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ORIGINAL ARTICLE

Is signet-ring cell carcinoma a specific entity among gastric cancers?

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Abstract

Background The prognosis and chemoresistance of signet-ring cell (SRC) gastric adenocarcinoma have been reported and debated, and the utility of perioperative chemotherapy for such a tumor has been questioned. This study was performed to assess the impact of the SRC type on survival following resection of gastric adenocarcinoma, and to assess whether the prognostic factors (including perioperative chemotherapy) for non-SRC adenocarcinoma differed from those for SRC adenocarcinoma.

Methods 1799 cases of adenocarcinoma that were consecutively treated from 1997 to 2010 in 19 French centers by subtotal or total gastrectomy were included in a retrospective study. A D2 lymphadenectomy was performed for antropyloric tumors, and a modified D2 for upper tumors. SRC adenocarcinoma was diagnosed based on the presence of isolated carcinoma cells containing mucin.

Results A total gastrectomy was performed in 979 (54.4 %) patients. SRC adenocarcinoma was diagnosed in 899 (50 %) patients. Patients with an SRC tumor were more frequently female, younger, and malnourished, had lower ASA scores, and had larger tumors than non-SRC patients. Median survival in patients with non-SRC carcinoma was 51 months, as compared to 26 months in patients with SRC carcinoma ($p < 0.001$). At multivariate analysis, SRC type remained an independent adverse prognostic factor (HR = 1.182). Factors that were prognostic in the SRC subgroup but not in the non-SRC subgroup were age >60 years, linitis, and involvement of adjacent organs. In contrast to non-SRC tumors, pre- and postoperative chemotherapy did not significantly impact on survival following resection of SRC adenocarcinoma.

On behalf of the FREGAT (French Eso-GAstric Tumours) working group–FRENCH (Fédération de Recherche en Chirurgie).

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Conclusion In comparison to non-SRC adenocarcinoma, the SRC type has a worse prognosis, different prognostic factors, and is only poorly sensitive to perioperative chemotherapy. Non-SRC and SRC adenocarcinomas should be considered different entities in future therapeutic trials.

Keywords Gastric adenocarcinoma · Signet-ring cell · Chemotherapy · Surgery · Prognosis

Introduction

With an estimated 988,000 new cases in 2008, gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of death from cancer in the world [1]. Although the global incidence of gastric adenocarcinoma has declined in the last few years, the incidence of the signet-ring cell (SRC) type increased in the USA between 1973 and 2000 from 0.1 to 1.4 cases per 100,000 persons [2], and represents 3.5 % to 45.4 % of gastric carcinoma in recent publications [3–12]. According to the World Health Organization (WHO) classification, SRC carcinoma is an adenocarcinoma in which more than 50 % of the tumor consists of isolated or small groups of malignant cells containing intracytoplasmic mucins [13]. This type has also been classified as the "diffuse type" (by Lauren [14]), "infiltrative type" (by Ming [15]), and "undifferentiated type" (by Nakamura [16]) of adenocarcinoma, and as "high-grade" adenocarcinoma by the UICC.

The prognosis of SRC adenocarcinoma is debated and may depend on the stage of the cancer. For early gastric cancer (described by the Japanese Endoscopy Society as gastric cancer that does not extend beyond the submucosa, whatever the lymph node status [17]), the prognosis of the SRC type has been reported to be better than that of non-SRC adenocarcinoma in four recent studies [7, 12, 18, 19], but this could be biased by the tendency of patients with SRC to be younger [20]. For advanced gastric cancer, the clinicopathological characteristics and prognosis are again controversial. While some studies have shown a better prognosis for the SRC type [12, 21], other studies have reported either a poorer prognosis of this histological type [3, 5, 10, 22] or no statistically significant difference in overall survival between patients with SRC and non-SRC tumors [4, 7, 8, 11] throughout the whole population studied or when adjustments were made to account for tumor stage [23].

Moreover, a few retrospective studies have indicated that SRC gastric adenocarcinoma may be more chemoresistant, and therefore may not respond to current therapeutic approaches available for gastric cancer in Europe (based on perioperative chemotherapy (CT) with cisplatin–fluorouracil with or without epirubicin) according to two randomized trials [24, 25], and in the USA (based on postoperative adjuvant chemoradiotherapy) [26]. These distinct epidemiologies, prognoses, and responses to chemotherapy of the SRC and non-SRC types suggest that each histological type should be considered an independent disease with its own specific prognostic factors and efficient therapeutic strategies.

In the study reported in the present paper, we aimed to assess the impact of the SRC type on survival following resection of gastric adenocarcinoma, and to assess whether the prognostic factors for SRC (including perioperative chemotherapy) and non-SRC adenocarcinoma differ.

Methods

Patients

The FREGAT multicentric database gathered 3010 patients from 19 participating surgical centers who were consecutively operated on for gastric or junctional adenocarcinoma between January 1997 and March 2010. Among them, 1799 fulfilled the following inclusion criteria: the gastric adenocarcinoma did not involve the gastroesophageal junction, it was considered resectable on preoperative assessment, and it was treated by either subtotal or total gastrectomy.

