The Impact of Perioperative Chemotherapy on Survival in Patients With Gastric Signet Ring Cell Adenocarcinoma

A Multicenter Comparative Study

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Objective: The aim of this retrospective study was to evaluate the survival impact of perioperative chemotherapy (PCT) in patients with gastric signet ring cell (SRC) adenocarcinoma.

Background: PCT is a standard treatment for advanced resectable gastric adenocarcinoma (GA). SRC has a worse prognosis compared to non-SRC and the chemosensitivity of SRC is uncertain.

Methods: Among 3010 patients registered in 19 French centers between January 1997 and January 2010, 1050 (34.9%) were diagnosed with SRC. Of those treated with curative intent (n = 924), 171 (18.5%) received PCT with surgery (PCT group), whereas 753 (81.5%) were treated with primary surgery (S group). PCT was based mainly on a fluorouracil-platinum doublet or triplet regimen.

Results: The groups were comparable regarding age, gender, American Society of Anesthesiologists (ASA) score, malnutrition, tumor location and cTNM stage. 60 patients did not undergo resection because of tumor progression (10) or metastases (50) found at operation. The R0 resection rates were 65.9% and 62.3% in the S and PCT groups, respectively ($P = 0.308$). Fewer patients received adjuvant chemotherapy in the S group than in the PCT group (35.2% vs. 66.5%, $P < 0.001$). At a median follow-up of 31.5 months, the median survival was shorter in the PCT group (12.8 vs. 14.0 months, $P = 0.043$). On multivariate analysis, PCT was found to be an independent predictor of poor survival (HR = 1.4, 95% CI 1.1–1.9, $P = 0.042$).

Conclusions: PCT provides no survival benefit in patients with gastric SRC. Clinical Trial.gov record: ADCI001, Clinical Trial.gov identifier NCT01249859.

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Despite a decreasing overall incidence, gastric adenocarcinoma (GA) remains the fifth most frequently diagnosed cancer and the second most common cause of cancer-related death worldwide.[1,2]

Among all GA histological entities, there has been a striking increase in the incidence of diffuse GA, specifically the signet ring cell (SRC) subtype, which has increased by more than 400% in the United States since the 1970s and composes 32% to 70% of GA cases in recent Western studies.[3–5] We previously reported that the prognosis is worse in patients with SRC compared to non-SRC gastric cancers, with a median survival of 21 vs. 44 months, respectively ($P = 0.004$).[3] This poorer prognosis is due to (i) a higher prevalence of peritoneal carcinomatosis and lymph node invasion at initial diagnosis, (ii) a lower R0 resection rate due to the infiltrating character that leads to more positive vertical margins despite more extensive surgery, and (iii) an earlier relapse primarily due to peritoneal carcinomatosis in patients with SRC.[3] Because of this poorer prognosis, neo- and/or adjuvant treatments are of special interest in an effort to decrease recurrence and enhance survival.

Different therapeutic strategies have been demonstrated to enhance survival in GA patients in different parts of the world. This has led to different guidelines for each continent, such as perioperative chemotherapy (PCT) in Europe, adjuvant chemoradiotherapy in the United States and adjuvant chemotherapy in Asia.[6,7] To date, no trials have been dedicated to the study of SRC, and no stratification according to the SRC subtype has been performed. However, several retrospective studies have suggested that there is a poor response to chemotherapy in patients with SRC. In a phase II study, Rougier *et al*. studied the impact of neoadjuvant chemotherapy with 5-fluorouracil and cisplatin in 30 patients with locally advanced GA;[8] the tumor response rate was 56% in the overall population compared to only 16% in patients with diffuse GA (linitis plastica). The lower response rate was associated with significantly worse survival ($P = 0.002$).[8] Using the same chemotherapy regimen as used by Rougier et al,[8] Takiuchi *et al.* showed that the response rate was significantly lower in patients with the diffuse GA subtype compared to the intestinal type (22.2% vs. 83.3%).[9]

The SRC type of GA has several characteristics that make it significantly different from the non-SRC type of GA. SRC GA can affect relatively younger patients,[10] it typically presents with a more advanced tumor stage at initial diagnosis, and there is a worse prognosis when compared to non-SRC GA.[3,11,12] These facts, in combination with the absence of data regarding chemosensitivity in the SRC population, illustrate the importance of addressing the question of chemosensitivity in this subpopulation of patients with GA. Therefore, the aim of this study was to test the survival impact of PCT in patients with gastric SRC in a large multicenter comparative cohort.

PATIENTS AND METHODS

Patients

This retrospective national survey was conducted at 19 French surgical centers that registered all the consecutive GA cases between January 1997 and January 2010. The patient lists were verified through double checking performed by independent observers (MM, AP, and FV). All investigators completed a standardized questionnaire for each patient concerning the clinical, morphological, biological, surgical, pathological, and outcomes parameters including whether the patient was operated on or not. The clinical, surgical, pathological

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and outcomes parameters were double-checked by independent observers (MM, AP, and FV) and all data were entered into a dedicated database.

Among the 3010 patients with GA, 1050 (34.9%) were diagnosed with SRC with analyzable data. Of these, 126 received only palliative chemotherapy because of clinical or morphological metastases at diagnosis. The remaining study population (n = 924) was considered for curative treatment and therefore was included in the intent-to-treat analysis (Fig. 1). Those patients who underwent primary surgery (S group, n = 753, 81.5%) were compared to those who received PCT (PCT group, n = 171, 18.5%).

