An Insight into the Peculiarities of Signet-Ring Cell Carcinoma of the Colon – a Narrative Review

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Abstract

Background: Signet-ring cell carcinoma of the colon (SRCC) is a rare and distinct form of colon cancer associated with a poor prognosis. Despite the rapid advancement of personalized cancer treatments, there is currently no recommended specific treatment for this histological subtype.

Materials and Methods: In this literature review, we explored and described the features that distinguish SRCC from other forms of colorectal cancer, focusing on clinical presentation, pre-operative workup, and treatment.

Results: One of the aspects that makes SRCC unique is that it is detected more often in the ascending vs other parts of the colon, regardless of age and gender. As a result, patients, unfortunately, present with a more advanced stage than other locations upon the initial diagnosis. Imaging techniques and tumor markers alone often fall short of revealing the extent of a tumor, and curative surgery procedures are rare. Neoadjuvant therapy in SRCC is currently recommended only in the context of a clinical trial. Adjuvant chemotherapy, on the other hand, appears promising in improving survival, especially in the stage III subgroup. SRCC have a higher incidence of BRCA1 and BRAF gene mutations when compared to adenocarcinomas, alongside to an increase in microsatellite instability. These particularities suggest that a targeted therapeutic approach may sometimes be considered.

Conclusion: Given its specific clinical characteristics and poor survival outcomes, SRCC should be considered a distinct colon cancer entity. Although its rarity makes prospective trials difficult, a timely diagnosis and a correct treatment decision-making algorithm is important.

Keywords: signet-ring cell carcinoma, colon cancer, ctDNA, microsatellite instability
1. Introduction

The incidence of cancer is increasing, accompanied by a shift towards more targeted, molecular-based, and personalized treatments. However, for rare tumors, pinpointing an exact target is difficult due to the limited statistical power of many epidemiological studies.

Signet-ring cell carcinoma of the colon (SRCC) is included in this category, accounting for 0.9 – 4% of all colon cancer histology subtypes (1). Characterized by excessive intracytoplasmic mucin vacuoles and a compressed peripheral nucleus, these signet-ring cells are an independent predictor of poor outcomes (2). To classify as a true SRCC, the World Health Organization requires at least 50% of the histopathological specimen to represent signet-ring cells.

This literature review aims to outline the clinical, morpho-pathological, and treatment-related particularities of SRCC to offer a more in-depth understanding of this disease.

2. Materials and methods

We performed a literature review of the PubMed database, using the following keywords in different combinations: “colon cancer,” “signet-ring cell carcinoma,” “epidemiology,” tumor marker,” “microsatellite instability,” “surgery,” “neoadjuvant therapy,” “adjuvant therapy.”

We first analyzed articles published from 2010 to 2023 by title and abstract and later focused only on those relevant to the current review (Figure 1). We then reviewed the reference lists from the selected studies to identify additional relevant studies.

The primary studies selected for this literature review focused on demographics and tumor characteristics. The studies outlined in Table 1 reported mainly treatment strategies and molecular features (Table 1).

![Figure 1. Flowchart illustrating our literature search and study selection method.](image-url)
Table 1. Outline the studies focusing on molecular alterations and treatment strategies in patients with SRCC, showing which treatment strategies are discussed.

<table>
<thead>
<tr>
<th>AUTHORS ET AL. (YEAR)</th>
<th>STRATEGIES OF TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td>Wenzai S et al. (3) 2023</td>
<td></td>
</tr>
<tr>
<td>Allart M et al. (4) 2021</td>
<td>x</td>
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<tr>
<td>Emile SH et al. (5) 2023</td>
<td></td>
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<tr>
<td>Sibio S et al. (6) 2019</td>
<td>x</td>
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<tr>
<td>Chalabi M et al. (7) 2020</td>
<td>x</td>
</tr>
<tr>
<td>Li C et al. (8) 2019</td>
<td></td>
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<tr>
<td>Luo D et al. (9) 2021</td>
<td>x</td>
</tr>
<tr>
<td>Hyung J et al. (10) 2022</td>
<td></td>
</tr>
<tr>
<td>Prabhu A et al. (11) 2020</td>
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<tr>
<td>Hugen N et al. (12) 2014</td>
<td></td>
</tr>
<tr>
<td>Zhao Z et al. (13) 2020</td>
<td></td>
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<tr>
<td>Jiang H et al. (14) 2021</td>
<td></td>
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<tr>
<td>Body A et al. (15) 2020</td>
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</table>

