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ORIGINAL ARTICLE

Prognosis of Signet Ring Cell Carcinoma of the Colon and Rectum and their Distinction of Mucinous Adenocarcinoma with Signet Ring Cells. A Comparative Study

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Abstract Signet ring cell carcinoma (SRCC) of the colorectum is very rare, comprising between <1% and 2.4% cases of colorectal cancer. Patients' prognoses are poor. Several case reports had described as SRCC cases that are mucinous adenocarcinomas (MAC) with signet ring cells (SRC). In order to clearly delineate between MAC with SRC and SRCC, we performed a retrospective study at a national cancer referral center in which survival and clinicopathological characteristics between these two forms were compared and also SRCC were characterized by immunohistochemistry. We retrieved 32 cases that had been classified as either SRCC or MAC with SRC subtypes. It was noted that SRCC patients presented at older ages, demonstrated more advanced clinical stages, lymphovascular invasion, lymph node metastases, and higher carcinoembrionic levels than MAC with SRC patients. Regarding SRCC immunophenotype, 50% showed loss of CDX2 expression, 33% were CK20 negative, 41.7% were CK7 positive, and 25% were negative for both CK7 and CK20. For the MAC with SRC and SRCC groups, the median disease-specific survival (DSS) was 46.1 months (95% CI 36.9–55.25) and 22.4 months (95% CI 5.1–39.7 [$p = 0.039$]), respectively. The 3-year DSS was 80.7% and 28.6% ($p = 0.017$) for the MAC and SRCC patients, respectively. Univariate and multivariate analyses showed that SRCC was associated with decreased survival. SRCC had several clinicopathological features that permitted differentiation of MAC with SRC from SRCC patients, who had a poor DSS. A differential diagnosis for metastatic gastric cancer is only possible with a good clinicopathological correlation.

Keywords Signet ring cell · Colorectal · Carcinoma · Survival · Mucinous adenocarcinoma

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Background

Colorectal cancer is one of the leading causes of cancer mortality worldwide [1]. The term signet ring cell carcinoma (SRCC) is a descriptive term denoting a carcinoma cell retaining abundant intracytoplasmic mucin that causes the nucleus to be displaced to the periphery. The majority of these tumors originates in the stomach but have also been described in breast, lung, bladder, pancreas, gall bladder, and colon. In affected sites, the tumor permeates the entire wall, thus transforming it into a rigid and contracted structure called the *linitis-plastica*.

Colorectal SRCC is very rare, comprising between <1% and 2.4% of colorectal cancer cases [2]; however, it represents up to 18% of colorectal carcinomas in children and adolescents [3]. SRCC was reported for the first time in 1951 by Laufman and Saphir, and since then, only a few hundred cases have been reported mostly in Asian patients as case reports or a small series of cases [4]. Only a few comparative and/or experimental studies with a significant number of cases have been performed (the longest series had 45 cases) [2].

Several published studies had classified cases of mucinous adenocarcinomas (MAC) with signet ring cells (SRC) as SRCC since the classic definition described by Laufman and Saphir does not clearly delineate

between the two types of cancer. This definition consists of several parameters: 1) presence of SRC; 2) immature or abortive glands; and 3) anaplastic and undifferentiated cells with diffuse infiltration into the tissue from which they originated [4]. There is no mention about a mucinous component. The World Health Organization (WHO) classification of tumors is also confusing because it defines MAC as a carcinoma conformed by >50% of extracellular mucin pools that contain malignant epithelial or individual tumor cells including SRC; it defines SRCC as a carcinoma conformed by >50% of SRC but states that SRC can occur within the pools of MAC or in a diffusely infiltrative process with minimal extracellular mucin in a *linitis-plastica* pattern [5].

Patients' prognoses are poor, but not well defined, as they are mainly determined by the advanced stage that is presented rather than by the histology. In addition, most of the published studies have shown miscellaneous results regarding the clinicopathological characteristics of the patient that are partially due to the small number of cases in addition to the poor definition of what is considered an SRCC [6–12].

To clearly determine patient prognosis and histopathological characteristics of SRCC, this tumor should be strictly defined. In order to clearly delineate between MAC with SRC and SRCC, we performed a study comparing patient survival and clinicopathological characteristics between these two subtypes and we also determined its immunophenotype.