Pretreatment Work-Up

Pretreatment investigations included a physical examination, standard laboratory tests, an esophagogastroduodenal barium study, a digestive endoscopy with biopsies and a computed tomography (CT) of the thorax, mediastinum and abdomen. Endoscopic ultrasound (EUS) was not routinely performed because of the grade C recommendation in the French guidelines for GA.[13]

Clinical tumor staging (cTNM) was assessed before treatment and was based on the CT and EUS results or on the CT results alone in the absence of EUS results. The following tumor staging guidelines were used:

- On the basis of the CT scan, the T1-T2 stages were defined by a parietal thickness >1 cm or >50% of the opposite nontumor wall. T3 was defined by the involvement of the serosa. T4 was defined by adjacent organ involvement.[14]
- On the basis of the EUS results, T1 was defined by the invasion of the lamina propria. T2 was defined by the invasion of the muscularis propria. T3 was defined by serosa involvement. T4 was defined by adjacent organ involvement.[15]

The lymph nodes were considered to be involved when (i) the maximum diameter was ≥10 mm on the CT or when (ii) the following features were observed on the EUS: a size of 1 cm or more, a rounded shape, well-demarcated borders, and homogeneous and hypoechoic patterns.

Perioperative Treatment

Starting in 2005 when the results of the MAGIC study were presented,[6] PCT based on epirubicin-cisplatinum-5-fluorouracil (ECF) was recommended for GA for stages IB and above by the French guidelines.[13] The following year, the CF regimen was proposed as an alternative to the ECF regimen following the presentation of the FNCLCC94012-FFCD9703 trial results.[16] Despite this recommendation, some French centers did not offer neoadjuvant chemotherapy for SRC after multidisciplinary discussion due to suspected chemoresistance and they preferred adjuvant treatment. However, other French centers strictly followed the recommendations due to the absence of large studies testing the chemosensitivity and the lack of specific recommendations on gastric SRC management. For patients who underwent primary surgery, the adjuvant chemotherapy decision was made at the discretion of the multidisciplinary staff clinicians. Therapeutic strategies did not differ from 1 patient to another within each center. Before 2005 and the results of the MAGIC's

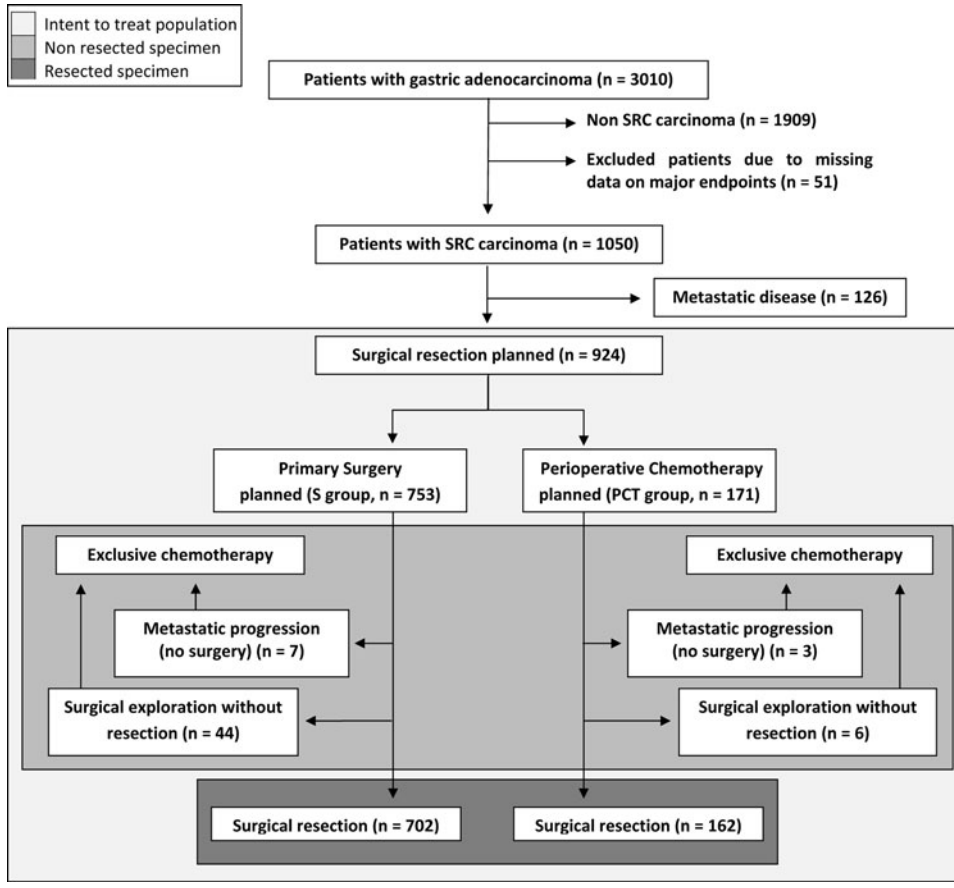

FIGURE 1. Flow chart of the study.

study,[6] the vast majority of patients did not receive any neoadjuvant treatment, regardless of the histological GA subtype.

Neoadjuvant chemotherapy was usually initiated between 4 and 6 weeks after the first oncological consultation, and the treatment typically lasted for 2 to 4 cycles. Adjuvant chemotherapy was usually commenced 4 to 8 weeks after surgery and also usually lasted for 2 to 4 cycles. Grade III or IV treatment toxicities were reported according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale (version 2.0).

Surgical Approach

Surgery was usually performed 4 to 8 weeks after the end of the neoadjuvant treatment. In the case of primary surgery, resection was performed 2 to 4 weeks after the first oncological consultation. Before resection, complete examination of the peritoneal cavity, lymph nodes, adjacent organs, and liver was performed. Patients with localized adjacent peritoneal carcinomatosis underwent resection in a curative attempt.[17] Distant metastases (lymphatic, peritoneal carcinomatosis/tumor ascitis, or hematogenous) were generally considered a contraindication for surgery except in the case of major symptoms, such as gastric outlet obstruction, bleeding, or perforation.

