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Research Article

Perioperative Chemotherapy (CAPOX 3X3) in Resectable Non-Metastatic Gastric Adenocarcinomas: What is the Benefit on Survival?

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Abstract

Although the incidence of gastric cancer has been declining spontaneously and steadily for over 50 years, stomach cancer remains common. The World Health Organization's 2020 annual report indicates a global incidence of gastric cancer estimated at 1,089,103 new cases per year, representing 5.6% of all cancers, with a mortality rate of approximately 768,793 deaths per year, accounting for 7.7% of all cancer deaths and ranking gastric cancer third in cancer mortality worldwide.

Keywords: Perioperative chemotherapy; Gastric cancer; Stomach cancer; Mortality rate.

INTRODUCTION

Although the incidence of gastric cancer has been declining spontaneously and steadily for over 50 years, stomach cancer remains common. The World Health Organization's 2020 annual report indicates a global incidence of gastric cancer estimated at 1,089,103 new cases per year, representing 5.6% of all cancers, with a mortality rate of approximately 768,793 deaths per year, accounting for 7.7% of all cancer deaths and ranking gastric cancer third in cancer mortality worldwide [1]. In Algeria, it ranks fifth men with an incidence of 9.5 new cases per 100,000 inhabitants, and sixth among women with an incidence of 7.6 new cases per 100,000 inhabitants [2]. Surgery is the only curative treatment for resectable gastric cancers. However, surgery alone has shown its limitations in the management of gastric cancers, with an R0 resection rate of 60% [3,4], a 24-month postoperative recurrence rate of approximately 69% [3-5], in the form of local and locoregional recurrences in 87% of cases [6,7], and a median 5-year survival rate of 25% [4,8]. To improve surgical outcomes and the prognosis of this cancer, several therapeutic strategies and combinations exist worldwide. Adjuvant chemoradiotherapy is the standard treatment in the United States and Canada [9]. Perioperative chemotherapy is the standard in Europe. Adjuvant chemotherapy after D2 gastrectomy and lymphadenectomy in Asia; postoperative chemotherapy with S-1 (oral prodrug of 5FU) for 1 year in Japan, capecitabine and oxaliplatin for 6 months in Korea [10-14].

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In Algeria, there is no well-defined therapeutic strategy for the management of gastric adenocarcinomas. This motivated us to conduct this prospective, comparative, randomized study, which aimed to answer the following question: Is there a recurrence-free survival benefit for patients with resectable, non-metastatic gastric adenocarcinoma treated with radical surgery followed by perioperative CAPOX chemotherapy? We also aimed to evaluate patient adherence, tolerability, and the impact on postoperative morbidity and mortality, as well as the feasibility, safety, and reproducibility of this strategy regardless of patient-related parameters, tumor location, histological type, and stage; with the intention of establishing it as a national consensus recommendation.

MATERIALS AND METHODS

This is a prospective comparative randomized study, carried out in 10 medical oncology centers across the national territory in collaboration with the oncological surgery department "A" of the Pierre and Marie Curie Center of Algiers (CPMC).

Patients eligible for inclusion in this study had histologically confirmed gastric adenocarcinoma (regardless of Lauren type) and a clinical stage ≥ Ib (>T1N0) assessed by Thoracoabdominopelvic CT scan.

In the protocol, all perigastric lymph nodes visible on the CT scan were considered potential N+ nodes; there were no specific criteria for lymph node positivity. Other inclusion criteria were age between 18 and 80 years, a WHO performance status of 0 to 2, a normal complete blood count, normal liver, heart, and kidney function, and no uncontrolled concomitant medical conditions.

Diagnostic laparoscopy was not routinely recommended for all patients; it was performed only when peritoneal involvement was suspected. Endoscopic ultrasound was not considered an essential examination in our series. Patients were excluded if they had distant metastases (peritoneum, liver, lung, or other), infiltration of adjacent structures or organs that were not resectable, or if they had previously undergone chemotherapy or radiotherapy for another disease. Ineligible comorbidities included active coronary artery disease, congestive heart failure (stage 3 or 4 according to the New York Heart Association functional classification), cirrhosis, and renal insufficiency.

The study protocol was approved by our institution's ethics committee. Written informed consent was obtained from all patients prior to enrollment.

The management, coordination of this work and the collection of data was carried out through the weekly multidisciplinary consultation meeting on digestive oncology which meets regularly within our institution.

Patient monitoring and follow-up were carried out simultaneously by medical oncologists and surgeons in medical oncology and surgery consultations.

RANDOMIZATION

Randomization was performed using a balanced block randomization method with permutations of 4 to ensure an equal distribution of the required number of subjects in both arms. Four patients were randomly selected at a time. The randomization table is held by a third party who provides us with the randomization results as patients are deemed eligible.

The evaluated therapeutic protocol includes optimal curative surgery framed by perioperative chemotherapy, 3 courses of chemotherapy before and 3 courses after surgery, compared to the standard therapeutic protocol (carcinological gastric resection with a D2 type dissection).