Material and Methods

Case Selection and Clinicopathological Features

This retrospective study of colorectal adenocarcinomas with SRC cases from 1995 to 2015 was conducted at a national cancer referral center. We searched all cases with a pathological diagnosis of primary colorectal adenocarcinomas with SRC. We retrieved 32 cases, and the histological material was evaluated in order to classify the cases into SRCC or MAC with SRC subtypes according to several criteria.

The SRCCs were defined according to a modification of the original description of Laufman and Saphir [4]: 1) tumors are surrounded by >90% of cells with prominent intracytoplasmic mucin with displacement and molding of the nucleus (SRC); 2) the remaining percentage consists of immature or abortive glands; 3) neoplastic diffuse cell infiltration into the tissues from which they originated; and 4) no evidence of mucin pools and/or extracellular mucin accumulation of mucin (Fig. 1). MAC with SRC, as defined by the WHO criteria [5] consists of an adenocarcinoma composed by >50% of pools of extracellular mucin that contain neoplastic cells including any amount of SRC (even >50%) (Fig. 2). Of the 32 cases, 12 were classified as SRCC and 20 as MAC with SRC [5].

Clinical and follow-up information was obtained from patients' clinical files. The patients were staged using the seventh edition of the American Joint Committee on Cancer Tumor Node Metastasis staging system [13]. Clinicopathological parameters consisted of age, sex, tumor location, lymphovascular invasion (LVI), perineural invasion (PNI), lymph node metastasis (LNM), tumor stage, metastasis, operation date, recurrence, surgical margins, most recent follow-up date, adjuvant treatment, serum carcinoembrionic antigen (CEA), and survival status.

Immunohistochemistry and Interpretation Paraffin blocks from 29 cases with available material were cut into 4-mm thick sections for immunohistochemical slides, which were processed on an automated immunostainer (Biotek System, Ventana, Tucson, AZ) using the standard avidin-biotin peroxidase complex technique. The antibodies used were CK7 (Dako, Carpinteria, CA, US, clone OVTL 12/30, dilution 1:200), CDX2 (Dako, clone DK-CDX2, dilution 1:1009, CK20 (Dako, clone Ks20.8, dilution 1:100), MUC1 (Novocastra, Newcastle, UK, clone Ma695, dilution 1:100), MUC2 (Novocastra, clone Ccp58, dilution 1:100), MUC5AC (Novocastra, (clone CLH2, dilution 1:150), and MUC6 (Novocastra, clone CLH5, dilution 1:150). All cases were subjected to a heat-induced epitope retrieval buffer. Positive and negative controls were used in each assay. For all antibodies, any staining on the tumoral population was considered positive, whereas absence of staining was considered negative (nuclear for CDX2 and cytoplasmic/membrane for cytokeratins and mucins).

Statistical Analysis

Data was analyzed using the Statistical Package for the Social Sciences (version 12.0, SPSS, Inc., Chicago, IL). For continuous variables comparison a Student's t test was done. The chi-square or Fisher exact tests were carried out to examine associations between categorical variables. In all the cases, p values were two sided, and statistical significance was accepted when $p < 0.05$.

Survival Analysis

The primary endpoint was disease specific survival (DSS) defined as death from cancer determined from

