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REVIEW

# Current adjuvant treatment modalities for gastric cancer: From history to the future

Leyla Kilic, Cetin Ordu, Ibrahim Yildiz, Fatma Sen, Serkan Keskin, Rumeysa Ciftci, Kezban Nur Pilanci

Leyla Kilic, Department of Medical Oncology, Acibadem University Hospital, Istanbul 34394, Turkey

Cetin Ordu, Department of Medical Oncology, Istanbul Bilim University, Istanbul 34394, Turkey

Ibrahim Yildiz, Fatma Sen, Serkan Keskin, Rumeysa Ciftci, Department of Medical Oncology, Institute of Oncology, Istanbul University, Istanbul 34394, Turkey

Kezban Nur Pilanci, Department of Medical Oncology, Haseki Training and Research Hospital, Istanbul 34394, Turkey

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Correspondence to: Cetin Ordu, MD, Department of Medical Oncology, Istanbul Bilim University, Büyükdere Cad. No.120, Şişli, Istanbul 34394, Turkey. cetinordu@hotmail.com
Telephone: +90-532-2276179
Fax: +90-212-2889812

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## Abstract

The discrepancy between the surgical technique and the type of adjuvant chemotherapy used in clinical trials and patient outcomes in terms of overall survival rates has led to the generation of different adjuvant treatment protocols in distinct parts of the world. The adjuvant treatment recommendation is generally chemoradiotherapy in the United States, perioperative chemotherapy in the United Kingdom and parts of Europe, and chemotherapy in Asia. These options mainly rely on the United States Intergroup-0116, United Kingdom British Medical Research Council Adjuvant Gastric Infusional Chemotherapy, and the Asian Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer and Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer trials. However, the benefits were evident for only certain patients, which were not very homogeneous regarding the type of surgery, chemotherapy regimens, and stage of disease. Whether the dissimilarities in survival are attributable to surgical technique or intrinsic biological differences is a subject of debate. Regardless of the extent of surgery, multimodal therapy may offer modest survival advantage at least for diseases with lymph node involvement. Moreover, in the era of individualized treatment for most of the other cancer types, identification of special subgroups comprising those who will derive more or no benefit from adjuvant therapy merits further investigation. The aim of this review is to reveal the historical evolution and future reflections of adjuvant treatment modalities for resected gastric cancer patients.

**Key words:** Adjuvant chemoradiotherapy; Biomarker; Gastric cancer; Lymph nodes



**Core tip:** Despite extensive surgery, gastric cancer will likely recur for most patients. Fortunately, additional treatment modalities either in the perioperative or post-operative setting provide varying degrees of survival

advantage. Although there is considerable data regarding adjuvant chemotherapy and chemoradiotherapy since the Intergroup-0116 study, there is still no established uniform treatment protocol depending on the type of surgery, histological subgroup, or extent of disease. The present review is aimed at identifying the advances in treatment strategies and discussing the pros and cons of each strategy.

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## INTRODUCTION

Gastric cancer is the fifth most common cancer in the world, with 952000 new cases being diagnosed in 2012[1]. The cornerstone for treatment of gastric cancer is surgical resection with lymph node dissection (LND). An extended lymph node resection, which is commonly defined as a D2 resection for gastric cancer, includes the removal of the whole stomach, the greater and lesser omentum, and the N1 and N2 (groups 1-11) lymph nodes. For tumours located in the proximal stomach, resection of the spleen and the tail of the pancreas may be necessary for removing groups 10 and 11 lymph nodes. While a D2 lymph node dissection is considered a standard surgical procedure for resectable gastric cancer in Japan and Korea, the necessity of a D2 dissection still remains a subject of controversy in Western countries. The overall 5-year survival rates in the United States is around 10% to 40%; however, in Japan and South Korea, it is reported to be 50% or higher[2-4]. It is unclear whether removing additional lymph nodes during the operation contributes to a difference in survival. Additional information on lymph nodes may provide more accurate staging, which is currently only available for patients that undergo a D2 dissection. Other factors such as early diagnosis, case selection, surgical skill, and post-operative care may also contribute to this observed difference in survival.

Despite difficulties with surgical techniques, data from the National Cancer Data Base in the United States points at a 10-year survival rate of 65% for patients with resected stage IA disease and 3%-42% for those with more advanced disease[5]. Thus, the high rate of both locoregional and distant relapse, even after complete resection, makes adjuvant treatment mandatory for patients with stomach cancer.

The timing and sequence of adjuvant/neoadjuvant strategies and combination therapies have been questioned in numerous phase Ⅱ and phase Ⅲ trials. The landmark Intergroup (SWOG 9008/INT-0116) trial demonstrated a survival benefit for resected stage IB-Ⅳ, M0 gastric cancer patients following adjuvant chemoradiotherapy[6]. However, the extent of surgery and the chemotherapy (CT) regimen, which was associated with high rates of toxicity, was seriously critiqued in this study. Although an extensive (D2) LND was recommended, only 10% of the patients had undergone a D2 dissection. The relative inadequacy of locoregional control with limited LND was supposed to be compensated with adjuvant radiotherapy.