MOLECULAR FEATURES

<table>
<thead>
<tr>
<th>AUTHORS ET AL. (YEAR)</th>
<th>RAS, BRAF</th>
<th>Microsatellite instability</th>
<th>Other molecular alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allart M et al. (4) 2021</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Inamura K et al. (16) 2015</td>
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<td>Arifi S et al. (17) 2015</td>
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<td>Benedix F et al. (1) 2013</td>
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<tr>
<td>Sung CO et al. (18) 2008</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Voer RM et al. (19) 2020</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Liu X et al. (20) 2022</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Kakar S et al. (21) 2005</td>
<td></td>
<td></td>
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<tr>
<td>Puccini A et al. (22) 2022</td>
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<td>x</td>
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<tr>
<td>Nitsche U et al. (23) 2013</td>
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<tr>
<td>Therkildsen C et al. (24) 2014</td>
<td>x</td>
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3. Results and discussion

3.1. Demographics
SRCC is shown to be age and gender independent (1), with a median age at diagnosis of 67 years old (25). Some studies suggest an earlier age at presentation when compared to the more frequent adenocarcinoma subtype (26,27), as well as an upward trend to more advanced disease and poor outcomes with metastatic spread in female patients (28). On the other hand, signet-ring cell histology is shown to occur more frequently in younger patients than adenocarcinoma. When comparing the two subtypes in this group, SRCC generally has a more unfavorable prognosis than adenocarcinoma (Table 2).

Table 2. Studies presenting clinicopathologic features of SRCC in younger patients.

<table>
<thead>
<tr>
<th>AUTHORS ET AL.</th>
<th>OBSERVATIONS</th>
</tr>
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</table>
| de Voer RM et al. (19) | - 135 patients with colorectal cancer < 25 years old  
- 11% with signet-ring cell histology  
- worse prognosis than adenocarcinoma |
| Benmoussa A et al. (29) | - 54 patients with colorectal cancer < 50 years old  
- 18.5% with mucinous and signet-ring cell histology |
| Tawadros PS et al. (30) | - 1274 patients with colorectal cancer aged between 20-39 years  
- 3% with signet-ring cell histology  
- mOS: 14 months |
| Huang B et al. (31) | - 78 patients with SRCC < 35 years old  
- 73.1% with N1 disease  
- poorer cancer specific survival (CSS) than patients > 35 years old with SRCC  
- 5-year CSS: 31.1% |
| Li C et al. (8) | - 75 patients with SRCC of which 62.7% < 55 years old  
- 18.7% of patients with SRCC were under 35 years old, compared with only 3% of those with adenocarcinoma |

Abbreviations: mOS – median overall survival, SRCC – signet-ring cell carcinoma, CSS – cancer specific survival

Due to the rarity of this histology, the only current demonstrated demographic risk factor is that Caucasians appear to have a higher susceptibility to SRCC (14,27) than other races. Additionally, Burón Pust A et al. (32) uncovered a correlation between smoking, obesity, and signet-ring cell histology in female colorectal cancer patients. Another observational study indicated a three-fold increase in the risk of developing SRCC in individuals with mutations in the CDH1 gene, mostly known for its role in hereditary diffuse gastric cancer (33). Patients diagnosed with SRCC generally exhibit a shorter median survival time than those with non-mucinous subtypes, with one study reporting 18.6 months vs 46 months respectively (25).

3.2. Tumor characteristics
SRCC is most commonly found in the ascending colon (55.3%) (28) and is seldom observed in the sigmoid and rectum (34). Although it has a poor overall survival across all anatomic locations, the hazard ratio for the latter is worse than that for adenocarcinoma cases (28). Another essential aspect is that the signet-ring cells mostly infiltrate the colon wall rather than forming an exophytic mass or arising within a polyp, a characteristic usually associated with the more common adenocarcinoma subtype.

SRCC is generally a poorly differentiated tumor (25) with a large diameter (1) and a more advanced T and N stage at diagnosis (25). In patients with a pT1 tumor, the incidence of lymph node involvement is 33.3%, compared to 10.6% for adenocarcinoma (27).
A large percentage of patients present initially with metastatic disease to multiple sites, and a propensity toward peritoneal carcinomatosis has been observed. Also, in a cohort of 67 patients with SRCC, half of the patients developed metastasis to the peritoneal wall. In the same cohort, the disease was more likely to spread in uncommon areas such as the heart, bone, pancreas, ovary, and skin (35).

