Is the negative prognostic impact of signet ring cell histology maintained in early gastric adenocarcinoma?

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Background. *Although the signet ring cell histologic subtype (SRC) is an independent predictor of poor prognosis in advanced gastric adenocarcinomas (GA), its prognostic value in early GA remains highly controversial. The aim of the study was to evaluate the prognostic impact of SRC in mucosal and submucosal GAs.*

Methods. *Based on a multicenter cohort of 3,010 patients operated on for GA between January 1997 and January 2010, patients with pTis or pT1 tumors were extracted and analyzed comparatively between the SRC and non-SRC groups. The primary objective was to compare the 5-year survival rate between groups.*

Results. *Among 421 patients with a pTis or pT1 tumor, 104 (25%) were SRC and 317 (75%) were non-SRC. Demographic variables were comparable between groups, except median age, which was less in the SRC group (59.6 vs 68.8 years;* $P < .001$*). Submucosal involvement was more frequent in the SRC group (94% vs 85%;* $P = .043$*), whereas lymph node involvement and number of invaded nodes were comparable between the 2 groups. When comparing SRC and non-SRC, recurrence rates (6% vs 9%;* $P = .223$*) and sites of recurrence were similar. The 5-year overall survival benefit in SRC patients (85% vs 76%, respectively;* $P = .035$*), was not evident when considering exclusively disease-specific survival or in multivariable analysis.*

Conclusion. *Contrary to more advanced GA, SRC morphologic subtype is not a negative prognostic factor in early GA. Better survival identified in some reports may be related to the younger age in SRC patients. (Surgery 2013;154:1093-9.)*

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Despite a decreasing overall incidence, gastric adenocarcinoma (GA) remains the second leading cause of cancer death worldwide with a frequency that varies widely with geographic location.[1,2] Because GA is generally a mixture of histologic patterns, the 2000 World Health Organization classification defined signet ring cell (SRC) as a GA in which the predominant component consists of isolated or small groups of malignant cells containing intracytoplasmic mucins.[3] The SRC histologic subtype corresponds to the diffuse type of the old Lauren classification.[4] Despite a decline in the incidence worldwide of the intestinal type of GA, the incidence of diffuse type has been increasing in Western studies.[5,6] Numerous reports have identified SRC as an independent predictor of poor prognosis, especially in Western countries, in which the vast majority of these tumors are diagnosed at an advanced stage, with greater incidence of lymph node metastases, a greater rate of peritoneal carcinomatosis,[6-8] and a lesser sensitivity to chemotherapy.[9] To the contrary, numerous reports from Asian countries, where the majority of GAs are diagnosed at an early stage owing to systematic screening, do not identify SRC as a predictor of poor prognosis.[10-12] Consequently, there is an interest in examining at oncologic outcomes in a large

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Western cohort of early GA patients. Because early presentations are rare in the West, the aim of the study was to test the hypothesis that SRC was an independent factor of poor prognosis in a Western, retrospective, multicenter cohort of early GA.

METHODS

Patients. This retrospective survey was conducted at 19 French surgical centers that registered all the consecutive junctional and GA cases between January 1997 and January 2010. The patient lists were verified through double checking performed by independent observers (MM, AP, and FV). A standardized questionnaire was completed for each patient concerning the preoperative, operative, and outcome parameters, including whether the patient underwent resection or not. The clinical, surgical, pathologic, and outcome parameters were double checked by independent observers, and all data were entered into a dedicated database. Inclusion criteria were patients with resected pTis or pT1 GA without neoadjuvant therapy, independent of nodal or metastatic status and type of resection. Patients' characteristics and outcomes were compared between SRC and non-SRC neoplasms.

Pretreatment workup. Pretreatment investigations included a physical examination, standard laboratory tests, an upper endoscopy with biopsies, and computed tomography (CT) of the thorax and abdomen. Endoscopic ultrasonography and esophagogastroduodenal barium studies were not performed routinely.

Operative approach. Details of the resection have been described previously.[9] Briefly, for antropyloric GA, a subtotal gastrectomy was most often performed, whereas for more proximal GA, a total gastrectomy and D2 lymphadenectomy was standard, preserving the spleen and the pancreatic tail. Lymphadenectomy was classified according to the number of lymph nodes resected (<15 lymph nodes, between 15 and 25 lymph nodes, and ≥25 lymph nodes).