For antropyloric SRC, a subtotal gastrectomy was most often performed, provided that a distance of at least 5 cm between the proximal resection margin and the neoplasm could be maintained. For other gastric tumor locations, a total gastrectomy was usually performed. For reconstruction, the Billroth II (after subtotal gastrectomy) or Roux-en-Y (after total gastrectomy) techniques were used. For patients undergoing resection with a curative intent, an extended lymphadenectomy with preservation of the spleen and pancreatic tail was attempted. Distal pancreatectomy and splenectomy were only performed in cases of contiguous organ invasion or the macroscopic involvement of the splenic artery lymph nodes. D0 lymphadenectomy was defined as a total number of resected lymph nodes <15, D1 lymphadenectomy as between 15 and 25 resected lymph nodes, and D2 lymphadenectomy as ≥ 25 resected lymph nodes.[18]

Resection of the neighboring organs was performed in cases of suspected or confirmed neoplastic involvement. An enlarged resection was defined as gastric resection including the removal of the esophagus, spleen, colon, pancreas, or liver.

For SRC invasion of the esophagogastric junction, resection was extended to the esophagus to achieve R0 resection using either a transthoracic or transhiatal approach with dedicated mediastinal lymphadenectomy.[19]

Histopathologic Analysis

Tumors were classified as SRC according to the World Health Organization classification method[20] and as previously reported.[3] Unless otherwise stated, the tumors were classified as SRC after discussion with the pathologist in cases of the diffuse type (Lauren classification) or in cases of tumors with isolated, independent, or anaplastic cells.[20,21] Pathological staging was based on the sixth UICC/TNM classification.[22] Resections were designated as R0 when the clearance was complete after both macroscopic and microscopic examination, as R1 when the clearance was microscopically incomplete with histological evidence of invasion of the longitudinal or lateral margins, and as R2 when the clearance was grossly incomplete with macroscopic residual tumor. All patients at pTNM stage IV were considered as R2 resections.

Postoperative Course

The postoperative mortality and morbidity rates at 30 days were specified, as well as the in-hospital (60 days) mortality and morbidity rates. All patients with events by these time points were included in the analysis. Postoperative complications were assessed using the Dindo-Clavien classification.[23]

Follow-Up

All patients who survived the operation were followed until death or until the time of manuscript preparation. During follow-up, patients underwent clinical examination, abdominal ultrasonography or CT, and chest radiography approximately every 6 months for 5 years and annually thereafter. In cases of suspected recurrence, a thoraco-abdominal CT scan and upper gastrointestinal endoscopy were performed. Histologic, cytologic, or unequivocal radiologic proof was required before a diagnosis of recurrence was made. In the R0 population, the first site of recurrence was used to define whether locoregional or distal relapse had occurred. Locoregional relapse included cancer recurrence within the regional resection area, local anastomotic sites, or peritoneal recurrence. A peritoneal recurrence was any recurrence within the abdominal cavity resulting in intraperitoneal implantation. Distant recurrence included liver metastasis, metastasis at other extra-abdominal sites, and nodal metastasis beyond the regional nodes. Mixed recurrences included concomitant locoregional and distant relapses. To analyze the recurrence as a binary variable, a fixed time point of 36 months was used. Event-free patients who did not reach that cut-off were excluded from the analysis. Only patients who had the event by that time or those who had not had the event but had at least 36 months of follow-up (censored) were included. The survival status of the patients was determined in March 2010, and the median follow-up was 31.5 (range, 0.6–106.9) months. Eighty-one patients (7.7%) were lost at follow-up.

Variables Studied

Data were collected retrospectively and maintained in a database. Patients with gastric SRC were identified, and the intent-to-treat analysis was performed. This analysis included all patients that were deemed to have resectable tumors after the preoperative work-up. The pretherapeutic demographic and perioperative parameters (Table 1), postoperative mortality and morbidity rates (Table 2), histomorphological tumor characteristics (Table 3), recurrent disease (Table 4), and survival (Table 5) were studied comparatively between the S and PCT groups. The primary objective of this study was the 3-year overall survival, and the secondary objectives were the R0 resection rate, the recurrence rate and the recurrence location.

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 software (SPSS, Chicago, IL). Data are shown as the prevalence, mean (standard deviation), or median (range). Continuous data were compared using the Mann-Whitney U test. Ordinal data were compared using the χ^2 test or the Fisher exact test as appropriate. Tests for independent samples were used. Survival was estimated using the Kaplan-Meier method and included postoperative deaths. The time of participation began at the time of the first oncological consultation in both groups and was used for survival calculation. All causes of death were considered for overall survival estimation. The log-rank test was used to compare survival curves. The predictive factors of survival were analyzed by Cox proportional hazard regression analysis using a stepwise procedure; the 0.1 level was defined for entry into the model. Multivariable χ^2 and P values were used to characterize the independence of these factors. The hazard ratio (HR) and 95% confidence interval (CI) were used to quantify the relationship between survival and each independent factor. All statistical tests were 2-sided, with the threshold of significance set at $P < 0.050$. The study was accepted by the regional institutional review board on April 13, 2010 and was registered on the ClinicalTrials.gov website (record ADCI001; identifier NCT01249859).

