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Risk factors of peritoneal recurrence in eso-gastric signet ring cell adenocarcinoma: Results of a multicentre retrospective study

C. Honoré [a], D. Goéré [a,*], M. Messager [b], A. Souadka [a], F. Dumont [a], G. Piessen [b], D. Elias [a], C. Mariette [b]
On behalf of the FREGAT Working Group – FRENCH[c]

[a] Department of Surgical Oncology, Institut Gustave Roussy, Cancer Center, 114, rue Edouard Vaillant, 94805 Villejuif, Cedex, France
[b] Department of Digestive and Oncological Surgery, University Hospital C. Huriez, Lille, France

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Abstract

Introduction: The poor prognosis of signet ring cell (SRC) eso-gastric adenocarcinoma (EGA) might be explained by its great affinity for the peritoneum. The aim of this study was to identify predictors of peritoneal carcinomatosis recurrence (PCR) after curative surgery and hence identify high risk patients.
Methods: A retrospective national survey was conducted over 19 French surgical centers between 1997 and 2010. Patients with non-metastatic disease who benefited from curative surgery without postoperative death were included. Event-free patients who did not reach the time point of 24 months were excluded.
Results: In a cohort of 3010 patients, 1050 were SRC EGA and 424 patients met the selection criteria. The tumor location was mainly gastric (68.9%) and a total gastrectomy was performed in 218 patients (51.4%). Chemoradiotherapy or chemotherapy alone was given preoperatively to 71 (16.7%) and postoperatively to 150 (35.4%) patients. After a median follow-up of 54 months, recurrence was diagnosed in 214 patients (50.5%) within a mean delay of 17 ± 10.7 months. PCR was diagnosed in 81 patients (19.1%). In multivariable analysis, four factors were identified as predictors of PCR: linitis plastica ($p < 0.001$; OR = 4.83), tumor invasion of/or through the peritoneal serosa ($p = 0.022$; OR = 1.58), lymph node involvement ($p = 0.005$; OR = 1.7) and tumors of gastric origin ($p = 0.026$; OR = 2.36), with PCR rates of 55%, 26%, 23% and 22%, respectively.
Conclusion: Identification of strong predictors for PCR among this large series of SRC EGA patients helps to identify subgroups of patients that may benefit from specific therapeutic strategies such as prophylactic hyperthermic intraperitoneal chemotherapy.

Keywords: Gastric cancer; Signet ring cell adenocarcinoma; Peritoneal carcinomatosis; Surgery; Multicentre study

Introduction

With more than 930 000 cases per year, eso-gastric adenocarcinoma (EGA) is the second most diagnosed cancer in the world.[1] Among all the different histological subtypes, signet ring cell carcinoma (SRC) represents 32–70% of all EGA in Western countries with an increasing incidence.[2–4] SRC is defined by the World Health Organization (WHO) as an adenocarcinoma in which more than 50% of the tumor is represented by isolated or small groups of malignant non cohesive cells containing intracytoplasmic mucin.[5] SRC is an independent predictor of poor prognosis, with a median survival of less than half of the median survival observed in non-SRC GA.[2] This is linked to higher rates of positive lymph nodes and peritoneal carcinomatosis (PC) at initial diagnosis[2] and to higher rate of PC recurrence (PCR) that occurs in up to half of the patients.[2,6] PCR is isolated in 20%–40% of cases[7–9] and for these patients some teams advocate local aggressive treatments with a curative intent such as complete cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) with encouraging results.[10,11] However, when PC

* Corresponding author. Tel.: +33 42114439; fax: +33 42115330.
E-mail address: goere@igr.fr (D. Goéré).
[c] The collaborators of "FREGAT Working Group – FRENCH" are listed in Appendix section.

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is diagnosed prognosis remains poor, a fact mainly related to the poor accuracy of current imaging tools for detecting PCR early in its course, meaning that diagnosis is usually late.[12] To improve patient prognosis by decreasing the PCR rate, some teams have looked at the benefit of prophylactic intraperitoneal therapy after curative surgery such as chemotherapy or HIPEC.[13] In order to tailor these aggressive and costly therapeutic approaches to patients that may benefit most, there is an urgent need to determine robust predictive factors of PCR. SRC and non curative surgery having been already shown to be a strong predictor of PCR,[2,14] the aim of our study was to identify further predictive factors of PCR in a large multicenter cohort of patients with SRC tumors operated on with a curative intent with a long-term follow-up.

