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**Interpretation of the development of neoadjuvant therapy for gastric cancer based on the vicissitudes of the NCCN guidelines**

Wang XZ *et al.* The development of neoadjuvant therapy for gastric cancer

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**Abstract**

Gastric cancer is one of the most common digestive system tumors in China, and locally advanced gastric cancer (LAGC) accounts for a high proportion of newly diagnosed cases. Although surgery is the main treatment for gastric cancer, surgical excision alone cannot achieve satisfactory outcomes in LAGC patients. Neoadjuvant therapy (NAT) has gradually become the standard treatment for patients with LAGC, and this treatment can not only achieve tumor downstaging and improve surgical rate and the R0 resection rate, but it also significantly improves the long-term prognosis of patients. Peri/preoperative neoadjuvant chemotherapy and preoperative chemoradiotherapy are both recommended according to a large number of studies, and the regimens have also been evolved in the past decades. Since the NCCN guidelines for gastric cancer are one of the most authoritative evidence-based guidelines worldwide, here, we demonstrate the development course and major breakthroughs of NAT for gastric cancer based on the vicissitudes of the NCCN guidelines from 2007 to 2019, and also discuss the future of NAT.

**Key words:** Gastric cancer; Locally advanced gastric cancer; Neoadjuvant therapy; Neoadjuvant chemotherapy; Neoadjuvant chemoradiotherapy; NCCN guidelines

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**Core tip:** Surgical excision is one of the most effective ways in treating nonmetastatic gastric cancer. However, surgery alone cannot achieve satisfactory therapeutic effects in locally advanced gastric cancer (LAGC), and the 5-year survival rate of LAGC patients is less than 50%. Neoadjuvant therapy (NAT) aims at improving the surgical and R0 resection rate and decreasing the recurrence of micrometastases of LAGC. The strategies of NAT have been continuously developed in the past decades, and the evolvements can be reflected from the vicissitudes of the NCCN guidelines. Moreover, targeted therapy and individualized treatment may be the next hotspots of NAT, and may further improve the prognosis of LAGC patients.

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**INTRODUCTION**

Gastric cancer (GC) is the most common tumor of the digestive system. GLOBOCAN estimated approximately 1.034 million newly diagnosed GC cases worldwide in 2018, which accounted for 5.7% of all tumors and ranked fifth among all cancers. GC is also the third leading cause of cancer-related deaths, as 0.783 million deaths were caused by GC in 2018, which accounted for 8.2% of all cancer deaths[[1](#_ENREF_1)]. The incidence of GC in Asia is much higher than that in other countries and regions. The incidence of GC in East Asia is approximately 32.1/100000, and the mortality rate is as high as 13.2/100000[[1](#_ENREF_1)]. Moreover, the current situation of GC in China is far more serious. First, the number of GC patients in China accounts for a substantial proportion of all GC cases worldwide, with approximately 679000 newly diagnosed cases and 498000 deaths each year[[2](#_ENREF_2),[3](#_ENREF_3)]. Second, the early diagnosis of GC in China is still in its initial stage. Patients with stage II-III GC account for 58.0% of the GC cases in China, while in South Korea and Japan, patients with stage II-III account for only 22.5% and 24.9% of all GC cases, respectively[[4](#_ENREF_4),[5](#_ENREF_5)]. As the 5-year survival rate of patients with locally advanced gastric cancer (LAGC) plunges dramatically, ways to improve the treatment effect and prognosis of these patients have become a primary focus in China and even worldwide.

**THE RISE OF NEOADJUVANT THERAPY FOR GC**

Surgery is the most effective treatment for nonmetastatic GC, and the cure rate for stage T1 cancer can reach 90% after surgery. However, many patients with LAGC will experience tumor recurrence within 1 year after surgery, even those with R0 resection, and the 5-year survival rate of these patients is less than 50%[[6](#_ENREF_6),[7](#_ENREF_7)]. Most scholars believe that surgical excision alone cannot achieve satisfactory outcomes in LAGC, and thus neoadjuvant therapy (NAT) was developed.

The concept of NAT was first proposed by Frei in 1982[[8](#_ENREF_8)], and it has also been referred to as preoperative chemotherapy. In the 1990s, Wilke, Plukker, Mai, and other scholars began to apply preoperative chemotherapy in the treatment of GC. They found that preoperative chemotherapy could achieve tumor downstaging, improve the tumor resection rate, and prolong the postoperative survival time of LAGC patients[[9-11](#_ENREF_9)]. The above study served as the prelude to NAT for LAGC, but conceptually, they should be considered as the conversion therapy. Currently, NAT is applicable to LAGC patients with resectable lesions at initial diagnosis. The purpose of NAT is to further reduce the lesion size, improve the R0 resection rate, inhibit micrometastases, reduce the risk of tumor recurrence, and determine the sensitivity of patients to the corresponding treatment in advance[[9](#_ENREF_9),[12](#_ENREF_12),[13](#_ENREF_13)].

NAT strategies for LAGC patients have been developed and continuously improved in recent decades. Studies have mainly focused on the patterns, indications, and the optimal regimens of NAT, as well as the response assessment and additional management after NAT and surgery. We will elaborate on the development and major breakthroughs of NAT for GC based on the vicissitudes of the NCCN guidelines for GC, and assess the future of this therapy.

**THE PATTERN OF NAT FOR LAGC**

Most NAT schemes referred to adjuvant therapy for gastric cancer. Currently, the NCCN guidelines recommend both perioperative chemotherapy (category 1) and preoperative chemoradiotherapy (category 2B) as alternatives to NAT for LAGC (see related studies and detailed recommendations in Tables 1 and 2).

***Pre/perioperative neoadjuvant chemotherapy***

Although Wilke *et al*[10] have revealed the positive effect of preoperative chemotherapy on LAGC patients through various studies, it was not until 2006 that the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) study in the United Kingdom verified this conclusion through a large-scale randomized controlled trial (RCT). The MAGIC study confirmed that perioperative chemotherapy could achieve tumor downstaging and improve the R0 resection rate in patients with resectable LAGC. Additionally, perioperative chemotherapy and surgery can significantly prolong the progression-free survival (PFS) and overall survival (OS) of patients compared with surgery alone[[14](#_ENREF_14)]. This landmark study prompted the NCCN guidelines to incorporate preoperative neoadjuvant chemotherapy (NACT) into the standard treatment procedures for LAGC in 2007.

The conclusions of the MAGIC study were subsequently validated by other clinical trials. In 2010, the European Organization for Research and Treatment of Cancer Randomized Trial 40954 (EORTC 40954) study confirmed the significant effect of preoperative chemotherapy in improving the R0 resection rate (81.9% *vs* 66.7%, *P* = 0.036) and reducing the lymph node metastasis rate (61.4% *vs* 76.5%, *P* = 0.018) of LAGC patients[[15](#_ENREF_15)]. The Fédération Nationale des Centres de Lutte contre le Cancer and Fédération Francophone de Cancérologie Digestive 9703 (FNCLCC and FFCD 9703) study published in 2011 not only reached similar conclusions, but also verified the advantages of perioperative chemotherapy in prolonging the 5-year disease-free survival rate (DFS) and OS of patients compared with surgery alone[[16](#_ENREF_16)]. The FLOT4 (Fluorouracil, leucovorin, oxaliplatin, docetaxel) study published in 2016 and 2019 indicated that NACT can achieve a high pathological complete regression (pCR) rate and significantly prolong the survival of patients[[17](#_ENREF_17),[18](#_ENREF_18)]. At this point, pre/perioperative NACT became a mature scheme with definite efficacy and sufficient evidence and has been listed as a category 1 recommendation in the NCCN guidelines since 2007 (Table 2).

The specific schedules of NACT proposed by the MAGIC, FNCLCC and FFCD 9703, and FLOT4 trials all consist of preoperative and postoperative chemotherapy (also known as perioperative chemotherapy). However, due to the dissatisfactory commencing rates of postoperative chemotherapy in these studies (137/209 (65.6%), 54/109 (49.5%), and 78/119 (65.5%) for MAGIC, FNCLCC and FFCD 9703, and FLOT4 studies, respectively) and even lower completion rates (104/209 (49.8%), 25/109 (22.9%), and 60/119 (55.0%), respectively), the benefits of postoperative chemotherapy were inconclusive. Thus, NCCN guidelines only initially recommended preoperative chemotherapy as the primary treatment for certain LAGC patients, and this recommendation was revised to include perioperative chemotherapy when more evidence became available in 2016.

Although undisputed benefits of perioperative chemotherapy have been presented by many clinical trials (Table 1), the category 1 recommendation made by NCCN guidelines was mainly derived from the above three landmark studies (the MAGIC, FNCLCC and FFCD 9703, and FLOT4 studies)[[14](#_ENREF_14),[16](#_ENREF_16),[17](#_ENREF_17)]. Sequentially, the dosing schedules of recommended regimens were also based on these three or their relevant studies (except for fluorouracil and oxaliplatin regimen, Table 2)[[19-21](#_ENREF_19)].

***Preoperative neoadjuvant chemoradiotherapy***

Chemoradiotherapy plays an important role in treating esophageal cancer. The Fédération Francophone de Cancérologie Digestive 9102 (FFCD 9102) study reported that, for locally advanced thoracic esophageal cancer patients who responded to chemoradiation, the additional surgery could provide no benefit comparing with the continuation of additional chemoradiation[[22](#_ENREF_22)]. Due to the successful treatment of esophageal cancer with chemoradiotherapy, scholars attempted to expand this treatment to GC, especially to lower esophageal and esophagogastric junction (EGJ) cancers[[23](#_ENREF_23)].

In 2001, the Intergroup-0116 (INT-0116) study found that postoperative chemoradiotherapy could significantly prolong the median OS of patients with EGJ or gastric adenocarcinoma (36 mo *vs* 27 mo, *P* = 0.005) compared with surgery alone[[24](#_ENREF_24)]. In 2006, the Radiation Therapy Oncology Group 9904 (RTOG 9904) study reported that preoperative induction chemotherapy and sequential chemoradiotherapy could achieve a high pCR rate and R0 resection rate in patients with localized gastric adenocarcinoma[[25](#_ENREF_25)]. Subsequently, both of the large-scale clinical trials in the United States (Cancer and Leukemia Group B 9781 study, CALGB 9781 study) and the Netherlands (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study, CROSS study) confirmed that preoperative chemoradiotherapy could indeed achieve a satisfactory pCR rate and improve the R0 resection rate, and it could also prolong the median survival time and 5-year survival rate of patients with lower esophageal and EGJ cancers[[26](#_ENREF_26),[27](#_ENREF_27)]. As a result, preoperative chemoradiotherapy was recommended as the preferred approach for localized EGJ adenocarcinoma (for Siewert type III EGJ cancer, hereinafter the same) according to the NCCN guidelines from 2012 to 2014[[27](#_ENREF_27)]. In 2017, the PreOperative therapy in Esophagogastric adenocarcinoma Trial concluded that preoperative induction chemotherapy and chemoradiotherapy might have better therapeutic effects on EGJ cancer than preoperative chemotherapy alone, which would significantly improve the local PFS after resection (*P* = 0.01) and had a trend in prolonging the OS of patients (39.5% *vs* 24.4%, *P* = 0.055)[[28](#_ENREF_28)].

