

**REVIEW****Schistosomal Colorectal Cancer: Biomarkers and Treatment Strategies****Hytham K. S. Hamid\***

Department of Surgery, Soba University Hospital, Khartoum, Sudan

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**ABSTRACT**

About 15.4% of human cancers worldwide have been attributed to infections. Among these, blood and liver flukes, notably *Schistosoma* sp, *Clonorchis Sinesis*, and *Opisthorchis Viverrini* have been associated with the development of various cancer types. *Schistosoma* sp. promotes colorectal cancer (CRC) progression through multiple mechanisms including production of toxins, symbiotic action with bacterial agents, and more importantly chronic inflammation. Diagnosis of schistosomal colorectal cancer (SCC) requires high index of clinical suspicion in endemic areas. Novel biomarkers may aid early diagnosis of SCC in patients with chronic intestinal schistosomiasis. Treatment should be tailored to individual patients according to the stage and biologic characteristics of the tumour, and the extent of hepatosplenic schistosomiasis. Long-term survival after surgical resection of SCC is lower than that reported in patients with sporadic CRC.

**1. Introduction**

Colorectal cancer (CRC) is the third most common human cancer. Accounting for approximately 1.8 million new cases and 861,000 deaths in 2018, it was considered the second leading cause of cancer death worldwide.<sup>[1]</sup> In addition to genetic factors, several environmental influences may interplay in a complex multi-step process to promote colorectal carcinogenesis. These include cigarette smoking, high alcohol consumption, obesity, lifestyles, and oncogenic viral and bacterial agents.<sup>[2-4]</sup> Recently, we highlighted the role of *Schistosoma* sp., a digenetic blood fluke, on the aetiology of colorectal cancer, disease progression and the characteristics of patients.<sup>[5,6]</sup>

*Schistosomal* colorectal cancer (SCC) has been linked to *S. japonicum* and *S. mansoni*, the leading causative

agents of intestinal schistosomiasis, and it has been mainly reported in areas of high endemicity of schistosomal infection; Southeast Asia, Africa, and the Middle East.<sup>[5]</sup> The disease occurs in younger age group with male to female ratio being consistently higher than sporadic colorectal cancer.<sup>[7-9]</sup> Moreover, SCC exhibits more aggressive biological behaviour with a larger tumour size at presentation, frequent multifocal and multi-centric distribution, and mucinous histology.<sup>[7,10-13]</sup>

The therapeutic landscape of CRC has evolved significantly in recent years. Current and emerging treatment options include surgical resection, chemoradiation, biologic therapy, and immunomodulation.<sup>14</sup> Recent research works keep insight into predictive and prognostic biomarkers of CRC, which may aid diagnosis and the development of new treatment strategies. In the current review, we discuss

\*Corresponding Author:

Hytham K. S. Hamid,

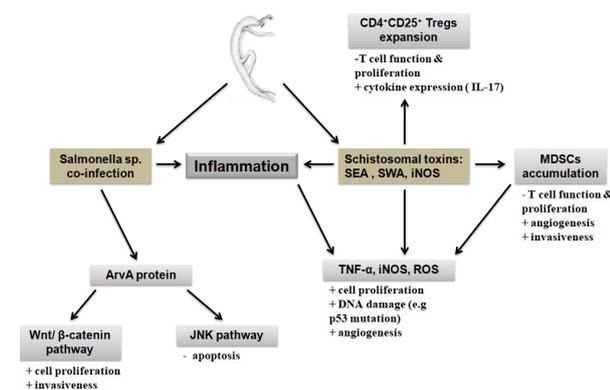
Department of Surgery, Soba University Hospital, Khartoum, Sudan;

Email: kujali2@gmail.com

the pathogenesis, diagnosis, and treatment options of SCC pointing to novel biomarkers and potential therapeutic targets in context.

## 2. Pathogenesis

The underlying pathogenesis of SCC involves several mechanisms, with chronic inflammation seems to play a pivotal role (Figure 1). These include production of schistosomal toxins notably schistosome worm antigen (SWA), soluble egg antigen (SEA), and inducible nitric oxide synthase (iNOS), the presence of endogenously produced carcinogens such as reactive nitrogen and oxygen species, down-regulation of immune surveillance, thereby favouring tumour progression and conferring a survival advantage to *Enterobacteriaceae* infections, particularly *Salmonella* sp.<sup>[6]</sup> The latter, in turn, promotes tumorigenesis directly through multiple epigenetic mechanisms, or indirectly through activation of environmental carcinogens.<sup>[15-17]</sup>



