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Signet ring cell adenocarcinomas: Different clinical–pathological characteristics of oesophageal and gastric locations

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Abstract

Aims: The incidence of oesogastric (OG) signet ring cell adenocarcinoma (SRC) is increasing in Western countries. The differential characteristics between oesophageal and gastric SRC tumours are unknown. We aimed to investigate the role of tumour location on prognosis in OG SRC.
Methods: Among 924 OG SRC resected in 21 centres from 1997 to 2010, consecutive patients who had oesophageal tumours (group OESO, $n = 136$) were matched to randomly selected patients who had gastric tumours (group GASTRIC, $n = 363$). Matching variables were gender, age, American Society of Anaesthesiologists score, malnutrition, pretherapeutic clinical TNM stage and neoadjuvant treatment. Patients and tumour characteristics were compared between groups and prognostic factors were identified.
Results: The two groups were well matched. Tumours in group GASTRIC were more advanced at surgical exploration, with higher rates of linitis plastica ($P < 0.001$), peritoneal carcinomatosis ($P = 0.001$), and advanced pTNM stages ($P = 0.034$). Radicality of resection and recurrence rates were similar ($P > 0.480$). Recurrences were more frequently distant ($P < 0.001$) and peritoneal ($P < 0.001$) in group GASTRIC. After adjustment on confounding variables, gastric location ($P = 0.034$) was independently associated with a better prognosis than oesophageal location.
Conclusion: Gastric and oesophageal SRC tumours are distinct diseases. Despite similar pretherapeutic factors, gastric tumours were more advanced with a greater propensity for the peritoneal surface at the diagnosis and recurrence and associated with a better prognosis.

Keywords: Gastric; Oesophagus; Cancer; Signet ring cell; Prognosis; Case control study

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Introduction

Oesogastric (OG) adenocarcinoma (ADC), ranks second amongst digestive cancers worldwide, with an incidence which is expected to continue to rise.[1,2]

Gastric signet ring cell adenocarcinoma (SRC) is a histological entity based on the microscopic characteristics of the predominant component of the tumour cells as described by the World Health Organization.[3] Recent studies have shown a striking increase in the incidence of the SRC tumours, which has risen by more than 400% in the United States since the 1970s[4–6] and composes 33%–71% of gastric ADC in recent western studies.[7–9]

We recently demonstrated that, due to specific characteristics, SRC histology was an independent predictor of poor prognosis in gastric ADC. These characteristics included the tendency for these tumours to be more infiltrative, with high affinity for lymphatic tissue, a high rate of associated peritoneal carcinomatosis and evidence of chemoresistance when the primary tumour remains in situ.[8–10] These results prompted us to consider the need for a dedicated work-up, with particular surgical and therapeutic strategies for patients with gastric SRC.[11]

SRC is a rare histologic variant of oesophageal ADC that has been recently increasing reported in the literature.[12–14] A recently published study showed that patients with a SRC ADC of the oesophagus or OG junction responded less well to induction therapy and had decreased overall survival compared with patients with non-SRC histology.[15] The pathologic appearance and clinical behaviour of oesophageal SRCs are still not well defined and comparative studies between oesophageal and gastric tumours have never been conducted. Whether specific prognosis and tumour characteristics that were identified for gastric SRCs are applicable to oesophageal SRCs remains unknown.

The aim of the study was to evaluate whether oesophageal SRCs differed from gastric SRCs in terms of long-term oncological outcomes and patterns of dissemination.

Patients and methods

Patients

A multicentre database of 2670 patients undergoing resection for OG ADC in 21 French centres from January 1997 to January 2010 was established with an independent monitoring team auditing data capture to minimize missing data and to control concordance, as well as inclusion of consecutive patients. All patients undergoing OG ADC resection during this period were included in the database. Criteria for inclusion in the study were patients with a pretherapeutic clinical TNM stage I–III, considered for curative treatment, and resected for a SRC ($n = 864$).

A matched cohort analysis was constructed to test the hypothesis that SRC tumours differed depending on their main tumour location (i.e. gastric including Siewert III tumours vs. oesophageal including Siewert I tumours). Considering, that in France the vast majority of Siewert II tumours are treated like oesophageal tumours,[16] we arbitrarely considered Siewert II tumours as oesophageal tumours.

