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Adjuvant Therapy in Gastric Cancer: What Is The Optimal Approach?

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Abstract Gastric cancer confers a poor prognosis even when diagnosed as localized disease. Multimodality therapy improves the cure rate of patients with localized cancer. However, adjunctive therapeutic approaches differ in different regions of the world. This review focuses on the current standards and unresolved issues based on updated literature on therapy for localized gastric cancer. In the USA, the Intergroup 0116 trial established the use of postoperative chemoradiotherapy as a standard for patients who have surgery first for treatment of gastric cancer. In Europe, the MAGIC trial investigating perioperative chemotherapy demonstrated a survival benefit for gastric cancer patients. Finally, in Asia, the ACTS-GC and CLASSIC trials investigating postoperative chemotherapy established this as the standard of care after primary surgery that included D2 dissection. It is clear, however, that surgery alone is insufficient to achieve the highest possible cure rates.

Keywords Gastric cancer · Adjuvant therapy · Preoperative · Postoperative · Biomarker

Introduction

Worldwide, nearly one million cases of gastric cancer are diagnosed per year, and more than 730,000 patients die annually [1]. Eastern Asia, eastern Europe, and South America are major endemic areas with high incidences of gastric cancer. In the USA, approximately 25,000 newly diagnosed cases of gastric cancer and 10,300 cancer deaths occurred in 2011 [2].

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The overall 5-year relative survival rate from 2002 to 2008 was approximately 27 % using Surveillance, Epidemiology, and End Results (SEER) outcomes data [3]. The main reason for this poor prognosis is the advanced stage of cancer at diagnosis in most patients. Appropriate staging is important in subgrouping patients with potentially curable localized gastric cancer versus those with more advanced metastatic and incurable cancer. Once it is determined that a patient has a localized and potentially curable condition, a multidisciplinary evaluation and multimodality therapy are recommended. In the following sections we discuss the variety of adjunctive approaches developed over recent years.

Postoperative Chemotherapy

The goal of adjuvant chemotherapy is to eliminate micrometastases after an R0 resection to improve both overall survival and relapse-free survival (RFS). For two decades, ten phase III randomized controlled trials [4–13] have been conducted to compare adjuvant chemotherapy with observation after surgery (Table 1). Most Western trials have produced negative findings, but two Asian trials have demonstrated benefit from postoperative adjuvant therapy [10, 13]. A meta-analysis has also demonstrated that adjuvant chemotherapy can be associated with longer overall survival [14].

The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer

In Japan, the standard surgical technique for gastric cancer includes gastrectomy plus D2 lymphadenectomy and not ≤D1 lymphadenectomy as commonly practiced in North America and in some Western countries. An earlier Japanese study (the NSAS-GC study) demonstrated an overall survival benefit for patients receiving postoperative chemotherapy [9]. In this

Table 1 Phase III randomized trials of postoperative chemotherapy versus surgery alone

Authors, year	Patient selection	Number of patients	Tumor location	Surgery D0/D1/D2<	Treatment	Outcome	
						5-year OS	Hazard ratio (95 % CI)
Nakajima et al. [4], 1998	Gastric adenocarcinoma (R0) Stage IB–III	A: 285 B: 288	Stomach	NR	MMC + FU + UFT	A: 85.8 % B: 82.9 %	NS
Nashimoto et al. [5], 2003	Gastric adenocarcinoma (R0) Stage IB–III	A: 123 B: 127	Stomach	0 %/2 %/98 %	MMC + FU + Ara C	A: 91.2 % B: 86.1 %	NS
Bouche et al. [6], 2005	Gastric or GEJ adenocarcinoma (R0) Stage II–IV(M0)	A: 127 B: 133	Stomach: 84.2 % GEJ: 15.8 %	40.4 %/32.7 %/ 26.9 %	FP	A: 46.6 % B: 41.9 %	NS
Nitti et al. [7], 2006	Gastric or GEJ adenocarcinoma (R0) Stage IB–IV(M0)	A: 103 B: 103	Stomach: 87.4 % GEJ: 12.6 %	1 %/9.7 %/89.3 %	MTX + FU/LV + DXR	A: 52 % B: 51 %	NS
De Vita et al. [8], 2007	Gastric or GEJ adenocarcinoma (R0) Stage IB–IIIB	A: 112 B: 113	Stomach: 87.1 % GEJ: 12.9 %	NR	FU/LV + VP-16 + EPI	A: 48.0 % B: 43.5 %	NS
Nakajima et al. [9], 2007	Gastric cancer (R0) T2, N1-2	A: 95 B: 93	Stomach	0 %/0 %/100 %	FU + tegafur	A: 86 % B: 73 %	0.48 (0.26–0.89)
Sakuramoto et al. [10], 2007	Gastric cancer (R0) Stage II, III	A: 529 B: 530	Stomach	0 %/0 %/100 %	S-1	A: 80.1 %[a] B: 70.1 %[a]	0.68 (0.52–0.87)
Di Costanzo et al. [11], 2008	Gastric adenocarcinoma (R0) Stage IB–IV(M0)	A: 130 B: 128	Stomach	0 %/34.4 %/65.6 %	FU/LV + EPI	A: 47.6 % B: 48.3 %	NS
Kulig et al. [12], 2010	Gastric adenocarcinoma (R0) Stage IB–IV (M0)	A: 141 B: 154	Stomach	0 %/20.3 %/79.7 %	DXR + VP-16 + CDDP	A: 44 % B: 40 %	NS
Bang et al. [13], 2012	Gastric or GEJ adenocarcinoma (R0) Stage II, III	A: 520 B: 515	Stomach: 97.7 % GEJ: 2.3 %	0 %/0 %/100 %	CAP + L-OHP	A: 74 %[b] B: 59 %[b]	0.56 (0.44–0.72)