Although there is large amount of data from randomized, controlled trials (RCT) and recommendations from several guidelines, recent analysis from the National Cancer Data Base have revealed that real-life practices somewhat diverge from the evidence-based results[7]. Trends in American cancer centres have shown that out of stage Ⅲ patients who received surgery at community hospitals, less than 50% also received adjuvant chemoradiotherapy in 2009. However, the large number of patients involved in the RCTs constitute a heterogeneous population where the benefit from adjuvant therapy may be difficult to interpret for some specific subgroups of patients. Moreover, there is still no phase Ⅲ data supporting the tailoring of treatment according to stage of disease after surgery, unlike colon and breast cancers, since each stage may benefit from adjuvant therapy to a varying degree. This review will focus on the evidences of adjuvant treatment strategies dependent on the recent RCTs and future directions for optimal approach.

## ADJUVANT CHEMOTHERAPY REGIMENS

Surgical resection is the only hope for curative treatment in early stages of gastric cancer. However, only 40% of the patients with gastric cancer will remain disease free after complete resection of their tumour. Therefore, adjuvant and neoadjuvant treatment modalities are crucial for establishing better prognosis for gastric cancer patients. Extensive studies were conducted to determine the efficacy of adjuvant chemotherapy for gastric cancer. Some previous phase Ⅲ randomized trials did not demonstrate absolute benefit for adjuvant chemotherapy. However, these studies usually did not enrol large datasets and generally included early stage patients[8-10]. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) study was a pioneer phase Ⅲ study showing a significant survival benefit following adjuvant chemotherapy after D2 LND for gastric cancer patients. The trial documented that one year adjuvant chemotherapy with an oral fluoropyrimidine, S-1 provided a clear survival benefit for stage Ⅱ and Ⅲ gastric cancer patients after D2 LND[3]. Since the publication of the results of the ACTS-GC trial, chemoradiation was excluded from adjuvant treatment modalities for D2 resected gastric cancer in Japan, but this was not the case in Western countries. However, the results of the ACTS-GC study conflicted with a similar large scaled phase Ⅲ Japanese trial that utilized mitomycin C, fluorouracil (FU), and oral UFT (a combination of tegafur, a prodrug of 5-FU and uracil treatment) as adjuvant chemotherapy[11]. The investigators considered that this

result was due to high proportion of pT1 gastric cancer patients included in the trial for which surgery alone may yield a good prognosis, and there seemed to be no requirement for adjuvant therapy. Consequently, further trials usually did not include early stage patients (*i.e.,* ≤ stage Ib).

Apart from the Asian studies, most of the trials performed with adjuvant chemotherapy have not demonstrated a significant survival benefit[12-14]. However, the results of the meta-analysis by the Global Advanced/Adjuvant Stomach Tumour Research International Collaboration (GASTRIC) group with an extended follow-up time have revealed a modest but statistically significant survival advantage with adjuvant chemotherapy after curative resection of gastric cancer[15]. There was an absolute improvement in overall survival (OS) of 6% after 5 years that was maintained at 10 years. The treatment benefit was sustained in the majority of the investigated groups of FU-based regimens, with reductions in the risk of death between 20% and 40%. This meta-analysis pointed out that adjuvant FU-based chemotherapy is associated with improved OS, and combination chemotherapy could be recommended for patients who have not received treatment in the perioperative setting.

S-1, an orally active FU analogue, is a combination of tegafur (a prodrug of 5-FU), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase), and oteracil (inhibitor of the phosphorylation of FU in the gastrointestinal tract). Pharmacokinetics studies have shown that the absorption of FU derived from S-1 is not affected by gastrectomy[16]. The response rates with S-1 alone were higher than 40% in two phase Ⅱ trials among patients with advanced gastric cancer[17,18]. Similarly, S1 demonstrated a clear survival benefit in the ACTS-GC study. After 3 years of median follow-up, the OS in the S-1 group was 33% higher than the surgery-only group[3]. Grade 3 or grade 4 adverse events occurred in less than 5% of patients in the S-1 group. The OS rate was 80.5% in the S-1 group and 70.1% in the surgery-only group at 3 years. Thus, S-1 was approved as an effective option for adjuvant chemotherapy for patients with resected gastric cancer.

Recently Zhang *et al*[19] have published the analysis of 31 RCTs, which included 7120 gastric cancer patients. There was no significant difference in terms of overall mortality among the four chemotherapy regimens including FU + mitomycin (MMC) + adriamycin, FU + MMC (FM), Tegafur and MMC. The evidence for the FM regimen and MMC regimen was not strong enough. According to this meta-analysis, Tegafur was recommended as the first-line adjuvant chemotherapy regimen for patients after complete resection. However, RCTs published after 2000 have consisted of primarily combinations of cisplatin and FU. Collectively, S1 or 5-FU-cisplatin combination regimens in neo-adjuvant, adjuvant, and perioperative settings have yielded a favourable impact on survival[20-32]. Moreover, chemotherapy seems to provide prolongation of survival for patients with mostly node-positive and T3-T4 disease (Table 1).