The chemotherapy protocol was a combination of capecitabine and oxaliplatin (CAPOX or XELOX), one cycle every 3 weeks, 3 cycles before surgery with an interval of 4 to 6 weeks between the last chemotherapy cycle and surgery, 3 cycles post-operatively with an interval of 4 to 6 weeks between surgery and the first post-operative chemotherapy cycle.

Capecitabine: 1000 mg/m2 in two oral doses per day, morning and evening with a large glass of water, 30 minutes after breakfast and dinner continuously for 14 days followed by a 7-day break, treatment from day 1 to day 14, then stopped from day 15 to day 21.

Oxaliplatin: 130 mg/m2 of body surface area in an infusion of 500cc of 5% glucose serum, to be administered over 2 hours, once every 21 days.

Insertion of a central venous catheter is not essential. Hematopoietic growth factors have not been used for primary prophylaxis; their use, along with symptomatic treatments, is left to the discretion of the oncologist based on the patient's needs.

In the event of grade 3 toxicity related to capecitabine, its administration is suspended and treatment is not resumed until the toxicity is fully controlled. In the event of a second toxic event of grade ≥ 2, the initial dose of capecitabine is reduced by 25% in subsequent cycles. In the event of grade 3 toxicity related to oxaliplatin, the oxaliplatin dose is reduced to 100 mg/m^2 in the following cycle. In the event of grade 4 toxicity, treatment is discontinued. In the event of toxicity related to only one drug, a dose reduction of the second drug is not necessary. If the dose of one drug is reduced, the dose of the other drug is not increased.

The reasons for stopping treatment were toxicity, disease progression, or at the patient's request.

A post-chemotherapy reassessment was carried out two weeks after the last chemotherapy treatment by a somatic clinical examination to reassess the general and nutritional condition of the patients in order to prepare them for surgery in addition to a morphological reassessment by an injected thoraco-abdomino-pelvic scan.

Patients randomized to the surgery arm were scheduled and operated on within a period not exceeding 4 weeks from the day of randomization.

Patients randomized to the perioperative chemotherapy arm were scheduled and operated on within 4 to 6 weeks after the last course of chemotherapy.

Depending on the histological type and location of the tumor, a total or partial gastrectomy was performed with a D2 lymph node dissection without left splenopancreatectomy. This gastrectomy was extended to a neighbouring organ or structure only if a complete R0 oncological resection was possible. Restoration of bowel continuity after total gastrectomy was achieved via a side-to -end esophagojejunal anastomosis, either using a circular mechanical stapler (CDH 21/25mm) or manually with two running sutures of braided absorbable suture (000) over a Roux-en-Y loop passed transmesocolicly. After a 4/5 gastrectomy, restoration of bowel continuity was achieved by a gastrojejunal anastomosis using an omega- shaped loop in an end -to-side configuration. The gastric suture was performed on the lower portion of the gastric resection margin, and the upper portion was sutured in a racquet-tail fashion (Finsterer -type gastrojejunal anastomosis), with or without an anastomosis at the base of the loop. The loop was then presented in a transmesocolic fashion. Peritoneal drainage was not routinely performed.

The surgical specimens were oriented and sent unfixed immediately after resection to the pathology laboratory of the CPMC, accompanied by a comprehensive information sheet. The histopathological examination of the surgical specimen was performed according to a standardized form. The AJCC ypTNM classification, 8th edition 2017, and the Becker classification were used to classify patients and assess tumor response to chemotherapy.

Postoperative morbidity and mortality were graded according to the Clavien and Dindo classification; all adverse events were recorded, noted, monitored, and regularly reported to the RCP and the regional ethics committee.

The primary objective of this study was to improve 3-year recurrence-free survival by 15% in the perioperative chemotherapy arm. Secondary objectives included evaluating the feasibility of this protocol in terms of adherence, tolerability, and chemotherapy toxicity; the R0 resection rate in both arms; and 90-day postoperative morbidity and mortality according to the Clavien and Dindo classification . Overall survival at 3 and 5 years was also assessed.

Relapse-free survival was defined as the time from randomization to disease progression or death from any cause. Overall survival was defined as the time from randomization to death from any cause.

The sample size was calculated based on the two-sided log- rank test. This calculation was performed using the "Log- rank test" sub-module of the "Power and sample size" module of the Stata/SE statistical software version 11.2.

Our goal was to increase 3-year recurrence-free survival by 15% in the chemotherapy plus surgery group. This rate averages 19% in the surgery-only group, and we project an improvement of 34% in the perioperative chemotherapy group. Allowing for a 5% type I standard error (the risk of finding a false difference between the two arms) and using a trial power of 80% (the 20% risk of failing to find a difference that exists), the software estimates the number of patients in each arm at 50.

To compare the proportions between treatments, the chi-square and Fisher's exact tests (for expected frequencies less than 5) were used, and means were compared using Student 's t-test. Tumor sizes were compared using the Mann-Whitney U test. Survival curves were estimated using the Kaplan-Meier method and compared with the log- rank test.

For the multivariate analysis, a Cox regression model including the different covariates of interest (type of treatment allocated, age, sex, WHO status, histological type, tumor location, degree of parietal invasion "T", lymph node status "N", type of surgery, histological type, morbidity and

mortality, mode of recurrence, time to recurrence) were used.

