

Gastric Signet Ring Cell Carcinoma: A Comparative Analysis of Clinicopathologic Features

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Abstract

Signet ring cell carcinoma (SRC) is a distinct histological subtype of gastric carcinoma. Our aim is to investigate differential characteristics between gastric SRC and other non SRC carcinomas (nSRC). It was a retrospective study including 183 patients diagnosed with gastric carcinoma over a period of 5 years at our pathology department. We performed statistical comparison of clinicopathological features between patients with SRC and those with nSRC. 127 patients (69.4%) had nSRC, 56 had SRC (30.6%), the mean age was 56.67 ± 14.03 years. Patients with SRC were younger than those with nSRC (mean age of 49.66 versus 59.76, $P = 0.030$). Patients with SRC tend to have more diffuse tumors in the stomach ($P = 0.005$), with flat macroscopic appearance ($P = 0.001$). Patients with SRC present more often with pT3 tumors ($P < 0.001$), lymph node metastasis ($P = 0.024$) and perineural invasion ($P = 0.003$). There were no significant differences between SRC and nSRC in gender, vascular invasion or distant metastasis ($P > 0.05$). The median survival time was 42.82 ± 1.70 months. Patients with nSRC live longer than those with SRC, but the difference was not significant ($P = 0.28$). SRC is a histological subtype of gastric carcinoma with distinctive clinicopathologic features. The clinical management of patients should take into account these particular features.

Keywords

gastric cancer, signet ring cell carcinoma, adenocarcinoma, histopathology

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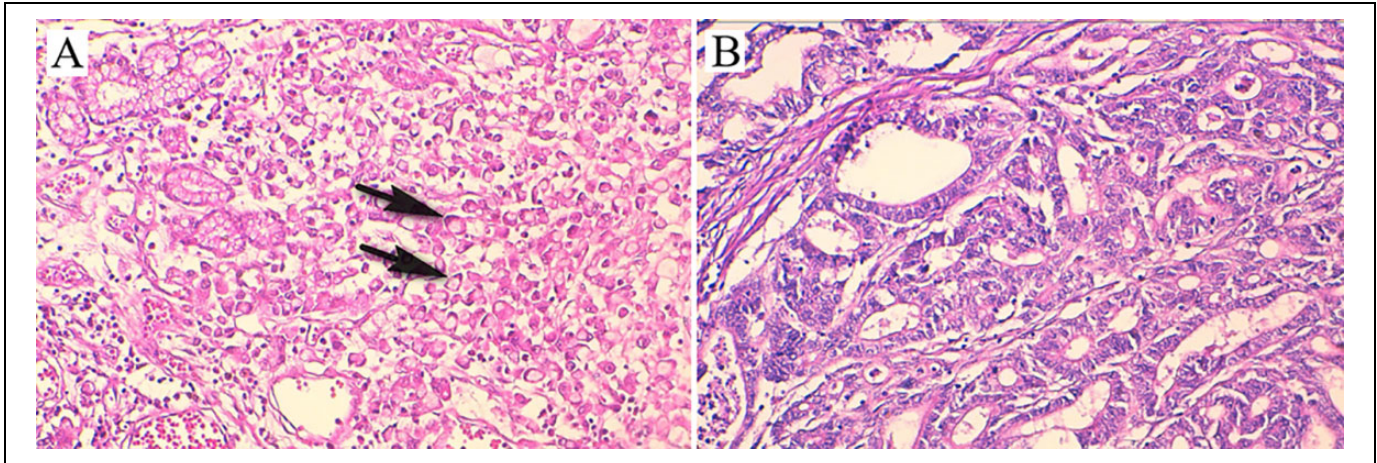


Figure 1. Histological aspects of gastric carcinomas. **A:** The signet ring cell carcinoma has a diffuse architecture with discohesive cells that have eccentrically placed irregular nuclei with abundant intracytoplasmic mucin (arrows) (HES x 100). **B:** A well differentiated adenocarcinoma with a predominant glandular structures (HES x 200).

