-3 Adjuvant chemoRadiation Therapy In STomach cancer (ARTIST) trial randomized 458 patients with locally advanced gastric carcinoma and who had been initially treated with D2 lymph-node dissection. The trial compared postoperative capecitabine–cisplatin chemotherapy vs capecitabine–cisplatin chemotherapy plus chemoradiotherapy with capecitabine. In this trial, it is important to note that 60% of patients had early stages of gastric carcinoma (IB and II) and, therefore, had a spontaneously better prognosis than patients with locally advanced-stage carcinoma. Treatment was completed as planned in 75.4% of patients in the chemotherapy arm vs 81.7% in the chemoradiotherapy arm.

After a median follow-up of 53.2 mo, there was no difference in 3-year disease-free survival (78.2% in the

**Table 4 Adjuvant chemoradiotherapy in gastric carcinoma: Randomized trials**

Studies	Country	Years	Randomization arms	Surgery	Protocol	Patients (n)	Overall survival	P value	Disease free survival	P value
INT 0116 trial <sup>[28,29]</sup>	United States	2001	Chemoradiotherapy and surgery	10% D2 surgery	5FU Mayo clinic/5FU RT	281	50% at 3 yr <sup>1</sup>	0.005	48% at 3 yr <sup>1</sup>	< 0.001
Chinese multicentre trial <sup>[33]</sup>	China	2012	Chemoradiotherapy and surgery	D2 surgery	5FU RT	186	48.4% at 5 yr	0.122	45.2% at 5 yr <sup>1</sup>	0.029
			Chemotherapy and surgery		5FU chemotherapy	165	41.8% at 5 yr		35.8% at 5 yr	
ARTIST trial <sup>[31]</sup>	South Korea	2012	Chemoradiotherapy and surgery	D2 surgery	Xeloda CDDP/Xeloda RT	230	-	-	74.2% at 3 yr	0.086
			Chemotherapy and surgery		Xeloda CDDP	228	-	78.2% at 3 yr		
CALGB 80101 trial <sup>[30]</sup>	United States	2011	Chemoradiotherapy and surgery	Not available	ECF/5FU RT	266	52% at 3 yr	0.8	47% at 3 yr	0.99
			Chemoradiotherapy and surgery		5FU Mayo/5FU RT	280	50% at 3 yr		46% at 3 yr	

<sup>1</sup>Statistically significant result. 5FU: 5-fluorouracil; RT: Radiotherapy; CDDP: Cisplatin.

chemotherapy arm vs 74.2% in the chemoradiotherapy arm;  $P = 0.0862$ <sup>[31]</sup>. However, in a subgroup analysis of 396 patients with positive pathological lymph nodes, there was statistically better 3-year disease-free survival in patients treated with chemoradiotherapy compared to those treated with chemotherapy (77.5% vs 72.3%,  $P = 0.0365$ ). There were no significant differences between the two arms in terms of locoregional recurrence or distant metastases (8.3% vs 4.8%;  $P = 0.353$  and 24.6% vs 20.4%;  $P = 0.557$ , respectively). Due to the lack of events at the time of analysis, the secondary end point for overall survival was not analyzed.

In a Korean observational study, Kim *et al.*<sup>[32]</sup> compared 544 patients who had received postoperative chemoradiotherapy after a curative D2 dissection with 446 patients who had received surgery without any further treatment. In this study, it is important to note that the proportion of patients with advanced-stage carcinoma was significantly greater in the chemoradiotherapy group than in the surgery-only group (stage IIIA: 34.1% vs 26.0%, and stage IV: 21.9% vs 13.9%).

Twenty-five percent of patients treated with chemoradiotherapy did not complete the planned protocol: the main reasons for this were its toxic side-effects (40%) and the patient's refusal to continue (35%). Thirty percent of patients experienced  $\geq$  grade 3 hematological toxicity and 15% experienced  $\geq$  grade 3 gastrointestinal toxicity. After a median follow-up of 66 mo, the 5-year overall survival and relapse-free survival rates were better in patients treated with chemoradiotherapy compared to those treated with surgery only (57.1% vs 51%;  $P = 0.0198$ , and 54.5% vs 47.9%;  $P = 0.0161$ , respectively). Locoregional recurrence rate was significantly lower in patients treated with chemoradiotherapy compared to those treated with surgery alone (14.9% vs 21.7%,  $P = 0.005$ ). The occurrence of distant metastases did not differ between the treatment groups (37.7%).