The study group was composed of 136 patients fulfilling the inclusion criteria who had an oesophageal, or a Siewert I or II OG junction SRC (group OESO, $n = 136$). According to the frequency matching technique, the database was subdivided into strata determined by each of known strong confounders linked to (i) the patient: gender, age ($\leq$60 vs. $>$60 years), American Society of Anaesthesiologists score, and preoperative malnutrition (weight loss $\geq$10% of baseline body mass over a 6-month period), (ii) the tumour: pretherapeutic clinical tumour stage (cTNM) and (iii) the therapeutic approach: administration of neoadjuvant treatment. A broadly matched control group of patients who underwent resection for a Siewert III or gastric SRC (group GASTRIC, $n = 363$) was thus constructed, in which control subjects were randomly chosen, during the same study period, to ensure that the distribution of the matching variables was similar as found in the case group. The maximum number of patients in group GASTRIC who could be matched was considered. The sampling fraction was allowed to vary across strata. Investigators were blinded to the oncological outcomes during the selection process.

Pretreatment work-up

Diagnostic investigations routinely included physical examination, routine laboratory tests, a barium study and an oesophago-gastro-duodenoscopy with biopsies, a thoraco-abdominal CT scan and selective endoscopic ultrasound evaluation.

Surgical approach

Details of the surgical approach to resection have been previously described.[9] Briefly, for antropyloric tumours a subtotal gastrectomy was most often performed, whereas for more proximal gastric tumours a total gastrectomy was standard with a D2 lymphadenectomy preserving the spleen and the pancreatic tail. Extended resections were performed for suspected or confirmed neoplastic invasion of adjacent structures and included resections of liver, spleen, pancreas and colon. For Siewert type II tumours either a total gastrectomy extended to the lower oesophagus or an oesophagectomy was performed depending upon surgeon preference. When gastric resection was extended to the oesophagus either a transthoracic or transhiatal approach with a dedicated mediastinal lymphadenectomy was used.[9] An oesophagectomy was performed for OG Siewert I and oesophageal tumours. Patients with metastatic disease at the time of surgery were included in the analysis.

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Preoperative and postoperative treatments

Preoperative treatment was initiated between 4 and 6 weeks after the first oncological consultation. After 2006, subsequent to the results of the MAGIC study being reported,[17] epirubicin-cisplatin-5-flourouracil (ECF) perioperative chemotherapy was included in the French guidelines for treatment of OG ADC staged IB and greater. The subsequent presentation of the FNCLCC94012-FFCD9703 results provided an alternative cisplatin/5-Fluorouracil regimen.[18] Concomitant neoadjuvant radiotherapy was considered for patients with locally advanced tumours predominantly invading the oesophagus. Usually 45 Gy were administered in 25 fractions of 1.8 Gy each. For patients who underwent primary surgery, a decision regarding adjuvant chemotherapy or radiochemotherapy was made at the discretion of the multidisciplinary team meeting in accordance with the French guidelines.[19]

Histopathological analysis

Histological staging of tumours was based on the 6th edition of the UICC/TNM classification, being the one of reference at the time of study accrual. Oesophageal and OG junction Siewert II and III tumours were classified as gastric tumours whereas oesophageal and OG junction Siewert I tumours were classified as oesophageal tumours. SRCs were defined by the World Health Organization classification as those where more than 50% of the tumour consisted of isolated or small groups of malignant cells containing intracytoplasmic mucins.[3] A radical resection, with macroscopically and microscopically tumour free margins, was considered as a R0 resection, a R1 resection indicated a microscopically positive resection margin and a R2 resection a macroscopically positive resection margin. The circumferential resection margin was considered positive if tumour was found within 1 mm of it. All patients with pTNM stage IV disease were graded as having an R2 resection and tumours showing a complete pathological response were graded as pT0.

Follow-up

All patients were followed until death or the time of closing the database (March 2010). 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. All patients surviving operation were followed until death or the time of closing the database (March 2010), and the median follow-up was 48.1 (range, 0.3–151.8) months.