Histopathologic analysis. Histologic staging of the GA was based on the 6th edition of the UICC/TNM classification, being the one of reference at the time of study accrual. GA were classified as pTis for in situ carcinoma or pT1 for tumor invading the lamina propria, the muscularis mucosa, or the submucosa. SRC GAs were defined by the World Health Organization classification as those where >50% of the tumor had SRC morphology.[3] A radical resection, with macroscopically and microscopically tumor-free margins was considered as R0 resection; an R1 resection indicated a microscopically positive resection margin, and a R2 resection a macroscopically positive resection margin. Metastatic patients were graded as having a R2 resection.

Table I. Perioperative and histomorphologic variables

Variables	*Total (%)*	*SRC group (%)*	*Non-SRC group (%)*	P *value*
n	421	104	317	—
Gender				.070
Male	293 (70)	65 (63)	228 (72)	
Female	128 (30)	39 (37)	89 (28)	
Age (y)				<.001
≤60	137 (33)	54 (52)	83 (26)	
>60	284 (67)	50 (48)	234 (74)	
ASA score*				.095
I	102 (24)	33 (32)	69 (22)	
II	220 (52)	54 (52)	166 (52)	
III	90 (22)	15 (14)	75 (24)	
IV	9 (2)	2 (2)	7 (2)	
Malnutrition*				.374
No	359 (85)	82 (79)	277 (87)	
Yes	30 (7)	9 (9)	21 (7)	
Not reported	32 (8)	13 (12)	19 (6)	
Gastrectomy extent				
Subtotal	244 (58)	44 (42)	200 (63)	<.001
Total	177 (42)	60 (58)	117 (37)	
Lymphadenectomy extent				
D0	137 (32)	25 (24)	112 (35)	<.001
D1	141 (34)	24 (23)	117 (37)	
D2	143 (34)	55 (53)	88 (28)	
pT				
pTis	54 (13)	6 (6)	48 (15)	.013
pT1	367 (87)	98 (94)	269 (85)	
pN				
pN0	337 (80)	79 (76)	258 (81)	.486
pN1	74 (18)	22 (21)	52 (17)	
pN2	10 (2)	3 (3)	7 (2)	
pM				
pM0	416 (99)	104 (100)	312 (98)	.198
pM1	5 (1)	0 (0)	5 (2)	
Resection				
R0	411 (98)	102 (98)	309 (97)	.900
R1	5 (1)	2 (2)	3 (1)	
R2	5 (1)	0 (0)	5 (2)	
Adjuvant treatment				.313
No	397 (94)	96 (92)	301 (95)	
Yes	24 (6)	8 (8)	16 (5)	

*Malnutrition indicates a weight loss >10% of the physical weight.
ASA, American Society of Anesthesiologists; *SRC*, signet ring cell histologic subtype.

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 radiograph

Table II. Patterns of recurrence in R0 and alive patients discharged from hospital (n = 396)

Variable	*Total (%)*	*SRC group (%)*	*Non-SRC group (%)*	P *value*
N	396	100	296	—
Recurrence				
No	365 (92)	95 (95)	270 (91)	.223
Yes	31 (8)	5 (5)	26 (9)	
Recurrence type (n = 31)				
Locoregional	4 (1)	1 (1)	3 (1)	.391
Distant	18 (5)	3 (3)	15 (5)	
Mixed	9 (2)	1 (1)	8 (3)	
Peritoneal recurrence				
No	389 (98)	98 (98)	291 (98)	.838
Yes	7 (2)	2 (2)	5 (2)	
Median time (mos) to first recurrence (range)	23.8 (3–118)	16 (8–39)	24 (3–118)	.617

SRC, Signet ring cell histologic subtype.

approximately every 6 months for 5 years and annually thereafter. In cases of suspected recurrence, a thoracoabdominal CT 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. The survival status of the patients was determined in March 2010, and the median follow-up was 46.2 months (range, 1–169). Three patients (1%) were lost to follow-up.

Variables studied. Data were collected retrospectively. The demographic, perioperative, and histomorphologic parameters (Table I), 30-day and in-hospital postoperative mortality and morbidity rates, recurrent disease, and overall and disease-specific survivals were studied comparatively between the SRC and non-SRC groups. The primary objective of this study was to compare the 5-year overall survival between the 2 groups. Secondary objectives were comparative analysis of the R0 resection and recurrence rates, recurrence sites, and disease-specific survival.