**Figure 1.** Illustration of the possible mechanisms of schistosome-induced colorectal carcinogenesis

## 3. Molecular Biomarkers

Several molecular changes have been described with SCC. Zhang et al. observed a different mutation types in the p53 gene, and a marginally significant higher proportion of base-pair substitutions at CpG dinucleotides and arginine missense mutations in the p53 gene among *S. japonicum*-associated rectal cancer patients compared to those with ordinary rectal cancer.<sup>[18]</sup> For *S. mansoni*-associated CRC, it was shown that schistosomal infection is associated with microsatellite instability, which is a sign of defective DNA repair.<sup>[19,20]</sup> This genomic instability results in DNA replication errors that preferentially affect target genes such as transforming growth factor (*TGF*) *bRII* and insulin-like growth factor (*IGF*)*2R*, and render

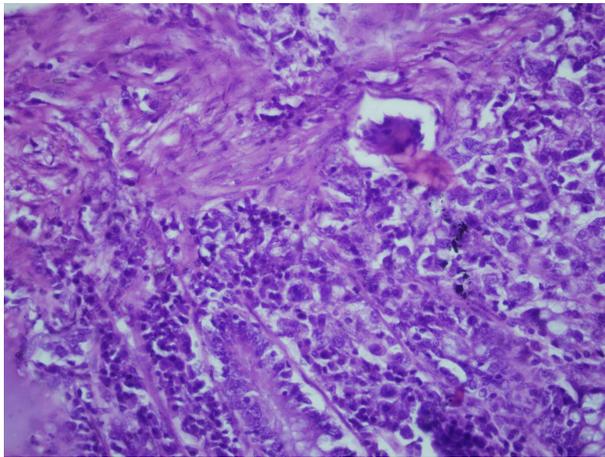
them incapable of normal colonocytes homeostasis resulting in malignant growth.<sup>[21]</sup> Madbouly et al. evaluated the expression of p53 in patients with SCC, and found that mutant p53 overexpression was significantly more frequent in schistosomal than in non-schistosomal colorectal cancer. Moreover, p53 overexpression in SCC correlated well with nodal metastasis, mucinous carcinoma, and tumour multicentricity, thereby serving as a useful prognostic biomarker.<sup>[22]</sup> Zalata and his associates developed a more comprehensive study of the expression pattern of p53, Bcl-2, and C-Myc in 75 CRC cases; 24 of these had pathological evidence of *S. mansoni* infection. Although they did not find a significant association between parasitism and p53 and C-Myc expression, their results showed that SCC are characterized by Bcl-2 overexpression and less apoptotic activity than ordinary colorectal tumours.<sup>[23]</sup>

## 4. Diagnosis

The clinical presentation of SCC is often non-specific with common gastrointestinal symptoms such as altered bowel habits and rectal bleeding which could be attributed to chronic schistosomiasis or other gastrointestinal diseases.<sup>[7,24]</sup> Therefore, in non-endemic areas, the diagnosis requires high index of clinical suspicion in patients with history of schistosomal infection. Recent reports have evidenced that *S. mansoni*-associated CRC is associated with significantly higher serum levels of Telomerase, LDH, clusterin protein, and CEA when compared to intestinal *S. mansoni* infection only.<sup>[25,26]</sup> These biomarkers might serve as promising tools for early tumour detection in patients with chronic intestinal schistosomiasis.

Current methods of investigation of SCC involve colonoscopy and computed tomographic (CT) scanning, whereas histological analysis remains the gold standard to confirm the diagnosis. Colonoscopy not uncommonly reveals features of concomitant colonic schistosomiasis; acute colitis, chronic colitis, or mixed-type colitis, with presence of typical yellow nodules in the majority of these cases.<sup>[7,27]</sup> The endoscopic appearance of SCC is heterogeneous, but the most prevalent findings are ulcerative and fungating masses in the colonic wall, which are not uncommonly multi-focal.<sup>[7,10,11]</sup> Histology frequently reveals mucinous adenocarcinomas, with deposited ova in the tumour or the adjacent lamina propria (Figure 2).<sup>[12,13]</sup> Enhanced CT scan and virtual CT colonography were both shown to be highly valuable tools in the detection, characterization, and management of the SACC. The intestinal wall appears irregularly thickened in all patients, involving a wide range of the intestine. Other common CT features include spotty and patchy calcifications with obscured margins, tram-track calcifications and soft tissue

masses.<sup>[10,11]</sup>



**Figure 2.** Photomicrograph showing *S. mansoni* egg shell inside the tumour and dysplastic glands. H&E × 40

## 5. Treatment and Outcome

### 5.1 Surgical

Complete mesorectal excision (CME) remains the best treatment modality for localized colon cancer that is amenable for curative surgical resection (70-80%), and provides effective palliation for metastatic disease.<sup>[28]</sup> For rectal cancer, curative surgery options are trans-anal and trans-sphincteric local excision, and total mesorectal excision (TME) with or without sphincter preservation. Laparoscopic-assisted approach is preferred over open colorectal resection, and confers better short-term outcomes.<sup>[29]</sup> In a series of 280 patients with SCC, 87 patients had laparoscopic resection, and 193 had open surgery. The laparoscopic group had earlier postoperative recovery, shorter hospital stay, and less surgical morbidities, with no increase in intra-operative adverse events. Higher rates of schistosomiasis-related complications were noted among the open surgery group. It was concluded that laparoscopic treatment is safe and effective for SCC with Child-Pugh grade A and B.<sup>[30]</sup> These results were recently replicated in CRC patients with liver cirrhosis caused by various infectious and non-infectious aetiologies.<sup>[31]</sup>

