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Feasibility of preoperative and postoperative chemoradiotherapy in gastric adenocarcinoma. Two phase II studies done in parallel. Fédération Francophone de Cancérologie Digestive 0308 ☆

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Abstract ***Background:*** For resectable gastric cancer, both postoperative chemoradiotherapy and perioperative chemotherapy demonstrate high-level evidence for improved survival in Western populations. To evaluate the feasibility of pre- or postoperative chemoradiotherapy, we proposed two multicentre phase II studies.
Patients and methods: Patients with localised, histologically confirmed gastric cancer and Eastern Cooperative Oncology Group (ECOG) performance status <2 judged suitable for curative resection were eligible. Eligible patients were assigned to either preoperative chemo-

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radiotherapy followed by surgical resection or surgical resection followed by chemoradiotherapy depending on each centre. Chemoradiotherapy regimen included four courses of FOLFIRI (5 Fluorouracil, Leucovorin, Irinotecan) regimen then Concurrent fluorouracil at 200 mg/m^2/d by continuous infusion 5 days each week. A dose of 50 Gy in 25 fractions in the preoperative study, or 45 Gy in 25 fractions in the postoperative study, was delivered. The primary end-point for both studies was the proportion of patients, who completed the therapeutic sequence.

Results: Between September 2007 and January 2010, 63 patients were included in both studies. The postoperative study was stopped for futility at the first step. In the preoperative study, 31 patients (73.8%, confidence interval (CI) 95%: 65.8–90.1%) received complete therapeutic sequence. Serum albumin and dietary restriction evaluated by QLQ-STO22 (Quality of Life-Stomach module) score were significantly linked with chemoradiotherapy feasibility in univariate analysis with respectively Odds-ratio (OR) 1.16 [CI 95%: 1.01–1.33] and 0.17 [0.03–0.89], $p = 0.04$. Median overall survival time was 26.4 months in the preoperative study.

Conclusion: Feasibility of chemoradiotherapy was not achieved for these studies: 73.8% (CI 95%: 65.8–90.1) and 42.9% (CI 95%: 21.8–66%) in preoperative and postoperative settings respectively.

1. Introduction

For resectable gastric cancer, adjuvant treatment strategy remains debated [1]. Currently, both postoperative chemoradiotherapy and perioperative chemotherapy demonstrate high-level evidence for improved survival in Western populations [2–4]. Recent data from the INT-0116 trial, after a 10-year median follow-up, has confirmed benefits in both overall survival and recurrence free survival for patients treated by postoperative chemoradiotherapy [5]. Only one Asian trial has directly compared postoperative chemotherapy with chemoradiotherapy [6]. In this trial, disease free survival was significantly superior in node-positive patients receiving chemoradiotherapy ($p = 0.036$). In gastric cancer, several preoperative chemoradiotherapy regimens have been evaluated at phase II [8–13]. In cancer of the oesophagogastric junction (OGJ), preoperative chemoradiotherapy improved 3-year survival rate from 27.7% to 47.4% ($p = 0.07$) in comparison with chemotherapy alone [14]. These different studies argue in favour of radiotherapy associated with chemotherapy in adjuvant treatment of gastric cancer. However, the feasibility of postoperative and preoperative chemoradiotherapy has never been studied according to the same criteria. In preoperative chemoradiotherapy studies, feasibility was defined by intention-to-treat approach including for analysis, all patients before treatment [8–13]. However, in postoperative chemoradiotherapy studies, feasibility analysis was limited to selected patients, with good post operative nutritional status [5–7]. To evaluate the feasibility of pre- or postoperative chemoradiotherapy, in intent to treat approach, we proposed two parallel multicentre phase II studies. Each centre determined either a preoperative or postoperative strategy.

