

Resectable gastric signet ring cell carcinoma: clinicopathological characteristics and survival outcomes

Ines Zemni^{1*}, Houyem Mansouri¹, Ines Ben Safta¹, Mohamed Ali Ayadi¹, Tarek Ben Dhiab¹, Riadh Chargui¹, Khaled Rahal¹

¹Department of surgical oncology, Salah Azaiez Institute, Faculty of Medicine of Tunis, University Tunis el Manar, Tunisia.

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*Correspondence to

Dr. Ines Zemni
Department of surgical oncology
Salah Azaiez Institute
Faculty of Medicine of Tunis
University Tunis el Manar
Avenue 9 Avril Bab Saadoun
1006 Tunis, Tunisia
Telephone: +216 71 563 980
ines.zemni@yahoo.fr

ABSTRACT

Background:

Gastric signet ring cell carcinoma (SRCC) appears to have clinical features and survival rates particularly different from other histological types. The aim of this study was to investigate clinicopathological features and survival outcomes of SRCC and to compare them with non-signet ring cell carcinoma (NSRCC).

Methods:

We retrospectively studied 145 patients with non-metastatic gastric carcinoma who underwent gastrectomy in our institute from 2005 to 2015. Among them, 36 patients (9.4%) with SRCC were compared to 109 patients (90.6%) with NSRCC.

Results:

Patients with SRCC presented at a younger age ($p=0.001$) with more advanced stage III-IV disease ($p=0.005$) and advanced N stages with a higher rate of pN3 ($p=0.0001$), a higher number of invaded lymph nodes ($p=0.002$) and a higher rate of patients with a lymph node ratio exceeding 25% (63.9% vs 36.7, $p=0.004$). After a median follow up of 35.30 months, there was no significant difference in the 5 years overall (OS) survival between SRCC and NSRCC ((36.7% vs 45.7%, $p=0.206$). However, the 5 years progressive free survival (PFS) was significantly decreased in case of SRCC (38.7% vs 50.9%, $p=0.038$) with a higher rate of metastasis in (52.9% vs 29.5%, $p=0.013$) and peritoneal recurrence (35.3% vs 9.5%, $p<0.0001$). The main prognostic factors of PFS and OS in SRCC were tumoral stenosis, hypoprotidemia, tumor size, depth of invasion ($p=0.001$), perineural and lymphovascular invasion, the UICC stage and complete surgical resection.

Conclusion:

Gastric SRCC have a particular clinicopathological behavior compared to NSRCC suggesting its more aggressive character.

Keywords:

gastric cancer, signet ring cell carcinoma, pathology, prognosis.

Background

Gastric signet ring cell carcinoma (SRCC) is defined as an adenocarcinoma composed of isolated or small groups of malignant cells with abundant intracytoplasmic mucinas predominant component (more than 50% of the tumor).[1, 2]According to Lauren’s classification, SRCC and gastric linitis, are part of the diffuse type. [3]Another Japanese classification separates gastric adenocarcinoma into two groups: differentiated and undifferentiated.[4]“Differentiated” cancers include well-differentiated, moderately differentiated and papillary adenocarcinoma. “Undifferentiated” cancers consist of poorly differentiated adenocarcinoma and SRCC.[5] SRCC appears to have clinical features and survival rates particularly different from other histological types according to the stage at diagnosis. The aim of this study was to investigate clinicopathological features and survival outcomes of SRCC and to compare them with non-signet ring cell carcinoma (NSRCC).

Methods

The medical records of 145 patients who underwent curative or palliative gastrectomy for non-metastatic gastric adenocarcinoma from January 2005 to December 2015 were retrospectively reviewed. From all, 36 patients had histologically proven gastric SRCC. Exclusion criteria were as follows: metastatic disease, other synchronous tumoral location, unknown surgery status, unknown vital status; incomplete pathological data, and less than 50% of signet ring cells. Demographic data (Sex, age), clinical presentation, tumor size, tumor location, histopathological variables, (lymph node ratio (LNR), microscopic invasions (venous, perineural or lymphovascular invasion), TNM stage, type of surgery and associated resection were recorded. Lymph node metastasis (N stage) and depth of tumor invasion (T stage) were classified according to the 8th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging system.