A Chinese randomized trial compared postoperative fluorouracil–leucovorin chemotherapy vs intensity modulated radiation therapy plus fluorouracil–leucovorin chemotherapy in 380 patients initially treated with a D2 dissection for locally advanced gastric carcinoma (70% had stage III or IV disease). Five-year overall survival in those that received postoperative radiotherapy was better than for those treated with chemotherapy only, but this difference was not statistically significant (48.4% vs 41.8%,  $P = 0.122$ ). The 5-year recurrence-free survival rate in patients receiving chemoradiotherapy was also better (45.2% vs 35.8%,  $P = 0.029$ )<sup>[33]</sup>. Patients treated with chemoradiotherapy also had less local relapses than those treated with chemotherapy only (15.6% vs 24.2%;  $P = 0.042$ ). However, the occurrence of distant metastases did not differ between the treatment arms (24.2% vs 26.7%,  $P = 0.595$ ). In this study, multivariate analyses showed that pathological lymph node involvement and TNM stage were both independent prognostic factors.

## ONGOING TRIALS AND FUTURE DIRECTIONS

The ongoing CRITICS phase-III study (ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach) (NCT00407186) is comparing patients undergoing preoperative epirubicin, cisplatin, capecitabine (ECC) chemotherapy followed by a D1 dissection, with patients receiving postoperative ECC chemotherapy alone, with patients receiving radiotherapy plus concurrent capecitabine + cisplatin<sup>[34]</sup>. The study plans to accrue 788 patients with gastric carcinoma. The primary endpoint of the study is overall survival; secondary endpoints are disease-free survival, toxicity, health-related quality of life, prediction of response, and recurrence risk, assessed by genomic and expression profiling (Table 5).

**Table 5 Ongoing phase-III randomized trials**

Study	Country	No. registration	Standard arm	Experimental arm	Patients (n)
EORTC 22114 - 40111 TOP GEAR study	Europe	Neoadjuvant chemoradiotherapy NCT01924819	ECC/ECF preoperative CT	ECC/ECF preoperative CT and RTCT preoperative	752
MAGIC-B/ST03 study	United Kingdom	Perioperative chemotherapy NCT00450203	ECC perioperative CT	ECC + bevacizumab perioperative CT	1100
PRODIGY trial	South Korea	NCT01515748	S-1 adjuvant CT	Neoadjuvant DOS CT and S-1 postoperative CT	640
ARTIST II Trial	South Korea	Adjuvant chemotherapy NCT01761461	S-1 adjuvant CT (arm 1)	SOX adjuvant CT (arm 2), S-1 and RT adjuvant (arm 3)	1000
CRITICS Trial	The Netherlands	Adjuvant chemoradiotherapy NCT00407186	ECC perioperative CT	ECC preoperative CT and RTCT postoperative	788

CT: Chemotherapy; RTCT: Radiochemotherapy; ECC: Epirubicin, cisplatin and capecitabine; ECF: Epirubicin, cisplatin, and fluorouracil; DOS: Docetaxel, oxaliplatin, and S-1; SOX: S-1 and oxaliplatin.

The international ongoing phase- II /III European Organisation for Research and Treatment of Cancer (EORTC) 22114–40111 TOP GEAR study (Trial Of Preoperative therapy for Gastric and Esophagogastric junction Adenocarcinoma) (NCT01924819) is currently testing whether adding chemoradiotherapy to ECF or ECC chemotherapy is superior to ECF or ECC chemotherapy alone for the preoperative treatment of resectable esophagogastric-junction or gastric carcinoma when treated with at least a D1 dissection (D2 dissection recommended). The phase- II part of this study is being conducted in 35 medical centers in nine countries: Belgium, France, Germany, Israel, Czech Republic, Slovenia, Spain, Turkey, and Italy, and is planning to accrue 120 patients. The study is designed to demonstrate the efficacy of chemoradiotherapy. The phase-III trial plans to accrue 752 patients and will determine whether chemoradiotherapy is superior to chemotherapy in these patients.

