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Upper Gastrointestinal Cancers (L Rajdev, Section Editor)

# Optimizing Therapies in the Perioperative Management of Gastric Cancer

*Uqba Khan, MD*
*Manish A. Shah, MD*[*]

**Address**
[*]Division of Hematology and Oncology, Weill Cornell Medicine/New York Presbyterian Hospital, 1305 York Avenue, Room Y1247, New York, NY, 10021, USA
Email: mas9313@med.cornell.edu

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## Opinion statement

Gastric cancer is a major health burden worldwide. Only about one-third of all the gastric cancer patients survive beyond 5-years. Management of this deadly disease has evolved over the last few decades due to the incorporation of better staging techniques, surgical approach, effective systemic treatment, and sequencing of different therapeutic modalities. There are some global differences in how local-regional gastric cancer is managed and treated. In the USA and some parts of Europe, perioperative chemotherapy is a preferred management approach. Adjuvant chemoradiation is considered if the surgical resection is performed upfront. However, in Asia, postoperative chemotherapy alone after D2 surgical resection is considered standard of care treatment. Based on recent evidence, perioperative treatment with triplet chemotherapy regimen FLOT (5FU, leucovorin, oxaliplatin, docetaxel) is the preferred regimen. However, doublet fluoropyrimidine/platinum combination is a reasonable alternative if triplet regimen cannot be given. At present, there are no approved targeted or immunotherapy agents in perioperative setting; however, there are a number of ongoing trials designed to examine the efficacy of targeted therapy and checkpoint inhibitors in various combinations with systemic therapy in perioperative setting.

## Introduction

Gastric cancer is the fifth most common cancer in the world [1]. However, there are striking differences in epidemiology of gastric cancer across various regions of the world. In western countries especially in the USA, gastric cancer is one of the least common cancers. On the contrary, it is one of the most common types of cancer in Japan. Gastric cancer carries a significant global health burden due to its high morbidity and mortality rate [2]. In the USA, an estimated 10,800 people will die of this disease in 2018 and 26,240 will likely to be diagnosed [3].

Over the past few decades, survival of the patients with gastric cancer has improved significantly; however, potentially resectable early-stage gastric cancer still carries significant mortality, as only about one-third of these patients with locally advanced disease survive more than 5 years [4]. Treatment of localized gastric cancer has evolved over the last few years especially with the incorporation of better staging approach, surgical techniques, effective systemic treatment, and sequencing of different therapeutic modalities. Treatment of early-stage disease involves multidisciplinary approach; however, surgical resection with lymph node dissection is the cornerstone for curative treatment. There are some global differences in surgical techniques especially for lymph nodes dissection [5]. In Asia, D2 dissection is routinely done which is done by removing nodes along the perigastric area, left gastric, celiac, splenic, and hepatic arteries [6]. While in the USA, D1 lymphadenectomy is usually the standard in which dissection of only the perigastric lymph nodes is performed. While D2 is preferred and recommended by NCCN [7], there is higher postoperative mortality associated with D2 surgery [8]. The conclusion of a meta-analysis of five randomized clinical trials showed that D2 resection can improve disease-specific survival in patients, although the increased incidence of postoperative mortality diminishes its therapeutic benefit [8]. Therefore, it is recommended that surgical planning should be done by an experienced surgeon in high volume center to perform optimal surgery without increasing postoperative mortality.

Systemic chemotherapy and radiation are used adjunctively with surgery in various combinations and sequence [9]. Management approach of localized gastric cancer also varies according to regional preferences in various parts of the world. In the USA and many European countries [10], perioperative chemotherapy or adjuvant chemoradiation are preferred treatment approaches. While in Asian countries, postoperative chemotherapy after D2 resection is considered standard of care. All these different management approaches will be discussed in the following review of literature and also summarized in Table 1.

