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Retrospective analysis of metastatic signet ring cell colon cancer and determination of prognostic factors

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Abstract

Aim: Signet ring cell tumor (SRCRC) is a rare form of colorectal carcinoma. Due to its rarity, there is no randomized controlled study. Data are generally derived from retrospective data or obtained by adapting data on signet ring cell gastric cancer and classical colon adenocarcinoma for this patient group. Therefore, we retrospectively examined patients with SRCRC followed in our center to contribute to the literature.

Material and Methods: Between 2009 and 2022, 51 patients with metastatic SRCRC were retrospectively analyzed in our center.

Results: Overall survival was 18.4 (16.2-20.5) months. In univariate analysis, a significant association was found between survival and the presence of right tumor location (p=0.044), RAS mutation type (p=0.006), stage (p=0.002), grade (p=0.001), tumor diameter (p=0.032), peritoneum metastasis (p=0.033), lymph node metastasis (p=0.001), lymphatic invasion (p=0.008), perineural invasion (p=0.002). In the multivariate analysis, a correlation was found between the survival time and the location of the right tumor (p=0.002), RAS mutation (p=0.044), stage (p=0.001), grade (p=0.001), presence of peritoneal (p<0.0001) and lymph node metastasis (p=0.005) and tumor diameter (p=0.044).

Discussion: SRCRC is a rare, aggressive tumor that has different characteristics. Stage, grade, right-sided location, tumor diameter, lymphatic invasion, presence of peritoneum and lymph node metastasis are related to prognoses.

Keywords

Colorectal Cancer, Signet-Ring Cell Colorectal Cancer, Signet ring cell, Prognosis

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Introduction

Colorectal cancer (CRC) is the third most common cancer in the US and the second leading cause of death [1]. SRCRC is seen in less than 1% of all CRCs [2]. Signet ring cell carcinomas usually occur in the stomach, but may rarely occur in other organs such as the breast, gallbladder, pancreas, bladder and colon [3]. In 1951, Laufman and Sphir first described signet-ring cell carcinoma of the colon [4]. SRCRC, classified by the World Health Organisation, has a signet ring appearance in more than 50% of tumor cells and is characterized by a conspicuous intracytoplasmic mucin deposition [5]. It is usually localized in the right colon and can occur at any age. It is more common in female patients and has a poor prognosis in the advanced stage and generally in the metastatic phase [6-7]. Because of their clinically delayed findings, they are in advanced stages and have a poor prognosis [7]. TNM stage has been shown to be the most effective prognostic factor in SRCRC [8]. Despite adjuvant therapy in stage 3 CRC, the presence of a signet ring cell tumor in both the colon and rectum shows a worse prognosis [9]. The 5-year survival rate for SRCRC varies between 9-36% [10]. Due to its rarity there is no randomized controlled study. Data are generally derived from retrospective data or obtained by adapting data on signet ring cell gastric cancer and classical colon adenocarcinoma for this patient group. Sometimes in clinical practice, the prognosis of patients with the same stage, the same number of metastases and the same metastasis site may be different, for this reason other prognostic markers other than stage are needed in patients. Therefore, we retrospectively examined patients with SRCRC followed in our center to contribute to the literature.

Material and Methods

Between 2009 and 2022, 51 patients with metastatic SRCRC were retrospectively analyzed at our center. In the study, age, sex, history of acute intestinal obstruction, tumor location, tumor diameter, TNM stage, tumor grade, lymphatic invasion, pan-RAS (KRAS and NRAS codon 12, 13, 59, 61, 117,146), BRAF mutation, presence of perineural-lymphatic invasion, metastasis site, overall survival and their relationship to overall survival were evaluated. Overall survival time was calculated as the time from the date of diagnosis to mortality for deceased patients and the last follow-up for the survivors.

Statistical analysis

Descriptive statistics were presented as numbers and percentages for categorical variables, median values as minimum and maximum for numerical variables, and means as standard deviations. Survival analysis was performed using the Kaplan-Meier method. Significant variables in univariate analysis were introduced into a multivariate Cox model. P<05 was considered significant in all statistics.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Fifty-one patients, 27 (52.9 %) women and 24 (47.1 %) men, were evaluated. The median age of patients was 48 (25-80) years. Metastasis developed at the time of diagnosis in 43 (84.3 %) cases and during the course of the disease in 8 (15.6 %) cases. Tumor localization was in the left colon in 30 (58.8 %) patients and in the right colon in 21 (41.2%) patients. RAS Mutations of the patients were detected in 27 (52.9 %) of the wild type and in 24 (47.1 %) of the mutated type. The mean tumor diameter in patients was 7.67 (± 0.27) cm. Twenty-two (43.1 %) of the patients were diagnosed after surgery due to bowel obstruction. Thirty-nine (76.5 %) poorly/undifferentiated and 12 (23.5 %) well-moderately differentiated grade tumors were detected. The lymphatic invasion was positive in 21 (41.2 %) patients and perineural invasion in 18 (35.5 %) patients. At