Preoperative investigations

In all centers, preoperative assessment included a complete medical history, physical examination, upper gastrointestinal endoscopy with biopsies, and abdominopelvic and chest computed tomographic scans. Endoscopic ultrasound and positron emission tomography (PET) were performed when indicated according to the French National Guidelines [27]. The suitability of patients for gastrectomy, with or without perioperative chemotherapy, was considered in multidisciplinary weekly meetings of surgeons, oncologists, pathologists, and radiologists. Linitis was defined macroscopically as partial or complete thickening and rigidity of the gastric wall observed on both preoperative endoscopy and intraoperative exploration. Preoperative malnutrition was defined as a weight loss exceeding 10 % of the baseline weight in the last six months. The American Society of Anesthesiologists (ASA) score was used to stratify patients according to their perioperative risk. It was assigned either in the preoperative period or at the time of surgery by the anesthesiologist according to the following guidelines: ASA 1, normal healthy patient; ASA 2, patient with mild systemic disease; ASA 3, patient with severe systemic disease; ASA 4, patient with severe systemic disease—a constant threat to life.

Perioperative treatment

According to reported prospective trials [24, 25], perioperative CT using cisplatin and fluorouracil with/without epirubicin is recommended for operable gastric or lower esophageal adenocarcinoma by the French Guidelines [27]. The preoperative and postoperative CT regimens used since 2005 have varied among participating French centers, and have always included a bitherapy utilizing fluorouracil with cisplatin or oxaliplatin. In some of them, epirubicin or taxotere has also been included. Prior to 2005, upfront surgical resection was performed routinely for gastric adenocarcinoma that was deemed resectable, and postoperative CT (FOLFOX or 5-FU/cisplatin) or radioCT was considered on a case-by-case basis, taking the histological characteristics of the resected tumor and the patient's status into account. Preoperative CT was defined here as at least one cycle of preoperative CT, and was considered in this study on an intention-to-treat basis, whatever the number of cycles of CT performed pre- and postoperatively. Postoperative CT was defined here as postoperative CT carried out in patients who had not received previous neoadjuvant chemotherapy, whatever the CT regimen and number of cycles.

Surgical technique

Surgery was performed 4–8 weeks after the end of the neoadjuvant chemotherapy (when administered) and 2–4 weeks after referral for patients with upfront resection.

At laparotomy, a surgical exploration of the peritoneal cavity was performed to search for liver metastasis and peritoneal carcinomatosis. The presence of ascites or localized resectable carcinomatosis was also recorded. A subtotal gastrectomy was an option for pyloric and antral tumors, providing a margin of at least 6 cm between the proximal resection line and the superior edge of the macroscopic tumor. The Billroth II technique was used for reconstruction. For tumors of the gastric body and fundus, a total gastrectomy with a Roux-en-Y reconstruction was always performed. If localized carcinomatosis or involvement of adjacent organs was discovered, an en bloc resection was performed with curative intent.

The recommended standard lymphadenectomy with curative intent was D2 for antropyloric tumors and modified D2 (without splenectomy and left pancreatectomy; only performed in cases where there was involvement of these organs by the gastric tumor) for upper tumors requiring total gastrectomy. Both D2 and modified D2 are termed D2 lymphadenectomy in this work, in accordance with the guidelines of the Japanese Research Society for the Study of Gastric Cancer (JRSGC) [28]. D1 resection was an option, depending on patient status and tumor extent. Because of the lack of available control lymphadenectomies in this retrospective multicentric study, we classified lymphadenectomies in which 15–24 lymph nodes were harvested as D1 and those in which 25 or more lymph nodes were harvested as D2. Palliative resections were defined as microscopically or macroscopically incomplete (R1/R2). Simultaneous resection of localized carcinomatosis or hepatic metastasis was a possibility.

Pathological analysis

The histological classification of gastric carcinoma types followed the criteria of the WHO classification [13]. Diagnosis of an SRC tumor was based on the presence of isolated carcinoma cells containing mucin in the gastric adenocarcinoma. A predominant SRC component (>50 % of the tumor) was usually observed, but the predominance of this component could not be ascertained precisely in this retrospective study. We therefore considered any tumor with a predominant (>50 %) SRC component and any diffuse-type gastric cancer with identified signet-ring cells (percentage not specified) to be an SRC gastric adenocarcinoma. Specimens were examined by pathologists experienced in digestive diseases. Retrieved lymph nodes, surgical margins, and the mural extension of the tumor were systematically assessed. TNM stages were defined according to the seventh edition of the UICC/TNM classification [29].

Curative resection (R0) was defined as macroscopically and microscopically complete resection. An R1 resection indicated microscopically positive margins and R2 indicated macroscopic residual tumor.

Postoperative outcomes

Morbidity and mortality at 30 and 90 days were recorded and classified according to Dindo and Clavien's classification of surgical complications [30] by retrospectively reviewing each patient record. Briefly, postoperative complications were ranked by severity based on the therapy used to treat the complications. A complication was classified grade I or II if it represented any deviation from the normal postoperative course or if it required any pharmacological treatment. Postoperative complications that were classified grade III required surgical, endoscopic, or radiological intervention, whereas complications that were classified grade IV represented life-threatening complications requiring intensive care unit management. A grade V complication corresponded to the death of the patient.

Follow-up

Data on long-term (>90 days) postoperative outcome were lacking in only 2 patients. Follow-up was performed in most centers every 6 months for at least 5 years, according to French guidelines [27]; each follow-up examination involved a physical examination, tumor marker measurement, and either abdominal ultrasound and chest radiography or a chest and abdominopelvic computed tomography scan.

