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ORIGINAL ARTICLE

Retrospective Study

Signet ring colorectal carcinoma: Do we need to improve the treatment algorithm?

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Abstract

AIM

To elaborate about this peculiar variant from a tertiary cancer center from India.

METHODS

It's a retrospective study (2011-2014) of all patients diagnosed with signet ring colo-rectal cancer (SRCC). Various clinico-pathological variables were studied.

RESULTS

One hundred and seventy consecutive patients with SRCC were diagnosed (11.4% of all colorectal cancers). Median Age of the cohort was 41 years. Most common location was recto-sigmoid area (54.7%). Majority patients presented in stage III and IV (91.2%). Most of the stage IV patients had isolated peritoneal metastases (86.5%). Colonic tumors had higher incidence of peritoneal metastases (91.8% *vs* 83.3%) as well as isolated peritoneal recurrences (37.5% *vs* 16.7%) than rectal primaries. Thirty-seven point five percent of patients recurred after curative surgery. Amongst them 63.63% patients had isolated peritoneal recurrences. Circumferential resection margin (CRM) was involved in 17.9% patients. Median relapse free survival (RFS) and overall

survival (OS) of the cohort were 14.9 and 18.13 mo respectively. CRM involvement, colonic primary were associated with poorer RFS and OS.

CONCLUSION
SRCC has predilection for peritoneal dissemination. More aggressive and/or extended chemotherapy schedules as well as prophylactic hyperthermic intra-peritoneal chemotherapy at the time of primary surgery may be attempted in these patients.

Key words: Colorectal cancer; Signet ring cell carcinoma; Peritoneal metastases; Hyperthermic intra-peritoneal chemotherapy

Core tip: The incidence of Signet Ring Colo-Rectal Cancer appears to be higher in Indian subcontinent than the world literature. It has predilection for peritoneal lining. It affects younger age group. Majority cases present in stage III and IV. Recto-sigmoid region is affected commonly. The most common metastatic site and site of recurrence is peritoneal cavity. Probably it should be treated with a different protocol than the conventional adenocarcinoma with focus on aggressive peritoneal cytoreductions and hyperthermic intra-operative intraperitoneal chemotherapy (HIPEC). Further research is needed to evaluate molecular biology of this variant and utility of prophylactic HIPEC during curative surgery.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide[1]. There are three subtypes described in the literature based on the amount and location of mucin in the tumor. These are conventional adenocarcinoma (AC), mucinous carcinoma (MC) and signet ring cell carcinoma (SRCC)[2,3]. SRCC constitutes 1% of all colorectal carcinomas[4-9]. It is an aggressive variant which affects younger population and has poorer prognosis[5]. The literature explaining the biology as well as the optimum treatment algorithm of this particular variant is scarce due to its low incidence. So we look into the incidence, demographics, clinico-radiological presentation and outcome of treatment of this peculiar variant from a tertiary cancer centre from India (Tata Memorial Centre, Mumbai).

MATERIALS AND METHODS

All patients diagnosed with colorectal carcinoma from 1st January 2011 to 31st December 2013, registered under the Department of Gastro-intestinal Oncology services, Tata Memorial Centre, were included. The data was collected retrospectively from Electronic database as well as case files from Department of Surgical Oncology. The histopathology specimens of all these patients were reviewed at Department of Surgical pathology, Tata Memorial Centre. Signet ring cell colorectal cancers were defined as per WHO criteria (AC with more than 50% of signet-ring cells). Patients were staged as per AJCC classification (7th edition). Response to neoadjuvant chemoradioatherapy (NACTRT) was assessed as per RECIST criteria. The decision about the same was taken in the multidisciplinary meeting held for every patient. Pathological complete response was defined as absence of viable tumor cells in the primary, the lymph nodes and peri-rectal soft tissue. Circumferential resection margin (CRM) positivity was defined as presence of viable tumor cells at or within 1 mm of it. Follow up data was obtained from electronic medical records and/or telephonic questionnaire. Recurrences were based on biopsy or strong clinico-radiological evidence. Peritoneal metastases or recurrences constituted peritoneal deposits, malignant ascites, omental deposits and ovarian deposits. Relapse free survival (RFS) was assessed from the date of cancer directed surgery to date of recurrence. Overall survival (OS) was measured from the date of diagnosis of malignancy to date of death. SPSS-21 (IBM corporation) was used for the statistical analysis. Categorical variables were compared with χ^2 test. Survival functions were analyzed with Kaplan Meir curves and compared with log rank test.