Introduction

Gastric cancer is one of the leading cause of cancer-related death worldwide.¹⁻⁴ Mostly, carcinomas constitute the predominant histologic variant of gastric malignancies.^{1,5} Gastric carcinomas are mainly categorized as tubular or papillary adenocarcinoma (ADC), mucinous adenocarcinoma (MAC) and signet ring cell carcinoma (SRC).¹ Adenocarcinomas (ADC) are histologically graded as well, moderately or poorly differentiated according to the extent of glandular formations; MAC is defined as a carcinoma with a predominant extracellular mucinous component ($\geq 50\%$). Signet ring cell carcinoma (SRC) is defined as a tumor with at least 50% of discohesive cells with intracytoplasmic mucin and eccentrically placed nuclei, leading to the characteristic histologic aspect of the “signet ring.”^{1,2,6} According to Lauren’s classification, gastric carcinomas are subdivided into 2 major groups: intestinal type and diffuse type. The intestinal type comprises ADC and some types of MAC, while the diffuse type includes SRC and some poorly to undifferentiated carcinomas with isolated infiltrative tumor cells.^{1,7,8}

In fact, gastric carcinomas are a wide group of histologic neoplasms with varying clinical, epidemiological and prognostic features. Environmental risk factors are supposed to induce intestinal type carcinomas (*Helicobacter pylori* gastritis, salt or dried diet, alcohol or tobacco consumption, . . . etc.) while genetic risk factors seem to play a major role in SRC.^{1,2,9} In fact, familial gastric diffuse carcinoma harbors germline mutations of the *CDH1* gene (E-cadherin gene), and SRC is the histological subtype of these familial carcinomas. Sporadic gastric SRC also bear mutations on *CDH1* gene, but these are somatic hypermethylation of the *CDH1* promoter.^{1,9} However, the exact etiology of sporadic gastric SRC remains unknown despite some similar molecular features with the familial diffuse gastric carcinoma.

Also, there is a trend worldwide suggesting a decline in gastric nSRC incidence compared to SRC, as etiologic

environmental factors can be controlled (diet, *Helicobacter pylori* gastritis, . . . etc.). Several studies have focused on differential characteristics between gastric nSRC and SRC with contradicting results. Controversy still remain as some studies showed that SRC has a better prognosis, while others concluded that SRC has a worse prognosis or did not harbor any different prognostic features compared to nSRC.^{2,3,6-14} Another drawback is that most of these previous studies on gastric carcinomas were from Western or Asian countries while fewer studies come from African countries.^{9,15-17} The aim of our current study is to provide some epidemiological and clinicopathologic insights of gastric carcinomas and to investigate differential characteristics between gastric SRC and nSRC, from an African country.

Methods

Patients

We retrospectively retrieved all patients diagnosed with primary gastric carcinomas from 2014 to 2018 at our pathology department, from a Northern African country. All the available clinical and histological datas were retrieved from the pathology request forms and the patients’ medical online records.

Histopathological Diagnosis

Patients have been diagnosed with primary gastric carcinomas on biopsy and on surgical specimens. Secondary tumors or other gastric malignancies (lymphomas, gastrointestinal stromal tumors, neuroendocrine tumors) have been excluded. The histological diagnosis has been made on formal fixed and paraffin-embedded specimens, and stained by hematoxylin-eosin-saffron (HES). Signet ring cell carcinoma was defined according to WHO criteria: an adenocarcinoma with the presence of more than 50% of tumor cells (signet ring cells) with prominent intracytoplasmic mucin.¹

The staging system applied on surgical specimens was in accordance with the American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma of the Stomach (Seventh Edition, 2010).

Statistical Analysis

Patients have been divided into 2 groups: SRC group and nSRC group.

Differences in the distribution of variables between the 2 groups were assessed using the Fisher exact test or chi-square test (for categorical variables) and Student-test (for non-categorical variables). Survival curves were generated by using the Kaplan-Meier method and compared with the log-rank test. Survival was determined using cause-specific mortality.