However, most scholars still believe that, since the incidence, geographical distribution, etiology, disease course, and biological behavior of EGJ cancers are different from those of true gastric (noncardia) cancers, the overall efficacy of neoadjuvant chemoradiotherapy remains inconclusive[[29](#_ENREF_29)]. Since the effects of preoperative chemoradiotherapy in resectable GC were only proposed by small-scale and single-arm studies, the regimens and dosing schedules listed in NCCN guidelines were based on trials that recruited esophageal and/or EGJ cancers patients[[22](#_ENREF_22),[25-27](#_ENREF_25),[30-35](#_ENREF_30)]. Therefore, the recommendation category of preoperative chemoradiotherapy remains in category 2B according to the latest NCCN guidelines. More than that, since there have not been enough studies compared the effect of pre/perioperative chemotherapy with chemoradiotherapy, the preferred recommendation of preoperative chemoradiotherapy for localized EGJ (Siewert type III) adenocarcinoma was also deleted in the 2015 NCCN guidelines. In the following sections, we will focus more on the development of neoadjuvant chemotherapy for LAGC.

**THE APPLICABLE POPULATION OF NAT**

Studies that specifically focused on the applicable population of NAT are still lacking. However, since NAT aims to improve the surgical outcomes in LAGC patients and the cure rate of T1 gastric cancer could reach 90% after surgery, most clinical trials enrolled patients with tumor ≥ T2/T3 and with/without lymph node metastasis invariably. Meanwhile, cytotoxic agents used in NACT are more efficient for metabolically active and/or proliferating tumor cells. Since the proliferation of tumor cells *in vivo*, which conforms to the Gompertzian model[[36](#_ENREF_36)], will be retarded along with the growth of tumor and the accumulation of necrosis and metabolites, the sensitivity to chemotherapy will also decline. These concepts serve as the basis for establishing the applications of NAT and reflect its original intention.

The NCCN guidelines have made minor alterations on the applicable population of NAT in the past decade. NAT was initially recommended for patients who are medically fit and with potentially resectable LAGC with clinical stage ≥ T2 or N+. Since 2012, the guidelines have neglected lymph node metastasis and recommend NAT for the abovementioned patients with clinical stage ≥ T2.

**THE EVOLUTION OF NEOADJUVANT CHEMOTHERAPY REGIMENS**

The efficacy and side effect must be weighted before performing NACT. Two-drug regimens were preferred according to the NCCN guidelines in principle because of their lower toxicity. And three-drug regimens may be applied in medically fit patients with access to frequent evaluation during treatment, to ensure that they can still tolerate surgery after NACT.

***Ecf and ecf modifications***

Fluorouracil, doxorubicin, and methotrexate (FAMTX) was one of the first attempts used in NACT for gastric cancer, but it failed to bring benefits to LAGC patients[[37](#_ENREF_37)]. Some scholars attributed the failure to the low effectiveness of this regimen, and Webb *et al*[38] did confirm that the efficacy of epirubicin, cisplatin, and fluorouracil (ECF) significantly surpassed that of FAMTX in patients with unresectable GC. With forethought, Cunningham *et al*[39], one of the originators of the ECF regimen, conducted the MAGIC study with landmark significance.

The MAGIC study enrolled 503 patients with nonmetastatic and operable lower esophageal cancer or GC who randomly received perioperative chemotherapy (ECF regimen, 3 cycles before and after surgery) and surgery or surgery alone. The results indicated that preoperative chemotherapy did not increase either postoperative complications or 30-day mortalities. Moreover, NACT resulted in tumor downstaging (T stage, *P* = 0.002; N stage, *P* = 0.01) and a higher R0 resection rate (79.3% *vs* 70.3%, *P* = 0.03). The PFS (*P* < 0.001) and 5-year survival rates (36.3% *vs* 23.0%, *P* = 0.009) were also improved significantly in patients who received NACT. Therefore, the NCCN guidelines began to adopt ECF as the standard regimen for neoadjuvant chemotherapy (category 1) in 2007.

To control the adverse effects and clinical practice difficulties of the ECF regimen, Cunningham *et al*[39] initiated the Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) study in 2000[[40](#_ENREF_40)]. Based on the ECF regimen, the REAL-2 study inspected the substitution of oxaliplatin (O) and capecitabine (X) for cisplatin (C) and fluorouracil (F) in patients with inoperable or metastatic esophageal, EGJ, or gastric cancer. The results confirmed that the incidences of side effects among ECF, ECX, EOF, and EOX (E, epirubicin) were similar (*P* > 0.05); it was also found that the EOX regimen was superior to the ECF regimen in prolonging the OS (*P* = 0.02) of patients. Moreover, the advantages of oral administration of capecitabine and the needlessness of persistent intravenous hydration of oxaliplatin reduce the admission time and frequency for patients. The REAL-2 study was published in 2008, and the three ECF modifications were subsequently adopted by the NCCN as the standard regimens (category 1). In addition, the substitutability between cisplatin and oxaliplatin, as well as infusional fluorouracil and capecitabine, was recognized by the guidelines. At this point, Cunningham *et al*[39] established the first-line status of ECF and ECF modifications in GC NACT, which dominated for a decade (Table 2).

***Fluorouracil and platinum-based regimens***

Over the next five years, after the rise of the ECF and ECF modifications, few regimens could achieve comparable results or be tested by high-quality clinical trials. This situation finally changed in 2011, when YChou *et al*[16] published the phase III clinical trial FNCLCC and FFCD 9703 and proposed the fluorouracil and cisplatin (FP) regimen.

This two-drug regimen was reported by Rougier *et al*[41] in 1994 and achieved satisfactory results including a 77% surgical rate and a 60% R0 resection rate in patients with nonresectable LAGC. The FNCLCC and FFCD 9703 study further tested the efficacy of the FP regimen as NACT. In this study, 224 patients with resectable lower esophageal, EGJ, or gastric cancer were randomized to receive perioperative FP chemotherapy (2-3 cycles before surgery, 3-4 cycles after surgery) and surgery or surgery alone. The results indicated that preoperative FP chemotherapy can significantly improve the R0 resection rate of patients (84% *vs* 74%, *P* = 0.04) and can achieve downstaging of lymph node metastasis (metastatic lymph node rate, 67% *vs* 80%, *P* = 0.054). More importantly, the perioperative FP regimen significantly increased the 5-year OS (38% *vs* 24%, log-rank *P* = 0.02) and 5-year DFS (34% *vs* 19%, log-rank *P* = 0.003) of patients. Compared with ECF, the two-drug regimen of FP could not only achieve a similar effect in terms of improving the long-term prognosis of patients, but also had the advantages of reducing chemotherapy-related complications, especially grade 3 to 4 leukopenia[[16](#_ENREF_16)].

In addition, the two-drug regimen of fluorouracil and oxaliplatin also came into view. Kim *et al*[20] verified that both S-1 + oxaliplatin and capecitabine + oxaliplatin had similar efficacy and good tolerance in patients with GC. In the CALGB 80403/E1206 study, Enzinger *et al*[19] also confirmed that the FOLFOX regimen (fluorouracil, leucovorin, and oxaliplatin) had similar effectiveness and better tolerance than the ECF regimen.

Considering the results of the MAGIC, FNCLCC and FFCD 9703, and other studies, as well as the safety priority principle of NACT, the two-drug regimens of fluorouracil and platinum (oxaliplatin/cisplatin) have gradually become the mainstream of neoadjuvant chemotherapy for LAGC. The FP regimen was adopted as a category 1 recommendation in the NCCN guidelines in 2013, and the fluorouracil + oxaliplatin regimen was also adopted in 2017 as a category 2A recommendation, while the recommendation categories of the ECF and ECF modifications were gradually demoted to 2A and 2B (Table 2).

***FLOT regimen***

After the MAGIC and FNCLCC and FFCD 9703 studies, the FLOT4 study published by German scholars Al-Batran *et al*[21] was considered as another landmark in the history of NACT for LAGC. The highlight of the FLOT regimen was the introduction of docetaxel.

The V325 study published in 2006 was the first large clinical trial that applied docetaxel in GC. Although the DCF regimen (docetaxel, cisplatin, and fluorouracil) used in this study improved the response rate to chemotherapy and prolonged the OS and PFS of patients with metastatic or locally recurrent disease, severe side effects have prevented it from being widely accepted[[42](#_ENREF_42)]. On this basis, Al-Batran *et al*[43,44] proposed the FLOT (docetaxel, fluorouracil, leucovorin, and oxaliplatin) regimen in 2008, which combined docetaxel with a safer skeleton regimen of FLO (fluorouracil, leucovorin, and oxaliplatin). The effectiveness and safety of the FLOT regimen were then validated through two clinical trials. These results encouraged researchers to further challenge the classical ECF and ECF modifications with the newly developed FLOT regimen.

The FLOT4 phase II study published in 2016 enrolled 300 patients with resectable EGJ or gastric cancer. In that study, patients randomly received perioperative ECF/ECX or FLOT chemotherapy[[17](#_ENREF_17)]. According to the study, the FLOT regimen not only significantly improved the surgical rate (93% *vs* 81%, *P* = 0.01) and the R0 resection rate (85% *vs* 74%, *P* = 0.02), but also promoted the downstaging of tumors (≤ ypT2, 44% *vs* 27%, *P* = 0.01). Most importantly, the pCR rate (tumor regression grade TRG1a) and the complete or subtotal regression rate (TRG1a/b) of the FLOT group were significantly higher than those of the ECF/ECX group (TRG1a, 16% *vs* 6%, *P* = 0.02; TRG1a/b, 37% *vs* 23%, *P* = 0.02). The phase III portion of the FLOT4 study indicated that the incidence of serious side effects of the FLOT regimen was similar to the ECF/ECX regimen (27% *vs* 27%), but the tumor resection rate (94% *vs* 87%, *P* = 0.001) and the R0 resection rate (85% *vs* 78%, *P* = 0.0162) of the FLOT group (*n* = 356) were significantly higher than those of the ECF/ECX group (*n* = 360). The median OS (50 mo *vs* 35 mo, *P* = 0.012) and median DFS (30 mo *vs* 18 mo, *P* = 0.0036) were also significantly longer than those of the ECF/ECX group[[18](#_ENREF_18)]. In view of the excellent pathological regression rate and the absolute advantages of FLOT over ECF/ECX, the NCCN guidelines adopted FLOT as the preferred regimen with a category 1 recommendation in 2018, and completely removed the ECF regimen and its modifications in the same year (Table 2).

From the domination of ECF and its modifications when NACT was developed in 2007 to the rally of the two-drug regimens of fluorouracil and platinum five years later, and the budding of the FLOT regimen in 2018, the development of chemotherapy drugs and the polishing of chemotherapy regimens have never stopped.

