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MINIREVIEWS

Neoadjuvant therapy for gastroesophageal adenocarcinoma

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Abstract

Gastric and esophageal adenocarcinomas are one of the main causes of cancer-related death worldwide. While the incidence of gastric adenocarcinoma is decreasing, the incidence of gastroesophageal junction adenocarcinoma is rising rapidly in Western countries. Considering that surgical resection is currently the major curative treatment, and that the 5-year survival rate highly depends on the pTNM stage at diagnosis, gastroesophageal adenocarcinoma management is very challenging for oncologists. Several treatment strategies are being evaluated, and among them systemic chemotherapy, to decrease recurrences and improve overall survival. The MAGIC and FNCLCC-FFCD trials showed a survival benefit of perioperative chemotherapy in patients with operable gastric and lower esophageal cancer, and these results had an impact on the European clinical practice. New strategies, including induction chemotherapy followed by preoperative chemoradiotherapy, targeted therapies in combination with perioperative chemotherapy and the new cytotoxic regimens, are currently assessed to improve current standards and help developing patient-tailored therapeutic interventions.

Key words: Gastric adenocarcinoma; Lower esophagus adenocarcinoma; Gastroesophageal junction adenocarcinoma; Preoperative treatment; Neoadjuvant treatment

Core tip: Gastric and esophageal adenocarcinomas are one of the main causes of cancer-related death worldwide. The incidence of gastroesophageal junction adenocarcinoma is rapidly rising in Western countries. Surgical resection is currently the major curative treatment. As the 5-year survival rate highly depends on the pTNM stage, the treatment strategy is very challenging for oncologists. Several treatments, including systemic chemotherapy, are being assessed to prevent recurrences and improve overall survival. New strategies, such as induction chemotherapy followed by preoperative chemoradiotherapy, targeted therapies and new cytotoxic regimens in perioperative chemotherapy, are currently assessed to improve current standards and develop more tailored therapeutic interventions.

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INTRODUCTION

Survival of patients with esophageal, gastric or gastro-esophageal junction adenocarcinoma is poor because they are frequently locally-advanced or with distant metastases at diagnosis. Even if the incidence of gastric adenocarcinoma is decreasing, it stays the second most frequent cause of cancer-related death worldwide. In 2012, 952000 new cases of gastric cancer were diagnosed with 723000 estimated deaths worldwide[1]. In Western countries, a faster increase of the incidence of gastroesophageal junction adenocarcinoma compared to that of other gastrointestinal adenocarcinomas has been reported over the last 25 years[2,3]. Surgical resection of the primary tumor is the major curative treatment for these upper gastrointestinal cancers. Esophageal cancers can be treated with exclusive radiochemotherapy[4], but this review will focus on (neo)adjuvant therapies. The 5-year survival rate is correlated with the pTNM stage, lymph node metastases being the major poor prognostic factor. A 5-year survival of 20% to 30% is reported in localized tumors, which extend beyond the submucosa[5-7]. Also, gastroesophageal adenocarcinomas (GEA) are often detected at an already advanced stage, in Western countries, about 30% of resectable patients were not identified at an early stage. For this group, the rate of recurrence following resection of a gastric cancer is high. Currently, various strategies (including nutritional management) are developed and tested to reduce this risk and improve patient's survival[8].

ADJUVANT THERAPIES FOR GASTROESOPHAGEAL ADENOCARCINOMA

Adjuvant chemotherapy

Like in colorectal cancer, adjuvant systemic therapy in patients with GEA is used to treat post-resection occult residual micro-metastatic disease and to increase survival. Many clinical studies have investigated the possible positive impact of adjuvant therapy on the patients' outcomes. Between 1994 and 2002, meta-analyses of the data from these trials suggested that adjuvant chemotherapy slightly increases overall survival, with a reduction of the risk of death between 12% and 18%[9-12]. However, no recommendation for the treatment of resectable gastric cancer could be proposed because of the heterogeneity of the methodology used in these meta-analyses including studies with a small number of patients, and because old chemotherapy regimens were often followed in these trials. Several clinical studies have focused on chemotherapy drugs that are currently used in the clinical practice. For instance, in France, the randomized phase Ⅲ trial of the French Federation of Digestive Oncology [Fédération Française de Cancérologie Digestive (FFCD)] on adjuvant chemotherapy combined with 5-fluorouracil (5-FU) and cisplatin (CDDP) after curative resection of gastric cancer showed no benefit on survival compared with surgery alone[13]. In Japan, a randomized phase Ⅲ trial on adjuvant chemotherapy with the S-1 fluoropyrimidin derivative in patients with stage Ⅱ-Ⅲ GEA found that the 5-year overall survival (OS) rate was 71.7% in the S-1 arm compared with 61.1% in the surgery alone arm (HR = 0.68, 95%CI: 0.52-0.87, P = 0.003)[14]. More recently, the CLASSIC study reported a higher 5-year OS in patients with stage Ⅱ or Ⅲ gastric cancer who received adjuvant chemotherapy treatment with capecitabine plus oxaliplatin compared to patients who underwent only D2 gastrectomy (5-year OS rate: 78% *vs* 69%; HR = 0.58, 95%CI: 0.47-0.72, P < 0.0001)[15].

