JOURNAL OF CANCEROLOGY REVIEW ARTICLE

Adjuvant Therapy in Resectable Gastric Cancer

JORGE GALLARDO[1], PAOLA MONTENEGRO[2], GUILLERMO MÉNDEZ[3], ANDRÉ M. MURAD[4], SEBASTIÁN SOLÉ[5] AND MANUEL ALVAREZ[6]

[1]Fundación CáncerChile, Providencia, Santiago, Chile; [2]Instituto Oncológico Perú, Lima, Peru; [3]Hospital Udaondo, Buenos Aires, Argentina; [4]Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brasil; [5]IRAM, Santiago, Chile; [6]Clínica las Condes, Metropolitana, Chile

ABSTRACT

Early detection of gastric adenocarcinomas is neither possible nor practiced around the world except, on a limited basis, in Japan. Therefore, gastric carcinoma is frequently detected late in most patients. Surgical resection in the early stages is potentially curative, with a high level of post-surgical relapse. Due to this, additional strategies with radiotherapy and neoadjuvant and adjuvant chemotherapy have been developed in order to improve the surgical results in patients with gastric carcinoma that is locally advanced and in the early stages. (J CANCEROL. 2016;3:109-24)

Corresponding author: Jorge Gallardo, dr.jgallard@gmail.com

Key words: Gastric carcinoma. Adjuvant. Neoadjuvant. Treatment. Radiotherapy. Chemotherapy.

Correspondence to:
Jorge Gallardo
E-mail: dr.jgallard@gmail.com

Received for publication: 01-09-2016
Accepted for publication: 15-09-2016

INTRODUCTION

Gastric cancer is the fourth most common type of cancer and the second leading cause of cancer-related deaths worldwide[1].

If surgery is still the only potentially therapeutic treatment for gastric cancer, in the early stages of the disease it has higher healing rates. However, less than 25% of cases are detected in the initial stages, and survival rates are significantly reduced when the tumor spreads to the muscle tissue and when lymph nodes are compromised[3].

Many of the symptoms produced by the disease may not appear in the early stages. Some of these symptoms can also appear in benign tumors, which, together with the lack of a standard screening process, contributes to the detection of the disease in more advanced stages, thus reducing the chances of cure in patients.

Treatment strategies have been developed, in addition to surgery, which allow for improved outcomes. They are neoadjuvant, adjuvant, or perioperative strategies, including chemotherapy (CT) and/or radiotherapy (RT), and are increasingly used to treat gastric cancer patients in early and locoregional advanced stages. Neoadjuvant therapy is aimed at increasing curative resections, reducing the tumor size, eliminating micro-metastasis, and improving the symptoms produced by the disease. The different regimens designed as an adjuvant therapy have an impact on the progression-free survival and overall survival[4].

Conversely, patients who are initially operated on and, depending on their clinical-pathological stage, may receive adjuvant treatment with chemotherapy (CTx) or chemoradiotherapy (CRTx), which has also been demonstrated to have an impact on the overall survival (OS) and progression-free survival (PFS)[5].

The controversy over which of these strategies is the most suitable continues worldwide, with a highlight on several trends, among them the Asian one, favoring adjuvant therapy with CTx only; in the USA, CRTx is combined with the adjuvant therapy, and European specialists favor perioperative CTx.

The present article focuses on the main perioperative treatment strategies, neoadjuvant and adjuvant therapy, showing the results for the different strategies in an impartial manner.

SURVIVAL PROGNOSIS ACCORDING TO STAGING

The prognosis of gastric cancer patients is related to the tumor extension, how compromised the lymph nodes are, and the tumor size beyond the gastric wall[6,7].

In the cases of stomach cancer, only 26% of patients are diagnosed in the local stage, 29% of patients are diagnosed in the regional stage, 35% of cancer patients in distant metastasis or metastasis, and approximately 10% of them without known staging[8]. In the SEER 1973-2005 study from the USA of 10,601 gastric cancer patients, only 17.4% of them were in IA-IB stages and 58% of patients were diagnosed in IV stage[9].

The five-year survival for stomach cancer in all stages is 29.3%, for the local stage it is 65.4%, 29.9% for the regional stage, and only 4.5% of survival in cancer patients with distant metastasis[8]. At a global level, nearly 60% of patients who undergo R0 resection relapse and die. Consequently, the overall five-year survival rate of resectable gastric cancer patients oscillates between 10 and 30%.

In the abovementioned SEER study[9], we can see that in the IA stage, the group with the best prognosis has a five-year survival rate of 87.8% and

Table 1. Survival rates observed in 10,601 surgically resected gastric adenocarcinomas

Stage	Al Dg	1	2	3	4	5
IA	100	90.2	84.8	79.8	74.8	70.8
IB	100	87.4	77.9	69.9	62.7	57.4
IIA	100	82.1	67.4	57.2	50.2	45.5
IIB	100	76.8	58.3	46.0	38.4	32.8
IIIA	100	66.5	42.4	29.9	23.5	19.8
IIIB	100	61.6	35.4	22.9	17.8	14.0
IIIC	100	47.4	21.8	14.2	11.0	9.2
IV	100	27.0	10.0	5.6	4.5	4.0

Stage IA included 1,194 cases; Stage IB, 655 cases; Stage IIA, 1,161 cases; Stage IIB, 1,195 cases; Stage IIIA, 1,031 cases; Stage IIIB, 1,660 cases; Stage IIIC, 1,053 cases; and Stage IV with 6,148 cases.
Source: SEER 1973-2005 Data. Public archives diagnosed in the years 1991-2000.

this drops drastically to 57.4% for the IB group (Table 1).

The depth of the primary tumor invasion on the wall is related to the worst prognosis, but lymph node involvement is possibly deemed as the most powerful prognostic factor. The location of the tumor inside the stomach (proximal tumors have a worse prognosis than distal tumors), the histological grading, and lymph-vascular invasion also have an influence on fully resected gastric cancers. Asians, women, and young patients are the predictors of a better prognosis, while high levels of CEA and CA-19-9 predict a poor prognosis[9].

NEOADJUVANT AND PERIOPERATIVE TREATMENT OF GASTRIC CANCER

Neoadjuvant and perioperative strategies, including CTx and/or CRTx, are being increasingly used to treat patients with locoregional advanced gastric cancer and in the early stages. A number of advantages have been described for the neoadjuvant treatment strategy in the treatment of aggressive solid tumors, including gastric cancer. Firstly, this focus allows for an early treatment of the micro-metastatic disease. On the other hand, it makes it possible for the evaluation of the chemosensitivity and *in vivo* treatment response, including the possibility of tumor reduction, as well as the complete pathological response, and this can be translated into improved outcomes[10,11]. In addition, it allows for treatment administration when the patient is in better clinical conditions without having to wait for the postoperative recovery, which leads to an improvement in adherence to therapy by patients to complete the treatment[4,12], and finally, it allows for an improved chance of an adequate oncological surgery (R0)[4,12].