All statistical analyses were performed by using SPSS 23.0 version software for Windows (SPSS, Inc., Chicago, IL, USA), and R 3.6.0 version software for Windows. *P* value was considered statistically significant at *P* < 0.05.

Results

General Features of the Patients

Over a period of 5 years (2014-2018), we have recorded 183 cases of gastric carcinomas. Of these 183 carcinomas, 127 (69.4%) had nSRC and 56 had SRC (30.6%) (Figure 1). Among our 183 patients, 75 had surgical specimens (41%) while the remaining 108 cases had gastric biopsies (59%). The mean age was 56.67 years (± 14.03) with a male predominance (115 cases, 62.8%). The majority of our patients had <60 years (101 cases, 55.2%). The mean tumor size (as assessed by macroscopic examination of the resected specimens) was 6.2 cm (± 3.48), 48 patients (64%) had tumor size ≥ 5 cm. Table 1 summarizes the clinicopathological features of our entire cohort.

Comparison of Patients With SRC and Those With nSRC

Patients with SRC were younger than those with nSRC (mean age of 49.66 versus 59.76, and 69.6% of patients with SRC were <60 years, versus 48.8%, *P* = 0.03, *P* = 0.009 respectively) (Figure 2). There was no statistical significant difference in gender between the 2 groups of patients (*P* = 0.949). Most patients have tumors located in the antro-pyloric area of the stomach (n = 81 cases, 45.5%), with ulcero-fungating aspects (n = 61 cases, 40.9%). Patients with SRC tend to have more diffuse tumors in the stomach (n = 10 cases, 17.9% versus n = 6 cases, 4.9%; *P* = 0.005) (Figure 3), with flat macroscopic appearance (n = 12 patients, 27.9% versus n = 10 patients, 9.4%; *P* = 0.001).

Patients with SRC present more often with pT3 tumors (sub-serosal invasion) (90.9% of SRC, n = 20, versus 43.4% of nSRC, n = 23; *P* < 0.001) with lymph node metastasis (*P* = 0.024). Also, perineural invasion was more frequently found in patients with SRC than those with nSRC (40.9% of

Table 1. Clinicopathological Features of Our Patients.

| Variables | Number | Percentage |
|--------------------------------------|--------|------------|
| Age (n = 183) | | |
| – < 60 years | 101 | 55.2% |
| – ≥ 60 years | 82 | 44.8% |
| Sexe (n = 183) | | |
| – Female | 68 | 37.2% |
| – Male | 115 | 62.8% |
| Specimens (n = 183) | | |
| – Biopsy | 108 | 59% |
| – Surgical | 75 | 41% |
| Tumor site (n = 178) | | |
| – Cardia | 23 | 12.9% |
| – Fundus | 58 | 32.6% |
| – Antro-pyloric | 81 | 45.5% |
| – Diffuse location | 16 | 9% |
| Tumor size (n = 75) | | |
| – < 5 cm | 27 | 36% |
| – ≥ 5 cm | 48 | 64% |
| Macroscopic aspects (n = 149) | | |
| – Ulcerated | 44 | 29.5% |
| – Fungating | 22 | 14.8% |
| – Ulcero-fungating | 61 | 40.9% |
| – Flat | 22 | 14.8% |
| Histological type (n = 183) | | |
| – SRC | 56 | 30.6% |
| – nSRC | 127 | 69.4% |
| Vascular invasion (n = 75) | | |
| – Absent | 54 | 72% |
| – Present | 21 | 28% |
| Perineural invasion (n = 75) | | |
| – Absent | 61 | 81.3% |
| – Present | 14 | 18.7% |
| Tumor stage (n = 75) | | |
| – pT2 | 21 | 28% |
| – pT3 | 43 | 57.3% |
| – pT4 | 11 | 14.7% |
| Lymph node status (n = 75) | | |
| – pN0 | 37 | 49.3% |
| – pN1 | 11 | 14.7% |
| – pN2 | 11 | 14.7% |
| – pN3 | 16 | 21.3% |
| Distant metastasis (n = 183) | | |
| – Absent | 131 | 71.6% |
| – Present | 52 | 28.4% |
| Survival (n = 183) | | |
| – Alive | 156 | 85.2% |
| – Dead | 27 | 14.8% |

SRC, n = 9, versus 9.4% of nSRC, n = 5; *P* = 0.003). However, there were no significant differences between SRC and nSRC in vascular invasion or in distant metastasis (*P* > 0.05). Table 2 summarises differential characteristics between patients with SRC and those with nSRC.