Statistical analysis

Continuous data were summarized using descriptive statistics (mean, standard deviation (SD), median, minimum, and maximum values). Categorical data were summarized using frequency and percentages. Clinicopathological differences between NSRCC and SRCC were compared with the Chi-square test for categorical variables. Overall survival (OS) was calculated as the time from surgery to death of any cause or the last follow-up date. Progressive-free survival (PFS) was measured from the time of surgery to initial tumor relapse (local or distant recurrence) or the initial tumor progression in patients with incomplete resection. Survival curves were generated using the Kaplan-Meier (KM) method and then compared with the log-rank test. Differences were considered to be statistically significant when $p < 0.05$. All statistical analyses were performed using SPSS version 20.0.

Results

Of 145 patients, there were 93 males and 52 females (1.78:1) with a mean age of 61.48 ± 12.86 years. 36 patients (9.4%) had signet ring cell carcinoma and 109

patients (90.6%) had non-signet ring cell carcinoma. Clinical and therapeutic features of patients with SRCC are summarized in Table 1.

Table 1: Clinical, and therapeutic features of patients with gastric signet ring cell carcinoma.

Variables		No of patients	%
Age (mean, range, years) 54.25 (29-85)	≥60 years	9	25%
	<60 years	27	75%
Gender	Men	21	58.3%
	Women	15	41.7%
Symptoms	Gastric pain	34	94.9%
	Vomiting	15	41.7%
	Melena	1	2.8%
	Hematemesis	3	8.3%
	Abdominal mass	1	2.8%
	Asthenia	28	77.8%
	Anorexia	29	80.6%
	Weight Loss	31	86.1%
Tumor location	Dysphagia	31	2.8%
	Cardia	3	8.3%
	Gastric fundus	12	33.3%
	Gastric antrum	19	52.8%
Whole stomach	Whole stomach	2	5.6%
	Stenosis		
Stenosis	No	27	75%
	Yes	9	25%
Surgical resection	TG	23	63.9%
	PG	13	36.1%
MVR	No	28	77.8%
	Yes	8	22.2%
LND	D1	4	11.1%
	D1.5	8	22.2%
	D2	24	66.7%

Treatment	Surgery alone	10	27.8%
	NACT+S+CT/RT	4	11.1%
	S+ADJ CT	8	22.2%
	S+ADJ RTCT/RT	14	38.9%

TG: total gastrectomy, PG: partial gastrectomy, MVR: multi-visceral resection, LND: Lymph node dissection; S: surgery, NACT: neoadjuvant chemotherapy, ADJ: adjuvant chemotherapy, ADJ RTCT/RT: adjuvant radio-chemotherapy or radiation therapy

The mean age of patients with SRCC was 54.25 ± 11.49 years. The most common complaint was abdominal pain (34 patients, 94.9%). The tumor was located in the cardia in three cases (8.3%), in the gastric fundus in twelve cases (33.3%), in the gastric antrum in 19 cases (52.8%) and in the whole stomach in 2 cases (30.4%). Total gastrectomy (TG) was the most common surgical procedure, performed in 63.9% of cases (23 patients) while 36.1% of patients had partial gastrectomy (PG). Multivisceral organ resection was necessary in eight patients (22.2%). We performed a D2 lymph node dissection (LND) in 24 cases (66.7%), a D1.5 LND in eight patients (22.2%) and four patients (11.1%) underwent a D1 lymph node dissection (LND).

Neoadjuvant chemotherapy was administered in four cases (11.1%). Thirty two patients (88.9%) underwent primary surgical resection which was followed by adjuvant chemotherapy in eight cases (22.2%), adjuvant radiation therapy or concomitant radio chemotherapy in 14 cases (38.9%) and ten patients (27.8%) were treated by exclusive surgical resection (Table 1).

The pathological features of patients with SRCC are listed in table 1. Complete surgical resection R0 was achieved in 32 patients (88.9%) and four patients (11.1%) had incomplete resection (R1/R2). The mean tumor size was 74.3 ± 46.53 mm and 61.1% of lesions exceeded 50mm. Perineural and lymphovascular invasion were found in 21 patients (58.3%). Depth of tumor invasion according to the 8th edition AJCC/ UICC TNM system was pT1 in 2 cases (5.6%), pT2 in 5 cases (13.9%), pT3 in 17 cases (47.2%) and pT4 in 12 cases (33.3%).