The perception that neoadjuvant treatment can compromise the chances of cure in those patients with progression during the preoperative treatment that generally demands two to three months is unfounded. Furthermore, it would allow the identification of poor surgical candidates that carry biologically aggressive and incurable tumors. This could also be considered an advantage of the neoadjuvant model.

The incorporation of CRTx into the neoadjuvant strategy could be beneficial. When finding an intact tumor as well as the patient's anatomy, it facilitates planning with a better preservation of the toxicity of adjacent organs. This strategy has been translated into better tolerance and better locoregional control in cases of rectal cancer and esophageal cancer, to mention two examples[13,14].

The FAMTX Dutch study was one of the first randomized clinical trials assessing the role of neoadjuvant CTx in gastric cancer. The study included 59 patients, of which 29 patients randomly received four cycles of 5FU, doxorubicin, and methotrexate followed by surgery, and 30 patients were assigned to surgery only. The resectability rate was similar in both treatment arms. The neoadjuvant FAMTX allowed around 32% of responses (full plus partial responses), but it did not improve the OS significantly compared to surgery alone (30 vs. 18 months; $p = 0.17$), but it was a study with a low number of patients[15].

The MAGIC English study was the first to demonstrate the benefit of the perioperative strategy in gastric cancer and gastroesophageal cancer patients. A total of 503 patients with cancer in stages Ib and IVa were randomly assigned to three preoperative cycles and three postoperative cycles of CTx with epirubicin (50 mg/m^2), cisplatin (60 mg/m^2) administered on day 1, plus 5FU in continuous infusion (200 mg/m^2), for 21 days in three-week interval cycles. Twenty-six percent of patients with gastroesophageal cancer were included in the study. The primary objective of the study was OS.

Patients in the perioperative CT group had a higher likelihood of a R0 surgery (79.3 vs. 70.3%; p = 0.03) and the resected tumors were significantly smaller (T1/T2 52 vs. 37%) and lesser lymph node involvement (N0/N1 84 vs. 71%) compared to the group subjected to surgery only. The postoperative complication rates and mortality rates were similar in both treatment groups.

The patients in the perioperative CTx group obtained a significant benefit in OS (24 vs. 20 months), five-year survival (36 vs. 23%; HR: 0.75; p = 0.009) as well as in PFS (HR: 0.66; p < 0.001). It is worth highlighting that while 91% of the patients in the CT group completed the preoperative part, only 50% of them could complete the postoperative part, particularly due to early recurrence and delayed postoperative recovery. This finding suggests that the survival benefit especially results from the preoperative CT. The most common adverse event related to CT was neutropenia (23%), although only 12% experienced grade 3-4 neutropenia. It is worth noting that in the subgroup analysis, patients with gastroesophageal cancer were the ones who had the greatest benefits regarding this strategy[4].

A similar benefit was observed in the FNLCC/FFCD French study[12], similar to the MAGIC study design. Patients with similar characteristics (Ib-IVa stages) were randomized to 2-3 preoperative CT cycles and 2-3 postoperative CT cycles with cisplatin (100 mg/m^2) on day 1 with 5FU 800 mg/m^2 in continuous infusion of four days in four-week cycles, or surgery alone (113 and 111 patients, respectively). Sixty percent of the patients had gastroesophageal cancer as primary site.

A higher probability of R0 surgery (84 vs. 73%; p = 0.004), higher OS (32 vs. 22 months), a higher five-year disease-free survival (DFS) rate (34 vs. 19%; HR: 0.65; p = 0.003) and a better five-year OS (38 vs. 24%; HR: 0.69; p = 0.02) were observed in the perioperative CT group compared to the surgery only group. As in the MAGIC study, the greatest benefit was obtained by gastroesophageal cancer patients.

Aiming to intensify and improve the perioperative strategy, the ST03 English study randomly assigned 1,063 gastric cancer and gastroesophageal cancer patients, stage Ib-IVa, to receive three preoperative CTx cycles and three postoperative CTx cycles with the regimen epirubicin 50 mg/m^2 day 1, cisplatin 60 mg/m^2 day 1, capecitabine 1,250 mg/m^2 days 1-21 in three-week cycles followed by surgery, versus the same regimen plus bevacizumab 7.5 mg/kg on day 1.

A similar percentage of patients with R0 surgery was observed in both groups (74 vs 75%) as well as a similar OS. A higher rate of postoperative complications (particularly fistulas) was noticed in the bevacizumab group. Notably, only 37% of patients in both groups could complete the postoperative CTx[16].

In order to demonstrate the benefits of the neoadjuvant strategy, the EORTC planned the 40954 study[17]. The patients were randomly assigned to four preoperative CTx cycles with cisplatin and 5FU or surgery only. Only 144 patients were recruited and the study was prematurely closed due to recruitment failure. A higher probability of R0 surgery (81.9 vs. 66.7%) and lower lymph node involvement (61.4 vs. 76.5%; p = 0.018) was no-

ticed in the CTx group. Although a much higher DFS and higher OS were achieved in the neoadjuvant CTx group, this did not reach statistical significance (p = 0.2 and 0.466, respectively), probably due to the low statistical power of the study.

In addition, several meta-analyses have evaluated the role of neoadjuvant CTx in gastric cancer[18-20]. In 2014, Xiong, et al. published the results of 1,820 patients from 12 different studies, of which six studies were performed in Asia and six were performed in the West[21]. The meta-analysis showed that patients treated with neoadjuvant CTx followed by surgery only had a marginal benefit in OS compared to surgery alone (odds ratio: 1.32; p = 0.001). However, a greater benefit was observed in the three-year DFS rate, "down-staging" rate, and R0 surgery rate for patients treated with CTx.

The subgroup analysis also showed that the benefit rates in five-year OS of patients treated with neoadjuvant CT were significantly improved in studies conducted in the West (p < 0.01), but not in studies conducted in Asia (p = 0.32).