For toxicity analysis, we used an answer sheet where all events were listed and graded for each patient and for all chemotherapy cycles.

The entire analysis was performed on an intention-to-treat basis, and all randomized patients were included. All study values were reported within a 95% confidence interval (with an accepted risk of error of 5%), and tests were performed using a two-sided approach.

The computer processing and analysis of the data were carried out using the software " Epi -info version 6.04 d" and SPSS version 14.

RESULTS

From June 2016 to June 2018, 198 gastric adenocarcinomas were treated. Twenty-eight patients underwent immediate surgery without preoperative chemotherapy due to the symptomatic nature of their tumors, including stenosis in 25 patients and hemorrhage in 3 patients. Twenty-four patients received neoadjuvant chemotherapy. Twenty- one patients received a perioperative chemotherapy protocol other than the study protocol (CAPOX). Consequently, 121 patients were included and randomized: 60 patients were included in the perioperative chemotherapy arm and 61 patients in the surgery-only arm (Figure 1).

Two patients were subsequently excluded from the surgery-only arm:

A patient operated on for a poorly differentiated fundic adenocarcinoma, the anatomopathological results of the surgical specimen were in favor of a gastric neuroendocrine carcinoma.

A patient operated on for a subcardial independent cell carcinoma whose intraoperative exploration revealed diffuse subcentimeter peritoneal carcinomatosis.

There were 113 R0 resections, the R0 curative oncological resectability rate was (93.38%), 98% R0 resection in the CPO arm versus 90.7% in the surgery arm (p: 0.089).

The median follow-up period was 51 months.

The perioperative chemotherapy regimen, as described in the protocol, was to consist of 6 cycles per patient, for a total of 360 cycles, divided into two phases: 180 preoperative cycles and 180 postoperative cycles. The total number of cycles completed by all patients was 349, representing 96.94% of the planned chemotherapy cycles. 180 chemotherapy cycles were administered preoperatively (100%), and 167 chemotherapy cycles were administered postoperatively, resulting in a postoperative chemotherapy adherence rate of 92.77%.

83.63% of patients received all 6 cycles as planned in the protocol. 81 toxicity events were reported out of 347 chemotherapy cycles, resulting in an overall toxicity rate of 23.34%. These were primarily grade 2 toxicities, accounting for 53 events (65.43% of all overall toxicity). Grade 3 toxicity occurred 13 times during preoperative chemotherapy, and 14 grade 3 events, mainly gastrointestinal (diarrhea), occurred during postoperative chemotherapy.

Two patients required hospitalization for toxicity (3.33%).

Chemotherapy was discontinued due to toxicity in two patients (3.33%), one for preoperative grade 3 gastrointestinal toxicity and the other for postoperative mucosal toxicity (grade 3 mucositis with very painful ulcerations and difficulty eating). There were no deaths due to chemotherapy toxicity (Tables 1 and 2).

SURGERY

Of the 121 randomized and operated patients, only one patient in the surgery-only arm was not resected (diffuse peritoneal carcinomatosis), giving us a macroscopic oncological resection rate of 99.09%.

A D2 lymph node dissection was performed in all resected patients.

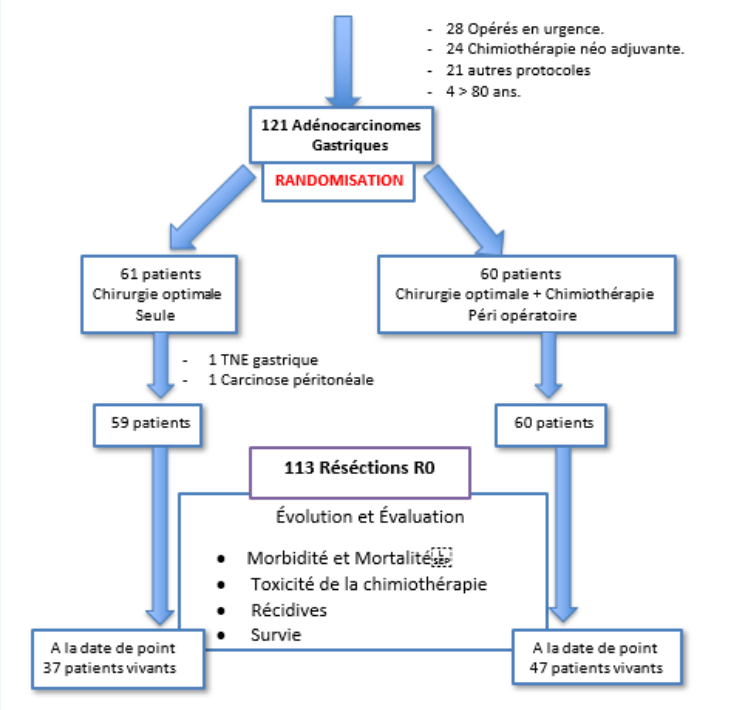

Figure 1 Summary of patients, randomization, and progress

Table 1: Distribution of Chemotherapy Toxicities

Toxicity	Number of events	Percentage %
General (asthenia)	16	5.01
Hematological (neutropenia + thrombocytopenia)	11	3.44
Nausea and vomiting	13	4.07
Diarrhea	7	2.19
Abdominal pain	16	5.01
Hand-foot syndrome	3	0.94
Mucositis	1	0.31
Neurological (neuropathy) Peripheral)	13	4.07
SAE (renal insufficiency)	1	0.31
Mortality	0	--
Total toxicity	**81**	**25.39**
Total cycles	347	100

