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## Neo-adjuvant chemo(radio)therapy in gastric cancer: Current status and future perspectives

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### Abstract

In the last 20 years, several clinical trials on neo-adjuvant chemotherapy and chemo-radiotherapy as a therapeutic approach for locally advanced gastric cancer have been performed. Even if more data are necessary to define the roles of these approaches, the results of preoperative treatments in the combined treatment of gastric adenocarcinoma are encouraging because this approach has led to a higher rate of curative surgical resection. Owing to the results of most recent randomized phase III studies, neoadjuvant chemotherapy for locally advanced resectable gastric cancer has satisfied the determination of level I evidence. Remaining concerns pertain to the choice of the optimal therapy regimen, strict patient selection by accurate pre-operative staging, standardization of surgical procedures, and valid criteria for response evaluation. New well-designed trials will be necessary to find the best therapeutic approach in pre-operative settings and the best way to combine old-generation chemotherapeutic drugs with new-generation molecules.

**Key words:** Gastric Cancer; Neo-adjuvant treatment; Chemotherapy; Radiotherapy

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randomized phase III studies, neoadjuvant chemotherapy for locally advanced resectable gastric cancer has satisfied the determination of Level I evidence. Remaining concerns pertain to the choice of the optimal therapy regimen, strict patient selection by accurate pre-operative staging, standardization of surgical procedures, and reliable criteria for response evaluation. New well-designed trials will be necessary to identify the best treatment plan in pre-operative settings and to understand how to combine the conventional chemotherapeutic drugs with new-generation molecules.

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## INTRODUCTION

Currently, gastric carcinoma remains one of the most widespread tumors in the world<sup>[1]</sup>. Surgical resection has a relative role in cancers with early lymphatic diffusion, distant metastasis or peritoneal involvement. Thanks to the introduction of screening protocols in high-incidence nations such as Japan and Korea, almost 50% of patients with gastric cancer receive an early diagnosis<sup>[2]</sup>. However, this screening approach has not shown a cost-effective advantage in lower-incidence countries like Europe and North America. As a consequence, most gastric cancers in the West are already in a locally advanced stage and with lymphatic spread at diagnosis<sup>[3]</sup>. Many attempts have been made to improve patients' survival, tailoring the extent of surgery and adding the administration of pre-operative and/or post-operative treatment.

In the last twenty years, large-scale randomized trials have demonstrated the efficacy of three different multimodal approaches: Adjuvant chemoradiation treatment (Unites States INT-0116 trial)<sup>[4]</sup>, adjuvant single-drug chemotherapy (Japanese ACTS-GC trial)<sup>[5]</sup> and perioperative three-drug combination chemotherapy (European MAGIC trial)<sup>[6]</sup>. After the publication of the results of these trials, standard treatment in patients with locally advanced gastric cancer is no longer based on surgery alone, and the goal of an R0-resection is not exclusively a surgical target. In this review, we discuss the rationale and the state of the art of preoperative neoadjuvant therapy in light of recent evidence and new perspectives.

## NEOADJUVANT TREATMENT: THEORETICAL RATIONALE AND LIMITATIONS

Preoperative treatment (*i.e.*, neoadjuvant treatment)

has led to higher rates of curative surgical resection in many solid tumors such as rectum and breast carcinoma. In gastric adenocarcinoma, the mainstay of therapeutic treatment still remains surgical resection, and neoadjuvant therapy appears to be justified by similar advantages<sup>[7]</sup>.

### Theoretical rationale

**Biological rationale:** (1) neoadjuvant treatment gives the chance to downstage and downsize the primary gastric tumor and to reach a more probable curative R0 resection; (2) the use of chemo or radiotherapy before surgery provides the theoretical advantage of treating an "untouched" neoplasia (lack of treatment-induced resistance) with intact vessels and without fibrotic remodeling of the tumor bed following surgery; and (3) pre-operative systemic therapy targets micro-metastases, being administered when there is an high growth fraction of the cells and the total tumor volume is relatively low for gastric cancer.

**Upfront randomization and feasibility:** Randomized clinical trials studying adjuvant therapy in gastric cancer may be not representative of the entire curatively operated population because poor patient compliance is often seen after surgery. In addition, due to frequent dose reductions and treatment delays, it is harder to demonstrate a reliable advantage for the treatment arm. Conversely, randomized studies of neoadjuvant systemic treatment allow an appropriate randomization without significant pre-selection and with greater feasibility.

**Monitoring:** In contrast to adjuvant treatment, which is administered on the basis of clinical trial results with no chance to demonstrate its efficacy on an individual basis, the efficacy of pre-operative treatment can be assessed during its administration. Thus, therapy can be adjusted according to patient response.

### Limitations

**Pre-operative staging:** While adjuvant therapy is based on the pathologic staging performed at the time of the resection of a given tumor, pre-operative treatment is based on clinical staging. In gastric cancer, as discussed earlier, the decision of whether to perform neoadjuvant therapy, based only on clinical staging, remains difficult.