# Perioperative treatment

## Benefits of preoperative chemotherapy

There are many potential benefits of giving preoperative systemic chemotherapy to gastric cancer patients [19]. One of the main advantages is to downstage the tumor which will in turn aid in performing R0 resection. This is especially important in locally advanced large, bulky tumors at the time of initial diagnosis, when curative resection is difficult to perform. Another potential advantage is to determine the natural behavior of the tumor during the phase of preoperative treatment, as patients who have high risk of distant metastasis may avoid gastrectomy if cancer metastasizes after/during preoperative chemotherapy. By this way, morbidity and mortality involved with gastrectomy can be avoided in such patients. And lastly, giving preoperative chemotherapy will provide the best chance to deliver maximum systemic treatment, as some patients may not be able to complete adjuvant chemotherapy due to delay in recovery from surgery. Therefore, it is our common practice to do perioperative chemotherapy as opposed to upfront surgery, especially for T2 and above or node-positive gastric cancers. Following review of literature justifies this approach.

## MAGIC trial (ECF versus no chemotherapy)

Over a decade ago, the UK Medical Research Council MAGIC trial was done to study the role of perioperative chemotherapy [11]. It was a multicenter, randomized phase III trial to compare surgery alone versus perioperative chemotherapy with epirubicin, cisplatin, and 5-flourouracil (ECF). In this trial, distal esophageal and gastro-esophageal junction (GEJ) adenocarcinomas were also included. In the perioperative group, patients were supposed to receive three cycles of preoperative ECF and three cycles postoperatively. Eligibility criteria included patients with T2 or higher tumors with no evidence of metastatic disease. Five hundred three patients were randomized to either group. About 74% were gastric, 15% distal esophageal, and 11% were GEJ. Eighty-six percent of patients who were assigned to receive perioperative chemotherapy completed preoperative chemotherapy. Only 65.6% of patients who underwent surgery started postoperative chemotherapy. Five-year survival rates were 36.3% for patients in perioperative chemotherapy group and 23% for patients in surgery alone group.

**Table 1. Major clinical trials in perioperative treatment of gastric cancer**

| Trial | Treatment setting | Treatment groups | Number of patients | Outcome results |
|---|---|---|---|---|
| MAGIC [11] | Perioperative | Surgery alone versus perioperative ECF | 503 | 5-year OS 23% versus 36% ($p = 0.009$) |
| FNCLCC-FFCD [12] | Perioperative | Surgery alone versus perioperative CF | 224 | 5-year OS 24% versus 38% ($p = 0.02$) |
| FLOT [13] | Perioperative | Perioperative ECF/ECX versus perioperative FLOT | 716 | Median OS 35 versus 50 months ($p = 0.012$) |
| INT-0116 [14] | Adjuvant | Surgery alone versus adjuvant 5-FU/leucovorin plus Radiation | 559 | 5-year OS 27% versus 36% ($p = 0.005$) |
| ACTS-GC [15] | Adjuvant | Surgery alone versus adjuvant S-1 | 1059 | 5-year OS 61% versus 72% |
| CLASSIC [16] | Adjuvant | Surgery alone versus adjuvant CapeOx | 1035 | 3-year DFS 59% versus 74% ($p \leq 0.0001$) |
| JACCRO GC-7 [17] | Adjuvant | Adjuvant S-1 versus S-1/Docetaxel | 915 | 3-year RFS 50% versus 66% ($p = 0.0007$) |
| ARTIST [18] | Adjuvant | Adjuvant capecitabine/cisplatin versus chemoradiation | 458 | 3-year DFS 74% versus 78% ($p = 0.086$) |

This study clearly showed benefit of perioperative chemotherapy over surgery alone with 13% absolute difference in survival at 5 years. However, only 41.6% of all patients randomly assigned to perioperative chemotherapy completed all six cycles of ECF which highlights the difficulty in delivering complete chemotherapy in perioperative setting.

Since this study, there have been several clinical trials performed in perioperative setting with different chemotherapy agents and biological agents to potentially enhance the outcomes of the patients.