The mean number of retrieved lymph node was 22.28 ± 9.48 (range, 9 - 50) with less than 15 extracted LN in seven cases (19.4%). Lymph node metastasis was found in 32 patients (88.9%) and the mean number of metastatic lymph node was 11.81 ± 8.61 (range, 1-38). LNR was greater than 25% in 66.7% of cases. Thirty patients were staged pN2-N3 (83.3%) and six patients (16.7%) were staged pN0-N1. Advanced stages (stage III and IV) were found in 78.8% of cases according to the AJCC classification.

Clinicopathologic characteristics were compared between signet ring cell carcinoma (SRC) and non-signet ring cell carcinoma (NSRC) and represented in Table 2.

Table 2: Pathological characteristics of patients with SRCC

Variables	No of patients	%	
Tumor size (mean, range, mm)	<50mm	14	38.9%
	≥50mm	22	61.1%
34 mm (range, 15mm-60mm)			
pT stage	pT1	2	5.6%
	pT2	5	13.9%
	pT3	17	47.2%
	pT4	12	33.3%
pN stage	pN0	4	11.1%
	pN1	2	5.6%
	pN2	7	19.4%
	pN3a	14	38.9%
	pN3b	9	25%
pM stage	pM0	32	88.9%
	pM1	4	11.1%
AJCC stage	I	2	5.6%
	II	6	16.7%
	III	25	66.7%
	IV	4	11.1%
NRLN (mean, range) 22 (min 9-max 50)	NRLN <15 LN	7	19.4%
	NRLN ≥15 LN	29	80.6%
NMLN (mean, range) 11.81 (min 1-max38)	LNR0	4	11.1%
	LNR1	2	5.6%
	LNR2	6	16.7%
	LNR3	26	66.7%
PNI	No	15	41.7%
	Yes	21	58.3%

LVSI	No	15	41.7%
	Yes	21	58.3%
Resection	R0	32	88.9%
	R1/R2	4	11.1%
NRLN: number of retrieved lymph node, NMLN: number of metastatic lymph node, LNR: lymph node ratio, LNR0: LNR=0; LNR:0%<LNR≤10%; LNR2: 10%<LNR≤25%, LNR3: LNR>25%, PNI: Perineural evasion; LVSI: lympho-vascular space invasion.			

Signet ring cell carcinoma presented at a younger age ($p=0.001$) with no significant difference in gender.

Most of cases of SRCC were located in the middle and lower third of the stomach (33.3% and 52.8% respectively). Patients with signet ring cell carcinoma were more likely to present with more advanced stage III-IV disease (77.8% vs 51.4%, $p=0.005$). A depth of tumor invasion greater than T2 was found more frequently in patients with SRCC (80.6%) than in those with NSRCC (69.7%). Advanced N stages were significantly more prevalent in SRCCs with particularly a higher rate of pN3 (63.9% vs 22%, $p=0.0001$), a higher number of invaded lymph nodes (11.81 vs 6.82, $p=0.002$), and a higher rate of patients with a lymph node ratio exceeding 25% (63.9% vs 36.7, $p=0.004$).

The median follow up was 35.30 months (range 2-139 months). After exclusion of five cases of postoperative death and one patient lost of view, there was no significant difference in the 5 years overall survival between SRCC and NSRCC (36.7% vs 45.7%, respectively, $p=0.206$).

Table 3: Comparison of the Clinicopathological Characteristics and survival outcomes of Patients with Signet-Ring Cell Carcinoma (SRC) and non-signet ring cell carcinoma (NSRC)

Variables	SRCC	NSRCC	P
Gender	Male	72 (66.1%)	0.402
	Female	15 (41.7%)	
Tumor location	Upper third	18 (16.5%)	0.06
	Middle third	33 (30.3%)	
	Lower third	58 (53.2%)	
	Whole	0	
Age	≤ 65 years	59 (54.1%)	0.001
	> 65 years	50 (45.9%)	
Tumor size	<50 mm	44 (40.4%)	0.875
	≥50 mm	65 (59.6%)	
pT stage	pT1-T2	33 (30.3%)	0.207
	pT3-T4	76 (69.7%)	

However, patients with SRCC stage pT4 seems to have a worse 5 years OS compared to those with NSRCC without statistically significant difference (0 vs 23.6% respectively, $p=0.068$).