SRCC is known to metastasize through the lymphatic vessels and frequently spreads to distant lymph nodes (23). The tumor budding grade directly correlates with lymphatic and venous invasion, substantially increasing in patients with signet-ring cell tumors (36).

Compared to adenocarcinoma, SRCC presents a higher recurrence rate following curative treatment, with a 10-year cumulative incidence for distant recurrence of 48% (37). Research has shown that relapse occurs early, mainly during the first two years of follow-up (9). Prabhu A. et al. evaluated 40 patients after complete cytoreduction and reported that 37 patients experienced systemic recurrence – peritoneal, liver, lung, bone, and distant lymph nodes (11).

3.3. Pathology overview

An accurate pathologic diagnosis of SRCC requires immunohistochemical analysis (Figure 2). This is essential for distinguishing between a primary tumor and metastasis. Signet-ring cell carcinoma of the stomach presents positive stains for MUC2, CDX2 (heterogenous), and HepPar1, while signet-ring cell carcinoma of the breast is identified based on the positive expression of MUC1 and ER. The high expression of MUC2 and MUC5AC in SRCC cases might suggest a different pathogenesis of these tumors (17).

**Table:**

<table>
<thead>
<tr>
<th>Positive stains</th>
<th>Negative stains</th>
<th>Variable stains</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK20, CDX2 (nuclear positivity, MUC2, MUC5AC)</td>
<td>CK7, ER</td>
<td>MUC1, HepPar1</td>
</tr>
</tbody>
</table>

Additionally, immunohistochemistry is needed to differentiate SRCC from benign processes such as pseudomembranous colitis, ulcerated tubular adenoma, and signet ring cell change. These conditions lack the expression of p53 and Ki-67 (39).

3.4. Molecular features

In contrast with the adenocarcinoma subtype, SRCC has more frequent mutations in the BRCA1 gene (11% vs 1%, p<0.001) (22) and B-RAF genes (25). In a cohort of metastatic SRCC cases, 9% had BRAF mutations (p.V600E, p.V600G), with 3 out of 16 patients presenting microsatellite instability (MSI-H). Although not prognostic in that subgroup (4), BRAF gene alterations demonstrate a shorter PFS and OS, with tumors responding poorly to anti-epidermal growth factor receptor (anti-EGFR) therapy (24). Several clinical trials evaluate BRAF-targeted treatments in solid tumors, irrespective of the histology (Table 3).

In contrast to mucinous carcinoma, signet-ring cell histology is negatively associated with KRAS mutations (20). Mutations in TP53, ARID1A, and APC are rare (20,22). This suggests SRCC might have a different pathogenesis, arising de novo, without following the classical adenoma-carcinoma sequence described by Fearon and Vogelstein (22).

Decreased expression of E-cadherin and β-catenin are found on SRCC samples (26). These proteins have a suppressor role in tumor invasiveness, so their low expression might explain the aggressive behavior of this histological subtype.

Another particularity of SRCC is the presence of MSI-H, which has no significant impact on overall survival (16,18). MSI-H SRCC tumors are associated with larger tumor size and proximal colon location, with a study reporting no MSI-H tumors in the rectal region for 22 patients included in the research (21). Thymidylate-synthase and glutathione S-transferase π expression is significantly higher in mucinous tumors. Since these enzymes contribute to the detoxification of platinum agents, their increased expression correlates with tumor resistance to chemotherapy. However, their influence on the prognosis of patients with SRCC who receive adjuvant chemotherapy remains to be demonstrated (40).
Table 3 Clinical trials for B-RAF mutated solid tumors.

<table>
<thead>
<tr>
<th>ClinicalTrials.gov ID</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00888134</td>
<td>Selumetinib</td>
</tr>
<tr>
<td>NCT05786924</td>
<td>BDTX-4933</td>
</tr>
<tr>
<td>NCT04913285</td>
<td>KIN-2787</td>
</tr>
<tr>
<td>NCT01791309</td>
<td>Vemurafenib + Panitumumab</td>
</tr>
<tr>
<td>NCT04984369</td>
<td>HLX208 + Cetuximab</td>
</tr>
<tr>
<td>NCT03727763</td>
<td>Cetuximab + Vemurafenib + FOLFIRI</td>
</tr>
</tbody>
</table>

3.5. Laboratory aspects

Data concerning the predictive and prognostic value of different tumor markers in SRCC cases are limited. However, higher carcinoembryonic antigen (CEA) levels were observed (25), correlating with metastatic spread and increased mortality (41).