Statistical analysis

Categorical data were compared using the chi-square test or Fisher's exact test. For continuous data, the independent-samples *t*-test was used. Survival rates and relapse rates were calculated using the Kaplan–Meier method and included postoperative deaths. Survival curves were calculated from the date of referral, and all causes of death were considered when estimating survival. The log-rank test was used to compare survival curves and to identify the prognostic factors of survival in univariate analysis. Multivariate analyses were performed using a Cox proportional hazards stepwise procedure, including nonredundant variables chosen by univariate analysis. A $p < 0.2$ was necessary for systematic entry into the model. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). A p value ≤ 0.05 was considered to indicate significance.

Results

Preoperative data

Table 1 summarizes the clinical characteristics of the whole studied population and shows the results of the univariate analysis of preoperative prognostic factors for overall survival. Median age at diagnosis was 67 years (range 21–100). Preoperative malnutrition was noted in 333 patients (21.1 %). Linitis was described on preoperative assessment for 241 patients (13.4 %).

At univariate analysis, the preoperative variables that were statistically significantly associated with poorer overall survival in the whole population were age >60 years, malnutrition, high American Society of Anesthesiologists (ASA) score, high clinical TNM stage, and linitis.

Surgical management and postoperative outcome

A total gastrectomy was performed in 979 patients (54.4 %). Seventy-four patients died within the first postoperative month, and 27 others in the next two months, accounting for postoperative mortality rates at 1 and 3 months of 4.1 and 5.6 %, respectively. Postoperative complications, either surgical or medical, occurred within the first and the third postoperative month in 664 patients (36.9 %) and 814 patients (45.2 %), respectively. At 1 month, according to Dindo–Clavien, complications were classified grade I or II in 328 (18.2 %) patients and grade III or IV in 262 (14.6 %) patients. At univariate analysis, the operative findings that were statistically associated with poorer overall survival were tumor involvement of the neighboring organs, distant metastasis, and peritoneal carcinomatosis (Table 2). Performance of a total gastrectomy, performance of a D1 lymphadenectomy, postoperative complication, and postoperative chemotherapy also adversely impacted overall survival.

Histological data

Among the 1799 patients included, 899 patients (50.0 %) were found to have SRC adenocarcinoma, as compared to 900 patients with non-SRC adenocarcinoma (50.0 %) (Table 2). Histological examination showed that 19.5 % were early gastric cancers (pT0, pTis, or pT1) and 80.5 % were more invasive tumors (T2, T3, T4). Sixty-five percent of the patients exhibited nodal metastases. The resection margin was R0 in 1528 patients (85.0 %).

Six histological variables were found to be associated with poor overall survival in univariate analysis: a positive resection margin (R0 vs R1/R2), pT, pN, pM, and pTNM stages, and an SRC-type tumor. Thus, median survival in patients with non-SRC carcinoma was 51 months, as compared to 26 months in patients with SRC carcinoma ($p < 0.001$) (Fig. 1).

In order to better understand the impact of histological type on overall survival, a stage-stratified analysis was conducted (Fig. 2). When comparing stage I cancers, the survival of patients with SRC carcinoma was found to be longer than that of patients with the non-SRC type (median survival not reached, mean overall survival of 120 vs. 105 months; $p = 0.043$). In stage II cancers, the prognosis of the SRC adenocarcinoma group was poorer than that of the non-SRC group, albeit not statistically significantly (43.9 vs. 129 months; $p = 0.191$). Median survival for the stage III SRC group was significantly shorter than that for the stage III non-SRC group (18.8 vs. 25.1 months; $p = 0.001$). Survival of patients with stage IV SRC carcinoma did not vary significantly depending on the histological type of the tumor (10.1 months for SRC vs. 8.9 months for non-SRC, $p = 0.576$).

Comparison between SRC and non-SRC groups

Females were more frequent in the SRC group (360/899 = 40.0 vs 282/900 = 31.3 %, $p < 0.001$). To better understand the poor prognosis associated with SRC, we

Table 1 Preoperative prognostic factors for overall survival in the whole population at univariate analysis

Variable	$N = 1799$ (%)	Median survival		p
		Months	95 % CI	
Gender				<0.337
Male	1157 (64.3)	34.2	30.0–38.5	
Female	642 (35.7)	35.2	28.2–42.1	
Age (years)				<0.001
≤60	1198 (66.6)	43.0	30.9–55.1	
>60	601 (34.4)	31.8	30.0–55.1	
Malnutrition				<0.001
No	1322 (73.5)	41.9	34.3–49.4	
Yes	333 (18.5)	19.2	16.6–21.8	
Unknown	144 (8.0)			
ASA score				<0.001
1	518 (28.8)	42.6	30.9–54.2	
2	832 (46.2)	39.2	29.3–49.0	
3	418 (23.2)	23.2	19.3–27.0	
4	31 (1.7)	12.2		
Pretherapeutic cTNM stage				<0.001
I	470 (26.1)	nr	27.4–59.2	
II	396 (22.0)	43.3		
III	858 (47.7)	23.0	21.1–24.9	
IV	75 (4.2)	11.1	08.1–14.0	
Linitis				<0.001
No	1558 (86.6)	41.1	35.0–47.3	
Yes	241 (13.4)	17.7	15.2–20.1	
Antropyloric location				<0.215
No	1043 (58.0)	30.8	25.9–35.8	
Yes	756 (42.0)	35.1	29.9–40.3	
Preoperative chemotherapy				<0.172
No	1509 (83.9)	36.7	31.9–41.4	
Yes	290 (16.1)	27.3	23.3–31.2	