Finally, a meta-analysis by the Global Advanced/Adjuvant Stomach Tumor RESEARCH International Collaboration (GASTRIC) Group that combined data from 3838 patients (17 trials) showed a benefit of 5-FU-based adjuvant chemotherapy *vs* surgery alone on OS (55.3% *vs* 49.6%, respectively; HR = 0.82, 95%CI: 0.76-0.90, P < 0.001) with stable results at 10 years (48% *vs* 40%, respectively)[16]. For this reason, 5-FU-based adjuvant chemotherapy is now considered as a therapeutic option and has been included in the French National Thesaurus of Digestive Oncology (www.snfge.asso.fr) for patients with resected GEA.

Adjuvant chemoradiotherapy

The efficacy of adjuvant chemoradiotherapy after a R0 resection in GEA patients (stage Ⅰb to Ⅳ M0) was studied with the SWOG 9008/INT 0116 phase Ⅲ trial in 603 patients[17,18]. They were randomized in two therapeutic arms: Surgery alone *vs* surgery combined with adjuvant chemoradiotherapy. The patients' characteristics, including the tumor stage, were similar in the two groups: 65% of patients had pT3/T4 stage tumors and 85% N^+ stage tumors. Treatment started with chemotherapy (1 cycle of the FUFOL Mayo Clinic regimen) followed with chemoradiotherapy after 1 mo. Radiotherapy was delivered in 25 fractions (45 Gy each) and FUFOL was administered during the first 4 d and the last 3 d of irradiation. Two additional FUFOL cycles were then given 1 mo after the end of chemoradiotherapy. In this study, 64% of patients completed the therapeutic protocol. The digestive and hematological toxicity rates were respectively of 33% and 54%. The administration of adjuvant chemoradiotherapy resulted in an improvement of the 5-year OS rate compared with surgery alone (40% *vs* 26%; HR = 1.31, 95%CI: 1.09-1.39, P = 0.005) and of the median disease-free survival (27 mo *vs* 19 mo; HR

= 1.52, 95%CI: 1.25-1.53, $P < 0.0001$), with a median follow-up of more than 10 years. The risk of death was reduced by 31%, and relapses were decreased by 52%. However, D2 lymph node dissection was reported in 10% of patients (36% had a D1 resection, and 54% a < D1 resection). In conclusion, adjuvant chemoradiotherapy appears to be a reasonable option for the treatment of resectable GEA, for patients with inadequate lymph node dissection and/or at high risk of recurrence (pT3/T4 and/or N^+ cancer).

Recently, the ARTIST study reported a benefit of adjuvant chemoradiotherapy with capecitabine and cisplatin on disease-free survival of patients with node-positive and intestinal-type gastric adenocarcinoma compared with patients treated with adjuvant chemotherapy alone[19].

In all cases, the nutritional status of patients should systematically and safely be evaluated before initiating adjuvant therapy at 6 wk post-surgery[20].

NEOADJUVANT SYSTEMIC THERAPIES IN GEA

The choice of administering systemic chemotherapy to the patients before surgery of resectable GEA is mainly based on the possibility of improvement of the R0 resections and primary tumor downstaging/downsizing. Systemic neoadjuvant therapy may also remove occult micro-metastatic disease and facilitate the preoperative chemo-sensitivity assessment. Possible disadvantages of neoadjuvant systemic therapies include the risk of disease progression until surgery, the increase in secondary morbidity and chemotherapy-related toxicity and the difficulty of assessing the preoperative treatment response.

In all clinical trials, patients with gastric, gastro-esophageal junction and lower esophagus adenocarcinomas were considered together as a single population. In this review, we will distinguish the different tumor sites, and, concerning esophageal cancer, we will focus on the results of neoadjuvant chemoradiotherapy.

Neoadjuvant chemotherapy

The feasibility of neoadjuvant chemotherapy as treatment of resectable gastric cancers was initially shown in phase Ⅱ studies[21-23], which reported an acceptable toxicity and no increase of the surgical mortality and morbidity rates using this therapeutic approach. The R0 resection rates following neoadjuvant chemotherapy were of 61% and 77%, with or without intra-peritoneal chemotherapy, respectively.

A randomized clinical trial coordinated by the Dutch Gastric Cancer Group, compared two groups of patients who underwent surgery alone ($n = 30$) or received neoadjuvant chemotherapy after surgery ($n = 29$), *i.e.*, 4 cycles of the FAMTX regimen (5-FU, doxorubicin and methotrexate)[24,25]. The R0 resection rates were 62% *vs* 56% in the surgery alone arm and in the neoadjuvant chemotherapy plus surgery arm, respectively. Although the trial was stopped early due to the small number of patients included ($n = 59$), the authors concluded to the poor efficacy of the FAMTX regimen in the treatment of resectable gastric cancer.