The Korean ARTIST II phase-III trial (Adjuvant chemoRadiation Therapy In STomach cancer II) (NCT01761461) plans to accrue 1000 patients with stage- II or -III gastric or gastroesophageal carcinoma with positive lymph nodes (AJCC 2010), and who are being treated with curative gastrectomy and more than a D2 lymph-node dissection. This three-arm trial is currently comparing surgery + adjuvant S-1 chemotherapy for 1 year, vs surgery + adjuvant SOX (S-1 and oxaliplatin) chemotherapy, vs surgery + adjuvant SOX (S-1 and oxaliplatin) chemotherapy + radiotherapy. The primary endpoint of the study is disease-free survival.

The United Kingdom MRC MAGIC-B/ST03 study (NCT00450203) is an ongoing phase- II /III study being conducted in 106 United Kingdom centers, which plans to accrue 1100 patients with histological stage Ib (T1 N1, T2a/b N0), II, III or stage IV (T4 N1 or N2) gastric or gastroesophageal-junction carcinoma. This randomized trial is currently comparing standard surgery + ECC (epirubicin, cisplatin, capecitabine) perioperative

chemotherapy vs standard surgery + ECC perioperative chemotherapy + bevacizumab. Primary endpoints are the safety and efficacy of the phase- II trial and overall survival in the phase-III trial. Secondary endpoints are response rates to preoperative treatment, surgical-resection rates, disease-free survival, quality of life, and cost-effectiveness. A pilot study within ST03, which is randomizing *HER2*-positive patients to standard ECX with modified ECX plus Lapatinib (Tyverb), will assess the safety and *HER2* positivity rate in 40 patients.

The Japanese JCOG 0501 phase-III trial (NCT00252161) plans to accrue 316 patients, from 35 institutions, with type-4 and large type-3 gastric carcinoma and who have undergone a gastrectomy + more than a D2 dissection. The primary endpoint will be overall survival; secondary endpoints will be progression-free survival, response rate, proportion completing treatment, proportion having a curative resection, and adverse events.

The ongoing Korean PRODIGY phase-III randomized trial (NCT01515748) plans to accrue 640 patients with resectable advanced GC (T2–3, N+, or T4 tumors). This study is currently testing neoadjuvant DOS (docetaxel, oxaliplatin, S-1) chemotherapy + surgery + adjuvant S-1 chemotherapy for 1 year vs surgery + adjuvant S-1 chemotherapy for 1 year. The primary endpoint is progression-free survival; the secondary endpoints are overall survival, stage distribution between the groups assessed after surgery, and R0 resection rate.

**Targeted therapy in GO**

Several molecular pathways are known to be involved in gastric carcinogenesis, such as *HER2*, *HER3*, *EGFR*, *HGFR/c-MET*, *E-Cadherin*, *MMP*, *VEGF/VEGFR*, *WNT/β-catenin*, *FGFR* and *Akt/PI3K/mTOR*<sup>[35]</sup>. Targeted and biological therapies are promising treatments in advanced GC. Combining chemotherapy with a targeted therapy may improve the complete pathological response (pCR) and survival, but also individualize

therapies and reduce toxicities.

HER2 is a transmembrane growth-factor receptor encoded by the proto-oncogene *ERBB2*, which is located on chromosome 17q21. The frequency of HER2-positive GC varies considerably between studies, ranging from 6.0%-36.6%<sup>[36]</sup>.

HER2 overexpression has been shown to predict the response to trastuzumab, a humanized recombinant monoclonal antibody that selectively binds to the extracellular domain of HER2, thereby blocking its downstream signaling. In the randomized ToGA trial, the addition of trastuzumab to cisplatin + capecitabine-fluorouracil significantly improved the objective response rate from 35% to 47% ( $P = 0.0017$ ), progression-free survival from 5.5 to 6.7 mo ( $P = 0.0002$ ), and overall survival from 11.1 to 13.8 mo ( $P = 0.0046$ )<sup>[37]</sup>.