## FNCLCC ACCORD 07 trial (5FU/cisplatin versus no chemotherapy)

This randomized phase III trial was initiated by the Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC) and the Fédération Francophone de Cancérologie Digestive (FFCD) in 28 centers in France. This phase III trial was designed to compare surgical resection with or without perioperative chemotherapy. Chemotherapy comprised two or three preoperative cycles of 5FU as continuous intravenous infusion for 5 consecutive days and cisplatin as a 1-h infusion, every 28 days, and three to four postoperative cycles, for a total of six cycles of chemotherapy. The primary endpoint was overall survival while secondary endpoints were disease-free survival, R0 resection rate, and safety. Two hundred twenty-four patients were randomly assigned to either the chemotherapy/surgery (CS) group ($n = 113$) or the surgery (S) group ($n = 111$). Twenty-five percent of patients were gastric, 64% were GEJ, and 11% of patients were lower esophageal. Of the 113 patients assigned to the CS group, 98 patients (87%) received at least two cycles. Forty-one (38%) of the 109 treated patients experienced at least grade 3 to 4 toxicity during preoperative chemotherapy. Among the 109 patients who received at least one cycle of preoperative chemotherapy, only 54 patients (50%) received postoperative chemotherapy. Five-year survival rates were 38% in the chemotherapy-surgery group compared with 24% in the surgery alone group. R0 resection rate was 84% in the CS group versus 74% in the S group ($p = 0.04$) [12]. The results of this trial further exemplified the role of perioperative chemotherapy.

## FLOT4-AIO trial (FLOT versus ECF)

This was phase II/III randomized trial comparing two different chemotherapy approaches in perioperative manner for gastric and GEJ cancers [13, 20•]. The study arm included four cycles of 5FU, leucovorin, oxaliplatin, and docetaxel (FLOT) given before and after the resection. It was compared with three cycles of epirubicin, cisplatin, and 5FU (or capecitabine) (ECF/ECX) given before and after the resection. There were more patients who achieved R0 resection in FLOT, 84% compared with 77% in ECF/ECX ($p = 0.011$). There was significant improvement in median overall survival of 50 months in FLOT arm compared with 35 months in ECF/ECX arm (HR 0.77 [0.63–0.94]; $p = 0.012$). Perioperative complications were similar in each arm, 50% with ECF/ECX and 51% with FLOT. However, there were more adverse events of sensory neuropathy, neutropenia, and infections in FLOT arm. Ninety-day postoperative mortality was 8% in ECF/ECX versus 5% in FLOT.

The results of this trial establish perioperative FLOT chemotherapy as new standard of care treatment in western countries, especially for medically fit patients with good performance status and ability to tolerate taxane-based chemotherapy. FOLFOX is a reasonable alternative for perioperative treatment in patients who cannot tolerate FLOT combination.

### Role of perioperative bevacizumab

VEGF inhibitors have a significant role in management of various malignancies. Ramucirumab, a VEGFR2 inhibitor, is approved in advanced, metastatic gastric cancer in second-line setting either alone or with paclitaxel [21, 22]. However, addition of bevacizumab to chemotherapy in perioperative setting did not improve the outcomes. Therefore, bevacizumab should not be used in perioperative setting. This recommendation comes from investigators from the UK Medical Research Council (MRC) who conducted a multicenter, randomized, open-label phase II/III trial to examine the safety and efficacy of adding bevacizumab to perioperative chemotherapy in patients with resectable gastric, GEJ, or lower esophageal adenocarcinoma [23•]. Eligible patients were randomly assigned to receive either perioperative epirubicin/cisplatin/capecitabine chemotherapy or epirubicin/cisplatin/capecitabine plus bevacizumab, in addition to surgery. A total of 1063 patients were randomized to receive perioperative chemotherapy only or perioperative chemotherapy plus bevacizumab. About 36% of patients were gastric, 50% were GEJ and 14% were lower esophageal. This trial was unable to achieve its primary efficacy endpoint of overall survival, with no significant difference in 3-year overall survival in the chemotherapy alone group (50·3%) versus chemotherapy plus bevacizumab group (48·1%) (HR 1·08, 95% CI 0·91–1·29; $p = 0·36$). In addition, the safety analysis also indicated that bevacizumab administration was associated with increased rate of anastomosis leak after surgery. Although the results of this trial were disappointing, however, this is an important piece of data to guide the future research in gastric-esophageal cancers in the direction of other targeted therapies instead of investing further into anti-angiogenic drugs.