The role of CA 72-4 as a tumor marker, commonly elevated in poorly differentiated gastric cancers (including signet-ring cell histology), needs further evaluation. It is elevated more often than CEA, representing an independent risk factor for hematogenous spread and reduced patient survival (42). Alpha-fetoprotein, another tumor marker that predicts disease-free survival and overall survival in poorly differentiated gastric cancers (43), might be worth considering in monitoring SRCC cases.

3.6. Imaging particularities

Usually, the specimens obtained during biopsy are scant precluding an extensive evaluation of tumor histology, and therefore, often, the preoperative assessment is challenging (1).

Computed tomography (CT) is the preferred imaging technique for colon cancer workup, but its sensitivity appears to be lower in mucinous subtypes (44). Most patients present with the li- nitis plastica phenotype (4), with long segmen- tal wall thickening ranging from 4.4 to 11.6 cm (17,45). On the other hand, magnetic reso- nance imaging (MRI) has an excellent contrast resolution, facilitating the recognition of SRCC tumors with an elevated water content.

Usually mucinous tumors are PET-negative (44). In a study of 14 patients with mucinous colo- n cancer subtype (including one with signet- ring histology), the SUVmax was 6.62 ± 3.36 g/ml, which is lower than the adenocarcinoma group (46). Therefore, a CT scan of the abdomen is more useful than a PET when evaluating a po- tential SRCC case.

The metastatic pattern of SRCC patients may be unusual, so a high level of suspicion should be raised when uncommon imaging findings are found on a CT.

3.7. Treatment particularities

3.7.1. Surgery

Both for early and locally advanced colon cancer, the international guidelines recom- mend following the same surgical strategies, ir- respective of the histological subtype. How- ever, the proportion of incomplete resections (R1, R2) with positive circumferential margin are 8% higher in the SRCC subgroup (25). In addition, open surgery, either upfront or by con- version of a laparoscopic procedure, is the most commonly used approach. The reason for the open approach is the increased number of SRCC patients presenting with advanced dis- ease (6). Regardless of the surgical approach, unfortunately, these cases have a higher risk of recurrence and a poor prognosis (44).

Curative surgery may still be an option for patients with stage IV colon cancer presented with a limited number of liver or lung metastases (6). Allart et al. report that in a cohort of 168 metastatic SRCC cases, 38 patients were able to receive curative treatment. Notably, half of them were treated with prior neoadjuvant chemotherapy (4).

Signet-ring cell histology tends to spread to the peritoneal wall. Thus, a complete cyto- ductive surgery (CRS) with intraperitoneal chemotherapy (HIPEC) is recommended for an R0 resection (11). Currently, the data regarding HIPEC remains controversial, with some
reports reporting a better mOS (11), while the NCCN guidelines highlights its increased morbidity and mortality.

3.7.2. Systemic treatment
Neoadjuvant chemotherapy seems to reduce the risk of distant relapse and increase the OS by downstaging the tumor, thus allowing for a more complete surgical resection (15). However, achieving tumor regression in SRCC cases needs further research. Due to their lower proliferative activity, signet-ring cells are known to have a limited response to common therapeutic drugs (22). Furthermore, in the FOxTROT trial, the MSI-H subgroup performed worse than MSS tumors, with no pathological response in 74% vs 27% of patients (15). Considering the higher frequency of MSI-H in the SRCC subtype, this might be another disadvantage for the use of upfront chemotherapy in this subgroup of patients. In contrast, the NICHE trial indicates that dual-checkpoint inhibition in MSI-H patients leads to better outcomes (7).

Studies on SRCC cohorts have shown that adjuvant treatment improves survival (14), regardless of the MSI status (21). Research revealed that for patients with stage III tumors, the cancer-specific survival rate was 53.1% in the chemotherapy arm vs 49.3% for those without any postoperative systemic treatment. However, the ratio was reversed in stage II, with 74.9% and 87.2% respectively (14). The lack of benefit of adjuvant chemotherapy in the stage II population was also confirmed by Zhao et al (13) and Emile SH et al (5). The limited number of patients included in the studies warrants further research. At present, the addition of chemotherapy after surgery in stage III SRCC remains the standard, as it prolongs OS by more than ten months (12).