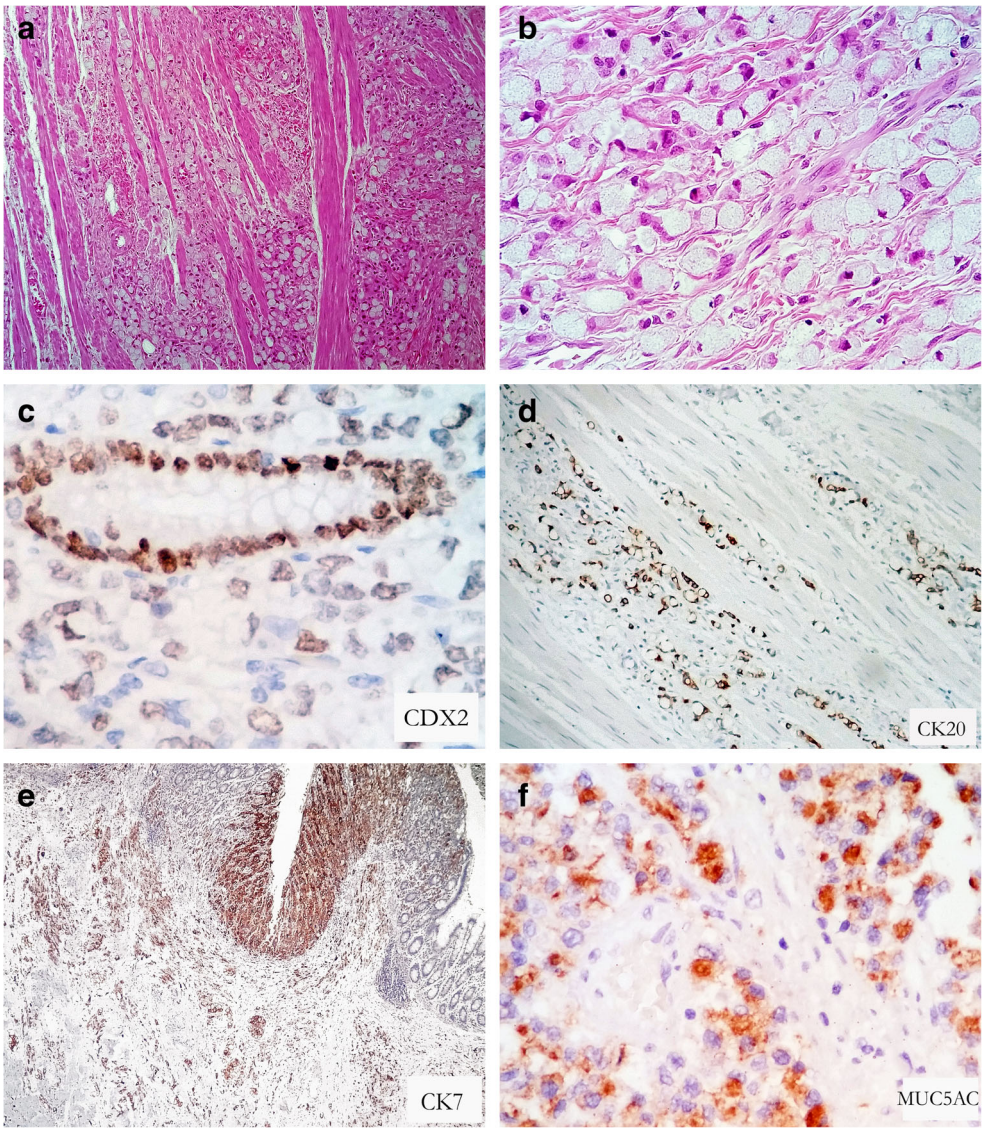

Fig. 1 Pathologic characteristics of the signet ring cell carcinoma. A) Low magnification shows signet ring cells (SRC) infiltrating diffusely into the *muscularis propria.* Note the absence of extracellular mucin. B) High magnification of the SRC. C) Nuclear expression of CDX2 in the SRC. Note the intensity is heterogeneous (even negative in some cells) and lesser than an entrapped gland. D) CK20 expression in the SRC. The expression is strong and diffuse but not all SRC are positive. E) CK7 expression is diffuse and strong. The SRC infiltrates diffusely all the intestinal wall. In the right upper corner SRC infiltrates and substitutes the epithelium. F) Cytoplasmic MUC5AC reactivity. The reaction is intense and granular at the cytoplasm of the SRC

the date of first treatment, including palliative care (event) or last follow-up (censored). DSS curves were estimated with the Kaplan-Meier method. The univariate Mantel-Cox (log rank) regression model was used to examine the association of clinicopathological variables with DSS. Significant characteristics in the univariate analysis were entered into a multivariate Cox proportional hazards model adjusted for age and gender.

Results

Patients and Pathological Characteristics

The data are summarized in the Table 1. The median age was 58.3 ± 16.4 years (range 28–87), 18 patients (56.3%) were women. Of all cases, 23 (71.9%) underwent surgery, and the remaining only had a biopsy. Twenty-two (68.7%) cases presented with cancer in the right colon (six at the cecum and 16 in the ascending colon), and three (9.4%) in the transverse and seven (21.9%) in the left colon (one in the descending, four in the sigmoid, and two in the rectum). Fourteen (43.7%) cases presented with metastasis, and of those, nine (64.3%) were in the peritoneum. Fifteen cases (46.5%) presented with LNM (mean of 14.3 positive lymph nodes), 20 (62.5%) with LVI, eight (25%) with PNI, 18 (56.3%) with elevated CEA (mean 342 ± 777.6 ng/dL; reference range 1.71–3118 ng/dL), and a clinical stage at presentation of 18.8% for stage II, 37.5% for stage III, and 43.8% for stage IV.

