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Review Article

Update on treatment of gastric cancer

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Abstract

Surgery is the main treatment for curing gastric cancer. Early diagnosis provides an excellent survival outcome via an improved detection of early gastric cancer and an improved resection rate. The extent of lymphadenectomy surgery has been under debate for a long time. In East Asian countries, especially Japan, Korea, and Taiwan, gastrectomy with D2 dissection is routinely performed. By contrast, in most Western countries, gastrectomy with D1 dissection is performed, due to lower mortality and morbidity. Recently, acceptance of D2 surgery has increased in Western countries because: (1) modified D2 lymphadenectomy (preservation of pancreas and spleen) improves operative morbidity and mortality; (2) Western surgeons can be trained to performed D2 lymph node dissection on Western patients safely; and (3) D2 resection decreases locoregional recurrence and prolongs survival. Current guidelines in the United States and Europe suggest modified D2 dissection is recommended, but needs to be performed by high-volume centers with experienced surgeons. Adjuvant or perioperative chemotherapy should be prescribed for gastric cancer with Stage II or III disease, due to its marked benefits of reducing disease recurrence and increasing long-term survival. Patients with inoperable advanced gastric cancer should receive chemotherapy to improve their survival and quality of life if an acceptable performance status can be achieved. Targeted therapy with trastuzumab should be considered in patients with HER-2/neu overexpression who have a higher response rate and a longer survival.

Keywords: adjuvant; chemotherapy; gastric cancer; surgery; targeted therapy

1. Introduction

Gastric cancer remains a major health problem around the world, despite declined incidence in recent decades.[1,2] It is the fourth most common cancer worldwide, with about one million (988,000) new cases annually and the second leading cause of cancer death (736,000 deaths per year) in 2008, according to the World Health Organization GLOBOCAN database.[3] The incidence is geographically related. Rates are highest in Eastern Asia (such as in Korea, Japan, and China), Eastern Europe, and South America, and the lowest rates are in North America.

Surgery is the only curative modality to treat gastric cancer. However, the cancer has a high recurrence rate after operation, especially in advanced stages. Adjuvant therapy with chemotherapy, chemoradiotherapy, or perioperative chemotherapy can provide survival benefit. Two large randomized controlled trials (RCTs) showed a lower recurrence rate and better survival after prescription of adjuvant chemotherapy.[4,5] Early diagnosis is crucial to provide excellent survival benefit. The 5-year survival rate by the seventh edition of *American Joint Committee on Cancer (AJCC)* is 89.2–95.1% in Stage IA, 84.9–88.4% in

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Stage IB, 76.8–84% in Stage IIA, 65.1–71.7% in Stage IIB, 43.8–58.4% in Stage IIIA, 31.1–46.8% in Stage IIIB, and 13.1–28.1% in Stage IIIC.[6–8] In Japan and Korea, where screening is widely performed, early detection is often possible.[9] In Japanese annual and nationwide registry data from 13,626 patients in 2002, the resection rate is high (95.4%) and the incidence of early gastric cancer (pT1) from resection patients is 49.7%. The overall 5-year survival is 68.9%.[8] By contrast, in Western countries, gastric cancer is often detected at an advanced stage and prognosis remains poor. In this article, we will review the treatment of gastric cancer, including resectable and unresectable diseases.

2. Surgery

Surgical intervention is the only modality that is potentially curative for gastric cancer. Standard gastrectomy is the principal surgical procedure, involving resection of at least two-thirds of the stomach, with lymph node dissection and adequate margin (≥4 cm).[10] Standard gastrectomy is comprised of total gastrectomy and distal subtotal gastrectomy for clinically node-positive or T2–4a tumors. Some patients with clinical T1 and N0 can receive modified gastric resection according to tumor location as follows: (1) pylorus-preserving gastrectomy for tumors in the middle part of the stomach with a distal tumor border at least 4 cm proximal to the pylorus; and (2) proximal gastrectomy for proximal tumors where more than half of the distal stomach can be preserved.[11]

