Research Article

Colorectal Cancer Prognosis: The Impact of Signet Ring Cell

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Keywords

Prognosis · Signet-ring cell carcinoma · Colorectal carcinoma

Abstract

Background: The prognosis for patients with colorectal cancer shows variation. The characteristics of colorectal cancer patients with signet-ring cell carcinoma (SRCC) are still not clear.

Materials and Methods: A retrospective comparison was made of the data of signet-ring cell colorectal carcinoma patients operated on between 2009 and 2018 in respect of clinicopathological and operative results, morbidity, mortality, and long-term survival. **Results:** The study included a total of 34 patients comprising 26 (76%) males and 8 (24%) females with a mean age of 58 ± 11.7 years. Incidence of SRCC was determined as 1.8%. Lymphovascular invasion was determined in 22 (64%) patients. Tumors were determined as stage T2 in 8 (32%) patients, stage T3 in 9 (36%), and stage T4 in 8 (32%). According to the TNM classification, 5 (14.7%) patients were diagnosed with stage 1, 7 (20.6%) with stage 2, 15 (44.1%) with stage 3, and 7 (20.6%) with stage 4. The mean follow-up period was 40.6 ± 30.4 months, and mean disease-free follow-up was determined as 33.1 ± 36.1 months. Fifteen (44.1%) patients died because of the disease. **Conclusion:** Although SRCC is a poor prognostic factor, it should be kept in mind when determining adjuvant therapies and prognosis of patients determined with advanced-stage SRCC.

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Introduction

Colorectal cancer is the third most frequently seen cancer worldwide [1]. Signet-ring cell carcinoma (SRCC), which is an uncommon type of colorectal cancer constituting 0.5–2.6% of all adenocarcinomas [2, 3], is defined by the presence of signet ring cells as the dominant (50%) malignant cell type, and the formation of immature glands [4]. SRCC has been shown to be a poor prognostic factor in several studies [2, 3, 5–7], and the AJCC Cancer Staging Guidelines (7th edition) qualified it to be an independent prognostic factor [6, 7]. SRCC has been reported to be seen generally at a young age with greater lymph node involvement and more peritoneal carcinomatosis. However, no full consensus has yet been reached on this subject. Several colorectal cancers are seen in different forms. Therefore, it is important to define the characteristics of the CRC subtype to be able to treat CRC patients appropriately.

The aim of this study was to determine the clinical-pathological features and postoperative long-term prognosis of colorectal SRCC.

Material and Methods

A retrospective scan was made of 3,180 patients for those histologically diagnosed with SRCC between 2009 and 2018.

The preoperative clinical evaluation included physical examination, colonoscopy, abdominopelvic computed tomography (CT), chest radiography or CT, complete blood cell count, liver function test, and carcinoembryonic antigen level. Depending on the extent of the disease, rectal or liver magnetic resonance imaging and CT combined with positron emission tomography were also performed.

Tumor sections were examined histologically, and the following features were recorded: depth of tumor invasion, vascular invasion, and lymph-node metastasis. The depth of tumor invasion, lymph-node metastasis, and clinical information were used to assign a tumor stage using the TNM classification as described in the American Joint Committee on Cancer, AJCC Cancer Staging Manual.

The following criteria were used for the diagnosis of a SRCC: the presence of signet-ring cells as the dominant (50%) malignant cell type, and the formation of immature glands. All cases were reviewed by a specialist pathologist who is an expert in this field.

Neoadjuvant and adjuvant treatments were applied according to the disease stage. Neoadjuvant therapy was applied to patients thought to have metastasis and carcinomatosis. Adjuvant therapy was applied to stage III patients with no medical contraindications, and to stage II patients with a high risk of recurrence.

Follow-Up

The patients were followed up clinically every 3 months for 1 year, every 6 months for the subsequent 2 years, and annually thereafter. Tumor progression was defined either pathologically or radiologically as local recurrence and distant metastases.

Statistical Analysis

The mean survival time of patients in SRCC stage was estimated using Student's *t* test, and the cumulative survival rate was estimated according to the Kaplan-Meier method. The significance of differences in survival rates were calculated using the log-rank test.