SRCC patients presented at older ages and with more advanced clinical stages, more LVI, higher LNM numbers, and higher CEA levels (Table 1). According to

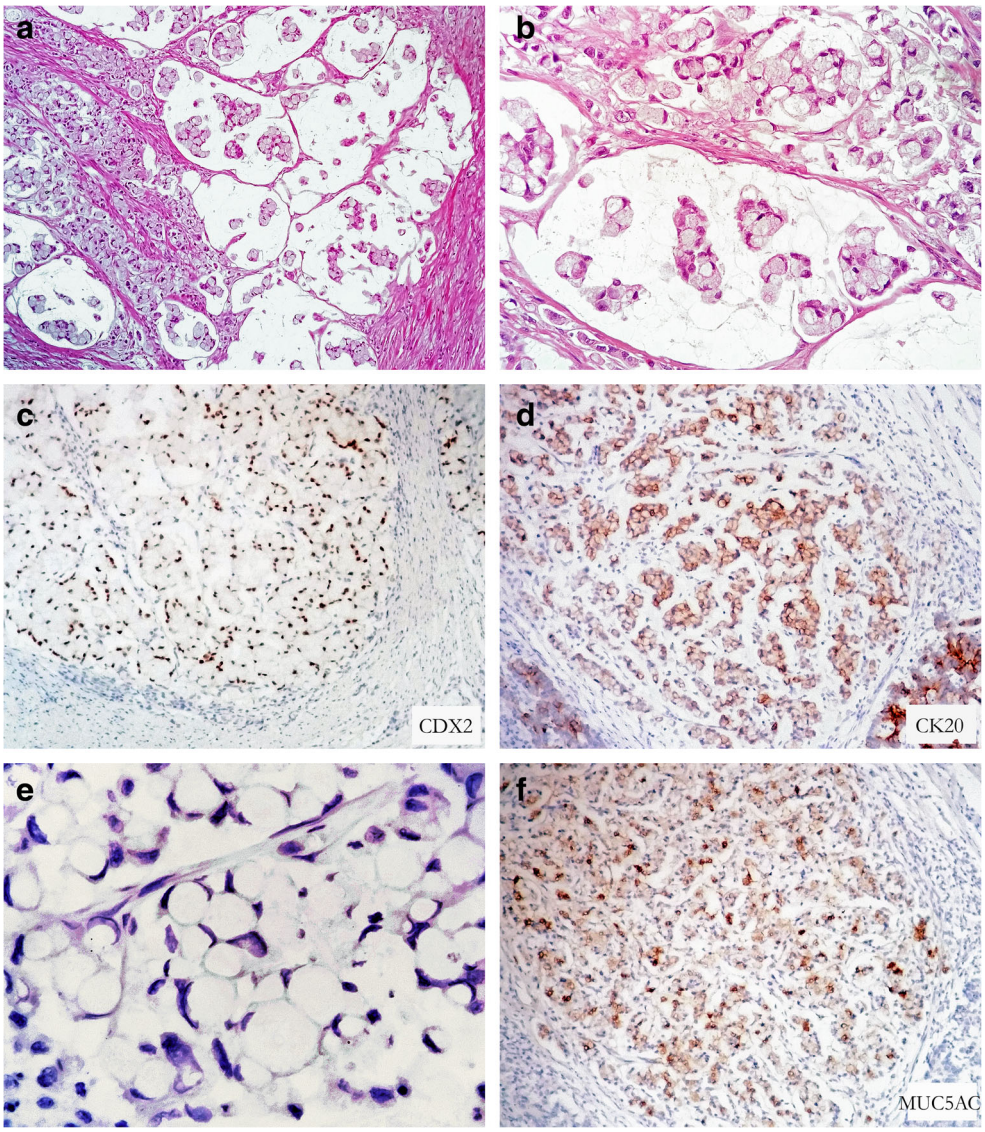

Fig. 2 Pathologic characteristics of the mucinous adenocarcinoma. A) Mucin pools are filled by signet ring cells (SRC) in different proportions, at the right are <50% and in the left, the pools are almost filled by SRC. B) High magnification of the mucin pools with SRC. C) CDX2 is positive in the nuclei of all neoplastic cells. D) CK20 is positive in the cytoplasm of all neoplastic cells. E) CK7 negativity in the SRC. F) MUC5AC was positive in some cases of mucinous adenocarcinoma

immunohistochemical analysis, 50% were CDX2 negative, 33% were CK20 negative, 41.7% were CK7 positive, and 25% were negative for both CK7 and CK20 (Table 2).