The combination of adjuvant with neo-adjuvant chemotherapy has proven its value in two randomized trials. As the pioneer study of perioperative chemotherapy for gastric cancer, the British Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial demonstrated a significant downstaging of the primary tumour and a 10% higher resectability rate with a survival benefit of 13% at 5 years[31]. The primary goals of the ECF perioperative CT were to increase the likelihood of R0 resection while downstaging the tumour, predicting tumour sensitivity to chemotherapy, improving obstructive symptoms, and eliminating micrometastases. One of the major limitations of the MAGIC trial was that only 42% of patients in the chemotherapy group were able to receive all protocol treatment; 34% of patients who completed preoperative chemotherapy and surgery could not be administered postoperative chemotherapy, possibly due to postoperative complications, early disease progression, or the patients' will. Nevertheless, patients in the perioperative chemotherapy section had a survival advantage when compared with those who underwent surgery alone (5 years OS rate for CT group *vs* surgery-alone; 36% *vs* 23%, respectively).

New questions have arisen regarding the optimal adjuvant therapy following the increased acceptance of D2 gastrectomy. The primary goal of design for Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) study was to answer these questions. The investigators aimed to evaluate the effect of adjuvant capecitabine plus oxaliplatin after D2 gastrectomy[25]. The CLASSIC study reported a 44% improvement in disease-free survival (DFS) for patients randomly assigned to postoperative capecitabine and oxaliplatin (XELOX) when compared with observation. Subgroup analysis confirmed the beneficial effect of adjuvant capecitabine and oxaliplatin for all disease stages (Ⅱ, ⅢA or ⅢB), and the extent of nodal involvement correlated with substantially more benefit (N2 > N1 > N0) from adjuvant CT. Three-year DFS was defined as the primary endpoint because the majority of the recurrences occur within 3 years of surgery according to the preliminary data from the GASTRIC group. Although not formally validated as a surrogate measure yet, 3-year DFS is strongly correlated with 5-year OS, which is the reference point for judging effectiveness of adjuvant therapy in gastric cancer[15]. Additionally, after a median follow-up of 62.4 mo, the updated results supported the interim analysis findings; the estimated 5-year DFS was 68% in the adjuvant capecitabine and oxaliplatin group *vs* 53% in the observation alone group[33]. The OS data from this study are not yet known; however, the data suggest an improvement in OS with capecitabine and oxaliplatin compared with surgery alone (78% *vs* 69%).

Whether the results of CLASSIC trial could be adapted to geographical regions where management practices differ is unclear. The CLASSIC trial had considerably better survival outcomes when compared with Western counterparts; the 3-year OS rate in the surgery-only group was 78% in the CLASSIC trial, while it was only 30%-40% in the United States Intergroup-0116 and

**Table 1 Randomized trials of chemotherapy for resected gastric cancer, published after 2000s**

| Ref. | Regimen | LN (+) % (chemo) | T3-T4 % (chemo) | No. of patients | D2 % (chemo) | % 5-yr survival | *P* value |
|---|---|---|---|---|---|---|---|
| Neoadjuvant | | | | | | | |
| Schuhmacher *et al*[20] | 5-FU, LV, cisplatin | 94.4 | 100 | 72 | 95.7 | 72.7 | 0.2 |
| | Surgery alone | | | 72 | | 69.9 | |
| Adjuvant | | | | | | | |
| Bajetta *et al*[21] | EAP, 5-FU + LV | 91 | 51 | 137 | 73 | 52 | 0.87 |
| | Surgery alone | | | 137 | | 48 | |
| Chipponi *et al*[22] | 5-FU, cisplatin | 80 | 75 | 101 | | 39.0 | NS |
| | Surgery alone | | | 104 | | 38.7 | |
| Bouché *et al*[23] | 5-FU, cisplatin | 80.3 | 77.9 | 127 | 55.9 | 46.6 | 0.22 |
| | Surgery alone | | | 133 | | 41.9 | |
| Sasako *et al*[24] | S-1 | 90.4 | 45.1 | 529 | 100 | 71.7 | |
| | Surgery alone | | | 530 | | 61.1 | |
| Bang *et al*[25] | Capecitabine, oxaliplatin | 91 | 45 | 520 | 100 | 83 | 0.493 |
| | Surgery alone | | | 515 | | 78 | |
| Kang *et al*[26] | MMC + 5'FDR (MF') *vs* | 90 | 43 | 424 | 100 | 66.5 | 0.33 |
| | MF' + CDDP | | | 431 | | 65 | |
| Di Costanzo *et al*[27] | PELF | 83.8 | 49.2 | 130 | 55 | 47.6 | 0.41 |
| | Surgery alone | | | 128 | | 48.7 | |
| De Vita *et al*[28] | ELFE | 72 | 80 | 112 | 79 | 48 | 0.610 |
| | Surgery alone | | | 113 | | 43.5 | |
| Nitti *et al*[29] | FAMTX or FEMTX | 82 | 61 | 194 | 88 | 43 | 0.86 |
| | Surgery alone | | | 203 | | | |
| Neri *et al*[30] | EPI, LV, 5-FU | 100 | 84 | 69 | | 30 m's (median) | < 0.01 |
| | Surgery alone | | | 68 | | 18 | |
| Perioperative | | | | | | | |
| Cunningham *et al*[31] | EPI, 5-FU, cisplatin | 71 | 56 | 250 | 28 | 36.3 | 0.009 |
| | Surgery alone | | | 253 | | 23.0 | |
| Ychou *et al*[32] | 5-FU, cisplatin | 67 | 58 | 113 | 100 | 38 | 0.02 |
| | Surgery alone | | | 111 | | 24 | |