2. Patients and methods

2.1. Patient selection

Patients with localised, histologically confirmed gastric cancer or gastroesophageal junction Siewert III and Eastern Cooperative Oncology Group (ECOG) performance status <2 judged suitable for curative resection were eligible. Patients underwent the following investigations: computed tomography (CT) of the chest, abdomen and pelvis and blood tests (CBC Cell Blood Count, hepatic function, renal function and serum albumin). Oesophagogastroduodenoscopy with endoscopic ultrasonography (EUS) was performed only in patients with node size below 2 cm on CT scan. Only patients over 18 years of age and with adequate renal, haematological and hepatic functions were enrolled (creatinine <120 μmol/L, neutrophils $\geqslant 1500/mm^3$, platelets $\geqslant 100{,}000/mm^3$, serum albumin >30 g/L). Patients with $T > 2$ imaging (CT or EUS) or perigastric node involvement (CT or EUS) without detectable distant metastases or peritoneal carcinomatosis were included. Exclusion criteria were personal history of thoracic or abdominal radiation therapy, known pregnancy or total bilirubin >3 upper limit level. Local ethics committees approved the protocol and patients' written informed consent was obtained (N°EudraCT:2006-005576-40).

2.2. Study treatment

These phase II trials were initiated in 24 centres by the Fédération Francophone de Cancérologie Digestive (FFCD). Each centre selected preoperative study or postoperative study participation according to preference. Only one of the two studies was opened in each centre. Both studies were done in parallel.

2.2.1. Chemotherapy

Four courses of FOLFIRI (5 Fluorouracil, Leucovorin, Irinotecan) regimen (D1, 15, 29, 43) were planned. FOLFIRI regimen included Leucovorin 400 mg/m^2 and irinotecan 180 mg/m^2 intravenous (IV) over 2 h, followed by fluorouracil (FU) 400 mg/m^2 IV bolus, then FU 2400 mg/m^2 continuous infusion over 46 h, repeated every 14 days. In the postoperative study, chemotherapy was begun 4–8 weeks after surgical resection of the tumour.

2.2.2. Chemoradiotherapy

Chemoradiotherapy was started 14 days after the final course of FOLFIRI. Fields included the entire stomach plus perigastric extension, if present, and draining lymph nodes (gastric, coeliac, portal hepatic gastroduodenal, splenic-suprapancreatic and retropancreaticoduodenal). For lesions involving the cardia or OGJ, a 3-cm margin of oesophagus was included, and for distal lesions at or near the gastroduodenal junction, the duodenum was included. In the preoperative study, pretreatment diagnostic studies were used to determine the maximum extent of disease relative to both the primary tumour and nodal groups. In the postoperative study, pathologic examination was used to determine the maximum extent. Idealised fields were modified, as necessary, to shield at least two-thirds of one kidney. For proximal lesions, cardiac shielding was recommended, along with evaluation of lateral fields for part of the treatment. Linear accelerators were used to deliver a dose of 50 Gy in 25 fractions of 2 Gy over 5 weeks in the preoperative study, or 45 Gy in 25 fractions of 1.8 Gy in the postoperative study, using anterior–posterior/posterior–anterior plus paired laterals. The minimum energy allowed was 10 MV photons. Concurrent outpatient fluorouracil was given at 200 mg/m^2/d by continuous infusion via a portable pump 5 days each week (usually starting on a Monday and ending on Friday, after radiation).

2.2.3. Surgery

Surgery was scheduled within 4–6 weeks after completion of radiotherapy in the preoperative study. Surgery consisted in complete excision of the tumour with extended lymphadenectomy (D2 recommended) and, partial or total gastrectomy was recommended according to the tumour site. Perioperative nutritional support with at least 1500 Kcal/d was recommended.