Endpoints of the study

The primary endpoint of the study was to evaluate whether SRCs located in the oesophagus had the same unfavourable long-term oncological outcomes (survival and recurrence) than gastric SRCs. The secondary endpoints were to evaluate whether oesophageal SRC shared the same characteristics in terms of peritoneal dissemination, lymphatic spread and tumour infiltration than gastric SRC.

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 Chi squared 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 predictive factors of survival were analysed by Cox proportional hazard regression analysis using a stepwise procedure; the 0.1 level was defined or clinical relevance in relation with the present study for entry into the model. Multivariate 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 and the database was previously registered on the Clinicaltrials.gov website (identifier NCT01249859).

Results

Demographic and perioperative parameters (Table 1)

The male to female ratio was 1.4:1 and the median age of patients was 62.9 (range 19–86) years. Patients' ASA grade was I or II in 81.8% of the cases. Malnutrition affected 22.2% of the patients. The OESO and GASTRIC groups were, as planned, comparable regarding gender, age, ASA grade, weight loss, pretherapeutic clinical stage and administration of neoadjuvant treatment. Neoadjuvant chemoradiotherapy was, as expected, more frequently administered in the OESO group (14.7% vs. 1.3%,

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Table 1
Demographic and perioperative parameters of all patients ($n = 499$).

Variables		Total $n = 499$ (%)	ESO $n = 136$ (%)	GASTRIC $n = 363$ (%)	P
Study period	<January 2006	279 (55.9)	84 (61.8)	195 (53.7)	0.107
	≥January 2006	220 (44.1)	52 (38.2)	168 (46.3)	
Gender[a]	Female	206 (41.3)	54 (39.7)	152 (41.9)	0.661
	Male	293 (58.7)	82 (60.3)	211 (50.1)	
Age (years)[a]	≤60	205 (41.1)	54 (39.7)	151 (41.6)	0.702
	>60	294 (58.9)	82 (60.3)	212 (58.4)	
ASA score[a]	I	134 (26.9)	37 (27.2)	97 (26.7)	0.932
	II	274 (54.8)	73 (53.7)	201 (55.4)	
	III	91 (18.3)	26 (19.1)	65 (17.9)	
Malnutrition[a]	No	373 (74.7)	98 (72.1)	275 (75.8)	0.472
	Yes	111 (22.2)	33 (24.3)	78 (21.5)	
	Unknown	15 (3.1)	5 (3.6)	10 (2.7)	
Pretherapeutic clinical TNM stage[a]	I	33 (6.6)	8 (5.9)	25 (6.9)	0.521
	II	108 (21.7)	34 (25.0)	74 (20.4)	
	III	358 (71.7)	94 (69.1)	264 (72.7)	
Neoadjuvant treatment[a]	No	317 (63.5)	81 (59.6)	236 (65.0)	0.260
	Yes	182 (36.5)	55 (40.4)	127 (35.0)	
Macroscopic aspect of linitis plastica	No	375 (75.2)	123 (90.4)	252 (69.4)	<0.001
	Yes	124 (24.8)	13 (9.6)	111 (30.6)	
Solid organ metastasis discovered during surgical exploration	No	485 (97.2)	135 (99.3)	350 (96.4)	0.086
	Yes	14 (8.8)	1 (0.7)	13 (3.6)	
Peritoneal carcinomatosis	No	457 (91.6)	133 (97.8)	324 (89.3)	0.002
	Yes	42 (8.4)	3 (4.4)	39 (10.7)	
Surgical approach	Laparotomy	354 (70.9)	31 (22.8)	343 (94.5)	<0.001
	Thoracotomy + Laparotomy	125 (25.1)	105 (77.2)	20 (5.5)	
Resection extended to the neighbouring organs	No	418 (83.8)	126 (92.6)	292 (80.4)	0.001
	Yes	81 (16.2)	10 (7.4)	71 (19.6)	
Postoperative 30 day morbidity	No	279 (55.9)	67 (49.3)	212 (58.4)	0.067
	Yes	220 (44.1)	69 (50.7)	151 (41.6)	
Adjuvant treatment	No	272 (54.5)	93 (68.4)	179 (49.3)	<0.001
	Yes	227 (45.5)	43 (31.6)	184 (50.7)	

ESO: esophageal and Siewert I + II tumours; GASTRIC: Siewert III and gastric tumours; ASA: American Society of Anaesthesiologists; Malnutrition: Weight loss >10% of physical weight over a 6 months period.
[a] Matching variable.