Statistical analysis. Statistical analysis was performed using SPSS version 15.0 software (SPSS, Chicago, Ill). 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 Chi-square 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 operation. All causes of death were considered for overall survival estimation, whereas only gastric cancer-related deaths were considered for disease-specific survival. 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 Chi-square and P values were used to characterize the independence of these factors. The hazard ratio and 95% confidence interval were used to quantify the relationship between survival and each independent factor. All statistical tests were 2-sided.

RESULTS

Pre- and perioperative variables. Among the 3,010 patients with junctional and GA, 421 (14%) were diagnosed with early GA, 104 of whom were SRC (25%) and 317 non-SRC (75%) neoplasms. The 2 groups were comparable for gender, American Society of Anesthesiologists (ASA) score, and prevalence of malnutrition (defined as weight loss of >10% of baseline physical weight over a 6-month period; Table I). Patients in the SRC group were younger than non-SRC group patients (59.6 years [range, 22.3–88.7] vs 68.8 [range, 30.8–88.3], respectively; $P < .001$). Owing to the poor prognosis usually associated with SRC in Western

Table III. Univariable analysis for overall survival

Variables	n = *421 (%)*	*Survival probability (%)*				P *value*
		1 y	*3 y*	*5 y*	*10 y*	
SRC subtype						.035
No	317 (75)	94	82	76	59	
Yes	104 (25)	93	87	85	83	
Gender						.402
Female	128 (30)	94	83	79	71	
Male	293 (70)	94	83	78	61	
Age (y)						<.001
≥60	137 (33)	99	94	91	85	
>60	284 (67)	91	78	72	54	
ASA score*						<.001
I	102 (24)	98	93	89	73	
II	220 (52)	94	88	83	71	
III	90 (22)	90	62	56	38	
IV	9 (2)	67	44	44	44	
Malnutrition* (*n* = 389)						<.001
No	359 (85)	96	86	80	65	
Yes	30 (7)	77	60	60	51	
Gastrectomy extent						.421
Subtotal	244 (58)	95	81	77	64	
Total	177 (42)	93	86	80	64	
Lymphadenectomy extent						.411
D0	137 (32)	91	80	75	60	
D1	141 (34)	95	86	79	64	
D2	143 (34)	95	83	81	69	
pT						.489
pTis	54 (13)	92	81	71	64	
pT1	367 (87)	94	83	79	64	
pN						<.001
pN0	337 (80)	93	85	80	68	
pN1	74 (18)	97	82	74	51	
pN2	10 (2)	90	0	0	0	
pM						.074
pM0	416 (99)	94	83	79	64	
pM1	5 (1)	80	80	40	40	
Resection						<.001
R0	411 (98)	94	84	80	65	
R1	5 (1)	83	50	33	33	
R2	5 (1)	75	75	0	0	
Adjuvant treatment						.339
No	397 (94)	94	83	79	65	
Yes	24 (6)	96	86	73	53	

*Malnutrition indicates a weight loss >10% of the physical weight.
ASA, American Society of Anesthesiologists; *SRC*, signet ring cell histologic subtype.

series, total gastrectomy was performed more frequently in the SRC group (58% vs 37%, respectively; $P < .001$) with a more extended lymphadenectomy ($P < .001$; Table I).

Histopathologic analysis assessment of the resected specimen. Despite more frequent submucosal invasion (94% vs 85%; $P = .043$) and a greater median number of dissected lymph nodes (26 ± 13 vs 20 ± 11; $P < .001$) in the SRC group, pN stage ($P = .486$), pM stage ($P = .198$), the median number of invaded nodes (0.7 ± 1.9 vs 0.5 ± 1.4; $P = .386$) and the R0 resection rates ($P = .900$) were similar between the SRC and non-SRC groups (Table I). Among 5 patients (1%) in the non-SRC group, who benefitted from resection, metastatic disease was found to be present as localized peritoneal carcinomatosis ($n = 2$) and isolated liver metastases ($n = 3$). In patients with incomplete

