

## Research Article

# Primary Signet-ring Cell Carcinoma of Colorectal Origin: A Poor Prognostic Entity

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### Abstract

**Objectives:** In this retrospective study, we aimed to evaluate the clinicopathologic characteristics and survival outcomes of colorectal cancer patients with signet-ring cell component.

**Methods:** 2673 patients diagnosed with colorectal cancer who presented to two different institutions from 2004 to 2019 were investigated. A total of 75 patients with primary signet-ring cell component were included in the study.

**Results:** A total of 75 patients with primary signet-ring cell component were included in the study. 49 (65.3%) were patients with signet-ring cell components more than 50%, 26 (34.7%) were patients with signet-ring cell components less than 50%. At the time of diagnosis, 8 (10.7%) patients had Stage 1-2, 53 (70.7%) patients had Stage 3 and 14 (18.6%) patients had Stage 4 disease. The mean follow-up period of the patients was 54 months. Median overall survival (mOS) was 28.5 months. The mOS of patients who developed metastasis at the time of diagnosis was 9.3 months and mOS of patients without metastasis was 36.5 months.

**Conclusion:** It was observed that primary signet-ring cell carcinomas were mostly seen in males and localized in left colon and had a worse prognosis than classical adenocarcinomas.

**Keywords:** Signet-cell, colorectal adenocarcinoma, survival

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Colorectal cancers are one of the leading causes of cancer-related deaths worldwide. Histologically, the most common subtypes, at decreasing frequency, can be classified as; intestinal type adenocarcinoma, mucinous adenocarcinoma, signet-ring cell carcinoma and other less common types.<sup>[1–3]</sup> The rare histological subtype, colorectal signet-ring cell carcinomas were first described by Laufman and Saphir in 1951. Primary signet-ring cell cancers, a variant of colorectal adenocarcinomas according to WHO classification, are characterized with more

than 50% intracytoplasmic mucin cells in tumor cells<sup>[4,5]</sup> and seen in <1% to 2.4% of all colorectal cancers.<sup>[6]</sup> Compared to classical adenocarcinoma histology, patients are diagnosed at a more advanced stage and have a poor prognosis.<sup>[7]</sup> There are inadequate studies on the group of colorectal adenocarcinomas containing less than 50% signet-ring cell components. This group is also considered to have a similar course compared with tumors containing 50% or more mucin.

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**Table 1.** Clinicopathologic features of colorectal adenocarcinoma with signet-ring cell component

Characteristic	All patients		<50% SRCC		≥50% SRCC		p
	n	%	n	%	n	%	
Sex							
Male	43	57.3	13	50.0	30	61.2	0.350
Female	32	42.7	13	50.0	19	38.8	
Age							
Median (range)	55.8 (39.7-65.4)		55.1 (37.7-65.8)		58.7 (42.3-65.5)		0.764
<40 yr	19	25.3	8	30.8	11	22.4	0.430
≥40 yr	56	74.7	18	69.2	38	77.6	
ECOG PS							
0-1	70	93.3	25	96.2	45	91.9	0.653
≥2	5	6.7	1	3.8	4	8.1	
Grade							
1-2	41	54.7	15	57.7	26	53.1	0.701
3	34	45.3	11	42.3	23	46.9	
Stage							
1-2	8	10.7	3	11.5	4	8.1	0.695
3	53	70.7	19	73.1	35	71.4	
Metastasis on initial diagnosis							
Yes	14	18.7	4	15.1	10	20.4	0.759
No	61	81.3	22	84.9	39	79.6	
Tumour location							
Left	54	72.0	18	69.2	36	73.5	0.697
Right	21	28.0	8	30.8	13	26.5	
Locations of metastasis							
Lung	6	8.0	2	7.7	4	8.2	
Liver	12	16.0	3	11.5	9	18.4	
Peritoneum	13	17.3	4	15.4	9	18.4	
Others	19	25.3	9	34.6	10	20.4	

SRCC: Signet-ring cell carcinoma; ECOG PS: Eastern Cooperative Oncology Group performance status.