$P < 0.001$). There was a strong trend toward neoadjuvant treatment over the last years (before January 2006: 16.5% vs. from January 2006: 61.8%, $P = 0.015$).

At time of surgery, macroscopic aspect of linitis plastica ($P < 0.001$), extension to the neighbouring organs ($P = 0.001$) and peritoneal carcinomatosis ($P = 0.002$) (that was localized in 92.9%) were more frequent in the GASTRIC group. Surgical approach was, as expected, significantly different between the two groups with more thoracic operations in the OESO group ($P < 0.001$). Total gastrectomy with extended resection of the lower oesophagus was significantly more frequent in the OESO group (19.1% vs. 5.5%, $P = 0.001$).

The 30-day postoperative mortality rate was 2.6% ($n = 13$), and was similar between groups OESO and GASTRIC (3.7% vs. 2.2%, $P = 0.355$). Patients in the OESO group exhibited a trend towards higher 30-day postoperative morbidity ($P = 0.067$). Adjuvant treatment was more frequently administrated in the GASTRIC group (50.7% vs. 31.6%, $P < 0.001$) and included radiotherapy for 59 patients (16.3%) in group GASTRIC and 13 patients (9.1%) in group OESO ($P = 0.058$).

Histopathological analysis assessment of the resected specimen (Table 2)

R0 resection rates were comparable between groups ($P = 0.767$). The rate of longitudinal (proximal or distal) and lateral margin involvement did not significantly differ between the two groups ($P > 0.218$).

The median numbers of lymph nodes retrieved and invaded was significantly higher in the GASTRIC group ($P < 0.001$ and $P = 0.023$). There were no significant differences in pT ($P = 0.258$) and pN stages ($P = 0.405$). However, pM stage and pTNM stages were more advanced in the GASTRIC group ($P = 0.026$ and $P = 0.034$, respectively).

Long-term oncological outcomes

Recurrence (Table 3)

The median follow-up was comparable between groups OESO and GASTRIC (58 [0.3–148.0] vs. 46.8 [0.5–151.8], $P = 0.120$). The recurrence rate for R0 patients discharged from the hospital ($n = 369$) was 56.1%

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Table 2
Histopathological variables of the resected specimen ($n = 499$).

Variables		Total $n = 499$ (%)	ESO $n = 136$ (%)	GASTRIC $n = 363$ (%)	P
Resection	R0	379 (76.0)	102 (75.0)	277 (76.3)	0.099
	R1	99 (19.8)	32 (23.5)	67 (18.5)	
	R2	21 (4.2)	2 (1.5)	19 (5.2)	
Proximal margin	Negative	450 (90.2)	121 (89.0)	329 (90.6)	0.578
	Positive	49 (9.8)	15 (11.0)	34 (9.4)	
Distal margin	Negative	458 (91.8)	126 (92.6)	332 (91.5)	0.667
	Positive	41 (8.2)	10 (7.4)	31 (8.5)	
Longitudinal margin	Negative	422 (84.6)	113 (83.1)	309 (85.1)	0.575
	Positive	77 (15.4)	23 (16.9)	54 (14.9)	
Lateral margin	Negative	450 (90.2)	119 (87.5)	331 (91.2)	0.218
	Positive	49 (11.8)	17 (12.5)	32 (8.8)	
Median number of dissected lymph nodes		24.0 [4.0–98.0]	21.0 [4.0–59.0]	26.0 [4.0–98.0]	0.001
Median number of invaded lymph nodes		5.0 [0–63.0]	5.0 [0–48.0]	6.0 [0–63.0]	0.023
pT	pT0	2 (0.4)	1 (0.7)	1 (0.3)	0.258
	pTis	2 (0.4)	0 (0)	2 (0.6)	
	pT1	44 (8.8)	15 (11.0)	29 (8.0)	
	pT2	128 (25.7)	35 (25.7)	93 (25.6)	
	pT3	229 (45.9)	67 (49.4)	162 (44.6)	
	pT4	94 (18.8)	18 (13.2)	76 (20.9)	
pN	pN0	105 (21.0)	33 (24.3)	72 (19.8)	0.405
	pN1	158 (31.7)	47 (34.6)	111 (30.6)	
	pN2	133 (26.7)	32 (23.5)	101 (27.8)	
	pN3	103 (20.6)	24 (17.6)	79 (21.8)	
pM	pM0	449 (89.9)	129 (94.9)	320 (88.2)	0.026
	pM1	50 (10.1)	7 (5.1)	43 (11.8)	
pTNM stage	0–I	77 (15.5)	23 (16.9)	54 (14.9)	0.034
	II	79 (15.8)	29 (21.3)	50 (13.8)	
	III	293 (58.7)	77 (56.7)	216 (59.5)	
	IV	50 (10.0)	7 (5.1)	43 (11.8)	