Table IV. Multivariate analysis of overall survival

Variables	Hazard ratio	95% Confidence interval	P value
Incomplete resection	3.6	1.3–9.3	.009
Age ≥60	2.2	1.2–4.2	.014
Malnutrition*	2.2	1.1–4.2	.018
pN1/pN2	2.0	1.3–3.0	.002
ASA score*	1.8	1.3–2.4	<.0001
SRC type*	0.6	0.3–1.2	.137
pM1	0.6	0.1–5.0	.606

*Malnutrition indicates a weight loss >10% of the physical weight.
ASA, American Society of Anesthesiologists; *SRC*, signet ring cell histologic subtype.

resection, proximal, distal, and lateral margins (including radial margin and distant metastases) were positive in 1.0%, 0.5%, and 1.0% of cases, respectively, without any differences between the 2 groups. A linitis plastica appearance was noted in 3% of the cases, more frequently in the SRC group (10% vs 1%; $P < .001$).

Postoperative variables. The 30-day postoperative mortality rate was 3% ($n = 14$), without any difference between the SRC and non-SRC groups (2% vs 4%; $P = .532$). Causes of postoperative mortality were anastomotic leak ($n = 5$), myocardial infarction ($n = 4$), major pulmonary complications ($n = 3$), and ischemic small bowel infarction ($n = 2$). The 30-day postoperative morbidity rate was 42% ($n = 177$) without any difference between the SRC and non-SRC groups (36% vs 44%; $P = .190$). A therapy was prescribed in 6% of patients (Table I), 23 of whom had an R0 resection and 1 had residual macroscopic disease. All 24 of these patients had adjuvant chemotherapy, and 14 patients received concomitant radiotherapy.

Recurrence. Recurrence rates in R0 patients discharged from hospital were similar between SRC and non-SRC patients (5% vs 9%, respectively; $P = .223$; Table II); the type of recurrence and in particular recurrence as peritoneal carcinomatosis was also similar between groups ($P > .391$). The median time to first recurrence was 23.8 months, which was similar between the SRC and non-SRC groups (16 vs 24 months; $P = .617$).

Survival. *Overall/disease-specific survival.* The overall median survival was not reached with 3- and 5-year survival rates of 83% and 78%, respectively. The 3- and 5-year survival rates were 81% and 71% for pTis tumors and 83% and 79% for the pT1 tumors, respectively. The 5-year overall survival rate, the primary aim of this study, was better in the SRC group than in the non-SRC group (85% vs 76%, respectively; $P = .035$), but the SRC group was considerably younger than the non-SRC group. Therefore, disease-specific survival was assessed. The disease-specific median survival was not reached with 3- and 5-year disease-specific survival rates of 94% and 91%, respectively. The 3- and 5-year survival rates were 97% and 94% for pTis tumors and 93% and 90% for the pT1 tumors, respectively. The 5-year disease-specific survival rate did not differ between the SRC and non-SRC groups (92% vs 90%, respectively; $P = .403$). These results suggest no prognostic impact of SRC in early GA, and the greater rate of non–cancer-related deaths in the non-SRC group may be related to older age.

Multivariable analysis for overall survival. To confirm this hypothesis, we looked at the impact of SRC histologic subtype in multivariable analysis. Based on the variables found to be related to poor prognosis in univariable analysis (Table III), such as age >60 years ($P < .001$), high ASA score ($P < .001$), malnutrition ($P < .001$), non-SRC tumors ($P = .035$), pN+ stage ($P < .001$), incomplete resection ($P < .001$), and pM+ stage ($P = .074$), we constructed a multivariable model. After adjustment for potential confounding factors, SRC was found not to be an independent predictor of survival. Independent predictors of poor prognosis were incomplete tumor resection, age >60 years, malnutrition, pN+ stage, and ASA score III or IV (Table IV).

DISCUSSION

Despite the incidence of the SRC GA having increased dramatically in Western countries,[5] very few studies have focused on this distinct patient and tumor behavior, epidemiology, or the efficacy of treatments for early GA as SRC or non-SRC histologies. Our team has shown in previous studies that for comparable tumor stages, SRC is associated with a lesser survival rate owing to more infiltrative tumors with a greater incidence of lymphatic spread and peritoneal seeding.[6] Most of the published studies have included locally advanced GAs that are the most frequent clinical presentation of GA in Western countries.[6] Studies looking at the prognostic impact of SRC in early GA come exclusively from Asia and suggest a similar[13] or a better[10-12,14] survival. Thus, we decided to evaluate the prognosis of SRC in a homogeneous Western population of early (pTis and pT1) SRC GA. We did not find any significant differences between SRC and non-SRC histology regarding tumor presentation and recurrence patterns. Even if we identified a 5-year overall survival