Tumor location, age, sex, lymphatic invasion and distant metastasis are the parameters that determine colorectal tumor behavior.<sup>[8,9]</sup> Mucin secretion feature of signet-ring cell cancers is one of the important parameters in the biological behavior of the tumor. In this study, we aimed to evaluate the clinicopathologic features and survival outcomes of signet-ring cell colorectal cancers.

## Methods

### Patient Populations

2673 patients diagnosed with colorectal cancer who presented to outpatient clinics of Medical Oncology in Istanbul Ümraniye Training and Research Hospital and Dr. Lütfi Kırdar Kartal Training and Research Hospital, from 2004 to 2019 were investigated. Group 1 was determined as patients with signet-ring cell component more than 50% and Group 2 as patients with signet-ring cells component less than 50%. Clinicopathological data of the patients were obtained from patient records retrospectively. Ethical ap-

proval (B.10.1.TKH.4.34.H.GP.0.01/65) was obtained from the Ethics Committee of Istanbul Ümraniye Training and Research Hospital.

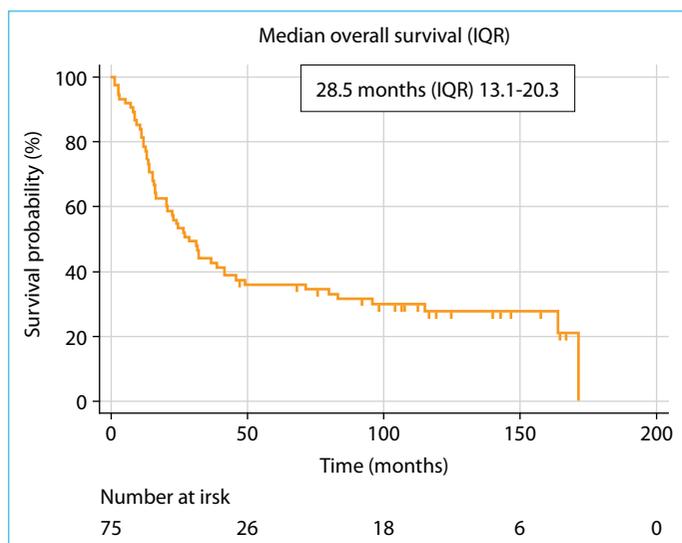
### Statistical Analysis

Statistical analyses were performed with SPSS 17.0 software. The quantitative variables were analyzed using proportions. Chi-square statistics and Mann-Whitney U tests were used to compare proportions and continuous variables. Survival distributions were estimated by the Kaplan-Meier method. The log-rank test was used to compare Kaplan-Meier survival curves. All tests were two-sided and p-value less than 0.05 was considered as significant.

## Results

### Clinicopathological Characteristics

A total of 75 patients with primary signet-ring cell component were included in the study. Forty-nine (65.3%) were