In our current study, the survival rate was 85.2% (156 patients were alive and 27 were dead of gastric carcinomas). The median survival time over the 5-year period of our study was 42.82 ± 1.70 months. Patients with nSRC live longer than those with SRC, but the difference was not statistically

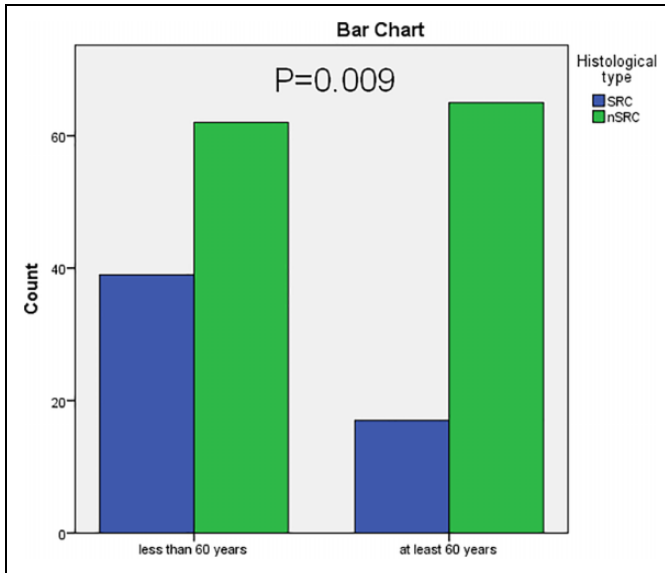


Figure 2. Patients' age by histological type (SRC versus nSRC).

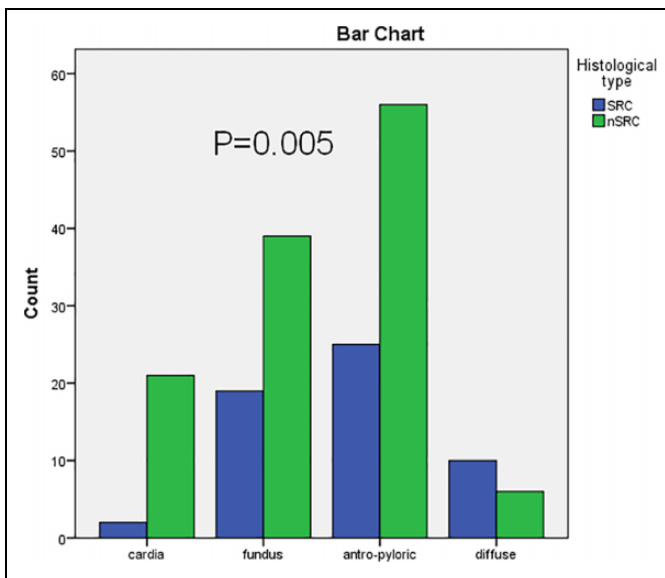


Figure 3. Tumor's location according to histological type (SRC versus nSRC).

significant ($P = 0.28$, median survival time of 44.23 ± 1.85 months for nSRC and 24.15 ± 1.89 months for SRC) (Figure 4).