**Delayed surgery:** The concept of "delayed surgery" is a relatively new entry among the therapeutic options available for gastric carcinoma. Several studies have shown that delaying surgical treatment in favor of preoperative systemic therapy does not reduce the benefits of a postponed but potentially curative resection and that it does not worsen surgical outcomes. However, there is a small number of cases in which the possibility of disease progression during adjuvant therapy persists, and this is the only justification for an

**Table 1** Pre-operative chemotherapy in non-resectable gastric cancer

Ref.	Regimen	No. patients	Stage	R0 resection (%)	Median survival (mo)
Wilkie <i>et al</i> <sup>[8]</sup>	EAP	34	NR	44	24
Plukker <i>et al</i> <sup>[9]</sup>	5-FU + MTX	20	NR	40	22
Rougier <i>et al</i> <sup>[10]</sup>	5-FU, P	30	NR	60	16
Kelsen <i>et al</i> <sup>[11]</sup>	FAMTX, IP 5FU-P	56	NR	61	15
Melcher <i>et al</i> <sup>[12]</sup>	ECF	27	R-NR	58 (R pts) 10 (NR pts)	10
Gallardo-Rincón <i>et al</i> <sup>[13]</sup>	P-ELF	60	NR	8,7	10
Cascinu <i>et al</i> <sup>[14]</sup>	EAFPLG	82	NR	45	17

NR: Non-resectable; EAP: Etoposide, doxorubicin, cisplatin; IP: Intraperitoneal; ECF: Epirubicin, cisplatin, 5-FU; R: Resectable; P-ELF: Cisplatin, etoposide, leucovorin, 5FU; EAFPLG: Epi-doxorubicin, 5-FU, cisplatin, leucovorin, glutathione; 5-FU: 5-fluorouracil.

unwillingness to carry out a multimodal preoperative treatment in gastric cancer. Actually, patients who progress while on chemotherapy are unlikely to benefit from resection and can be spared radical surgery. The long therapy developmental time period for neoadjuvant treatment in gastric cancer over the last thirty years partially explains some of the skepticism about this treatment option<sup>[7]</sup>.

**Contraindications:** Preoperative treatments are contraindicated in obstructive or hemorrhagic cancers. In particular, the lesions of the cardia or the prepyloric areas can already be completely obstructive at the time of diagnosis. In those situations, upfront surgery is the best treatment, but preoperative systemic therapy could be considered, *e.g.*, making a jejunostomy for enteral feeding or using parenteral feeding. Rarely does a gastric neoplastic lesion bleed acutely; however, it can be dramatic, and in this case, direct salvage surgery is the only chance.

As explained above, the feasibility, randomization, facility, biological rationale and monitoring represent several potential advantages that make neoadjuvant treatment an interesting path to consider for investigation and patient management. For this reason, many authors over the last 30 years have reported experiences with neoadjuvant treatments in locally advanced gastric cancer (preoperative chemotherapy, preoperative radiotherapy or both).

## PRE-/PERI-OPERATIVE CHEMOTHERAPY

Investigation of the efficacy and possible uses of chemotherapy (CT) in patients with advanced gastric cancer began in the late 1970s, but the first encouraging results were not reported until the early 1990s when two independent studies in patients with non-resectable gastric cancer demonstrated that chemotherapy treatment enabled subsequent surgical resection in 40%-50% of patients, with an increase in total median survival of 18 mo compared with unresected patients<sup>[8,9]</sup>. Following these encouraging preliminary results, neoadjuvant chemotherapy protocols were introduced not only for patients with non-resectable disease (Table 1)<sup>[8-14]</sup> but also for patients with

potentially resectable, locally advanced gastric cancer (Table 2)<sup>[6,11,15-27]</sup>. Nevertheless, the interpretations of the results of these pioneer studies were limited by their methodological drawbacks. These limitations included the heterogeneous criteria used in the recruitment of patients, such as the inclusion of patients with locally advanced gastric cancer and patients with cancer of unclear stages, and the absence of a clear distinction between resectable and non-resectable cancers. Moreover, other causes of bias in these first trials included the use of different chemotherapeutic protocols, non-standardized surgery or surgery of questionable quality, and the absence of accurate response criteria.

## Randomized controlled trials

The first randomized controlled trial of exclusively neoadjuvant chemotherapy for gastric cancer dates back to 1993 and was conducted by the Dutch Gastric Cancer Group<sup>[21]</sup>. In this trial, cardia tumors were not included, and the chemotherapeutic protocol was based on 5-fluorouracil, doxorubicin, and methotrexate (FAMTX) because at that time, it was the gold standard of treatment for gastric adenocarcinoma. The study was prematurely stopped because an interim analysis demonstrated that using FAMTX as neoadjuvant chemotherapy did not provide the goal of a 15% increase in curative resection. This trial contained many biases, though, such as the use of inappropriate staging procedures, with optional use of CT or laparoscopy, or the inadequacy of lymph node dissection. In this trial, a 36% rate of tumor progression during therapy was found in patients treated with neoadjuvant chemotherapy. Moreover, there was a decreased rate of curative resections (56% vs 62%) and a reduction in the median survival rate of treated patients vs untreated patients (18 mo vs 30 mo). The results of this trial were discouraging, even if the observed differences were statistically insignificant<sup>[28]</sup>.

Since the late 1990s, rigorous European phase III trials have been designed and performed to demonstrate the efficacy of neoadjuvant therapy, but in some cases, the selection criteria of patients were too strict, leading to premature cessations due to low patient accrual (EORTC 40954 and SWS-SAKK-43/99 trials)<sup>[25,27]</sup>.