nr median survival not reached, *ASA* America Society of Anesthesiology

compared the SRC and non-SRC groups in terms of the prevalence of each prognostic factor identified by the previous univariate analysis (Table 3). Patients in the SRC group were significantly younger, had lower ASA scores, and were more likely to have preoperative malnutrition. Linitis, pT3–T4 tumors (61.3 vs 23.8 %), and nodal and peritoneal metastases were more frequent in the SRC tumor group. Accordingly, resections in this latter group were more often palliative (R1–R2), and postoperative CT was used more frequently. All of these differences were statistically significant. The factors that were prognostic in the univariate analysis were all included in the multivariate analysis.

Prognostic factors for overall survival

In the multivariate analysis, neither the type of gastrectomy (subtotal or total) nor preoperative chemotherapy were found to be prognostic for overall survival (Table 4). Postoperative chemotherapy, which appeared to be associated with poorer overall survival in the univariate analysis, was instead identified as a protective factor in the multivariate analysis.

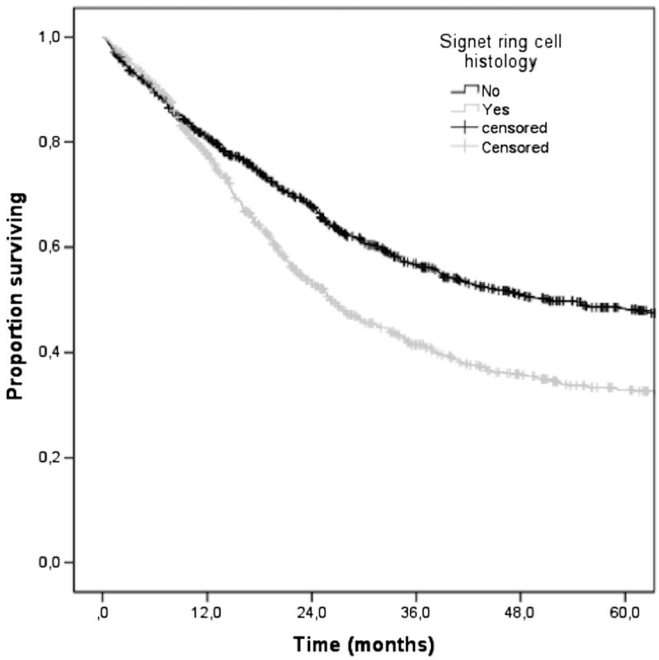
The other 12 variables examined in the multivariate analysis, including postoperative complication and extent of lymphadenectomy, remained significantly associated with overall survival. Thus, SRC type remained a significant and independent adverse prognostic factor (HR = 1.182).

Because advanced disease was seen more frequently in SRC patients, which meant that incomplete resections were also more frequent in this group, a multivariate analysis was performed on the R0 population. This multivariate analysis confirmed the independent pejorative prognosis of SRC type in this R0 population (see Online Resource 1 in the Electronic supplementary material, ESM).

Table 2 Pre- and postoperative prognostic factors for overall survival in the whole population at univariate analysis

Variable	$N = 1799$ (%)	Median survival		p
		Months	95 % CI	
Involvement of neighboring organs				<0.001
No	1548 (85.4)	41.3	34.6–48.0	
Yes	251 (14.6)	14.6	12.4–16.8	
Distant metastasis				<0.001
No	1732 (96.3)	36.9	32.5–41.2	
Yes	67 (3.7)	10.5	08.5–12.5	
Peritoneal carcinomatosis				<0.001
No	1672 (92.9)	39.2	34.1–44.2	
Yes	127 (7.1)	11.6	10.0–13.2	
Gastrectomy				<0.001
Total	979 (54.4)	30.2	25.9–34.6	
Subtotal	820 (45.6)	39.3	29.2–49.3	
Number of lymph nodes retrieved				<0.001
<25 lymph nodes	383 (21.3)	26.6	21.5–31.8	
>25 lymph nodes	1230 (68.4)	40.1	34.3–46.0	
Missing data	186 (10.3)			
Postoperative complication				<0.001
No	985 (54.8)	43.2	36.2–50.1	
Yes	814 (45.2)	24.9	20.8–29.0	
Postoperative chemotherapy				<0.027
No	1174 (65.3)	40.8	33.7–47.9	
Yes	625 (34.7)	28.9	25.5–32.3	
pT stage				<0.001
pT0	27 (1.5)	nr		
pTis	28 (1.6)	nr		
pT1	296 (16.5)	nr		
pT2	590 (32.8)	55.4	42.0–68.7	
pT3	604 (33.6)	21.0	19.1–22.8	
pT4	254 (14.1)	16.3	13.5–19.1	
pN stage				<0.001
pN0	637 (35.4)	148.1		
pN1	572 (31.8)	37.7	32.1–43.4	
pN2	372 (20.7)	18.8	17.0–20.6	
pN3	218 (12.18)	15.2	12.5–17.8	
pM stage				
pM0	1598 (88.8)	42.2	35.5–48.2	<0.001
pM1	201 (11.2)	11.7	10.1–13.3	
pTNM stage				
Stage I	541 (30.1)	nr		<0.001
Stage II	310 (17.2)	54.3	13.8–94.9	
Stage III	747 (41.5)	22.8	20.9–24.8	
Stage IV	201 (11.2)	11.7	10.2–13.1	
Histological type				
Non-SRC	900 (50.0)	51.1	39.2–63.1	<0.001
SRC	899 (50.0)	26.2	23.0–29.4	
Resection				
R0	1528 (84.9)	47.0	39.4–54.7	<0.001
R1	186 (10.3)	15.4	13.4–17.3	
R2	85 (4.7)	9.0	05.9–12.1	