TABLE 1. Pretherapeutic Demographic and Perioperative Parameters (n = 924)

Variables	Total n = 924 (%)	S Group n = 753 (%)	PCT Group n = 171 (%)	*P*
Gender				0.254
Female	321 (34.7)	268 (35.6)	53 (31.0)	
Male	603 (65.3)	485 (64.4)	118 (69.0)	
Age (yr)				0.295
≤60	426 (46.1)	341 (45.3)	85 (49.7)	
>60	498 (53.9)	412 (54.7)	86 (50.3)	
ASA grade				0.416
I	312 (33.8)	246 (32.7)	66 (38.6)	
II	433 (46.8)	356 (47.3)	77 (45.0)	
III	170 (18.4)	144 (19.1)	26 (15.2)	
IV	9 (1.0)	7 (0.9)	2 (1.2)	
Malnutrition*				0.358
No	664 (71.9)	546 (72.5)	118 (69.0)	
Yes	260 (28.1)	207 (27.5)	53 (31.0)	
Tumoral location				0.114
Antropyloric	243 (26.3)	213 (28.3)	30 (17.5)	
Nonantropyloric	586 (63.4)	450 (59.8)	136 (79.6)	
Unknown	95 (10.3)	90 (11.9)	5 (2.9)0	
Pretherapeutic cTNM stage				0.438
Stage I	180 (19.5)	151 (20.0)	29 (17.0)	
Stage II	238 (25.8)	197 (26.2)	41 (24.0)	
Stage III	506 (54.7)	405 (53.8)	101 (59.0)	

*Malnutrition indicates weight loss >10% of physical weight over a 6-months period.
ASA indicates American Society of Anesthesiologists.

TABLE 2. Operative Variables in Resected Patients (n = 864)

Variables	Total n = 864 (%)	S Group n = 702 (%)	PCT Group n = 162 (%)	*P*
Surgical procedure				<0.001
Subtotal gastrectomy	351 (40.6)	293 (41.7)	58 (35.8)	
Total gastrectomy	513 (59.4)	409 (58.3)	104 (64.2)	
Lymphadenectomy extent				0.100
D0	212 (24.5)	180 (25.6)	32 (19.7)	
D1	283 (32.8)	219 (31.2)	64 (39.5)	
D2	369 (42.7)	303 (43.2)	66 (40.8)	
Extended resection to neighboring organs				0.001
No	598 (69.2)	503 (71.7)	95 (58.6)	
Yes	266 (30.8)	199 (28.3)	67 (41.4)	
Postoperative 30-day mortality	28 (3.2)	26 (3.7)	2 (1.2)	0.110
Postoperative 30-day morbidity	364 (42.1)	298 (42.4)	66 (40.7)	0.691

RESULTS

Study Population

Among the 1050 registered SRC patients, 126 had metastases at the initial consultation and were not included in this study. Only patients with SRC who were determined to have resectable tumors (n = 924) were considered using an intent-to-treat process (Fig. 1).

Pre- and Perioperative Variables

The median age of the patients was 63.0 (range, 19.0–97.1). The male to female ratio was 1.9:1. The patient American Society of Anesthesiology (ASA) grades were I or II in 80.6% of patients. Malnutrition (weight loss greater than 10% of physical weight over a 6-month period) affected 28.1% of the patients. Tumors were mainly located in the upper or middle third of the stomach (63.4%) with 24.9% of patients suffering from junctional tumors. Most patients (80.5%) were diagnosed with a locally advanced cancer (cTNM stage II and III) at initial diagnosis.

The S and PCT groups were comparable regarding demographic (gender, age, ASA grade, and malnutrition) and tumor (tumor location and cTNM staging) parameters (Table 1).

Among the 924 patients whose tumors were determined to be resectable, 60 patients (51 in the S group and 9 in the PCT group) did not undergo resection due to diffuse metastatic progression by the time of surgery (n = 10) or extensive tumor infiltration at surgical examination (n = 50). In these nonresected patients, there was no significant difference in the number of metastatic progressions (7 vs. 3, $P = 0.347$) or the number of surgical examinations without resection (44 vs. 6, $P = 0.231$) between the S and PCT groups, respectively.

For the resected patients (n = 864, Table 2), extended resections to the stomach (total gastrectomy; 58.3% vs. 64.2%, $P < 0.001$), to the neighboring organs (28.3% vs. 41.4%, $P = 0.001$), and to the

TABLE 3. Histopathologic Variables of Resected Specimen (n = 864)

Variables	Total n = 864 (%)	S Group n = 702 (%)	PCT Group n = 162 (%)	*P*
pT				0.432
pTis	3 (0.3)	2 (0.3)	1 (0.6)	
pT1	108 (12.5)	96 (13.7)	12 (7.4)	
pT2	223 (25.8)	177 (25.2)	46 (28.4)	
pT3	363 (42.1)	290 (41.3)	73 (45.1)	
pT4	167 (19.3)	137 (19.5)	30 (18.5)	
pN				0.597
pN0	203 (23.5)	168 (23.9)	35 (21.6)	
pN1	276 (32.0)	229 (32.6)	47 (29.0)	
pN2	198 (22.9)	157 (22.4)	41 (25.3)	
pN3	187 (21.6)	148 (21.1)	39 (24.1)	
pM				0.472
pM0	742 (85.9)	600 (85.5)	142 (87.7)	
pM1	122 (14.1)	102 (14.5)	20 (12.3)	
pTNM stage				0.170
I	125 (14.5)	102 (14.5)	23 (14.2)	
II	338 (39.1)	283 (40.3)	55 (33.9)	
III	279 (32.3)	215 (30.6)	64 (39.5)	
IV	122 (14.1)	102 (14.6)	20 (12.4)	
Including peritoneal carcinomatosis	86 (9.9)	74 (10.5)	12 (7.4)	
Median number of dissected lymph nodes*	22.0	22.0	21.0	0.432
Median number of invaded lymph nodes*	4.0	4.0	5.0	0.480
Resection				
R0	564 (65.3)	463 (65.9)	101 (62.3)	0.222
R1	123 (14.2)	93 (13.2)	30 (18.6)	
R2	177 (20.5)	146 (20.9)	31 (19.1)	
Adjuvant treatment				<0.001
No	524 (60.7)	467 (66.5)	57 (35.2)	
Yes	340 (39.3)	235 (33.5)	105 (64.8)	

*Used as continuous variable.