Regional lymph node dissection is an important part of radical gastrectomy, due to frequent node metastases in gastric cancer.[12] Pathologic examination and evaluation of lymph node stations that surround the stomach have been suggested by the Japanese Research Society for the Study of Gastric Cancer since 1963.[13] The perigastric lymph node stations are grouped together as N1, including along the lesser curvature (stations 1, 3, and 5) and greater curvature (stations 2, 4, and 6) of the stomach. The nodes along the celiac artery and its branches are grouped together as N2, including the left gastric artery (station 7), common hepatic artery (station 8), celiac artery (station 9), and splenic artery (stations 10 and 11). More distant nodes, including the paraaortic (N3 and N4), are regarded as distant metastases. Minor modifications of the grouping system are necessary according to the location of the primary tumor [e.g., proximal lymph nodes at station 1 (right paracardial lymph nodes) were classified into the N1 group in upper third gastric cancer but classified into the N2 group in the lower third tumor]. D1 gastrectomy is defined as dissection of all the N1 group nodes, and D2 is defined as dissection of all the N1 and N2 group nodes.[14] In the new Japanese classification and treatment guidelines for gastric cancer published by the Japanese Gastric Cancer Association in 2011, the definition of lymphadenectomy has been simplified: the lymph node stations to be dissected in D1 and D2 are prescribed by the kind of gastrectomy, regardless of the tumor location. In total gastrectomy, D1 is defined as N1°+°station 7 (left gastric artery) lymph node dissection, D2 is N1°+°N2 lymph node dissection, and D0 is incomplete resection of N1 lymph nodes.[11,15]

The extent of lymphadenectomy is debated and there is no consensus in the world. In Japan, D2 dissection was introduced in the 1960s and has been recommended as standard practice with low morbidity and low mortality.[12] However, in most Western countries, gastrectomy with only D1 dissection is performed, due to having a lower mortality and morbidity than D2 dissection.[16,17]

Several large prospective, randomized trials investigated the extent of lymph node dissection and survival (Table 1).[16,19,20,24–26,28] In Western countries, there were two large randomized control trials (RCTs). The first one was conducted by the Medical Research Council in the United Kingdom, with 400 patients randomized to D1 or D2 lymphadenectomy.[16,18] There was no significant difference of 5-

Table 1
Phase III randomized trials comparing D1 with D2/D3 lymphadenectomy.

	Patient numbers	Postoperative morbidity	Postoperative mortality	Overall survival
Cuschieri et al[16] (The British Cooperative trial), 1999	D1: $n = 200$ D2: $n = 200$ (1987–1994)	28 46 $p < 0.001$	6.5 13 $p = 0.04$	35 33 $p = 0.43$ (5-year survival)
Dutch Gastric Cancer Group Trial: (1) Hartgrink et al,[19] 2004 (2) Songun et al[20] (15-year follow-up), 2010	D1: $n = 380$ D2: $n = 331$ (1989–1993) Lower local regional recurrence (13 vs. 19) and lower gastric-cancer-related death rates (37 vs. 48) in D2 lymphadenectomy	25 43 $p < 0.001$	4 10 $p = 0.004$	30 35 $p = 0.53$
Sasako et al[24] (Japan Clinical Oncology Group Study 9501, JCO), 2008	D2: $n = 263$ D2 + paraaortic node dissection: $n = 260$ (1995–2001)	20.9 28.1 $p = 0.067$	0.8 0.8 $p = 0.99$	69.2 70.3 $p = 0.85$ (5-year survival)
Wu et al[25,26] (Taiwan, single-institution randomized trial), 2004, 2006	D1: $n = 110$ D3: $n = 111$[a] (1993–1999)	7.3 17.1	0 0	59.5, 53.6 $p = 0.041$ (5-year survival)
Degiuli et al[28] (Italian Gastric Cancer Study Group, IGCSG), 2010	D1: $n = 133$ D2 with modification:[b] $n = 134$ (1998–2005)	12.0 17.9 ($p = 0.178$)	3.0 2.2 ($p = 0.722$)	No available data

Data are presented as %.