**Table 2 Peri-operative chemotherapy in resectable gastric cancer**

Ref.	Phase	Selection criteria	Study arms	No. of patients	R0 resection (%)	Pathologic CR (%)	Median survival (mo)
Ajani <i>et al</i> <sup>[15]</sup>	II	M0 Resectable + EGJ	EFP × 2 + surgery + EFP × 3	25	72	0	15
Leichman <i>et al</i> <sup>[16]</sup>	II	M0 resectable	PFL × 2 + surgery (IP FUDR + IP cisplatin × 2)	8	88	8	> 17
Kang <i>et al</i> <sup>[17]</sup>	III RCT	M0 Loc. advanced	EFP × 3 + surgery + EFP × 3-6 vs surgery + EFP × 3-6	107 (53 + 54)	79 vs 61	8	43 vs 30
Ajani <i>et al</i> <sup>[18]</sup>	II	M0 resectable	EAP × 3 + surgery + EAP × 2	48	90	0	16
Rougier <i>et al</i> <sup>[19]</sup>	II	M0 Loc. advanced + EGJ	FP × 6 + surgery	30	78	0	16
Kelsen <i>et al</i> <sup>[11]</sup>	II	M0 Loc. advanced	FAMTX × 3 + surgery + IP FP + F	56	77	NS	15
Crookes <i>et al</i> <sup>[20]</sup>	II	M0 resectable + EGJ	PFL × 2 + surgery (IP FUDR + IP cisplatin × 2)	59	71	9	52
Songun <i>et al</i> <sup>[21]</sup>	II RCT	T2-T4; M0	FAMTX × 3 + surgery vs surgery alone	56 (27 + 29)	75 vs 75	NS	18 vs 30
Schuhmacher <i>et al</i> <sup>[22]</sup>	II	III-IV; M0 + EGJ	EAP + surgery	42	86	0	19
D'Ugo <i>et al</i> <sup>[23]</sup>	II	T3-4 any N; T ≤ 2 N+; M0	EEP × 3 or ECF × 3 + surgery + EEP × 3 or ECF × 3	34	82	3	> 28
Cunningham <i>et al</i> <sup>[6]</sup> (MAGIC trial)	III RCT	Resectable GC (II-IV); M0 + adenocarcinomas EGJ	ECF × 3 + surgery + ECF × 3 s vs surgery alone	503 (250 + 253)	74 vs 68	NS	18 vs 30
Ychou <i>et al</i> <sup>[24]</sup> (ACCORD trial)	III RCT	Resectable GC + adenocarcinomas EGJ	FP × 2-3 + surgery + FP × 3-4 vs surgery alone	224 (113 + 111)	84 vs 73	NS	NS
Schuhmacher <i>et al</i> <sup>[25]</sup> (EORTC trial)	III RCT	Loc. advanced GC T3-T4N × M0	PFL × 2 vs surgery alone	144 (72 + 72)	81.9 vs 66.7	NS	> 36
Kinoshita <i>et al</i> <sup>[26]</sup>	II	Schirrous resectable	S-1 × 2 + surgery	55	80.8	0	NS
Biffi <i>et al</i> <sup>[27]</sup>	III RCT	T3-4 any N or any T N1-3 M0 + EGJ	TCF × 4 + surgery vs surgery alone	69 (34 + 35)	85	11.7	NS
Yoshikawa <i>et al</i> <sup>[30]</sup>	II RCT	T2-3/N+ or T4aN0 + EGJ	SC × 2 + surgery vs SC × 4 + surgery vs PC × 2 + surgery vs PC × 4 + surgery	83 (21 + 20 + 21 + 21)	NS	10	NS

EL: Exploratory laparotomies; R0: Curative (R0) resections; CR: Complete response; EFP: Etoposide, fluorouracil, and cisplatin; GC: Gastric cancer; IP: Intraperitoneal; FUDR: 5-fluoro-2'-deoxyuridine; RCT: Randomized controlled trial; EAP: Etoposide, doxorubicin, cisplatin; FP: Fluorouracil, cisplatin; F: Fluorouracil; NS: Not stated; EEP: Etoposide, epirubicin, cisplatin; TCF: Docetaxel, cisplatin, fluorouracil; SC: S1, cisplatin; PC: S, cisplatin.

Schuhmacher *et al*<sup>[25]</sup> reported data from the European Organization for Research and Treatment of Cancer 40954 phase III trial (EORTC) comparing neo-adjuvant cisplatin, folinic acid, and infusional fluorouracil (PLF protocol) with surgery alone in patients with locally advanced adenocarcinoma of the stomach. Unfortunately, this study had to be stopped before its conclusion because of poor accrual following the inclusion of only 144 patients instead of the 360 patients initially expected. Patients assigned to chemotherapy received 48-d cycles of neo-adjuvant biweekly cisplatin, weekly L-folinic acid and 5-fluorouracil (5-FU) for 2 cycles. Only 62.5% of patients assigned to the chemotherapy arm completed 2 cycles of treatment. Median follow-up was approximately 4 years. Pre-operative chemotherapy reduced tumor size and nodal involvement compared to surgery alone. Progression-free survival had a hazard ratio of 0.76 but was not statistically significant (95%CI: 0.49-1.16;  $P = 0.2$ ). The hazard ratio for overall survival was 0.84 in favor of chemotherapy, though it was not a statistically significant finding (95%CI: 0.52-1.35;  $P = 0.466$ ). The rate of R0 resection was higher in the group that received neo-adjuvant chemotherapy compared to

those undergoing primary surgery (81.9% vs 66.7%;  $P = 0.036$ ).

Although not statistically significant, patients undergoing preoperative CT showed a higher rate of postoperative complications than patients treated with primary surgery (27.1 vs 16.2%;  $P = 0.09$ ). In addition, postoperative death was more common among patients who underwent neoadjuvant chemotherapy (4.3% vs 1.5%).