## Global differences in treatment approach

### Role of adjuvant chemotherapy

Although perioperative chemotherapy is the preferred treatment for initially resectable localized gastric cancers, however, if the patient is resected initially and pathological stage reveals T3/T4 or node-positive disease then adjuvant treatment is warranted. In western countries, adjuvant chemoradiation is considered standard of care as per results of Intergroup 0116 trial (explained later); however, in Asian countries, adjuvant chemotherapy alone is considered as standard in postoperative setting after D2 resection. Following is the review of published trials supporting those recommendations.

### The GASTRIC group—meta-analysis

In this meta-analysis, data from all published randomized clinical trials (RCTs) (from 1970 to 2009) comparing adjuvant chemotherapy with surgery alone for resectable gastric cancers was analyzed [24]. The primary objective was to perform an individual patient-level meta-analysis of all

RCTs to quantify the potential benefit of chemotherapy after complete resection over surgery alone in terms of overall survival and disease-free survival. Individual patient data from 3838 patients from 17 different RCTs was obtained. There were 1000 deaths among 1924 patients assigned to chemotherapy groups and 1067 deaths among 1857 patients assigned to surgery-only groups. There was statistically significant benefit in median overall survival for patients who received adjuvant chemotherapy (HR, 0.82; 95% CI, 0.76–0.90; $p < 0.001$). The estimated median overall survival was 4.9 years (95% CI, 4.4–5.5) in the surgery-only group versus 7.8 years (95% CI, 6.5–8.7) in the group receiving adjuvant chemotherapy. Absolute benefits were 5.8% and 7.4% at 5 and 10 years respectively.

## ACTS-GC trial (role of S-1 chemotherapy)

S-1 is a combination of three different pharmacological compounds (tegafur, gimeracil, and oteracil potassium) in a 1:0.4:1 M ratio [25]. It is available in Asia and Europe but is not approved by the FDA in the USA. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) was a randomized phase III trial to examine the efficacy of S-1 given for 1 year postoperatively compared with surgery alone in patients with stage II or III gastric cancer who underwent D2 gastrectomy [15]. S-1 (80 to 120 mg per day) was given for 4 weeks, followed by 2 weeks of rest for a total of 1 year of treatment. The primary endpoint was overall survival, and the secondary endpoints were relapse-free survival and safety. A total of 1059 patients were enrolled at 109 centers throughout Japan; 529 were assigned to the S-1 group and 530 to the surgery-only group. The overall survival rate at 5 years was 71.7% in the S-1 group and 61.1% in the surgery-only group (hazard ratio, 0.669; 95% CI, 0.540 to 0.828). The adverse events of grade 3 or 4 that were more frequent in the S-1 group were anorexia, nausea, diarrhea, leukopenia, anemia, elevated total serum bilirubin level, stomatitis, and rash [26]. The results of this trial established the role of 1 year of S-1 in adjuvant setting in Asian countries.