[a] D3 lymphadenectomy by 1st edition of Japanese classification of Gastric Carcinoma in 1995.

[b] D2 with modification: spleen preservation in most patients.

year survival rates [35% for D1 resection and 33% for D2, hazard ratio (HR) = 1.03, 95% confidence intervals (CI) 0.82–1.29] in the two groups. However, the morbidity (28% vs. 46%) and mortality (6.5% vs. 13.5%) were higher in the D2 group. The second trial was the Dutch Gastric Cancer Trial (DGCT). A total of 711 patients were randomly assigned to undergo either a D1 or D2 lymphadenectomy.[19] The median follow-up was 11 years. The results demonstrated no significant difference in overall survival (30% vs. 35%, $p = 0.53$). In a subgroup analysis, there was a trend to benefit in the N2 disease group (positive lymph nodes between 7 and 15, *AJCC Cancer Staging Manual* 6th edition). In addition, the morbidity (25% vs. 43%) and mortality (4% vs. 10%) were also higher in the D2 group. After a median follow-up of 15 years, the D2 lymphadenectomy was associated with lower locoregional recurrence and lower gastric-cancer-related death rate than the D1 surgery.[20]

In Eastern Asian countries, such as Korea and Japan, where the incidence of gastric adenocarcinoma is the highest in the world, D2 lymphadenectomy is routinely performed by experienced surgeons with low morbidity and mortality and clinical trials. Comparing D1 to D2 would be considered unethical today.[21,22] Seoul National University Hospital, which performed almost 1000 operations for gastric cancer per year, reported a morbidity rate of 17.4% and mortality rate of 0.6%.[23] In a prospective, randomized trial (JCOG 9501) from Japan of D2 versus extended paraaortic lymphadenectomy, the morbidity rate was 20.9–28.1%, and the mortality rate was 0.8%.[24] Investigators in another Eastern Asian country, Taiwan, conducted a prospective randomized trial, enrolling 221 patients who were randomly assigned to D1 surgery or D3 surgery.[25] The three participating surgeons were well-trained and had done at least 25 independent D3 dissections prior to the start of the trial. Morbidity (10.1% vs. 17.1%) was higher in the extended lymphadenectomy (D3) group, but there were no deaths (mortality 0%) in either group. Overall 5-year survival was significantly higher in patients receiving D3 surgery (59.5% vs. 53.6%, $p = 0.041$).[26] The recurrence rates at 5 years were lower in D3 surgery but without statistical significance (40.3% vs. 50.6%, $p = 0.197$).[26]

In the Dutch Gastric Cancer trial, when hospital deaths were excluded, D2 resection had a trend for survival benefit. Survival rates were 32% for D1 ($n = 365$) and 39% for D2 ($n = 299$), and the relative risks of these patients favored the D2 lymphadenectomy ($p = 0.07$).[19,22] More recent studies have shown that Western surgeons can be trained to perform D2 lymph node dissection on Western patients with low morbidity and mortality. One retrospective trial in Spain assessed 85 patients who underwent D1 lymphadenectomy and 71 who received D2 lymphadenectomy in a single institution.[27] The results showed a longer 5-year survival in the D2 group than in the D1 group (50.6% vs. 41.4%, $p = 0.03$), with low postoperative mortality (0% vs. 2.3% for D2 and D1, respectively, $p = 0.295$). Another prospective RCT was conducted by the Italian Gastric Cancer Study Group (IGCSG) to compare D1 and D2 gastrectomy in specialized Western centers.[28] A total of 267 patients with gastric cancer were randomly assigned to either a D1 or a D2 resection in five specialized centers. The results demonstrated no difference in the postoperative mortality rates (D1: 3.0% vs. D2: 2.2%, $p = 0.722$) and overall morbidity rates (D1: 12.0% vs. D2: 17.9%, $p = 0.178$). In a trial employing randomized adjuvant chemoradiation study (Intergroup 0116), reanalysis of the impact of hospital volume on the outcome of patients who underwent D0 comparing with D1 or D2 lymphadenectomy was performed.[29] The results demonstrated there was a trend toward improved overall survival among patients who received a D1 or D2 lymphadenectomy at moderate- to high-volume cancer centers.