RESULTS

From 1st January 2011-31st December 2013, 1487 patients with colorectal cancer got registered under the department of Gastrointestinal Services Tata Memorial Centre. Amongst them, signet ring cell carcinoma was diagnosed in 170 consecutive patients (11.4%). Follow up of 18 of 170 patients (10.58%) was inadequate (< 1 mo) (Table 1). Median Age of the cohort was 41 years. Males were affected nearly twice more than females (M: F = 1.8:1). Most tumors were located in the rectum and sigmoid colon (Rectum: 41.2% and Sigmoid: 13.5%). Majority patients presented in stage III (51.8%) and stage IV (39.4%). Most of the stage IV patients had isolated peritoneal metastases (58/67, 86.5%) (Table 2). Curative surgery was feasible only in 51.76% (88/170) patients. Thirty-seven point five percent (33/88) patients recurred after curative surgery. Twenty-one thirty-thirds (63.63%) patients had isolated peritoneal recurrences (Table 3). Most patients had high nodal burden, pN1 being 23.2% (22/95), pN2 being 57.9% (55/95). Amongst node positive patients, 66.3% (53/77)

Table 1 Demographic parameters

Parameter	Statistics
Total No.	170
Sex ratio	
Male	110
Female	60
Age (median), yr	41
Stage, *n* (%)	
II	6 (3.5)
III	88 (51.8)
IV	67 (39.4)
Not available	9 (5.3)
Location, *n* (%)	
Right colon	49 (28.8)
Transverse colon	13 (7.6)
Descending colon	11 (6.5)
Sigmoid colon	23 (13.5)
Rectum	70 (41.2)
Appendix	1 (0.6)
Not available	3 (1.8)

Table 2 Pattern of metastases in stage IV patients

Site of metastases	*n* (%)
Liver	1 (1.5)
Lung	1 (1.5)
Isolated peritoneal	58 (86.5)
Retroperitoneal lymphnodes	2 (3.1)
Others	5 (7.4)

had perinodal extension. The rate of lymph node metastases and lympho-vascular invasion increased progressively with increasing pathological T stage.

Median RFS and OS of the cohort were 14.9 mo and 18.13 mo respectively. OS of peritoneal and non-peritoneal metastases were equivalent (16 mo *vs* 13 mo, $P = 0.729$) (Table 4).

Forty-eight rectal cancers were operated. Data for patients undergoing NACTRT was available for 37 cases only. Pathological complete response was seen in 21.6% (8/37) patients. CRM was involved in 17.9% (7/39) patients (data on CRM was not available for 9 cases). CRM involvement was associated with poorer RFS (15 mo *vs* 37.2 mo, $P = 0.060$) and OS (19.9 mo *vs* 41.5 mo, $P = 0.018$) as compared to patients with uninvolved CRM (Tables 4 and 5).

The location of primary had a significant impact on the clinico-pathological outcome of the patient. As compared to rectal primaries, colonic tumors had higher incidence of peritoneal metastases (83.3% *vs* 91.8%, $P = 0.074$) as well as isolated peritoneal recurrences (16.7% *vs* 37.5%, $P = 0.062$). Colonic primaries were associated with poorer OS than rectal tumors after curative resection (32.298 mo *vs* 40.089 mo, $P = 0.058$) and RFS (24.74 mo *vs* 34.02 mo, $P = 0.048$) (Table 6).

DISCUSSION

CRC is one of the most common cancers worldwide. Worldwide, it leads to 10% and 9.2% of cancers in

Table 3 Pattern of recurrence after curative surgery

Pattern of recurrence	*n* (%)
Locoregional	4 (12.12)
Distant	4 (12.12)
Isolated peritoneal	21 (63.63)
Peritoneal + second primary	2 (6.06)
Local + peritoneal	2 (3.4)

Regional recurrences: Regional lymph node recurrences; Distant recurrences: Non-regional lymph nodal and visceral recurrences.