Results

The study included a total of 34 patients comprising 26 (76%) males and 8 (24%) females with a mean age of 58 ± 11.7 years. Incidence of SRCC was determined as 1.06%, and 4 (11.7%) patients were aged <40 years. Operations were performed on 25 (73.5%) patients, of which 13 (52%) were laparoscopic. The mean tumor diameter was 4.6 ± 1.8 cm and a mean of 20 ± 4.1 lymph nodules were removed from the patients who underwent surgery.

Table 1. Demographic, anatomic-pathological, and oncological data according to the signet ring cell ($n = 34$)

Age, years	58±11.7
Males	26 (76)
Operation	25 (73.5)
Laparoscopic	13 (52)
Open	12 (48)
Tumor size, cm	4.6±1.8
Harvested lymph nodes	20±4.1
Lymph node+ patients	17 (68)
Invaded lymph node	3.7±3.9
lymphovascular invasion	22 (64)
Tumor location	
Left colon	8 (23.5)
Right colon	10 (29.4)
Rectosigmoid	16 (47.1)
T stage	
2	8 (32)
3	9 (36)
4	8 (32)
Stage	
1	5 (14.7)
2	7 (20.6)
3	15 (44.1)
4	7 (20.6)
Tumor recurrence	
Liver + pulmonary metastasis	10 (29.4)
Carcinomatosis peritonei	5 (14.7)
Distant metastasis + carcinomatosis peritonei	2 (5.8)
Neoadjuvant chemotherapy	8 (23.5)
Adjuvant chemotherapy	15 (44.1)
Data are presented as mean ± SD or n (%).	

Table 2. Long-term outcomes according to the signet ring cell ($n = 34$)

Died with disease	15 (44.1)
Died without disease	1 (2.9)
Survived without disease	16 (47)
Survived with disease	2 (5.8)
Follow-up time, months	40.6±30.4
Disease-free follow-up time, months	33.1±36.1
Data are presented as mean ± SD or n (%).	

Lymph node metastasis was determined in 17 (68%) patients, and a mean of 3.7 ± 3.9 invaded lymph nodes were determined. Lymphovascular invasion was determined in 22 (88%) patients.

Tumor localization was in the rectosigmoid colon in 16 (47.15) patients, the right colon in 10 (29.4%) and the left colon in 8 (23.5%). Tumors were determined as stage T2 in 8 (32%) patients, stage T3 in 9 (36%), and stage T4 in 8 (32%). According to the TNM classification, 5 (14.7%) patients were diagnosed with stage 1, 7 (20.6%) with stage 2, 15 (44.1%) with stage 3, and 7 (20.6%) with stage 4. Hepatic and pulmonary metastases were determined in 10 (29.4%) patients, carcinomatosis peritonei in 5 (14.7%), and distant organ metastasis and carcinomatosis peritonei together in 2 (5.8%). As 9 (26.4%) patients were metastatic at the time of diagnosis, neoadjuvant therapy was applied. Postoperative adjuvant chemotherapy was applied in 15 (44.1%) patients (Table 1).

Fig. 1. Survival according to the signet ring cell.

The mean follow-up period was 40.6 ± 30.4 months, and the mean disease-free follow-up was determined as 33.1 ± 36.1 months. Throughout the follow-up period, 16 (47%) patients were disease-free, 2 (3.8%) patients were followed up with disease, and mortality was seen in 15 (44.1%) patients because of the disease. Of these 15, the tumor was stage T1 in 1 (6.6%) patient, and stage T3–4 in the remainder. One (6.6%) patient died for other reasons (Table 2; Fig. 1).

Discussion

Compared to other cancer types, SRCC is a more uncommon cancer subtype, and the prognosis is worse [2, 3, 6, 7]. The aim of this study was to determine the clinical and pathological features and postoperative long-term prognosis of colorectal SRCC.

Various series have reported the mean age of SRCC patients ranging from 48 to 70 years, and have stated that it is seen generally at younger ages [8, 9]. A previous study showed young age (≤ 40 years) to be an independent predictive factor for disease outcome [10]. In our series, the mean age was 58 years, and age < 40 years was determined at a rate of 11.7%. There is no consensus on whether it is more prevalent in males or females, and while some studies have reported higher rates in males [11, 12], others have shown higher rates in females [13, 14]. There are also studies that have reported poor life expectancy in females [14]. In the current study, the number of males was greater.