5-FU: 5-fluorouracil; EAP: Etoposide, adriamycin, cisplatin; LV: Leucovorin; MMC: Mitomycin C; 5' FDR: Doksifluridine; EPI: Epirubicine; FAMTX: Fluorouracil, adriamycin; methtrexate; FEMTX: Fluorouracil, epirubicin; methtrexate; PELF: Cisplatin, epirubicin, leucovorin, 5- fluorouracil; ELFE: Epirubicin, leucovorin, 5-fluorouracil, etoposide; CDDP: Cisplatin; LN: Lymph node.

United Kingdom MAGIC populations. Although patients included in the CLASSIC trial had fewer T3 and T4 lesions (44% in CLASSIC *vs* 68% in Intergroup-0116 *vs* 64% in MAGIC), node-positive disease was more frequent (90% *vs* 85% *vs* 72%). The differences in survival rates are supposed to be not only due to prognostic differences but also due to intrinsic biological disparities and consistent use of D2 surgery. Since D2 gastrectomy is also a standard of care in Western countries currently, the findings of this study could be remarkable and generalized to the other regions where D2 surgery is performed by experienced surgeons.

## ADJUVANT CHEMORADIOTHERAPY

After surgery with curative intent, local or regional recurrence in the gastric or tumour bed, the anastomosis, or regional lymph nodes occurs in 40% to 65% of patients[34]. According to the preoperative analysis of the University of Minnesota, locoregional failure was the only evidence of relapse in 29% of patients and as any component of relapse in 88% of patients. Locoregional recurrences occurred in three major locations: (1) Gastric bed (organs and structures in proximity to the primary tumour); (2) regional nodes; and (3) gastric remnant, anastomoses, and duodenal stump[35]. Autopsies report even higher locoregional failure rates reaching up to 80%-93%[36]. Thus, radiotherapy is supposed to be an essential adjunct of postoperative treatment in gastric cancer patients.

Two randomized trials evaluating the benefit of adjuvant radiotherapy (RT) alone after resection for gastric cancer revealed conflicting results. The first trial by the British Stomach Cancer Group included 436 patients who were randomized to undergo surgery alone or surgery followed by RT or chemotherapy with mitomycin, doxorubicin, and fluorouracil[37]. However, more than one third of the patients had gross or microscopic residual disease following surgery. At the 5-year follow-up, there was no additional survival benefit for adjuvant RT or chemotherapy compared with surgery alone. However, there was a significant reduction in locoregional recurrence with the addition of RT to surgery. The second trial by Zhang *et al*[38] randomized 370 patients to preoperative RT or surgery alone. Survival and resection rates were significantly improved with preoperative RT compared with surgery alone (30% *vs* 20%; 89.5% *vs* 79%, respectively). However, there was not a significant reduction in distant recurrence rates (24.3% *vs* 24.7%). Because only cardiac lesions were included in the trial, it is not clear whether these results can be adapted to distal lesions.

The landmark trial regarding combined modality adjuvant treatment for gastric cancer has been the

Intergroup 0116 study[6]. A total of 556 patients with resected carcinoma of the stomach or gastroesophageal junction (stage IB through Ⅳ, M0) disease were randomized to surgery alone or surgery plus postoperative chemoradiotherapy. The median OS in the surgery only group was 27 mo, as compared with 36 mo in the chemoradiotherapy group ($P$ = 0.005). An important issue regarding the surgical procedure was the extent of surgery in this trial. Although the recommendation was an extensive D2 LND, only 10% of the patients underwent a D2 dissection, 36% had a D1 dissection, and more than half had a D0 lymphadenectomy (not all of the N1 nodes were resected). This situation raised the question of whether chemoradiation was compensatory for inadequate surgery. Thus, in high-volume centres where D2 LND is routinely performed, omitting adjuvant radiotherapy has been considered due to high morbidity rates and poor tolerance. However, an observational study including patients with D2 LND has demonstrated that chemoradiotherapy as an adjunct to surgery could be tolerable with acceptable toxicity and good tumour control[39]. The patients had received a postoperative chemoradiotherapy protocol similar to the Intergroup trial or surgery without further adjuvant treatment. The median duration of OS was significantly longer in the chemoradiotherapy (CRT) group than in the comparison group (95.3 mo *vs* 62.6 mo). However, these data rely on nonrandomized observation studies with suitable controls or unplanned subgroup analysis.