Table 4 Factors affecting overall survival

Parameter	OS (mo)	Significance
Location (After curative surgery)		
Colon	32.3	0.058
Rectum	40.1	
CRM		
Positive	19.9	0.018
Negative	41.5	
Metastases		
Peritoneal	14.85	0.729
Non-peritoneal	11.14	

CRM: Circumferential resection margin; OS: Overall survival.

males and females respectively. It is a cause of 8% and 9% of cancer related deaths in males and females respectively[1]. Several histological subtypes have been reported[2,3]. It has two different subgroups apart from classical AC. They are classified based on varying amounts of signet-ring cell and/or mucinous component. Signet-ring cell carcinoma (SRCC) is characterized by intra-cytoplasmic mucin which displaces the nucleus aside. MC is characterized by extracellular mucin pools. SRCC or MC (defined as carcinoma with more than 50% of signet-ring cells or mucinous component, respectively as per WHO classification) constitutes approximately 1% or 5%-15% of CRC cases, respectively in the world literature[4-9]. As compared to the world literature, the incidence of SRCC is much higher in our study (11.4% *vs* 1%). The median age of the cohort in our study was also lower than world literature (41 years *vs* 50-55 years)[5,6,10,11]. This could represent either a referral bias being a tertiary cancer centre in India or definite distinct disease biology in the Indian population. Further studies regarding the demographic profile of this particular variant in Indian population are under consideration currently.

The literature is divided about the most common site of colorectal cancer in young population with some indicating proximal colon[12] and others suggesting it to be recto-sigmoid region[13,14]. In our study, rectum and sigmoid colon region was most commonly affected. This may be related to preferential referral of locally advanced rectal cases to our institute. One of the studies has shown that colorectal cancers affecting younger age group (< 40 years) have significantly higher incidence of signet ring cell cancer. Such tumors also affect rectosigmoid area more commonly than rest of the colon in

Table 5 Factors affecting relapse free survival in operated patients

Parameter	RFS (mo)	Significance
CRM		
Positive	15.003	0.060
Negative	37.202	
Location		
Colon	24.74	0.048
Rectum	34.02	

RFS: Relapse free survival; CRM: Circumferential resection margin.

Table 6 Impact of location on outcome

Parameter	Colon	Rectum	Significance
Recurrence after curative resection			
Peritoneal, *n* (%)	15/40 (37.5)	8/48 (16.7)	0.062
Non-peritoneal, *n* (%)	3/40 (7.5)	7/48 (14.6)	
Pattern of Metastases at presentation			
Peritoneal, *n* (%)	45/49 (91.8)	15/18 (83.3)	0.074
Non-peritoneal, *n* (%)	4/49 (9.2)	3/18 (16.7)	
RFS (mo)	24.74	34.02	0.048
Overall Survival (mo)	26.011	30.32	0.062
OS after curative surgery (mo)	32.298	40.089	0.058

RFS: Relapse free survival; OS: Overall survival.

young patients[15].

SRCC has been associated with peculiar genomic changes such as high-degree microsatellite instability (MSI-high) (up to 40%), high-frequency of CpG island methylator phenotype, higher methylation level of long interspersed nucleotide element-1 and frequent BRAF mutation and low COX-2 expression[8,16-20]. Due to high frequency of MSI-H mutations[21] and associated poor prognosis, tumors with signet ring histo-morphology are recommended to be screened for MSI-H mutations as per revised Bethesda guidelines[22]. The serrated adenoma-carcinoma pathway has been proposed for development of these tumors. Terada *et al*[23] found that epithelial membrane antigen was downregulated in colorectal SRCC. Kim *et al*[24] showed that focal loss of epithelial cell adhesion molecule was associated with development of SRCC in colonocytes. These molecular changes may be related to preferential peritoneal spread of this subtype. Currently the studies are under consideration at our institute to assess genomic changes related to this specific phenotype which may be the cause of higher incidence of signet ring colorectal cancer in Indian population than the world literature.