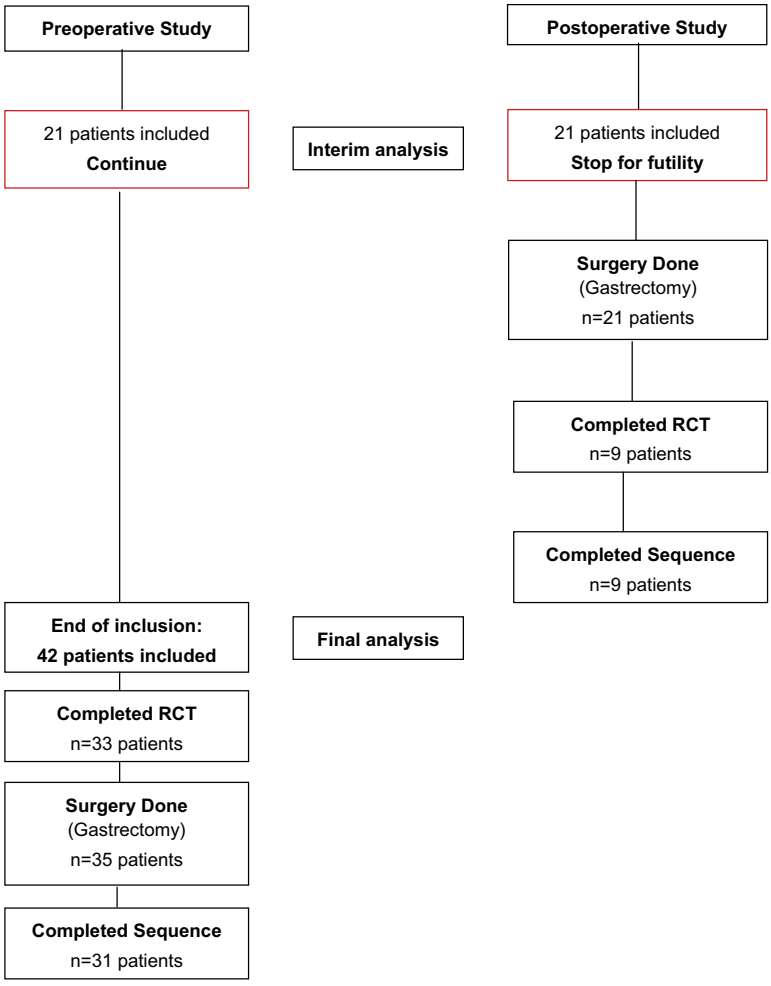

Fig. 1. Trial profile.

2.3. Statistics

The primary end-point for both studies was the proportion of patients, who completed the therapeutic sequence. This was defined by four courses of FOLFIRI infused with at least 90% of fractions of radiation delivered and, at least 75% of the total dose of 5-fluorouracil (5FU) infused during radiotherapy and surgical exploration. A feasibility rate of 70% was considered uninteresting and a rate of 88% was expected. Fleming's two-stage design required inclusion of 42 patients in each study (unilateral alpha 5%, power 83%) [15].

Secondary end-points were: toxicities evaluated by National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (version 2), overall survival, progression-free survival. Quality of life was evaluated by QLQC-30 (Quality of Life) and the questionnaire specific to gastric pathology ST022.

Survival curves were plotted using Kaplan–Meier estimates and Logistic regression models were used to calculate the odds-ratios (ORs) with a 95% confidence interval (CI). All analyses were performed on an intention-to-treat principle using SAS software (V9.1 SAS Institute Cary, NC) at a level of significance of 0.05.

3. Results

3.1. Study population

Between September 2007 and January 2010, 63 patients were included in both studies. Fig. 1 shows the trial profile. In the preoperative study, 42 patients were included by 16 centres and in the postoperative study, 21 patients were included by 10 centres. The postoperative study was stopped for futility at the first step and preoperative study continued to the final step. Patient baseline characteristics are presented in Table 1.

Table 1
Patient characteristics.