Initially, distal pancreatectomy and splenectomy (pancreaticosplenectomy) were performed routinely to remove lymph node metastases at the splenic artery (station 11) and splenic hilum (station 10) in D2 gastrectomy for proximal third gastric cancer.[30,31] There was a marked adverse effect on both mortality and morbidity of distal pancreatectomy and splenectomy in two RCTs in Western countries[18,32] and no survival benefit of pancreaticosplenectomy compared with splenectomy alone by two Japanese retrospective trials.[33,34] Pancreas-preserving splenectomy has been considered an effective and safe procedure without decreasing surgical curability.[35,36] Currently, distal pancreatectomy is considered beneficial only when the primary tumor or metastatic lymph node directly invades the pancreas, but is not performed for prophylactic resection.[21,22]

Unlike the distal pancreatectomy, resection of the spleen continues to be controversial. According to the Japanese experience with lymph node dissection at the splenic hilus with splenectomy, the incidence of hilar node metastasis ranged from 15% to approximately 21% for tumors located at or infiltrate to the proximal third of the stomach.[31] About 20–25% of patients with lymph node metastasis have survived over 5 years following lymphadenectomy with splenectomy. Two prospective RCTs of total gastrectomy and lymphadenectomy, with or without splenectomy, have been performed in Chile and South Korea.[37,38] Both studies demonstrated a marginally better 5-year survival rate in patients with splenectomy, but the survival difference was not statistically significant. A higher rate of infectious complications in the spleen resection group from the Chile study was noted. However, the numbers of patients in these two studies were 187 and 207, respectively, and thus the power of these studies to confirm a modest improvement in survival for splenectomy is limited. In Japan, a large multicenter randomized trial (JCOG 0110, recruiting 500 patients) to evaluate the role of splenectomy for proximal gastric cancer is currently ongoing.[39] In Japan, in patients with potentially curable T2–T4 tumors invading the greater curvature of the upper stomach, complete clearance of No. 10 nodes by splenectomy should be considered by Japanese treatment guidelines.[11]

In conclusion, the D2 dissection has been the standard procedure in eastern Asia for a long time and also recommended in Western countries in recent years. In the treatment guidelines of gastric cancer in the United States and Europe, gastrectomy with modified D2 dissection is recommended, but

should be performed in specialized centers with adequate surgical expertise and postoperative care.[40,41]

3. Endoscopic therapy

Endoscopic resection for gastric cancer is considered as curative when there is an extremely low possibility of lymph node metastasis and it is suitable for en bloc resection.[11] The endoscopic resection comprises endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The absolute indications for EMR and ESD include a differentiated-type adenocarcinoma without ulcerative findings, depth of invasion in the mucosa (clinically diagnosed as T1a), and diameter <2 cm. ESD has a higher rate of en bloc resection and a better cumulative recurrence-free rate (97.6% vs. 92.5%, $p = 0.01$) than EMR.[42] In two large retrospective studies, 3843 and 5265 patients with early gastric cancer received D2 gastrectomy, respectively.[12,43] Tumors of the following categories have a very low possibility for lymph node metastasis (0%)[12,43] and are regarded as expanded indications: tumors clinically diagnosed as invasion in the mucosa (cT1a) and: (1) of differentiated-type without ulcer formation and irrespective of tumor size; (2) differentiated-type with ulcer formation and tumor size ≤3 cm; or (3) undifferentiated-type without ulcer formation and tumor size ≤2 cm. Under the expanded indications, ESD but not EMR should be employed for en bloc resection and may provide potential curative treatment. One large retrospective trial in Korea with 1152 patients who received ESD for early gastric cancer showed no statistically significant difference of recurrence rates in the absolute indication and in the expanded indication groups (7.7% vs. 9.3%, $p = 0.524$).[44] The long-term follow-up and survival data remain insufficient for ESD under the expanded criteria, and the procedure should be performed with caution.[11] A prospective clinical trial to evaluate the efficacy and safety of ESD under the expanded indications by the Japan Clinical Oncology Group (JCOG0607) is ongoing.[45]