The ongoing German Herceptin in combination with Fluorouracil, Leucovorin, Oxaliplatin, and Taxotere AIO-STO-0310 multicenter phase-II study is currently testing perioperative chemotherapy with 5-FU, leucovorin, docetaxel, and oxaliplatin (FLOT) in combination with trastuzumab in patients with HER2-positive, locally advanced, resectable adenocarcinoma of the gastroesophageal junction or stomach (NCT01472029). The primary endpoint is the rate of pCR. Hofheinz *et al.*<sup>[38]</sup> reported the preliminary results from the first 25 patients at the 2014 ASCO meeting: A pCR was found in 22% of patients and near complete regression (< 10% residual tumor cells) was observed in 24% of patients. The complete resection rate was 90%.

The Spanish NEOHX multicenter phase-II study evaluated the efficacy and toxicity profile for perioperative XELOX-T (capecitabine, oxaliplatin, trastuzumab) followed by adjuvant trastuzumab as a monotherapy in patients with advanced resectable stomach or esophagogastric-junction adenocarcinoma that was HER-2+. The primary endpoint was 18-mo disease-free survival. By the end of the study, 36 patients had been included. Preliminary results were reported at the 2013 ASCO meeting: pCR was observed in 19% and complete-resection rate (R0) was observed in 78% of patients. However, the follow-up period was too short for disease-free survival or overall survival to be assessed<sup>[39]</sup>.

The future EORTC randomized phase-II trial (INNOVATION) will test neoadjuvant chemotherapy with cisplatin-capecitabine plus trastuzumab vs cisplatin-capecitabine plus trastuzumab plus pertuzumab in HER2-positive resectable gastric or gastroesophageal-junction adenocarcinoma (NCT02205047). Pertuzumab is a humanized monoclonal antibody that binds to extracellular dimerization domain II of HER2, and inhibits heterodimerization of HER2 with other HER family members, especially HER2-HER3, which is the most potent signaling HER heterodimer. The primary endpoint will be the rate of major pathological response (*i.e.*, < 10% vital tumor cells).

carcinoma is based on R0 surgical resection with D2 lymph-node dissection. A D1 lymph-node dissection, with at least 15 lymph nodes resected, could also be performed in less experienced centers. Complementary treatment after curative surgical resection in T3 and/or N+ gastric carcinoma should be discussed. Perioperative chemotherapy and adjuvant chemoradiotherapy have significantly improved overall survival compared to surgery alone in Europe and the United States. In Asia, adjuvant chemotherapy, with S-1 or XELOX delivered after surgery + a D2 lymph-node dissection has shown significantly improved survival compared to surgery alone. Ongoing randomized trials are currently testing the efficacy of adjuvant chemoradiotherapy after neoadjuvant chemotherapy; intensified chemotherapy, and targeted therapy plus chemotherapy.

## REFERENCES

- 1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
- 2 **Siegel R**, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; **64**: 9-29 [PMID: 24399786 DOI: 10.3322/caac.21208]
- 3 **Karimi P**, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev* 2014; **23**: 700-713 [PMID: 24618998 DOI: 10.1158/1055-9965.EPI-13-1057]
- 4 **Meyerhardt JA**, Fuchs CS. Adjuvant therapy in gastric cancer: can we prevent recurrences? *Oncology* (Williston Park) 2003; **17**: 714-21, 728; discussion 728-9, 732-3 [PMID: 12800796]
- 5 **Abad A**, Manzano JL, Martí C. Reflections on adjuvant treatment of gastric cancer. *Ther Clin Risk Manag* 2007; **3**: 563-567 [PMID: 18472977]
- 6 **Bonenkamp JJ**, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999; **340**: 908-914 [PMID: 10089184 DOI: 10.1056/NEJM199903253401202]
- 7 **Cuschieri A**, Weeden S, Fielding J, Banciewicz J, Craven J, Joypaul V, Sydes M, Fayers P. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999; **79**: 1522-1530 [PMID: 10188901 DOI: 10.1038/sj.bjc.6690243]
- 8 **Songun I**, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; **11**: 439-449 [PMID: 20409751 DOI: 10.1016/S1470-2045(10)70070-X]
- 9 **Okines A**, Verheij M, Allum W, Cunningham D, Cervantes A. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** Suppl 5: v50-v54 [PMID: 20555102 DOI: 10.1093/annonc/mdq164]
- 10 **NCCN**. Clinical Practice Guidelines in Oncology. *Gastric Cancer* 2011; **1**: 2015
- 11 **D'Angelica M**, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. *Ann Surg* 2004; **240**: 808-816 [PMID: 15492562]
- 12 **Maehara Y**, Hasuda S, Koga T, Tokunaga E, Kakeji Y, Sugimachi K. Postoperative outcome and sites of recurrence in patients following curative resection of gastric cancer. *Br J Surg* 2000; **87**: 353-357 [PMID: 10718807 DOI: 10.1046/j.1365-2168.2000.01358.x]
- 13 **He LF**, Yang KH, Tian JH, Bai ZG. [Meta analysis of clinical effectiveness of neoadjuvant chemotherapy for gastric cancer]. *Acta*