A randomized phase Ⅲ trial compared in 503 patients with resectable stomach, lower esophagus or esophageal-gastric junction adenocarcinomas, surgery alone ($n = 253$) with perioperative chemotherapy ($n = 250$)[26]. This Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial comprised the ECF regimen (50 mg/m² epirubicin on day 1, 60 mg/m² CDDP on day 1 and continuous venous infusion of 5-FU, 200 mg/m² per day, for 3 wk). Three cycles were administered pre- and post-surgery, which took place within the 6 wk after randomization for patients in the surgery group, or 3 to 6 wk after the third chemotherapy cycle for the perioperative chemotherapy group. The surgical procedure, which was left to the surgeon's discretion, included D1 or D2 lymphadenectomy. The patients' characteristics were similar in both arms; 26% of patients had a lower esophageal or gastroesophageal junction tumor. In the chemotherapy arm, 86% of patients completed the neoadjuvant treatment, 55% initiated postoperative treatment and 42% completed the chemotherapy protocol. Concerning surgery, 88% and 95% patients underwent the intervention in the chemotherapy and surgery alone arms. The pathological analysis of the resected specimens showed significant tumor downsizing in the chemotherapy group compared to the surgery alone arm (mean tumor size: 3 cm *vs* 5 cm; $P < 0.001$). An improvement of T stage ($P = 0.009$) and N stage ($P = 0.01$) was also reported in the chemotherapy group. The 79% R0 resection rate was significantly higher in the chemotherapy arm than in the surgery alone group (70%; $P = 0.03$). Grade 3-4 hematological toxicities during pre- and postoperative chemotherapy were not significantly different in the two groups, with 24% and 28% of neutropenia, respectively. With a median follow-up of 3 years, the median OS was 24 mo *vs* 20 mo in the chemotherapy and surgery alone groups, respectively (HR = 0.75, 95%CI: 0.60-0.93, $P = 0.009$) and the 5-year survival rates were 36% and 23%, respectively. Progression-free survival was significantly longer in the chemotherapy than in the surgery alone group (HR = 0.66, 95%CI: 0.53-0.81, $P = 0.0001$) (Table 1). The therapy efficacy was independent of the tumor site. The ECF chemotherapy regimen was chosen based on the results of a phase Ⅲ trial that compared the ECF and FAMTX regimens in patients with advanced GEA. In this study, ECF was associated with better response rate (45% *vs* 21%; $P < 0.001$), better median OS (8.7 mo *vs* 6.1 mo) and acceptable hematological toxicity (grade 3-4 neutropenia: 36% *vs* 58%) compared to FAMTX[27]. Recently, a meta-analysis showed that addition of an anthracycline to the CDDP and 5-FU regimens increased the OS of patients with advanced disease, but this

Table 1 Two neoadjuvant chemotherapy schedules offered for the treatment of resectable gastroesophageal adenocarcinomas

	MAGIC[24]			FNCLCC-FFCD[27]		
	ECF *n* = 250	Surgery *n* = 253	*P*	FP *n* = 113	Surgery *n* = 111	*P*
Median age, yr (range)	62 (29-85)	62 (23-81)		63 (36-75)	63 (38-75)	
Sex, male (%)	82%	76%		85%	82%	
Performance status, 0/1	68/32	68/32		74/26	75/25	
Gastric ADK (%)	74%	74%		25%	24%	
GOJ ADK (%)	26%	26%		75%	76%	
Downstaging/downsizing (%)						
T1/T2	52%	38%	0.09	42%	32%	0.16
T3/T4	48%	62%		58%	68%	
N0/N1	84%	76%	0.01	(N0) 33%	20%	0.54
N2/N3	16%	29%		(N+) 67%	80%	
R0 resection rate (%)	79%	70%	0.03	84%	73%	0.04
5-yr overall survival rate (%)	36%	23%	0.009 (HR = 0.75)	38%	24%	0.002 (HR = 0.69)

ADK: Adenocarcinomas; GOJ: Gastro-esophageal junction; ECF: Epirubicin, cisplatin and 5-FU; FP: 5-fluorouracil and cisplatin; MAGIC: Medical research council; FNCLCC-FFCD: Fédération nationale des centres de lutte contre le cancer - fédération française de cancérologie digestive.

advantage was not reported in the GASTRIC meta-analysis that combined data from 3226 patients[16,28].

A recently published French trial (FNCLCC 94012-FFCD 9703) evaluated another perioperative (two neoadjuvant cycles and four postoperative cycles) chemotherapy regimen (continuous protracted intravenous infusion of 5-FU 800 mg/m² per day from days 1 to 4 and 100 mg/m² CDDP on day 1 or 2 every 4 wk)[29]. It included 224 patients who were randomized between perioperative chemotherapy (*n* = 113) and surgery alone (*n* = 111) Patients underwent surgery 4 to 6 wk after neoadjuvant chemotherapy, and postoperative chemotherapy started 4 to 6 wk after surgery. The patients' characteristics were similar in the two groups. The originality in this study was the high percentage (75%) of patients with tumor in the cardia and in the lower esophagus. Preoperative staging was evaluated by endoscopic ultrasound examination and CT scan. In the perioperative chemotherapy arm, 96% underwent surgery compared with 99% in the surgery alone arm, and 87% of patients completed neoadjuvant chemotherapy. The pathological assessment of the resected specimens was similar in the two groups in terms of pT, whereas slightly less tumors were classified as N+ in the chemotherapy arm than in the surgery alone arm (67% *vs* 80%; not significant difference). The R0 resection rate was of 87% in the chemotherapy group, higher than the 74% rate in the surgery alone group (*P* = 0.004). The 5-year disease-free survival rates were 34% (95%CI: 26%-44%) *vs* 19% (95%CI: 13%-28%), and the 5-year OS rates were 38% (95%CI: 29%-47%) *vs* 24% (95%CI: 17%-33%) (HR = 0.69, 95%CI: 0.50-0.95, *P* = 0.02).