For patients with metastatic SRCC, response rates to standard first-line chemotherapy regimens remain low. Furthermore, only 50% of them are able to receive a second line of therapy (4). Data regarding the benefit of vascular endothelial growth factor (VEGF) or EGFR inhibitors is conflicting. Although there seems to be an increase in PFS following treatment with anti-VEGF or anti-EGFR antibodies, the benefit is limited to approximately 1.1 months (4). In a study evaluating the role of CRS and HIPEC in SRCC patients with peritoneal carcinomatosis, 39% received anti-VEGF or anti-EGFR as part of their preoperative therapy (11). However, the benefit of these targeted agents on the rate of complete cytoreduction could not be evaluated. In theory, systemic use of immune checkpoint inhibitors (ICI) in patients with tumors exhibiting MSI-H should be beneficial. Contrary to what may have been expected, three clinical trials demonstrated that this histology had an inferior response to ICI compared to the adenocarcinoma subtype (10).

3.7.3. Other treatment modalities
Radiotherapy is an established treatment for rectal cancer. In a cohort of 123 patients with rectal SRCC, of which 90 patients were treated with radiotherapy, the risk of death was reduced by 39% (3). However, this did not influence the OS, which remained poor compared to rectal adenocarcinoma.

3.8. Future perspectives
Circulating tumor DNA (ctDNA) represents an emerging investigational tool. Evaluated in the neoadjuvant setting of various types of cancers, ctDNA helped redirect nonresponding tumors to a more potent systemic therapy or upfront surgery (15). Based on preliminary data, the signet-ring cell subtype appears to display lower levels of ctDNA compared to the adenocarcinoma histology when evaluated in the gastric cancer subpopulation (47). Data on ctDNA expression in SRCC patients remains to be further investigated.

In the following table are summarized several ongoing clinical trials investigating the role of ctDNA in colon cancer (all histological findings are included) (Table 4):
Table 4. On-going clinical trial evaluating the role of ctDNA in the SRCC population.

<table>
<thead>
<tr>
<th>ClinicalTrials.gov ID</th>
<th>Study Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT05529615</td>
<td>ctDNA guided adjuvant chemotherapy in colon cancer</td>
</tr>
<tr>
<td>NCT03416478</td>
<td>ctDNA as a predictive and surveillant method for tumor recurrence in stage II and III colorectal cancer</td>
</tr>
<tr>
<td>NCT06167967</td>
<td>ctDNA guiding postoperative adjuvant chemotherapy in stage III colon cancer</td>
</tr>
<tr>
<td>NCT04752930</td>
<td>ctDNA as an assisted diagnosis, early intervention, and prognostic marker for peritoneal metastases from colorectal cancer</td>
</tr>
<tr>
<td>NCT05131243</td>
<td>ctDNA in predicting the recurrence risk of colorectal cancer</td>
</tr>
<tr>
<td>NCT04084249</td>
<td>ctDNA-guided surveillance for stage III colorectal cancer</td>
</tr>
<tr>
<td>NCT04920032</td>
<td>The efficacy of adjuvant trifluridine and tipiracil (TAS-102) in combination with irinotecan in patients with ctDNA positive colon adenocarcinoma</td>
</tr>
</tbody>
</table>

4. Conclusion

Given its specific clinical characteristics and poor survival outcomes, SRCC should be considered a distinct colon cancer entity. Although its rarity makes prospective trials difficult, a timely diagnosis and a correct treatment decision-making algorithm is paramount.

Abbreviations

CEA – carcinoembryonic antigen
CRS – cytoreductive surgery
CSS – cancer specific survival
CT – computed tomography
ct DNA – circulating tumor DNA
EGFR – epidermal growth factor receptor
HIPEC – hyperthermic intraperitoneal chemotherapy
ICI – immune checkpoint inhibitors
MRI – magnetic resonance imaging
MSI-H – microsatellite instability
OS – overall survival
PET – positron emission tomography
SRCC – signet-ring cell carcinoma of the colon
VEGF – vascular endothelial growth factor

Statements

Authors’ contributions: Study conception and design: L.F. Acquisition and analysis of data: L.F. Drafting of the manuscript: L.F. Writing – review and editing: All authors. Critical revision: All authors.

Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all named authors.

Conflict of interests: None.

Funding: This research received no external funding.

Statement of Ethics: This study was not subject to ethical review and approval due to its article format.
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