	Preoperative study $N = 42$	Postoperative study $N = 21$
Age (years)		
Median (range)	61 (29.8–78.0)	59.5 (39.2–77.7)
Sex		
Male	33 (78.6%)	14 (66.7%)
Eastern Cooperative Oncology Group (ECOG)		
0	25 (59.5%)	15 (71.4%)
1	16 (38.1%)	6 (28.6%)
Unknown	1 (2.4%)	0 (0%)
Haemoglobin (g/100 ml)		
Median (range)	12.2 (7.4–16.2)	12.6 (8.6–15.9)
Serum albumin (g/L)	$n = 37$	$n = 18$
Median (range)	40 (18–52)	39.5 (29.0–45.0)
Tumour site		
Lower third	19 (45.2%)	7 (33.3%)
Middle third	15 (35.7%)	11 (52.4%)
Cardia III	8 (19%)	3 (14.3%)
Histology	$n = 35$*	
Tubulous	12 (34.3%)	7 (33.3%)
Signet-ring cell	11 (31.4%)	9 (42.8%)
Other	12 (34.3%)	5 (23.8%)

* Calculated on operated patients $n = 35$.

3.2. Treatment sequences (Table 2)

3.2.1. Preoperative study

In the preoperative study, 31 patients (73.8%) [CI 95%: 65.8–90.1%] received complete therapeutic sequence. To assess the feasibility of the trial we expected at least 35 patients with complete therapeutic sequence. In two cases, treatment was stopped for toxicity. Reasons for incomplete sequence were: less than four FOLFIRI courses for three patients, radiotherapy not delivered for six patients, incomplete doses of 5FU during radiotherapy for eight patients and no surgery for seven patients. During preoperative chemoradiotherapy, metastatic progression of the disease was reported in five cases. Results of surgery are presented in Table 2. Delay between inclusion and surgery was in accordance with protocol in 85.7% of operated patients. Complete pathologic response was present in 8.6% of operated patients. Serum albumin and dietary restriction evaluated by score QLQ-STO22 (Quality of Life-Stomach module) were significantly linked with chemoradiotherapy feasibility in univariate analysis with respectively OR 1.16 [CI 95%: 1.01–1.33], $p = 0.04$ and 0.17 [0.03–0.89], $p = 0.04$ (Table 3).

3.2.2. Postoperative study

In the postoperative study, nine patients (42.9%), [CI 95%: 21.8–66.0%] had complete therapeutic sequence before interim analysis. Two patients died postoperatively. In one case, surgical exploration showed a peritoneal lesion. In four cases, treatment was modified because of chemoradiotherapy toxicity. In three cases, the tumour was over-staged by pretherapeutic investigations and the pathologic result of surgical specimen did not confirm the utility of chemoradiotherapy. In two cases, medical decision was not justified.

3.3. Toxicities (Table 4)

3.3.1. Preoperative study

Seventeen (40.5%) patients reported at least one severe toxic event (grade 3–4) related to chemoradiotherapy. During FOLFIRI courses, 11 patients (26.2%) reported at least one toxicity grade 3–4. In one case a digestive toxicity grade 3–4 was observed. During radiotherapy, eight patients (19%) reported toxicity grade 3–4. NCI CTC grade 3 or 4 non-haematological toxic effects were asthenia ($n = 2$), diarrhoea ($n = 1$), dysphagia ($n = 1$), stomatitis ($n = 1$), anorexia ($n = 1$), hand-foot skin reaction ($n = 1$) and radio der-

Table 2
Treatment sequences.

	Preoperative study $N = 42$	Postoperative study $N = 21$
Complete therapeutic sequence	31 (73.8%)	9 (42.9%)
Four courses of FOLFIRI	39 (92.9%)	12 (57.1%)
90% radiotherapy (RT)	36 (85.7%)	12 (57.1%)
75% of fluorouracil (FU) during CTRT	34 (80.9%)	9 (42.9%)
Surgery	35 (83.3%)	21 (100%)
Causes of arrest		
Progression of disease or death	5 (11.9%)	3 (14.3%)
Toxicity or side-effect	5 (11.9%)	4 (19%)
Patient refusal	1 (2.4%)	0 (0%)
Medical decision	0 (0%)	5 (23.8%)
Carcinomatosis	4 (11.4%)*	1 (4.8%)
Metastasis	2 (5.71%)*	0 (0%)
Total gastrectomy	26 (74.2%)*	15 (71.4%)
Number of nodes		
Median (range)	25 (9–37)	21 (8–65)
Resection		
R0	28 (80%)	12 (57.1%)
R1	1 (2.9%)	4 (19.1%)
Unknown	2 (5.7%)	5 (23.8%)
Postoperative mortality at 60 days	6 (17.1%)*	2 (9.5%)
Pathologic complete response	3 (8.6%)*	0 (0%)