nr median survival not reached



Non SRC	900	684	512	368	281	223
SRC	899	657	395	260	191	147

Fig. 1 Survival curves for the non-SRC and SRC groups. The number of subjects at risk at each interval is shown in the table at the *bottom* of the graph

Specific prognostic factors for overall survival in SRC adenocarcinoma

As the two histological types of gastric adenocarcinoma had distinct presentations and prognoses, a subgroup multivariate analysis based on histological type was conducted to determine whether the SRC and non-SRC gastric adenocarcinoma groups exhibit distinct prognostic factors for overall survival.

In the non-SRC group, the independent adverse prognostic factors for overall survival were high ASA score, preoperative malnutrition, limited lymphadenectomy, postoperative complication, high histological T or N stage, and a positive margin (Table 5). Preoperative chemotherapy was also associated with poorer overall survival, whereas postoperative chemotherapy was statistically associated with better survival.

The prognostic factors that were independently associated with poor survival differed somewhat for the SRC group (Table 5). Age older than 60 years, linitis, and involvement of adjacent organs were statistically associated with poor survival, but administration of preoperative or postoperative chemotherapy did not independently influence survival in the SRC group.

Prognostic factors for relapse-free survival

Among the 1799 patients included in the study, 152 were treated by performing a complete (R0) resection. The relapse rate in the R0 patients followed-up during this study was 41.36 % (632 patients). During follow-up, a relapse of the cancer occurred in 304 patients (37.49 %) in the non-SRC group and 328 patients (45.75 %) in the SRC group ($p < 0.001$).

Online Resource 2 in the ESM presents the results of the multivariate analysis performed to assess independent prognostic factors for relapse-free survival in the R0 population. Among the variables included in the Cox model, 12 independent prognostic factors were identified, including age older than 60 years, high ASA score, preoperative malnutrition, neoadjuvant chemotherapy, linitis, involvement of adjacent organs, number of lymph nodes retrieved, postoperative complications, pT stage, pN stage, pM stage, and SRC-type tumor.

Discussion

Despite improvements in diagnostic tools and changes in therapeutic strategy during the last decade in Europe, overall survival for patients with gastric cancer remains poor, with a mean age-standardized 5-year relative survival rate of 25.1 % [31]. Moreover, several recent studies have reported a decreased incidence of gastric adenocarcinoma but an increased incidence of the SRC type of gastric adenocarcinoma in Western countries [2]; this type accounted for 35–45.4 % of gastric ADC cases in recent studies [4, 5, 7, 8]. Given the worse prognosis of the SRC type than the non-SRC