4. Laparoscopic resection

Laparoscopic surgery has been increasingly employed, largely for early gastric cancer (T1 tumor) which is unsuitable for EMR. A recent meta-analysis study of laparoscopy-assisted versus open distal gastrectomy for early gastric cancer, including 22 trials and 3411 patients, demonstrated that: (1) the long-term outcome of cancer recurrence rate or survival was similar between both groups; (2) the numbers of retrieved lymph nodes were close in the two groups; and (3) there was significantly less postoperative morbidity (such as blood loss, postoperative analgesic consumption, and hospital stay) in the laparoscopic surgery group.[46] In gastric cancer more advanced than early cancer, there is less solid evidence regarding safety and long-term outcome. One small prospective randomized study of laparoscopic versus open subtotal gastrectomy for distal gastric cancer from Huscher and colleagues[47] showed: (1) no significant difference in operative mortality, with 3.3% for the laparoscopic surgery versus 6.7% for open surgery and morbidity of 26.7% versus 27.6%, respectively; (2) the number of resected lymph nodes was also not significantly different; and (3) 5-year overall survival (58.9% vs. 55.7%) and 5-year disease-free survival (57.3% vs. 54.8%) were similar between laparoscopic surgery and open surgery groups. However, laparoscopic surgery is technically demanding, and solid evidence regarding safety and long-term outcome remains lacking. It should be considered as an investigational treatment and requires further investigation in randomized clinical trials.

5. Radiation

5.1. Neoadjuvant chemoradiation therapy

The role of preoperative chemoradiation treatment for patients with resectable gastric cancer still remains uncertain. In resectable adenocarcinoma of the lower esophagus, esophagogastric junction, or gastric cardia, preoperative chemoradiation provides survival benefit, from two small-scale randomized studies.[48,49] The multicenter German PreOperative chemotherapy or radiochemotherapy in Esophagogastric adenocarcinoma Trial (POET) study included 119 patients with locally advanced adenocarcinoma of the lower esophagus or esophagogastric junction.[48] Patients who received preoperative chemoradiotherapy followed by surgery had a significantly higher pathologic complete response (15.6% vs. 2.0%) or tumor-free lymph nodes (64 vs. 38%). The 3-year survival rate showed improvement (47% vs. 28%). Although the study was ended prematurely due to low accrual, and statistical significance was not achieved, there was a trend towards survival advantage. Another randomized study demonstrated that preoperative chemoradiation was superior to surgery alone in patients with resectable adenocarcinoma of the esophagus (74 patients) and gastric cardia (39 patients).[49] The results showed: (1) a lower rate of lymph node metastasis (42% vs. 82%, $p < 0.001$); and (2) improved overall survival (16 months vs. 11 months, $p = 0.01$) in the preoperative chemoradiation group.

However, there have been no randomized studies to survey the benefits of preoperative chemoradiotherapy in noncardiac gastric cancer. Only several Phase II trials were done, which showed that preoperative chemoradiation provided pathologic complete response rates which ranged from 20% to 30%, and 70% to 78% achieved complete (R0) resection.[50–52] Neoadjuvant chemoradiotherapy for patients with resectable gastric cancer remains unclear. An international prospective Phase III randomized trial is still ongoing.[53]

5.2. Adjuvant chemoradiation therapy

Adjuvant chemoradiation therapy has become the standard in America, since the landmark Intergroup randomized trial SWOG 9008/INT-0116 demonstrated the survival benefit of the therapy when compared with surgery alone.[54] The study showed that five monthly cycles of chemotherapy (5-fluorouracil and leucovorin) with concurrent radiotherapy (45 Gy) during cycles 2 and 3 resulted in an approximately 22% improvement in 3-year overall survival. However, only