* Calculated on operated patients $n = 35$.

matitis ($n = 1$). There was no preoperative-treatment related death. Mortality rate at 60 days after surgery was 17.1%.

3.3.2. Postoperative study

Six (28.6%) patients reported at least one severe toxic event (grade 3–4) related to chemoradiotherapy. During FOLFIRI courses, five patients (23.8%) reported at least one toxic effect grade 3–4. For three patients non-haematological toxicities were reported (two patients with digestive toxicity and, one patient with cardiac toxicity). During radiotherapy, two patients reported toxicity grade 3–4.

3.4. Survival (Figs. 2 and 3)

After median follow-up of 38.1 months, there were 18 surviving patients (42.9%) in the preoperative study, and after a median follow-up of 26.6 months, 12 surviving patients (57.1%) in the postoperative study. Cause of death was evolution of cancer in 16 (66.7%) and four (44.4%) patients in the preoperative and postoperative study respectively. Median overall survival time was 26.4 and 32.9 months in the preoperative and postoperative study respectively. Progression-free survival was 12.3 and 22.8 months in the preoperative and postoperative study respectively. Site of recurrence was distant metastasis in 16 (55.2%) and five (41.7%) patients in the preoperative and postoperative studies respectively.

4. Discussion

The main result of these studies is the difference in chemoradiotherapy feasibility between pre- and postoperative settings. Feasibility of chemoradiotherapy was not achieved for these studies: 73.8% [CI 95%: 65.8–90.1] and 42.9% [CI 95%: 21.8–66%] in preoperative and postoperative settings respectively. Each centre had previously determined their option for pre- or postoperative chemoradiotherapy before the study and performed regimen according to their practice and preference. The results of these studies are an accurate

Table 3
Univariate and multivariate analysis for feasibility of preoperative chemoradiotherapy.

		Univariate analysis		Multivariate analysis ($N = 30$)	
	N	Odds-ratio (OR) [confidence interval (CI) 95%]	p-Value	OR [CI 95%]	p-Value
Eastern Cooperative Oncology Group (ECOG)					
1 versus 0	41	1.17 [0.28–4.87]	0.83	1.34 [0.15–11.80]	0.79
Serum albumin	37	1.16 [1.01–1.33]	0.04	1.15 [0.96–1.38]	0.14
Tumour site					
Cardia versus others	41	0.53 [0.10–2.74]	0.45	0.20 [0.02–2.12]	0.18
Score QLQ-C30					
Global health					
>60 versus ⩽60	35	4.5 [0.89–22.67]	0.067	3.68 [0.44–30.61]	0.23
Physical health					
>70 versus ⩽70	37	7.71 [0.61–97.78]	0.12		
Constipation	35	0.98 [0.95–1.01]	0.12		
Score QLQ-STO22					
Dysphagia					
>15 versus ⩽15	37	0.27 [0.06–1.28]	0.1	0.33 [0.04–2.75]	0.31
Dietary restrictions					
>20 versus ⩽20	37	0.17 [0.03–0.89]	0.04		

Table 4
Number of patients with at least one severe toxicity (grade 3–4).