Updated analysis of the Intergroup trial with longer follow-up has supported the persistent benefit of adjuvant CRT[40]. The OS and recurrence-free survival data demonstrated continued strong benefit from postoperative radiochemotherapy. Hazard ratios were virtually unchanged since the original report. Moreover, two meta-analyses comparing the efficacy of adjuvant CRT *vs* CT after R0 resection have confirmed the superiority of the combined modality in terms of disease-free survival[41,42]. However, there was no OS advantage with the addition of radiotherapy in both analyses.

## OPTIMAL CHEMOTHERAPY REGIMEN DURING RADIOTHERAPY

One of the most criticized aspects of the Intergroup trial was the toxicity profile of the FU/LV regimen. Therefore, other investigators have sought alternative postoperative chemoradiation regimens. In a pilot study by Lee *et al*[43] patients with stage Ⅲ-Ⅳ (M0) gastric cancer who had undergone extensive D2 LND were administered postoperative chemoradiation with fluorouracil and cisplatin before and after capecitabine and concurrent RT. A total dose of 4500 cGy in 25 fractions over five weeks was delivered to the target volume similar to the INT-0116 trial. This study demonstrated a 3-year disease free and OS of 82.7% and 83.4%, respectively, with the use of adjuvant chemoradiotherapy. Leong *et al*[44] reported that postoperative chemotherapy with epirubicin, cisplatin, and 5-FU (ECF) before and after concurrent chemoradiation with infusional fluorouracil was tolerable and efficient. A similar regimen with ECF before and after radiation with infusional fluorouracil has been compared with the INT-0116 regimen in a randomized phase Ⅲ trial (CALGB 80101)[45]. Although the ECF regimen had a more favourable toxicity profile compared with bolus fluorouracil and leucovorin, there was no significant improvement in survival.

Alternative regimens for concomitant and adjuvant treatment have also been experienced. The efficacy of paclitaxel - cisplatin and 5-FU regimen against oesophageal and gastroesophageal junction adenocarcinomas has been demonstrated previously[46]. Results of a phase Ⅰ trial conducted among patients with locally advanced gastric cancer using weekly cisplatin and RT with paclitaxel as a 96-h continuous infusion were also promising[47]. Another trial from MD Anderson included patients with gastric cancer who received two cycles of induction chemotherapy with infusional 5-FU, cisplatin on days 1 to 5, and paclitaxel over 24 h on day 1 of each 28-d cycle[48]. During the 5-wk course of RT, infusional 5-FU and paclitaxel were administered weekly. Complete and partial response rates were 22% and 15%, respectively, which were quite promising. In the light of these findings, a phase Ⅱ trial (RTOG-0114) was designed to integrate paclitaxel and cisplatin with or without 5-FU concomitantly through radiotherapy. However, the paclitaxel, cisplatin, and 5-FU (PCF) arm were closed due to the high gastrointestinal toxicity rates, which were significantly worse than INT0116 results[49]. For the paclitaxel and cisplatin (PC) arm, the 2-year DFS was 52% (95%CI: 36%-68%). Although the PC arm was tolerable, the DFS failed to exceed the predefined lower bound of DFS at 2 years. Thus, this regimen could not be recommended as an adjuvant modality for future randomized phase Ⅲ studies. These trials suggested that intensification of adjuvant chemotherapy or chemoradiation regimens may not be as effective as expected. Table 2 summarizes the major trials evaluating adjuvant CRT.

Whether an intensified CRT regimen prolonged survival after D2 dissection was another subject of debate. The ARTIST trial was designed to answer this question; comparing six cycles of capecitabine and cisplatin (XP) chemotherapy with two cycles of XP followed by concurrent capecitabine and RT followed by two additional cycles of XP after D2 dissection[4]. However, the study failed to demonstrate a significant DFS benefit with the addition of radiotherapy to XP (3-year DFS rates 78.2 *vs* 74.2% for CRT and CT arms, respectively). Treatment was completed as planned by 75.4% of patients in the chemotherapy arm and 81.7% in the CRT arm. The updated analysis with longer follow-up did not reveal DFS or OS benefit either[50]. However, the subgroup of patients with pathologic lymph node metastasis in the CRT arm had superior DFS when compared with those who received CT alone (3-year DFS; 76% *vs* 72%). Besides,