Only the MAGIC trial (started in the United Kingdom in 1994) and the FFCD 9703 trial (started in France in 1996) have been completed<sup>[6,24]</sup>. The MAGIC trial is presently the most recognized landmark study for perioperative CT. Between 1994 and 2002, 45 centers in the United Kingdom, Europe and Asia recruited patients with resectable gastric cancer and adenocarcinomas of the esophagogastric junction (EGJ)<sup>[6]</sup>. Patients were randomized in two arms. In the first arm, patients underwent surgery associated with perioperative chemotherapy ( $n = 250$ ), based on three cycles of neoadjuvant and three cycles of adjuvant epirubicin cisplatin and continuous 5-fluorouracil (ECF). In the second arm, patients underwent surgery only ( $n = 253$ ). Only 49.5% of the patients who underwent



pre-operative treatment also received the full courses of the planned post-operative CT because of poor performance status, complications or compliance issues in the post-operative period. Median follow-up was approximately 4 years. The group of patients who underwent perioperative treatment had a higher rate of curative resection (79% vs 70%;  $P = 0.03$ ), smaller tumors (T1-T2: 51% vs 36%;  $P = 0.002$ ) and lower nodal involvement (N0-N1: 84% vs 70%;  $P = 0.01$ ). Overall, survival and progression-free survival were significantly increased in patients receiving perioperative CT compared with patients treated by surgery only (HR = 0.75;  $P = 0.009$  and HR = 0.66;  $P < 0.001$ ). The 5-year survival rate was 36% for patients receiving perioperative CT and 23% for patients treated by surgery only.

A retrospective study from the United Kingdom on a series of 66 patients undergoing perioperative CT according to the MAGIC protocol confirmed the benefit in terms of disease-free survival for patients receiving neo-adjuvant as well as adjuvant treatment compared with patients who did not undergo post-operative CT<sup>[29]</sup>.

The results of the French FNLCC ACCORD 07 FFCD 9703 trial confirmed data in favor of the establishment of perioperative CT for patients with resectable gastric cancer and esophageal adenocarcinoma<sup>[24]</sup>. Only 25% of the patients in this study had gastric cancer, while the remaining patients had esophageal or EGJ tumors. The chemotherapeutic regimen consisted of 2 or 3 pre-operative cycles and 3 or 4 post-operative cycles of 5-fluorouracil and cisplatin. A total of 224 patients were randomized to receive pre-operative CT ( $n = 113$ ) or primary surgery ( $n = 111$ ). The median follow-up was 5.7 years. The R0 resection rate was 84% in the chemotherapy group compared to 74% in the surgery group ( $P = 0.04$ ). Overall, survival and disease-free survival were significantly prolonged after CT (HR = 0.69;  $P = 0.02$  and HR = 0.65;  $P = 0.003$ , respectively). The 5-year survival rates were 38% in the CT- and 24% in the surgery-only arm.

More recently, early results from a Japanese phase II randomized study (the COMPASS trial) have shown a high rate (approximately 10%) of complete pathologic response after neo-adjuvant chemotherapy with four cycles of S1/cisplatin or paclitaxel/cisplatin regimens without a marked increase of toxicities<sup>[30]</sup>.

### Meta-analyses

To date, four meta-analyses regarding neo-adjuvant chemotherapy have been published. The first systematic review and meta-analysis was published by Wu *et al*<sup>[31]</sup> in 2007, which included only 4 randomized controlled trials, and concluded that neo-adjuvant chemotherapy should not be used routinely in clinical settings until further results are available. Similarly, the second meta-analysis performed in 2008 by He *et al*<sup>[32]</sup>, which included 5 randomized controlled trials, concluded that evidence for the efficacy of neo-adjuvant chemotherapy on gastric cancer was weak and that pre-operative

treatment should not be recommended as a regular treatment for gastric cancer.

In 2010, Li *et al*<sup>[33]</sup> conducted the third meta-analysis that included randomized and non-randomized controlled trials. This study showed a marginal improvement in the 3-year overall survival rate for patients who received perioperative chemotherapy (OR = 1.27; 95%CI: 1.04-1.55) in addition to surgery. Furthermore, this study found that perioperative chemotherapy was more beneficial in improving overall survival in later-stage (pT3-4) gastric cancer vs earlier stage (pT1-2) (OR = 1.91; 95%CI 1.24-2.96).

The small number of studies included within the meta-analyses from Wu *et al*<sup>[31]</sup> and He *et al*<sup>[32]</sup> and the non-randomized controlled trials included in the meta-analysis by Li *et al*<sup>[33]</sup> may together compromise the reliability of the results of those meta-analyses.

The most recent meta-analysis was published in 2014 by Xiong *et al*<sup>[34]</sup> and has provided, by its strict inclusion criteria as well as its population subgroup and regimen-subgroup analyses, the most robust evidence so far on neo-adjuvant chemotherapy. This review concluded that while neo-adjuvant chemotherapy offered a marginal survival benefit over the control group with an OR of 1.32 (95%CI: 1.07-1.64,  $P < 0.01$ ), it significantly improved the 3-year progression-free survival (OR = 1.85; 95%CI: 1.39-2.46;  $P < 0.0001$ ), tumor down-staging rate (OR = 1.71, 95%CI: 1.26-2.33;  $P < 0.0006$ ) and R0 resection rate (OR = 1.38; 95%CI: 1.08-1.78;  $P < 0.01$ ) of patients with advanced gastric cancer.

Finally, a Cochrane Systematic Review conducted by Ronellenfitsch *et al*<sup>[35]</sup> in 2013 on perioperative chemoradiotherapy vs primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus. The findings showed an absolute improvement in survival of 9% at 5 years for patients undergoing perioperative chemotherapy. This benefit was evident 18 mo after surgery and was maintained for 10 years. The odds of a R0 resection in patients treated with perioperative CT were 1.4 times higher than in untreated patients. Moreover, in subgroup analyses, the authors demonstrated a higher survival benefit for patients with tumors of the EGJ compared to other sites.