The efficacy of these regimens was further verified in many studies (Table 3). However, the absolute advantages of different regimens can hardly be concluded, because of the different regions, dosing schedules, completion rates, surgery/R0 resection rates and so on. Generally, the fluorouracil plus platinum regimens are more popular in Asia, while the ECF/ECF modifications and the FLOT regimen are widely accepted in Europe[[45-61](#_ENREF_45)]. An excellent 4-year OS was achieved by Li *et al*[51] with perioperative FOLFOX regimen. In this prospective non-randomized study, LAGC patients received a total of 6 cycles of FOLFOX chemotherapy perioperatively or postoperatively. The clinical and pathological response rates of FOLFOX were 69.7% and 39.4%, respectively, and the 4-year OS, as well as the 4-year DFS, of the neoadjuvant arm was 78%[[51](#_ENREF_51)]. Meanwhile, the highest pathological response rate was achieved by Favi *et al*[48] with preoperative FLOT regimen. Patients with advanced distal esophageal and EGJ cancer in this study received 3-6 cycles of FLOT chemotherapy before surgery, the tumor regression rate of Cologne regression grade 1-3 was 52%, and the 3-year OS was 37%[[48](#_ENREF_48)]. Nevertheless, disease recurrences were still common among all the studies and regimens, with the recurrence rates ranging from 32% to 62.5% (Table 3).

**RESPONSE ASSESSMENT AND ADDITIONAL MANAGEMENT FOR NAT**

Since more and more patients have received neoadjuvant treatment in the past decade, the 2018 NCCN guidelines proposed a response assessment for those patients in order to improve additional management strategies.

According to the 2018 NCCN guidelines, a chest/abdomen/pelvis CT scan with contrast was used as the method to evaluate disease status. If the outcome showed persistent local disease, surgical treatment was preferred. For patients with unresectable or metastatic disease, and those who were not medically fit for surgery, palliative management was recommended. For patients with no evidence of disease, the guidelines allowed clinicians to perform surveillance on those who refused surgery on the premise that surgery was still preferred.

However, both “surveillance” and “no evidence of disease” are controversial in GC. First, the definition of “no evidence of disease” is vague, and CT scanning with contrast cannot evaluate the disease status accurately[[62-64](#_ENREF_62)]. Second, although pCR is a predictor of a favorable prognosis, it is still not equivalent to the clinical cure[[58](#_ENREF_58),[65](#_ENREF_65),[66](#_ENREF_66)]. Finally, even if patients who achieved pCR after chemotherapy can be screened out by nonsurgical methods, sequential therapy should be recommended as an alternative to surgery[[67](#_ENREF_67)]. Therefore, the 2019 NCCN guidelines contained major revisions in this chapter, the phrase “no evidence of disease” was deleted, and additional managements were recommended according to the resectability of the lesion. For patients with resectable tumors, surgery was still the preferred treatment, while for other patients, including those with nonresectable/metastatic lesions and those who were not medically fit for surgery, palliative care, but not surveillance, was recommended.

The postoperative treatment strategy for patients who received NAT was based on the cutting-edge of tumors and NAT modes. Due to the lack of direct studies that enrolled post-NAT patients, the recommendations proposed by the NCCN guidelines were derived from indirect studies with a relatively low level of evidence. The vicissitudes of this chapter were focused primarily on four aspects: (1) Before 2016, the stratification of postoperative NAT patients depended on their ypT and ypN stages, and only ypT2 and ypN0 patients were included in the low-risk group. In recent years, the status of lymph nodes has been elevated, and the current stratification is now only based on the presence of metastatic lymph nodes, partially according to the study of Smyth *et al*[[68](#_ENREF_68)]; (2) The unification of postoperative treatment became a trend, especially for those who achieved R0 resection after NAT. The latest guidelines now do not adhere to the stratification of R0 resected patients and gave highly unified treatment recommendations, partially due to the lack of relevant studies; (3) Chemoradiotherapy is now preferred for non-R0 resected patients after NAT. The INT-0116 study established the “operation and postoperative adjuvant chemoradiotherapy” pattern in North America. Based on this study, the NCCN guidelines recommend that non-R0 resected patients without preoperative chemoradiotherapy should receive postoperative chemoradiotherapy for additional management; and (4) Reconsiderations of selecting the postoperative NACT regimens. The NCCN guidelines previously recommended R1 resected patients who underwent NACT to receive the same NACT regimens after surgery, in order to ensure the integrity and unity of perioperative treatment. However, the 2019 guidelines only recommended those patients with R0 resection to continue their preoperative NACT regimens.

**THE FUTURE OF NAT FOR GC**

NAT is one of the breakthroughs of GC treatment in recent decades, and has the trend to become the standard strategy of this disease. However, the indications and strategies of NAT still need to be perfected, and researchers may gain ground in the following aspects in the future.

Above all, the validation of NAT in a wider range is necessary. The NCCN guidelines may only reflect a corner of NAT from the Western view, and the acceptability of NAT worldwide is still improving, especially in Asia. Chinese GC guidelines recommended that patients with advanced resectable GC (clinical stage III or above) could either receive surgery directly (Grade I recommendations) or receive neoadjuvant chemotherapy (Grade II recommendations)[[69](#_ENREF_69)]. In Japan, preoperative chemotherapy has just been accepted in the latest guidelines for LAGC patients with bulky lymph nodes[[70](#_ENREF_70)]. And in South Korea, the efficacy of preoperative chemotherapy and chemoradiotherapy for potentially resectable GC patients remains inconclusive[[71](#_ENREF_71)]. Meanwhile, numerous trials in Asia, such as JCOG0405, JCOG1002, NCT01515748, NCT01534546, NCT02555358, and NCT00252161[[55](#_ENREF_55),[72](#_ENREF_72),[73](#_ENREF_73)], have provided or will provide more evidence about the best indications for NAT, and physicians should always be critical when adopting the recommendations from foreign guidelines.

Second, the enhancement and delicacy management of NACT are required. Fluorouracil and platinum have been used as skeleton regimens of NACT for years, and their efficiency and tolerance in patients have been tested. However, it is an eternal rule that old regimens will be eliminated and that the development of new drugs may further improve the prognosis of patients[[74](#_ENREF_74),[75](#_ENREF_75)]. Besides traditional cytotoxic regimens, the development of targeted therapy, immunotherapy, and metabolism based anticancer therapy may help us usher in a new era of LAGC treatment. Targeted drugs such as trastuzumab (anti-HER2) and ramucirumab (anti-VEGF2) have shown potential in improving clinical outcomes for late staged patients[[74-85](#_ENREF_74)]. Immunotherapy, such as anti-PD-1/PD-L1 and anti-CTLA-4 drugs (nivolumab, pembrolizumab, avelumab, tremelimumab, *etc.*), adoptive cell therapy, and VEGF related cancer vaccine have also been evaluated in gastric cancer and have shown promising effects[[86-92](#_ENREF_86)]. Studies about cancer metabolomics also provided new insights in cancer treatment. Drugs targeting at hexokinase II may intervene the glycolysis of tumor cells[[93](#_ENREF_93)], and others that altered the metabolism of lipid, amino acid, *etc*. also presented exciting prospects in treating GC *in vitro*[[94-96](#_ENREF_94)]. In addition, the continuous monitoring of NACT efficacy can also help to clarify the optimal operation timing for chemotherapy-sensitive patients, or it can encourage the termination of unnecessary treatment for chemotherapy-resistant patients in advance to avoid disease progression[[97](#_ENREF_97),[98](#_ENREF_98)].

Besides, the individualized treatment and efficacy prediction of neoadjuvant chemotherapy may be a trend. It is true that the antitumor effects of cytotoxic drugs are extensive and without high selection, but the correlation between genetic traits and chemosensitivity may also be underestimated. Polymorphisms, gene mutations, and unique genetic backgrounds may lead to different response rates to the same chemotherapy regimen[[99](#_ENREF_99),[100](#_ENREF_100)]. The advantages of the S-1 and cisplatin regimens reported by the SPIRITS (S-1 Plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer) study in Japan were not consistently concluded in the non-Asian trial of the First-Line Advanced Gastric Cancer Study study (median OS, 13.0 mo *vs* 8.6 mo, respectively)[[101](#_ENREF_101),[102](#_ENREF_102)]. Scholars have also found that genetic polymorphisms play an important role in selecting NAT for each patient[[103](#_ENREF_103)]. Additionally, the Trastuzumab for Gastric Cancer study confirmed that chemotherapy combined with HER-2 targeted therapy resulted in a better therapeutic effect than chemotherapy alone for patients with high HER-2 expression[[76](#_ENREF_76)], which may enlighten us about the possibility of neoadjuvant chemotherapy plus targeted therapy. The heterogeneity of histopathology in GC also results in different response rates to the same regimen. Although the latest NCCN guidelines of GC (2019.V2) did not recommend the best regimen for each pathological type, clinical trials such as the FLOT study have proposed different histopathological regression rates among different histology types. We should never handle GC as one kind of disease, and preoperative treatment will eventually be recommended based on the histopathology types (Lauren, JGCA, WHO classification, *etc.*) and/or the molecular types (TCGA, ACRG classification, *etc.*)[[104-108](#_ENREF_104)]. In the future, the individual differences of patients may be carefully considered before performing NACT, and cytotoxic regimens combined with targeted therapy may be a new option for certain patients[[79](#_ENREF_79),[81](#_ENREF_81),[82](#_ENREF_82),[109-111](#_ENREF_109)].

Finally, the strategic flow of NAT will be continuously perfected. The booming of NAT in the past decade benefited from abundant high-quality clinical trials, while the decision-making process of NAT still needs to be perfected. For example, there is still no consensus on whether surgery can bring absolute benefits to patients who exhibit an excellent response to NACT. And for patients who have received NACT but did not achieve R0 resection, which treatment (either chemoradiotherapy or alternative chemotherapy) should be administered remains unclear. The clarity of such decisions will have substantial impacts on patients’ prognosis and quality of life. We believe that the NCCN guidelines will continue perfecting the strategic flow to allow better choices for patients base on future studies and trials.

**CONCLUSION**

NAT is becoming the standard treatment for patients with resectable, nonmetastatic LAGC. Although the universality of present evidence is insufficient, and the frontier of NAT is still led by Western scholars, we are always confident in Asian researchers for their unremitting efforts[[112](#_ENREF_112),[113](#_ENREF_113)]. We are also looking forward to more high-quality studies such as the NCT01534546, NCT02555358, and NCT00252161, which will help to establish a characteristic NAT strategy that is more appropriate for Asian populations.