10% of patients underwent a D2 dissection, 36% had a D1 dissection, and 54% had a D0 lymphadenectomy. There was no survival difference in patients who received D2 resection. In Europe, postoperative chemoradiation has not gained wide acceptance due to concerns about (late) toxicity with abdominal chemoradiation, and the quality of surgery used.[41] In Japan, where standardized D2 lymph node dissection provides good local tumor control, postoperative chemoradiation is usually not performed.[11] A recent randomized Phase III trial in Korea (ARTIST trial, $n = 458$) which compared adjuvant chemoradiation (capecitabine and cisplatin plus radiotherapy) with adjuvant chemotherapy after curative D2 lymph node dissection of gastric cancer showed that adjuvant chemoradiation did not improve disease-free survival.[55]

6. Chemotherapy

6.1. Adjuvant chemotherapy

Two large Asian randomized Phase III studies (the ACTS GC and CLASSIC trials) have confirmed the survival benefit for postoperative chemotherapy after curative D2 lymph node dissection in patients with gastric cancer.[4,5] Postoperative chemotherapy with oral S-1 (ACTS GC trial) or capecitabine plus oxaliplatin (CLASSIC trial) were prescribed in patients with Stage II or Stage III after D2 lymph node dissection. In the CLASSIC study, the 3-year disease-free survival was 74% in the chemotherapy and surgery group and 59% in the surgery only group (HR 0.56, 95% CI 0.44–0.72). The 3-year survivals were 83% and 78%, respectively in the surgery with chemotherapy group and surgery alone group (HR 0.72, 95% CI 0.52–1.00).[4] In the ACTS-GC study, the 5-year disease-free survival was 65.4% in the S1 group and 53.1% in the surgery only group (HR 0.653, 95% CI 0.537–0.793). The 5-year survivals were 71.7% and 61.1% (HR 0.669, 95% CI 0.540–0.828), respectively, in the surgery with chemotherapy group and surgery-alone group.[55]

6.2. Perioperative chemotherapy

The first well-powered Phase III trial (MAGIC trial) for perioperative chemotherapy was conducted by the British Medical Research Council.[56] In this trial, 503 patients with adenocarcinoma of the stomach (74%), lower esophagus (15%), or esophagogastric junction (11%) were randomized to receive either perioperative chemotherapy (ECF: epirubicin, cisplatin, and fluorouracil) followed by surgery or surgery alone. The 5-year survival rates were 36% among those who received perioperative chemotherapy and 23% in the surgery group. The results of this study showed that perioperative chemotherapy with the ECF regimen significantly improved progression-free and overall survival in patients with resectable gastroesophageal adenocarcinomas.

6.3. Chemotherapy for advanced metastatic disease

Chemotherapy can provide improved survival and delay the appearance of disease-related symptoms compared to the best supportive care in patients with unresectable gastric cancer.[12–14] Although chemotherapy regimens have achieved

Table 2
Phase III randomized trials of chemotherapy in patients with gastric cancer.

	Regimen (patient's number)	Response rate, %	Median PFS/TTP (mo)	Median overall survival (mo)
Al-Batran,[60] (in Germany) 2008	FLP ($n = 108$)	24.5	3.9	8.8
	FLO ($n = 112$)	34.8	5.8	10.7
			$p = 0.077$	$p = 0.506$
Van Cutsem et al[62] (V325 trial), 2006	DCF ($n = 221$)	37	5.6	9.2
	CF ($n = 224$)	25	3.7	8.6
		$p = 0.01$	$p < 0.001$	$p = 0.02$
Cunningham et al[63] (REAL-2 trial), 2008	ECF ($n = 249$)	40.7	6.2	9.9
	ECX ($n = 241$)	46.4	6.7	9.9
	EOF ($n = 235$)	42.7	6.5	9.3
	EOX ($n = 239$)	47.9	7.0	11.2
Kang et al[58] (ML 17032), 2009	XP ($n = 139$)	41	5.6	10.5
	FP ($n = 137$)	29	5.0	9.3
		$p = 0.020$	$p < 0.001$ (noninferiority)	$p = 0.008$ (noninferiority)
			$p = 0.080$ (superiority)	$p = 0.265$ (superiority)
Bang et al[61] (TOGA trial), 2010	XP or FP ($n = 290$)	35	5.5	13.8
	T + XP or FP ($n = 294$)	47	6.7	11.1
		$p = 0.0017$	$p = 0.0002$	$p = 0.0046$
Ajani et al[59] (FLAGS trial), 2010	5-FU + cisplatin ($n = 526$)	29.1	5.5	8.6
	S-1 + cisplatin ($n = 527$)	31.9	4.8	7.9
		$p = 0.40$	$p = 0.92$	$p = 0.20$
Ohtsu et al[74] (AVAGAST trial), 2011	XP or FP ($n = 387$)	37.4	5.3	10.1
	bevacizumab + XP or FP ($n = 387$)	46	6.7	12.1
		$p = 0.0315$	$p = 0.0037$	$p = 0.0301$