The results of the EORTC study showed an improvement of the R0 resection rate in patients treated with neoadjuvant chemotherapy (two courses of 50 mg/m² CDDP, Ⅳ on days 1, 15 and 29 followed by 500 mg/m² folinic acid, IV and 2000 mg/m² 5-FU by continuous infusion for 24 h on days 1, 8, 15, 22, 29 and 36; day 1 = day 48) compared to patients treated with surgery alone (81.9% *vs* 66.7%; *P* = 0.036). OS was comparable between the two arms, but this study lacked statistical power due to recruitment failure (expected patients per arm = 180; patients included in each arm = 72)[30].

The MAGIC and the FNCLCC 94012-FFCD 9703 studies reported similar benefits as those of the MRC OE02 trial that assessed the effect of CDDP (80 mg/m² administered by intravenous infusion for 4 h on day 1, day 1 = day 21) and 5-FU (1000 mg/m² by continuous protracted venous infusion from days 1 to 4, day 1 = day 21) in patients with resectable esophageal cancer[31]. In this study, 802 patients (66% had tumors located in the lower portion of the esophagus or in the cardia) were randomized in two arms, surgery alone (*n* = 402) *vs* preoperative chemotherapy (*n* = 400). The median OS was significantly higher in the chemotherapy group (17 mo *vs* 13 mo; 95%CI: 30-196 d) as well as the 5-year OS (23% *vs* 17%; HR = 0.84, 95%CI: 0.72-0.98, *P* = 0.03) according to the updated results[32].

At the 2015 ASCO annual meeting, Alderson *et al*[33] reported the results of the OEO5 trial that compared the ECX (4 cycles, *n* = 446) and 5-FU with CDDP (2 cycles, *n* = 451) regimens as neoadjuvant chemotherapy in patients with resectable adenocarcinoma of the esophagus or of gastroesophageal junction (Siewert type Ⅰ and Ⅱ). No significantly survival difference was observed between treatments even when an anthracycline was added to the CDDP and 5-FU regimen [3-year OS: 42% (95%CI: 37-46) in the 5-FU/CDDP arm *vs* 39% (95%CI: 35-44) in the ECX arm; HR = 0.92, 95%CI: 0.79-1.08, *P* = 0.8]. However, grade 3-4 toxicities were more frequent in patients treated with ECX (diarrhea, neutropenia, hand-foot syndrome and mucitis).

These two trials (MAGIC and FNCLCC 94012-FFCD 9703) were the first studies to demonstrate better survival rates with a perioperative systemic approach for the treatment of localized GEA (Table 1). These results

Table 2 Neoadjuvant chemoradiotherapy schedule offered in the treatment of resectable gastroesophageal junction and lower esophagus adenocarcinomas

Trials	Patients (*n*)	Pathology	CT-RT	5-yr OS rate (%)
Walsh 1996	CT-RT = 58	ADK (100%)	CDDP-5FU	CT-RT 32%
	S = 55		40 Gy	S 6% (3-yr OS) (P = 0.01)
Urba 2001	CT-RT = 50	ADK (75%)	CDDP-VLB-5FU	CT-RT 30%
	S = 50	SCC	45 Gy	S 16% (3-yr S) (P = 0.15)
Burmeister 2005	CT-RT = 128	ADK (62%)	CDDP-5FU	CT-RT 22 mo
	S = 128	SCC	35 Gy	S 19 mo (P = 0.38)
Tepper 2008	CT-RT = 30	ADK (75%)	CDDP-5FU	CT-RT 39%
	S = 26	SCC	50.4 Gy	S 16% (P < 0.008)
CROSS 2010	CT-RT = 180	ADK (75%)	Paclitaxel-carboplatin	CT-RT 47%
	S = 188	SCC	41.4 Gy	S 34% (P = 0.03)

CT-RT: Chemoradiotherapy; OS: Overall survival; S: Surgery; ADK: Adenocarcinoma; SCC: Squamous cell carcinoma; VLB: Vinblastin.

have been confirmed in the meta-analysis by Li *et al*[34], and neoadjuvant chemotherapy is now considered as standard treatment for GEA in Europe. Moreover, based on the first OEO5 trial results, neoadjuvant chemotherapy with 5-FU and CDDP seems to be the best option in this setting.