**REFERENCES**

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Chen W**, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]

3 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

4 **Jeong O**, Park YK. Clinicopathological features and surgical treatment of gastric cancer in South Korea: the results of 2009 nationwide survey on surgically treated gastric cancer patients. *J Gastric Cancer* 2011; **11**: 69-77 [PMID: 22076206 DOI: 10.5230/jgc.2011.11.2.69]

5 **Nashimoto A**, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y, Tsujitani S, Seto Y, Furukawa H, Oda I, Ono H, Tanabe S, Kaminishi M. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. *Gastric Cancer* 2013; **16**: 1-27 [PMID: 22729699 DOI: 10.1007/s10120-012-0163-4]

6 **Siewert JR**, Böttcher K, Roder JD, Busch R, Hermanek P, Meyer HJ. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. *Br J Surg* 1993; **80**: 1015-1018 [PMID: 8402053 DOI: 10.1002/bjs.1800800829]

7 **Gee DW**, Rattner DW. Management of gastroesophageal tumors. *Oncologist* 2007; **12**: 175-185 [PMID: 17296813 DOI: 10.1634/theoncologist.12-2-175]

8 **Frei E 3rd**. Clinical cancer research: an embattled species. *Cancer* 1982; **50**: 1979-1992 [PMID: 7127245 DOI: 10.1002/1097-0142(19821115)50:10<1979::aid-cncr2820501002>3.0.co;2-d]

9 **Plukker JT**, Mulder NH, Sleijfer DT, Grond J, Verschueren RC. Chemotherapy and surgery for locally advanced cancer of the cardia and fundus: phase II study with methotrexate and 5-fluorouracil. *Br J Surg* 1991; **78**: 955-958 [PMID: 1913116 DOI: 10.1002/bjs.1800780820]

10 **Wilke H**, Preusser P, Fink U, Gunzer U, Meyer HJ, Meyer J, Siewert JR, Achterrath W, Lenaz L, Knipp H. Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase II study with etoposide, doxorubicin, and cisplatin. *J Clin Oncol* 1989; **7**: 1318-1326 [PMID: 2769330 DOI: 10.1200/JCO.1989.7.9.1318]

11 **Mai M**, Takahashi Y, Fujimoto T, Omote K. [Neoadjuvant chemotherapy for far-advanced gastric carcinoma]. *Gan To Kagaku Ryoho* 1994; **21**: 431-439 [PMID: 8129383]

12 **Plukker JT**, Sleijfer DT, Verschueren RC, Van der Graaf WT, Mulder NH. Neo-adjuvant chemotherapy with carboplatin, 4-epiadriamycin and teniposide (CET) in locally advanced cancer of the cardia and the lower oesophagus: a phase II study. *Anticancer Res* 1995; **15**: 2357-2361 [PMID: 8572652]

13 **Melcher AA**, Mort D, Maughan TS. Epirubicin, cisplatin and continuous infusion 5-fluorouracil (ECF) as neoadjuvant chemotherapy in gastro-oesophageal cancer. *Br J Cancer* 1996; **74**: 1651-1654 [PMID: 8932350 DOI: 10.1038/bjc.1996.604]

14 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]

15 **Schuhmacher C**, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, Haag C, Mauer ME, Hasan B, Welch J, Ott K, Hoelscher A, Schneider PM, Bechstein W, Wilke H, Lutz MP, Nordlinger B, Van Cutsem E, Siewert JR, Schlag PM. 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**: 5210-5218 [PMID: 21060024 DOI: 10.1200/JCO.2009.26.6114]

16 **Ychou M**, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; **29**: 1715-1721 [PMID: 21444866 DOI: 10.1200/JCO.2010.33.0597]

17 **Al-Batran SE**, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, Meiler J, Homann N, Lorenzen S, Schmalenberg H, Probst S, Koenigsmann M, Egger M, Prasnikar N, Caca K, Trojan J, Martens UM, Block A, Fischbach W, Mahlberg R, Clemens M, Illerhaus G, Zirlik K, Behringer DM, Schmiegel W, Pohl M, Heike M, Ronellenfitsch U, Schuler M, Bechstein WO, Königsrainer A, Gaiser T, Schirmacher P, Hozaeel W, Reichart A, Goetze TO, Sievert M, Jäger E, Mönig S, Tannapfel A. 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**: 1697-1708 [PMID: 27776843 DOI: 10.1016/S1470-2045(16)30531-9]

18 **Al-Batran SE**, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K, Lindig U, Schmiegel W, Pohl M, Stoehlmacher J, Folprecht G, Probst S, Prasnikar N, Fischbach W, Mahlberg R, Trojan J, Koenigsmann M, Martens UM, Thuss-Patience P, Egger M, Block A, Heinemann V, Illerhaus G, Moehler M, Schenk M, Kullmann F, Behringer DM, Heike M, Pink D, Teschendorf C, Löhr C, Bernhard H, Schuch G, Rethwisch V, von Weikersthal LF, Hartmann JT, Kneba M, Daum S, Schulmann K, Weniger J, Belle S, Gaiser T, Oduncu FS, Güntner M, Hozaeel W, Reichart A, Jäger E, Kraus T, Mönig S, Bechstein WO, Schuler M, Schmalenberg H, Hofheinz RD; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019; **393**: 1948-1957 [PMID: 30982686 DOI: 10.1016/S0140-6736(18)32557-1]

19 **Enzinger PC**, Burtness BA, Niedzwiecki D, Ye X, Douglas K, Ilson DH, Villaflor VM, Cohen SJ, Mayer RJ, Venook A, Benson AB 3rd, Goldberg RM. CALGB 80403 (Alliance)/E1206: A Randomized Phase II Study of Three Chemotherapy Regimens Plus Cetuximab in Metastatic Esophageal and Gastroesophageal Junction Cancers. *J Clin Oncol* 2016; **34**: 2736-2742 [PMID: 27382098 DOI: 10.1200/JCO.2015.65.5092]

20 **Kim GM**, Jeung HC, Rha SY, Kim HS, Jung I, Nam BH, Lee KH, Chung HC. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. *Eur J Cancer* 2012; **48**: 518-526 [PMID: 22243774 DOI: 10.1016/j.ejca.2011.12.017]

21 **Al-Batran SE**, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, Rethwisch V, Seipelt G, Homann N, Wilhelm G, Schuch G, Stoehlmacher J, Derigs HG, Hegewisch-Becker S, Grossmann J, Pauligk C, Atmaca A, Bokemeyer C, Knuth A, Jäger E; Arbeitsgemeinschaft Internistische Onkologie. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26**: 1435-1442 [PMID: 18349393 DOI: 10.1200/JCO.2007.13.9378]

22 **Bedenne L**, Michel P, Bouché O, Milan C, Mariette C, Conroy T, Pezet D, Roullet B, Seitz JF, Herr JP, Paillot B, Arveux P, Bonnetain F, Binquet C. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007; **25**: 1160-1168 [PMID: 17401004 DOI: 10.1200/JCO.2005.04.7118]

23 **Yin S**, Wang P, Xu X, Tan Y, Huang J, Xu H. The optimal strategy of multimodality therapies for resectable gastric cancer: evidence from a network meta-analysis. *J Cancer* 2019; **10**: 3094-3101 [PMID: 31289579 DOI: 10.7150/jca.30456]

24 **Macdonald JS**, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730 [PMID: 11547741 DOI: 10.1056/NEJMoa010187]

25 **Ajani JA**, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, Greskovich JF, Anne PR, Bradley JD, Willett C, Rich TA. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *J Clin Oncol* 2006; **24**: 3953-3958 [PMID: 16921048 DOI: 10.1200/JCO.2006.06.4840]

26 **Tepper J**, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, Kiel K, Willett C, Sugarbaker D, Mayer R. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008; **26**: 1086-1092 [PMID: 18309943 DOI: 10.1200/JCO.2007.12.9593]

27 **van Hagen P**, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074-2084 [PMID: 22646630 DOI: 10.1056/NEJMoa1112088]

28 **Stahl M**, Walz MK, Riera-Knorrenschild J, Stuschke M, Sandermann A, Bitzer M, Wilke H, Budach W. 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**: 183-190 [PMID: 28628843 DOI: 10.1016/j.ejca.2017.04.027]

29 **Van Cutsem E**, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet* 2016; **388**: 2654-2664 [PMID: 27156933 DOI: 10.1016/S0140-6736(16)30354-3]

30 **Lowy AM**, Feig BW, Janjan N, Rich TA, Pisters PW, Ajani JA, Mansfield PF. A pilot study of preoperative chemoradiotherapy for resectable gastric cancer. *Ann Surg Oncol* 2001; **8**: 519-524 [PMID: 11456051]

31 **Ajani JA**, Mansfield PF, Janjan N, Morris J, Pisters PW, Lynch PM, Feig B, Myerson R, Nivers R, Cohen DS, Gunderson LL. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. *J Clin Oncol* 2004; **22**: 2774-2780 [PMID: 15254045 DOI: 10.1200/JCO.2004.01.015]

32 **Ajani JA**, Mansfield PF, Crane CH, Wu TT, Lunagomez S, Lynch PM, Janjan N, Feig B, Faust J, Yao JC, Nivers R, Morris J, Pisters PW. Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. *J Clin Oncol* 2005; **23**: 1237-1244 [PMID: 15718321 DOI: 10.1200/JCO.2005.01.305]

33 **Rivera F**, Galán M, Tabernero J, Cervantes A, Vega-Villegas ME, Gallego J, Laquente B, Rodríguez E, Carrato A, Escudero P, Massutí B, Alonso-Orduña V, Cardenal A, Sáenz A, Giralt J, Yuste AL, Antón A, Aranda E; Spanish Cooperative Group for Digestive Tumor Therapy. Phase II trial of preoperative irinotecan-cisplatin followed by concurrent irinotecan-cisplatin and radiotherapy for resectable locally advanced gastric and esophagogastric junction adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2009; **75**: 1430-1436 [PMID: 19540072 DOI: 10.1016/j.ijrobp.2008.12.087]

34 **Conroy T**, Galais MP, Raoul JL, Bouché O, Gourgou-Bourgade S, Douillard JY, Etienne PL, Boige V, Martel-Lafay I, Michel P, Llacer-Moscardo C, François E, Créhange G, Abdelghani MB, Juzyna B, Bedenne L, Adenis A; Fédération Francophone de Cancérologie Digestive and UNICANCER-GI Group. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. *Lancet Oncol* 2014; **15**: 305-314 [PMID: 24556041 DOI: 10.1016/S1470-2045(14)70028-2]

35 **Khushalani NI**, Leichman CG, Proulx G, Nava H, Bodnar L, Klippenstein D, Litwin A, Smith J, Nava E, Pendyala L, Smith P, Greco W, Berdzik J, Douglass H, Leichman L. Oxaliplatin in combination with protracted-infusion fluorouracil and radiation: report of a clinical trial for patients with esophageal cancer. *J Clin Oncol* 2002; **20**: 2844-2850 [PMID: 12065561 DOI: 10.1200/JCO.2002.12.032]

36 **Norton L**. A Gompertzian model of human breast cancer growth. *Cancer Res* 1988; **48**: 7067-7071 [PMID: 3191483]

37 **Hartgrink HH**, van de Velde CJ, Putter H, Songun I, Tesselaar ME, Kranenbarg EK, de Vries JE, Wils JA, van der Bijl J, van Krieken JH; Cooperating Investigators of The Dutch Gastric Cancer Group. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. *Eur J Surg Oncol* 2004; **30**: 643-649 [PMID: 15256239 DOI: 10.1016/j.ejso.2004.04.013]

38 **Webb A**, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997; **15**: 261-267 [PMID: 8996151 DOI: 10.1200/JCO.1997.15.1.261]

39 **Cunningham D**, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR; Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 36-46 [PMID: 18172173 DOI: 10.1056/NEJMoa073149]

40 **Sumpter K**, Harper-Wynne C, Cunningham D, Rao S, Tebbutt N, Norman AR, Ward C, Iveson T, Nicolson M, Hickish T, Hill M, Oates J. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. *Br J Cancer* 2005; **92**: 1976-1983 [PMID: 15928658 DOI: 10.1038/sj.bjc.6602572]