DCF = docetaxel + cisplatin + 5-fluorourcail (5-FU); ECF = epirubicin + cisplatin + 5-FU; ECX = epirubicin + cisplatin + capecitabine; EOF = epirubicin + oxaliplatin + 5-FU; FLO = 5-FU + leucovorin + oxaliplatin; FLP = 5-FU + leucovorin + cisplatin; FP = 5-FU + cisplatin; PFS = progression-free survival; T = trastuzumab; TTP = time to progression; XP = capecitabine + cisplatin.

remarkable advances, these responses have not led to complete cure. The median survival time remains 8.6–11.1 months in large clinical trials (Table 2).[57–64,74]

A meta-analysis of randomized gastric cancer trials has revealed that combination chemotherapy results in substantially improved overall survival compared with single-agent chemotherapy.[65] There is no single well-established standard regimen in current use, but fluoropyrimidine- and platinum-based combinations are the most widely used in the world. It remains controversial whether a triplet regimen is needed. The meta-analysis showed significant benefits from adding an anthracycline to a platinum and fluoropyrimidine doublet, and ECF (epirubicin plus cisplatin plus protracted infusion 5-fluorouracil) is among the most active and well-tolerated regimens.[65] The combination of docetaxel, cisplatin, and 5-fluorouracil (DCF) was evaluated in a randomized Phase III study (V325 trial).[62] The median overall survival was significantly longer for DCF compared with CF (9.2 months vs. 8.6 months; $p = 0.02$). However, DCF was associated with increased myelosuppression and infectious complications. Twenty-nine percent developed neutropenia. Modification of the regimen can obtain similar activity and is better tolerated.[66]

Oxaliplatin is the third generation of platinum and is as effective as cisplatin. One Phase III trial conducted by a German Study Group in 2008, randomly assigned patients to receive combination treatment of fluorouracil, leucovorin, and oxaliplatin (FLO) or fluorouracil, leucovorin, and cisplatin (FLP). The results demonstrated no statistically significant difference in median overall survival (10.7 months vs. 8.8 months) between the FLO and FLP groups.[60] Another Phase III trial (REAL-2) compared capecitabine with fluorouracil and oxaliplatin with cisplatin in 1003 patients with advanced esophagogastric cancer.[63] Results from this study showed oxaliplatin was as effective as cisplatin and associated with lower incidences of Grade 3 or Grade 4 neutropenia, alopecia, renal toxicity, and thromboembolism, but with slightly higher incidences of Grade 3 or Grade 4 diarrhea and neuropathy.

Capecitabine is an oral fluoropyrimidine which is converted to 5-fluorouracil intracellularly. Two Phase III trials (REAL-2 and ML 17032) demonstrated that capecitabine was not inferior to fluorouracil in terms of progression-free and overall survival.[58,63]