Table 1. Demographic, clinical and pathological characteristics of all patients

		Number (n)	Percentage (%)
Sex	Male	24	52.9
	Female	27	47.1
ECOG performance score	ECOG≤2	20	39.2
	ECOG>2	31	60.7
Site of metastasis	Lymph node	35	68.6
	Peritoneum	27	52.9
	Liver	27	52.9
	Lung	15	29.4
	Bone	11	21.5
Ileus at diagnosis	Yes	22	43..1
RAS	Wild	24	47.1
	Mutant	27	52.9
BRAF	Wild	51	100
Stage	3	8	15.6
	4	43	84.3
Lymphatic invasion	Positive	21	4.4
	Negative	10	17.6
Perineural invasion	Positive	18	35.3
	Negative	18	35.3
Pathological Grade	Poorly/undifferentiated	39	76.5
	Well + moderately differentiated	12	23.5

ECOG; Eastern cooperative oncology group

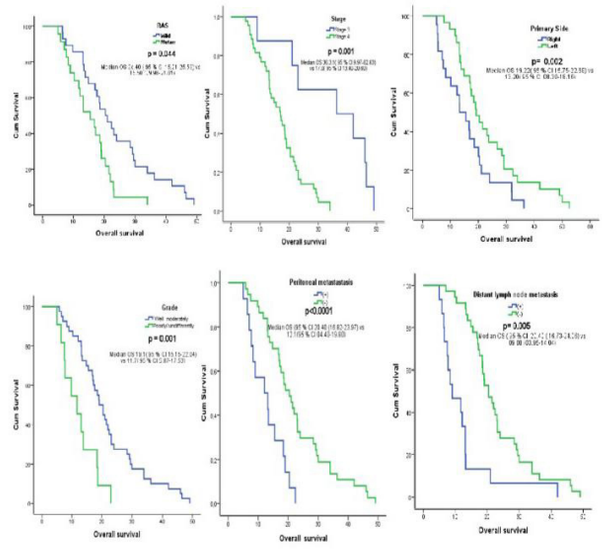

Figure 1. Kaplan-Meier curves showing overall survival (RAS,stage, primary tumor site, Grade, peritoneal und lymph node metastasis)

Table 2. Correlation between overall survival and clinical factors

	Univariate analysis (HR, 95% CI)	P value	Multivariate analysis (HR, 95% CI)	P value
Age	1.00 (0.98-1.02)	0.86		
sex	1.07 (0.60-1.90)	0.81		
ECOG	1.06 (0.99-1.14)	0.11		
LVI	2.88 (1.32-6.28)	0.008	2.18 (0.82-5.82)	0.12
PNI	2.90 (1.49-5.65)	0.002	1.05(0.50-2.22)	0.90
Grade	2.29 (1.60-6.79)	0.001	5.65 (2.06-15.53)	0.001
Tumor side	1.80(1.02-3.22)	0.044	3.13(1.5-6.56)	0.002
RAS	2.32 (1.27-4.25)	0.006	2.07 (1.02-4.2)	0.044
Tumor diameter	1.18 (1.01-1.37)	0.032	1.20 (1.03-1.41)	0.023
Peritoneum	1.37 (1.03-1.83)	0.033	9.50(3.45-26.29)	<0.001
Lymph node	1.673 (1.23-2.28)	0.001	3.15 (1.40-7.02)	0.005
Lung	1.14 (0.65-2.00)	0.65		
liver	1.21 (0.69-2.15)	0.51		
Ileus	1.12 (0.64-1.97)	0.69		
Stage	6.92 (2.08-22.97)	0.002	10.64(2.60-43.39)	0.001

HR: Hazard ratio, CI: confidence interval, ECOG: Eastern cooperative oncology group, LVI: lymphatic invasion, PNI: perineural invasion

diagnosis or recurrence, lymph node metastasis was found in 35 (68.6%) patients, peritoneal metastasis in 27 (52.9 %), liver metastasis in 27 (52.9 %), lung metastasis in 15 (24%) and bone metastasis in 15 (24.9 %) (Table 1). Overall survival was 18.4 (95 % CI 16.2-20.5) months. In univariate analysis, a significant association was found between survival and the presence of right tumor location (p=0.044), RAS mutation type (p=0.006), stage (p=0.002), grade (p=0.001), tumor diameter (p=0.032), peritoneum metastasis (p=0.033), lymph node metastasis (p=0.001), lymphatic invasion (p=0.008), perineural invasion (p=0.002). In the multivariate analysis, a correlation was found between the survival time and the location of the right tumor (p=0.002), RAS mutation (p=0.044), stage (p=0.001), grade (p=0.001), presence of peritoneal (p<0.0001) and lymph node metastasis (p=0.005) and tumor diameter (p=0.044) (Table 2).

Discussion

SCCRC is a rare but aggressive cancer. It occurs in 0.5% to 1% of all CRCs [11]. It has a poorer prognosis than other colorectal cancers due to late diagnosis, high grade, aggressive behavior and frequent recurrence after surgery [7,12]. SCCRC can occur at any age. Although some studies have reported that it is more common over the age of 60 [6,13], other studies have reported that it is more common at younger ages than other subtypes [12,14-15]. In our study, the mean age at diagnosis was 48 years. A clear assessment of the incidence of SRCRC between the sexes could not be made. While it was observed more frequently in women in some studies [5,14], it was observed more frequently in men in some studies [12,13]. In our study, it was observed more frequently in women .