TABLE 4. Recurrence in R0 Patients Discharged from Hospital (n = 610)

Variables	Total n = 610 (%)	S Group n = 497 (%)	PCT Group n = 113 (%)	*P*
Recurrence				0.843
No	335 (54.9)	272 (54.8)	63 (55.7)	
Yes	275 (45.1)	225 (45.2)	50 (44.3)	
Recurrence type (n = 275)				0.849
Locoregional	49 (17.8)	44 (19.6)	5 (10.0)	
Distant	156 (56.7)	126 (56.0)	30 (60.0)	
Both	59 (21.5)	46 (20.4)	13 (26.0)	
Unknown	11 (4.0)	9 (4.0)	2 (4.0)	
Peritoneal recurrence				0.252
No	495 (81.1)	399 (80.3)	96 (85.0)	
Yes	115 (18.9)	098 (19.7)	17 (15.0)	
Median time to first recurrence* (months)	11.6	12.2	7.9	0.015
[range min–max]	[0.4–111.0]	[0.4–111.0]	[2.2–34.6]	

*Used as continuous variable.

esophagus (16.1% vs. 27.8%, $P < 0.001$) were less common in the S group compared to the PCT group, respectively.

Perioperative Chemotherapy

When PCT was given (n = 171, 18.5%), the regimen was based mainly on a fluorouracil-platinum therapy, with doublet (39.2%) or triplet (in association with epirubicin, 42.3%) therapy used. Other combinations reported included fluorouracil-irinotecan (8.8%) and other various therapies, such as combinations in doublet or triplet forms with docetaxel (8.8%). The median delay between the first oncological consultation and the beginning of the neoadjuvant chemotherapy was 1.4 months (range, 0–6.1), with surgery performed 1.6 months (range, 0.2–17.7) after the end of the neoadjuvant treatment. The median duration of neoadjuvant treatment was 1.5 months (range, 0–15.0), and 83.9% of patients received 2 to 4 cycles of neoadjuvant chemotherapy. For those patients who received PCT, adjuvant chemotherapy was used in 106 patients (64.8%) and was based mainly on the fluorouracil-platinum platform in doublet form (39.3%) or triplet form (mainly with epirubicine; 33.7%). The drug combinations used were comparable with those used for neoadjuvant

TABLE 5. Survival in the Overall Population (N = 924): Variables Issued From Univariate Analysis

	Survival Probabilities (%)			
Variables	**1 Year**	**2 Years**	**3 Years**	***P***
ASA grade				0.052
I	65	28	10	
II	56	26	13	
III	46	20	12	
IV	25	0	0	
Gender				0.102
Female	53	23	7	
Male	58	26	14	
Antropyloric location				0.530
No	60	32	11	
Yes	55	22	12	
Age (yr)				0.978
≤60	64	23	7	
>60	50	26	15	
Pretherapeutic cTNM stage				<0.001
Stage I	82	50	34	
Stage II	75	37	20	
Stage III	47	17	6	
Resection				<0.001
R0	67	34	19	
R1	51	18	7	
R2	48	22	6	
30-day postoperative morbidity				0.005
No	66	28	13	
Yes	45	21	10	
Malnutrition*				0.021
No	59	28	13	
Yes	49	18	8	
Perioperative chemotherapy				0.043
No	49	24	14	
Yes	69	26	8	
Surgical procedure				0.582
Subtotal gastrectomy	60	30	16	
Total gastrectomy	60	26	11	
Lymphadenectomy extent				0.635
D0	59	30	16	
D1	52	25	12	
D2	67	28	12	
Enlarged resection to neighboring organs				0.001
No	61	29	13	
Yes	49	19	10	
Macroscopic aspect of linitis plastica				0.035
No	59	28	14	
Yes	55	20	9	
pT				<0.001
pT1	60	40	40	
pT2	72	39	23	
pT3	62	25	10	
pT4	35	19	5	
pN				<0.001
pN0	75	46	31	
pN1	68	35	18	
pN2	50	23	8	
pN3	51	12	3	
pM				<0.001
pM0	63	31	16	
pM1	46	16	3	
pTNM stage				<0.001
I	89	56	41	
II	72	37	22	
III	49	19	5	
IV	41	12	2	
Adjuvant treatment				0.608
No	49	25	14	
Yes	69	26	8	

*Malnutrition indicates weight loss >10% of physical weight over a 6-months period; ASA: American Society of Anesthesiologists.

treatment. Adjuvant chemotherapy in PCT was performed with a median delay between surgery and the first chemotherapy cycle of 1.6 months (range, 0.2–12.9), with a median duration time of 2.7 months (range, 0–12.4) and a median number of cycles of 3.0 (range, 0–13).

For patients who received primary surgery, adjuvant chemotherapy, when performed (n = 235, 33.5%), was based mainly on a fluorouracil-platinum regimen in doublet (40.3%) or triplet (mainly with epirubicin; 19.9%) form. Other associations were fluorouracil-irinotecan (11.3%) and fluorouracil-hydroxyurea (10.2%). The median delay between surgery and the first chemotherapy cycle was 1.6 months (range, 0.1–13.2), with a median duration time of 1.3 months (range, 0–12.4) and a median number of cycles of 6.0 (range, 1–16).