Discussion

Our current study reports about clinicopathological characteristics of gastric carcinoma and differential features between non signet ring cell carcinomas (nSRC) and signet ring cell carcinoma (SRC), in a single institution from a northern African country. Gastric carcinoma is the fifth most common cancer worldwide with a high incidence in developing countries from Asia and South America.² Africa is considered to

Table 2. Differential Characteristics Between Patients With SRC and Those With nSRC.

| Variables | SRC, No. (%) | nSRC, No. (%) | P |
|--------------------------------------|--------------|---------------|--------|
| Age (n = 183) | | | |
| - Mean (years) | 49.66 | 59.76 | 0.030 |
| < 60 ans | 39 (69.6%) | 62 (48.8%) | 0.009 |
| ≥ 60 ans | 17 (30.4%) | 65 (51.2%) | |
| Total | 56 (100%) | 127 (100%) | |
| Sexe (n = 183) | | | |
| - Female | 21 (37.5%) | 47 (37%) | 0.949 |
| - Male | 35 (62.5%) | 80 (63%) | |
| Total | 56 (100%) | 127 (100%) | |
| Tumor site (n = 178) | | | |
| - Cardia | 2 (3.6%) | 21 (17.2%) | 0.005 |
| - Fundus | 19 (33.9%) | 39 (32%) | |
| - Antropyloric. | 25 (44.6%) | 56 (45.9%) | |
| - Diffuse location | 10 (17.9%) | 6 (4.9%) | |
| Total | 56 (100%) | 122 (100%) | |
| Macroscopic aspects (n = 149) | | | |
| - Ulcerated | 14 (32.6%) | 30 (28.3%) | 0.001 |
| - Fungating | 9 (20.9%) | 13 (12.3%) | |
| - Ulcero-fungating | 8 (18.6%) | 53 (50%) | |
| - Flat | 12 (27.9%) | 10 (9.4%) | |
| Total | 43 (100%) | 106 (100%) | |
| Vascular invasion (n = 75) | | | |
| - Absent | 17 (77.3%) | 37 (69.8%) | 0.583 |
| - Present | 5 (22.7%) | 16 (30.2%) | |
| Total | 22 (100%) | 53 (100%) | |
| Perineural invasion (n = 75) | | | |
| - Absent | 13 (59.1%) | 48 (90.6%) | 0.003 |
| - Present | 9 (40.9%) | 5 (9.4%) | |
| Total | 22 (100%) | 53 (100%) | |
| Tumor stage (n = 75) | | | |
| - pT2 | 0 (0%) | 21 (39.6%) | <0.001 |
| - pT3 | 20 (90.9%) | 23 (43.4%) | |
| - pT4 | 2 (9.1%) | 9 (17%) | |
| Total | 22 (100%) | 53 (100%) | |
| Lymph node status (n = 75) | | | |
| - pN0 | 5 (22.7%) | 32 (60.4%) | 0.024 |
| - pN1 | 4 (18.2%) | 7 (13.2%) | |
| - pN2 | 5 (22.7%) | 6 (11.3%) | |
| - pN3 | 8 (36.4%) | 8 (15.1%) | |
| Total | 22 (100%) | 53 (100%) | |
| Distant metastasis (n = 183) | | | |
| - Absent | 39 (69.6%) | 92 (72.4%) | 0.724 |
| - Present | 17 (30.4%) | 35 (27.6%) | |
| Total | 56 (100%) | 127 (100%) | |
| Survival (n = 183) | | | |
| - Alive | 45 (80.4%) | 111 (87.4%) | 0.259 |
| - Dead | 11 (19.6%) | 16 (12.6%) | |
| Total | 56 (100%) | 127 (100%) | |

have a low gastric cancer incidence, however this fact seems to be linked to few data from African countries likely due to the lack of diagnostic resources.⁹ In our study, the mean age was 56.67 years and most patients were <60 years (55.2%), with a male predominance. These epidemiological features were quite