Table 2: Grade and toxicity of chemotherapy

Toxicity	Grade 2	Grade 3	Grade 4
Asthenia	10	6	0
Neutropenia	5	2	0
Thrombocytopenia	4	0	0
Nausea and vomiting	8	5	0
Diarrhea	6	1	0
Abdominal pain	9	7	0
Peripheral neuropathy	9	4	0
Hand-foot syndrome	2	1	0
Mucositis	0	1	0

Table 3: Intraoperative and postoperative parameters of patients

	Perioperative chemotherapy	Surgery alone	P
GT	45	42	0.347
G4/5	15	18	0.286
G Enlarged	7	8	0.971
Non-resectable	0	1	--
Operating time	238 min	232.09 min	0.530
Bleeding during surgery	150.18 cc	151.45 cc	0.909
Transfusion during surgery	6	3	0.284
Hospital stay	7.14 days	7.78 days	0.427
Post-operative mortality at 30 days	0	2	--
Post-operative morbidity at 90 days	13	15	0.761

Total gastrectomy was the most frequently performed surgical procedure in our series (76.36%), while partial gastrectomy was performed in 26.36% of patients. In 15 patients, it was necessary to extend or combine the gastrectomy with an additional procedure due to oncological requirements (R0 oncological resection) (Table 3).

The mean operative time was 235 minutes, ranging from 120 to 390 minutes: 238 minutes in the CPO arm versus 232.09 minutes in the Surgery arm (P = 0.530). Blood loss was measured by the total volume of surgical aspiration at the end of the procedure minus the volume of saline used intraoperatively. Mean blood loss was 150 cc, ranging from 50 to 400 cc: 150.18 cc in the CPO arm versus 151.45 cc in the Surgery arm (P = 0.909). Nine patients received an intraoperative blood transfusion (8.18%), with an average of two units of packed red blood cells per transfusion: 6 patients in the CPO arm and 3 patients in the Surgery arm. The average postoperative length of stay was 7.53 days, ranging from 4 to 37 days (7.24 days in the CPO arm versus 7.78 days in the surgery arm, P = 0.427). Postoperative morbidity and mortality were calculated for the randomized and included patients over the 90-day postoperative period. Two deaths were recorded on days 37 and 68 postoperatively in the surgery-only arm, while no deaths were observed in the CPO arm, resulting in a 90-day postoperative mortality rate of 1.80%.

We observed 28 complications (23.14%) in 17 patients. Thirteen complications occurred in 9 patients in the perioperative chemotherapy arm and 15 complications in 8 patients in the surgery-only arm (P = 0.761). These were minor complications, grade I and II according to Clavien and Dindo, in 64.28% of cases, and major complications in 35.71% of patients, distributed equally between the two arms (Table 4).

The mean tumor size was 3.36 cm in the CPO arm versus 4.62 cm in the surgery arm (P = 0.019).

The total number of lymph nodes examined in our series was 2866. The mean number of lymph nodes examined per dissection was 25.90, with a range of 9 to 68. An average of 26.44 lymph nodes were found in the surgery arm versus 25.42 in the CPO arm (p = 0.640). The mean number of involved lymph nodes was 4.12 per dissection, with a range of 0 to 51. There were more metastatic lymph nodes in the surgery arm than in the CPO arm (5.59 versus 2.75, p = 0.048).

Eleven patients in the CPO arm had a Becker grade Ia complete pathological response (18.33%), 6 patients with a Becker grade Ib major guard response (%?).

Forty-two percent of patients were classified (T0, T1, T2) in the CPO arm versus 19% in the surgery-only arm (p = 0.009). Fifty-four percent of patients were classified as T3 in the CPO arm versus 70% in the surgery-only arm. Fifty-four percent of patients were classified as N0 in the CPO arm versus 33% in the surgery-only arm (Table 5 and Table 6).

The median follow-up time was 48 months in the surgery-only arm versus 53 months in the CPO arm; during this surveillance period, 35 recurrences were noted in 31 patients, resulting in a 36-month recurrence rate of 30.17%.

Thirteen recurrences in 11 patients in the CPO arm versus 22 recurrences in 20 patients in the surgery alone arm (P = 0.026).

The median overall survival (OS) for the entire series was 43.52 months, with a median of 52 months. In the surgery-only arm, it was 40.210 months versus 46.345 months in the CPO arm (p = 0.117). The 5-year OS was 67% in the CPO arm versus 48.3% in the surgery-only arm. The median recurrence-free survival (RFS) for the entire series was 40.24 months, and the median recurrence-free survival (RFS) was 35.88 months in the surgery-only arm versus 41.04 months in the CPO arm (p = 0.046). At 3 years, the RFS was 49% in the surgery-only arm versus 69.9% in the CPO arm.