Although these studies have demonstrated the neoadjuvant treatment benefits, their main weakness lies in the lack of postoperative adjuvant treatment in the standard group, which consisted of surgery only in all studies. Conversely, some questions were not answered: What is the most important part of the perioperative treatment? Would preoperative CTx be enough to yield survival benefits or should it be combined with postoperative adjuvant CTx? Are objectives achieved with adjuvant CTx alone? How do we view the use of neoadjuvant CTx in Asia, where the highest incidence of gastric cancer, the most sophisticated surgical techniques, and good adjuvant treatment strategies coexist? The key question is that we still do not know if perioperative CTx has the same additional advantage as adjuvant CTx in the treatment of operable gastric cancers.

In order to address these questions, a meta-analysis of neoadjuvant CTx was performed in the survival results of operable gastric cancers, with searches in the PubMed, Embase, and Cochrane Library for random clinical trials published through June 2014. Neoadjuvant CTx strategies were compared with neoadjuvant-free strategies in patients with stomach adenocarcinoma or gastroesophageal cancer who had undergone a potentially curative resection[22]. The combined adjusted hazard risk (HR) rate for OS was insignificant when comparing the arm containing neoadjuvant treatment with the free arm. The subgroup analysis showed that the treatment arm that included both adjuvant and neoadjuvant CTx was significantly improved in the control group (only adjuvant treatment) (HR: 0.48; 95% CI: 0.35-0.67; p < 0.001). While neoadjuvant CTx plus surgery did not show any benefit in survival compared with surgery alone, perioperative CTx showed a significant PFS increase and a significant reduction of distant metastasis compared to surgery only. However, in patients with resectable gastric cancer, neoadjuvant CTx only is not sufficient and adjuvant CTx itself is not sufficient for a definitive improvement in the OS of treated patients. The study reached the conclusion that perioperative CTx associated with surgery can be beneficial in the survival rate of resectable gastric cancer patients.

The scope in the potential indication of a neoadjuvant/perioperative strategy highlights the need for an optimal selection of patients who received the greater benefit.

Different clinical tools, such as age, weight loss, and need for splenectomy and/or pancreatectomy, have been used to predict the postoperative morbidity risk[23]. Those high-risk patients could be preserved in time for the start of postoperative treatment.

An adequate preoperative study is directly related to the selection of patients. Computed axial tomography (with its variants: hydrotomography and

pneumotomography), echo-endoscopy, PET-CT, and laparoscopy with different methods are used in the staging of patients. In addition to their strengths and weaknesses, it is likely that an optimal staging requires a combination of two or more studies[24-27].

ADJUVANT TREATMENT WITH CHEMOTHERAPY ONLY

There are a varied number of studies that have evaluated the administration of adjuvant CTx (CTx after surgery with curative intent) versus surgery alone. The impact of adjuvant CTx in the survival has contradictory results.

Multiple meta-analyses have been published; some of them support a significant benefit in the survival of patients who received postoperative or adjuvant CTx. The first meta-analysis published by Hermans, et al. included 2,096 patients. In this meta-analysis, adjuvant CTx did not have an improvement in the survival of patients with surgical resections with a curative intent. The odds ratio (OR) was assessed at 0.88[28].

Another meta-analysis limited to non-Asian patients published by Earle, et al. reported a 0.80 OR (95% CI: 0.66-0.97). It showed that 65% of patients who underwent gastrectomy and had recurrence ended up dying, compared to 61% of patients subjected to surgery plus adjuvant CTx. The reduction in absolute risk was 4%[29].

More recent meta-analyses that included a greater number of patients have demonstrated a statistically significant benefit in terms of OS and PFS in favor of adjuvant therapy with regimens that contain 5FU. Paoletti, et al. (6,390 patients) demonstrated an OS (HR: 0.82; 95% CI: 0.76-0.90; p = 0.0019) and DFS (HR: 0.82; 95% CI: 0.75-0.90; p = 0.001) in favor of adjuvant therapy with chemotherapy, with a five-year survival rate increase from 49.6 to 55.3%[30].

Table 2. Optimal adjuvant chemotherapy regimen

Author	Number of patients	Results	P
Paoletti, et al.[30]	3,838	HR 0.82	< 0.001
Hermans, et al.[28]	2,096	OR 0.88	NR
Earle, et al.[29]	1,990	OR 0.80	NR
Sun, et al.[31]	3,809	HR 0.78	< 0.001

However, Sun, et al. (3,809 patients) published some benefits in terms of OS in favor of adjuvant therapy with CTx (HR: 0.78; 95% CI: 0.71-0.85). No influence was found in the results obtained from the depth of the tumor invasion, lymph node metastasis grading, lymphadenectomy type, geographic distribution, or route of administration of the drug[31] (Table 2).

The optimal adjuvant chemotherapy regimen has not yet been established. There are several acceptable alternatives including epirubicin, cisplatin and 5-FU infusion (ECF); cisplatin-5FU (5FU, C) capecitabine plus oxaliplatin; and S-1, which is an oral fluoropyrimidine comprising three different agents: ftorafur (tegafur), gimeracil (5-chloro-2,4-dihydropyridine), a potent dihydropyrimidine dehydrogenase inhibitor), and oteracil (potassium oxonate), which inhibits intestinal phosphorylation.

Various adjuvant therapy studies have been conducted in Japan. Studies JCOG 8801 and 9206-1 of the Japanese group failed to demonstrate the adjuvant treatment benefits using combinations with S-1[32,33]. The latter (9206-1) published in 2003 included 252 patients, who after the D2 surgery or more, were randomly assigned to observation versus adjuvant treatment with CTx (mitomycin 1.33 mg/m^2, 5FU 166.7/m^2, and cytarabine 13.3 mg/m^2) twice a week for the first three weeks after surgery, and oral 5FU 134 mg/m^2, every day for the following 18 months until reaching a total dose of 67 mg/m^2). No statistically significant differences were found between both treatment arms in terms of OS or relapse-free survival[33].

These results are consistent with the preliminary meta-analysis results that show a death HR of 0.70-0.82 among patients who received S-1 compared to those who did not receive it[30,31].

In the USA, this adjuvant therapy is not a conventional treatment; however, this treatment is a standard in Asia, based on the results of the CLASSIC and ACTS-GC studies, which are further discussed.

The Japanese study with S-1 showed the benefits of adjuvant therapy with S-1 in gastric cancer patients stage II or III who had undergone a potentially curative surgery with D2 lymphadenectomy randomly assigned to S-1 (80-120 mg/day for four weeks, repeated every six weeks for one year) against surgery only[34].

A total of 1,059 patients were included in this study, which was initially published in 2007 and updated in 2011 after a five-year follow-up, with a five-year survival of 71.7% in the group receiving S-1 and 61.1% in the surgery only arm (HR: 0.669; 95% CI; 0.540-0.828). The five-year relapse-free survival was 65.4% in patients receiving S-1 and 53.1% in the surgery alone group (HR: 0.653; 95% CI: 0.537-0.793). The most common adverse events were anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%).