Patients and methods

Patients' selection and variables studied

A retrospective national survey was conducted over 19 French surgical centers and included all consecutive patients with an EGA between January 1997 and January 2010. The list of patients was verified with double checking by an independent monitoring team. All investigators were asked to complete for each patient, operated on or not, a standardized questionnaire for clinical, morphological, biological, surgical, pathological, and outcome parameters. After verification, by an independent team, of clinical, surgical and pathological variables, these data were entered in a dedicated electronic database. For the purpose of the study, inclusion criteria were SRC histology, non metastatic disease at time of surgery, a curative R0 resection, no postoperative death and a follow-up period of at least 24 months. Other histological subtypes, patients with metastatic disease at the time of diagnosis or discovered at surgery (including peroperative discovery of PC), non-curative surgery (residual microscopic (R1) or macroscopic (R2) disease), patients who suffered a postoperative death and patients with an event-free follow-up of less than 24 months were not included in the study.

Variables studied were preoperative and perioperative parameters, histopathological tumor characteristics, recurrence site and survival. The primary objective was to identify predictors of PCR. Secondary objectives were overall survival, rates and types of recurrence.

Pretherapeutic work-up

Pretherapeutic investigations included a complete physical examination, laboratory tests, esophagogastroduodenal barium study, an upper-GI endoscopy with multiple biopsies and computerized tomography (CT) of the thorax, mediastinum and abdomen. Endoscopic ultrasound (EUS) was not routinely performed.

Surgical technique

For antropyloric cancer, a subtotal gastrectomy was performed if a 5 cm proximal macroscopic margin was achievable. For other tumor locations and when the margin was less than 5 cm, a total gastrectomy was performed. The digestive renconstruction was made with an omega loop or a Roux-en-y after subtotal gastrectomy (left to the surgeon's discretion) and with a Roux-en-y after total gastrectomy. An extended lymphadenectomy preserving the spleen and pancreas was systematic. A distal pancreatectomy and splenectomy was only performed in cases of contiguous organ invasion or macroscopic involvement of the splenic artery lymph nodes. A D0 lymphadenectomy was defined as a <15 resected lymph nodes, a D1 as $15 \leq 25$ resected lymph nodes, a D2 as ≥ 25 resected lymph nodes. Resection was extended to the neighboring organs in cases of suspected macroscopic tumoral involvement. An enlarged resection was defined as a gastric resection extended to the esophagus, spleen, colon, pancreas or liver. For SRC adenocarcinoma invading the eso-gastric junction, the resection was extended to the esophagus either by a trans-thoracic or trans-hiatal approach, with a dedicated and appropriate lymphadenectomy.[15]

Histopathological analysis

Tumors were classified according to the World Health Organization (WHO) classification.[5] If not specifically mentioned, tumors were classified as SRC adenocarcinoma after discussion with the pathologist, in case of diffuse type tumors according to the Lauren classification or in the case of tumors with isolated, independent, or anaplastic cell. Pathological staging was based on the sixth UICC/TNM classification.

Follow-up

Patient underwent a clinical examination combined with an abdominal ultrasonography and chest X-ray or a thoraco-abdomino-pelvic CT-scan every 6 months for at least 5 years. In cases of suspected recurrence, a thoraco-abdomino-pelvic CT-scan and an upper-GI endoscopy were undertaken. The diagnosis of recurrence was made on histological, cytological or unequivocal radiological findings. The first site of recurrence was used to define the type of recurrence (loco-regional, peritoneal, or distant).

Statistical analysis

Statistical analysis was performed using the computer software SPSS version 15.0 (SPSS, Chicago, IL). Data are shown as prevalence or median (range). Categorical variables were compared using the Chi^2 or Fisher exact test as appropriate. Normally distributed continuous variables were analyzed by Student's *t*-test, whereas non-normally

distributed continuous variables were analyzed by the Mann–Whitney test. Survival was estimated by the Kaplan–Meier method including postoperative deaths. The log rank test was used to compare survival curves. To determine predictors of recurrence, a stepwise logistic regression model was used, in which all covariates were adjusted simultaneously. The 0.1 level was defined for entry into the model. All statistical tests were 2-sided with the threshold of significance set at $p < 0.05$.