Our study revealed that, though SRCC has an aggressive biology in general, it seems to respond well to NACTRT with pathological complete response rate of 21%. Literature assessing response of SRCC to NACTRT is scarce due to low incidence worldwide. Jayanand *et al*[25] showed that these tumors respond well to RT with high pathological complete response rates. It may be related to their aggressive nature and higher mitotic index. So potentially NACTRT should be included in the treatment protocol of rectal SRCC for improved outcomes.

Patients with SRCC are more likely to present in advanced stages (Stage Ⅲ/Ⅳ) than AC. SRCC patients more often present with metastatic disease and are more likely to develop peritoneal metastases. This may be related to their peculiar molecular origin which is yet to be proven. It is also shown that SRCC metastasizes to the lymph nodes, whereas AC metastasizes primarily to the liver[6,9,11]. Our study also showed similar findings.

SRCC has been associated with a poor prognosis compared with AC[5,6,10,11]. Studies have shown that peritoneal metastases of SRCC are associated with a poorer prognosis, and survival is even worse if other organs are also affected[26]. But in our study, patients with peritoneal metastases had similar OS as compared to those with non-peritoneal metastases. This may be due to small sample size of the study. Often, these metastases cannot be treated with curative intent. As of now, curative surgery is an option mainly limited to liver and lung metastases, which are the most common metastatic sites in AC patients. Systemic chemotherapy for peritoneal metastases may not yield the same results compared with hematogenous metastases due to blood-peritoneal barrier. As a result, outcome is poor in advanced SRCC cases[27].

The incidence of synchronous and metachronous peritoneal metastases in colorectal carcinoma (AC) seems to be in the range of 4%-5% (much lower than with SRCC)[26,28]. Studies have revealed that peritoneal carcinomatosis among patients with metastatic colorectal cancer is associated with a 30% reduction in overall survival (10.7 mo *vs* 17.6 mo)[29]. The overall survival of these patients is found to be less than 6 mo despite the use of 5FU and leucovorin based chemotherapy[30,31]. But palliative surgery and systemic chemotherapy, together have been shown to improve survival upto 12 mo in patients with isolated peritoneal metastases[29,32].

Hyperthermic intra-operative intra-peritoneal chemotherapy (HIPEC) has shown promising results for peritoneal metastases of colorectal origin[29]. Verwaal *et al*[29] reported outcome of 1427 patients with peritoneal metastases of colorectal origin treated with cytoreductive surgery (CRS) and HIPEC. Peri-operative morbidity and mortality were 34% and 3% respectively. Median hospital stay was 16 d. Median PFS was 15 mo and OS was 33 mo. Three- and five-year survival rates were 46% and 31% respectively. So authors concluded that CRS and HIPEC seems to be safe and beneficial in peritoneal metastases of colorectal origin[33]. But literature assessing benefit of HIPEC for SRCC is scarce and controversial with studies denying[34,35] and implying[36] benefit of HIPEC in this subgroup. But these reports are retrospective and are fraught with small sample sizes.

Recently, Hao *et al*[37] have proposed a study assessing the benefit of monoclonal antibody blocking EpCAM in CRC. This may be relevant in the further management

of SRCC as EpCAM also has altered expression in this subtype.

Klaver *et al*[38] have proposed a randomized controlled trial (COLOPEC) for assessing benefit of prophylactic HIPEC in patients at high risk of peritoneal carcinomatosis. They have included patients (non-metastatic) with T4 disease or on table tumor site perforation for prophylactic HIPEC followed by routine adjuvant chemotherapy. It has been postulated in assumption that very few patients with peritoneal carcinomatosis become eligible for CRS and HIPEC; as a result they have poor prognosis. So if a prophylactic HIPEC reduces the occurrence of peritoneal metastases in future, it may result in benefit in OS. The investigators have not considered signet ring cell pathology as inclusion criteria for the study; probably because of low incidence (1%-2%) of it in the western literature. A similar study may be considered in Indian patients with signet ring cell carcinoma to assess benefit of prophylactic HIPEC at the time of primary surgery as it has a peculiar tendency for isolated peritoneal recurrences and the incidence of this particular histopathological subtype seems to be higher in them (11.4%) as suggested by present study.