ESO: esophageal and Siewert I + II tumours; GASTRIC: Siewert III and gastric tumours.

($n = 207$) and was not significantly different between the OESO and GASTRIC groups (56.6% vs. 55.9%, $P = 0.913$). The median time to first recurrence after surgery was 11.7 months [1.0–111.0] and did not differ between OESO and GASTRIC groups (11.2 vs. 12.0 months, respectively $P = 0.393$). Locoregional recurrence rate was significantly higher in the OESO group ($P < 0.001$) whereas distant recurrence and more importantly peritoneal recurrence were more frequent in the GASTRIC group ($P = 0.005$ and $P < 0.001$, respectively).

Survival

The overall median survival was 19.7 months with 3- and 5-year survival rates of 31.2% and 19.8%, respectively. For patients who underwent R0 surgical resection, the 3- and 5-year survival rates were 38.5% and 25.3%, respectively when compared to 11.4% and 4.3% for R1 resections, respectively and 0% at 36 months for R2 resections ($P < 0.001$).

Median survivals were comparable between the GASTRIC and OESO groups (19.9 vs. 17.9 months,

Table 3
Recurrence in R0 patients discharged from hospital ($n = 369$).

Variables		Total $n = 369$ (%)	ESO $n = 99$ (%)	GASTRIC $n = 270$ (%)	P
Recurrence	No	162 (43.9)	43 (43.4)	119 (44.1)	0.913
	Yes	207 (56.1)	56 (56.6)	151 (55.9)	
Locoregional recurrence	No	345 (93.5)	85 (85.9)	260 (96.3)	<0.001
	Yes	24 (6.5)	14 (14.1)	10 (3.7)	
Distant recurrence	No	240 (65.0)	72 (72.7)	168 (62.2)	0.061
	Yes	129 (35.0)	27 (27.3)	102 (37.8)	
Peritoneal recurrence	No	242 (65.6)	81 (81.8)	161 (59.6)	<0.001
	Yes	127 (34.4)	18 (18.2)	109 (40.4)	
Mixed recurrence	No	315 (85.4)	84 (84.8)	231 (85.6)	0.865
	Yes	54 (14.6)	15 (15.2)	39 (14.4)	
Median time to first recurrence (months) [range min–max]		11.7 [1–111]	11.2 [1–90]	12.0 [1–111]	0.393

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$P = 0.277$) with 5-year survival rates of 21.1% and 16.8%, respectively (Fig. 1). In the R0 population, when comparing OESO and GASTRIC groups, median survival was 22.7 vs. 26.8 months ($P = 0.089$) and 5-year survival rates were 18.1% vs. 28.3% (Fig. 2).

Since pTNM stage and pM stage were more advanced in group GASTRIC, we performed a survival analysis stage by stage. Survival stage by stage was significantly different between groups ($P = 0.020$), favouring group GASTRIC. When comparing OESO and GASTRIC groups, median survival was 50.4 vs. 66.2 months in pTNM stages I and II patients, 16.9 vs. 18 months in pTNM stage III patients and 5.8 vs. 7.3 months in pTNM stage IV patients.