This study is the first large Japanese phase III trial, positive, with great clinical impact. However, the treatment according to its own authors could not be validated, while D1 resection is considered a recommended but not required surgery[35].

Conversely, the CLASSIC study (in South Korea, China and Taiwan), which included 1,035 patients, evaluated the administration of postoperative CTx with capecitabine (1000 mg/m^2 twice a day, on days 1-14) in combination with oxaliplatin (130 mg/m^2 on day 1), after curative resection with D2 nodal dissection, of at least 15 lymph nodes to ensure adequate classification in gastric cancer patients, stage II, IIIA or IIIB randomly assigned to eight 21-day cycles of capecitabine plus oxaliplatin, or surgery alone[36].

In this study, DFS was found at 62.4 months follow-up of 27% in a group that received adjuvant treatment vs. 39% in patients who received surgery alone (HR: 0.58). An estimated five-year DFS of 68 vs. 53% was found in patients who received adjuvant therapy vs. surgery alone, respectively, with statistical significance. The five-year OS was 78% in patients who received adjuvant CTx treatment vs. 69% in patients who were under observation.

In the subgroup analysis, the patients who benefited most from the treatment were patients with histological grade G1 and G2, lymph node involvement, and antral tumor localization.

The results of these two studies support the use of postoperative CTx after D2 curative surgery in patients with resectable cancer. However, it should be borne in mind that these results have not been documented in patients with D1 or D0 dissection; thus, some authors consider that CRTx would be the treatment of choice in these patients.

The ARTIST study[38], a randomized trial, which showed that postoperative CRTx has no benefit in gastric cancer patients, with D2 nodal dissection and curative resection, stages Ib-IVa, will be further reviewed in detail. In this trial, the standard arm indicated six CTx cycles with capecitabine and cisplatin, with a median follow-up of 53 months; the three-year DFS was 74% for CTx. From the adjuvant therapy viewpoint, this result is consistent with the CLASSIC study.

As for the use of adjuvant treatment in elderly patients, information is controversial, but they seem to benefit from adjuvant CTx. In a recent meta-analysis, the HR for OS in elderly and non-elderly patients was found to be 0.745 (95% CI: 0.552-1.006; $p = 0.055$), and 0.633 (95% CI: 0.533-0.753; $p < 0.001$), respectively. No heterogeneity was found between both groups, which may suggest

that a statistically relevant significance could be found if the sample size increased. Conversely, there was a statistically significant benefit in relapse-free survival in elderly patients (HR: 0.613; 95% CI: 0.466-0.806; $p < 0.001$)[39].

If the usefulness and benefit of adjuvant CTx therapy in patients with curative resections have been established, randomized positive studies mainly included Asian populations, and it is uncertain whether such results can be replicated in the Western population.

ADJUVANT CHEMORADIOTHERAPY

More than 80% of patients who die from gastric cancer experience local recurrence[40], which has caused interest in adjuvant CRTx. In randomized combined postoperative CRTx studies, after a complete resection of the gastric cancer, survival benefits have been demonstrated as compared to surgery alone.

The INT0116 study, published in 2001, is the most representative, though it is also the most controversial study. It established postoperative CRTx as a standard for completely resected gastric cancer.

The trial included 556 patients with gastric adenocarcinoma stages IB-IVA or gastroesophageal cancer, who, after a potentially curative surgery, were randomly assigned to surgery alone or to postoperative adjuvant therapy with concomitant CRTx followed by CTx. This consisted of radiotherapy (45 Gy in fractions of 1.8 Gy daily) administered with 5FU and leucovorin (400 and 20 mg/m^2, respectively) on days 1-4, and in the last three days of RT[41]. Furthermore, patients received four cycles of 5FU and leucovorin, one of them before CRTx and the remaining three patients after CRTx.

The majority of patients had T3 or T4 tumors and lymph node involvement (85%); only 31% of them had T1-T2 tumors, and 14% of patients had the disease without lymph node involvement (N0). Surgery was not scheduled. CRTx was offered to all patients with T1 or larger tumors, with or without lymph node involvement.

Adjuvant therapy versus surgery alone demonstrated benefits in several parameters: DFS improvement, 30 vs. 19 months; three-year survival benefit, 50 vs. 41%; improved OS, 36 vs. 27 months; a decrease in local treatment failure went from 29 to 19% and a reduction in the metastasis rate went from 40% for the surgery group alone vs. 32% for the group receiving experimental therapy.

Toxicity was significant, as there was a high hematological (54%) and gastrointestinal (33%) toxicity rate grade 3-4. Among the 281 patients assigned to CRTx, only 64% were able to complete the therapy. In addition, there was 1% (three cases) of death related to CRTx.

With more than 10 years of follow-up, the improvement in patient survival has been maintained. No increase in late toxicity was observed[42]. In the USA, the standard therapy is considered in patients with completely resected gastric cancer or gastroesophageal cancer, but the doses or the CTx regimen are no longer used due to toxicity. Therefore it is preferred to indicate 5FU in continuous infusion or capecitabine[43-45].

This study has been criticized for several reasons, with highlights on: a D0 surgery in 54% of cases; D1 surgery in 36%, and D2 surgery in only 10% of cases. The study was not designed to evaluate the role of CRTx in cases that had a D2 dissection. Moreover, 39 patients were classified at stage IB (T2N0) of the disease, in which a low risk of relapse is expected; in this case the benefit is not clear, due to the small number of enrolled patients.

Combined chemotherapy and radiotherapy treatment requires experience and a careful approach. Some argue that treatment with CTx received by these patients is not optimal.

According to the analysis of the results by subgroups of patients, the CRTx would be more effective in those cases with intestinal adenocarcinomas and smaller tumor volume (T1 N+, T2 NO) than those patients who have undergone non-oncologic D0 or D1 surgery. However, the effectiveness of this treatment would disappear in diffuse tumors and in patients who underwent D2 surgery.

It is not very clear whether the benefit was due only to CRTx or only to the adjuvant CTx or to their combination, as it happened in initial pancreatic adjuvant therapy studies, in which the benefit of CRTx was finally dismissed.

Leong, et al. in 2011 reported that postoperative CTx with epirubicin, cisplatin, and 5FU (ECF) before and after concomitant CRTx with 5FU infusion was safe and effective in patients with completely resected gastric adenocarcinoma[44]. With a follow-up of 36 months, the three-year OS rate was 62%. At three years, the DFS and OS rates were 82.7 and 83.4% respectively.