## CONCLUSION

Currently, the treatment for locally advanced gastric

- Zheng 2008; **27**: 407-412 [PMID: 18423128]
- 14 **Li W**, Qin J, Sun YH, Liu TS. Neoadjuvant chemotherapy for advanced gastric cancer: a meta-analysis. *World J Gastroenterol* 2010; **16**: 5621-5628 [PMID: 21105197]
  - 15 **Wu AW**, Xu GW, Wang HY, Ji JF, Tang JL. Neoadjuvant chemotherapy versus none for resectable gastric cancer. *Cochrane Database Syst Rev* 2007; **(2)**: CD005047 [PMID: 17443566 DOI: 10.1002/14651858.CD005047.pub2]
  - 16 **Xiong B**, Ma L, Cheng Y, Zhang C. Clinical effectiveness of neoadjuvant chemotherapy in advanced gastric cancer: an updated meta-analysis of randomized controlled trials. *Eur J Surg Oncol* 2014; **40**: 1321-1330 [PMID: 25239442 DOI: 10.1016/j.ejso.2014.01.006]
  - 17 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]
  - 18 **Ychou M**, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; **29**: 1715-1721 [PMID: 21444866 DOI: 10.1200/JCO.2010.33.0597]
  - 19 **Hermans J**, Bonenkamp JJ, Boon MC, Bunt AM, Ohyama S, Sasako M, Van de Velde CJ. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993; **11**: 1441-1447 [PMID: 8336183]
  - 20 **Earle CC**, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer* 1999; **35**: 1059-1064 [PMID: 10533448]
  - 21 **Mari E**, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, Cascinu S, Barni S, Labianca R, Torri V. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol* 2000; **11**: 837-843 [PMID: 10997811]
  - 22 **Panzini I**, Gianni L, Fattori PP, Tassinari D, Imola M, Fabbri P, Arcangeli V, Drudi G, Canuti D, Fochessati F, Ravaioli A. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori* 2002; **88**: 21-27 [PMID: 12004845]
  - 23 **Hu JK**, Chen ZX, Zhou ZG, Zhang B, Tian J, Chen JP, Wang L, Wang CH, Chen HY, Li YP. Intravenous chemotherapy for resected gastric cancer: meta-analysis of randomized controlled trials. *World J Gastroenterol* 2002; **8**: 1023-1028 [PMID: 12439918]
  - 24 **GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group**, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, Van Cutsem E, Buyse M. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010; **303**: 1729-1737 [PMID: 20442389 DOI: 10.1001/jama.2010.534]
  - 25 **Sakuramoto S**, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810-1820 [PMID: 17978289 DOI: 10.1056/NEJMoa072252]
  - 26 **Sasako M**, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011; **29**: 4387-4393 [PMID: 22010012 DOI: 10.1200/JCO.2011.36.5908]
  - 27 **Bang YJ**, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; **379**: 315-321 [PMID: 22226517 DOI: 10.1016/S0140-6736(11)61873-4]
  - 28 **Macdonald JS**, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730 [PMID: 11547741 DOI: 10.1056/NEJMoa010187]
  - 29 **Smalley SR**, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, Gunderson LL, Goldman B, Martenson JA, Jessup JM, Stemmermann GN, Blanke CD, Macdonald JS. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012; **30**: 2327-2333 [PMID: 22585691 DOI: 10.1200/JCO.2011.36.7136]