## PRE-OPERATIVE

### RADIO(CHEMO)THERAPY

Following the results of the SWOG 9008/INT-0116 trial, the use of a preoperative combination of chemotherapy and radiotherapy garnered increased interest<sup>[4]</sup>. There have been several pivotal randomized single center studies on preoperative radiotherapy. In the trial performed by Zhang *et al*<sup>[36]</sup>, 317 patients with adenocarcinoma of the cardia were randomly assigned to preoperative radiotherapy followed by surgical resection vs surgery alone. This study showed a

**Table 3** Pre-operative chemo-radiotherapy in gastric and esophagogastric junction cancer

Ref.	Phase	Selection criteria	Study arms	No. of patients	R0 resection (%)	Pathologic CR (%)	Median survival (mo)
Zhang <i>et al</i> <sup>[36]</sup>	RCT	EGJ	40 Gy EBRT + surgery <i>vs</i> surgery alone	370 (171 + 199)	89.5	0	5-yr OS 30% <i>vs</i> 20%
Shchepotin <i>et al</i> <sup>[37]</sup>	RCT	M0 resectable and unresectable	Surgery alone <i>vs</i> 20 Gy EBRT <i>vs</i> 20 Gy EBRT + Hy	293 (98 + 100 + 95)	NS	NS	5-yr OS 21.3%
Skoropad <i>et al</i> <sup>[38]</sup>	RCT	M0 resectable + EGJ	20 Gy EBRT + Hy + 20 Gy IORT <i>vs</i> surgery alone	122 (59 + 53)	66	0	16
Safran <i>et al</i> <sup>[39]</sup>	Phase I	Unresectable M0	45 Gy EBRT+ Paclitaxel	27	NS	11	2-yr OS 35%
Lowy <i>et al</i> <sup>[40]</sup>	Phase I	T > 2, Any N, M0	45 Gy EBRT, 5-FU	24	75	11	NS
Ajani <i>et al</i> <sup>[41]</sup>	Phase II	T > 2, Any N	5FU, LV, P + 45 Gy EBRT, 5FU	33	70	30	34
Ajani <i>et al</i> <sup>[42]</sup>	Phase II	M0 resectable + EGJ	FP, paclitaxel + 45 Gy EBRT, 5FU	41	78	20	> 36
Allal <i>et al</i> <sup>[43]</sup>	Phase I	T3-T4, N+	FP, Leucovorin + 31.2–45.6 Gy EBRT	19	NS	5	5-yr OS 35%
Ajani <i>et al</i> <sup>[44]</sup>	Phase II	M0 resectable	FP, LV, P + 45 Gy EBRT, 5FU, cis	49	63	26	23
Stahl <i>et al</i> <sup>[45]</sup> POET trial	Phase III RCT	EGJ	PFL × 3 + 30 Gy + cisplatin/ etoposide + surgery <i>vs</i> PFL × 2, 5 + surgery	126 (62+64)	72 <i>vs</i> 69	15.6 <i>vs</i> 2.0	33.1 <i>vs</i> 21.1
Van Hagen <i>et al</i> <sup>[48]</sup> CROSS trial	Phase III RCT	Esophageal or EGJ cancer	Carboplatin + paclitaxel + 41.1Gy + surgery <i>vs</i> surgery alone	366 (178 + 188)	92 <i>vs</i> 69	29 (CRT + surgery)	49.9 <i>vs</i> 24

R0: Curative (R0) resections; CR: Complete response; GEJ: Gastro-esophageal junction; RCT: Randomized controlled trial; EBRT: External beam radiotherapy; IORT: Intraoperative radiotherapy; Hy: Hyperthermia; FP: Fluorouracil and cisplatin; LV: Leucovorin; NS: Not stated; OS: Overall survival.

significant five-year survival advantage for patients who received neoadjuvant radiation treatment compared to patients treated with surgery alone (30.1% *vs* 19.8%, respectively), in addition to an improvement in the rate of complete curative resection after radiation therapy (80% *vs* 62%). Another single center trial was a three-arm study, performed in Ukraine from February 1984 to May 1986<sup>[37]</sup>. That study enrolled 293 patients with gastric cancer and then randomized by envelope assignment into three groups: (1) radiotherapy and subsequent surgery; (2) radiotherapy combined with local hyperthermia and subsequent surgical resection; or (3) only surgery. This study demonstrated a five-year survival rate of 30.1% for surgery alone, 44.7% for radiotherapy followed by surgery, and 51.5% for radiation therapy combined with hyperthermia and subsequent surgical resection: The last multimodal treatment was demonstrated to be significantly more effective than surgery alone ( $P < 0.05$ ). Moreover, in this study, an advantage in using radiotherapy and surgery *vs* surgical resection alone was demonstrated, but it was statistically insignificant. Skoropad *et al*<sup>[38]</sup> reported the 20-year follow-up results of a randomized trial on pre-operative radiotherapy (given at a dose of 20 Gy) compared to surgery alone. No significant difference in overall survival was detected between the two treatment groups. Published phase II studies have confirmed the efficacy of chemo-radiotherapy (CRT) in terms of complete pathological response (up to 30% in some series) and increased long-term survival without an increase in morbidity or mortality (Table 3)<sup>[28,36-44]</sup>.