A interventional arm, *B* control arm, *GEJ* gastroesophageal junction, *OS* overall survival, *CI* confidence interval, *NR* not recorded, *NS* not significant, *MMC* mitomycin C, *FU* 5-fluorouracil, *UFT* orally administered uracil–tegafur, *Ara-C* cytarabine, *FP* fruolouracil plus cisplatin, *MTX* methotrexate, *LV* leucovorin, *DXR* doxorubicin, *VP-16* etopocide, *EPI* epirubicin, *S-1* tegafur/gimeracil/oteracil, *CDDP* cisplatin, *CAP* capecitabine, *L-OHP* oxaliplatin

[a] Three-year OS

[b] Three-year disease-free survival

trial, the adjuvant agent was orally administered uracil–tegafur given daily for 16 months and it was compared with surgery alone for treatment of patients with T2N1-2 (by the Japanese classification of gastric carcinoma) tumors. Five-year overall survival and RFS rates were statistically higher for the chemotherapy group (86 % vs. 73 %, hazard ratio 0.48, p=0.017, and 85 % vs. 68 %, hazard ratio 0.44, p=0.005, respectively). However this was a small trial (n=190) and was terminated prematurely. In addition, its control arm was questioned because the RFS rate was approximately 10 % lower than that of JCOG9206-1 [5], a previous trial that also evaluated the benefit of adjuvant chemotherapy. Thus, orally administered uracil–tegafur was not adopted as standard adjuvant therapy. A much larger and well-executed study, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) [10], investigated the efficacy of adjuvant S-1 [an oral fluoropyrimidine that consists of triplet agents: tegafur (a prodrug for fluorouracil), gimeracil (a dihydropyrimidine dehydrogenase inhibitor), and oteracil potassium (a phosphoribosyltransferase inhibitor; prevents gastrointestinal toxicity)], recommended for 12 months, for treatment of stage II and stage III gastric cancer after D2 lymphadenectomy and compared it with observation after surgery. A total of 1,059 patients were studied. The 5-year overall survival rate was 71.7 % in the S-1 group and 61.1 % in the surgery-alone group [hazard ratio 0.67, 95 % confidence interval (CI) 0.54–0.83] and the 5-year RFS was 65.4 % in the S-1 group and 53.1 % in the surgery-alone group (hazard ratio 0.65, 95 % CI 0.54–0.79) [15]. These results established S-1 monotherapy as a standard approach for treatment of stage II and stage III gastric cancer after curative resection with D2 lymphadenectomy in Japanese patients.

The CLASSIC Trial

The CLASSIC trial investigated the benefit of capecitabine and oxaliplatin as adjuvant therapy for patients with stage II and stage III gastric cancer after gastrectomy and D2 lymphadenectomy [13]. A total of 1,035 patients were randomized to surgery then observation or 6 months of adjuvant treatment with capecitabine and oxaliplatin. During an interim analysis, the 3-year disease-free survival (DFS) rate, the primary end point in this trial, was 74 % (95 % CI 69–79) in the chemotherapy group and 59 % (95 % CI 53–64) in the surgery-alone group. The hazard ratio of the 3-year DFS was 0.56 [95 % CI 0.44–0.72, p<0.0001). Given this, it would be expected that an overall survival advantage is likely to be found following longer observation.