The rate of grade III–IV chemotherapy toxicities in the neoadjuvant setting was 20.8%. These toxicities were mainly digestive, hematologic and neurologic in nature. The rate of toxicities in the adjuvant setting was 21.5% (mainly hematologic and digestive).

Postoperative Setting

The 30-day postoperative mortality and morbidity rates were 3.2% and 42.1%, respectively, without any significant difference between the S and PCT groups (Table 2). Significant postoperative complications (including grades IIb, III and IV of the Dindo-Clavien classification) were similar between the S and PCT groups (27.3% vs. 32.1%, respectively; $P = 0.226$).

The 60-day postoperative mortality and morbidity rates were 4.4% and 45.0%, respectively, without any significant difference between the S and PCT groups (4.7% vs. 3.1%, $P = 0.422$ and 45.2% vs. 44.4%, $P = 0.870$, respectively).

Histopathologic Assessment of the Resected Specimen

When comparing the S and PCT groups during pathological examination, no significant differences were observed in the depth of tumor invasion ($P = 0.432$), degree of lymph node infiltration ($P = 0.597$), mean number of dissected lymph nodes ($P = 0.432$), mean number of invaded lymph nodes ($P = 0.480$), distant metastatic invasion ($P = 0.472$), and pTNM stage ($P = 0.170$; Table 3). Additionally, due to similar rates of R0 tumor resection between the 2 groups (65.9% vs. 62.3%, respectively, $P = 0.222$), it was clear that neoadjuvant chemotherapy did not result in any tumor downsizing.

Recurrence

The recurrence rate for R0 patients discharged from the hospital was 45.1% and was not significantly different between the S and PCT groups (45.2% vs. 44.3%, $P = 0.843$; Table 4).

Locoregional, distant, and both locoregional and distant recurrences were found in 17.8%, 56.7%, and 21.5% of patients, respectively. These recurrences were comparable between the 2 groups ($P = 0.849$). Peritoneal carcinomatosis recurrence did not occur more frequently in the S group (19.7% vs. 15.0%, $P = 0.252$).

The median time to recurrence after surgery was 11.6 months and was significantly longer in the S group (12.2 months vs. 7.9 months for the PCT group, $P = 0.015$).

Survival

The overall median survival of the study population (resected and nonresected patients) was 14 months, with 3- and 5-year survival rates of 11.7% and 2.9%, respectively (Fig. 2). The median survival was significantly longer in the S group compared to the PCT group (14.0 vs. 12.8 months, respectively, $P = 0.043$; Fig. 3), with better 3- and 5-year survival rates (13.1% for the S group vs. 3.6% for the PCT group and 3.4% for the S group vs. 0% for the PCT group,

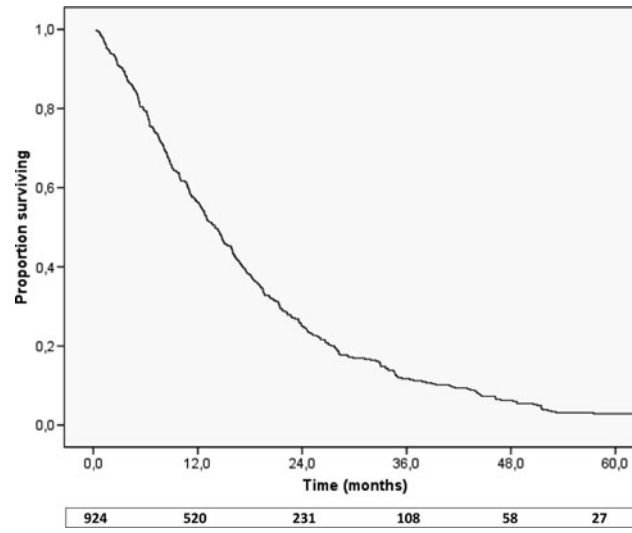

FIGURE 2. Survival curve for the overall population. The number of subjects at risk at each interval is shown in the table at the bottom of the graph.

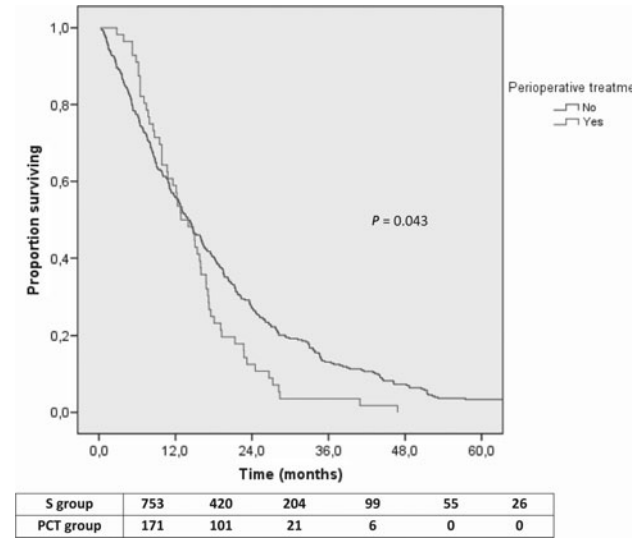

FIGURE 3. Survival curve for the S and PCT groups. The number of subjects at risk at each interval is shown in the table at the bottom of the graph.

respectively). For patients who underwent R0 surgical resection, the 3- and 5-year survival rates were 18.7% and 5.3%, respectively when compared to 9.1% and 0% for R1 resections and 5.2% and 0% for R2 resections, respectively ($P < 0.001$).