Results

Patients' characteristics

Among the 3010 patients included in the database, 1050 patients (34.9%) had an SRC EGA and 424 patients (14.1%) met the inclusion criteria [Fig. 1].

The median age was 62 (range 22–90) years with a male/female ratio of 1.75 to 1. The patients' general status was good, with 82.3% of the patients having an American Society of Anaesthesiologists (ASA) score of I or II and 78.5% showing no preoperative malnutrition (defined by a weight loss of more than 10%). Tumors were mainly of gastric origin (68.9%). A linitis plastica was notified in 10.6% of the patients. Total gastrectomy was the most common procedure, performed in 51.4% of the patients and the resection was extended to a neighboring organ in 27.4% of the procedures. The extent of lymphadenectomy was classified as D2 in 43.4% of cases. As defined in the selection criteria, all the patients had a curative resection (100% R0 resection). Seventy one patients (16.7%) received preoperative chemotherapy (associated with radiotherapy in 2.4% of them ($n = 10$)). One hundred and fifty patients (35.4%) received postoperative treatment (chemotherapy alone in 61.0%, chemoradiation in 38.0% and radiotherapy alone in 1.0%). Histological analysis revealed locally advanced disease (pT3-4) in 207 patients (49.7%) and 72.9% of them had invaded lymph nodes (Table 1).

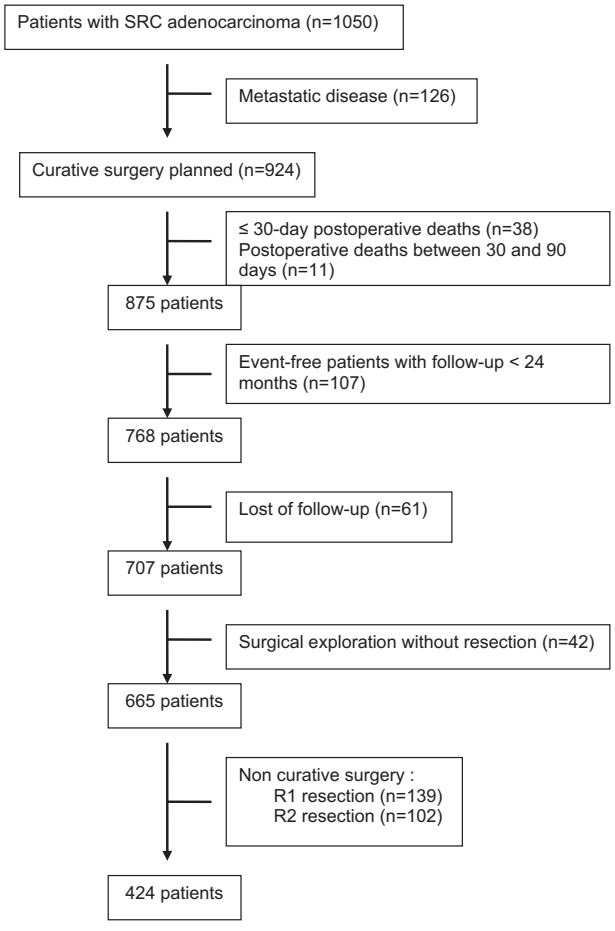

Figure 1. Flow chart of the study.

Recurrence

After a median follow-up of 54 months, a recurrence was reported in 214 patients (50.5%) within a mean delay of 17.0 ±10.7 months. The recurrence was classified as loco-regional in 41 patients (9.7%), distant in 121 patients (28.5%) and mixed in 52 patients (12.3%). Among recurrences, a peritoneal location was diagnosed in 81 patients (19.1%). The delay for recurrence was non significantly different according to the type of recurrence, with a mean delay of 16.5±10.9 months for loco-regional recurrence, 17.2±10.1 months for distant metastases, 15.1±8.5 months for PCR and 23.7±13.0 for mixed recurrences ($p > 0.086$).