	Preoperative study $N = 42$	Postoperative study $N = 21$
Severe toxicities during FOLFIRI courses	11 (26.2%)	5 (23.8%)
Haematological	6 (14.3%)	2 (9.5%)
Non-haematological*	7 (16.7%)	3 (14.3%)
Digestive	1 (2.4%)	2 (9.5%)
Severe toxicities during radiotherapy (RT)	8 (19.1%)	2 (9.5%)
Haematological	3 (7.1%)	1 (4.8%)
Non-haematological*	5 (11.9%))	2 (9.5%)
Digestive	2 (4.8%)	1 (2.2%)
All severe toxicities	17 (40.5%)	6 (28.6%)

* Included digestive toxicities.

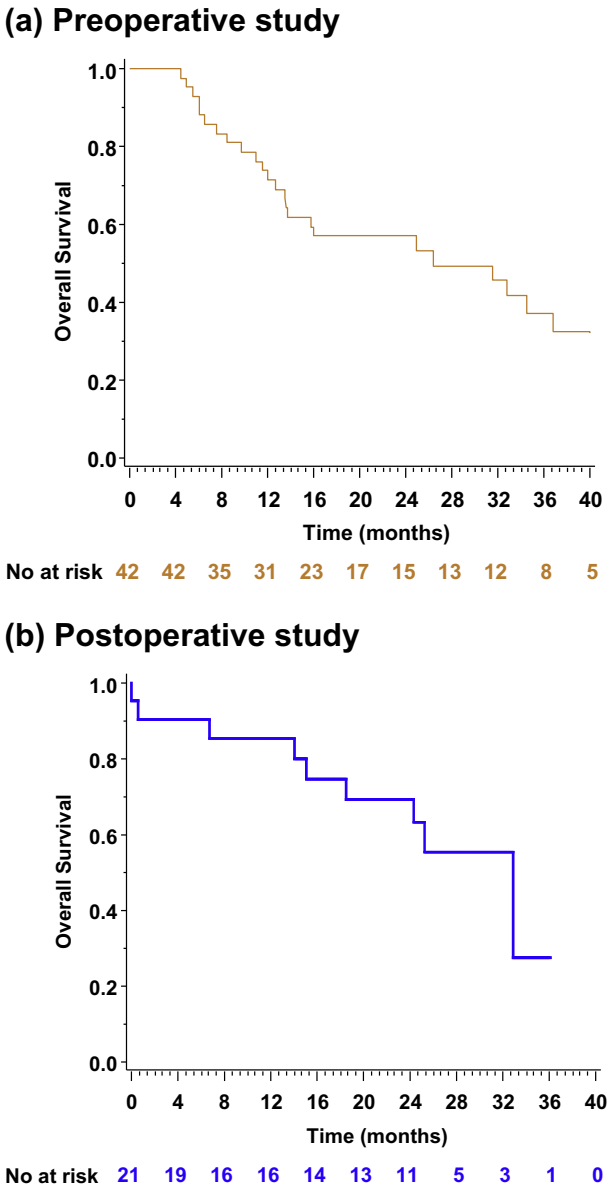

Fig. 2. Overall survival.