Some studies reported that tumor localization was more common in the right colon [16], in some studies, it was more common in the left colon [17], and in some studies, there was no difference in the frequency of localization [11,14]. In our study, 30 (58.8%) of the signet ring tumors were located in the left colon and 21 (41.2%) in the right colon, and a significant correlation was found with survival of tumors in the right colon (p= 0.002).

In their study, Tung et al. found that signet ring cell tumors have a larger tumor diameter than other adenocarcinomas [15]. They attributed this to local infiltration and involvement in the form of linitis plastica. Dai et al. found that a larger tumor diameter was associated with poor prognosis and short life expectancy in patients with colorectal cancer [18]. In our study, the mean tumor diameter in patients was 7.67 (± 0.27) and it was found to be significantly associated with survival (p=0.023).

Colon cancer with a signet ring feature is often observed with lymphatic invasion [12]. The presence of lymphovascular invasion and perineural invasion has been associated with poor prognosis [19]. In our study, a significant correlation was found between mean life expectancy (p=0.008) and lymphatic invasion in univariate analyses but this finding was not significant in multivariate analyses (p=0.12) . The diagnosis of metastatic patients is sometimes made by organ biopsies and sometimes by endoscopic biopsy. Lymphovascular and perineural invasion could not be evaluated, especially since it was performed primarily for diagnosis in organ biopsies, and the materials taken were smaller than the surgical materials. Therefore, LVI and PNI may not be significant in the multivariate analysis, since they were not evaluated in all patients.

In studies, tumors with signet-ring morphology have been found to be high grade. Due to poorly differentiated high grade, these tumors cause short survival and early recurrence [7,17,19]. In our study, a significant correlation was found between mean survival and high-grade tumor (p=0.001).

TNM stage has been found to be an independent factor for prognosis in SCCRC [9]. As SRCRC is usually diagnosed late and has an aggressive course, it is diagnosed at an advanced stage with diffuse lymph node involvement and distant metastatic findings [14,16-17]. Tumor invasion with T3 or more involvement is present at the time of diagnosis [14]. In these tumors, lymph node involvement is observed more frequently than adenocarcinoma morphology, and as a result, more advanced disease is noted [14,15]. In our study, 43 (84.3%) of patients developed metastases at diagnosis and 8 (15.6%) during the course of the disease. Detection of advanced disease in our study was associated with shorter life expectancy (p < 0.001). This situation was similar to that reported in the literature.

Loss of E-cadherin expansion is frequently observed in SRCRC tumor cells [20]. This loss of expiration enhances the development of local invasion. As a result, the peritoneal uptake of tumor cells is increased. In studies, this picture is often observed in signet ring cell morphology and consequently leads to advanced disease [18]. Peritoneal metastasis and lymph node involvement are evident at the time of diagnosis, and bone, lung and liver involvement is observed less frequently compared to adenocarcinoma morphology [21].

Local recurrence and the presence of peritoneal metastasis are associated with a poor prognosis for patients [22]. Peritoneal metastasis at the time of diagnosis indicates a short life expectancy [14]. In our study, metastasis developed in 43 (84.3%) cases at the time of diagnosis and in 8 (15.6%) cases during the course of the disease. Among SCCRC patients at the time of diagnosis or recurrence, 35 (68.6%) had intra-

abdominal lymph node metastasis, 27 (52.9%) had peritoneal metastasis, 27 (52.9%) had liver metastasis, 15 (24.9%) had lung metastasis and 15 (24.9%) had bone metastasis. The occurrence of peritoneal and intra-abdominal lymph node metastases proved to be statistically significant in relation to average life expectancy. These results are consistent with the literature.

In the treatment of metastatic colorectal cancer, RAS and other genetic evaluations are the most important target of treatment. RAS is a transducer in the epithelial growth pathway and a small G protein in the role of tumor suppression. Loss of function leads to activation of the mitogen-activated kinase and phospho-inositol phosphate 3 pathway. Loss of RAS mutation occurs in a type of colon cancer that is resistant to treatment [23]. This occurs in about 40% of all colon cancers [24]. In our study, a significant association was found between the average survival time and the RAS mutated tumor (p=0.044). In studies, no difference was found between the frequency of RAS mutations between the signet ring type and other subtypes of colon cancer [25].

The weaknesses of our study may be that it is retrospective, single-center, with a small number of patients and only Turkish patients, which may have led to racial bias. However, this study is important because it shows factors affecting the prognosis in SRCRCs, and due to their rarity, randomized studies cannot be performed.

Conclusion

SRCRCs are rare and aggressive cancers. They are diagnosed at advanced stages. Stage, grade, right side location, tumor diameter, lymphatic invasion, presence of peritoneum and lymph node metastasis are related to prognoses. SRCRC is a tumor that has different characteristics and its treatment needs further investigation. For a standardized treatment approach, more centered studies with a larger number of patients are needed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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