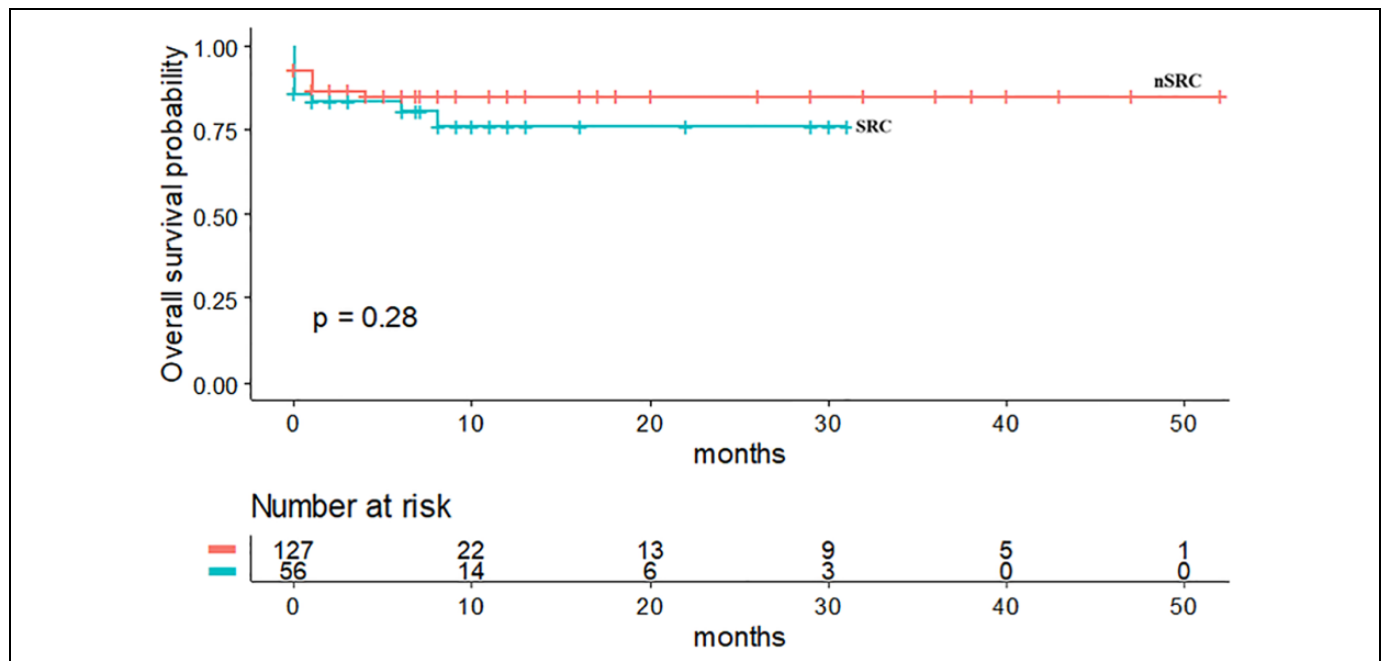


Figure 4. Kaplan-Meier survival curves by histological type (SRC versus nSRC).

similar to those reported previously in the literature from african countries.^{15,17,18} Afuwape et al. from a Nigerian study of gastric cancer, have reported a mean age of 56 years with a male predominance,¹⁵ while in Morocco, 2 studies on gastric cancer by Smith et al and Elmajjaoui et al have reported respectively a median age of 60 years and a mean age of 55 years.^{17,18}

We have also focused our study on differential features between gastric nSRC and SRC, as these histological subtypes harbor many epidemiological, clinical, histopathological and biological differences. In our study, 56 patients (30.6%) had SRC, and these patients were younger than those with nSRC ($P < 0.05$). These characteristic features of SRC have been widely reported in the literature. L. M. Postlewait et al. in their study of 768 patients with gastric carcinoma, have reported that SRC was present in 40.6% of patients and was associated with younger age and female sex.¹⁹ In 2009 J. Yu and Zhao have reported quite similar characteristics between SRC and nSRC.⁶ However, other studies have reported low incidence of SRC and did not find no statistically significant differences in patient gender.^{10,11} The frequent association of SRC with the female sex could be in part due to hormonal influence, and the younger age of patients is likely linked to risk factors that are different between SRC and nSRC.^{14,20} Environmental factors (*Helicobacter pylori*, salt or dried diet, alcohol or tobacco consumption, . . . etc.) play a major role in the pathogenesis of SRC, and these factors require a long individual exposition to lead to sequential changes of gastric mucosa that could end in malignant transformation (chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and carcinoma).^{1,2,9} The role of these environmental factors is controversial in SRC, and genetic factors are in part involved (in fact there are authentic familial gastric SRC that harbor well-established germline

mutations of the E-cadherin gene, and sporadic gastric SRC share some molecular genetic alterations of this gene although its exact risk factors still remain unknown), leading to an earlier onset of the disease in comparison to patients with nSRC.² However, our current study did not focus on gastric carcinomas risk factors, thus we cannot speculate on the contribution of these factors (environmental or genetic).