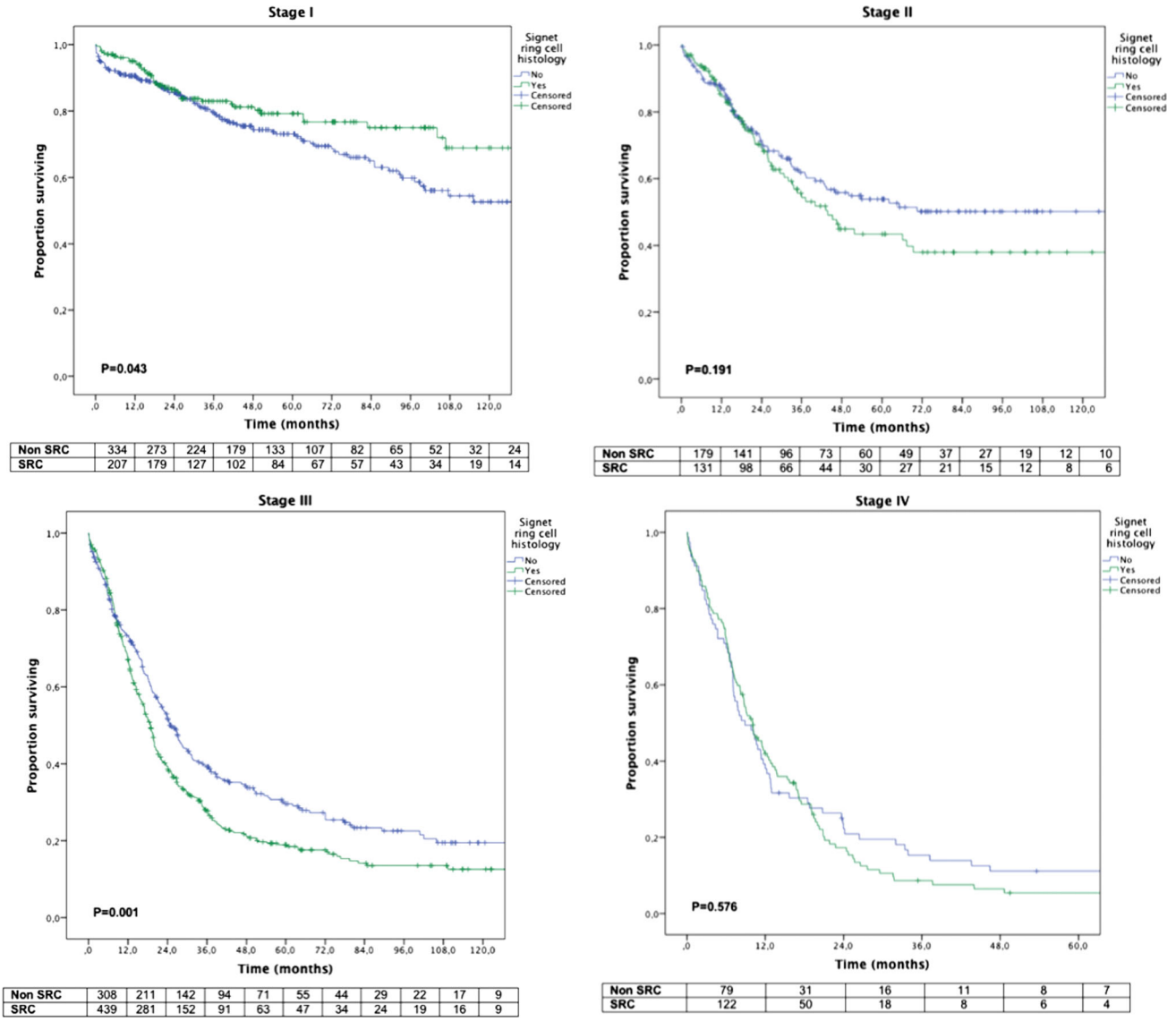


Fig. 2 Stage-stratified survival curves for the non-SRC and SRC groups

type, it may be that the increased incidence of the SRC type is contributing to the lack of improvement in overall survival of patients with gastric cancer. However, studies supporting this hypothesis are rare, especially in Europe, where only one retrospective single-center case-matched study addressing this issue has been published [5].

In the present study, using a large multicenter retrospective cohort of 1799 resected gastric carcinoma cases between January 1997 and March 2010, we confirmed that SRC histological type is an independent prognostic factor for mortality (HR = 1.182; $p = 0.041$) and for disease-free survival (HR = 1.227; $p = 0.019$) according to multivariate analysis when adjustments are made for other prognostic factors such as malnutrition, linitis, completeness of resection, tumor extension (pT stage), lymph node invasion (pN stage), and presence of distant metastasis.

In early gastric cancer (mostly described in Asian countries), it is clearly established that the prognosis of the SRC type is better than that of the non-SRC type [8, 10, 18, 19, 32], probably because the SRC-type tumor is more frequently confined to the mucosa and shows a lower rate of lymph node metastasis [18, 32]. This observed better survival may be related to the younger age of patients with SRC gastric cancer [20].

In contrast, the prognostic value of histological type in cases of advanced gastric carcinoma is still controversial. Thus, numerous studies from Asia have demonstrated that the SRC type was more frequently diagnosed at a later stage, with a higher proportion of such tumors invading subserosa (pT3) or serosa (pT4); a higher rate of lymph node metastasis is also seen for the SRC type [7, 10, 33, 34]. Furthermore, unsuspected peritoneal carcinomatosis

Table 3 Distribution of factors prognostic for overall survival in the non-SRC and SRC groups

Variable	Non-SRC $N = 900$	SRC $N = 899$	p
Gender: male	618 (68.7)	539 (59.9)	<0.001
Age >60 years	697 (77.4)	502 (55.8)	<0.001
ASA score			<0.001
1	212 (23.5)	306 (34.0)	
2	430 (47.8)	402 (44.7)	
3	238 (26.4)	180 (20.0)	
4	20 (2.3)	11 (1.3)	
Malnutrition (missing data in 144 cases)	150 (17.9)	183 (22.4)	<0.022
cTNM stage			<0.001
Stage I	275 (30.6)	195 (21.7)	
Stage II	211 (23.4)	185 (20.6)	
Stage III	387 (43.0)	471 (52.4)	
Stage IV	27 (3.0)	48 (5.3)	
Linitis	19 (2.1)	222 (24.7)	<0.001
Preoperative chemotherapy	131 (14.6)	159 (17.7)	<0.071
Involvement of adjacent organs	107 (11.9)	144 (16.0)	<0.011
Distant metastasis	34 (3.8)	33 (3.7)	<0.905
Ascites/carcinomatosis	39 (4.3)	88 (9.8)	<0.001
Total gastrectomy	433 (48.1)	546 (60.7)	<0.001
Number of lymph nodes retrieved (mean ± SD)	23.85 ± 12.47	26.41 ± 13.81	<0.001
Postoperative complication (90 days)	427 (47.4)	387 (43.0)	<0.061
Postoperative chemotherapy	251 (27.9)	374 (41.6)	<0.001
pT stage			<0.001
pT0–pTis–pT1	212 (23.5)	139 (15.5)	
pT2	338 (37.5)	252 (28.0)	
pT3	243 (27.0)	361 (40.2)	
pT4	107 (14.8)	147 (21.1)	
pN stage			<0.001
pN0	396 (44.0)	241 (26.8)	
pN1	290 (32.2)	282 (31.4)	
pN2	162 (18.0)	210 (23.4)	
pN3	52 (5.8)	166 (18.5)	
pM1 stage	79 (8.8)	122 (13.6)	<0.001
pTNM stage			<0.001
Stage I	334 (37.1)	207 (23.0)	
Stage II	179 (19.9)	131 (14.6)	
Stage III	308 (34.2)	439 (48.8)	
Stage IV	79 (8.8)	122 (13.6)	
Resection R1–R2	89 (9.9)	182 (20.2)	<0.001