Neoadjuvant chemoradiotherapy

Considering the improvement brought by systemic neoadjuvant chemotherapy for the management of patients with gastroesophageal junction and lower esophagus adenocarcinoma, several randomized phase Ⅲ study assessed the benefit of neoadjuvant chemoradiotherapy compared to surgery alone. The clinical trials by Urba *et al*[35] and Burmeister *et al*[36] did not show any benefit of chemoradiotherapy compared with surgery concerning the 3-year OS rate (30% *vs* 16%; P = 0.16) and the median OS (21.7 mo *vs* 18.5 mo; P = 0.38), in a population of patients among whom 75% had a gastroesophageal junction or lower esophagus adenocarcinoma (Table 2).

Only one phase Ⅲ trial found that chemoradiotherapy before surgery improved survival[37]. In this study, 113 patients with gastroesophageal junction and lower esophagus adenocarcinoma were randomized in two groups, PReoperative chemoradiotherapy plus surgery or surgery alone. Two cycles of 5-FU and CDDP were administered during radiotherapy, followed by surgery (multiple procedures) 8 wk after the beginning of the combined treatment. After a median follow-up of 10 mo, the median OS (16 mo *vs* 11 mo, P = 0.01) and the 3-year OS rates (32% *vs* 6%, P = 0.01) were significantly higher in the combined treatment arm than in the surgery alone arm, and the pathologic complete response rate was 25% in the chemoradiotherapy plus surgery arm. However, this monocentric study was closed prematurely after an intermediate analysis and with an unusually low survival rate in the surgery alone arm. Therefore, it is unclear how its results could be generalized.

The meta-analysis of 10 randomized trials (1209 patients) by Gebski *et al*[38] found an OS benefit of 13% at two years in patients treated with neoadjuvant chemoradiotherapy plus surgery *vs* surgery alone (HR = 0.81, 95%CI: 0.70-0.93, P = 0.002 and HR = 0.75, 95%CI: 0.59-0.95, P = 0.05) for the adenocarcinoma type in esophageal carcinoma. More recently, the CALGB Group reported a benefit of neoadjuvant chemoradiotherapy with a 5-FU-CDDP regimen in 56 patients (75% with a gastroesophageal or lower esophagus cancer)[39]. The 5-year OS rate was 39% in patients treated with neoadjuvant chemoradiotherapy compared with 16% (P < 0.008) in patients treated with surgery alone (median follow-up of 6 years). The complete pathologic response rate was 40%. These results are controversial due to the recruitment failure relative to the number of expected patients (n = 500).

Finally, the CROSS trial (n = 368 with esophageal or gastroesophageal junction cancer) clearly reported an improvement of the R0 resection rate (92% *vs* 69%; P < 0.0010) in patients treated with neoadjuvant chemoradiotherapy (paclitaxel-carboplatin regimen) plus surgery (n = 178) compared with patients who had only surgery (n = 188), with a complete pathologic response of 29%. The median OS was also significantly higher in the combined treatment arm than in the surgery arm (49 mo *vs* 24 mo; HR = 0.66, 95%CI: 0.49, 0.87, P = 0.003)[40].

COMBINATION OF NEOADJUVANT INDUCTION CHEMOTHERAPY AND CHEMORADIOTHERAPY

Ajani *et al*[41] proposed a three-step strategy combining induction chemotherapy (two cycles of 5-FU, levofolinate and cisplatin) with preoperative chemoradiotherapy (45 Gy of radiation concomitantly with 5-FU) and surgery. Their phase Ⅱ trial assessed response and survival in 33 patients with resectable gastric cancer. They showed a R0 resection rate of 70% and a 54% pathological response rate and a complete pathologic response of 30%. The median OS was 34 mo with a median follow-up of 5 years. The same authors assessed in another phase Ⅱ trial the same three-step strategy adding paclitaxel to 5-FU during chemoradiotherapy[42]. The trial

included 49 patients with resectable gastric carcinoma and showed a 77% R0 resection rate and a complete pathologic response rate of 26%. A median OS of 23 mo was reported, with a median follow-up of 22 mo.

A similar strategy (neoadjuvant chemoradiotherapy after two or three cycles of 5-FU-cisplatin induction chemotherapy followed by surgery) was also evaluated in patients with T3/T4 GEA who were randomized in the three-step protocol group or in the neoadjuvant chemotherapy alone plus surgery group. Although the trial was stopped early due to poor accrual, there was a trend towards a higher efficacy in the three-step protocol arm than in the neoadjuvant chemotherapy arm (3-year disease-free survival rate: 47.7% *vs* 27.7%; HR = 0.67; 95%CI: 0.41-1.07; $P = 0.07$)[43]. An Australian randomized phase Ⅱ study reported a significant reduction of the R1 resection rate in a similar population of patients treated with neoadjuvant chemoradiotherapy *vs* neoadjuvant chemotherapy alone (0% *vs* 11%, $P = 0.04$; pathological complete response rates of 31% *vs* 8%, respectively, $P = 0.01$)[44].

PERSPECTIVES IN THE GEA MANAGEMENT: UNANSWERED QUESTIONS

We described different treatment modalities and therapeutic strategies in the management of resectable GEA. However, some questions remain unresolved.