At 5 years, the SSR was respectively 34% versus 66%.

DISCUSSION

In this prospective, randomized, comparative study, the two arms were homogeneous and comparable for all pre-treatment and post-operative clinical, pathological, and anatomopathological parameters. There were no statistically significant differences between the two groups. Perioperative CAPOX-based chemotherapy (3x3) in resectable, non-metastatic gastric adenocarcinoma improved 3- year and 5-year recurrence-free survival by 20%.

The first study to demonstrate the benefit of perioperative chemotherapy compared to surgery alone in terms of recurrence-free survival and overall survival in resectable, non-metastatic gastric adenocarcinomas was the MAGIC trial [14]. Two thousand five hundred and three patients with clinical stage II or III gastric adenocarcinoma (75%), gastroesophageal junction adenocarcinoma (12%), or lower esophageal adenocarcinoma (15%) were treated with three cycles of epirubicin, cisplatin, and 5-FU (ECF) before and after surgery versus surgery alone. The authors showed a significant improvement in 5-year overall survival compared to surgery alone (36% vs. 23%; p = 0.009). The second pivotal study, the French phase 3 FNCLCC/FFCD trial, included 3,224 patients with adenocarcinoma of the gastroesophageal junction (64%), esophagus (11%), or stomach (24%). Patients received two to three cycles of cisplatin and 5-FU before and after surgery. Patients in the chemotherapy group had significantly improved 5-year overall survival compared to surgery alone (38% vs. 24%; p=0.02) [16].

Overall adherence to the postoperative chemotherapy regimen was 96.94%. All 180 cycles of preoperative chemotherapy were completed, resulting in a 100% adherence rate. Of the 180 postoperative chemotherapy cycles, 167 were completed, with an adherence rate of 92.77%. Compared to the two seminal studies in this area, Cunningham's Magic trial [15], and Marc Ychou 's FFCD study [15], adherence to preoperative chemotherapy was 90.7% and 87%, respectively, and adherence to postoperative chemotherapy was 50% and 54.8%, respectively. Of the 50% of patients who received postoperative chemotherapy, only 23% completed their protocol [15].

In the Magic trial, 41.6% of patients completed their perioperative chemotherapy cycles, whereas in our series, 84% of patients received all perioperative chemotherapy cycles [15].

In the trial published in The Lancet in April 2019 by Al Batran (perioperative chemotherapy ECF versus FLOT), adherence to preoperative chemotherapy was 91% in the ECF arm versus 90% in the FLOT arm. Adherence to postoperative chemotherapy was 52% in the ECF arm versus 60% in the FLOT arm, and 37% of patients completed their chemotherapy regimen in the ECF arm versus 46% in the FLOT arm. In this paper, 21% of patients discontinued chemotherapy in the ECF arm versus 13% in the FLOT arm, either due to disease progression, death, or at the patient's request following toxicity. In our study, 6 patients (10.9%) discontinued postoperative chemotherapy: one patient after one cycle and 5 patients after two cycles. In one patient, chemotherapy was discontinued due to toxicity, and in the other patients, at their request [17].

Compared to Asian adjuvant chemotherapy protocols, adherence to postoperative chemotherapy was 66% in the Japanese ACTS-GC trial and 67% in the Korean CLASSIC study [18,19]. Good adherence to pre- and postoperative chemotherapy was observed in our series.

During the 319 chemotherapy cycles administered, 81 toxic events occurred, representing an overall toxicity rate of 23.34%. Fifty-three toxic events were grade 2 (65.43%), and 28 were grade 3 (8.5%). Thirty-nine toxic events occurred in 27 patients during preoperative chemotherapy, and 41 toxic events occurred in 28 patients during postoperative

Table 4: Summary of postoperative morbidity of patients in both arms According to the Clavien and Dindo classification.

Grade of complications	Kind	Perioperative chemotherapy	Surgery alone	Total N	%
	Antibiotic therapy	4	6	10	
Minor Complications					**18**
(Grade II)	**Blood transfusion**	4	2	6	**(64.28%)**
	Pneumonia	0	1	1	
	Urinary tract infection	0	1	1	
Major Complications	**Intra-abdominal collection**	3	3	6	
(Grade IIIb ,					**10**
	Anastomotic fistula	1	0	1	
Grade IVa)	**Acute intestinal obstruction**	1	0	1	**(35.71%)**
	Hemoperitoneum	0	2	2	

Table 5: General parameters per arm of the series.