was found more frequently during surgery in patients with SRC-type gastric carcinoma [7, 33, 35]. Accordingly, Asian studies reported that the SRC histological type exhibited a lower curative resection rate and was associated with poorer overall survival [7, 10, 11, 22].

Although gastric adenocarcinoma seems to behave differently in Asian and Western countries [36, 37], the four studies performed in the United States and Europe that have compared SRC with non-SRC gastric adenocarcinoma obtained similar results [4, 5, 23, 38]. As also noted in those studies, we found that the SRC type was associated with a lower curative resection rate (79.8 vs 90.1 %; $p < 0.001$) and poorer median overall survival (26.2 ± 1.62 vs 51.13 ± 6.09 months; $p < 0.001$) than the non-SRC subtype, with significantly more frequent involvement of adjacent organs (16 vs 11.9 %), linitis (24.7 vs 2.1 %), peritoneal carcinomatosis (9.8 vs 4.3 %), advanced T stage (61.3 vs 41.8 % of pT3 and pT4 stage),

Table 4 Prognostic factors for overall survival at multivariate analysis for the whole population

Variable	X^2	HR	95 % CI	p
Age >60 years	10.225	1.330	1.117–1.584	<0.001
ASA score	20.531	1.265	1.143–1.401	<0.001
Cancer-related malnutrition	17.760	1.432	1.212–1.692	<0.001
Preoperative chemotherapy	3.437	1.207	0.989–1.474	<0.064
Linitis	5.133	1.252	1.031–1.521	<0.023
Involvement of adjacent organs	9.780	1.360	1.122–1.650	<0.002
Total or subtotal gastrectomy	0.048	1.018	0.869–1.193	<0.826
More than 25 lymph nodes retrieved	8.640	0.770	0.647–0.917	<0.003
Postoperative complication (90 days)	15.443	1.334	1.155–1.540	<0.001
Postoperative chemotherapy	7.137	0.802	0.683–0.943	<0.008
SRC tumor	4.182	1.182	1.007–1.387	<0.041
pT stage	25.990	1.243	1.143–1.352	<0.001
pN stage	153.842	1.638	1.515–1.771	<0.001
pM stage	4.326	1.257	1.013–1.560	<0.038
Completeness of resection R0/R1/R2	18.469	1.372	1.188–1.585	<0.001

Table 5 Prognostic factors for overall survival at multivariate analysis for patients with signet ring cell (SRC) carcinoma and patients with non-SRC carcinoma

Group	Variable	X^2	HR	95 % CI	p
Non-SRC	Age >60 years	0.809	1.149	0.849–1.553	<0.368
	ASA score	14.532	1.343	1.154–1.563	<0.001
	Cancer-related malnutrition	17.913	1.767	1.358–2.300	<0.001
	Preoperative chemotherapy	6.575	1.515	1.103–2.082	<0.010
	Linitis	0.028	0.947	0.503–1.784	<0.867
	Involvement of adjacent organs	1.850	1.232	0.912–1.664	<0.174
	Total or subtotal gastrectomy	1.115	1.131	0.900–1.423	<0.291
	More than 25 lymph nodes retrieved	4.802	0.752	0.583–0.970	<0.028
	Postoperative complication (90 days)	8.600	1.399	1.118–1.750	<0.003
	Postoperative chemotherapy	7.660	0.692	0.534–0.898	<0.006
	pT stage	7.186	1.180	1.045–1.331	<0.007
	pN stage	69.007	1.729	1.520–1.968	<0.001
	pM stage	1.809	1.281	0.893–1.837	<0.179
	Completeness of resection R0/R1/R2	13.151	1.518	1.211–1.902	<0.001
SRC	Age >60 years	14.133	1.513	1.219–1.877	<0.001
	ASA score	5.231	1.179	1.024–1.358	<0.022
	Cancer-related malnutrition	5.249	1.291	1.038–1.606	<0.022
	Preoperative chemotherapy	0.205	1.062	0.819–1.376	<0.651
	Linitis	5.406	1.291	1.041–1.601	<0.020
	Involvement of adjacent organs	9.960	1.500	1.166–1.930	<0.002
	Total or subtotal gastrectomy	0.841	0.900	0.718–1.128	<0.359
	More than 25 lymph nodes retrieved	4.350	0.774	0.609–0.985	<0.037
	Postoperative complication (90 days)	7.036	1.297	1.070–1.572	<0.008
	Postoperative chemotherapy	1.609	0.873	0.708–1.077	<0.205
	pT stage	22.094	1.336	1.184–1.508	<0.001
	pN stage	84.998	1.592	1.442–1.757	<0.001
	pM stage	2.169	1.229	0.934–1.617	<0.141
	Completeness of resection R0/R1/R2	6.070	1.272	1.050–1.539	<0.014