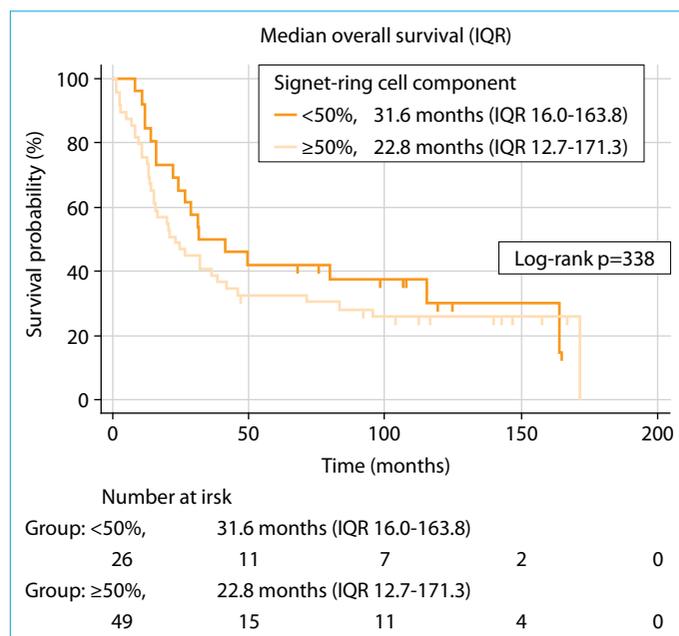


**Figure 1.** Kaplan-Meier overall survival curve.

patients with signet-ring cell components more than 50%, 26 (34.7%) were patients with signet-ring cell components less than 50%. 43 (57.3%) patients were male and 32 (42.7%) patients were female. The median age was determined as 55.8 (39.7-65.4). There were 19 (25.3%) patients diagnosed under the age of 40 and 56 (74.7%) patients over the age of 40. At the time of diagnosis, 8 (10.7%) patients had Stage 1-2, 53 (70.7%) patients had Stage 3 and 14 (18.6%) patients had Stage 4 disease. Tumor originated from left colon in 54 (72%) patients whereas from right colon in 21 (28%) patients. Clinicopathological characteristics of signet-ring cell colorectal carcinomas are shown in Table 1.

### Clinical Outcome of CRC with Signet-Ring Cell Component

The mean follow-up period of the patients was 54 months. Median overall survival (mOS) was 28.5 months (Fig. 1) The mOS of patients who developed metastasis at the time of diagnosis was 9.3 months and mOS of patients without metastasis was 36.5 months.



**Figure 2.** Survival analysis according to the signet-ring cell component of the tumor.

### Comparison of Clinical Parameters of Group 1 and Group 2 Patients

61.2% of Group 1 patients were male, whereas in Group 2 patients both genders were equal in frequency (p: 0.350). Median age was 58.7 (42.3-65.5) years in Group 1 and 55.1 (37.7-65.8) years in Group 2 (p: 0.350). There was no statistically important difference in terms of the stage of the disease at the time of diagnosis between both groups (p: 0.695). Stage 1-2 disease were seen less frequently in both groups. No difference was observed between the groups according to tumor localization, however, tumors were mostly located in the left colon (p: 0.697). The mOS of the group 1 patients was 22.8 months and the mOS of the group 2 patients was 31.6 months. There was no statistically important difference between the groups (p: 0.338, Fig. 2). The 5-year overall survival rate was 32% in Group 1 patients and 42% in Group 2 patients (Table 2). As a result of univariate analysis, ECOG performance score and presence

**Table 2.** Stage specific 5-year survivals for SRCC of the colon and the rectum

	n	Stage 1-2 %	Stage 3 %	Stage 4 %	All stages
Tumour location					
Rectum	26	50	48	0	42
Colon	49	100	25	18	32
Signet-ring cell component					
<50% signet-ring cells	26	100	37	25	42
≥50% signet-ring cells	49	80	32	10	32

SRCC: Signet-ring cell carcinoma.

**Table 3.** Univariate analysis (log-rank test) of OS, in SRCC patients

Variables	Median OS (months), IQR	p
Male	22.8 (13.4-95.9)	0.309
Female	36.5 (12.0-NR)	
Age <40 years	31.0 (13.1-163.8)	0.786
Age ≥40 years	26.4 (12.9-NR)	
ECOG PS 0-1	31.0 (14.0-163.8)	0.037
ECOG PS ≥2	2.5 (1.3-8.3)	
Right colon	41.6 (20.3-115.3)	0.409
Left colon	24.0 (12.7-163.8)	
Metastasis on initial diagnosis (+)	8.3 (2.5-15.7)	<0.001
Metastasis on initial diagnosis (-)	36.5 (16.0-163.8)	
≥50% signet-ring cells	22.8 (12.7-171.3)	0.338
<50% signet-ring cells	31.6 (16.0-163.8)	

OS: Overall survival; SRCC: Signet-ring cell carcinoma; ECOG PS: Eastern Cooperative Oncology Group performance status; IQR: Interquartile range; NR: Not reached.

of metastasis at the time of diagnosis were found to be effective on overall survival (Table 3).