## CLASSIC trial (CapeOx versus no chemotherapy)

The capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) study was a multicenter, randomized controlled phase III trial done in South Korea, China, and Taiwan [16]. In this trial, patients with stage II–IIIB gastric cancer who underwent curative D2 gastrectomy were randomly assigned to receive adjuvant eight 3-week cycles of oral capecitabine plus intravenous oxaliplatin for 6 months or surgery only. The primary endpoint was 3-year disease-free survival. Of 1035 patients which were enrolled, 520 were randomly assigned to adjuvant capecitabine and oxaliplatin, and 515 to observation. There was statistically significant benefit in estimated 5-year disease-free survival, which was 68% (95% CI 63–73) in the adjuvant capecitabine and oxaliplatin group versus 53% (47–58) in the observation alone group. Estimated 5-year overall survival was 78% (95% CI 74–82) in the adjuvant capecitabine and oxaliplatin group versus 69% (64–73) in the observation group [27]. The results of this trial established the role of 6 months of CAPEOX in adjuvant setting in Asian countries.

### JACCRO GC-7 trial (S-1/docetaxel)

In Asia, especially in Japan and South Korea, the outcome of stage III gastric cancer was thought to be suboptimal despite adjuvant treatment. Therefore, the JACCRO GC-07 trial, a randomized phase III trial for stage III gastric cancer, was initiated in 138 centers across Japan [17]. Nine hundred fifteen patients with stage III gastric cancer were randomized after R0 resection by D2 gastrectomy, either to S-1/docetaxel group or the control group with S-1 only for 1 year. The primary endpoint was relapse-free survival. The study results were presented at 2018 annual ASCO meeting, which showed statistically significant benefit of 3-year relapse-free survival of the S-1/docetaxel arm compared with S-1 arm (65.9% versus 49.6%) (HR 0.632, 99% CI 0.400~0.998, $p = 0.0007$) [28]. This could also be considered another option in stage III patients in Asian population.

### Standard of Care in Asia

In Asian countries especially in Japan and South Korea, the standard of care for stage II and stage III gastric cancer is D2 surgery followed by adjuvant chemotherapy. The evidence of this recommendation for Asian population comes from the results of above-mentioned trials (ACTS-GC, CLASSIC and JACCRO GC-7 trials). Either 1 year of S-1 or 6 months of capecitabine/oxaliplatin is considered standard of care adjuvant chemotherapy. S-1/docetaxel is also considered for stage III gastric cancers as well.

## Role of chemoradiation therapy

### Neoadjuvant chemoradiation

The role of preoperative chemotherapy is uncertain in gastric cancer due to lack of high-quality randomized trial data. Neoadjuvant chemoradiation therapy is utilized in esophageal and GEJ cancer as derived from the CROSS trial [29]. The German PreOperative therapy in Esophagogastric adenocarcinoma Trial (POET) was another major phase III trial designed to compare the preoperative chemotherapy and chemoradiation versus chemotherapy alone followed by surgery [30]. This trial only enrolled patients with GEJ cancer. This trial was terminated prematurely due to poor accrual. Overall survival showed a trend in favor of preoperative chemoradiation (HR 0.65, 95% CI 0.42–1.01, $p = 0.055$) but it was not statistically significant.

There is no prospective randomized phase III clinical trial in resectable gastric cancer (except for GEJ) to highlight the role of neoadjuvant chemoradiation. Therefore, preoperative chemoradiation cannot be recommended (outside of a clinical trial) in resectable non-GEJ gastric cancer.

### Adjuvant chemoradiation

As stated earlier, in western countries especially in the USA, the standard way of managing locally advanced gastric cancer is with perioperative chemotherapy. However, if gastric cancer resected upfront without any preoperative chemotherapy then standard of care is to give postoperative chemoradiation especially in ≥T3 and/or node-positive tumors. The results of following randomized trials justify the use of postoperative chemoradiation in resected gastric cancer.