The incidence of SRCC is unclear, which could be due to environmental and genetic reasons between different regions. Generally, the incidence of SRCC has been reported as 0.5–2.6% [15, 16]. In our study, the incidence was determined as 1.8%.

SRCC has generally been determined in the right colon, and while 20% have been reported in the rectum [17], other studies have considered colon localization to be an independent prognostic factor [18]. In the present study, SRCC was determined most in the rectosigmoid followed by the right colon.

In several studies, T3–4 tumors have been seen at a high rate of up to 90% in patients with SRCC, and it has been reported that patients are diagnosed when at an advanced stage [13–17]. Bonello et al. [19] suggested 3 reasons for the advanced stages of these patients; as the tumor is uncommon, there are few symptoms as a result of intramucosal spread, and it cannot be differentiated radiologically from inflammatory processes. Another reason that

patients are diagnosed at an advanced stage could be the high rate of lymphovascular invasion [20, 21]. Signet-ring cell histology is known to be more aggressive because the cellular abnormality does not involve cell-to-cell adhesions, which results in a greater spreading tendency [16, 22]. In our series, T3/T4 tumors were determined at a rate of 68%, which is consistent with the literature. In 64.7% of the current study patients, diagnosis was made at an advanced stage, and a high rate of lymphovascular invasion was determined, which was also consistent with the literature [10–17, 23].

Compared to other cancer types, this cancer has been reported to metastasize to the peritoneal surface more often [11, 12, 23]. Rates of 51.2 and 43.9% for peritoneal dissemination and distant lymph node, respectively, were reported by Hugen et al. [17]. The proportion of patients with dissemination to the peritoneum and distant lymph node was statistically different compared to non-SRCC patients. In the current study, peritoneal metastasis was determined at 20.5%. Previous studies have reported that distant metastases at presentation are found in approximately 22–40% of cases of SRCC of the colon and rectum [2, 16, 21]. In our patients, distant organ metastasis occurred at a rate of 35.3%, which is consistent with the literature.

Mucinous adenocarcinoma has been reported to have a more problematic prognosis than adenocarcinoma [3, 8]. As SRCC has been reported to have a worse prognosis than mucinous carcinoma [2, 3, 8, 10–14, 23], SRCC carcinoma has been reported to be an independent risk factor [24]. In a study by Börger et al. [25] in which signet ring histology was investigated in 1,530 patients with mucinous adenocarcinoma, it was suggested that SRCCs develop through a different genetic pathway than conventional adenocarcinomas. Wu et al. [26] suggested that rather than a relationship between disease-free and overall survival rates and the pathological subtype of the cancer, the survival rates could be related to differences at the presentation stage. Sung et al. [22] reported that the disease-free survival rates and overall survival rates of patients with SRCC were lower than those of patients with adenocarcinoma. In the present study, the mortality rate during follow-up was determined as 44.1%.

In previous studies, some authors have suggested extended resections and increased systemic chemotherapy because of the poor prognosis [27, 28]. The current guidelines published by the American Society of Clinical Oncology related to Stage II colon cancer recommend adjuvant treatment of patients with stage II only in the presence of high-risk criteria such as T4 stage, inadequate lymphadenectomy, poor histological differentiation, bowel obstruction or perforation, and lymphovascular or perineural invasion [29]. Moreover, recent studies have shown no difference between SRCC patients and those with adenocarcinoma in respect of chemotherapy efficacy in the adjuvant setting [17]. In a study by Ackermann et al. [30], it was reported that there was no need for the adjuvant treatment of stage 1 and 2 SRCC colon cancer treatments to differ from that of other patients as the prognoses were similar. The poor prognosis of SRCC was stated to be due to diagnosis made at an advanced stage and the presence of lymph node metastasis. In line with our results, the majority of patients were diagnosed at an advanced stage, and most of the patients with mortality had T3–4 tumor and were diagnosed at an advanced stage. The majority of patients with T2 tumor and early stage diagnosis survived disease-free.

In gastric adenocarcinoma, a link to E-cadherin CDH1 gene mutation has been shown to correlate with signet-ring cell histology, although patients with SRCC have been shown to have a high rate of familial stomach cancer [31]. In the current study, no family history of stomach cancer was determined in any patient.