Settings	Perioperative chemotherapy	Surgery alone	P
Average age	57 years old	60 years old	0.213
<45 years old	12	9	
45-60 years old	22	20	
61-70 years old	15	17	
>70 years old	11	15	
Sex F/M	31/29	28/33	0.637
BMI	24.73	23.78	0.272
Weight loss > 10%	7	4	0.105
ASA I/II/III	40/20/0	37/24/0	0.271
WHO 0	60	61	
Grouping A rh +	26	20	0.216
Location :			
Subcardiac	3	5	0.527
Fundique	11	9	0.773
Anthro -fundic	14	11	0.223
Angulus	5	6	0.974
Lair	27	30	0.390
Diffuse/intestinal type	26/34	29/32	0.647
cT1	--	--	
cT2	13	14	0.828
c T3	45	46	0.826
cT4	2	1	0.828
cN0	11	13	0.345
cN +	49	48	0.344

Table 6: Anatomopathological parameters

	Perioperative chemotherapy	Surgery alone	P
Tumor size	3.36 cm	4.62 cm	0.019
pT0	11	0	0.009
pT1	6	3	
pT2	10	8	0.293
pT3	31	41	
pT4	2	7	
pN0	30	18	0.151
pN1	9	10	
pN2	8	11	0.299
pN3	8	14	
M0	55	52	
M1	0	2	
Ratio N+/N	0.106	0.194	0.038
R0	59	54	0.089
R1	1	3	
EPN	8	11	0.423
EV	10	6	0.297
Peritoneal cytology	0	2	0.150

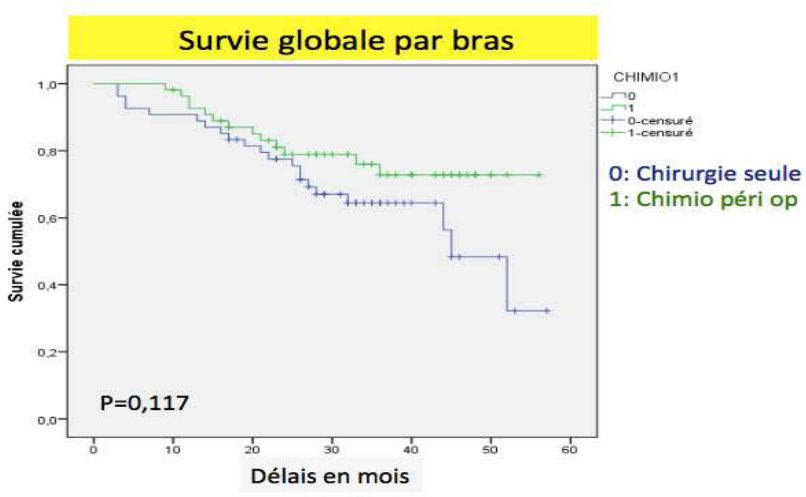

Figure 2 Overall survival curve

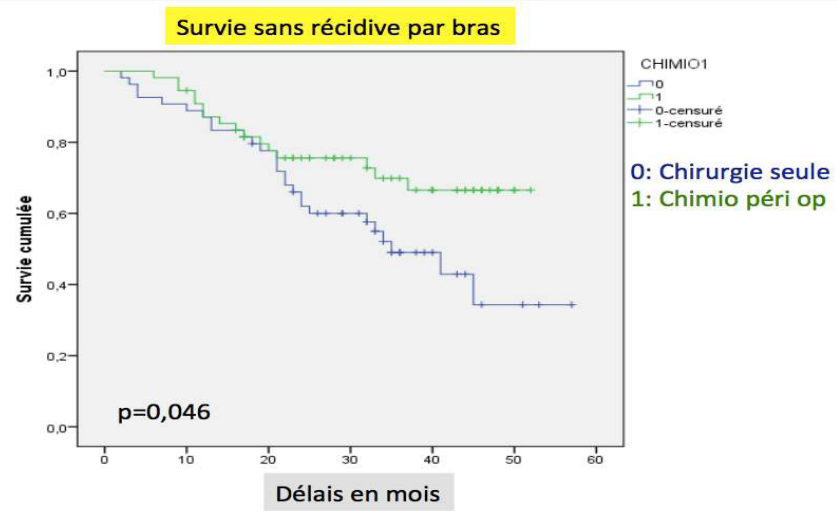

Figure 3 Relapse-free survival curve.

chemotherapy. Thirteen grade 3 toxic events occurred during preoperative chemotherapy, and 14 grade 3 toxic events occurred during postoperative chemotherapy. In our series, there was no difference in toxicity between preoperative and postoperative chemotherapy.

Grade 3 toxicity consisted primarily of asthenia (1.89%), neutropenia (0.63%), gastrointestinal toxicity (1.89%), abdominal pain (2.21%), hand-foot syndrome (0.63%), and peripheral neurological toxicity (1.26%). We observed only one grade 4 toxicity in our series, characterized by the development of functional renal failure in a patient following gastrointestinal toxicity consisting of vomiting and diarrhea, which required hospitalization for rehydration, symptomatic treatment, and discontinuation of chemotherapy.