### Intergroup 0116 study (adjuvant chemoradiation versus observation)

This trial was one of the historical, landmark studies to compare chemoradiation after surgery versus surgery alone for gastric and GEJ cancers [14]. In this trial, 559 patients with tumors ≥T3 and/or node-positive gastric cancer were randomly assigned to observation versus chemoradiation after R0 resection. The chemoradiation arm used bolus 5-FU/leucovorin-based chemotherapy with sandwiched chemoradiation therapy (45 Gy) and bolus 5-FU/ LV as a radiosensitizer. The median overall survival in the surgery-only group was 27 months, as compared with 36 months in the chemoradiotherapy group. The long-term update of this trial, with a more than 10-year median follow-up, demonstrated strong persistent benefit from adjuvant chemoradiation [31]. Although, results of this study set adjuvant chemoradiation after R0 resection as the standard of care in the USA; however, there was a criticism of this trial due to suboptimal surgery (< 50% of patients had D1 or D2 surgery).

### ARTIST trial (adjuvant chemotherapy versus chemoradiation)

The ARTIST (Adjuvant Chemoradiation Therapy in Stomach Cancer) trial was designed to investigate the role of postoperative chemoradiotherapy in comparison with chemotherapy alone in patients with curatively resected gastric cancer with D2 lymph node dissection in a single center in Korea [32]. This trial used capecitabine with cisplatin for six cycles in chemotherapy arm. Patients assigned to the chemoradiation arm received two cycles of capecitabine/cisplatin, then radiation therapy (45 Gy of radiation at 1.8 Gy per day), 5 days per week, for 5 weeks with continuous capecitabine, followed by two additional cycles of capecitabine/cisplatin. The primary endpoint was disease-free survival. The results showed that disease-free survival did not prolong significantly with the addition of radiation therapy to chemotherapy ($p = 0.0862$). However, in the subgroup of patients with pathologic lymph node metastasis at the time of surgery, patients randomly assigned to chemoradiation arm experienced better disease-free survival when compared with those who received chemotherapy alone ($p = 0.0365$). With updated 7-year follow-up, disease-free survival was similar in both arms but again chemoradiation significantly improved disease-free survival in patients with node-positive disease [18]. Due to these results, the ARTIST II trial was designed to specifically look at node-positive gastric cancer only. The trial is currently recruiting patients in Korea [33•].

## Future perspective

### FDG-PET/CT scan as predictive biomarker

Use of PET/CT scans as predictive biomarker has been explored in preoperative setting [34]. FDG-PET/CT has been examined for their ability to identify response to therapy early after the initiation of chemotherapy by evaluating the change in the standardized uptake value (SUV) of the administered FDG as compared with the baseline [35]. CALGB-80803, a randomized phase II trial, was conducted in esophageal and GEJ tumors to determine whether changing chemotherapy during pre-op chemoradiation based on response to induction FDG-PET imaging can lead to improved pathologic complete response. Efficacy endpoint of improvement in pathological complete response was met among patients who were PET non-responders after induction chemotherapy and

received alternative chemotherapy during chemoradiation therapy [36]. A randomized phase 2 trial (NCT02485834) was designed to study the impact of early FDG-PET-directed intervention on preoperative therapy for locally advanced gastric cancer; however, the trial was terminated due to poor accrual.

### HER2-directed therapy

HER2 amplification or overexpression is present in about 7–34% of gastric cancer patients [37]. It is an important biomarker in unresectable, metastatic gastric adenocarcinoma. Trastuzumab in combination with chemotherapy is considered standard option for patients with HER2-positive advanced gastric or GEJ cancer. Trials are designed to examine the role of HER2-directed therapy in early-stage gastric cancer and there are some promising results published from early feasibility trials [38]. The ongoing EORTC INNOVATION trial is a phase II randomized study to examine the efficacy of trastuzumab or the combination of trastuzumab and pertuzumab with standard chemotherapy compared with chemotherapy alone given before and after surgery. This trial is currently recruiting patients [39]. It is possible that the results of HER2-directed trials may change the way we treat early-stage HER2-positive gastric in future [40].