Limitations of the current study can be that it was retrospective, the chemotherapeutic agents given were not stated, there was a lack of molecular data and family history, and the patient group was small as SRCC is uncommon. There is a need for further studies to explore the differences in prognosis between mucin-rich and mucin-poor cells and to examine the long-term prognosis of early stage SRCC patients.

Conclusion

Signet cell is a poor prognostic factor, and the clinical characteristics of patients show variability. When determining the adjuvant therapies of patients determined with advanced-stage SRCC, it is necessary to take SRCC into consideration.

Statement of Ethics

In accordance with the protocol of the Ethics Committee of Clinical Investigation and the provisions of the protocol authorized by the Spanish Pharmaceutical and Health Products Agency, this study, which is processed and controlled for each subject, complies with ethical standards.

Disclosure Statement

There is no conflict of interest pertaining to this study among the authors.

Author Contributions

Refik Bademci: principal author; Jesus Bollo: primary operator, data collection and work; M. Carmen Martinez: primary operator, data collection and work; Maria Pilar Hernandez: primary operator, data collection and work; Eduardo Maria Targarona: primary operator.

References

- 1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010 Dec;127(12):2893–917.
- 2 Nitsche U, Zimmermann A, Späth C, Müller T, Maak M, Schuster T, et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. *Ann Surg*. 2013 Nov;258(5):775–82.
- 3 Ogino S, Brahmandam M, Cantor M, Namgyal C, Kawasaki T, Kirkner G, et al. Distinct molecular features of colorectal carcinoma with signet ring cell component and colorectal carcinoma with mucinous component. *Mod Pathol*. 2006 Jan;19(1):59–68.
- 4 Hamilton SR, Aaltonen LA. Pathology and genetics of tumours of the digestive system. In: WHO classification of tumors. Geneva: WHO; 2010.
- 5 Edge S, Byrd DR, Compton CC, Fritz AG, Greene F, Trotti A, editors. *AJCC Cancer Staging Manual*. 7th ed. Berlin: Springer; 2010.
- 6 Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th ed. Geneva: International Agency for Research on Cancer; 2010.
- 7 Hyngstrom JR, Hu CY, Xing Y, You YN, Feig BW, Skibber JM, et al. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. *Ann Surg Oncol*. 2012 Sep;19(9):2814–21.
- 8 Dajani YF, Zayid I, Malatjalian DA, Kamal MF. Colorectal cancer in Jordan and Nova Scotia: a comparative epidemiologic and histopathologic study. *Cancer*. 1980 Jul;46(2):420–8.
- 9 Ibrahim NK, Abdul-Karim FW. Colorectal adenocarcinoma in young Lebanese adults. The American University of Beirut-Medical Center experience with 32 patients. *Cancer*. 1986 Aug;58(3):816–20.
- 10 Tawadros PS, Paquette IM, Hanly AM, Mellgren AF, Rothenberger DA, Madoff RD. Adenocarcinoma of the rectum in patients under age 40 is increasing: impact of signet-ring cell histology. *Dis Colon Rectum*. 2015 May;58(5):474–8.
- 11 Tung SY, Wu CS, Chen PC. Primary signet ring cell carcinoma of colorectum: an age- and sex-matched controlled study. *Am J Gastroenterol*. 1996 Oct;91(10):2195–9.
- 12 Liang Z, Yan D, Li G, Cheng H. Clinical Analysis of Primary Colorectal Signet-Ring Cell Carcinoma. *Clin Colorectal Cancer*. 2018 Mar;17(1):e39–e44.
- 13 Fu J, Wu L, Jiang M, Tan Y, Li D, Chen F, et al. Signet ring cell carcinoma of resectable metastatic colorectal cancer has rare surgical value. *J Surg Oncol*. 2016 Dec;114(8):1004–8.
- 14 Inamura K, Yamauchi M, Nishihara R, Kim SA, Mima K, Sukawa Y, et al. Prognostic significance and molecular features of signet-ring cell and mucinous components in colorectal carcinoma. *Ann Surg Oncol*. 2015 Apr;22(4):1226–35.