Compared to data from the literature, in the FFCD trial, overall toxicity was 38% grade 3 and 4, with 20.2% neutropenia, 9.2% nausea and vomiting, and 5.5% thrombocytopenia [16]. In the Magic trial, overall grade 3 and 4 toxicity was not specified. However, during the preoperative chemotherapy cycles, the following were observed: 11.5% leukopenia, 4.7% anemia, 12% nausea and vomiting, 4.3% stomatitis, 2.6% diarrhea and 3.8% grade 3 and 4 neurotoxicity; and during the postoperative chemotherapy, the following were observed: 11.1 % leukopenia, 0.7% anemia, 22.4% nausea and vomiting, 3.6% stomatitis and diarrhea, 3.6% grade 3 and 4 neurotoxicity [15].

In the series published by Al Batran in 2019 [16], grade 3 and 4 toxicity in the FLOT arm was represented as follows: nausea in 27% of patients, vomiting in 2%, thrombocytopenia, anemia and febrile neutropenia in 6%, 20%, 2% of patients respectively in the FLOT.

In our series, chemotherapy was stopped due to toxicity in two patients (3.33%), whereas in Al Batran 's series, chemotherapy was stopped due to toxicity in 13% of patients in the ECF arm versus 10% in the FLOT arm.

In our series, two patients (3.33%) were hospitalized for chemotherapy toxicity: one patient during preoperative chemotherapy and one patient during postoperative chemotherapy. Compared to data from the literature, the hospitalization rate for chemotherapy toxicity was 26% in the ECF arm versus 25% in the FLOT arm in Al Batran's study.

There were no deaths from chemotherapy toxicity in our series, the same finding in the Magic trial, whereas in the FFCD trial one death from cardiac toxicity was reported, 4 deaths from toxicity in Al Batran, 2 deaths in the ECF arm versus 2 deaths in the FLOT arm [15-17].

In our series, 11 chemotherapy cycles were delayed by one week and 7 cycles (2.21%) by two weeks for various reasons: patient fatigue, abnormal blood test results, technical platform issues, and scheduling errors. For the same medical reasons, Al Batran reported in his series a delay of chemotherapy cycles exceeding 7 days in 2% of patients in the ECF arm versus 3% in the FLOT arm.

At the end of this comparative analysis of the tolerance, compliance and toxicity of the perioperative chemotherapy protocol of our series compared to data from the literature, our chemotherapy protocol was well observed and tolerated by our patients with less morbidity and toxicity than reported in the literature.

In our series, the 90-day mortality rate was 1.68 %. In the Albatran FLOT 4 study, the 90-day postoperative mortality rate was 8% in the ECF arm versus 5% in the FLOT arm. In the Magic trial, mortality was reported over 30 days postoperatively and was 5.6% in the perioperative chemotherapy arm versus 5.9% in the surgery-alone arm. In the FFCD trial, postoperative mortality was reported over 30 days postoperatively and was 4.5% in the perioperative chemotherapy arm versus 4.6% in the surgery-alone arm [15-17].

The mean tumor size was 3.36 cm in the perioperative chemotherapy arm versus 4.62 cm in the surgery- only arm (p = 0.019). The same finding was reported in the Magic trial, with a mean tumor size of 3 cm in the perioperative chemotherapy arm versus 5 cm in the surgery-only arm. Our results are consistent with the literature, concluding that perioperative chemotherapy induces tumor downsizing. Resection was deemed R0 in 103 patients (96%) after macroscopic and microscopic analysis by the pathologist of the proximal, distal, and circumferential resection margins. In the perioperative chemotherapy arm, 54 patients (98%) underwent R0 resection versus 49 patients (92.45%) in the surgery-only arm (p = 0.089).

Three patients (5.17%) in the surgery-only arm had circumferential margins less than 1 mm, versus one patient (1.66%) in the perioperative chemotherapy arm who had a circumferential margin less than 1 mm, classifying the resection as R1. Proximal and distal resection margins were negative in all patients and in both groups. In the literature, perioperative chemotherapy, regardless of the treatment protocol, has improved the R0 resection rate. In the FFCD study, the R0 resection rate increased from 74% in the surgery-only arm to 84% in the perioperative chemotherapy arm, with 4% R1 resections in the perioperative chemotherapy arm versus 5% in the surgery-only arm. In the Magic trial, this R0 resection rate was estimated at 69.4% in the perioperative chemotherapy arm versus 66.4% in the surgery-only arm. In the FLOT 4 study, R0 resection was 78% in the ECF arm versus 85% in the FLOT arm (p = 0.0162). In the pathology results, 11 patients in the perioperative chemotherapy arm were classified as ypT0 (18.33%), and 8 patients were classified as ypT1, 5 in the perioperative chemotherapy arm versus 3 patients in the surgery-only arm.

A major histological response (pT0/pT1) was found in 15 patients, or 25% in the perioperative chemotherapy arm versus 5.76% in the surgery-only arm (p = 0.009). Fifteen percent of patients in the perioperative chemotherapy arm were classified as pT2 versus 13.46% in the surgery-only arm (p = 0.293). 54.54% of patients were classified as ypT3 in the perioperative chemotherapy arm versus 71.15% were classified as pT3 in the surgery-only arm (p = 0.293). Whereas pre-treatment, 75% of patients were classified as cT3, in an identical and homogeneous manner in both arms. There were more patients classified as pT4 in the surgery-only arm than in the perioperative chemotherapy arm (13.46% versus 3.63%, p = 0.293). Through the analysis of these (Figures 2 and 3), we observe that there is a shift in ypT stages due to the tumor downstaging effect caused by perioperative chemotherapy, whereas in the surgery-only arm there is no difference between cT and pT stages.