Predictive factors for peritoneal recurrence

In univariable analysis, factors associated with the PCR and included in the multivariable model were a female gender ($p = 0.052$), age > 60 years ($p = 0.094$), a high ASA score ($p = 0.035$), a gastric tumor location ($p = 0.054$), a locally advanced tumor ($p < 0.001$), a linitis plastica ($p < 0.001$), a total gastrectomy ($p = 0.016$), the presence of invaded lymph nodes ($p < 0.001$) and administration of a postoperative treatment ($p < 0.001$) (Table 1). In the multivariable model, after adjustment for confounding variables, four pre- and/or per-operative factors were identified as independent predictors of PCR: a linitis plastica aspect ($p < 0.001$; OR = 4.8), tumor invasion of or through the peritoneal serosa ($p = 0.022$; OR = 1.6), the presence of invaded lymph nodes ($p = 0.005$; OR = 1.7) and gastric tumor location ($p = 0.026$; OR = 2.4), with corresponding PCR rates of 55%, 26%, 23% and 22%, respectively (Table 2).

Survival

After curative surgery for SRC EGA, the median overall survival was 17.7 months [95% CI 15.6–19.7], with 1-year, 3-year and 5-year overall survival of 69.2%, 18.1% and 5.9%, respectively [Fig. 2]. The median survival of patients with PCR was significantly lower when compared to

Table 1
Demographic and perioperative parameters and their relationship with the peritoneal recurrence variable (univariable analysis).

Variable	Total $n = 424$ (%)	PCR $n = 81$ (%)	Absence of PCR $n = 343$ (%)	P value
Gender				0.052
Female	154 (36.3)	37 (45.7)	117 (34.1)	
Male	270 (63.7)	44 (54.3)	226 (65.9)	
Age				0.094
≤60 years	195 (46.0)	37 (45.7)	158 (46.0)	
>60 years	229 (54.0)	44 (54.3)	185 (54.0)	
ASA score				0.035
I-II	349 (82.3)	68 (84.0)	281 (81.9)	
III-IV	75 (17.7)	13 (16.0)	62 (18.0)	
Preoperative malnutrition				0.627
No	333 (78.5)	62 (76.5)	271 (79.0)	
Yes	91 (21.5)	19 (23 0.5)	72 (21.0)	
Tumor location				0.006
Esophageal	26 (6.1)	2 (2.5)	24 (7.0)	
EGJ	106 (25.0)	13 (16.0)	93 (27.1)	
Gastric	292 (68.9)	66 (81.4)	226 (65.9)	
Linitis plastica				< 0.001
Yes	45 (10.6)	25 (30.9)	20 (5.8)	
No	254 (59.9)	45 (55.5)	209 (61.0)	
Not determined	125 (29.5)	11 (13.6)	114 (33.2)	
Preoperative treatment				0.852
Yes	71 (16.7)	13 (16.0)	58 (16.9)	
No	353 (83.3)	68 (84.0)	285 (83.1)	
Type of surgery				0.063
Total gastrectomy	218 (51.4)	31 (38.3)	187 (54.5)	
Subtotal gastrectomy	202 (47.7)	49 (60.5)	153 (44.6)	
Missing data	4 (0.9)	1 (1.2)	3 (0.9)	
Extent of lymphadenectomy				0.945
D0	102 (24.1)	18 (22.2)	84 (24.5)	
D1	133 (31.4)	22 (27.2)	111 (32.4)	
D2	184 (43.4)	38 (46.9)	146 (42.6)	
Missing data	5 (1.1)	3 (3.7)	2 (0.5)	
Extended resection to a neighboring organ				0.381
Yes	116 (27.4)	19 (23.5)	97 (28.3)	
No	308 (72.6)	62 (76.5)	246 (71.7)	
pT classification				< 0.001
pTis	3 (0.7)	0 (0)	3 (0.9)	
pT1	69 (16.3)	0 (0)	69 (20.1)	
pT2	141 (33.3)	27 (33.3)	114 (33.2)	
pT3	168 (39.6)	50 (61.8)	118 (34.4)	
pT4	43 (10.1)	4 (4.9)	39 (11.4)	
Serosal invasion and beyond				< 0.001
Yes	211 (49.7)	54 (66.7)	157 (45.8)	
No	213 (50.3)	27 (33.3)	186 (54.2)	
pN classification				< 0.001
pN0	115 (27.1)	9 (11.1)	106 (30.9)	
pN1	155 (36.6)	27 (33.3)	128 (37.3)	
pN2	87 (20.5)	30 (37.0)	57 (16.6)	
pN3	67 (15.8)	15 (18.5)	52 (15.2)	
Invaded lymph nodes				< 0.001
Yes	309 (62.9)	72 (88.9)	237 (69.1)	
No	115 (27.1)	9 (11.1)	106 (30.9)	
pTNM stages				< 0.001
I	79 (18.6)	4 (4.9)	75 (21.9)	
II	215 (50.7)	41 (50.7)	174 (50.7)	
III	130 (30.7)	36 (44.4)	94 (27.4)	
Postoperative treatment				< 0.001
Yes	150 (35.4)	47 (58.0)	103 (30.0)	
No	274 (64.6)	34 (42.0)	240 (70.0)	