**Table 2 Features of major adjuvant chemoradiotherapy trials for gastric cancer**

| Ref. | CT Regimen without RT/with RT | *n* (total) | D2 rates | G3-G4 toxicity (hem/GI) | Completeness of treatment | RT technique |
|---|---|---|---|---|---|---|
| Macdonald *et al*[6] | Bolus 5-FU + LV/bolus 5-FU + LV | 556 | 10% | 54%/33% | 64% | 2D |
| Lee *et al*[43] | FP/capecitabine | 31 | 100% | 50.2%/12.8% | 74.20% | 2D |
| Zhu *et al*[57] | Bolus 5-FU + LV/bolus 5-FU + LV | 380 | 100% | 5.9%/7.5% | NA | IMRT |
| Leong *et al*[44] | ECF/inf 5-FU | 54 | NA | 66%/28% | NA | 3D |
| Schwartz *et al*[49] | PC (PCF arm closed)/PC | 78 | NA | 24%/33% (for PC arm) | NA | 3D |
| Lee *et al*[4] | XP/capecitabine | 458 | 100% | 48.4%/19% | 81.7% | 3D |

CT: Chemotherapy; RT: Radiotherapy; D2: D2 lymph node dissection; G3-G4: Grade 3-grade 4; hem: Hematologic; GI: Gastrointestinal; NA: Not available; 5-FU: 5-fluorouracil; LV: Leucovorin; inf: Infusional; FP: 5-FU, cisplatin; ECF: Epirubicin, cisplatin, 5-FU; PC: Paclitaxel, cisplatin; PCF: Paclitaxel, cisplatin, 5-FU; XP: Capecitabine, cisplatin; 2D: Two-dimensional; 3D: Three-dimensional; IMRT: Intensity modulated radiotherapy.

intestinal-type gastric cancer derived more benefit from CRT (3-year DFS rates were 83% and 94% in the CT and CRT arms, respectively).

The most commonly encountered nonhaematologic grade 3 to 4 side effects were stomatitis, hand and foot syndrome, diarrhoea, and vomiting, each of which occurred in 1% to 12% of patients in both arms. The rate of grade 3 and 4 neutropenia was 39% in the CT arm and 48% in the CRT arm; however, the rate of febrile neutropenia was quite low in both arms (< 1%), suggesting that postoperative treatment with cisplatin and capecitabine and is tolerable following a D2 LND. In conclusion, capecitabine at a dose of 1650 mg/m$^2$ per day with RT was well tolerated.

In the light of the studies mentioned above, combination regimens other than 5-FU/LV are still under investigation for gastric cancer. The NCCN guidelines, however, do not recommend the standard bolus 5FU/LV regimen utilized in the INT0116 trial. Relying on the data from gastric cancer trials, such as the ARTIST trial and colorectal cancer studies, capecitabine or infusional 5-FU is recommended concomitantly with RT by the NCCN due to their better toxicity profile and tolerability[51].

## RADIOTHERAPY TECHNIQUE

Since the publication of the INT0116 results, the radiotherapy technique and planning of the target volume has changed over time. Patients involved in this trial received 45 Gy of radiation in 25 fractions to the surgical bed, regional lymph nodes, and preoperative tumour volume. The regional lymph nodes included perigastric, splenic, hepatoduodenal, pancreatoduodenal, celiac, and local paraaortic lymph nodes based on patterns of failure after a D0/D1 dissection. In the Intergroup-0116 trial, two-dimensional (2D) radiation therapy was utilized and the CRT arm was associated with high rates of toxicity, with nearly three-quarters of patients experiencing grade 3/4 toxicities. Only 64% of patients in the CRT arm completed the planned treatment program, and 17% discontinued treatment due to toxicity. However, treatment-related mortality was low (1% on the chemoradiation arm *vs* 0% on the surgery alone arm). In addition, overall chemoradiation appeared tolerable.

Fortunately, technology has improved over time to allow conformal radiation therapy, sparing normal tissues and allowing dose escalation. Three-dimensional (3D) conformal radiotherapy reduces the damage to normal tissues to some extent and is considerably superior to 2D radiation[52]. Currently, modern 3D RT techniques are applied for the resected gastric cancer patients at most of the oncology centres in the world. 3D planning enables exact description of the target volume and organs at risk by visualization of anatomic changes in the internal organs after surgery[53].

Whether or not to change the RT target volumes for patients undergoing D2 dissection is another subject of debate. The findings of the study by Chang *et al*[54] have revealed that the most prevalent sites of regional recurrence after D2 dissection were the lymph nodes around the superior mesenteric vessels, the abdominal aorta from the upper margin of celiac trunk to the lower margin of aortic bifurcation, and the hepatoduodenal lymph nodes, which were primarily in the nodal basin outside the D2 dissection field. Consistent with these findings, the RT target volume in the ARTIST trial did not involve lymph nodes in the perigastric region and splenic hilum[4]. The investigators have noted higher locoregional relapse rates in the CT arm (13% *vs* 7%, $P = 0.0033$) which supports the addition of CRT even in the presence of D2 dissection with the modified RT target volume.