Survival Analysis

The median follow-up period was 17.25 ± 18.18 months (range 0–59). For the MAC patients, the median DSS was 46.1 months (95% confidence interval [CI] 36.9–55.25) and 22.4 months (95% CI 5.1–39.7) for the SRCC patients (p = 0.039, Fig. 3). The 3-year DSS was 80.7% for the MAC group and 28.6% for the SRCC patients (p = 0.017). In the comparison of clinical stages, the MAC group showed a 3-year DSS for stages II, III, and IV of 100%, 78%, and 73%, respectively, while for the SRCC group they were 100%, 33%, and 0%, respectively (p = 0.017).

Univariate analysis showed that the only factor associated with decreased survival was the histological subtype (SRCC), and this factor remained as a predictor of decreased survival in the multivariate analysis in conjunction with clinical stages (Stage III versus IV) (Table 3).

Discussion

Colorectal SRCC is very rare despite reports by several published studies in which any adenocarcinoma with SRC (including MAC with SRC) were classified as SRCC. The WHO classification is also confusing because it defines MAC as a carcinoma conformed by >50% of pools of extracellular mucin that may have SRC; it defines SRCC as a carcinoma conformed by >50% of SRC and states

Table 1 Comparison of pathological and clinical characteristics between patients with colorectal mucinous adenocarcinoma with signet ring cells and signet ring cell carcinoma

Variable	Mucinous adenocarcinoma (n = 20)	Signet ring cell carcinoma (n = 12)	P*
Age, median (range)	56.5 (28–86)	65 (30–87)	0.176
Sex			
Female	12 (60%)	6 (50%)	0.581
Male	8 (40%)	6 (50%)	
Clinical stage			
I-II	5 (25%)	1 (8.3%)	0.248
III-IV	15 (75%)	11 (91.7%)	
Lymph node metastasis			
No	10 (50%)	3 (25%)	0.040
Si	10 (50%)	9 (75%)	
Median lymph node resected (range)	22 (10–56)	14 (6–42)	0.191
Median positive lymph nodes (range)	4 (0–51)	9 (0–30)	0.830
Median carcinoembryonic antigen serum level (interquartile range)	8.44 (2.83–17.7)	40.65 (12.29–136.65)	0.002
Basal carcinoembryonic antigen			
Normal	12 (60%)	2 (16.7%)	0.017
Elevated	8 (40%)	10 (83.3%)	
Lymphovascular invasion			
No	7 (35%)	5 (41.7%)	0.706
Si	13 (65%)	7 (58.3%)	
Perineural invasion			
No	13 (65%)	10 (83.3%)	0.238
Yes	7 (35%)	2 (16.7%)	
Peritoneal metastasis			
No	14 (70%)	8 (75%)	0.457
Yes	6 (30%)	4 (25%)	
Resection			
R0	14 (87.5%)	6 (100%)	0.331
R1	1 (6.25%)	0	
R2	1 (6.25%)	0	
Overall recurrence			
No	17 (85%)	8 (66.7%)	0.963
Si	3 (15%)	4 (33.3%)	
Status			
Alive without disease	6 (30%)	3 (25%)	0.351
Dead with disease	3 (15%)	5 (41.7%)	
Alive with disease	10 (50%)	4 (33.3%)	
Dead without disease	1 (5%)	0	
Follow-up in months, median (range)	16 (1–55)	5 (0–59)	0.304
Median disease specific survival in months (95% confidence interval)	46.1 (36.95–55.25)	22.43 (5.12–39.7)	0.039
3-year disease specific survival	80.7%	28.6%	0.017
CDX2 expression[a]			
Negative	2 (11.8%)	6 (50%)	0.023
Positive	15 (88.2%)	6 (50%)	
MUC1 expression[a]			
Negative	15 (88.2%)	8 (66.7%)	0.158
Positive	2 (11.8%)	4 (33.3%)	
MUC2 expression[a]			
Negative	0	1 (8.3%)	0.226
Positive	17 (100%)	11 (91.7%)	
MUC5AC expression[a]			
Negative	11 (64.7%)	7 (58.3%)	0.728
Positive	6 (35.3%)	5 (41.7%)	
MUC6 expression[a]			
Negative	17 (100%)	11 (91.7%)	0.081
Positive	0	1 (8.3%)	
CK20 expression[a]			
Negative	4 (23.5%)	4 (33.3%)	0.561
Positive	13 (76.5%)	8 (66.7%)	
CK7 expression[a]			
Negative	16 (94.1%)	7 (58.3%)	0.019
Positive	1 (5.9%)	5 (41.7%)	