The univariate analysis of the prognostic factors associated of the 5 years OS of SRCC showed that the tumoral stenosis ($p=0.039$), hypoprotidemia (<0.0001), the depth of invasion ($p=0.003$), perineural invasion (PNI) (<0.0001), lymphovascular space invasion (LVSI) (<0.0001), and UICC stage ($p=0.007$) (Figure 1) were the main prognostic factors of overall survival in SRCC (Table 3).

The overall survival was not correlated to the type of

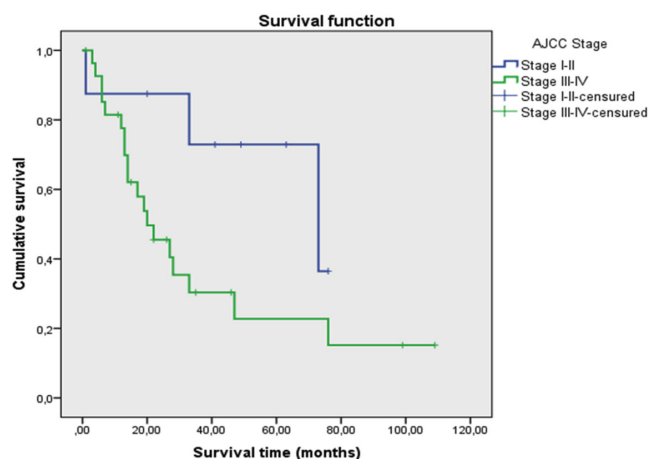


Figure 1: Kaplan-Meier (KM) survival curves of OS according to the AJCC stage. There were significant differences ($p=0.007$).

pN stage	pN0	4 (11.1%)	22 (20.2%)	<0.0001
	pN1	2 (5.6%)	29 (26.6%)	
	pN2	7 (19.4%)	34 (31.2%)	
	pN3	23 (63.9%)	24 (22%)	
LNR	≤ 25%	13 (36.1%)	69 (63.3%)	0.004
	>25%	23(63.9%)	40(36.7%)	
NMLN		11.81 ±8.611	6.82±7.297	0.002
UICC stage	Stage I-II	8 (22.2%)	53 (48.6%)	0.005
	Stage III-IV	28 (77.8%)	56 (51.4%)	
LVSI	No	15 (41.7%)	58 (53.2%)	0.230
	Yes	21 (58.3%)	51 (46.8%)	
PNI	No	15 (41.7%)	61 (56%)	0.136
	Yes	21 (58.3%)	48 (44%)	
Metastatic recurrence	No	16 (47.1%)	74 (70.5%)	0.013
	Yes	18 (52.9%)	31 (29.5%)	
Peritoneal recurrence	No	24 (64.7%)	95 (90.5%)	<0.0001
	Yes	12 (35.3%)	10 (9.5%)	
5 years OS		36.7%	45.7%	0.206
5 years PFS		38.7%	50.9%	0.038

gastrectomy and the lymphadenectomy extend.

The 5 years overall survival was higher when complete surgical resection (R0) is achieved, compared to R1/R2 resection (41% vs 0% respectively, $p=0.069$). The number of retrieved lymph node exceeding 15 seems to enhance the 5 years OS (38.7% in case of more than 15 retrieved LN and 21.4% if the NRLN was less than 15 LN, $p=0.330$). According to N stage, patients with pN0-N1 stages had better 5 years OS rate compared to patients with pN2-N3 (62.5% vs 30%, $p=0.431$).

The 5 years progressive free survival (PFS) was significantly decreased in SRCC compared to NSRCC (38.7% vs 50.9% respectively, $p=0.038$) (Figure 2).

From the 145 patients, 49 patients (33.8%) presented a metastatic recurrence with significant higher rate of metastasis in SRCC compared to NCRCC (52.9% vs 29.5% respectively, $p=0.013$). Moreover, we found that the rate of peritoneal recurrence was significantly higher in patients with SRCC compared to those with NSRCC (35.3% vs 9.5% respectively, $p<0.0001$).