Among other reported controversial features of SRC, were tumor site and macroscopic aspects. In the current study, patients with SRC tend to have more diffuse tumors in the stomach ($P = 0.005$) with flat macroscopic appearance ($P = 0.001$). In the literature, there were contradictory reports about tumor location. While some showed that SRC have a predilection to distal location (middle part or lower parts of the stomach), other studies did not find any significant difference in tumor site between SRC and nSRC.^{10-13,19} SRC is considered to derive from in situ carcinoma from oxyntic glands (gastric fundus and body), in contrast to intestinal type carcinomas that develop from other part of the stomach (through the histological sequence atrophic gastritis, intestinal metaplasia, dysplasia and infiltrative carcinoma).^{14,21} However this remains theoretical as locations of these carcinoma subtypes overlap in the gastric's different anatomical parts.

The depth of tumor invasion is one of the most important prognostic factors in gastric cancer. We found in the current study that SRC presents more often as pT3 when compared to nSRC (90.9% versus 43.4%, $P < 0.001$). These findings are not in agreement with certain studies that have reported a high rate of SRC in stage T1 (early gastric carcinoma).^{12,22} Also, some previous studies showed that SRC was associated with an advanced stage,^{3,19,14} in contrast to our current study, as only 2 patients (9.1%) with SRC had pT4 tumors, whereas 9 (17%)

with nSRC had this stage. Similar to our findings, Zhang et al. showed that serosal invasion (pT4 stage) was less prominent in SRC compared to nSRC.¹² We have found a significant statistical difference between SRC and nSRC in lymph node and perineural invasion. SRC was associated with lymph node and perineural invasion in comparison with nSRC ($P < 0.05$). There were no significant differences between SRC and nSRC in other adverse prognostic factors such as distant metastasis or vascular embolus ($P > 0.05$). In the literature, controversies remain as previous studies have reported inconsistent results regarding differences in prognostic factors between SRC and other gastric carcinomas.^{2,3,6-14} As our study, some previous studies have reported that SRC had a higher rate of lymph node invasion,^{11,13} while others have shown that SRC had a low rate of lymph node metastasis.¹⁰ Also, some authors have reported no significant differences between SRC and nSRC in vascular or perineural invasion.^{1,2} Similar controversies have been reported by several studies in survival rate between these 2 types of gastric carcinomas.⁶⁻¹⁴ In our study, the median survival time was 42.82 ± 1.70 months. Patients with nSRC live longer than those with SRC, but the difference was not statistically significant ($P = 0.28$). Some studies have reported a significant difference between SRC and nSRC, with a better overall survival rate for SRC.^{8,14} In fact, it seems that advanced SRC has similar prognosis than advanced nSRC. A recent meta-analysis including 19 studies comparing SRC and nSRC found that there was no difference in overall survival between SRC and non-SRC patients.²³ However, controversies still remain on the issue of comparative features between gastric SRC and nSRC, some very recent studies arguing that even a small proportions of signet ring cells correlates with a worse prognosis.²⁴⁻²⁶

In this current study, although retrospective and mono-centric, we have found that gastric SRC presents some particular differential features in comparison with nSRC, implying that management strategies could be designed in regards to histological type of gastric carcinoma.

Conclusion

Gastric carcinomas constitute a group of tumors frequently diagnosed in the digestive tract. Signet ring cell carcinoma (SRC) is a distinct type of gastric carcinoma associated with a younger age, perineural invasion and lymph node metastasis. The clinical management of patients with this histological subtype of carcinoma should take into account these particular features.

Authors' Note

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Declaration of Conflicting Interests

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