On the basis of the univariate analysis, 8 variables were found to be statistically related to poor survival: advanced pretherapeutic cTNM stage ($P < 0.001$), incomplete tumor resection ($P < 0.001$), the presence of postoperative complications at 30 days ($P = 0.005$), pretherapeutic malnutrition ($P = 0.021$), PCT administration ($P = 0.043$), enlarged resection to neighboring organs ($P < 0.001$), the macroscopic aspect of linitis plastica ($P = 0.035$), and an advanced

pTNM stage (P <0.001; Table 5). Adjuvant chemotherapy did not have any impact on overall survival ($P = 0.608$).

On the basis of the multivariate analysis, after adjusting for potential confounding factors (Table 6), 4 independent variables were predictive of a poor prognosis: pretherapeutic cTNM stages II or III (HR = 1.4, $P < 0.001$), the presence of postoperative complications (HR = 1.5, $P = 0.001$), incomplete tumor resection (HR = 1.2, $P = 0.011$), and PCT administration (HR = 1.4, $P = 0.042$). Furthermore, no survival benefit from chemotherapy was identified in any subgroup analysis based on variables listed in Tables 1–3 (data not shown).

As the French recommendation that considered PCT as a standard treatment in GA[13] changed in 2006, a subgroup analysis was conducted on patients operated on during the first study period (from January 1997 to December 2005) compared with those operated on during the second study period (from January 2006 to January 2010). These 2 groups were strictly comparable regarding variables listed in Tables 1–3. Median survival was longer in the former study period group when compared to the most recent one (14.7 vs. 13.0 months, $P < 0.001$).

Finally the potential effect on survival of the treating center was looked at. Because of the fact that use of PCT was directly related to the treating center, the center effect was only studied in the primary surgery group. No variation in survival was found ($P = 0.120$).

DISCUSSION

The incidence of SRC GA has been dramatically increasing, especially among young patients in the USA and other Western countries.[3–5,10] Previous studies have strongly suggested that SRC histology is associated with a worse prognosis when compared to non-SRC histology. Therefore, there is an urgent need for studies that related surgery with systemic treatments. In 2 published studies, a 5-year survival benefit for GA with PCT when the ECF[6] or CF[16] regimen was used. However, neither stratification nor SRC subgroup analysis were performed. Thus, this study used a large multicenter comparative cohort to investigate the impact of PCT on survival in patients with SRC GA.

This results were based on the largest study conducted on this GA histological subtype and confirm the poor prognosis of SRC. An overall median survival of 14.0 months and a 3-year survival rate of 11.7% was found. The patients who received PCT did not exhibit any survival benefit over patients treated with primary surgery. Although the data in Figure 2 may give the impression that PCT benefits patients during the first 12 months, it should be emphasized that such apparent benefit is artificial related to the time of participation for survival calculation began at the time of the first oncological consultation and not at the time of surgery. Consequently, postoperative deaths appears earlier in the S group. When starting survival calculation at time of surgery, the survival benefit for the primary surgery group is higher ($P < 0.001$, data not shown).

Neoadjuvant chemotherapy did not result in tumor downstaging or downsizing, as evidenced by comparable pT and pTNM stages between the S and PCT groups, without any R0 resection rate improvement in the PCT group. In addition, neoadjuvant chemotherapy did not result in lymph node downstaging because the pN stages were comparable between the S and PCT groups without any decrease in the mean number of invaded lymph nodes. Finally, neoadjuvant chemotherapy did not decrease the risk of recurrence, with a median time to first recurrence that was significantly shorter in the PCT group. Whereas in GA, PCT usually downstages and downsizes the tumor, as well as improving the R0 resection rate and eradicating micrometastases, the present results strongly suggest that there is no cytotoxic effect of chemotherapy on GA of SRC histology.

Some disease progression appears to have occurred during neoadjuvant treatment because surgeons more commonly performed an extended resection to the stomach to the esophagus, or to the neighboring organs in the PCT group. This indicates no cytostatic effect of chemotherapy on SRC GA. The absence of survival impact of adjuvant chemotherapy in SRC patients combined with a longer median survival in the first study period supports this observation.

The absence of cytotoxic and cytostatic effects may explain why PCT was associated with worse survival when compared to primary surgery and was identified as an independent predictor of poor survival in the multivariate analysis. There may be a number of explanations for this phenomenon. Systemic chemotherapy is known to have little effect on peritoneal tumor invasion, whereas such tropism is a feature of SRC histology. The patients' performance status deterioration during chemotherapy leads to relative immunodeficiencies as a result of chemotherapeutic toxicities. Usually, the possibility of serious drug adverse events on the patient's general status is counterbalanced by a clear survival benefit of PCT.[6,16] In the absence of an improvement in survival, chemotherapy toxicities may negatively impact the general status of the patient and may contribute to tumor progression, earlier relapse and death.[24]

Looking at the efficacy of other standard gastric cancer treatments on SRC histology, such as adjuvant chemoradiotherapy in the USA or adjuvant oral S1-based chemotherapy in Asia, no conclusions can be made because of the absence of SRC subtype analyses in both pivotal trials.[7,25] It is of specific interest to note that the 10-year follow-up of the INT0116 trial suggests that the diffuse histology subgroup does not benefit from adjuvant chemoradiation.[26]

Today, there is no true understanding of the chemoresistance mechanisms of SRC. However, it has been suggested that the massive intracytoplasmic vacuole of mucinous content (which defines the histological features of SRC)[27] could play an important role by competing with drug–cell interactions within the tumor. Hypothetically, specific patterns of the secretion and membranous expression of mucins could play a crucial role in drug–cell interactions, leading to chemoresistance.[28] In a similar situation, Ott *et al*. suggested that the high mucin content in SRC could lead to a reduced fluorodeoxyglucose concentration within the tumor, which in turn leads to the misevaluation of positron emission tomography (PET) signals.[29] This could explain why PET is a poor tool to evaluate this histological subtype. Therefore, there is a pressing need to explore SRC biology to understand the chemoresistance mechanisms involved and to identify specific signaling pathways that can be targeted.