Prognostic factors in the overall population

Based on univariate analysis, 11 variables were found to be statistically related to poor prognosis (Table 4): high ASA score ($P = 0.016$), malnutrition ($P < 0.001$), advanced pretherapeutic clinical TNM stage ($P < 0.001$), macroscopic aspect of linitis plastica ($P < 0.001$), total gastrectomy with extended resection of the lower oesophagus ($P = 0.019$), 30-day postoperative morbidity ($P = 0.003$), advanced pT, pN, pM and pTNM stages ($P < 0.001$ for each) and incomplete tumoural resection (R1 or R2) ($P < 0.001$).

After adjustment for potential confounding factors, gastric tumour location was an independent predictor of good prognosis (HR 0.76, $P = 0.033$), whereas advanced pTNM stage (HR 2.03, $P < 0.001$), incomplete resection (HR 1.81, $P < 0.001$), 30-day postoperative morbidity (HR 1.34, $P = 0.009$), macroscopic aspect of linitis plastica (HR 1.36, $P = 0.011$) and malnutrition (HR 1.36, $P = 0.014$) were independent factors of poor prognosis (Table 5).

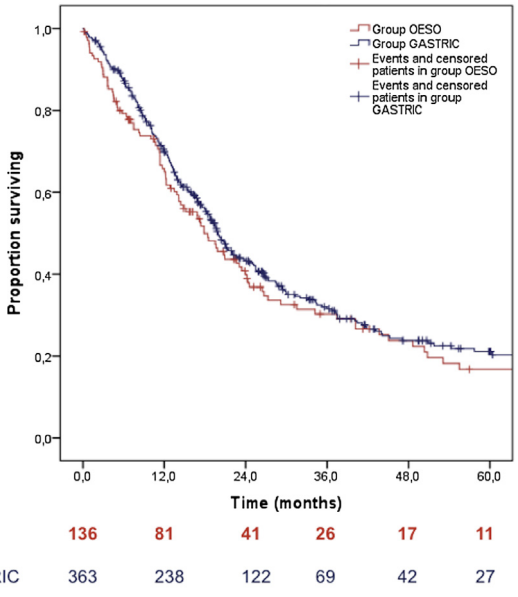

Figure 1. Overall survival curves in group OESO ($n = 136$ oesophageal and Siewert I + II tumours) vs. group GASTRIC ($n = 363$ Siewert III and gastric tumours).

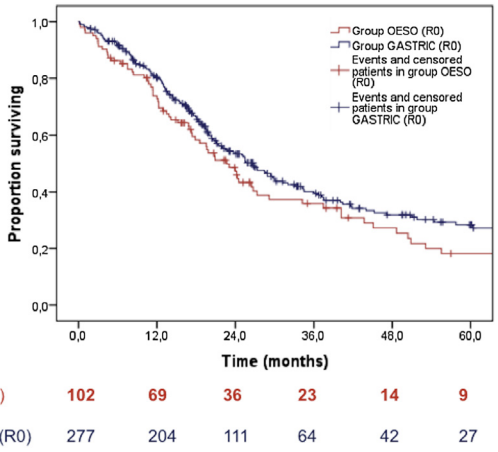

Figure 2. Overall survival curves in R0 resected patients in group OESO ($n = 102$ oesophageal and Siewert I + II tumours) vs. group GASTRIC ($n = 277$ Siewert III and gastric tumours).

Discussion

Several studies recently demonstrated the specific characteristics of gastric SRCs when compared to non-SRCs. Such characteristics include their highly infiltrative nature, high affinity for both lymphatic and peritoneal spread, and evidence of chemoresistance. All these factors lead to a dismal prognosis and hence demand the development of a dedicated oncological and surgical strategy for this histological subtype.[8,9,20] The growing incidence of oesophageal SRC[12–14] prompted us to question whether this tumour location was associated with similar long-term oncological outcomes and tumour seeding characteristics as seen in gastric SRC tumours.

In the present case matched study, we demonstrate that gastric and oesophageal SRCs are two distinct diseases. Despite similar pretherapeutic clinical stage and preoperative treatment, gastric tumours were more advanced with a tendency for more peritoneal disease both at the time of surgical exploration and of recurrence. Oesophageal tumour location was independently predictive of poor prognosis.