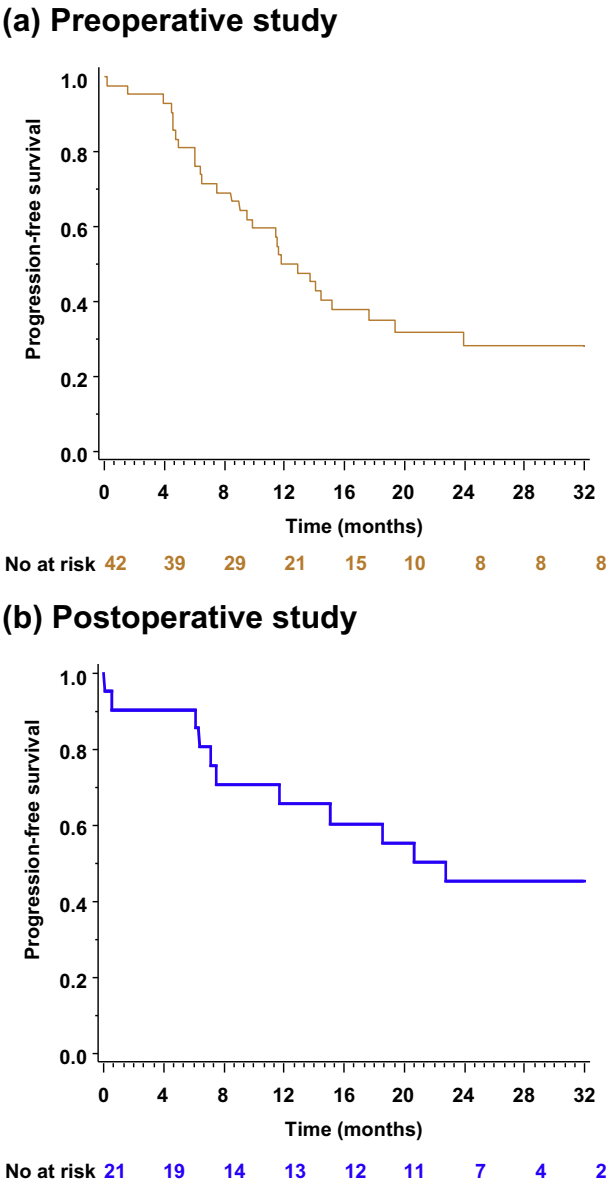

Fig. 3. Progression-free survival.

representation of current practices. The weak feasibility rate of postoperative chemoradiotherapy is coherent with published data in Western countries. In INT-0116 trial, the completion rate observed was 64% in living/surviving patients with good performance and nutritional status after gastrectomy [2]. When inclusion was performed before surgical resection, postoperative chemotherapy was carried out in only 40–50% of patients in the two largest studies recently performed in a European population [3,4]. However, in an Asian study the completion rate of postoperative chemoradiotherapy associated with capecitabine and radiation was superior to 80% [6].

In a preoperative setting, other chemoradiotherapy regimens showed a feasibility of 75–85% [8–13]. Radiation dose and fraction, as well as chemotherapy

associated at radiation (5-fluorouracil) were the same as in previous studies [8,10]. Several data supported the FOLFIRI regimen for chemotherapy. In metastatic situations, the usefulness of FOLFIRI regimen has been demonstrated [16,17]. According to previous studies, FOLFIRI regimen is less toxic than the chemotherapy regimen with cisplatin [16]. In preoperative treatment, CPT-11 based chemotherapy downstaged locally advanced gastric cancer [18]. Two main differences between the present study and previously reported phase II trials of preoperative chemoradiotherapy could explain these discordant results. First, in previous studies, inclusion was limited to 1–3 centres [8,10–13]. In the present study, the high number of centres involved, decreased selection bias, with recruitment from the general population. Second, the sites of tumours were different. In the present study, more than 80% of tumours were in the middle third or lower third of the stomach, while in previous studies, the majority of tumours were proximal [8,10]. Radiation volume was different according to the site of the tumour. In distal tumours, treated volume could explain an increase in digestive toxicity. In the present study, only serum albumin was significantly linked with chemoradiotherapy feasibility in univariate analysis with OR 1.16 [CI 95%: 1.01–1.33], $p = 0.04$. Albumin level was previously reported as a predictive factor of response in oesophageal cancer treated by definitive chemoradiotherapy [19]. Nutritional status must be included in criterion selection before chemoradiotherapy.

The complete pathologic response of 8.6% in preoperative study was disappointing in comparison to 26–30% in studies by Ajani et al. [8,10]. Chemotherapy with cisplatin or paclitaxel seemed more efficient than CPT-11 in preoperative settings on pathologic response.

In conclusion, present studies showed that the feasibility of postoperative chemoradiotherapy was lower than that of preoperative chemoradiotherapy. However, the chemoradiotherapy regimen evaluated in this phase II study did not achieve a feasibility rate superior to 70%. Based on our results, we recommend performing chemoradiotherapy in a preoperative setting in future studies for treatment of localised gastric cancer.

Conflict of interest statement

None declared.

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