This study has several limitations. First, its retrospective nature may introduce some bias. However, the large number of patients

TABLE 6. Survival in the Overall Population (N = 924): Results From The Multivariate Analysis

Variables	χ^2	HR	95% CI	*P*
Pretherapeutic cTNM stages II or III	12.9	1.4	1.2–1.6	<0.001
Presence of postoperative complications	10.2	1.5	1.2–1.8	0.001
Incomplete tumoral resection	6.5	1.2	1.1–1.4	0.011
Perioperative chemotherapy administration	4.1	1.4	1.1–1.9	0.042
ASA score 3 or 4	0.4	1.1	0.9–1.2	0.516
Pretherapeutic malnutrition	00.3	1.1	0.8–1.4	0.590
Macroscopic aspect of linitis plastica	0.1	1.1	0.7–1.4	0.978

ASA indicates American Society of Anesthesiologists.

included, the multicentric nature of the study, the intent-to-treat analysis, and the comparability between the groups for many of the prognostic parameters may limit the impact of any bias on the results. One can argue that some patients with tumor progression and/or chemotherapy-related mortality during neoadjuvant chemotherapy have not been included in this study because they had not been seen by a surgeon. However, if this were the case, it would have reinforced the results with enhancing the mortality rate in the PCT group. Others may argue that the only patients who received PCT presented with more advanced stages at diagnosis. However, the study groups were comparable at pretherapeutic tumor staging, with a trend toward more patients with metastatic disease due to the higher incidence of peritoneal carcinomatosis at surgical examination in the primary surgery group. In addition for patients deemed to be resectable considered in this study, PCT was usually offered in some centers whereas others did not, whatever the cTNM stage. This allows confident comparisons between the 2 therapeutic strategies. Another potential limitation is that only Western patients were included in this study, whereas individual and epidemiological differences probably exist for GA across continents. For example, the S1 oral chemotherapeutic agent exhibited higher efficacy in Asian populations with regard to metastatic disease,[30] whereas bevacizumab may provide some survival benefit only in Western patients.[31] Moreover, a specific therapeutic approach with trastuzumab for metastatic tumors that overexpressed HER2 has been demonstrated to enhance survival.[32] This leads one to consider different therapeutic strategies for some GA subpopulations. The incidence of SRC is dramatically increasing and presents in a more advanced form in patients from Western countries when compared to Eastern countries.[3–5]

This study provides the best evidence that PCT does not provide any survival advantage in SRC GA due to an absence of both cytotoxic and cytostatic effects. Tumors continue to progress during treatment. As previously reported in GA, a tailored approach should be proposed according to the TNM stage, performance status, tumor protein expression and histological subtype. For SRC tumors deemed to be resectable, primary surgery should be considered as a standard therapy, with adjuvant chemotherapy considered according to the GASTRIC study results.[33] The study also highlights the urgent need for (i) randomized trials dedicated to SRC (or stratified on the SRC subtype) to test different therapeutic strategies and/or chemotherapeutic regimens and (ii) studies of chemoresistance biology to find specific signaling pathway targets for SRC.

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DISCUSSANTS

D. Henne-Bruns (Ulm, Germany):

I think the question raised in this study is of great importance and we are in agreement with the clinical observations. However I think the study's methodology, because of its retrospective nature, is not really strong enough to support the conclusion. In my opinion it remains unclear how treatment decisions were made and it seems that the therapeutic strategies were left to the discretion of the attending surgeon or oncologist. This is supported by the fact that surgery was performed within a range of zero to nearly 18 months after the end of the neoadjuvant treatment and that the duration of this neoadjuvant treatment varied between zero and 15 months. Also the adjuvant chemotherapy was initiated with a duration range of zero to 13 months postoperatively. Chemotherapy was performed as doublet or triplet association but with many variations regarding the drugs used. Because of this wide variation in therapeutic approaches, in my opinion, the data collection does not fulfill the criteria of a study population. Therefore, the results of the study cannot be reliably interpreted due to the study design. I think to investigate this very important question, it would be better to simply evaluate those patients who meet the strict study criteria for preoperative as well as postoperative chemotherapy in accordance with the French guidelines.

Response From C. Mariette:

Regarding the therapeutic decisions, they were the conclusion of a multidisciplinary meeting with oncologists, surgeons, gastroenterologists, radiotherapists, radiologists, and pathologists based on French national recommendations mixed with each center's practice. What is of importance is that, among the 19 centers that included patients, some strictly followed the French recommendations whereas others, which were frequently high volume centers, never proposed neoadjuvant chemotherapy for signet ring cell adenocarcinoma (SRC), on the basis of their own clinical experience of poor efficacy of chemotherapy in this gastric cancer subpopulation. Consequently, I think that comparison between the 2 groups of patients, those who received and those who did not received neoadjuvant chemotherapy, is reliable. Regarding your comment on analyzing only eligible patients, French recommendations stated that neoadjuvant chemotherapy should be discussed for patients with at least stage Ib tumors. This is the reason why all patients with stage I, II, or III tumors were included. Moreover due to the infiltrating character of SRC, it should be emphasized that precise pretherapeutic staging may be difficult, reinforcing the choice of our inclusion criteria. Variation in chemotherapy regimen used reflects "real life" and is not, per se, a limitation for questioning the SRC chemosensitivity. Finally, important delays that you mentioned are probably related to the fact that all time calculations, including survival calculations, have been done with a start time at the first oncological consultation, to achieve a reliable intent to treat comparison between the 2 groups.