Another novel oral fluoropyrimidine, S-1, has shown promise in advanced gastric cancer. In the Phase III randomized trial [First Line Advanced Gastric Cancer Study, (FLAGS) trial], 1053 patients with advanced gastric or esophagogastric junction adenocarcinoma were randomized to either cisplatin plus S-1 or cisplatin plus 5-fluorouracil.[59] The results showed no difference in median overall survival (8.6 months and 7.9 months, respectively; $p = 0.20$), but cisplatin and S-1 were associated with a significantly improved safety profile. In a randomized Phase III trial (SPIRITS trial), 298 patients with advanced gastric cancer were randomly assigned to S-1 plus cisplatin or S-1 alone.[67] Median overall survival (13.0 months vs. 11.0 months, $p = 0.04$) and progression-free survival (6.0 months vs. 4.0 months, $p < 0.0001$) were significantly longer in patients with a combination of S-1 and cisplatin compared with S-1 alone. In Japan, the first-line regimen of chemotherapy for advanced gastric cancer is S-1 plus cisplatin.[15]

Irinotecan is a topoisomerase I inhibitor widely used for colorectal cancer. In several Phase II studies, irinotecan showed activity in advanced gastric cancer, with response rates ranging from 15% to 23%.[68–70] The results of a Phase III study in 2008, randomly comparing irinotecan plus 5-fluorouracil and folinic acid (IF) to cisplatin combined with 5-fluorouracil (CF), demonstrated slightly superior results in the IF group, with response rates 31.8% versus 25.8%, time to tumor progression (TTP) 5.0 months versus 4.2 months, and overall survival 9.0 months versus 8.7 months, but no significant superiority or noninferiority was found.[57] Irinotecan was less toxic (improved tolerance) and showed a marginally significant noninferiority in terms of TTP (HR 1.23, 95% CI 0.97–1.57 for a margin of noninferiority of 0.93), thus it can be an alternative when platinum-based therapy cannot be delivered.

7. Targeted therapy

Some selective targeted agents have been developed in recent years. The only one showing strong evidence for improved survival is trastuzumab. The ToGA trial was a Phase III, multicenter, randomized study. A total of 594 patients with gastric and esophagogastric junction adenocarcinoma with HER2 overexpression were included.[61] Of these, 298 received trastuzumab plus chemotherapy (5-fluorouracil or capecitabine and cisplatin) and 296 received chemotherapy alone. There was a significant improvement in overall survival (13.8 months vs. 11.1 months, $p = 0.0046$) and progression-free survival (6.7 months vs. 5.5 months, $p = 0.0002$) when adding trastuzumab to chemotherapy. Subgroup analysis demonstrated that, in patients with immunohistochemistry (IHC) 2+ and fish fluorescence in situ hybridization (FISH)-positive tumors or IHC 3+, there was a marked improvement in overall survival (16.0 months vs. 11.8 months, HR 0.65, 95% CI 0.51–0.83) when trastuzumab was combined with chemotherapy. The toxicity was similar in both study arms. There was also no difference in symptomatic congestive heart failure between both arms. The study established the addition of trastuzumab to chemotherapy as a new standard treatment for patients with HER2-neu overexpression advanced gastric or esophagogastric junction adenocarcinoma.

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor A. Clinical trials have shown that bevacizumab, in combination with chemotherapy, has efficacy against several malignancies, including colon cancer, breast cancer, and lung cancer.[71–73] In a recent Phase III study (AVAGAST trial), 774 patients were randomly assigned to the bevacizumab combination in chemotherapy (cisplatin plus 5-fluorouracil or capecitabine) or chemotherapy alone.[74] Although the primary end point, overall survival, was not reached (12.1 months vs. 10.1 months; $p = 0.1002$), adding bevacizumab significantly increased progression-free survival

and overall response rate in the first-line treatment of advanced gastric cancer. In the subgroup analysis, in patients recruited in the United States, a benefit for overall survival was found, although the improvement was not significant for patients treated in Europe or in Asia.

In conclusion, gastrectomy with modified D2 dissection is the acceptable standard treatment worldwide now, but needs to be performed in high-volume centers by experienced surgeons. Adjuvant or perioperative chemotherapy can lower the recurrence rate and provide survival benefit. In patients with unresectable gastric cancer, chemotherapy and target therapy should be considered to improve survival and delay the appearance of disease-related symptoms.

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