41 **Rougier P**, Mahjoubi M, Lasser P, Ducreux M, Oliveira J, Ychou M, Pignon JP, Elias D, Bellefqih S, Bognel C. Neoadjuvant chemotherapy in locally advanced gastric carcinoma--a phase II trial with combined continuous intravenous 5-fluorouracil and bolus cisplatinum. *Eur J Cancer* 1994; **30A**: 1269-1275 [PMID: 7999411 DOI: 10.1016/0959-8049(94)90171-6]

42 **Van Cutsem E**, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA; V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991-4997 [PMID: 17075117 DOI: 10.1200/JCO.2006.06.8429]

43 **Al-Batran SE**, Hartmann JT, Hofheinz R, Homann N, Rethwisch V, Probst S, Stoehlmacher J, Clemens MR, Mahlberg R, Fritz M, Seipelt G, Sievert M, Pauligk C, Atmaca A, Jäger E. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol* 2008; **19**: 1882-1887 [PMID: 18669868 DOI: 10.1093/annonc/mdn403]

44 **Al-Batran SE**, Pauligk C, Homann N, Hartmann JT, Moehler M, Probst S, Rethwisch V, Stoehlmacher-Williams J, Prasnikar N, Hollerbach S, Bokemeyer C, Mahlberg R, Hofheinz RD, Luley K, Kullmann F, Jäger E. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). *Eur J Cancer* 2013; **49**: 835-842 [PMID: 23063354 DOI: 10.1016/j.ejca.2012.09.025]

45 **Reece-Smith AM**, Saha S, Cunnell ML, Hameed K, Bessell EM, Duffy JP, Madhusudan S, Parsons SL. MAGIC in practice: experience of peri-operative ECF/X chemotherapy in gastro-esophageal adenocarcinomas. *J Surg Oncol* 2012; **106**: 748-752 [PMID: 22674046 DOI: 10.1002/jso.23187]

46 **Achilli P**, De Martini P, Ceresoli M, Mari GM, Costanzi A, Maggioni D, Pugliese R, Ferrari G. Tumor response evaluation after neoadjuvant chemotherapy in locally advanced gastric adenocarcinoma: a prospective, multi-center cohort study. *J Gastrointest Oncol* 2017; **8**: 1018-1025 [PMID: 29299362 DOI: 10.21037/jgo.2017.08.13]

47 **Al-Batran SE**, Homann N, Pauligk C, Illerhaus G, Martens UM, Stoehlmacher J, Schmalenberg H, Luley KB, Prasnikar N, Egger M, Probst S, Messmann H, Moehler M, Fischbach W, Hartmann JT, Mayer F, Höffkes HG, Koenigsmann M, Arnold D, Kraus TW, Grimm K, Berkhoff S, Post S, Jäger E, Bechstein W, Ronellenfitsch U, Mönig S, Hofheinz RD. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial. *JAMA Oncol* 2017; **3**: 1237-1244 [PMID: 28448662 DOI: 10.1001/jamaoncol.2017.0515]

48 **Favi F**, Bollschweiler E, Berlth F, Plum P, Hescheler DA, Alakus H, Semrau R, Celik E, Mönig SP, Drebber U, Hölscher AH. Neoadjuvant chemotherapy or chemoradiation for patients with advanced adenocarcinoma of the oesophagus? A propensity score-matched study. *Eur J Surg Oncol* 2017; **43**: 1572-1580 [PMID: 28666624 DOI: 10.1016/j.ejso.2017.06.003]

49 **Lorenzen S**, Pauligk C, Homann N, Schmalenberg H, Jäger E, Al-Batran SE. Feasibility of perioperative chemotherapy with infusional 5-FU, leucovorin, and oxaliplatin with (FLOT) or without (FLO) docetaxel in elderly patients with locally advanced esophagogastric cancer. *Br J Cancer* 2013; **108**: 519-526 [PMID: 23322206 DOI: 10.1038/bjc.2012.588]

50 **Schulz C**, Kullmann F, Kunzmann V, Fuchs M, Geissler M, Vehling-Kaiser U, Stauder H, Wein A, Al-Batran SE, Kubin T, Schäfer C, Stintzing S, Giessen C, Modest DP, Ridwelski K, Heinemann V. NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma-Very good response predominantly in patients with intestinal type tumors. *Int J Cancer* 2015; **137**: 678-685 [PMID: 25530271 DOI: 10.1002/ijc.29403]

51 **Li ZY**, Koh CE, Bu ZD, Wu AW, Zhang LH, Wu XJ, Wu Q, Zong XL, Ren H, Tang L, Zhang XP, Li JY, Hu Y, Shen L, Ji JF. Neoadjuvant chemotherapy with FOLFOX: improved outcomes in Chinese patients with locally advanced gastric cancer. *J Surg Oncol* 2012; **105**: 793-799 [PMID: 22189752 DOI: 10.1002/jso.23009]

52 **Yoshikawa T**, Morita S, Tanabe K, Nishikawa K, Ito Y, Matsui T, Fujitani K, Kimura Y, Fujita J, Aoyama T, Hayashi T, Cho H, Tsuburaya A, Miyashita Y, Sakamoto J. Survival results of a randomised two-by-two factorial phase II trial comparing neoadjuvant chemotherapy with two and four courses of S-1 plus cisplatin (SC) and paclitaxel plus cisplatin (PC) followed by D2 gastrectomy for resectable advanced gastric cancer. *Eur J Cancer* 2016; **62**: 103-111 [PMID: 27244537 DOI: 10.1016/j.ejca.2016.04.012]

53 **Ott K**, Sendler A, Becker K, Dittler HJ, Helmberger H, Busch R, Kollmannsberger C, Siewert JR, Fink U. Neoadjuvant chemotherapy with cisplatin, 5-FU, and leucovorin (PLF) in locally advanced gastric cancer: a prospective phase II study. *Gastric Cancer* 2003; **6**: 159-167 [PMID: 14520529 DOI: 10.1007/s10120-003-0245-4]

54 **Kochi M**, Fujii M, Kanamori N, Mihara Y, Funada T, Tamegai H, Watanabe M, Takayama Y, Suda H, Takayama T. Phase II Study of Neoadjuvant Chemotherapy With S-1 and CDDP in Patients With Lymph Node Metastatic Stage II or III Gastric Cancer. *Am J Clin Oncol* 2017; **40**: 17-21 [PMID: 24662266 DOI: 10.1097/COC.0000000000000058]

55 **Tsuburaya A**, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M; Stomach Cancer Study Group of the Japan Clinical Oncology Group. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. *Br J Surg* 2014; **101**: 653-660 [PMID: 24668391 DOI: 10.1002/bjs.9484]

56 **Feng D**, Leong M, Li T, Chen L, Li T. Surgical outcomes in patients with locally advanced gastric cancer treated with S-1 and oxaliplatin as neoadjuvant chemotherapy. *World J Surg Oncol* 2015; **13**: 11 [PMID: 25634099 DOI: 10.1186/s12957-015-0444-6]

57 **Yu Y**, Fang Y, Shen Z, Wang Y, Yan M, Cao H, Liu Y, Wang X, Cui Y, Liu F, Chen W, Li W, Li Q, Jiang H, Sun Y, Liu T. Oxaliplatin plus Capecitabine in the Perioperative Treatment of Locally Advanced Gastric Adenocarcinoma in Combination with D2 Gastrectomy: NEO-CLASSIC Study. *Oncologist* 2019; [PMID: 31239311 DOI: 10.1634/theoncologist.2019-0416]

58 **Mingol F**, Gallego J, Orduña A, Martinez-Blasco A, Sola-Vera J, Moya P, Morcillo MA, Ruiz JA, Calpena R, Lacueva FJ. Tumor regression and survival after perioperative MAGIC-style chemotherapy in carcinoma of the stomach and gastroesophageal junction. *BMC Surg* 2015; **15**: 66 [PMID: 25997454 DOI: 10.1186/s12893-015-0054-9]

59 **Bichev D**, Treese C, von Winterfeld M, Breithaupt K, Dogan Y, Schmidt SC, Daum S, Thuss-Patience PC. High Impact of Histopathological Remission for Prognosis after Perioperative Chemotherapy with ECF and ECF-Like Regimens for Gastric and Gastroesophageal Adenocarcinoma. *Oncology* 2015; **89**: 95-102 [PMID: 25823985 DOI: 10.1159/000376550]

60 **Mongan AM**, Kalachand R, King S, O'Farrell NJ, Power D, Ravi N, Muldoon C, O'Byrne K, Reynolds JV. Outcomes in gastric and junctional cancer using neoadjuvant and adjuvant chemotherapy (epirubicin, oxaliplatin, and capecitabine) and radical surgery. *Ir J Med Sci* 2015; **184**: 417-423 [PMID: 24879337 DOI: 10.1007/s11845-014-1135-y]

61 **Xue K**, Ying X, Bu Z, Wu A, Li Z, Tang L, Zhang L, Zhang Y, Li Z, Ji J. Oxaliplatin plus S-1 or capecitabine as neoadjuvant or adjuvant chemotherapy for locally advanced gastric cancer with D2 lymphadenectomy: 5-year follow-up results of a phase II<b>-</b>III randomized trial. *Chin J Cancer Res* 2018; **30**: 516-525 [PMID: 30510363 DOI: 10.21147/j.issn.1000-9604.2018.05.05]

62 **Yoshikawa T**, Tanabe K, Nishikawa K, Ito Y, Matsui T, Kimura Y, Hasegawa S, Aoyama T, Hayashi T, Morita S, Miyashita Y, Tsuburaya A, Sakamoto J. Accuracy of CT staging of locally advanced gastric cancer after neoadjuvant chemotherapy: cohort evaluation within a randomized phase II study. *Ann Surg Oncol* 2014; **21 Suppl 3**: S385-S389 [PMID: 24595801 DOI: 10.1245/s10434-014-3615-8]

63 **Fujikawa H**, Yoshikawa T, Hasegawa S, Hayashi T, Aoyama T, Ogata T, Cho H, Oshima T, Rino Y, Morita S, Masuda M. Diagnostic value of computed tomography for staging of clinical T1 gastric cancer. *Ann Surg Oncol* 2014; **21**: 3002-3007 [PMID: 24687153 DOI: 10.1245/s10434-014-3667-9]

64 **Hwang SW**, Lee DH, Lee SH, Park YS, Hwang JH, Kim JW, Jung SH, Kim NY, Kim YH, Lee KH, Kim HH, Park DJ, Lee HS, Jung HC, Song IS. Preoperative staging of gastric cancer by endoscopic ultrasonography and multidetector-row computed tomography. *J Gastroenterol Hepatol* 2010; **25**: 512-518 [PMID: 20370729 DOI: 10.1111/j.1440-1746.2009.06106.x]

65 **Blackham AU**, Greenleaf E, Yamamoto M, Hollenbeak C, Gusani N, Coppola D, Pimiento JM, Wong J. Tumor regression grade in gastric cancer: Predictors and impact on outcome. *J Surg Oncol* 2016; **114**: 434-439 [PMID: 27199217 DOI: 10.1002/jso.24307]

66 **Becker K**, Langer R, Reim D, Novotny A, Meyer zum Buschenfelde C, Engel J, Friess H, Hofler H. Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. *Ann Surg* 2011; **253**: 934-939 [PMID: 21490451 DOI: 10.1097/SLA.0b013e318216f449]