PCR: Peritoneal recurrence; EGJ: Eso-Gastric Junction; ASA: American Score of Anesthesiologists.

loco-regional recurrence (17.2 vs. 23.5 months, $p = 0.015$), whereas no significant difference was observed when comparing PCR with distant recurrences, with median survivals of 17.2 vs. 18.1 months, respectively ($p = 0.187$).

Discussion

Our study shows that patients operated on for an SRC EGA with a curative intent have a poor prognosis with a 5-year overall survival of only 5.9%. We confirm that this population is exposed to a significant risk of PCR for which we identified four predictive factors that can be determined a priori: the appearance of a linitis plastica, a tumor invading the peritoneal serosa and beyond, the presence of invaded lymph nodes and a tumor of gastric origin.

In the literature, the most frequently reported factors associated with an increased risk of PCR after surgery for EGA are palliative surgery, an invasion of the serosa and beyond, a large tumor size, invaded lymph nodes and the histological diffuse type, leading to PCR rates ranging from 17 to 49%.[7,8,16–19] These factors are consistent with our results even if probably underestimated because of the retrospective nature of the study and the varying PCR diagnosis methods among the participating centers. We should however mention that our rate of PCR is as expected much higher for pT3 tumors when compared to pT1-T2

Table 2
Predictive factors of peritoneal recurrence after curative surgery in patients with SRC EGA: multivariable analysis.

Variable	p	OR [95% CI]
Linitis plastica	>0.001	4.8 [2.2–10.7]
Invaded lymph nodes	0.005	1.7 [1.2–2.5]
Serosal invasion and beyond	0.022	1.6 [1.1–2.3]
Gastric location	0.026	2.4 [1.1–5.0]
ASA score III-IV	0.088	0.7 [0.5–1.1]
Postoperative treatment	0.423	1.3 [0.7–2.4]
Female gender	0.448	1.3 [0.7–2.2]
Age > 60 years	0.937	1.0 [0.6–1.9]

OR: Odd Ratio; 95% CI: 95% Confidence Interval.

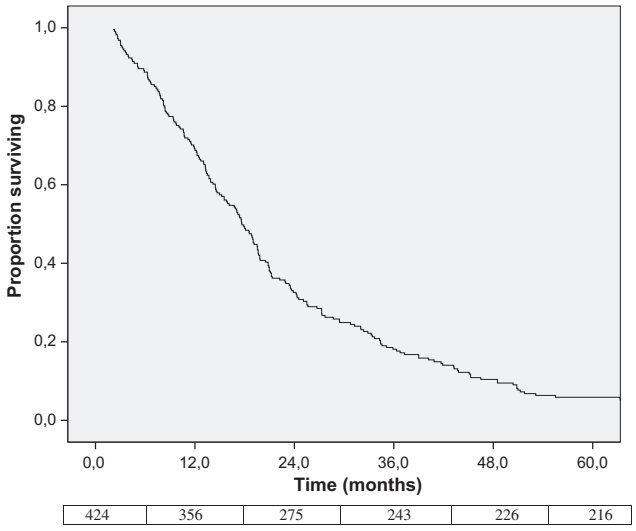

Figure 2. Overall survival curve after curative surgery for SRC OGA. The number of subjects at risk at each interval is shown in the table at the bottom of the graph.