## Discussion

Among all colorectal carcinomas, primary signet-ring cell colorectal carcinomas are seen at a rate of <1% to 2.4%.<sup>[6]</sup> This rate can reach up to 20% in various publications.<sup>[8]</sup> In our study, primary signet-ring cell (group 1) carcinoma was found to be 1.83% of all our colorectal cancer patients. The rate of colorectal carcinomas in Group 2 (signet-ring cell component less than 50%) was 2.8% and these results are consistent with the literature.

In the general population, more than 70% of patients are diagnosed with colorectal cancer over the age of 65.<sup>[10]</sup> Signet-ring cell tumors are generally seen in the young patient population (under 40 years of age) and female gender.<sup>[11-13]</sup> In the literature, the majority of primary signet-ring cell colon cancers was presented as a case report or series. The median age varies from 48 to 70 years in some studies probably due to the small number of patients. However, in all studies, primary signet-ring cell carcinomas are diagnosed at an earlier age than classical adenocarcinomas.<sup>[14,15]</sup> In our study, the median age was 55.8 years. Although the median age was younger than the general population, it was found to be older than the majority of studies conducted in this group of patients. In our study, male gender was seen slightly higher. There are also studies showing male gender predominance in the literature.<sup>[6,16]</sup> In our study, the majority of patients were diagnosed in the locally- advanced and metastatic stages. These findings were also consistent with the literature.<sup>[6,9,16]</sup> Primary signet-ring cell cancers were found generally to be located in the right colon in many studies,<sup>[17,18]</sup> however, in our study, unlike the existing lit-

erature, they were generally located in the left colon and rectum. In the study conducted by Lee et al.,<sup>[19]</sup> the majority of patients' localization of tumor was the left colon.

Median overall survival of primary signet-ring cell carcinomas varies between 20-45 months. In our study, overall survival was 28.5 months in accordance with the literature. 3-year overall survival was 44% and 5-year overall survival was 36%. The median overall survival of patients with Stage 4 at the time of diagnosis was 9.3 months. In classical colon adenocarcinomas, this duration is around 24 months.<sup>[20]</sup> A numerical significant difference was observed between the overall survival of Group 1 and Group 2 patients, even though it was not statistically significant (22.8 months vs. 31.6 months). A recent study concluded that greater amount of extracellular mucin, lymphovascular and perineural invasion, advanced pathological stage, and old age at the time of diagnosis were found to be prognostic factors for poor overall survival.<sup>[21]</sup> Huang et al.<sup>[22]</sup> found in their analysis on patients with signet-ring cell Carcinoma of the Colon without distant Metastasis, that patients ≤35 years of age were more likely to have a poorer survival outcome compared with patients aged >35 years. Also in our study, univariate analysis showed that patients with an ECOG performance score of ≥2 and above and patients with metastasis at the time of diagnosis had a negative effect on overall survival.

In our study, we aimed to evaluate the clinicopathologic characteristics and overall survival outcomes of primary signet-ring cell colorectal carcinomas. Since our study is retrospective, it is open to selection bias. In addition, molecular analyzes are lacking.

## Conclusion

It was observed that primary signet-ring cell carcinomas were mostly seen in males and in left colon, diagnosed at locally- advanced and advanced stages at the time of diagnosis and had a worse prognosis than classical adenocarcinomas. Histopathological examination revealed that the overall survival results were worse as the signet-ring cell component increased.

## Disclosures

**Ethics Committee Approval:** The study was performed according to the institutional ethical standards (University of Health Sciences, Umraniye Training and Research Hospital, Number: B.10.1.TKH.4.34.H.GP.0.01/65) and Helsinki Declaration.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – A.O.; Design – A.O.; Supervision – A.O.; Materials – A.O.; Data collection &/or processing – A.O., M.B.; Analysis and/or interpretation – M.B.; Literature search – A.O.; Writing – A.O.; Critical review – A.O., M.B.

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