67 **Mokadem I**, Dijksterhuis WPM, van Putten M, Heuthorst L, de Vos-Geelen JM, Haj Mohammad N, Nieuwenhuijzen GAP, van Laarhoven HWM, Verhoeven RHA. Recurrence after preoperative chemotherapy and surgery for gastric adenocarcinoma: a multicenter study. *Gastric Cancer* 2019; [PMID: 30949777 DOI: 10.1007/s10120-019-00956-6]

68 **Smyth EC**, Fassan M, Cunningham D, Allum WH, Okines AF, Lampis A, Hahne JC, Rugge M, Peckitt C, Nankivell M, Langley R, Ghidini M, Braconi C, Wotherspoon A, Grabsch HI, Valeri N. Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial. *J Clin Oncol* 2016; **34**: 2721-2727 [PMID: 27298411 DOI: 10.1200/JCO.2015.65.7692]

69 **Wang FH**, Shen L, Li J, Zhou ZW, Liang H, Zhang XT, Tang L, Xin Y, Jin J, Zhang YJ, Yuan XL, Liu TS, Li GX, Wu Q, Xu HM, Ji JF, Li YF, Wang X, Yu S, Liu H, Guan WL, Xu RH. The Chinese Society of Clinical Oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer. *Cancer Commun (Lond)* 2019; **39**: 10 [PMID: 30885279 DOI: 10.1186/s40880-019-0349-9]

70 **Japanese Gastric Cancer Association.** Japanese Gastric Cancer Treatment Guidelines. 5th ed. Japan: Jinyuan Press, 2018

71 Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group and Review Panel. Korean Practice Guideline for Gastric Cancer 2018: An Evidence-based, Multi-disciplinary Approach. *J Gastric Cancer* 2019; **19**: 1-48 [PMID: 30944757 DOI: 10.5230/jgc.2019.19.e8]

72 **Katayama H**, Ito S, Sano T, Takahari D, Mizusawa J, Boku N, Tsuburaya A, Terashima M, Sasako M; Stomach Cancer Study Group of the Japan Clinical Oncology Group. A Phase II study of systemic chemotherapy with docetaxel, cisplatin, and S-1 (DCS) followed by surgery in gastric cancer patients with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1002. *Jpn J Clin Oncol* 2012; **42**: 556-559 [PMID: 22525210 DOI: 10.1093/jjco/hys054]

73 **Kodera Y**. Neoadjuvant chemotherapy for gastric adenocarcinoma in Japan. *Surg Today* 2017; **47**: 899-907 [PMID: 28247105 DOI: 10.1007/s00595-017-1473-2]

74 **Hecht JR**, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, Jeziorski K, Shparyk Y, Hoff PM, Sobrero A, Salman P, Li J, Protsenko SA, Wainberg ZA, Buyse M, Afenjar K, Houé V, Garcia A, Kaneko T, Huang Y, Khan-Wasti S, Santillana S, Press MF, Slamon D. Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2-Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC--A Randomized Phase III Trial. *J Clin Oncol* 2016; **34**: 443-451 [PMID: 26628478 DOI: 10.1200/JCO.2015.62.6598]

75 **Satoh T**, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, Tsuji A, Omuro Y, Li J, Wang JW, Miwa H, Qin SK, Chung IJ, Yeh KH, Feng JF, Mukaiyama A, Kobayashi M, Ohtsu A, Bang YJ. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. *J Clin Oncol* 2014; **32**: 2039-2049 [PMID: 24868024 DOI: 10.1200/JCO.2013.53.6136]

76 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. 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**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]

77 **Lordick F**, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, Park JO, Sawaki A, Celik I, Götte H, Melezínková H, Moehler M; Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 490-499 [PMID: 23594786 DOI: 10.1016/S1470-2045(13)70102-5]

78 **Waddell T**, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, Wotherspoon A, Saffery C, Middleton G, Wadsley J, Ferry D, Mansoor W, Crosby T, Coxon F, Smith D, Waters J, Iveson T, Falk S, Slater S, Peckitt C, Barbachano Y. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 481-489 [PMID: 23594787 DOI: 10.1016/S1470-2045(13)70096-2]

79 **Ohtsu A**, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, Starnawski M, Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29**: 3968-3976 [PMID: 21844504 DOI: 10.1200/JCO.2011.36.2236]

80 **Shen L**, Li J, Xu J, Pan H, Dai G, Qin S, Wang L, Wang J, Yang Z, Shu Y, Xu R, Chen L, Liu Y, Yu S, Bu L, Piao Y. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer* 2015; **18**: 168-176 [PMID: 24557418 DOI: 10.1007/s10120-014-0351-5]

81 **Fuchs CS**, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, Dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalcberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; **383**: 31-39 [PMID: 24094768 DOI: 10.1016/S0140-6736(13)61719-5]

82 **Wilke H**, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A; RAINBOW Study Group. 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**: 1224-1235 [PMID: 25240821 DOI: 10.1016/S1470-2045(14)70420-6]

83 **Ohtsu A**, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; **31**: 3935-3943 [PMID: 24043745 DOI: 10.1200/JCO.2012.48.3552]

84 **Catenacci DVT**, Tebbutt NC, Davidenko I, Murad AM, Al-Batran SE, Ilson DH, Tjulandin S, Gotovkin E, Karaszewska B, Bondarenko I, Tejani MA, Udrea AA, Tehfe M, De Vita F, Turkington C, Tang R, Ang A, Zhang Y, Hoang T, Sidhu R, Cunningham D. Rilotumumab plus epirubicin, cisplatin, and capecitabine as first-line therapy in advanced MET-positive gastric or gastro-oesophageal junction cancer (RILOMET-1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; **18**: 1467-1482 [PMID: 28958504 DOI: 10.1016/S1470-2045(17)30566-1]

85 **Shah MA**, Bang YJ, Lordick F, Alsina M, Chen M, Hack SP, Bruey JM, Smith D, McCaffery I, Shames DS, Phan S, Cunningham D. Effect of Fluorouracil, Leucovorin, and Oxaliplatin With or Without Onartuzumab in HER2-Negative, MET-Positive Gastroesophageal Adenocarcinoma: The METGastric Randomized Clinical Trial. *JAMA Oncol* 2017; **3**: 620-627 [PMID: 27918764 DOI: 10.1001/jamaoncol.2016.5580]

86 **Matsueda S**, Graham DY. Immunotherapy in gastric cancer. *World J Gastroenterol* 2014; **20**: 1657-1666 [PMID: 24587645 DOI: 10.3748/wjg.v20.i7.1657]

87 **Kono K**, Takahashi A, Ichihara F, Amemiya H, Iizuka H, Fujii H, Sekikawa T, Matsumoto Y. Prognostic significance of adoptive immunotherapy with tumor-associated lymphocytes in patients with advanced gastric cancer: a randomized trial. *Clin Cancer Res* 2002; **8**: 1767-1771 [PMID: 12060615]

88 **Jiang J**, Xu N, Wu C, Deng H, Lu M, Li M, Xu B, Wu J, Wang R, Xu J, Nilsson-Ehle P. Treatment of advanced gastric cancer by chemotherapy combined with autologous cytokine-induced killer cells. *Anticancer Res* 2006; **26**: 2237-2242 [PMID: 16821594]

89 **Jiang JT**, Shen YP, Wu CP, Zhu YB, Wei WX, Chen LJ, Zheng X, Sun J, Lu BF, Zhang XG. Increasing the frequency of CIK cells adoptive immunotherapy may decrease risk of death in gastric cancer patients. *World J Gastroenterol* 2010; **16**: 6155-6162 [PMID: 21182234 DOI: 10.3748/wjg.v16.i48.6155]

90 **Ralph C**, Elkord E, Burt DJ, O'Dwyer JF, Austin EB, Stern PL, Hawkins RE, Thistlethwaite FC. Modulation of lymphocyte regulation for cancer therapy: a phase II trial of tremelimumab in advanced gastric and esophageal adenocarcinoma. *Clin Cancer Res* 2010; **16**: 1662-1672 [PMID: 20179239 DOI: 10.1158/1078-0432.CCR-09-2870]

91 **Janjigian YY**, Bendell J, Calvo E, Kim JW, Ascierto PA, Sharma P, Ott PA, Peltola K, Jaeger D, Evans J, de Braud F, Chau I, Harbison CT, Dorange C, Tschaika M, Le DT. CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients With Metastatic Esophagogastric Cancer. *J Clin Oncol* 2018; **36**: 2836-2844 [PMID: 30110194 DOI: 10.1200/JCO.2017.76.6212]

92 **Muro K**, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, Eder JP, Golan T, Le DT, Burtness B, McRee AJ, Lin CC, Pathiraja K, Lunceford J, Emancipator K, Juco J, Koshiji M, Bang YJ. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2016; **17**: 717-726 [PMID: 27157491 DOI: 10.1016/S1470-2045(16)00175-3]

93 **Maher JC**, Krishan A, Lampidis TJ. Greater cell cycle inhibition and cytotoxicity induced by 2-deoxy-D-glucose in tumor cells treated under hypoxic vs aerobic conditions. *Cancer Chemother Pharmacol* 2004; **53**: 116-122 [PMID: 14605866 DOI: 10.1007/s00280-003-0724-7]

94 **Cai Z**, Zhao JS, Li JJ, Peng DN, Wang XY, Chen TL, Qiu YP, Chen PP, Li WJ, Xu LY, Li EM, Tam JP, Qi RZ, Jia W, Xie D. A combined proteomics and metabolomics profiling of gastric cardia cancer reveals characteristic dysregulations in glucose metabolism. *Mol Cell Proteomics* 2010; **9**: 2617-2628 [PMID: 20699381 DOI: 10.1074/mcp.M110.000661]

95 **Wiggins T**, Kumar S, Markar SR, Antonowicz S, Hanna GB. Tyrosine, phenylalanine, and tryptophan in gastroesophageal malignancy: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2015; **24**: 32-38 [PMID: 25344892 DOI: 10.1158/1055-9965.EPI-14-0980]

96 **Duan J**, Sun L, Huang H, Wu Z, Wang L, Liao W. Overexpression of fatty acid synthase predicts a poor prognosis for human gastric cancer. *Mol Med Rep* 2016; **13**: 3027-3035 [PMID: 26936091 DOI: 10.3892/mmr.2016.4902]

97 **Martin-Romano P**, Solans BP, Cano D, Subtil JC, Chopitea A, Arbea L, Lozano MD, Castanon E, Baraibar I, Salas D, Hernandez-Lizoain JL, Trocóniz IF, Rodriguez J. Neoadjuvant therapy for locally advanced gastric cancer patients. A population pharmacodynamic modeling. *PLoS One* 2019; **14**: e0215970 [PMID: 31071108 DOI: 10.1371/journal.pone.0215970]

98 **Liu Y**, Zhang KC, Huang XH, Xi HQ, Gao YH, Liang WQ, Wang XX, Chen L. Timing of surgery after neoadjuvant chemotherapy for gastric cancer: Impact on outcomes. *World J Gastroenterol* 2018; **24**: 257-265 [PMID: 29375211 DOI: 10.3748/wjg.v24.i2.257]

99 **Aichler M**, Luber B, Lordick F, Walch A. Proteomic and metabolic prediction of response to therapy in gastric cancer. *World J Gastroenterol* 2014; **20**: 13648-13657 [PMID: 25320503 DOI: 10.3748/wjg.v20.i38.13648]