Safran *et al*<sup>[39]</sup> showed that patients treated concurrently with paclitaxel and radiotherapy had an overall

response of 56%, with 11% of the sample achieving complete response (3 cases) in patients with local-regional unresectable gastric cancer. The 2-year progression-free and overall survivals were 29% and 31%, respectively. Lowy *et al*<sup>[40]</sup> performed a pilot study of preoperative chemo-radiotherapy (combined with IORT) in patients with a diagnosis of gastric tumor, which used a staging protocol based on the results of computed tomography, endoscopic ultrasonography, and staging laparoscopy to determine the possibility of surgical resection. Twenty-four patients with a potentially resectable disease, but who had a poor prognosis tumor (T2 or higher at EUS), were treated with 45 Gy of external-beam radiation at 1.8 Gy/d and 5 d/wk with continuous-infusion 5-FU (300 mg/m<sup>2</sup> per day). All but one patient were able to complete the treatment. The radiation field included the entire stomach and regional lymph nodes. A restaging CT scan was performed at 4 to 6 wk after neoadjuvant therapy and before surgery. Nineteen patients (83%) were treated with a spleen-preserving D2 gastrectomy after the end of chemo-radiotherapy, and the surgical resection was accompanied by IORT (10 Gy). Two patients (11%) showed a complete pathological response.

In 2004, Ajani *et al*<sup>[41]</sup> treated patients with two courses of 5-FU, folinic acid, and cisplatin (P), following those with 5FU-potentiated radiotherapy (45 Gy). This study enrolled 34 patients with localized gastric adenocarcinoma, and 85% of them underwent surgical resection after neoadjuvant chemo-radiotherapy, without an increase in postoperative complications. Thirty percent of patients showed a complete pathologic response, while 24% showed a partial response. The

**Table 4** Currently recruiting trials for pre and peri-operative chemo(radio)therapy

Country	Title	Phase	Study arms	Trial registration
United Kingdom <sup>[51]</sup>	Chemotherapy with or without bevacizumab or lapatinib to Treat Operable Oesophagogastric Cancer (ST03)	II/III	ECX + bevacizumab <i>vs</i> ECX <i>vs</i> ECX + lapatinib	NCT00450203
United Kingdom <sup>[52]</sup>	A study of bevacizumab in combination with capecitabine and cisplatin as first-line therapy in Patients With Advanced Gastric Cancer (AVAGAST)	III	Bevacizumab + ECX <i>vs</i> ECX	NCT00548548
Multicenter study (24 countries) <sup>[53]</sup>	ToGA study - A study of herceptin (trastuzumab) in combination with chemotherapy compared with chemotherapy alone in patients with HER2-positive Advanced Gastric Cancer	III	Trastuzumab + fluorouracil/capecitabine + cisplatin <i>vs</i> fluorouracil/capecitabine + cisplatin	NCT01041404
Australia and New Zealand	Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR)	II/III	Epirubicin + cisplatin + 5-fluorouracil + 45 Gy <i>vs</i> Epirubicin + cisplatin + 5-fluorouracil	NCT01924819
Netherlands <sup>[54]</sup>	Randomized phase III trial of adjuvant chemotherapy or Chemoradiotherapy in Resectable Gastric Cancer (CRITICS)	III	ECC + surgery + ECC <i>vs</i> ECC + surgery + 45 Gy + capecitabine + cisplatin	NCT00407186
China	Peri-operative chemotherapy with ECX or XP in the treatment of advanced gastric cancer	III	Epirubicin + cisplatin + capecitabine <i>vs</i> capecitabine + cisplatin	NCT01558947
Korea	DOS regimen as neoadjuvant chemotherapy in advanced gastric cancer (PRODIGY)	III	Docetaxel + oxaliplatin + tegafur <i>vs</i> surgery only	NCT01515748
China	Peri-operative chemotherapy with ECX (epirubicin + cisplatin + capecitabine) or XP (capecitabine + cisplatin) in the treatment of advanced gastric cancer: A randomized, multicenter, parallel controlle	III	Epirubicin + cisplatin + capecitabine <i>vs</i> capecitabine + cisplatin	ChiCTR-TRC-11001319
Ireland	MAGIC <i>vs</i> CROSS Upper GI. ICORG 10-14	III	MAGIC regimen <i>vs</i> CROSS protocol	NCT01726452

AVAGAST: The Avastin in gastric cancer; ECX: Epirubicin, cisplatin and xeloda; TOPGEAR: Trial of preoperative therapy for gastric and esophagogastric junction adenocarcinoma; CRITICS: Chemoradiotherapy after induction. chemotherapy in cancer of the stomach; XP: Xeloda and cisplatin; DOS: Docetaxel, oxaliplatin and S1; MAGIC: Medical research council adjuvant gastric infusional chemotherapy; CROSS: Chemoradiotherapy for oesophageal cancer followed by surgery study; ICORG: Ireland cooperative oncology research group.

overall median survival duration was 33.7 mo, but in patients who reached a complete response, the median survival time was 64 mo. For those with a partial response, the median survival duration was 12.6 mo ( $P < 0.05$ ). The results from this trial demonstrate that patients with cancers responding to treatment can achieve a substantial survival benefit. Similar results were obtained by the same authors in two subsequent studies using a different combination of chemotherapeutic drugs<sup>[42-44]</sup>.