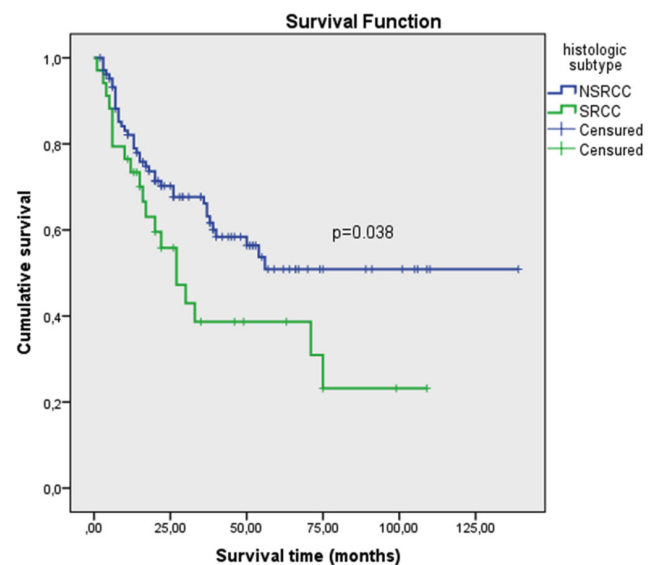


Figure 2: Kaplan-Meier survival curves of PFS by Histological type. There were significant differences between SRC and NSRC ($p=0.038$).

The 5 years PFS rate of SRCC was 38.7% and the 10 years PFS rate was 23.2%.Univariate analysis showed that

tumoral stenosis ($p=0.042$), hypoprotidemia (<0.0001), tumor size ($p=0.049$), depth of invasion ($p=0.001$), PNI (<0.0001), LVSI (<0.0001), UICC stage ($p=0.026$) (Figure 3) and complete surgical resection ($p=0.021$) were the main prognostic factors of PFS in SRCC (Table 3).

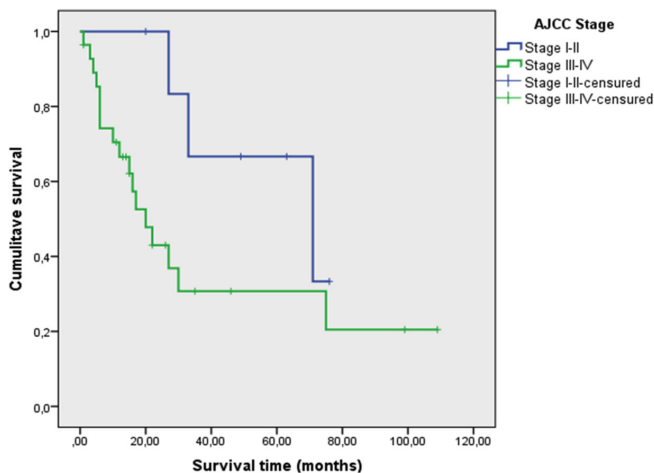


Figure 3: Kaplan-Meier (KM) survival curves of PFS according to AJCC stage. There were significant differences between stage I-II and stage III-IV ($p=0.026$).

The PFS was not correlated to the type of gastrectomy and the lymphadenectomy extend. However, the 5 years PFS of patients with more than 15 retrieved lymph nodes seems to be improved compared to those with less than 15 retrieved lymph nodes (41.4% vs 25.7% respectively, $p=0.588$). According to N stage, patients with pN0-N1 stages had a better 5 years PFS rate compared to patients with pN2-N3 (50% vs 37%, $p=0.514$).

Discussion

Our study suggests that SRCC are frequently characterized by larger tumor size with stenosis, advanced stage, and presence of LNI, PNI and lymph node metastasis as well as a different pattern of spread and recurrence. The study of predictive factors of survival and recurrence suggest that the prognosis of SRCC depends not only on the classic prognostic factors recognized in all gastric adenocarcinoma, but also on the stenotic nature of the lesions and the nutritional status of patients. The type of gastrectomy does not affect long-term results if resection margin is adequate.

SRCC have clinical features that distinguish them from other histological types and the prognosis of these cancers remains controversial because of their specific behavior that may suggest an adjustment of therapeutic modalities.