Compared to the histological results reported in the FLOT4 study, ypT0 was found in 6% of patients in the ECF arm versus 16% in the FLOT arm (p = 0.02), ypT1 was found in 6% of patients in the perioperative chemotherapy arm versus 17% in the FLOT arm (p = 0.01), and the major histological response rate was 9% in the ECF arm versus 33% in the FLOT arm. In contrast, in the FFCD trial, ypT0 was found in 3% of patients in the perioperative chemotherapy arm.

Recurrence-free survival in the entire series was 40.24 months, in the surgery-alone arm it was 35.88 months, while in the perioperative chemotherapy arm it was 41.04 months, a statistically significant difference (p=0.046). Chemotherapy improved three-year recurrence-free survival from 49% in surgery-alone to 69.9% in the perioperative chemotherapy arm, regardless of tumor location, histological type, or stage.

Overall survival in the entire series was 43.52 months, while in the surgery-only arm it was 40.21 months versus 46.34 months in the perioperative chemotherapy arm.

At 3 years, overall survival was 68.2% in the entire series, 72.8% in the perioperative chemotherapy arm versus 64.4% in the surgery-only

arm. Compared to data in the literature, our results support and reinforce those reported in the MAGIC trial and the ACCORD 07 trial by the FFCD. In the MAGIC trial, overall survival was 36% in the chemotherapy arm versus 23% in the surgery-only arm. In the ACCORD 07 trial, overall survival was 38% in the perioperative chemotherapy arm versus 24% in the control arm. Three-year recurrence-free survival in the MAGIC trial was not specified. However, in the ACCORD 07 trial by the FFCD, it was 34% in the perioperative chemotherapy arm versus 19% in the surgery-only arm. In FLOT4, the 3-year overall survival was 57% in the FLOT arm with a median of 50 months versus 48% with a median of 35 months in the ECF arm, and a median recurrence-free survival of 18 months in the ECF arm versus 30 months in the FLOT arm [15-17].

Compared to the data reported by the Japanese and Koreans, which focus exclusively on adjuvant chemotherapy after oncological resection for gastric adenocarcinoma, the two seminal studies are the ACTS-GC trial published by Sakuramoto in 2007 [18], and subsequently updated by Sasako in 2011 [20]. This phase III trial compared patient survival after R0 resection for gastric adenocarcinoma. Patients were randomized into two groups: observation alone versus adjuvant chemotherapy based on S-1 (an oral fluoropyrimidine prodrug). The 3-year overall survival rate was 80.1% in the adjuvant chemotherapy arm versus 70.1% in the observation arm. Three-year recurrence-free survival increased from 59.6% in the surveillance arm to 72.2% in the adjuvant chemotherapy arm ($p = 0.003$, HR for death = 0.68, 95% CI = 0.52–0.87). The second study is the Korean CLASSIC trial published in 2012 by Bang [18]. This prospective phase III trial compared patient survival after R0 resection and D2 lymph node dissection for gastric adenocarcinoma. Patients were randomized to two arms: surveillance versus adjuvant chemotherapy with XELOX for 6 months, with a median follow-up of 34 months. Three-year recurrence-free survival was 74% in the adjuvant chemotherapy arm versus 59% in the surgery-only arm (HR = 0.56, 95% CI: 0.44–0.72, $p < 0.0001$). The 5-year recurrence-free survival confirmed previous results: 68% versus 53%, HR = 0.58, 95% CI: 0.47-0.72, $p < 0.0001$. The 3-year overall survival was 83% in the adjuvant chemotherapy arm versus 78% in the surgery-alone arm with an HR for death: 0.72 (0.52-1.00), $p < 0.0001$ [18-20].

In our work, patient quality of life was a central priority. While we did not use a specific questionnaire to measure it in this series, we relied on a general assessment using questions during consultations related to physical activity, the patients' social, family, and professional lives, the presence of pain, discomfort, or specific limitations, and their nutritional and psychological status. In our series, all patients resumed a normal diet (solid food) two months after surgery, experienced an improvement in their weight status, and reintegrated into their family and social environments. Three patients remain in chronic convalescence after two years of follow-up. The other active patients, without disease recurrence, all returned to work starting six months post-surgery. One patient resumed her postgraduate studies four months post-surgery. Two patients experienced depression, requiring psychiatric treatment and follow-up; two patients are being treated at the Pierre and Marie Curie Center's pain clinic for chronic pain. The symptoms of fatigue and asthenia disappeared after three months post-surgery. There was no difference in quality of life between the two groups of patients.

CONCLUSION

Through the results of this work, perioperative chemotherapy has allowed us to significantly improve the 3-year recurrence-free survival of patients, with good compliance and tolerance and without impact on either short-term postoperative results or on the quality of life of patients with very encouraging and satisfactory oncological results pending more follow-up and a larger sample size.

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