100 **Biondi A**, Agnes A, Del Coco F, Pozzo C, Strippoli A, D'Ugo D, Persiani R. Preoperative therapy and long-term survival in gastric cancer: One size does not fit all. *Surg Oncol* 2018; **27**: 575-583 [PMID: 30217321 DOI: 10.1016/j.suronc.2018.07.006]

101 **Koizumi W**, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215-221 [PMID: 18282805 DOI: 10.1016/S1470-2045(08)70035-4]

102 **Ajani JA**, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, Vynnychenko I, Garin A, Lang I, Falcon S. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol* 2010; **28**: 1547-1553 [PMID: 20159816 DOI: 10.1200/JCO.2009.25.4706]

103 **Goekkurt E**, Al-Batran SE, Hartmann JT, Mogck U, Schuch G, Kramer M, Jaeger E, Bokemeyer C, Ehninger G, Stoehlmacher J. Pharmacogenetic analyses of a phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil and leucovorin plus either oxaliplatin or cisplatin: a study of the arbeitsgemeinschaft internistische onkologie. *J Clin Oncol* 2009; **27**: 2863-2873 [PMID: 19332728 DOI: 10.1200/JCO.2008.19.1718]

104 Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]

105 **Cristescu R**, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, Liu J, Yue YG, Wang J, Yu K, Ye XS, Do IG, Liu S, Gong L, Fu J, Jin JG, Choi MG, Sohn TS, Lee JH, Bae JM, Kim ST, Park SH, Sohn I, Jung SH, Tan P, Chen R, Hardwick J, Kang WK, Ayers M, Hongyue D, Reinhard C, Loboda A, Kim S, Aggarwal A. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med* 2015; **21**: 449-456 [PMID: 25894828 DOI: 10.1038/nm.3850]

106 **LAUREN P**. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675 DOI: 10.1111/apm.1965.64.1.31]

107 **Nagtegaal ID**, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington MK, Carneiro F, Cree IA. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2019; [PMID: 31433515 DOI: 10.1111/his.13975]

108 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]

109 **Qiu MZ**, Li Q, Wang ZQ, Liu TS, Liu Q, Wei XL, Jin Y, Wang DS, Ren C, Bai L, Zhang DS, Wang FH, Li YH, Xu RH. HER2-positive patients receiving trastuzumab treatment have a comparable prognosis with HER2-negative advanced gastric cancer patients: a prospective cohort observation. *Int J Cancer* 2014; **134**: 2468-2477 [PMID: 24155030 DOI: 10.1002/ijc.28559]

110 **Van Cutsem E**, de Haas S, Kang YK, Ohtsu A, Tebbutt NC, Ming Xu J, Peng Yong W, Langer B, Delmar P, Scherer SJ, Shah MA. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol* 2012; **30**: 2119-2127 [PMID: 22565005 DOI: 10.1200/JCO.2011.39.9824]

111 **Okines AF**, Langley RE, Thompson LC, Stenning SP, Stevenson L, Falk S, Seymour M, Coxon F, Middleton GW, Smith D, Evans L, Slater S, Waters J, Ford D, Hall M, Iveson TJ, Petty RD, Plummer C, Allum WH, Blazeby JM, Griffin M, Cunningham D. Bevacizumab with peri-operative epirubicin, cisplatin and capecitabine (ECX) in localised gastro-oesophageal adenocarcinoma: a safety report. *Ann Oncol* 2013; **24**: 702-709 [PMID: 23108952 DOI: 10.1093/annonc/mds533]

112 **Yoshikawa T**, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, Oshita H, Ito S, Kawashima Y, Fukushima N. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. *Br J Surg* 2009; **96**: 1015-1022 [PMID: 19644974 DOI: 10.1002/bjs.6665]

113 **Inoue T**, Yachida S, Usuki H, Kimura T, Hagiike M, Okano K, Suzuki Y. Pilot feasibility study of neoadjuvant chemoradiotherapy with S-1 in patients with locally advanced gastric cancer featuring adjacent tissue invasion or JGCA bulky N2 lymph node metastases. *Ann Surg Oncol* 2012; **19**: 2937-2945 [PMID: 22466666 DOI: 10.1245/s10434-012-2332-4]

114 **Sakuramoto S**, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K; ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810-1820 [PMID: 17978289 DOI: 10.1056/NEJMoa072252]

115 **Mandard AM**, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994; **73**: 2680-2686 [PMID: 8194005 DOI: 10.1002/1097-0142(19940601)73:11<2680::aid-cncr2820731105>3.0.co;2-c]

116 **Becker K**, Mueller JD, Schulmacher C, Ott K, Fink U, Busch R, Böttcher K, Siewert JR, Höfler H. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. *Cancer* 2003; **98**: 1521-1530 [PMID: 14508841 DOI: 10.1002/cncr.11660]

117 **Kajitani T**. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. *Jpn J Surg* 1981; **11**: 127-139 [PMID: 7300058]

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**Table 1 Important studies of neoadjuvant therapy for gastric cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Number** | **Characteristics of patients** | **Arms and interventions** | **Outcomes and conclusions** |
| FAMTX, Hartgrink *et al*[[37](#_ENREF_37)], 2004 | 59 | Nonmetastatic resectable cancer of the stomach | Preoperative FAMTX chemotherapy and surgery *vs* surgery alone | FAMTX could not bring benefits to resectability rates or survival |
| MAGIC, Cunningham *et al*[[14](#_ENREF_14)], 2006 | 503 | Operable and nonmetastatic cancer of the stomach or lower esophagus, ≥ stage II | Perioperative ECF chemotherapy and surgery *vs* surgery alone | Perioperative ECF decreased tumor sizes and stages and improved PFS and OS |
| REAL-2, Cunningham *et al*[[39](#_ENREF_39)], 2008 | 1002 | Inoperable or metastatic cancer of the esophagus, EGJ, or stomach | Randomly received ECF, ECX, EOF, and EOX chemotherapy | Capecitabine and oxaliplatin were as effective as fluorouracil and cisplatin, respectively |
| EORTC 40954, Schuhmacher *et al*[[15](#_ENREF_15)], 2010 | 144 | Stages III and IV (cM0) cancer of the EGJ or stomach | Preoperative chemotherapy (cisplatin, leucovorin, and fluorouracil) and surgery *vs* surgery alone | Increased R0 resection rate, failed to demonstrate a survival benefit |
| FNCLCC and FFCD 9703, Ychou *et al*[[16](#_ENREF_16)], 2011 | 224 | Resectable lower esophagus, EGJ, or stomach cancer | Perioperative FP chemotherapy and surgery *vs* surgery alone | Perioperative FP improved curative surgical rate, OS, and DFS |
| V325, van Cutsem *et al*[[42](#_ENREF_42)], 2006 | 445 | Gastric or EGJ cancer with measurable metastatic disease or locally recurrent disease of lymph nodes | DCF chemotherapy *vs* CF chemotherapy | DCF prolonged the time-to-progression and OS, but associated with more adverse events |
| FLOT AIO, Al-Batran *et al*[[43](#_ENREF_43)], 2008 | 59 | Measurable metastatic cancer of the EGJ or stomach | Single arm, biweekly FLOT chemotherapy | Biweekly FLOT was effective and well tolerated |
| FLOT65+, Al-Batran *et al*[[44](#_ENREF_44)], 2013 | 143 | Locally advanced or metastatic esophagogastric cancer, age ≥ 65 | FLO chemotherapy *vs* FLOT chemotherapy | FLOT improved response rates and PFS, but increased adverse events |
| Kim *et al*[[20](#_ENREF_20)], 2012 | 129 | Metastatic or recurrent gastric cancer | SOX chemotherapy *vs* CAPOX chemotherapy | SOX and CAPOX were equally effective and well tolerated |
| FLOT4, AI-Batran *et al*[[17](#_ENREF_17),[18](#_ENREF_18)], 2016, 2019 | 300 (phase II), 716 (phase III) | Resectable gastric or EGJ cancer, staged ≥ cT2 and/or cN+ | Perioperative ECF/ECX chemotherapy *vs* perioperative FLOT chemotherapy | FLOT achieved more pCR and increased medial survival time and OS than ECF/ECX |
| CALGB 80403/E1206, Enzinger *et al*[[19](#_ENREF_19)], 2016 | 245 | Measurable metastatic cancer of the esophagus or EGJ | ECF-C chemotherapy *vs* IC-C chemotherapy *vs* FOLFOX-C chemotherapy | FOLFOX and ECF regimen had similar efficacy, and FOLFOX was better tolerated |
| ACTS-GC, Sakuramoto *et al*[[114](#_ENREF_114)], 2011 | 1059 | Nonmetastatic gastric cancer staged as II, IIIA, or IIIB | Surgery and postoperative S-1 chemotherapy *vs* surgery alone | S-1 could prolong the 5-year OS and 5-year RFS rate |
| FLAGS, Ajani *et al*[[102](#_ENREF_102)], 2010 | 1053 | Unresectable, locally advanced or metastatic gastric or EGJ cancer | Cisplatin/S-1 chemotherapy *vs* cisplatin/fluorouracil chemotherapy | Cisplatin/S-1 could not prolong the OS but could improve safety profile |
| INT-0116, Macdonald *et al*[[24](#_ENREF_24)], 2001 | 556 | Operable cancer of the EGJ or stomach | Surgery and postoperative chemoradiotherapy *vs* surgery alone | Postoperative chemoradiotherapy prolonged the OS and RFS time |
| RTOG 9904, Ajani *et al*[[25](#_ENREF_25)], 2006 | 49 | Localized cancer of the EGJ or stomach, staged as T2-3N0-1 or T1N1 | Single arm, induction chemotherapy, chemoradiotherapy, and surgery | Achieved a pCR rate of 26% and a R0 resection rate of 77% |
| CROSS, van Hagen *et al*[[27](#_ENREF_27)], 2012 | 368 | Resectable cancer of the esophagus or EGJ, staged as T1N1M0 or T2-3N0-1M0 | Preoperative chemoradiotherapy and surgery *vs* surgery alone | Preoperative chemoradiotherapy improved survival and was well tolerated |
| FFCD 9102, Bedenne *et al*[[22](#_ENREF_22)], 2007 | 444 | Operable T3N0-1M0 cancer of the thoracic esophagus | Additional surgery *vs* additional chemoradiotherapy | Additional surgery had no benefits among patients who responded to chemoradiotherapy |
| CALGB 9781, Tepper *et al*[[26](#_ENREF_26)], 2008 | 56 | Operable cancer of the thoracic esophagus or EGJ, staged as T1-3, N1 | Preoperative induction chemotherapy, chemoradiotherapy, and surgery *vs* surgery alone | The trimodality therapy improved median survival and 5-year survival |
| POET, Stahl *et al*[[28](#_ENREF_28)], 2017 | 119 | Locally advanced cancer of the EGJ, staged as T3 and T4 | Chemotherapy and surgery *vs* induction chemotherapy, chemoradiotherapy, and surgery | Induction chemotherapy and chemoradiotherapy could prolong PFS |

FAMTX: Fluorouracil, doxorubicin, and methotrexate; ECF: Epirubicin, cisplatin, and fluorouracil; ECX: Epirubicin, cisplatin, and capecitabine; EOF: Epirubicin, oxaliplatin, and fluorouracil; EOX: Epirubicin, oxaliplatin, and capecitabine; DCF: Docetaxel, cisplatin, and fluorouracil; CF: Cisplatin and fluorouracil; FLO: Fluorouracil, leucovorin, and oxaliplatin; FLOT: Docetaxel, fluorouracil, leucovorin, and oxaliplatin; SOX: S-1 and oxaliplatin; CAPOX: Capecitabine and oxaliplatin; ECF-C: ECF and cetuximab; IC-C: Irinotecan, cisplatin, and cetuximab; FOLFOX-C: Oxaliplatin, fluorouracil, leucovorin, and cetuximab; EGJ: Esophagogastric junction; pCR: Pathological complete regression; PFS: Progression-free survival; OS: Overall survival; RFS: Relapse-free survival.