The US Intergroup study, CALGB 80101, which included patients with gastric cancer or gastroesophageal cancer who had undergone curative surgery, compared the regime of INT0116 protocol (5FU bolus and leucovorin with FU plus concurrent RT) versus postoperative ECF before and after FU plus concurrent RT[45]. Patients who received ECF had lower rates of diarrhea, mucositis, and grade 4 neutropenia. The OS was not significantly better with ECF at three years (52 vs. 50% for ECF and FU/leucovorin, respectively[7]).

In Korea[46], a study was conducted and published in 2003 that evaluated the benefits of adjuvant CRTx in gastric cancer patients stages IB to IV (MO), adequately operated with radical surgery, D2 dissection. Patients received a regimen similar to that given in the INT 0116 study. A total of 290 patients were included, of which 79% completed adjuvant treatment; with a follow-up of 49 months, 114 (34%) patients relapsed; 33 (29%) patients had a locoregional relapse, 76 (67%) patients had peritoneal relapse, and 41 (36%) patients had distant metastasis. Overall survival and relapse-free survival at five years was 60 and 57% of patients, respectively, all with acceptable toxicity. This study demonstrated that postoperative CRTx can be beneficial in patients with radical D2 surgery; however, this study was not randomized.

The ARTIST study[47], a phase III randomized trial, investigated the role of postoperative CRTx in patients with D2 lymph node dissection and gastric cancer curative resection, stages Ib-IVa, and was designed to compare postoperative treatment with capecitabine plus cisplatin (XP) versus the same CTx (XP) plus concomitant CRTx with capecitabine.

Six CTx XP cycles (capecitabine on days 1-14 and cisplatin on day 1, repeated every three weeks) were indicated in the standard treatment arm. The experimental treatment arm received two XP cycles followed by 45 Gy (capecitabine 1,650 mg/m^2 per day for five weeks) and then two XP cycles. A total of 458 randomly assigned patients were studied. Treatment was completed as expected by 75.4% of patients in XP and 81.7% in the experimental treatment arm. Patients with T2a, positive microscopic border, lymph node involvement N0, or distant metastases, and those who only had D1 resection were excluded from this study.

With a median follow-up of 53 months, the three-year DFS was 78 and 74%, respectively for CRTx vs. CTx ($p = 0.862$). Thus, the addition of CRTx to postoperative CTx did not significantly improve DFS in patients with D2 resection. However, in the subgroup of patients with lymph node metastasis, patients randomly assigned to the experimental treatment arm had a higher DFS compared to those only receiving XP (77.5 and 72.0%, respectively; $p = 0.0365$), and the statistical significance was maintained in the multivariate analysis. The conclusion is that the addition of CRTx did not significantly reduce recurrence after curative resection and D2 lymph node dissection in gastric

cancer, and a subsequent trial (ARTIST-II) will be performed in gastric cancer patients with lymph node involvement to confirm or dismiss this finding in the subgroup analysis.

This study demonstrated again that CTx with cisplatin/capecitabine is viable after D2 dissection.

The CRITICS study[48] was a phase III randomized study that included 788 patients with gastric adenocarcinoma or gastroesophageal cancer stages Ib-IVA. Patients with T2a, positive microscopic border, M1 lymph node involvement or distant metastasis, and those who only had R1 resection, were excluded from the study. Of the patients, 87% had at least one D1+ dissection, without splenectomy or pancreatectomy, and an average extirpation of 20 lymph nodes.

All patients received preoperative CTx at standard doses of epirubicin, cisplatin, and capecitabine (ECC), or epirubicin, oxaliplatin, capecitabine (EOC). After surgery, patients were randomly assigned to receive only CTx (393 patients), with the same preoperative regimen or concomitant CRTx.

With a median follow-up of 4.2 years for the primary endpoint, the five-year OS was similar in both treatment arms: 40.8 for CTx and 40.9 for CRTx, with a corresponding mean survival of 3.5 and 3.3 years. The PFS was also similar in both arms. However, only 47 and 52% of patients completed CTx and CRTx, respectively. A number of patients did not receive postoperative treatment for several reasons, including personal preference, disease progression, and toxicity in the preoperative phase. This study showed that CRTx does not significantly reduce recurrence after D2 dissection in curatively resected gastric cancer patients.

A retrospective analysis[49] of various phase I/II studies conducted in the Netherlands, which compared the outcomes of patients treated with surgery only versus those treated with surgery followed by fluoropyrimidine-based CRTx, showed no benefits in the recurrence rate for patients operated with a D2 dissection, but in patients who had a D1 nodal dissection, the postoperative CRTx reduced the recurrence rate from 8 to 2%.

CONCOMITANT CHEMORADIOTHERAPY IN LOCALLY ADVANCED GASTRIC CANCER

Radiotherapy perspective

Surgery has poor results in patients with locally advanced cancer, partly because of the large number of locoregional recurrences, which can be avoided with CRTx.

The first randomized study that demonstrated a benefit in OS for adjuvant treatment is that of MacDonald, et al. published in 2001[50]. Radiotherapy (RTx) with concomitant CTx (CRTx) improved OS by 9%. However, as mentioned earlier, this study has multiple criticisms.

The only randomized study comparing CTx versus adjuvant CRTx in gastric cancer patients with gastrectomy and D2 dissection is the ARTIST study. It has three publications that should be reviewed[47,51,52]. The objective was to show differences in DFS (not OS). It included 458 patients only. The CRTx treatment arm was better tolerated and could be completed in 81.7% of patients vs. 75.4% of patients receiving CTx. The three-year DFS was higher for CRTx versus CTx (78 vs. 74%), but it did not achieve statistical significance, although the p value was close ($p = 0.0862$). Unfortunately, patients without lymph node involvement were included, who do not require RTx, since with adequate surgery and adjuvant CTx, the risk of local or regional relapse is low. When analyzing the DFS of patients with lymph node involvement in this study, it was better for those patients who received CRTx with a significant p value ($p = 0.0365$). In addition, the adjuvant CTx treatment arm had more than 3% of N0 patients, and therefore, a