First, there is no strong evidence of the benefit of preoperative chemoradiotherapy over perioperative chemotherapy in patients with gastroesophageal junction adenocarcinoma. As surgical findings showed a higher incomplete tumor resection in locally-advanced T3/T4 gastroesophageal junction adenocarcinomas, the evaluation of the effects of preoperative chemoradiotherapy is urgently needed in this setting[45]. One ongoing phase Ⅲ clinical trial is focusing on this question. The all-Ireland Cooperative Oncology Research Group trial is currently comparing preoperative chemoradiotherapy (as it was done in the CROSS study) and perioperative chemotherapy with the epirubicin, cisplatin and 5-FU (ECF) regimen. The Dutch Colorectal Cancer Group is currently assessing postoperative chemoradiotherapy, comparing perioperative epirubicin, cisplatin, capecitabin (ECC) chemotherapy and preoperative ECC chemotherapy combined with postoperative chemoradiotherapy (the CRITICS study) in GEA.

Second, during chemotherapy/chemoradiotherapy, many patients experience life-threating effects and cannot complete the treatment. Conroy *et al*[46] showed that in patients with non-resectable esophageal carcinoma treated only with chemoradiotherapy, using oxaliplatin instead of CDDP (the FOLFOX4 regimen), reduced toxicities and toxic deaths compared with the standard 5-FU-CDDP regimen. A neoadjuvant FOLFOX6 chemotherapy regimen could be substituted to 5-FU-CDDP and proposed as ambulatory treatment.

In patients with metastatic GEA, the intensification of chemotherapy with docetaxel, 5-FU and cisplatin (TCF) is more effective than with 5-FU plus cisplatin alone, but with a significantly higher level of hematologic toxicities. The FLOT regimen (50 mg/m² docetaxel and infusion of 5-FU, leucovorin and oxaliplatin (TEF regimen) was compared with 5-FU plus oxaliplatin (the FLO regimen) in a randomized phase Ⅱ clinical trial. This study included patients older than 65 years and showed an improvement of the response rate and the progression-free survival in patients with locally-advanced cancer[47]. The combination of docetaxel, 5-FU, leucovorin and oxaliplatin as first-line treatment was effective with an intention-to-treat objective response rate of 66% (95%CI: 50.55-78.44) and two confirmed complete responses, progression-free survival of 6.3 mo (95%CI: 4.5-7.3) and OS of 12.1 mo (95%CI: 6.5-15.3)[48]. At the 2015 ASCO meeting, the authors presented preliminary results on the pathologic response in patients with resectable lower esophagus or gastroesophageal junction adenocarcinomas treated with FLOT or ECF. The complete pathologic response rate was significantly higher in patients who received FLOT than in those treated with ECF (15.6% *vs* 5.8%, $P = 0.015$)[49].

For T3/T4 and or N+ GEA, using hyperthermic intraperitoneal chemotherapy (HIPEC) could reduce the frequent peritoneal recurrences in this setting. The PRODIGE French scientific group study is currently assessing HIPEC as adjuvant treatment.

Concerning targeted therapies, the use of trastuzumab combined with neoadjuvant chemotherapy is not recommended in patients with resectable GEA that overexpress HER2. Also, the MAGIC group is currently assessing the association of bevacizumab and the ECC (capecitabine instead of 5-FU) chemotherapy regimen in a perioperative setting compared to chemotherapy with ECF alone.

Finally we need predictive markers of neoadjuvant treatment response as early PET-scan metabolic response or assessment of biomarkers using systematic pre-therapeutic or liquid biopsies.

CONCLUSION

Currently, two main therapeutic options can be proposed for the treatment of resectable GEA: (1) adjuvant chemoradiotherapy (Macdonald *et al*[17]) and (2) perioperative chemotherapy with 5-FU and platin salts-based regimens (Cunningham *et al*[26] or Ychou *et al*[29]). But what is best for our patients? Comparing the two strategies is not possible because the patients' profiles are too different. In both the MAGIC and FNCLCC 94012-FFCD 9703 trials, patients were identified at diagnosis, and not after surgery as it was done in the INT-0116 trial regarding the pT3/T4 or pN stage, the OMS (0 or 1) and the nutritional status.

Therefore, the treatment choice could be summarized

between two unsatisfactory options: A preoperative approach in which patients with a good-prognosis tumor may be over-treated, or a postoperative approach in which patients with high risk of recurrence and poor nutritional status after surgery might be under-treated. We recommend deciding the therapeutic management of each individual patient in a multidisciplinary committee, before the primary tumor surgery. Future applications of cytotoxic therapies, *e.g.*, oxaliplatin, capecitabine or docetaxel, or targeted therapies may help improving resectable GEA management.

For patients with gastroesophageal junction or lower esophagus adenocarcinomas, neoadjuvant chemoradiotherapy could be a viable option, but needs to be compared with perioperative chemotherapy.