  - 30 **Fuchs C**, Tepper J, Niedzwiecki D, Hollis D, Mamon H, Swanson R, Haller D, Dragovich T, Alberts S, Bjarnason G, Willett C, Enzinger P, Goldberg R, Mayer R. Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: Intergroup trial CALGB 80101. *J Clin Oncol* 2011; **29**: 4003
  - 31 **Lee J**, Lim do H, Kim S, Park SH, Park JO, Park YS, Lim HY, Choi MG, Sohn TS, Noh JH, Bae JM, Ahn YC, Sohn I, Jung SH, Park CK, Kim KM, Kang WK. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol* 2012; **30**: 268-273 [PMID: 22184384 DOI: 10.1200/JCO.2011.39.1953]
  - 32 **Kim S**, Lim DH, Lee J, Kang WK, MacDonald JS, Park CH, Park SH, Lee SH, Kim K, Park JO, Kim WS, Jung CW, Park YS, Im YH, Sohn TS, Noh JH, Heo JS, Kim YI, Park CK, Park K. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1279-1285 [PMID: 16099596 DOI: 10.1016/j.ijrobp.2005.05.005]
  - 33 **Zhu WG**, Xua DF, Pu J, Zong CD, Li T, Tao GZ, Ji FZ, Zhou XL, Han JH, Wang CS, Yu CH, Yi JG, Su XL, Ding JX. A randomized, controlled, multicenter study comparing intensity-modulated radiotherapy plus concurrent chemotherapy with chemotherapy alone in gastric cancer patients with D2 resection. *Radiother Oncol* 2012; **104**: 361-366 [PMID: 22985776 DOI: 10.1016/j.radonc.2012.08.024]
  - 34 **Dikken JL**, van Sandick JW, Maurits Swellengrebel HA, Lind PA, Putter H, Jansen EP, Boot H, van Grieken NC, van de Velde CJ, Verheij M, Cats A. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). *BMC Cancer* 2011; **11**: 329 [PMID: 21810227 DOI: 10.1186/1471-2407-11-329]
  - 35 **Wong H**, Yau T. Molecular targeted therapies in advanced gastric cancer: does tumor histology matter? *Therap Adv Gastroenterol* 2013; **6**: 15-31 [PMID: 23320047 DOI: 10.1177/1756283X12453636]
  - 36 **Boku N**. HER2-positive gastric cancer. *Gastric Cancer* 2014; **17**: 1-12 [PMID: 23563986 DOI: 10.1007/s10120-013-0252-z]
  - 37 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro A, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]
  - 38 **Hofheinz R**, Hegewisch-Becker S, Thuss-Patience P, Kunzmann V, Fuchs M, Graeven U, Homann N, Heinemann V, Pohl M, Tannapfel A, Al-Batran S. HER-FLOT: Trastuzumab in combination with



FLOT as perioperative treatment for patients with HER2-positive locally advanced esophagogastric adenocarcinoma: A phase II trial of the AIO Gastric Cancer Study Group. *Proceedings of the J Clin Oncol* 2014; Abstract 4073

- 39 **Rivera F**, Jiménez P, Garcia Alfonso P, Lopez C, Gallego J, Limon M, Alsina M, Lopez-Gomez L, Galán M, Falco E, Manzano J,

González E, Serrano R, Fernandez Parra E, Jorge M. NeoHx study: Perioperative treatment with trastuzumab in combination with capecitabine and oxaliplatin (XELOX-T) in patients with HER2 resectable stomach or esophagogastric junction (EGJ) adenocarcinoma—R0 resection, pCR, and toxicity analysis. *J Clin Oncol* 2013; **13**: Abstract 4098

**P- Reviewer:** Aurello P, Christodoulidis G, Fujiwara T

**S- Editor:** Ma YJ **L- Editor:** A **E- Editor:** Jiao XK





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