A gastric location has been identified in previous publications to expose patients to higher risk of peritoneal metastasis at diagnosis when compared to oesophageal or junctional ADC (28.8% vs. 6–11%).[21] In the present study, the same observations have been made (10.8% vs. 2.2%, $P = 0.002$, respectively), with however a lower incidence of peritoneal carcinomatosis in both groups, possibly because surgical resection is less likely to be performed in cases of peritoneal tumour seeding, a fortiori palliative oesophagectomy. This higher rate of peritoneal seeding at surgical exploration in the GASTRIC group mainly explains the more advanced pTNM stage observed since pT and pN stages were well balanced. We did not show any difference regarding margin involvement between groups, but total gastrectomy with extended resection of the lower

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Table 4
Survival in resected patients ($n = 499$): variables issued from univariate analysis.

Variables		Median survival (months)	CI (95%)	P
Study period	<January 2006	19.0	16.9–21.2	0.291
	≥January 2006		17.9–27.5	
Tumour location	ESO	17.9	13.3–22.4	0.277
	GASTRIC	19.9	17.9–21.9	
Gender	Female	19.8	16.9–22.6	0.684
	Male	19.5	17.1–22.0	
Age (years)	≤60	19.9	15.7–24.0	0.250
	>60	19.5	17.3–21.8	
ASA score	I	36.9	14.5–25.2	0.016
	II	48.3	17.9–24.1	
	III	26.1	11.9–17.4	
Malnutrition	No	18.1	18.1–23.5	<0.001
	Yes	10.6	10.6–16.2	
Pretherapeutic clinical TNM stage	I	81.5	24.5–138.5	<0.001
	II	32.0	21.3–42.7	
	III	16.7	14.2–19.2	
Neoadjuvant treatment	No	20.4	18.3–22.5	0.712
	Yes	18.0	14.5–21.5	
Macroscopic aspect of linitis plastica	No	22.6	18.9–26.2	<0.001
	Yes	13.5	11; 1–15.9	
Total gastrectomy with extended resection of the lower oesophagus	No	20.4	18.0–22.8	0.019
	Yes	14.1	3.6–24.7	
30-day postoperative morbidity	No	24.4	20.8–28.1	0.003
	Yes	13.9	10.8–16.9	
Postoperative treatment	No	19.1	16.8–21.4	0.466
	Yes	20.8	17.7–24.0	
pT	pT0	60.0	48.8–73.0	<0.001
	pTis	96.0	60.9–123.0	
	pT1	144.0	124.1–161.2	
	pT2	36.1	33.4–39.2	
	pT3	18.8	15.3–21.2	
	pT4	10.6	8.9–12.7	
pN	pN0	55.5	22.7–88.3	<0.001
	pN1	26.8	20.1–33.6	
	pN2	13.7	11.2–16.2	
	pN3	12.0	9.7–14.3	
pM	pM0	44.7	18.5–23.7	<0.001
	pM1	10.8	4.3–9.8	
pTNM stage	0–I	N. R		<0.001
	II	37.2	23.9–50.6	
	III	17.3	14.9–19.7	
	IV	7.2	4.8–9.6	
Resection	R0	49.3	21; 5–29.0	<0.001
	R1	16.8	9.7–12.9	
	R2	7.3	1.9–9.2	

ESO: esophageal and Siewert I + II tumours; GASTRIC: Siewert III and gastric tumours; CI: confidence interval; NR: not reached; ASA: American Society of Anaesthesiologists; Malnutrition: Weight loss >10% of physical weight over a 6 months period.

oesophagus was more frequently required in the OESO group. Overall, the established propensity of SRCs for the peritoneal surfaces especially in group GASTRIC[8] and the longitudinal infiltration characteristic in group OESO, make the argument for systematic laparoscopic exploration for OG SRC regardless of the tumour location.

With regards to the recurrence pattern, we recently published a study dedicated to identifying predictive factors of peritoneal recurrence among 424 curatively resected patients.[22] Similar to our current findings, gastric tumour location was a predictive factor of peritoneal recurrence.[22] The intra abdominal location of the stomach covered by a peritoneal surface may be part of the explanation, favouring "contact" and transcoelomic tumoural seeding more than a hematogeneous dissemination.