**Table 2 The vicissitudes of the recommendation categories of different neoadjuvant chemotherapy regimens in the NCCN gastric cancer guidelines**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **2007** | **2008** | **2009** | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019.V1** | **2019. V2** |
| ECF[[14](#_ENREF_14)] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2B | 2B |  |  |  |
| ECF modifications[[39](#_ENREF_39),[40](#_ENREF_40)] |  | 1 | 1 | 1 | 1 | 1 | 1 | 2A | 2A | 2B | 2B |  |  |  |
| Fluorouracil  and cisplatin[[16](#_ENREF_16)] |  |  |  |  |  |  | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| aFluorouracil  and oxaliplatin[[19-21](#_ENREF_19)] |  |  |  |  |  |  |  |  |  |  | 2A | 2Ab | 2Ab | 2Ab |
| FLOT[[17](#_ENREF_17)] |  |  |  |  |  |  |  |  |  |  |  | 1b | 1b | 1b |

References quoted in Table 2 for each regimen were based on NCCN guidelines from 2007 to 2019. 1, 2A, 2B: Categories of recommendations. b: Preferred intervention. a: This regimen was based on extrapolations from literature and clinical practice according to NCCN guidelines, and was revised to fluoropyrimidine and oxaliplatin in 2017 NCCN guidelines. ECF: Epirubicin, cisplatin, and fluorouracil; FLOT: Docetaxel, fluorouracil, leucovorin, and oxaliplatin.

**Table 3 Short-term and long-term effects of different pre/perioperative chemotherapy regimens**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Region** | **Regimen** | ***n*** | **Median age** | **EGJ/gastric (%)** | **pT stage (%)** | | | | | **pN stage (%)** | | | | **Short-term effect** | | **Long-term effect**  **(mo; yr)** |
| **0** | **1** | **2** | **3** | **4** | **0** | **1** | **2** | **3** | **aSurgery/R0 (%)** | **Response** |
| Mongan *et al*[[60](#_ENREF_60)], 2015 | EU | EOX | 59 | 65 | 71/29 | 6 | 9 | 23 | 58 | 4 | 30 | 44 | 17 | 9 | 80/54 | Mandard *et al*[[115](#_ENREF_115)], TRG 1-3: 34% | Median OS: 22 mo; 4-yr survival: 47%; recurrence rate: 40%; median time to recurrence: 13 mo |
| Bichev *et al*[[59](#_ENREF_59)], 2015 | EU | ECF/mECF | 77 | 62.1 | 61/40 | 0b | | 4 | 91 | 5 | 14 | 86 | | | 88/69 | Becker *et al*[[116](#_ENREF_116)], TRG 1 + 2: 44.2% | 5-yr cumulative survival: 36.3%; median OS: 23.7 mo; 5-yr TSS: 42.2%; median TSS: 32.9 mo; recurrence rate: 32% |
| Mingol *et al*[[58](#_ENREF_58)], 2015 | EU | ECF/ECX | 53 | 64 | 17/83 | 33 | | | 67 | | 35 | 17 | 48 | | 91/72 | Becker *et al*[[116](#_ENREF_116)], TRG 1a + 1b: 17% | 5-yr OS: 18%; 5-yr DSS: 22%; recurrence rate: 61.9% |
| Achilli *et al*[[46](#_ENREF_46)], 2017 | EU | ECF/ECX | 67 | 67 | 0/100 | 0 | 8 | 18 | 65 | 9 | NA | NA | 73 | | 99/96 | CR + PR: 37%; Becker TRG 1: 29% | Median OS: 36.6 mo; median DFS: 25.7 mo; recurrence rate: 54% |
| REECE-SMITH *et al*[[45](#_ENREF_45)], 2012 | EU | ECF/ECX | 100 | 66 | 68/32 | 4 | 9 | 32 | 46 | 9 | 50 | 32 | 14 | 5 | 78/76 | Histological regression > 50%: 45.8% | Median survival: 31.7 mo; 2-yr survival: 53% |
| Favi *et al*[[48](#_ENREF_48)], 2017 | EU | FLOT | 40 | 61.5 | 100/0 | 12 | 15 | 17 | 43 | 10 | 40 | 17 | 28 | 15 | 97/85 | Cologne Regression Scale 1-3: 52% | 1-yr OS: 72%; 2-yr OS: 60%; 3-yr OS: 37%; median OS: 2.4 yr |
| Al-Batran *et al*[[47](#_ENREF_47)], 2017 | EU | FLOT | 51 | 66 | 39/61 | 0b | | 18 | 69 | 8 | 26 | 75 | | | 96/78 | NA | Median OS and PFS not achieved |
| Schulz *et al*[[50](#_ENREF_50)], 2015 | EU | FLOT | 58 | 61 | 59/38 | 20 | 12 | 16 | 40 | 8 | 54 | 16 | 16 | 10 | 86/74 | Becker *et al*[[116](#_ENREF_116)], TRG 1a + 1b: 40% | 1-yr survival: 79.3%; 1-yr PFS: 67.2%; median DFS: 32.9 mo |
| Lorenzen *et al*[[49](#_ENREF_49)], 2013 | EU | FLOT | 21 | 69 | 62/38 | 10 | 48 | | 5 | | 29 | 38 | | | 71/67 | CR + PR: 59.1% | 1.5-yr OS: 78%; 2-yr OS: 78%; median PFS: 21.1 mo |
| FLO | 22 | 71.5 | 41/59 | 0 | 68 | | 5 | | 32 | 41 | | | 77/68 | CR + PR: 18.2% | 1.5-yr OS: 70%; 2-yr OS: 56%; median PFS: 12.0 mo |
| Yoshikawa *et al*[[52](#_ENREF_52)], 2016 | AS | SC-2 | 21 | 66 | 33/67 | 0 | | | 5 | 95 | 5 | 60 | 20 | 15 | 95/81 | NA | 3-yr OS: 67% |
| SC-4 | 20 | 63 | 25/75 | 0 | | | 5 | 95 | 20 | 40 | 20 | 20 | 90/75 | NA | 3-yr OS: 55% |
| Tsuburaya *et al*[[55](#_ENREF_55)], 2014 | AS | SC | 53 | 63 | NA | 4 | 14 | 47 | 33 | 2 | 16 | 10 | 43 | 31 | 94/82 | CR + PR: 65%; JCGC[[108](#_ENREF_108)] grade 1b-3: 51% | 3-yr OS: 59%; 5-yr OS: 53%; 3-yr and 5-yr RFS: 50% |
| Kochi *et al*[[54](#_ENREF_54)], 2017 | AS | SC | 50 | 64 | 0/100 | NA | 12 | 8 | 40 | 36 | 22 | 14 | 32 | 30 | 98/88 | pCR: 2%; clinical response for LN: 75.5%, for primary tumor: 59.2% | 3-yr OS: 48%; 3-yr RFS: 42% |
| Ott *et al*[[53](#_ENREF_53)], 2003 | EU | FLP | 49 | 58 | 0/100 | 0 | 10 | 55 | 24 | 12 | 26 | 36 | 21 | 17 | 86/76 | Major pathological tumor regression: 17% | Median survival: 25.4 mo (for ITT patients) and 32 mo (for R0 patients); recurrence rate: 62.5%; median recurrence: 19 mo |
| Li *et al*[[51](#_ENREF_51)], 2012 | AS | FOLFOX | 33 | 65 | 0/100 | 12 | 6 | 12 | 61 | 9 | 36 | 33 | 27 | 3 | 100/91 | CR + PR: 69.7%; JRSGC[[117](#_ENREF_117)] grade 2-3: 39.4% | Mean survival: 74 mo; 4-yr OS: 78%; 4-yr DFS: 78% |
| Xue *et al*[[61](#_ENREF_61)], 2018 | AS | SOX | 25 | ≥ 65: 48% | 0/100 | 12 | 8 | 36 | 8 | 36 | 60 | 16 | 8 | 16 | 100/100 | JCGC[[108](#_ENREF_108)] grade 2-3: 40% | 5-yr OS: 70% |
| CAPOX | 25 | ≥ 65: 24% | 0/100 | 4 | 8 | 32 | 20 | 36 | 44 | 20 | 16 | 20 | 100/100 | JCGC[[108](#_ENREF_108)] grade 2-3: 36% |
| Yu *et al*[[57](#_ENREF_57)], 2019 | AS | XELOX | 54 | 65 | 30/70 | 13 | 13 | 17 | 33 | 25 | 31 | 15 | 31 | 23 | 91/83 | CR + PR: 50%; JCGC[[108](#_ENREF_108)] grade 1b-3: 41.6% | Median OS: 30.77 mo; 3-yr OS: 47.2%; disease progression: 55.6%; median PFS: 20.1 mo; 3-yr PFS: 43.8% |
| Feng *et al*[[56](#_ENREF_56)], 2015 | AS | SOX | 80 | 60 | 40/60 | 15 | 11 | 30 | 19 | 25 | 59 | 16 | 14 | 11 | 100/95 | CR + PR: 68.8%; pCR: 12.5% | NA |

a: Some data were amended in order to increase comparability. b: T and N stages in this study were clinical stages. EU: Europe; AS: Asia; EOX: Epirubicin, oxaliplatin and capecitabine; ECF: epirubicin, cisplatin and fluorouracil; mECF: ECF modifications; ECX: Epirubicin, cisplatin and capecitabine; FLOT: Docetaxel, fluorouracil, leucovorin and oxaliplatin; FLO: Fluorouracil, leucovorin and oxaliplatin; SC: S-1 and cisplatin; SC-2/4: S-1 and cisplatin for 2 cycles/4 cycles; FLP: 5-FU, cisplatin and leucovorin; FOLFOX: Oxaliplatin, fluorouracil and leucovorin; SOX: S-1 and oxaliplatin; CAPOX: Capecitabine and oxaliplatin; XELOX: Capecitabine and oxaliplatin; EGJ: Esophagogastric junction; LN: Lymph node; TRG: Tumor regression grade; JRSGC: Japanese research society for gastric cancer; JCGC: Japanese classification of gastric cancer; CR: Complete regression; PR: Partial regression; pCR: Pathological complete regression; OS: Overall survival; TSS: Tumor specific survival; DSS: Disease specific survival; DFS: Disease free survival; PFS: Progression-free survival; RFS: Relapse-free survival; ITT: Intention to treat; NA: Not available.