tumors (42.3% vs. 14.7%), but lower in pT4 tumors (10.2% (Table 1)). This could be explained by either a higher rate of non-curative surgery in pT4 tumors (with these resections having been excluded), or by the en bloc tumoral resection to neighboring organs required for such patients to achieve an R0 resection. Despite having excluded non R0 resections and consequently some patients with tumors invading the peritoneal serosa and beyond, this factor remains significant as a predictor of PCR, witness of its robustness in our model. Lymph node involvement has been also reported in different studies to be associated with PCR.[7] Of course linked to advanced pT stage, lymph node involvement remains independently significant in the multivariable model suggesting that hematogenic dissemination is also involved in the PC disease in addition to the well-known mechanism of gradual metastatic seeding. Of interest a gastric location has been identified to expose patients to higher risk of PCR when compared to esophageal or junctional tumors. The intra-abdominal location of the stomach covered by a peritoneal surface may be part of the explanation. Linitis plastica is commonly associated with advanced tumoral stages in gastric SRC, especially with serosal and lymph node invasion, and it remains highly significant in the multivariable model after adjustment for these prognostic variables. This strongly suggests a specific carcinogenetic pathway of the linitis plastica form through the tumoral micro-environment represented by the abundant stroma which is a characteristic of this tumor presentation.[20]

PCR has been demonstrated to worsen the prognosis of patients operated on for EGA. Fanelli et al. showed that in patients with no PCR after surgery for GA (combining SRC and non-SRC), the median and 5-year overall survival were 65 months and 45% respectively, compared to 15 months and 0% for patients exhibiting a PCR.[21] Systemic chemotherapy for synchronous or metachronous GA PC adds no clear survival benefit compared to the natural history of the disease, although some favorable responses have been reported.[22,23] For these reasons, some teams advocate treating PC aggressively combining complete cytoreductive surgery with intraperitoneal chemotherapy (with or without hyperthermia). Such treatment, in a selected population of 159 patients with exclusive PC disease, offered a 5-year overall survival of 23%.[10,11] However, macroscopically complete surgical resection was achievable in only half of the patients and the 5-year overall survival dropped to 3% for incomplete cytoreductive surgery.[10] PC is difficult to diagnose since current radiological imaging tools are disappointingly poor at detecting it at an early stage. Whereas no specific studies are available for EGA, the best tool for PC diagnosis in colorectal cancer has been shown to be CT-scan offering a sensitivity of only 60–79%, with a drop to less than 30% for peritoneal lesions smaller than 5 mm in size.[12] To overcome this issue, Inoue et al. evaluated the feasibility of an aggressive strategy by a systematic second-look laparoscopy in 21 patients with positive peritoneal cytology and/or PC at initial curative surgery. PC was found in 43% of the patients despite a negative morphological work-up after a median delay of 9.8 months.[24] These data highlight the importance of predicting PCR, as reported in the present study, in order to tailor both the follow-up diagnostic strategy and the therapeutic approach.

Because of the disappointing accuracy of radiological imaging in the diagnosis of PC, drawbacks in making the diagnosis by invasive surgical exploration and relatively poor long-term results obtained with HIPEC in established PC, an alternative attractive strategy would be to anticipate and prevent the occurrence of PC in patients who are at high risk of its development. Whereas perioperative chemotherapy is the standard option for enhancing survival in GA,[25,26] a recent large retrospective comparative study strongly suggests there is both no survival benefit of preoperative chemotherapy in SRC and no impact on PCR when compared to surgery alone.[27] Similarly, in the present study, perioperative chemotherapy was not identified as an independent protective factor against PCR. Consequently, assuming that metastatic dissemination occurred prior to, or at the time of surgery, another option would be to attempt to eradicate all residual disease at the time of surgery by using high concentration of intraperitoneal chemotherapy. A meta-analysis has demonstrated a positive impact on overall survival by the addition of intraperitoneal chemotherapy to surgery.[13] These results were confirmed in a recent large retrospective study of 360 patients with GA staged T2-4bN0-3M0, showing a 5-year overall survival of 60.4% after surgery plus intraperitoneal chemotherapy compared to 42.9% when surgery alone was performed ($p = 0.001$).[28] It has been also suggested that hyperthermia may act as a synergistic antitumor effect.[13] Latest results combining surgery to a preventive HIPEC offers 5-year

overall survival rates from 42 to 72%.[29,30] Usually associated with a higher rate of postoperative complications, this costly procedure should consequently only be considered for patients at high risk of PCR, identified in the present study. According to our results, preventive HIPEC after curative surgery could be considered in patients with SRC GA having a linitis plastica, a tumor invading the peritoneal serosa and beyond and/or a macroscopic lymph node invasion.