Our data confirm established parameters like pTNM stage and R status to be correlated with overall survival in OG SRCs.[8,9] In addition, the present study identified oesophageal tumour location as an independent factor of poor prognosis. We included tumour location in the multivariate analysis because of the clinical relevance of this analysis. Moreover, despite matching of pretherapeutic variables, the different pTNM stage between groups (more advanced in group GASTRIC) was a potentially confounding variable

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Table 5
Survival in resected patients: variables issued from multivariate analysis.

Variables	Multivariate analysis		
	P	χ^2	Hazard ratio (95% confidence interval)
pTNM stage	<0.001	62.51	2.03 (1.70–2.41)
Radicality of resection	<0.001	33.58	1.81 (1.48–2.20)
Postoperative 30 day morbidity	0.009	6.80	1.34 (1.07–1.67)
Malnutrition	0.014	6.08	1.36 (1.07–1.75)
Macroscopic linitis plastica	0.011	6.45	1.37 (1.07–1.75)
Tumour location (GASTRIC vs. ESO)	0.034	4.50	0.76 (0.59–0.98)
Neoadjuvant treatment	0.082	3.02	1.25 (0.97–1.59)
Age (<≤60 vs. >60)	0.159	1.99	1.18 (0.94–1.49)
ASA grade	0.684	0.17	0.97 (0.81–1.14)

as shown by the difference of survival stage by stage between groups ($P = 0.020$). Among series of gastric ADC including OG junction tumours, location of the primary tumour has long since been known to carry prognostic information, with a worse prognosis for proximal cancers when compared to distal lesions.[23,24] When focussing on OG junction tumours, long-term outcome has repeatedly been shown to be better for Siewert I and II tumours relative to Siewert III tumours in univariate analysis.[25,26] However the prognostic impact of tumour location was lost in multivariate analysis,[26] without consideration being taken of the SRC histological subtype. One can argue that proximal OG junction cancers may be detected earlier due to Barrett's oesophagus surveillance programs or due to earlier symptoms such as dysphagia related to a narrowed oesophagus.[25] The SRC infiltrative characteristics may lead to a later onset of dysphagia compared with non-SRCs and may explain the worse prognosis identified in the present work.

The occurrence of surgical complications and malnutrition were also identified as independent predictors for poorer long-term survival, correlating closely with previous studies.[27–29] Linitis plastica is commonly associated with advanced tumoural stages in gastric SRC cancers, especially with serosal and lymph node invasion and remains of high prognostic value after adjustment for these variables. This strongly suggests a specific carcinogenetic pathway of the linitis plastic form may be through the tumoural micro-environment characterized by the abundant stroma.[30] Of importance, and as previously published by our group,[9] administration of neoadjuvant chemotherapy in resected OG SRC was not associated with improved survival.

This study is limited by its retrospective nature, which may lead to missing data and may introduce bias. The overall sample size, however, gives sufficient statistical robustness and the multicentre data collection allows for more universal results. Moreover, intent to treat analysis has limited the selection bias and a rigorous and blinded matching process has allowed comparisons of homogenous groups and robust conclusions. Follow-up end date was March 2010, time of closing the database and could not be updated afterwards due to the high number of patients and centres included. However median follow-up raised 48.1 months with no missing data due to an independent monitoring team auditing data capture. This study covers a long period, with a strong trend toward neoadjuvant treatment from 2006 ($P = 0.015$). However patients were matched according to the administration of neoadjuvant treatment. Moreover, survival was similar between groups when comparing patients operated on with or without neoadjuvant treatment and according to the study period.

To conclude, gastric and oesophageal SRCs are two distinct diseases. Gastric tumours were more advanced with a greater propensity for peritoneal spread at diagnosis and peritoneal recurrence after resection. Oesophageal tumour location is an independently predictive factor for poor prognosis in OG SRCs. In these highly infiltrating tumours, staging laparoscopy should be performed and an extended resection should systematically be attempted to achieve an R0 resection which remains a major prognostic factor.

Conflict of interest statement

We have no disclosure of any financial and personal relationships with other people or organizations that could inappropriately influence our work: no potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. The authors declare that they have no competing interests.

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