It is unclear whether different histological subtypes should influence treatment decisions, since it is often not addressed in clinical trials. In the literature, studies concerning outcome after adjuvant or palliative chemotherapy for SRCC are rare. However, due to the aggressive behavior and high incidence of SRCC in young patients, it is imperative to develop understanding of potential adjuvant treatment options as it is likely to alter quality of life and have significant socio-economic impact. Colonic SRCC are more likely to have peritoneal dissemination and poorer survival than rectal SRCC. So more aggressive treatment options, like HIPEC may be useful in these patients at the time of primary surgery or after peritoneal limited recurrence in order to improve survival and quality of life. This can only be addressed in a randomized control trial setting. Due to high nodal disease burden and high incidence of failure after curative surgery (up to 40%), more extended and/or aggressive adjuvant chemotherapy options should also be explored in this subset of population which is younger and is likely to tolerate the aggressive treatment better.

Signet ring colorectal cancer has poor prognosis. It has a higher incidence in Indian subcontinent. It affects young patients and has predilection for peritoneal dissemination.

Isolated peritoneal metastases as well as isolated peritoneal recurrences are very frequent in these patients. SRCC responds well to radiation. So whenever indicated, neoadjuvant radiation should be included in the treatment protocol for rectal SRCC.

More aggressive and/or extended chemotherapy schedules as well as prophylactic HIPEC at the time of primary surgery, especially for colonic tumors, should be explored in a trial setting in order to improve dismal survival in these patients.

COMMENTS

Background

Signet ring colorectal cancer (SRCC) is a subtype of colorectal adenocarcinoma. It tends to affect younger age group. Most of the patients present in stage III or IV. The most common site affected is rectosigmoid region. It has a peculiar affection for peritoneal lining. Most of the metastases and recurrences happen exclusively in the peritoneal cavity. Visceral metastases are rare. Average prognosis of these patients is poor. There is no effective adjuvant or palliative treatment for this entity. Early studies in the field of cytoreductionandhyperthermic intra-operative intraperitoneal chemotherapy (HIPEC) have shown promising results and prolongation of survival in peritoneal carcinomatosis of colorectal cancer. The trials are underway to test the impact of prophylactic HIPEC during primary surgery for cT4N1/2 diseases. Since SRCC has a different natural course than the conventional adenocarcinoma of colon, it may be worthwhile to evaluate the possible role of extended chemotherapy or prophylactic HIPEC at the time of curative surgery for SRCC.

Research frontiers

Currently trials are underway (COLOPEC and Prophylochip) to assess efficacy of prophylactic HIPEC in high risk colorectal cancers to prevent occurrence of peritoneal metastases and prolongation of survival. Though aggressive, SRCC has shown its peculiar nature to remain confined to peritoneal cavity in majority patients. This makes it a potential target for peritoneum directed therapies (Cytoreduction and HIPEC). Also monoclonal antibodies blocking EpCAM are being evaluated in CRC. This may be relevant in the further management of SRCC as EpCAM also has altered expression in this subtype.

Innovations and breakthroughs

Cytoreduction and HIPEC has shown survival benefit in peritoneal carcinomatosis of colorectal origin in a large randomized trial by Verwaal *et al* SRCC has not been evaluated widely in the western literature, probably due to lower incidence. But in Indian subcontinent, the incidence of this disease entity appears to be higher than rest of the world. It also affects younger population; as a result has significant bearing on the socioeconomic outcome of entire family. There is a strong need to develop a modified treatment protocol for this disease than conventional adenocarcinoma as the disease biology appears to be different and standard chemotherapy doesn't act well on the peritoneal disease. Certain molecular abnormalities are also noted in SRCC such as high microsatellite instability, EpCAM mutations, high-frequency of CpG island methylator phenotype, higher methylation level of long interspersed nucleotide element-1 and frequent *BRAF* mutation and low COX-2 expression. Further research needs to be carried out to understand the biology of this disease entity well which might give us an insight into potential treatment options for the same.

Applications

To summarize, SRCC seems to be a suitable target for peritoneum directed therapies which include aggressive cytoreduction and HIPEC. Extended/modified chemotherapy protocols may improve survival. Further understanding of molecular biology of this disease may open new methods for its treatment.

Peer-review

It is a retrospective study of an uncommon subtype of colorectal carcinoma. The author statisized some information of this cancer including the age, location, stages, metastasis, recurrence and survival.

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