Many studies reported that gastric SRCC is commonly more frequent in young patients and females [6, 7] and seems to be related to hormonal status [8]. Similar results were found in our study with a significantly higher rate of patients under 65 years of age in SRCC compared to NSRCC (86.5% vs 54.1%; $p=0.001$). However, we observed that the male to female ratio was similar for the two groups which is line with the results of Li and al who compared 4097 cases of NSRCC to 662 cases of SRCC without significant difference in gender (the rate of male was 67.3% vs 68% respectively and the rate of

female was 32.7% vs 31.1% respectively, $p=0.418$). [9] Nie et al reported in their recent meta-analysis of 19 studies including 35947 cases, that SRCC tends to be located in the middle and lower third of the stomach (OR=0.62, 95% CI=0.47-0.81, $P<0.001$; $I^2=82.0\%$, $P<0.001$) compared to non-signet ring cell carcinoma (NSRCC). [10] We also reported that most of cases of SRCC were located in the lower third (52.8%) and the middle third (33.3%) of the stomach. We found that patients with SRCC were more likely to present at later stages, with a greater proportion of patients presenting at AJCC stage III (66.7%), with deeper parietal invasion and a higher rate of lymph node metastasis which is in line with the results of Taghavi and Piessen. [7, 11]

Lymphovascular and perineural invasion are more commonly seen in gastric SRCC. In fact, Kwon et al. reported that the rate of PNI and LVSI were respectively 7.8% and 11.8% in early SRCC and 56.1% and 64.9% in advanced SRCC. [12] In our study, 58.3% of patients had PNI and LVSI compared to 44% and 46.8% respectively in NSRCC. We also found that patients with SRCC were more likely to present with larger tumor size, since 61.1% of tumors measured more than 50mm. Chen and al reported that according to Lauren classification, diffuse and mixed tumors were significantly associated with larger tumors exceeding 80mm. [13]

Although most authors agree on the poor prognosis of diffuse type of gastric carcinoma according to the Lauren classification, the prognosis of SRCCs as a particular entity remains debated and varies according to stage at diagnosis. Indeed, in early gastric cancer, some studies showed that early SRCC has a better prognosis than NSRCC. [12, 14, 15] Other authors demonstrated no difference in survival between the two histological groups in the early stages. [16, 17] However, in advanced gastric cancer, Li et al [9] and Piessen et al. [11] found that the 5-years survival rate of SRCC was significantly poorer than that of NSRCC.

In our study the 5-year overall survival rate was 35.7%. Regarding tumor stage, the 5 years overall survival was shorter in stage III and IV compared to stage I and II (22.8% vs 72.9%, $p=0.007$). Similar rates were reported by Liu et al with a 5 years OS of 93.9% in stage I, 58.7% in stage II and 25.3% in stage III and IV. [18] Few studies investigated the recurrence and progressive free survival in SRCC according the common prognostic factors. In our study, the rate of recurrence was 55.6% and the 5 years progression-free survival rate was 38.7%. Lower rates of relapses were reported by Voron et al (45.75%) and Zhang et al (45%). [19, 20] Moreover, in our study we reported a higher rate of distant metastasis in SRCC compared to NSRCC (52.9% vs 29.5%, $p=0.013$) which is in line with the results of Postlewait and al who compared the outcomes of 312 patients with SRCC to 456 patients with NSRCC and suggested a significant difference in term of distant relapses (28.2% vs 20.2%, respectively, $p=0.013$). [21] Piessen and al [11] analyzed the trend of recurrence after a complete resection between 23 cases of SRCC and 42 cases of NSRCC and found that peritoneal relapses occurred more frequently in patients with SRCC (52.2% vs 21.4%, $p=0.001$) which is similar to our finding.

Lymph node metastasis and depth of parietal invasion

are the most important prognostic factors of gastric carcinoma.[22-25] In the majority of studies analyzing the survival outcomes of SRCC, the depth of invasion, as well as LN metastasis, are the independent prognostic factors of recurrence and survival.[18-20] In our study, pT stage was also significantly correlated to survival outcomes and the 5-years OS rate and PFS rate were lower in patients with pN2-N3 compared to those with pN0-N1 (30% and 37% respectively vs 62.5% and 50%). However, the difference was not significant, and this could be explained by the particularly high rate of lymph node involvement in our series (only 4 patients were staged pN0) but also the reduced number of patients.