The German POET trial<sup>[45]</sup> compared neo-adjuvant chemotherapy with neo-adjuvant chemo-radiotherapy in patients with locally advanced adenocarcinoma of the lower esophagus or gastric cardia. Patients were randomly allocated to one of two treatment groups: induction chemotherapy (15 wk of cisplatin, fluorouracil, leucovorin) followed by surgery or chemotherapy (12 wk of cisplatin, fluorouracil, leucovorin) followed by 3 wk of chemo-radiotherapy (30 Gy, cisplatin/etoposide) followed by surgery. The median length of survival was 33.1 mo for patients in the chemo-radiotherapy arm and 21.1 mo for those in the chemotherapy arm.

Although the study was closed early due to low accrual and no evidence of a significant survival benefit for chemo-radiotherapy, the results suggest a survival

advantage for pre-operative chemo-radiotherapy compared with pre-operative chemotherapy. Based on this study, most European guidelines consider neo-adjuvant or perioperative chemo-radiotherapy as an alternative to chemotherapy in adenocarcinomas of the EGJ<sup>[46,47]</sup>.

A recent multicenter, randomized phase III trial investigated the role of neo-adjuvant chemo-radiotherapy in the treatment of esophageal or EGJ cancer (CROSS trial)<sup>[48]</sup>. Patients with resectable tumors were randomly assigned to receive surgery alone ( $n = 188$ ) or CRT (carboplatin, paclitaxel, 41.4 Gy in 23 fractions) followed by surgery ( $n = 178$ ). Seventy five per cent of the patients had adenocarcinoma. Patients treated with CRT had a higher R0 resection rate than patients treated with surgery alone (92% and 69%,  $P < 0.001$ ), and 29% of patients showed a pathological complete response (23% in patients with adenocarcinoma and 49% in patients with squamous-cell carcinoma). The median overall survival duration was 49.9 mo in patients undergoing CRT associated with surgical resection and 24 mo in patients undergoing surgery only ( $P = 0.003$ ). Post-operative complications and in-hospital death rate (4% in both) were similar in both arms.

Based on the results of this trial, pre-operative

chemo-radiation is now the preferred approach for localized adenocarcinoma of the EGJ in the United States, whereas chemotherapy is regarded as an alternative, but less preferred option.

Recently, Kumagai *et al.*<sup>[49]</sup> conducted a meta-analysis regarding chemo-radiotherapy in resectable gastric and gastro-esophageal junction cancer. Eighteen studies were collected, from which data were available from 14. In this meta-analysis, pre-operative chemo-radiotherapy as well as chemotherapy for resectable gastric and gastro-esophageal cancers were associated with a significant survival benefit compared to surgery alone. Due to the lack of studies comparing pre-operative chemotherapy and chemo-radiotherapy in this study, the comparison between the two regimens was performed in adjusted indirect form. Despite this methodological bias, pre-operative chemo-radiotherapy showed a trend towards better long-term survival.

## ONGOING TRIALS

Many answers are expected from ongoing trials that are exploring ways of improving pre-operative treatment strategies for resectable gastric cancer<sup>[50-53]</sup> (Table 4).

In the field of neo-adjuvant chemotherapy, an ongoing phase II/III British trial (ST03) is actively recruiting localized gastric and EGJ tumor patients and comparing perioperative epirubicin, cisplatin and capecitabine (ECX) with or without bevacizumab (ECX-B)<sup>[50]</sup>. This chemotherapeutic protocol is based on the demonstrated beneficial effect of bevacizumab in the treatment of advanced gastric cancer (AVAGAST trial). The preliminary results of phase II about safety showed that chemotherapy is feasible with acceptable toxicity (specifically gastrointestinal perforation rates and cardio-toxicity) with no negative impact on surgical outcomes<sup>[51]</sup>.

The findings of the ToGA-study, which revealed the beneficial effects of trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive advanced gastric and GEJ cancers in combination with a platinum-based chemotherapy<sup>[52]</sup>, gave rise to studies investigating the HER2 positivity in advanced gastric cancer with bulky N2 or N3 nodal disease with possible implications in a neo-adjuvant setting (JCOG2005-A).

Several ongoing trials are currently investigating the role of a neo-adjuvant chemotherapeutic protocol. Most of these trials come from Eastern countries (JCOG 001, JCOG 0405, JCOG 0210, JCOG 0501, JCOG 1002, Kyoto trial, PRODIGY trial) and are recruiting patients with advanced and marginally resectable gastric cancer (T3-4, large type 3 gastric cancer, linitis plastica, and bulky N2-3 + tumor).

At the same time, ongoing trials are evaluating the role of radiotherapy in the setting of pre- and perioperative treatment. For instance, the TOPGEAR phase II/III trial is examining the addition of a neo-adjuvant chemo-radiotherapy strategy to perioperative chemotherapy in patients with resectable adeno-

carcinoma of the stomach or EGJ. Patients are randomized to receive three cycles of ECF alone or chemo-radiotherapy (two cycles of ECF followed by 45 Gy or radiation with concurrent 5-FU). Following surgery, both groups receive three cycles of ECF. Part I of the trial (phase II component) will recruit 120 patients with the aim of demonstrating the efficacy and safety of pre-operative CRT. The second part (phase III component) will recruit 632 additional patients. The primary endpoints are the pathological complete response rates and overall survival.

The CRITICS trial (Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach) is a phase III study that randomizes between pre-operative chemotherapy (three courses of epirubicin, cisplatin, capecitabine; ECC) and gastric surgery followed by post-operative chemotherapy (three courses of ECC) or chemo-radiotherapy (45 Gy in 25 fractions; concurrent capecitabine and cisplatin)<sup>[53]</sup>. The MAGIC vs CROSS Upper GI. ICORG 10-14 trial are randomizing patients with adenocarcinoma of the esophagus and EGJ in neo-adjuvant and adjuvant chemotherapy according to the MAGIC regimen vs neo-adjuvant chemo-radiation according to the CROSS protocol in order to assess 2- and 3-year patient survival, clinical and pathological response rate, tumor regression grade, and disease-free survival.