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REFERENCES

1 **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]

2 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078 DOI: 10.3322/canjclin.55.2.74]

3 **Blot WJ**, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; **265**: 1287-1289 [PMID: 1995976]

4 **Crehange G**, Maingon P, Peignaux K, N'guyen TD, Mirabel X, Marchal C, Verrelle P, Roullet B, Bonnetain F, Bedenne L. Phase III trial of protracted compared with split-course chemoradiation for esophageal carcinoma: Federation Francophone de Cancerologie Digestive 9102. *J Clin Oncol* 2007; **25**: 4895-4901 [PMID: 17971585 DOI: 10.1200/JCO.2007.12.3471]

5 **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]

6 **Watanabe S**, Tominaga S, Teds K. In: Cancer Treatment and Survival, Gann Monograph on Cancer Research. The Japanese Research Society for Gastric Cancer. Treatment results of gastric cancer patients: an analysis of nationwide database. Tokyo: Japan Sc Soc Press, 1995: 47-56

7 **Hundahl SA**, Menck HR, Mansour EG, Winchester DP. The National Cancer Data Base report on gastric carcinoma. *Cancer* 1997; **80**: 2333-2341 [PMID: 9404711 DOI: 10.1002/(SICI)1097-0142(19971215)80:12<2333::AID-CNCR15>3.0.CO; 2-V]

8 **Cohen DJ**, Leichman L. Controversies in the treatment of local and locally advanced gastric and esophageal cancers. *J Clin Oncol* 2015; **33**: 1754-1759 [PMID: 25918302 DOI: 10.1200/JCO.2014.59.7765]

9 **Hermans J**, Bonenkamp JJ, Boon MC, Bunt AM, Ohyama S, Sasako M, Van de Velde CJ. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993; **11**: 1441-1447 [PMID: 8336183]

10 **Earle CC**, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer* 1999; **35**: 1059-1064 [PMID: 10533448 DOI: 10.1016/S0959-8049(99)00076-3]

11 **Mari E**, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, Cascinu S, Barni S, Labianca R, Torri V. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol* 2000; **11**: 837-843 [PMID: 10997811 DOI: 10.1023/A: 1008377101672]

12 **Panzini I**, Gianni L, Fattori PP, Tassinari D, Imola M, Fabbri P, Arcangeli V, Drudi G, Canuti D, Fochessati F, Ravaioli A. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori* 2002; **88**: 21-27 [PMID: 12004845]

13 **Bouché O**, Ychou M, Burtin P, Bedenne L, Ducreux M, Lebreton G, Baulieux J, Nordlinger B, Martin C, Seitz JF, Tigaud JM, Echinard E, Stremsdoerfer N, Milan C, Rougier P. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). *Ann Oncol* 2005; **16**: 1488-1497 [PMID: 15939717 DOI: 10.1093/annonc/mdi270]

14 **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. 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]

15 **Bang YJ**, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; **379**: 315-321 [PMID: 22226517 DOI: 10.1016/S0140-6736(11)61873-4]

16 **Paoletti X**, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, Van Cutsem E, Buyse M. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010; **303**: 1729-1737 [PMID: 20442389 DOI: 10.1001/jama.2010.534]

17 **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]

18 **Smalley SR**, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, Gunderson LL, Goldman B, Martenson JA, Jessup JM, Stemmermann GN, Blanke CD, Macdonald JS. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012; **30**: 2327-2333 [PMID: 22585691 DOI: 10.1200/JCO.2011.36.7136]

19 **Park SH**, Sohn TS, Lee J, Lim do H, Hong ME, Kim KM, Sohn I, Jung SH, Choi MG, Lee JH, Bae JM, Kim S, Kim ST, Park JO, Park YS, Lim HY, Kang WK. 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**: 3130-3136 [PMID: 25559811 DOI: 10.1200/JCO.2014.58.3930]

20 **Braga M**, Zuliani W, Foppa L, Di Carlo V, Cristallo M. Food intake and nutritional status after total gastrectomy: results of a nutritional follow-up. *Br J Surg* 1988; **75**: 477-480 [PMID: 3390683]

21 **Crookes P**, Leichman CG, Leichman L, Tan M, Laine L, Stain S, Baranda J, Casagrande Y, Groshen S, Silberman H. Systemic chemotherapy for gastric carcinoma followed by postoperative intraperitoneal therapy: a final report. *Cancer* 1997; **79**: 1767-1775 [PMID: 9128994 DOI: 10.1002/(SICI)1097-0142(19970501)79:9<1767:: AID-CNCR19>3.0.CO;2-W]

22 **Kelsen D**, Karpeh M, Schwartz G, Gerdes H, Lightdale C, Botet J, Lauers G, Klimstra D, Huang Y, Saltz L, Quan V, Brennan M. Neoadjuvant therapy of high-risk gastric cancer: a phase II trial of preoperative FAMTX and postoperative intraperitoneal fluorouracil-cisplatin plus intravenous fluorouracil. *J Clin Oncol* 1996; **14**:

1818-1828 [PMID: 8656250]
23 **Ajani JA**, Mayer RJ, Ota DM, Steele GD, Evans D, Roh M, Sugarbaker DJ, Dumas P, Gray C, Vena DA. Preoperative and postoperative combination chemotherapy for potentially resectable gastric carcinoma. *J Natl Cancer Inst* 1993; **85**: 1839-1844 [PMID: 8230264 DOI: 10.1093/jnci/85.22.1839]
24 **Songun I**, Keizer HJ, Hermans J, Klementschitsch P, de Vries JE, Wils JA, van der Bijl J, van Krieken JH, van de Velde CJ. Chemotherapy for operable gastric cancer: results of the Dutch randomised FAMTX trial. The Dutch Gastric Cancer Group (DGCG). *Eur J Cancer* 1999; **35**: 558-562 [PMID: 10492627 DOI: 10.1016/S0959-8049(98)00429-8]
25 **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. 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]
26 **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. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]
27 **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: 10.1016/S0959-8049(97)86090-X]
28 **Wagner AD**, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; **24**: 2903-2909 [PMID: 16782930 DOI: 10.1200/JCO.2005.05.0245]
29 **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]
30 **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]
31 **Medical Research Council Oesophageal Cancer Working Group**. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; **359**: 1727-1733 [PMID: 12049861 DOI: 10.1016/S0140-6736(02)08651-8]
32 **Allum WH**, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009; **27**: 5062-5067 [PMID: 19770374 DOI: 10.1200/JCO.2009.22.2083]
33 **Alderson D**, Langley RE, Nankivell MG, Blazeby JM, Griffin M, Crellin A, Grabsch HI, Okines AF, Goldstein C, Falk S, Thompson J, Krysztopik R, Coxon FY, Pritchard S, Langer R, Stenning SP, Cunningham D. Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: Results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072). 2015 ASCO Annual Meeting 2015; 33: 4002. Available from: URL: http://meetinglibrary.asco.org/content/149773-156
34 **Li W**, Qin J, Sun YH, Liu TS. Neoadjuvant chemotherapy for advanced gastric cancer: a meta-analysis. *World J Gastroenterol* 2010; **16**: 5621-5628 [PMID: 21105197 DOI: 10.3748/wjg.v16.i44.5621]
35 **Urba SG**, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001; **19**: 305-313 [PMID: 11208820]
36 **Burmeister BH**, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, Ackland S, Gotley DC, Joseph D, Millar J, North J, Walpole ET, Denham JW. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005; **6**: 659-668 [PMID: 16129366 DOI: 10.1016/S1470-2045(05)70288-6]
37 **Walsh TN**, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; **335**: 462-467 [PMID: 8672151 DOI: 10.1056/NEJM199608153350702]
38 **Gebski V**, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007; **8**: 226-234 [PMID: 17329193 DOI: 10.1016/S1470-2045(07)70039-6]
39 **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]
40 **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. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074-2084 [PMID: 22646630 DOI: 10.1056/NEJMoa1112088]
41 **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]
42 **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]
43 **Stahl M**, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, Langer P, Engenhart-Cabillic R, Bitzer M, Königsrainer A, Budach W, Wilke H. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009; **27**: 851-856 [PMID: 19139439 DOI: 10.1200/JCO.2008.17.0506]
44 **Burmeister BH**, Thomas JM, Burmeister EA, Walpole ET, Harvey JA, Thomson DB, Barbour AP, Gotley DC, Smithers BM. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. *Eur J Cancer* 2011; **47**: 354-360 [PMID: 21084184 DOI: 10.1016/j.ejca.2010.09.009]
45 **Mariette C**, Piessen G, Briez N, Gronnier C, Triboulet JP. Oesophagogastric junction adenocarcinoma: which therapeutic approach? *Lancet Oncol* 2011; **12**: 296-305 [PMID: 21109491 DOI: 10.1016/S1470-2045(10)70125-X]
46 **Conroy T**, Yataghène Y, Etienne PL, Michel P, Senellart H, Raoul JL, Mineur L, Rives M, Mirabel X, Lamezec B, Rio E, Le Prisé E, Peiffert D, Adenis A. Phase II randomised trial of chemoradiotherapy with FOLFOX4 or cisplatin plus fluorouracil in oesophageal cancer. *Br J Cancer* 2010; **103**: 1349-1355 [PMID: 20940718 DOI: 10.1038/sj.bjc.6605943]
47 **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]

48 **Pernot S**, Mitry E, Samalin E, Dahan L, Dalban C, Ychou M, Seitz JF, Turki H, Mazard T, Zaanan A, Lepère C, Vaillant JN, Landi B, Rougier P, Taieb J. Biweekly docetaxel, fluorouracil, leucovorin, oxaliplatin (TEF) as first-line treatment for advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: safety and efficacy in a multicenter cohort. *Gastric Cancer* 2014; **17**: 341-347 [PMID: 23739764 DOI: 10.1007/s10120-013-0266-6]

49 **Pauligk C**, Tannapfel A, Meiler J, Luley KB, Kopp HG, Homann N, Hofheinz RD, Schmalenberg H, Probst S, Haag GM, Egger M, Behringer DM, Stoehlmacher J, Prasnikar N, Block A, Trojan J, Koenigsmann M, Schmiegel W, Jäger E, Al-Batran SE. Pathological response to neoadjuvant 5-FU, oxaliplatin, and docetaxel (FLOT) versus epirubicin, cisplatin, and 5-FU (ECF) in patients with locally advanced, resectable gastric/esophagogastric junction (EGJ) cancer: Data from the phase II part of the FLOT4 phase III study of the AIO. 2015 ASCO Annual Meeting 2015; **33**: 4016. Available from: URL: http://meetinglibrary.asco.org/content/147101-156

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