*Chi square test or Fischer's test

[a] Twenty-nine patients. In three patients the studies cannot be performed

Table 2 Immunohistochemical characteristics of the tumors

	CDX2	MUC1	MUC2	MUC5ac	MUC6	CK20	CK7
SRCC1	−	−	+	+	−	+/−	+
SRCC2	−	−	+/−	+	+	+	+/−
SRCC3	−	+	+	+	+	−	+
SRCC4	+	−	+	−	−	+	−
SRCC5	+	−	+	+	−	+	−
SRCC6	−	−	+	−	−	−	−
SRCC7	−	−	+	−	−	−	−
SRCC8	−	−	+	−	−	−	−
SRCC9	+	−	+	+	−	+/−	−
SRCC10	+	−	+	−	−	+	+
SRCC11	+	+	+	+	−	+	−
SRCC12	+	−	−	−	−	+	+/−
MAC1	+	−	−	+	−	+	−
MAC2	+	+	+	−	−	+	−
MAC3	+	−	+	−	−	+	−
MAC4	+	−	+	+	−	−	−
MAC5	+	−	+	−	−	+	−
MAC6	+	−	+	−	−	+	−
MAC7	−	+	+	−	−	−	−
MAC8	+	−	+	+	−	+	−
MAC9	+	−	+	+	−	+	−
MAC10	+	−	+	−	−	−	−
MAC11	+	−	+	+	−	+	−
MAC12	+	−	+	−	−	−	−
MAC13	−	−	+	−	−	+	−
MAC14	−	−	+	−	−	+	−
MAC15	−	−	+	−	−	+	−
MAC16	−	−	+	−	−	+	−
MAC17	−	−	+	+/−	−	+	+/−

that SRC can occur within the pools of MAC or in a diffuse infiltrative process [5]. We have presented a series of SRCC cases defined by strict criteria with a clear distinction of MAC and which is independent of the percentage of SRC in the mucin pools.

We found that SRCC showed some distinctive characteristics when compared with MAC: 1) patients presented a decade later (65 versus 56.5 years); 2) patients presented in a higher clinical stage; 3) patients presented with a high median serum CEA (40.65 versus 8.44 ng/dL); 4) patients presented with more LNM; and 5) patients had a poor 3-year DSS (28.6% with a median of 22.4 months) (Table 1). According to immunohistochemical analysis, a higher proportion of negativity for CDX2, CK20, MUC5AC, and a higher proportion of CK7 expression were shown (Table 2).

Most reported cases of SRCC in the literature occurred in male patients and contrary to our results, presented in younger people (<40 years). There were a few studies with patients >40 years (in a series of 15 Korean cases the median age was 56 years) [14–22]. Most patients described in the literature presented with SRCC in the right colon, which agrees with our results; however, in one study, 11 of 15 patients presented with SRCC in the left colon [22]. The overall prognosis is poor, with a maximal median survival of 30.09 months [14–22]. These data are similar to our results in which a median of 22.4 months was shown.

We speculate that this poor prognosis is strongly associated with the SRC, and there are studies corroborating this. Inamura et al. [23] proved that even a minor SRC component in colorectal cancers was associated with higher mortality, a 1–50% of SRC component was associated with cancer-specific mortality hazard ratio of 1.40 [95% confidence interval (CI) 1.02–1.93],