## INTERNATIONAL GUIDELINES AND AREAS OF UNCERTAINTY

The above-mentioned collection of study data led neoadjuvant therapy to be included into several national and international guidelines for gastric cancer management, but significant differences exist among different countries. Both United States and European guidelines<sup>[54,55]</sup> consider pre-operative chemotherapy as the preferred pathway for  $\geq T2$  and/or  $N \pm$  gastric cancer reaching the "level 1" of recommendation in the National Comprehensive Cancer Network Consensus. Similarly, pre-operative chemoradiation is the favorite approach to manage esophagogastric junction cancer in American guidelines.

In contrast, neoadjuvant therapy was still considered investigational by the last edition of the Japanese Gastric Cancer Association guidelines while researchers await the results of dedicated ongoing trials<sup>[56]</sup>.

This probably reflects the well-known diversity of gastric cancer epidemiology and pathology between the West and East, which leads to different treatment approaches.

Considering that locally advanced cancers are more frequent than earlier stages in the United States and Europe, the current guidelines suggest the use of neoadjuvant therapy in a majority of gastric cancers. Although potentially beneficial, this wide application of pre-operative treatment requires proper patient selection to avoid its potentially dangerous overuse<sup>[57]</sup>.



Several studies have reported that a tumor's response may depend on different factors such as the tumor site, grading and Lauren's histotype<sup>[58,59]</sup>, and a recent large retrospective study demonstrated that survival was mainly influenced by the disease stage after neoadjuvant chemotherapy, rather than the clinical stage at presentation<sup>[60]</sup>.

In particular, signet-ring cell cancer seems to be less responsive to pre-operative chemotherapy as shown in some large European retrospective studies<sup>[61,62]</sup>.

Interestingly, the subset analysis of the final report of the trial evaluating the role of adjuvant radiotherapy after D2 gastrectomy showed that chemoradiation significantly improved DFS in patients with intestinal-type cancer, but there was no benefit in diffuse histotype<sup>[63]</sup>. A French phase II/III multicenter trial evaluating the role of neoadjuvant therapy in resectable signet ring cell gastric cancer is currently ongoing (NCT01717924; clinicaltrials.gov) and will probably help clarify this issue.

Basically, in the last two decades, Western surgeons have tried to extend the overall lower survival rate of their gastric cancer patients - compared with Eastern patients - adding pre- and/or post-operative multimodal therapy to surgery. However, "high quality" surgery is still the cornerstone of the management of gastric cancer, and D2-lymphadenectomy has been recently introduced as the standard surgical procedure also in the Western Countries<sup>[54,55]</sup>. So far, the most evidence on neoadjuvant therapy comes from studies including patients generally treated by inadequate surgery, considering that in the MAGIC and FFCO trials, a D0-1 lymphadenectomy was the more common procedure<sup>[6,24]</sup>. Therefore, we could argue that pre-operative therapy could fill the survival gap of a limited surgery.

An emerging and unresolved question regards the management of gastric cancer in elderly patients. The incidence of gastric cancer increases with advancing age<sup>[64]</sup>, and the elderly population is dramatically growing due to increased life expectancy, especially in developed countries<sup>[65]</sup>. Several studies have demonstrated that age alone is not a contraindication for surgery<sup>[66-69]</sup>, but there are limited data on the role of perioperative therapy in older patients. The recent review by Ronellenfitsch *et al.*<sup>[35]</sup> reported no survival advantage from adding pre-operative therapy in elderly patients, but several important issues such as under-representation of older patients in clinical trials, heterogeneity of elderly definitions and non-specific analyzed end-points may have significantly affected the interpretation of the current available data<sup>[70,71]</sup>. Further specifically designed studies and reliable biologic indicators of real functional status are needed to properly select older patients for multimodal treatment.

## CONCLUSION

In gastric cancer, radical surgery (R0-resection), defined as the complete surgical resection of all the tumor

cells in the tumor bed, is considered the best chance of a cure. However, distant and loco-regional failure rates in radically resected patients with positive lymph nodes or involvement of the serosa make this definition somewhat contradictory. Currently, the tailoring of the treatment, both in terms of the extent of surgical resection and of the administration of pre- and post-operative therapies, represents the major goal. In the last ten years, three pivotal studies from three different areas of the world (United States, Europe and Japan) have shown that combined treatments can lead to a better prognosis for patients with resectable gastric cancer. Multimodal treatments aim to obtain an improvement in prognosis by means of a truly complete curative surgery (R0 resection) with minimal morbidity and mortality. In gastric cancer, surgical research has always proceeded slowly, and standardization is still far from being settled. Geographical differences in epidemiology and therapeutic approaches and the absence of a surgical gold standard have diverted attention from the development of an ideal multimodal approach.

More data are necessary to define the role of neo-adjuvant chemo-radiotherapy in the field of gastric cancer treatment. The results of pre-operative chemotherapy in the multimodal treatment of gastric adenocarcinoma are undoubtedly encouraging. Modern and unsolved concerns regarding the choice of the optimal chemotherapy regimen, the role of radiotherapy, a reliable pre-operative staging protocol for accurate patients selection, standardization of surgical procedures, and reliable criteria for response evaluation amid new well-designed trials will be necessary to identify the best treatment plan in the pre-operative setting and to understand how to combine the conventional chemotherapeutic drugs with new-generation molecules.

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