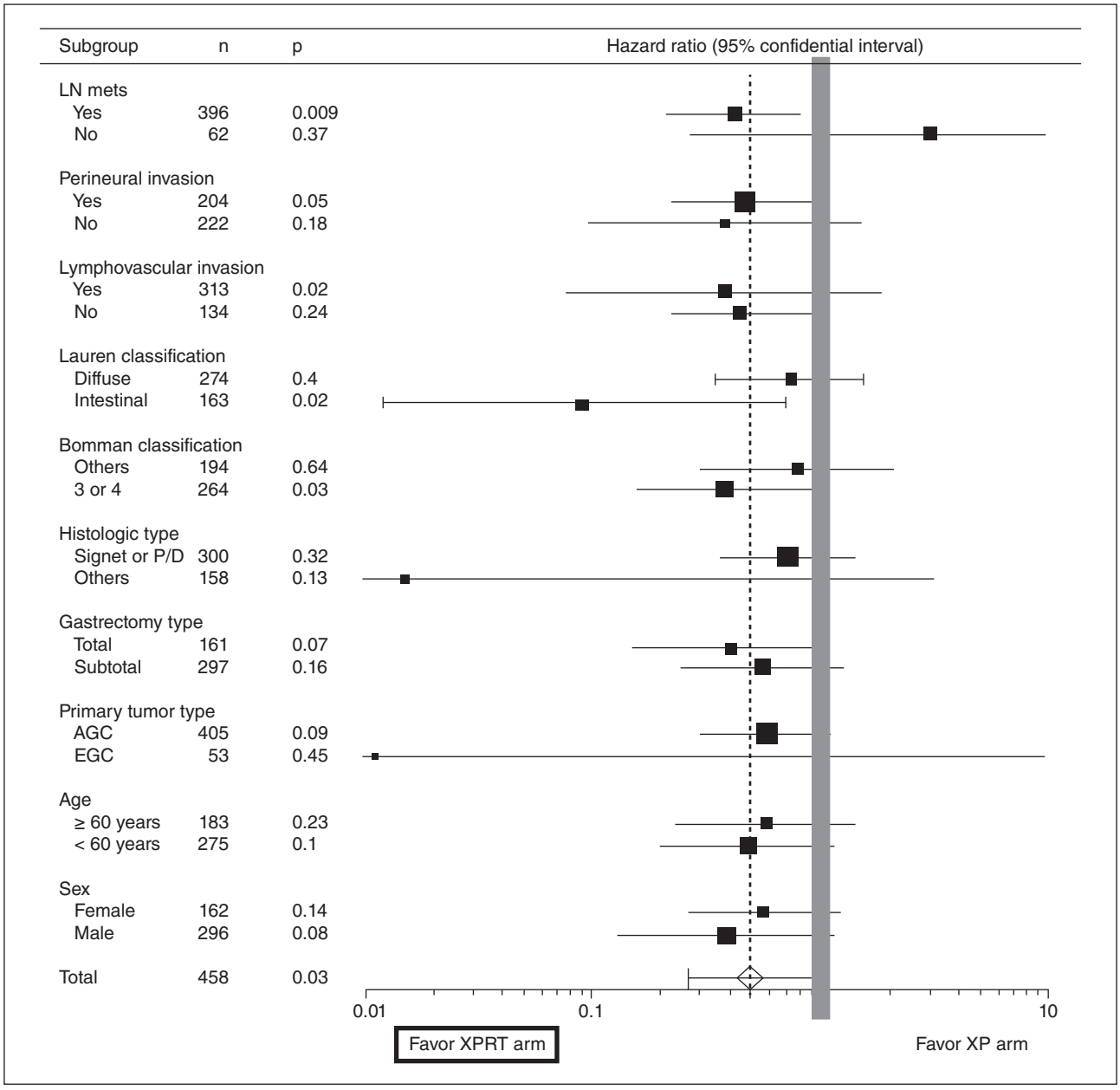

Figure 1. XP: capecitabine/cisplatin; XPRT: capecitabine/cisplatin/radiotherapy.

better prognosis. The third publication of this study is the most interesting as it conducted a more in-depth analysis of the results. In patients with lymph node involvement, locoregional recurrence was 14.5% for the adjuvant CTx treatment arm versus only 6.4% for the CRTx arm (p = 0.009). It should be noted that the surgery of these patients was excellent; all D2 and 99% with more than 15 resected nodes.

A key finding is that the RTx was with opposite parallel anterior-posterior fields (RTx 2D), extremely old, slightly homogeneous, not precise and not well formed for an irregularly shaped target (splenic

hilum, hepatic hilum, anastomosis, celiac trunk, etc.) and with many healthy regional organs to avoid (small intestine, large intestine, kidneys, liver, etc.). No simulation with computed tomography or 3D conformational dosimetry was used, both being the minimum standard nowadays worldwide for at least a decade. It is noteworthy that there has been a benefit in some patients with this RTx. There is even a study by the Princess Margaret Cancer Centre in Toronto that shows that their specialists prefer even more conformed treatments, such as intensity-modulated RTx (IMRT) for this pathology, because with this technique, the coverage of the area to be irradiated is better (it receives a corresponding dose, not less) and the doses of the healthy organs are smaller[53].

It must be emphasized in the ARTIST study that the Forest Plot shows benefits for CRTx in all subgroups, except for patients without lymph node involvement (Fig. 1).

In summary, D2 dissection gastrectomy plus adjuvant CTx is not sufficient for locally advanced gastric cancer. The only comparison of this strategy versus adjuvant CRTx (ARTIST) shows that with surgery and CTx, locoregional recurrence is 14.5% versus only 6.4% when CRTx is performed (p = 0.009). In addition, the CRTx regimen has less toxicity and can be completed by a higher proportion of patients.

Currently, the presented evidence demonstrates that the indications for adjuvant CRTx are: (i) for patients with gastrectomy and D2 dissection with compromised lymph nodes (ARTIST), (ii) for patients with insufficient D0-1 dissections (MacDonald), and (iii) for patients with positive R1 borders (Stiekema, et al. study not commented on in this publication[54]).

In conclusion, we must consider that the current RTx worldwide is better than the RTx of randomized trials that proved their benefit in gastric cancer.

THE FUTURE AND UNANSWERED QUESTIONS

There are many questions that remain unanswered, among which are the clinical or pathological stages at which adjuvant therapy should be indicated. In some trials, patients were included from stage Ib, in others only stage II + was considered, in some trials until stage III, and in others until stage IVa. We currently know relapse rates according to sub-stages, but we do not know the benefit of adjuvant therapies according to these sub-stages. We know that intestinal vs. diffuse histology, as well as antral vs. gastric background, male vs. female, Asian vs. non-Asian, have different prognoses, but we do not know the survival prognoses by combining two or more of these factors. In the near future we must have relapse risk tables according to the combination of these factors and the proportion of benefits according to the different therapy alternatives (similar to breast cancer).