Intensity modulated radiotherapy (IMRT) is a more sophisticated radiotherapy technique, with capability of delivering high doses of radiation to a targeted area with high geometrical accuracy. According to the recent studies, IMRT for gastric cancer is dosimetrically superior to conventional therapy, because IMRT is able to decrease the radiation dose to organs at risk, especially the spinal cord and kidney, while providing the intended radiation dose to the target areas[55,56]. The most recent phase Ⅲ trial comparing concomitant CT with IMRT and chemotherapy alone investigated the role of IMRT among gastric cancer patients with D2 LND[57]. The IMRT plus CT arm was tolerable with a significant improvement in DFS (5-year DFS, 45% *vs* 36%); however, the results of this trial could not point at an OS benefit like the previous comparative studies (5-year OS, 24% *vs* 27%, $P > 0.05$). According to some investigators, IMRT appears to provide only limited advantages when compared with sophisticated 3D conformal RT planning[58]. Moreover, the risk of a second cancer induced by radiation is reported

to increase in some patients[59,60]. Whether 3D conformal RT or IMRT provides better protection of organs at risk remains controversial.

## SELECTING PATIENTS FOR ADJUVANT CHEMORADIOTHERAPY

### *Stage*

Although the patients involved in the INT0116 trial were stage IB-Ⅳ (M0), the majority had advanced disease, whereas up to 60% of patients in the ARTIST trial were stage Ⅰ/Ⅱ. Furthermore, in the subgroup analysis of the ARTIST trial, improved DFS ($P < 0.05$) was observed in stage Ⅲ and Ⅳ patients in the CRT group. The proportion of stage Ⅲ/Ⅳ (M0) patients enrolled in the study by Zhu *et al*[57] was 71%, which demonstrated a DFS benefit for CT with IMRT after D2 dissection. The subset (node-positive) analyses of the ARTIST trial and the DFS advantage for stage Ⅲ and Ⅳ (M0) patients in the Chinese trial supported that the use of adjuvant CRT for the whole stage IB to stage Ⅳ (M0) population may be overtreatment. Similarly, adjuvant CT alone may be inadequate for resected stage Ⅲ-Ⅳ patients. Subgroup analysis of 5-year OS in the ACTS-GC trial from Japan showed an insufficient survival benefit of S1 for N3a and N3b stages (HR = 0.77, 95%CI: 0.53-1.13 and HR = 0.92, 95%CI: 0.47-1.79, respectively). The results indicated the necessity of adjuvant RT in these patients who were at high risk for locoregional relapse. Accordingly, in our study, which included D2 dissected pN3(M0) gastric cancer patients, the addition of RT to CT did not provide a statistically significant improvement in DFS or OS, but there was an evident difference between the CT and CRT arms numerically (median DFS 12.5 and 15.2 mo; median OS, 26.8 mo *vs* 34.2 mo for CT and CRT arms, respectively)[61]. Another retrospective study from China including stage Ⅲ gastric cancer patients with D2 dissection showed OS and DFS advantage for stage ⅢC patients undergoing adjuvant CRT compared with CT[62]. These studies indicate that patients with relatively advanced disease stages (Ⅲ or Ⅳ) would benefit the most from adjuvant CRT.

The presence of lymphovascular invasion (LVI) or perineural invasion (PNI) have been demonstrated as significant prognostic factors for both OS and DFS among patients undergoing adjuvant treatment[63]; however, thus far, there have not been any randomized trial data evaluating the administration of CT or CRT depending on the stage or presence of LVI or PNI, unlike for breast and colon cancers. However, the ARTIST Ⅱ trial is on track to evaluate the efficacy of all available adjuvant treatment modalities after D2 dissection for node positive patients (clinicaltrials.gov NCT01761461); chemotherapy with S-1 for 1 year *vs* chemoradiotherapy involving two cycles of SOX followed by S-1/radiotherapy and then four additional cycles of (SOX) *vs* combination chemotherapy with S-1 and oxaliplatin (SOX) for 6 mo. Patients were stratified according to stage, type of surgery, and the Lauren classification.

Another phase Ⅲ study is currently recruiting stage IB gastric cancer patients for evaluating adjuvant capecitabine *vs* observation (clinicaltrials.gov NCT01917552). The results of these trials are expected to answer the question regarding tailoring treatment to disease stages.