- 15 Chew MH, Yeo SA, Ng ZP, Lim KH, Koh PK, Ng KH, et al. Critical analysis of mucin and signet ring cell as prognostic factors in an Asian population of 2,764 sporadic colorectal cancers. *Int J Colorectal Dis.* 2010 Oct;25(10):1221–9.
- 16 Pande R, Sunga A, Levea C, Wilding GE, Bshara W, Reid M, et al. Significance of signet-ring cells in patients with colorectal cancer. *Dis Colon Rectum.* 2008 Jan;51(1):50–5.
- 17 Hugen N, van de Velde CJ, de Wilt JH, Nagtegaal ID. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. *Ann Oncol.* 2014 Mar;25(3):651–7.
- 18 Ishihara S, Watanabe T, Akahane T, Shimada R, Horiuchi A, Shibuya H, et al. Tumor location is a prognostic factor in poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma of the colon. *Int J Colorectal Dis.* 2012 Mar;27(3):371–9.
- 19 Bonello JC, Quan SH, Sternberg SS. Primary linitis plastica of the rectum. *Dis Colon Rectum.* 1980 Jul-Aug;23(5):337–42U.
- 20 Bittorf B, Merkel S, Matzel KE, Wein A, Dimmler A, Hohenberger W. Primary signet-ring cell carcinoma of the colorectum. *Langenbecks Arch Surg.* 2004 Jun;389(3):178–83.
- 21 Mizushima T, Nomura M, Fujii M, Akamatsu H, Mizuno H, Tominaga H, et al. Primary colorectal signet-ring cell carcinoma: clinicopathological features and postoperative survival. *Surg Today.* 2010 Mar;40(3):234–8.
- 22 Sung CO, Seo JW, Kim KM, Do IG, Kim SW, Park CK. Clinical significance of signet-ring cells in colorectal mucinous adenocarcinoma. *Mod Pathol.* 2008 Dec;21(12):1533–41.
- 23 Lee WS, Chun HK, Lee WY, Yun SH, Cho YB, Yun HR, et al. Treatment outcomes in patients with signet ring cell carcinoma of the colorectum. *Am J Surg.* 2007 Sep;194(3):294–8.
- 24 Kanemitsu Y, Kato T, Hirai T, Yasui K, Morimoto T, Shimizu Y, et al. Survival after curative resection for mucinous adenocarcinoma of the colorectum. *Dis Colon Rectum.* 2003 Feb;46(2):160–7.
- 25 Börger ME, Gosens MJ, Jeuken JW, van Kempen LC, van de Velde CJ, van Krieken JH, et al. Signet ring cell differentiation in mucinous colorectal carcinoma. *J Pathol.* 2007 Jul;212(3):278–86.
- 26 Wu CS, Tung SY, Chen PC, Kuo YC. Clinicopathological study of colorectal mucinous carcinoma in Taiwan: a multivariate analysis. *J Gastroenterol Hepatol.* 1996 Jan;11(1):77–81.
- 27 Lee DW, Han SW, Lee HJ, Rhee YY, Bae JM, Cho NY, et al. Prognostic implication of mucinous histology in colorectal cancer patients treated with adjuvant FOLFOX chemotherapy. *Br J Cancer.* 2013 May;108(10):1978–84.
- 28 Benedix F, Kuester D, Meyer F, Lippert H. [Influence of mucinous and signet-ring cell differentiation on epidemiological, histological, molecular biological features, and outcome in patients with colorectal carcinoma]. *Zentralbl Chir.* 2013 Aug;138(4):427–33.
- 29 Benson AB 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol.* 2004 Aug;22(16):3408–19.
- 30 Ackermann CJ, Guller U, Jochum W, Schmied BM, Warschkow R. The prognostic value of signet ring cell histology in stage I/II colon cancer—a population-based, propensity score-matched analysis. *Int J Colorectal Dis.* 2018 Sep;33(9):1183–93.
- 31 Richards FM, McKee SA, Rajpar MH, Cole TR, Evans DG, Jankowski JA, et al. Germline E-cadherin gene (CDH1) mutations predispose to familial gastric cancer and colorectal cancer. *Hum Mol Genet.* 1999 Apr;8(4):607–10.