Although the prognostic value of tumor size remains debatable, it has been reported to be an independent prognostic factor by many authors.[26, 27] In our study, a tumor size more than 50 mm was significantly associated with a decline in overall survival as well as progression-free survival which is consistent with the results of Liu et al who reported a decrease of the 5-years OS in tumors larger than 50mm (16.7% vs 48.8% $p < 0.001$).[18]

Several studies investigated the pejorative prognostic value of lymphovascular space invasion and perineural invasion in gastric cancer.[28-32] Moreover, this pejorative prognostic effect of PNI and LVI was also found in SRCC. In fact, in the study by Liu et al[18], the 5-years OS was significantly decreased in the presence of LVI (49.4% versus 15.1%, $p < 0.001$) and PNI (46.3% versus 21.4%, $p < 0.001$) which is in line with our finding. In a study comparing 218 patients with SRCC to 1221 patients with NSRCC, Zhang et al reported that curative resection with negative margins represents an independent predictor of overall survival in the subgroup of patients with SRCC (HR=2.878, 95% CI=1.865-4.440, $p < 0.001$).[20] In our study, both of OS and PFS were significantly improved by complete surgical resection. However, the extent of gastrectomy was not correlated to survival outcomes, in case of complete resection, and total gastrectomy resulted in a worse 5 years OS and PFS. These findings are supported by many other authors. In the retrospective study of Voron et al, including a total of 899 SRCC treated by total gastrectomy in 576 cases (60.7%) and partial gastrectomy in 353 cases (39.3%), complete surgical resection was achieved in 79.8% of cases and the overall survival was not correlated to the type of gastrectomy on multivariate analysis (HR=0.900, 95% CI= 0.718-1.128, $p < 0.359$).[19] Despite a higher risk of lymph node involvement in SRCC, there is no specific recommendation about the extent of lymphadenectomy for advanced SRCC. As for other histological types, a modified D2 lymphadenectomy retrieving at least 15 lymph nodes is recommended.[33] Thus, we found a gain in terms of OS and PFS if the number of removed lymph nodes was greater than 15 LN, even if the difference was not statistically significant (38.7% and 41.7% respectively if the NRLN was greater than 15 LN, 21.4% and 25.7% respectively if the NRLN was less than 15 LN).

Several studies showed that malnutrition, especially hypoprotidemia and weight loss, were a prognostic factor for survival and recurrence.[34, 35] However, in studies dedicated to gastric SRCC, the long-term prognostic value of hypoprotidemia has rarely been

evaluated. Voron et al reported that cancer related malnutrition was significantly associated to a worse OS in SRCC as well as NSRCC.[19] However, in the present report, the 5 years OS was significantly reduced with hypoprotidemia (52.5% vs 0%, $p < 0.0001$) and it was the same for the 5 years PFS (55.5% vs 0%, $p = 0.001$). Weight loss of more than 10% of the usual weight was also associated to lower rate of 5 years OS (23.7% vs 45.5% if the weight loss was less than 10%) and a lower rate of 5 years PFS (30.3% vs 54.5% if the weight loss was less than 10%). We also found that patients presenting with tumoral stenosis had a worse OS and PFS which is consistent with the report of Chen et al.[13]

Despite the limited number of patients enrolled in this retrospective and single institution study, we suggest that SRCC remain an aggressive clinical subtype of gastric cancer characterized with advanced stage and a worse survival outcome compared to NSRCC.

Conclusion

The incidence of SRCC is increasing in recent years and their prognosis seems to be equivalent to that of gastric adenocarcinoma or better in the early stages. However, it would be more reserved in the advanced stages. Although this study helped to describe clinical and histological features and survival outcomes, it has some limitations due to small sample size. Clinical studies with larger patient groups and comparative study with NSRCC could be helpful to understand its clinicopathological behavior.

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Contributors

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Competing interests

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Availability of data and materials

Further information is available from the corresponding author on reasonable request.

Ethics approval

The ethics review board approved this study and did not require informed consent from study participants since this was a strictly registry-based study.

Provenance and peer review

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