Meta-Analysis

A meta-analysis was published by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group in 2010 [14] that analyzed individual patient data of 3,838 patients from 17 randomized controlled trials of adjuvant chemotherapy. This analysis demonstrated that fluoropyrimidine-based therapy was associated with longer overall survival (hazard ratio 0.82, 95 % CI 0.76–0.90, p<0.001) and DFS (hazard ratio 0.82, 95 % CI 0.75–0.90, p<0.001).

Perioperative Chemotherapy

One can argue that systemic chemotherapy prior to surgery could improve the R0 resection rate, particularly in Western patients, where tumors are often bulky at diagnosis [16]. A mid-sized phase III randomized trial, the MRC Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) trial, established level 1 evidence for this approach [17].

The MAGIC Strategy

The MAGIC trial investigated the epirubicin, cisplatin, and 5-fluorouracil regimen [17] in 503 patients with gastric, gastro-esophageal junction, or esophageal cancer who were randomized to perioperative chemotherapy and surgery or surgery followed by observation. Overall survival and DFS were improved significantly in the group receiving epirubicin, cisplatin, and 5-fluorouracil (hazard ratio for overall survival 0.75, 95 % CI 0.60–0.93, p=0.009, and hazard ratio for DFS 0.66, 95 % CI 0.53–0.81, p<0.001). However, important limitations of this trial were that (1) the postoperative chemotherapy was difficult to deliver (only delivered in 34 % of patients who underwent surgery), (2) only 68 % of patients underwent curative resection, and (3) the control group had a relatively poor outcome.

Another multicenter, phase III randomized trial, from France (FNCLCC and FFCD trial), demonstrated improved overall survival from preoperative chemotherapy using cisplatin and 5-fluorouracil [18]. However, this trial was terminated prematurely, and only 25 % of patients had gastric cancer. Similar to the MAGIC trial, only half of patients received postoperative chemotherapy.

In contrast, a European Organisation for Research and Treatment of Cancer (EORTC) phase III randomized study (the EORTC 40954 trial) [19] demonstrated no benefit from preoperative chemotherapy; however, this trial was underpowered and terminated prematurely. The results of an ongoing phase III randomized trial by the Japanese Clinical Oncology Group (the JCOG0501 study) comparing preoperative S-1 therapy plus cisplatin therapy then surgery followed by S-1 therapy versus postoperative S-1 therapy are awaited.

Postoperative Chemoradiotherapy

In the USA, postoperative chemoradiotherapy has had appeal of long duration because of the work of Moertel et al. [20] and

Table 2 Recently published and ongoing trials of adjuvant therapy for resectable gastric cancer

Study	Start year	Phase	Target sample size	Patient selection	Preoperative treatments	Surgery	Postoperative treatments	Primary end point
Perioperative chemoradiation vs. perioperative chemotherapy alone								
CRITICS trial [25] (MAGIC + postoperative CRT)	2007	III	788	Stomach or GEJ Stage IB–IV(M0)	A: ECC/EOC B: ECC/EOC	D1 + lymphnode dissection	A: CC + RT (45 Gy) B: ECC/EOC	OS
TOPGEAR trial [26] (MAGIC + preoperative CRT)	2012	II/III	752	Stomach or GEJ Stage IB–IIIC	A: FU/X + RT (45 Gy) B: ECF/ECX	D1+ lymph node dissection	A: ECF/EOX B: ECF/EOX	OS
ARTIST-II trial	2013	III	1,000	Stomach or GEJ Stage II–III with any N (N0 will be excluded)	A: none B: none	D2+ lymph node dissection	A: S-1 + RT(45 Gy)/S-1 + CDDP + RT(45 Gy) B: S-1/S-1 + CDDP	DFS
Adding bevaxizumab to perioperative chemotherapy								
MAGIC-B trial (MAGIC + bevacizumab)	2008	II/III	1,100	Stomach or GEJ Stage IB–IV(M0)	A: ECX + bevacizumab B: ECX	D1+ lymph node dissection	A: ECX + bevacizumab B: ECX	OS
Perioperative chemotherapy vs. postoperative chemotherapy								
JCOG0501	2005	III	316	Stomach Type 3[a] (8 cm+), type 4[b] N0-2, H0, M0	A: S-1 + CDDP B: none	D2+ lymph node dissection	A: S-1 B: S-1	OS
Preoperative chemotherapy vs. postoperative chemotherapy								
EORTC 40954 trial [19]	Published 2010	III	144 (planned 360)	Stomach or GEJ Stage III, IV(M0)	A: FU/LV + CDDP B: none	D1 + lymph node dissection	A: none B: none	OS (NS)
Kyoto University	Completed	III	100	Stomach or GEJ Stage II, III	A: S-1 + CDDP B: none	D2+ lymph node dissection	A: none B: S-1	OS