We know that the biological characteristics of cancer in Asia and the West are partly different, as we also know that the efficacy and tolerance of some therapy regimens are different in these regions, but we do not yet know how similar they are in our population. In the future we shall know better the biological characteristics of cancer in our population and participate in international trials aimed to investigate the results of new therapies.

Biomarker-guided therapies and the development of new drugs aimed at molecular targets have paved the way in oncology since the beginning of the 21st century. According to this finding, the new molecular classification of the Gastric Cancer Genome Atlas could change the paradigm in the treatment of this disease[55]. Strategies seeking to incorporate targeted therapies and biological therapies to CTx, RTx, and surgery in a multimodal approach will be mandatory in the future to improve outcomes.

Trastuzumab is a humanized monoclonal antibody that blocks the HER2 receptor by preventing binding with its ligand. Such a receptor is overexpressed in 10-20% of gastric cancer patients. In the ToGA study, the addition of trastuzumab to CTx with cisplatin and 5FU or capecitabine in gastric cancer patients with overexpressed HER2 demonstrated benefit in PFS and OS. It also significantly increased the response rate[56]. These data make the idea of seeking similar benefits seem attractive with this strategy in adjuvant therapy and neoadjuvant therapy. Studies incorporating trastuzumab to this scenario are in progress.

The selection of patients to receive treatment is crucial to define the best treatment option as well as to optimize the results. In the future, progress is expected in the identification of populations and subgroups with specific characteristics at a molecular level to allow a more adequate selection of patients for different treatment strategies. We will have to stop treating gastric cancers according to their phenotype. The cancer genome should lead to future adjuvant trials with specific therapies, particularly as we move forward into the immunotherapy age.

There are many current questions that need to be resolved in the near future:

- Why use three neoadjuvant cycles in the MAGIC study when it will be more beneficial to indicate four, five, or six cycles? Conversely, the French study showed similar results to the MAGIC study although it used only two neoadjuvant cycles.

- How many cycles are appropriate in adjuvant therapy; six as in the ARTIST study or eight as in the CLASSIC study, or even more?

- Is it necessary to use epirubicin in adjuvant therapy? Is ECF equal to CF?

- Is the four-day cisplatin-5FU infusion regimen (from the French study) interchangeable with cisplatin/capecitabine or oxaliplatin/capecitabine? Is the EOC (epirubicin/oxaliplatin/capecitabine) regimen better than ECF in neoadjuvant therapy?

- Is the cisplatin/capecitabine regimen used in the ARTIST study equal in efficacy to oxaliplatin/capecitabine used in the CLASSIC study?

- Could the oxaliplatin/capecitabine regimen be changed by FOLFOX?

- In the oxaliplatin/capecitabine regimen, 130 mg/m^2 of oxaliplatin is indicated, which is not tolerable; however, in colon cancer 85 mg/m^2 is as effective as 130 mg/m^2.

- Is there a role for trastuzumab in adjuvant or neoadjuvant therapy?

- How could patients with very low, low, intermediate, and high risk be defined?

- Should the same neoadjuvant or adjuvant therapy be used in low-risk, intermediate-risk, or high-risk patients?

- Is there really a benefit to using CRTx in gastric cancer?

- Should a different strategy be used in D0, D1, or D2 resections; R0 or R1?

- How can clinical T and N be more accurately determined in gastric cancer?

- How can the effectiveness of neoadjuvant therapy be clinically evaluated?

SUMMARY AND CONCLUSIONS

The exclusive surgery of gastric cancer is associated with 70% or more of relapses, essentially systemic and also locoregional relapses. Therefore, various systemic or locoregional treatment

strategies have been studied, complementary to surgery, in the adjuvant form (postoperative) as well as neoadjuvant (preoperative), or perioperative form (pre- and post-surgery), using CTx and/or RTx in different sequences and giving results that have improved the potential for cure.

According to the most outstanding studies, there are three alternatives that have shown benefits in terms of survival of patients with operable gastric cancer and are suitable alternatives with a standard A approach in the therapy of resectable, locally advanced, proximal gastric adenocarcinomas or distal, intestinal, or diffuse tumors:

– If patients have had a potentially curative resection, adjuvant treatment with CRTx followed by chemotherapy with 5FU-leucovorin is an appropriate option, based on the results obtained with the INT-0116 study (standard in the USA), and would be appropriate in patients with D0 or D1 resections.

– Another potentially better alternative would be to use only adjuvant CTx, based on capecitabine/platinum, according to evidence from Asia. This adjuvant CTx is recommended for patients who have not received perioperative treatment following complete resection of gastric cancer, especially when D2 dissection was performed. The use of chemotherapy with S1 for one year as an adjuvant treatment has been shown to be effective in Asian patients; however, studies in other populations are required to extend its use.

– If patients are viewed prior to resection, in the European standard, they should receive perioperative CTx (neoadjuvant and adjuvant therapy). The optimal regimen is not yet defined and combinations with ECF, (according to the MAGIC study), or only CF (according to the French study) and it should be remembered that there is clear evidence for using neoadjuvant CTx alone.

As in most digestive tumors, neoadjuvant treatment has been incorporated into the multimodal approach of gastric cancer, especially as part of a perioperative treatment strategy. It has been shown to improve locoregional control, the possibility of R0 surgery, and OS, with a better tolerance and a greater probability of completing the planned treatment.

These three standard alternatives are not exempt from criticism and controversy. There is not yet a study that has compared these three strategies, and we cannot safely say which of these alternatives is superior. However, some studies suggest that in the prevention of locoregional recurrence, the preoperative adjustment should be emphasized where patients can have a better tolerance regarding the therapy and its effect can be more pronounced. One possible and easy way to improve its effectiveness is to modify the time of drug administration by applying the majority of cycles prior to surgery in order to increase protocol integrity.

Aggressive adjuvant therapy trials have not been as successful as desired, and possibly focus should be maintained on patients with high-risk of positive lymph nodes.

REFERENCES

1. Katherine DC, Alfred IN. Epidemiology of gastric cancer. World J Gastroenterol. 2006;12:354-63.
2. Edge SB, Byrd DR, Compton CC, et al. American Joint Committee on Cancer Staging Manual. 7th ed. New York: Springer, 2010.
3. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11-20.
4. Diaz-Nieto R, Orti-Rodríguez R, Winslet M. Post-surgical chemotherapy versus surgery alone for resectable gastric cancer. Cochrane Database Syst Rev. 2013;9:CD008415.
5. Siewert JR, Böttcher K, Stein HJ, et al. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. Ann Surg. 1998;228:449-61.
6. Nakamura K, Ueyama T, Yao T, et al. Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. Cancer. 1992;70:1030-7.
7. AJCC Cancer Staging Handbook, 7th ed. 2010:147 (145-152), Chapter 11, Springer, Cham, Switzerland.

8. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda. Available at: http://seer.cancer.gov/csr/1975_2012/
9. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994;73:2680-6.
10. Ajani JA, Mansfield PF, Crane CH, et al. Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. J Clin Oncol. 2005;23:1237-44.
11. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11-20.
12. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29:1715-21.
13. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27:851-6.
14. Stahl, M, Hansjochen, W, Martin, S et al. Clinical response to induction chemotherapy predicts local control and long-term survival in multimodal treatment of patients with locally advanced esophageal cancer. J Cancer Res Clin Oncol. 2005;V131:67-72.
15. Hartgrink HH, van de Velde CJ, Putter H, et al. Neoadjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. Eur J Surg Oncol. 2004;30:643-9.
16. STO3: A randomized trial of perioperative epirubicin, cisplatin plus capecitabine (ECX) with or without bevacizumab (B) in patients with operable gastric, esophagogastric junction, or lower esophageal adenocarcinoma.
17. Schuhmacher C, Gretschel S, Lordick F, et al: Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol. 2010;28:5210-18.
18. He LF, Yang KH, tian JH, Bai ZG. [Meta analysis of clinical effectiveness of neoadjuvant chemotherapy for gastric cancer]. AiZheng. 2008;27:407-12.
19. Li W, Qin J, Sun YH, Liu TS. Neoadjuvant chemotherapy for advanced gastric cancer: a meta-analysis. World J Gastroenterol. 2010;16:5621-8.
20. 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.
21. 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;40:1321-30.
22. Yang Y, Yin X, Sheng L, et al. Perioperative chemotherapy more of a benefit for overall survival than adjuvant chemotherapy for operable gastric cancer: an updated Meta-analysis. Sci Rep. 2015;5:12850.
23. Bartlett EK, Roses RE, Kelz RR, et al. Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database. Surgery. 2014;156:298-304.
24. Shimizu K, Ito K, Matsunaga N, et al. Diagnosis of gastric cancer with MDCT using the water-filling method and multiplanar reconstruction: CT-histologic correlation. AJR Am J Roentgenol. 2005:185;1152-8.
25. Javaid G, Shah OJ, Dar MA, et al. Role of endoscopic ultrasonography in preoperative staging of gastric carcinoma. ANZ J Surg. 2004;74:108-11.
26. Ott K, Herrmann K, Krause BJ, Lordick F. The value of PET imaging in patients with localized gastroesophageal cancer. Gastrointest Cancer Res. 2008;2:287-94.
27. Lavonius MI, Gullichsen R, Salo S, Sonninen P, Ovaska J. Staging of gastric cancer: a study with spiral computed tomography, ultrasonography, laparoscopy, and laparoscopic ultrasonography. Surg Laparosc Endosc Percutan Tech. 2002;12:77-81.
28. Hermans J, Bonenkamp JJ, Boo MC, et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol. 1993;11:1441-7.
29. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian: revisiting a meta-analysis of randomized trials. Eur J Cancer. 1999;35:1059-64.
30. Paoletti X, Oba K, Burzykowski T, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA. 2010;303:1729-37.
31. Sun P, Xiang JB, Chen ZY. Meta-analysis of adjuvant chemotherapy after radical surgery for advanced gastric cancer. Br J Surg. 2009;96:26-33.
32. Nakajima T, Nashimoto A, Kitamura M, et al. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomized trial. Lancet. 1999;354:273-7.
33. Nashimoto A, Nakajima T, Furukawa H, et al. Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology group 9206-1. J Clin Oncol. 2003;21:2282.
34. Sakuramoto S, Sakako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810-20.
35. Sasako M, Sakuramoto S, Katai H, et al. 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.
36. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379:315.
37. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15:1389.
38. Lee J, Lim do H, Kim S, et al. 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;30:268-73.
39. Chang SH, Kim SN, Choi HJ, et al. Adjuvant Chemotherapy for Advanced Gastric Cancer in Elderly and Non-Elderly Patients: Meta-Analysis of Randomized Controlled Trials. Cancer Res Treat. 2016;49:263-73.
40. Gunderson AU Sosin LL. Adenocarcinoma of the stomach: areas of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys. 1982;8:1-11.
41. Smalley SR, Benedetti JK, Haller DG, et al. 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;30:2327-33.
42. Lee HS, Choi Y, Hur WJ, et al. Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. See comment in PubMed Commons belowWorld J Gastroenterol. 2006;12:603-7.
43. Leong T, Joon DL, Willis D, et al. Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-fluorouracil before and after three-dimensional conformal radiotherapy with concurrent infusional 5-fluorouracil: a multicenter study of the Trans-Tasman Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2011;1;79:690-5.
44. André T, Quinaux E, Louvet C, et al. Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: final results of GERCOR C96.1. J Clin Oncol. 2007;25:3732-28.
45. Fuchs CS, Tepper JE, Niedzwiecke D, et al. 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:(Suppl 15). [Abstract 4003].
46. Park S H, Kim D Y, Heo J S, et al. Postoperative chemoradiotherapy for gastric cancers. Ann Oncol. 2003;14:1373-7.
47. Lee J, Lim do H, Kim S, et al. 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;30:268-73.See comment in PubMed Commons below
48. Verheij M, Jansen E, Cats A, et al. A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study. J Clin Oncol. 2016:(suppl). [Abstract 4000].

49. Dikken JL, Jansen EP, Cats A, et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. J Clin Oncol. 2010;28:2430-6.
50. MacDonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345:725-30.
51. Lee J, Lim DH, Kim S, et al. 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;30:268-73.
52. Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, including survival and subset analyses. J Clin Oncol. 2015;28:3130-6.
53. Yu JI, Lim do H, Ahn YC, et al. Effects of adjuvant radiotherapy on completely resected gastric cancer: A radiation oncologist's view of the ARTIST randomized phase III trial. Radiother Oncol. 2015;117:171-7.
54. Ringash J, Perkins G, Brierley J, et al. IMRT for adjuvant radiation in gastric cancer: a preferred plan? Int J Radiat Oncol Biol Phys. 2005; 63:732-8.
55. Stiekema J, Trip AK, Jansen EP, et al. Does adjuvant chemoradiotherapy improve the prognosis of gastric cancer after an R1 resection? Results from a Dutch Cohort Study. Ann Surg Oncol. 2015;22:581-8.
56. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202-9.
57. Bang YJ, Van Cutsem E, Feyereislova A, et al. 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;376:687-97.