Generally, patients with SCC have significantly lower disease-free and overall survival than those with sporadic CRC.<sup>[13,32]</sup> These observations could be ascribed to the aggressive biological behaviour of SCC and to the presence of concomitant hepatosplenic schistosomiasis. Furthermore, the pattern of *Schistosoma* eggs deposition correlates well with the overall survival, but it does not affect the risk of anastomotic leak, indicating that the current standard surgical resection of SCC appears to be sufficient.<sup>[33]</sup>

### 5.2 Non-surgical

Preoperative (neoadjuvant) 5-Fluorouracil (5-FU) based chemoradiation or short-course high dose radiation therapy is currently the standard of care for operable T3/4 or node-positive rectal cancer.<sup>34</sup> Following surgery for CRC, various regimens of adjuvant treatment are used to achieve local control and to prevent systemic tumour dissemination, among which combination chemotherapy with oxaliplatin has the best curative effect and gives most benefit to patients.<sup>35</sup> For metastatic disease, oxaliplatin-based (FOLFOX) and irinotecan-based (FOLFIRI) regimens are regarded as first-line chemotherapy with comparable efficacy and overall survival.<sup>[29]</sup> The former regimen is particularly beneficial in treatment of SCC which frequently expresses high levels of clusterin.<sup>[26]</sup> Nonetheless, as hepatic perlobular and periportal fibrosis, leading to portal blood flow obstruction are frequent pathological findings, and active HBV/HCV coinfection is not uncommonly seen in patients with schistosomal infection regardless of the development of colonic schistosomiasis,<sup>[36,37]</sup> the use of oxaliplatin-based chemotherapy should be cautiously considered in SCC patients with portal hypertension, even in those with good liver reserve. This is because of the risk of hepatotoxicity, sinusoidal obstruction syndrome, and subsequent upper gastrointestinal bleeding. Oxaliplatin-based regimen is furthermore associated with a significantly increased mortality in portal hypertension patients undergoing colorectal cancer surgery.<sup>[38,39]</sup> Other conventional (NON-OXALI) chemotherapeutic regimens can be acceptable alternatives in those patients.

In the last decade, novel biologic therapies, targeting either epidermal growth factor signalling or angiogenesis, have been used in combination with cytotoxic agents as standard regimens for metastatic and advanced CRC. Inhibitors of the vascular endothelial growth factor (VEGF), an angiogenic molecule expressed in many patients with CRC and preferentially over-expressed on SCC cells,<sup>[11]</sup> among others, were shown to improve the progression-free and overall survival in advanced CRC with variable efficacy depending on the concurrent chemotherapy regimen utilized.<sup>[29]</sup> More recently, immunotherapy has emerged as a promising therapeutic option that selectively targets cancer-dependent pathways and avoids chemotherapy-related toxicities, thereby improves patient tolerance. This modality comprises immune checkpoints modulation, adoptive cell transfer, cancer vaccines, and oncolytic viral therapy. Nevertheless, the immunomodulating agents that have been investigated so far showed either minimal efficacy or have not yet proceeded on to later phase studies.<sup>[40]</sup> The clinical response rate to immunothera-

py and progression-free survival could be significantly ameliorated by targeting certain subsets of CRC such as mismatch repair-deficient (MMR-d) and microsatellite instability-high (MSI-H) metastatic tumours, which account for approximately 15% of all CRC and 42% of SCC.<sup>[40,41]</sup> Additionally, modulating MDSC- and Treg-mediated immunosuppression may be a beneficial strategy to improve the efficiency of immunotherapeutic interventions, particularly in SCC cases.<sup>[42,43]</sup>

## 6. Conclusion

Although the carcinogenesis induced by *Schistosoma* sp. has been actively investigated, the causal relationship between the parasite and CRC is still poorly understood. The molecular biology of SCC must be further studied. Identification of predictive and prognostic biomarkers at an early stage is of paramount importance if the long-term outcome of surgery is to be improved. Further studies are warranted to explore new treatment strategies for SCC, and more effective means of controlling schistosomiasis in endemic areas.

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