Table V. Studies comparing early SRC with non-SRC gastric adenocarcinoma

		Overall survival				
	Number of patients	*Median age (y)*	*5-year survival (%)*	*Univariable analysis*	*Multivariable analysis*	
Author and year	*SRC/ Non-SRC*	*SRC/ Non-SRC*	*SRC/ Non-SRC*	P *value*	*HR (95% CI)*	P *value*
Jiang 2011[21]	54/215	51/55	94/91	.007	2.4 (1.2–4.6)	.011
Chiu 2011[12]	505/1,934	56/64	96/90	.010	NR	NR
Zhang 2010[20]	36/61	56/58	81/79	NS	—	—
Ha 2008[10]	333/1,032	NR	100/99	.001	NR	NR
Kunisaki 2004[16]	120/393	54/60	98/91	.030	3.6 (1.1–11.7)	.03
Kim 2004[14]	94/467	50/57	96/91	NS	—	—
Hyung 2002[11]	263/670	NR	90/79	.010	2.1 (1.1–4.0)	.001
Yokota 1998[18]	93/590	56/63	91/93	NS	—	—
Maehara 1992[19]	28/356	52/58	100/95	NS	—	—

CI, Confidence interval; *HR*, hazard ratio; *NR*, not reported; *NS*, not significant; *SRC*, signet ring cell.

benefit in SRC patients (85% vs 76%, respectively; $P = .035$), however, this apparent survival benefit was not found when considering the disease specific-survival, and SRC was not a predictor of prognosis in multivariable analysis. This observation leads us to conclude that, contrary to advanced forms, SRC is not a prognostic factor in early GA. Better survival identified in some reports may be related to the younger age at presentation that is common in SRC patients[9,15] and a greater rate of non–cancer-related deaths in the non-SRC patients owing to advanced age. If we look deeper at the literature results, studies that report a better overall prognosis for early SRC GA[10-14,16-21] also document older patients in the non-SRC group (Table V).

Some of these authors have reported tumors more frequently limited to the mucosa[11] with a lesser rate of lymph node invasion in early SRC GA,[10,11] suggesting a potential role for local therapy such as endoscopic mucosectomy, especially for mucosal SRC with a diameter <2 cm.[10,11] In Western patients in particular, this approach to treatment needs to be analyzed carefully and balanced owing to (1) the high incidence of locally advanced disease at presentation, associated with a poor prognosis and the requirement for a total gastrectomy[6,22] and (2) SRC familial syndrome linked to the CDH1 gene mutation. Hereditary diffuse gastric cancer, characterized by a dominant autosomic transmission, requires a preventive total gastrectomy and is responsible frequently for multifocal, superficial SRC GA on the operative specimen.[23] All these data may explain in part why in the present study SRC patients benefited more frequently from total gastrectomy with extended lymphadenectomy. Even if the need for such extensive surgery has been proven of interest in locally advanced SRC tumors,[9] the present study does raise the question of whether a lesser operation for early SRC GA would provide equivalent results.

Despite being limited to mucosal and submucosal tumors, this study underlines that the risk for tumor dissemination is not negligible, because 20% of patients experienced lymph node involvement, 1% metastatic disease, and 2% underwent a noncurative resection, all these variables being strong predictors of poor prognosis in multivariable analysis.

The retrospective nature of our study may have introduced some bias, but having included a large number of patients in an homogeneous population of mucosal and submucosal surgically resected tumors may have limited their impact. Moreover, monitoring and quality controls performed during data collection and database construction may contribute to limit these biases.

This large study dedicated to early Western SRC tumors does not support a poorer prognosis for early SRC and suggests 2 different steps in the SRC GA carcinogenetic pathway. Early SRC are characterized by a latent state with low aggressiveness, as already reported for mutated CDH1 tumors.[23] In contrast, when SRC has invaded the muscular layer, an accelerated tumor process leads to diffuse tumor invasiveness, associated with a greater risk of spread to lymph nodes and peritoneal surfaces and is linked to poor chemosensitivity and prognosis. Altogether, these data strongly suggest the need for a tailored therapeutic strategy for SRC GA according to tumor stages.

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