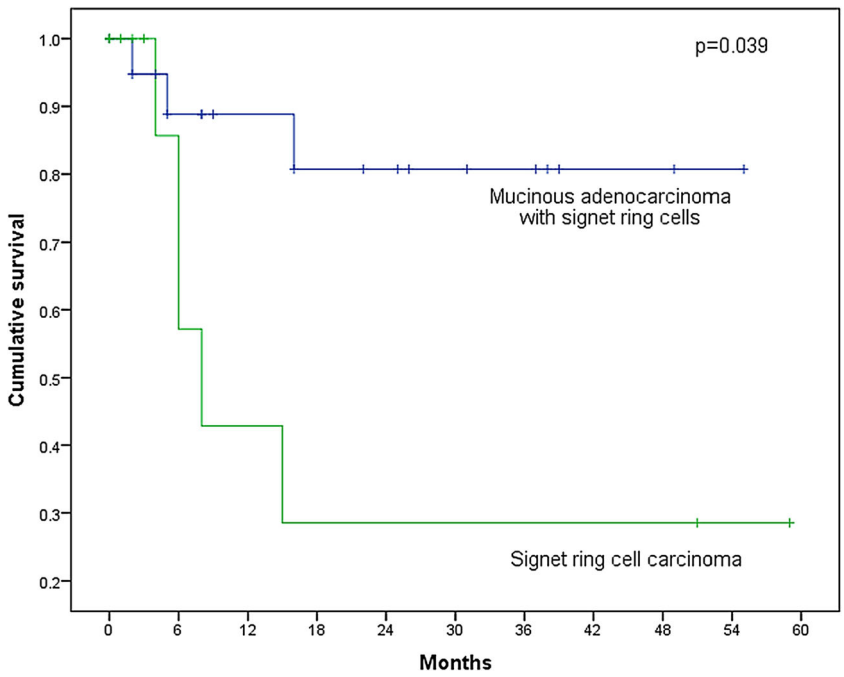

Fig. 3 Survival comparison between twelve signet ring cell carcinoma cases and mucinous adenocarcinoma with signet ring cell carcinoma cases

Table 3 Survival analysis of colorectal carcinomas with signet ring cells

Variable	Univariant			Multivariant		
	3-year Overall survival (%)	Chi square value	*p*-value	Cox Hazard Ratio|	CI (95%)	*P*
Subtype						
Mucinous adenocarcinoma with signet ring cells	80.7	4.468	0.035	4.388	1.031–20.686	0.049
Signet ring cell carcinoma	28.6					
Gender						
Male	68.8	0.101	0.750	1.400	0.287–6.825	0.677
Female	61.5					
Clinical stage[a]						
II	100	4.558	0.098	5.109	1.075–24.278	0.040
III	62.5					
IV	41.6					
Lymph node metastasis				1.883	0.338–10.495	0.470
No	100	3.089	0.079			
Yes	52					
Lymphovascular invasion						
No	83	1.202	0.273			
Yes	57.3					
Carcinoembrinoic antigen						
Normal	80	1.569	0.210			
Elevated	53					
CDX2 expression						
Present	61.3	0.006	0.941			
Absent	60					
CK7 expression						
Present	66.7	0.141	0.707			
Absent	60.4					

Mantel-Cox test

[a] stage III vs stage IV for the multivariant analysis

and >50% of SRC component was associated with cancer specific mortality Hazard ratio of 4.53 (95% CI 2.53–8.12) ($p < 0.001$) in multivariate analysis was shown; the presence of the mucinous component did not have an association with decreased survival. We found similar results, proving that SRCC without any mucinous material has a significantly poorer survival compared with an MAC independent of the percentage of SRC (3-year DSS of 28.6% versus 80.7%; $p = 0.017$).

The main differential diagnosis is a metastatic gastric carcinoma with SRC, and it is necessary to rule out this diagnosis before finalizing a diagnosis of primary colorectal SRCC. The differential diagnosis is very difficult because colorectal SRCC was CDX2 negative in up to 50% of the cases, CK20 negative in a third of cases, and could be MUC2 negative and MUC5AC positive in 41.7% of the cases. Three cases (25%) were negative for CK7 and CK20. According to the literature, one half to two thirds of gastric SRCC express MUC2, MUC5AC, CK20, and CK7; and 90% are CDX2 positive [24, 25]. These findings complicated the immunohistochemical distinction between gastric and colorectal SRCC. The more reasonable markers supporting colorectal SRCC appear to be MUC2 and CK20. We also recommend adding a broad-spectrum cytokeratin cocktail when appropriate in a case of negative CK7 and CK20.

In conclusion, SRCC presented with several clinicopathological features that permit differentiation from MAC with SRC. SRCC showed a poor patient DSS compared with MAC. Immunohistochemical differentiation between gastric and colorectal SRCC is not very feasible; this distinction relies on a good clinicopathological correlation.

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Compliance with Ethical Standards

Conflicts of Interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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