### *Histology and biomarkers*

The main carcinogenic event for the evolution of diffuse type of gastric cancer is loss of expression of E-cadherin, a key cell surface protein for establishing intercellular connections. Biallelic inactivation of the gene encoding E-cadherin, CDH1, can occur through germline or somatic mutation, allelic imbalance events (*e.g.,* loss of heterozygosity), or epigenetic silencing of gene transcription. Diffuse type cancers are highly metastatic and characterized by rapid disease progression and a poorer prognosis than intestinal cancers[64]. Thus far, there has been no adjuvant therapy trial designed according to histological subtype. However, exploratory subgroup analysis of randomized trials point at varying degrees of benefit according to histologic subtype. The investigators of the INT0116 study reported their observation of a reduced treatment benefit in patients with diffuse histology in their updated analysis[40]. Similarly, the patients with intestinal type gastric cancer were found to be more prone to benefit from CRT than those with diffuse type in subgroup analyses of the ARTIST trial[50]. Patients with intestinal type histology showed a significant improvement in DFS in the CRT arm compared with the CT arm (94% *vs* 83%, $P = 0.01$, respectively). Whether or not this is a random observation of an unplanned subset analysis or reflective of the biologic variations is unknown, but if chemoradiotherapy is less effective in diffuse gastric cancer, future clinical trials may consider different adjuvant strategies based on histological subtype. A phase Ⅱ/Ⅲ study is currently recruiting patients with resectable signet-ring cell gastric carcinoma to perioperative treatment similar to MAGIC trial or surgery followed by six cycles of ECF (clinicaltrials.gov NCT01717924). This study may help determining the efficacy of intense CT with cisplatin for diffuse type gastric cancer cases.

In addition to morphologic appearance and clinical behaviour, the two distinct types of gastric adenocarcinoma differ with respect to their pathogenesis and genetic profiles[65]. For the intestinal subtype, there is meticulous evidence for the role of *Helicobacter pylori* in the initiation of the events that lead from chronic active gastritis to atrophic gastritis, intestinal metaplasia, dysplasia, and finally adenocarcinoma. Many gene changes have been described in various stages of the preneoplastic/neoplastic cascade, but the alterations do not generally follow a sequential arrangement. Some changes are seen in early preneoplastic lesions but are not present in more advanced lesions. Therefore, it is not easy to develop an appropriate target for treatment.

Approximately 50% of intestinal-type gastric cancers have alterations in tumour suppressor genes, including

*TP53, TP73*, *APC*, *TFF*, *DCC*, and *FHIT*[66]. In addition, epigenetic alterations, such as DNA methylation of gene promoters, can silence the expression of certain genes, including *CDH1* (the E-cadherin gene), in not only diffuse type but also in intestinal-type cancers[67,68]. Unlike the complex molecular pathway for intestinal type, diffuse carcinomas display a discriminative molecular abnormality: Defective intercellular adhesions through the loss of expression of the cell adhesion protein E-cadherin as mentioned below. Although this knowledge has not resulted in a specific targeted therapy for diffuse gastric cancer yet, the recognition of germline *CDH1* mutations in families helps identify high-risk individuals and encourage them to receive prophylactic gastrectomy.

The struggle to identify specific biomarker for predicting a treatment benefit has not resulted in success in the adjuvant setting so far. In the ARTIST trial, the different status of the *EGFR*, *HER-2, MET, MLH1,* and *CDH1* genes were considered; however, differences in the expression of these genes between the CRT and CT groups had no effect on DFS[50]. Inhibition of HER-2 overexpression *via* trastuzumab in metastatic disease has revealed a median of 2.7 in OS benefit in the ToGA trial, and currently this strategy is being evaluated in the adjuvant setting (clinicaltrials.gov NCT01130337, NCT01748773). Previously, the amplification of mesenchymal-epithelial transition (MET) receptor has been linked to poorer clinical outcome in patients with gastric cancer[69]. There are some conflicting case reports on attempts to target MET in patients with gastric cancer[69,70]. However, it seems feasible to wait until the results of the trial, which is testing a MET antibody in the metastatic setting, are reported (clinicaltrials.gov NCT01662869).

## CONCLUSION

Currently, there is no doubt that adjuvant chemotherapy or chemoradiotherapy after resection of gastric cancer offers survival benefits. The major challenge for the clinicians is how and where to place the additional treatment modality (*i.e.*, CT or CRT; adjuvant or perioperative setting). The selection of the appropriate patient who will provide more or no benefit from therapy further complicates the situation. Obviously, there is lack of data to compare perioperative CT *vs* adjuvant CRT. However, the evidence for adjuvant CT with XELOX or S1 after D2 dissection is satisfactory. Although the evolution of the RT technique since the Intergroup study promises better tolerability, the addition of CRT after D2 dissection merits further investigation in the light of the findings from the ARTIST trial. Instead of the bolus 5-FU regimen or 5-FU combinations, infusional 5-FU or capecitabine concomitantly with RT may be preferred due to the improved toxicity profile. Nevertheless, the struggle to individualize treatment strategies for a robust combat with the resistant subgroups, such as the diffuse type of gastric cancer, should continue until optimal targets for therapy are defined.

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