### Immunotherapy

Checkpoint inhibitors have definitely changed the management of various tumors including GI malignancies. In gastric cancer, pembrolizumab is currently approved in advanced disease in third-line setting. Although the response rates were very modest in advance disease (objective response rate was 11.6%) [41], it is worthwhile to examine the role of checkpoint inhibitors in perioperative setting. There are a number of ongoing trials being designed to recruit patients to determine the efficacy of immunotherapy. Some of these exciting trials include the VESTIGE phase II randomized trial with the primary objective to investigate if nivolumab plus ipilimumab given as adjuvant treatment improve disease-free survival in patients with stage Ib-IVa gastric and GEJ adenocarcinoma following neoadjuvant chemotherapy and resection [42]. In Asia, NCT03006705 is a phase III trial designed to evaluate the efficacy and safety of adjuvant chemotherapy with nivolumab in combination with S-1 or CapeOX therapy, in comparison with placebo in combination with S-1 or CapeOX therapy, in pathological stage III gastric cancer after D2 lymph node dissection [43].

## Compliance with Ethical Standards

**Conflict of Interest**
Uqba Khan and Manish A. Shah declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance


1. GLOBOCAN 2012 v1.1. Cancer incidence and mortality worldwide: IARC CancerBase No. 11. Lyon: International Agency for Research on Cancer; 2014. Available from: http://www.globocan.iarc.fr. Accessed 1 Aug 2018
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
4. SEER Cancer statistics: survival by stage in stomach cancer. 2018 Available from: https://seer.cancer.gov/statfacts/html/stomach.html. Accessed 1 Aug 2018
5. Schmidt B, Yoon SS. D1 versus D2 lymphadenectomy for gastric cancer. J Surg Oncol. 2013;107(3):259–64.
6. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric cancer. 2017;20(1):1–19.
7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer. Available from: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed 1 Aug 2018
8. Mocellin S, McCulloch P, Kazi H, Gama-Rodrigues JJ, Yuan Y, Nitti D. Extent of lymph node dissection for adenocarcinoma of the stomach. Cochrane Database Syst Rev. 2015;8:Cd001964.
9. Raigani S, Hardacre JM, Kim J, Ammori JB. Trends in the surgical treatment of gastric adenocarcinoma. Ann Surg Oncol. 2014;21(2):569–74.
10. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v38–49.
11. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
12. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29(13):1715–21.
13. Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17(12):1697–708.
14. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725–30.
15. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, 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 Off J Am Soc Clin Oncol. 2011;29(33):4387–93.
16. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379(9813):315–21.
17. Kakeji Y, Kodera Y, Yoshida K, Kochi M, Takahashi M, Kii T, et al. Pre-planned feasibility and safety analyses of docetaxel/S-1 combination in a phase III study comparing docetaxel/S-1with S-1 alone as postoperative adjuvant chemotherapy for stage III gastric cancer (JACCRO GC-07). J Clin Oncol. 2015;33(15_suppl):e15000-e.
18. Park SH, Sohn TS, Lee J, Lim DH, Hong ME, Kim K-M, 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;33(28):3130–6.
19. Davies AR, Gossage JA, Zylstra J, Mattsson F, Lagergren J, Maisey N, et al. Tumor stage after neoadjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophagogastric junction. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32(27):2983–90.
20. • Al-Batran S-E, Homann N, Schmalenberg H, Kopp H-G, Haag GM, Luley KB, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. J Clin Oncol. 2017;35(15_suppl):4004

Phase 3 clinical trial in perioperative setting comparing ECF/ECX with FLOT regimen. The results of this trial suggest improvement in outcomes with FLOT.

21. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for

previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet (London, England). 2014;383(9911):31–9.

22. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224–35.

23.• Cunningham D, Stenning SP, Smyth EC, Okines AF, Allum WH, Rowley S, et al. Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2-3 trial. Lancet Oncol. 2017;18(3):357–7.

This phase 3 trial of bevacizumab showed lack of benefit of adding bevacizumab in perioperative setting.

24. Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA. 2010;303(17):1729–37.

25. Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anti-Cancer Drugs. 1996;7(5):548–57.

26. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357(18):1810–20.

27. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, 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(12):1389–96.

28. Kodera Y, Yoshida K, Kochi M, Ichikawa W, Kakeji Y, Sano T, et al. A randomized phase III study comparing S-1 plus docetaxel with S-1 alone as a postoperative adjuvant chemotherapy for curatively resected stage III gastric cancer (JACCRO GC-07 trial). J Clin Oncol. 2018;36(15_suppl):4007.

29. Shapiro J, van Lanschot JJB, Hulshof M, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090–8.

30. Stahl M, Walz MK, Riera-Knorrenschild J, Stuschke M, Sandermann A, Bitzer M, et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): long-term results of a controlled randomised trial. Eur J Cancer. 2017;81:183–90.

31. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, 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 Off J Am Soc Clin Oncol. 2012;30(19):2327–33.

32. Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, 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(3):268–73.

33.• Park SH, Lee J, Lim DH, Kim K-M, An JY, Choi M-G, et al. Results from the safety interim analysis of the Adjuvant chemoRadioTherapy In Stomach Tumors 2 (ARTIST 2) randomized, multi-center clinical trial. J Clin Oncol. 2018;36(15_suppl):e16029-e

The ARTIST trial was designed to investigate the role of post-operative chemoradiotherapy in comparison with chemotherapy alone in patients with curatively resected gastric cancer with D2 lymph node dissection in a single center in Korea. This trial showed no evidence of improvement in DFS; however, ARTIST 2 is currently enrolling patients with node-positive gastric cancer only.

34. Shah MA, Yeung H, Coit D, Trocola R, Ilson D, Randazzo J, et al. A phase II study of preoperative chemotherapy with irinotecan(CPT) and cisplatin(CIS) for gastric cancer(NCI 5917): FDG-PET/CT predicts patient outcome. J Clin Oncol. 2007;25(18_suppl:4502.

35. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007;8(9):797–805.

36. Goodman KA, Hall N, Bekaii-Saab TS, Ou F-S, Twohy E, Meyers MO, et al. Survival outcomes from CALGB 80803 (Alliance): a randomized phase II trial of PET scan-directed combined modality therapy for esophageal cancer. J Clin Oncol. 2018;36(15_suppl):4012.

37. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki 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(9742):687–97.

38. Rivera F, Jiménez P, Alfonso PG, Lopez C, Gallego J, Limon ML, et al. NeoHx study: perioperative treatment with trastuzumab in combination with capecitabine and oxaliplatin (XELOX-T) in patients with HER2 resectable stomach or esophagogastric junction (EGJ) adenocarcinoma—R0 resection, pCR, and toxicity analysis. J Clin Oncol. 2013;31(15_suppl:4098.

39. Neoadjuvant study using trastuzumab or trastuzumab with pertuzumab in gastric or gastroesophageal junction adenocarcinoma (INNOVATION). Available from: https://clinicaltrials.gov/ct2/show/NCT02205047. Accessed 1 Aug 2018

40. A study of the combination of oxaliplatin, capecitabine, and trastuzumab with chemoradiotherapy in the adjuvant setting in operated participants with human epidermal growth factor receptor-2 positive (HER2+) gastric or gastroesophageal junction cancer (TOXAG). Available from: https://clinicaltrials.gov/ct2/show/NCT01748773?term=01748773&rank=1. Accessed 1 Aug 2018
41. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol. 2018;4(5):e180013.
42. Postoperative immunotherapy vs standard chemotherapy for gastric cancer with high risk for recurrence (VESTIGE). Available from: https://clinicaltrials.gov/ct2/show/NCT03443856?term=immunotherapy&cond=Gastric+Cancer&phase=12&rank=5. Accessed 1 Aug 2018
43. Study of adjuvant ONO-4538 with resected gastric cancer. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03006705?term=nivolumab&cond=Gastric+Cancer&phase=2&rank=1&show_locs=Y#locn. Accessed 1 Aug 2018

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