A interventional arm, *B* control arm, *GEJ* gastroesophageal junction, *ECC* epirubicin/cisplatin/capecitabine, *ECF* epirubicin/cisplatin/5-fluorouracil, *EOC* epirubicin/oxaliplatin/capecitabine, *CC* cisplatin/capecitabine, *RT* radiotherapy, *CRT* chemoradiotherapy, *FU* 5-fluorouracil, *X* capecitabine, *ECX* epirubicin/cisplatin/capecitabine, *S-1* tegafur/gimeracil/oteracil, *CDDP* cisplatin, *LV* leucovorin

[a] Macroscopic type of advanced gastric cancer (Japanese classification of gastric cancer, third edition [34]): Ulcerated tumors with raised margins, surrounded by a thickened gastric wall without clear margins

[b] Macroscopic type of advanced gastric cancer (Japanese classification of gastric cancer, third edition [34]): tumors without marked ulceration or raised margins, the gastric wall is thickened and indurated and the margin is unclear

others [21]. The Intergroup 0116 trial showed a significant improvement in overall survival and therefore established adjuvant chemoradiotherapy as the standard of care [22].

The Intergroup 0116 and Adjuvant Chemoradiation Therapy in Stomach Cancer Trials

In the moderate-sized phase III randomized Intergroup 0116 trial, a total of 559 patients with stage IB to stage IV disease who had had resections were assigned to observation or postoperative chemoradiotherapy [22]. Most of the patients had a T3 or greater tumor and involved lymph nodes. Recently updated results continue to demonstrate improvement in both overall survival (hazard ratio 1.32, 95 % CI 1.10–1.60, $p<0.005$) and RFS (hazard ratio 1.51, 95 % CI 1.25–1.83, $p<0.001$) for the chemoradiotherapy group [22]. However, a major criticism of the trial was inadequate quality control of nodal dissection, as only 10 % of all patients underwent D2 lymph node dissection, and more than 50 % underwent D0 resection. A retrospective analysis from Korea [23] compared overall survival and RFS of 544 patients who received postoperative chemoradiotherapy after D2 gastrectomy and overall survival and RFS of 446 patients who were followed after D2 gastrectomy. The 5-year overall survival rate was 57.1 % in the chemoradiotherapy group and 51.0 % in the control group ($p=0.0198$).

This retrospective observation was the foundation for the Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial [24] comparing adjuvant chemoradiotherapy with adjuvant chemotherapy after an R0 resection in 458 patients. However, the 3-year DFS rate as the primary end point was not statistically different between the two groups. In the subgroup analysis, patients with node-positive cancer in the adjuvant chemoradiotherapy group had a significantly better 3-year DFS rate than those in the adjuvant chemotherapy group. This result suggests that the adjuvant chemoradiotherapy might have been beneficial compared with adjuvant chemotherapy among the node-positive populations. A further study to address this hypothesis has started (ARTIST-II trial). Furthermore, the results of two additional trials investigating chemoradiotherapy are awaited [25, 26].

Preoperative Chemoradiotherapy

Several studies in the USA that evaluated the feasibility of preoperative chemoradiotherapy have been reported [27–29]. However, this strategy remains a topic of study and is the subject of an ongoing phase III trial [26].

Biomarkers for Adjuvant Treatments

The molecular biology of gastric cancer in the adjuvant setting is not well characterized enough to implement any biomarker for patient selection. In the advanced setting, however, a biomarker analysis of the AVAGAST trial suggests that plasma vascular endothelial growth factor A and neuropillin-1 are of interest [30]. Terashima et al. [31] and Sasako et al. [32] retrospectively evaluated the impact of epidermal growth factor receptor or human epidermal growth factor receptor 2 expression and correlated this with the effect of pyrimidine metabolism (thymidylate synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase, and orotate phosphoribosyltransferase) on the outcomes of patients in the ACTS-GC trial. Thymidylate synthase and dihydropyrimidine dehydrogenase gene overexpression were associated with better overall survival in patients treated with S-1 after surgery. Another trial showed that epidermal growth factor receptor overexpression was associated with overall survival in patients receiving adjuvant 5-fluorouracil and cisplatin chemotherapy [33]. Much more work remains to be done in this regard.

Conclusion

Several adjunctive strategies have been developed for patients with localized gastric cancer, and each strategy appears to increase the cure rate by approximately 10 %. Therefore, surgery alone is not recommended. Multidisciplinary evaluation of localized gastric cancer is recommended. In-depth analysis of molecular biology will also be helpful to develop more specific strategies. We hope that several ongoing trials (Table 2) will also result in improvement in the outcome of our patients.

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