and lymph node involvement (73.2 vs 56 %). However, we also found that SRC adenocarcinoma still had a poor prognosis after including these potential confounding factors in the multivariate analyses of the whole population and the R0 population, suggesting that SRC histological type is an independent adverse prognostic factor for overall survival in gastric carcinoma cases. This result is concordant with a previous French retrospective and single-center study of 180 patients [5], and is also in line with an Asian study that used multivariate analysis and found that the SRC type was associated with a poorer prognosis, albeit not statistically significantly so [35]. In contrast, among the five multivariate studies available [39–44] on the prognostic impact of SRC type in gastric adenocarcinoma, the single Western study did not find any impact of SRC type on survival [23], but Taghavi et al. acknowledged that although radicality of surgery (R0 or R1–R2) and extent of lymphadenectomy were found to be prognostic factors for overall survival in the literature (and in our multivariate analysis) [39–44], these factors were neither controlled nor recorded in their retrospective analysis of the large SEER database [23].

Among the prognostic factors for poor survival found in our study, three are characteristics of patients: patient older than 60 years (HR = 1.33; $p = 0.001$), high ASA score (HR = 1.265; $p < 0.001$), and preoperative malnutrition (HR = 1.432; $p < 0.001$). Although age has usually been included in analyses of prognostic factors for survival in gastric cancer, the two other factors were not previously included in multivariate analyses, prognostic indices, or nomograms reporting patient outcomes after gastrectomy for gastric cancer [45, 46]. However, several studies have shown that malnutrition—which was observed in 21 % of oncological patients [47] (as in our study)—significantly increases mortality after surgery for cancer [48–51]. Further studies should therefore systematically include nutritional status in their prognostic analyses.

Interestingly, postoperative chemotherapy was found to be an independent favorable prognostic factor for survival (HR = 0.802; $p = 0.008$), as demonstrated with identical hazard ratio in two recent patient-level meta-analyses [52, 53] and in the CLASSIC randomized controlled trial [54, 55]. Our retrospective study suggests that adjuvant chemotherapy may have more impact than neoadjuvant chemotherapy, but this observation could be biased by the retrospective design of this study, with selective administration of neoadjuvant chemotherapy to more aggressive tumors and of adjuvant chemotherapy to patients without postoperative morbidity. Although perioperative chemotherapy has been adopted as the standard treatment in Europe, the respective merits of pre- and postoperative chemotherapy deserve further study.

The differences in presentation at diagnosis between SRC and non-SRC gastric carcinoma and the independent prognostic value of SRC type for overall survival support the emerging concept that SRC carcinoma is a distinct disease. This concept is supported by recent results of a large molecular and genomic analysis of gastric cancers by the Cancer Genome Atlas Research Network, which defined four major genomic gastric cancer subtypes [58]. Among these, genomically stable tumors (GS tumors), which were predominantly associated with the diffuse type in the Lauren classification, share some characteristics with SRC adenocarcinoma in the WHO classification. Thus, GS tumors were associated with RHOA mutations and CLDN18-ARHGAP fusion, which contribute to the invasive phenotype of this subtype of gastric cancer, exhibiting CDH1 mutations and deficient cell adhesion.

In line with this new concept, we have individualized distinct independent prognostic factors for SRC and non-SRC gastric adenocarcinoma. Although classical prognostic factors for overall survival were found for both of these types of gastric carcinoma (e.g., pT stage, pN stage, completeness of resection, extent of lymphadenectomy, and postoperative complications), a few prognostic factors appear to be specific to only one histological type. Thus, linitis, involvement of adjacent organs, and age >60 years were found to alter survival in patients with SRC carcinoma but were not statistically associated with poorer survival in patients with non-SRC carcinoma. Similarly, postoperative chemotherapy was efficient in the non-SRC group but did not impact on survival in the SRC group, whereas preoperative chemotherapy was associated with poorer survival in the non-SRC group but had no significant impact in the SRC group. This latter observation contrasts with results from a previous study by our group, which identified preoperative chemotherapy as an adverse prognostic factor for overall survival in SRC adenocarcinoma patients [6]. This discrepancy could be partly due to the inclusion of tumors of the esophagogastric junction in the first study [56]. Moreover, important prognostic factors identified in our more recent analysis, such as age, involvement of adjacent organs, extent of lymphadenectomy, and T, N, and M components of the TNM classification, were not included in the multivariate analysis performed in the first study. To better investigate the chemosensitivity of SRC carcinoma, an ongoing prospective randomized multicentric trial has been launched by our FREGAT group (NCT01717924) [57].

In conclusion, although SRC gastric adenocarcinoma is usually diagnosed at a more advanced stage, our study demonstrates that SRC histological type is a major and independent prognostic factor for overall survival in gastric cancer. This histological type should be considered a

distinct disease among gastric cancers, with its own specific prognostic factors.

Moreover, stratification according to the SRC component is warranted in further studies of chemosensitivity and response to (neo)adjuvant chemotherapy because SRC tumors may require distinct perioperative therapeutic strategies. Those future studies should take into account the specific prognostic factors for SRC tumors identified in our study.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have nothing to disclose.

Ethical statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients before they were included in the study.

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