The major strengths of our study are the large number of patients, its multi-centric nature representing different practices, a homogenous population resulting from an optimal selection process and a sufficient follow-up. However some limitations should be highlighted: (i) the retrospective nature of the study may be responsible for some biases even if the number of missing data is small. Stringent inclusion/exclusion criteria and the fact that major variables have been double-checked at the time of the data-base creation may have limited their impact; (ii) absence of data concerning peritoneal cytology. Since peritoneal cytology has been related to PCR with 11–100% of PCR in cases of positive cytology compared to 0–51% for negative cytology,[31] this might help for targeting high risk patients. However this procedure is not recommended in European and French guidelines,[32,33] no reliable and standard technique having been established, and its impact is still controversial[34]; (iii) as in all studies dealing with PCR, since the diagnosis is difficult, there may have been an underestimation of the PCR since no systematic surgical exploration was performed. This is highlighted by a cancer-related death rate of 84.6% in the present study, despite a rate of identified recurrence of 50.5%. However, further additional events would not have changed the significance of the variables already identified but might allow for the identification of additional relevant predictive parameters.

In conclusion, PCR after curative surgery for an SRC EGA is a major issue, occurring frequently and being associated with a poor prognosis. Identification of factors independently associated with PCR in this subpopulation such as linitis plastica, tumor invasion of the peritoneal serosa and beyond, lymph node invasion and/or gastric tumoral location, will help to identify patients that may benefit from intensive follow-up and the possibility of tailored innovative therapeutic approaches such as a preventive hyperthermic intraperitoneal chemotherapy.

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Conflict of interest

None to declare.

Appendix

Collaborators of the FREGAT Working Group – FRENCH that contributed significantly to the present study.

Arnaud J-P[3], Balon J-M[4], Borie F[5], Brachet D[3], Brigand C[6], Carrere N[7], D'Journo X-B[8], Dechelotte P[9], Delpero J-R[10], Dhari A[11], Fabre S[4], Fernandez M[6], Flamein R[12], Gillet B[12], Glaise A[13], Glehen O[14], Guilbert M[2], Guiramand J[10] Huten N[14], Kraft K[15], Lefevre JH[16], Leteurtre E[17], Louis D[7], Mabrut J-Y[14], Mathieu B[12], Meunier B[18], Michalak S[19], Michot F[20], Millat B[13], Paye F[16], Pichot-Delahaye V[14], Peschaud F[21], Pezet D[12], Pocard M[22], Poisson A[2], Prudhomme M[5], Regimbeau J-M[11], Thiébot T[18], Thomas P-A[8], Tsilividis B[20], Vandois F[2].

Departments of digestive surgery of [3]Angers University Hospital, [4]Clinique Jules Verne Nantes, [5]Nîmes University Hospital, [6]Strasbourg University Hospital, [7]Toulouse University Hospital, [8]Nord University Hospital Marseille, [9]Department of Pathology of Clermont-Ferrand University Hospital, Departments of digestive surgery of[10]Paoli Calmette Institute Marseille, [11]Amiens University Hospital, [12]Clermont-Ferrand University Hospital, [13]Montpellier University Hospital, [14]Lyon University Hospital, [15]Tours University Hospital, [16]St Antoine University Hospital Paris, [17]Department of Pathology of Lille University Hospital, [18]Department of digestive surgery of Rennes University Hospital, [19]Department of Pathology of Angers University Hospital, [20]Department of digestive surgery of Rouen University Hospital,, [21]Ambroise Paré University Hospital Boulogne-Billancourt, and [22]Lariboisière University Hospital Paris, France.

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