

# Colorectal sarcoma: more than a gastrointestinal stromal tumor

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**Abstract:** Primary colorectal sarcomas have been defined as a rare and diverse group of mesenchymal cancers distinct from gastrointestinal stromal tumors (GISTs). Primary colorectal sarcomas have been recognized as a distinct entity from GISTs due to the dramatically worse prognosis these sarcomas carry. Also, primary colorectal sarcomas when compared to the more common colorectal adenocarcinoma, demonstrate more aggressive biology, present at a younger age and carry worse outcomes. At this time, surgery remains the mainstay of treatment and adjuvant chemotherapy has an unclear role in treatment of primary colorectal sarcoma. This paper attempts to review the available data regarding primary colorectal sarcomas.

**Keywords:** Colorectal cancer; colorectal sarcoma; gastrointestinal stromal tumor (GIST); gastrointestinal sarcoma; colorectal adenocarcinoma

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## Introduction

Primary colorectal sarcomas are a rare and diverse group of mesenchymal cancers of the lower gastrointestinal tract, comprising only 0.1% of all colorectal malignancies (1-3). In a recent National Cancer Database review, excluding gastrointestinal stromal tumor (GIST), there were only 433 patients identified with primary colorectal sarcoma from 1998–2012. Given the rarity of the tumors, there is little data available regarding outcomes and prognosis. Historically, most information and inferences were drawn from several small case reports; many with patient populations in the single digits, and the largest containing 50 patients (1-6). Although once thought to be similar, these sarcomas are now recognized as a different entity from the other more common mesenchymal neoplasm, GIST. When compared to the more common colorectal adenocarcinoma, primary colorectal sarcomas behave more aggressively, present at a younger age and have worse outcomes (1). Surgery remains the mainstay of treatment and adjuvant chemoradiation has an unclear benefit. Given the rarity of the colorectal sarcomas, there is a paucity of high quality data regarding the optimal management of primary colorectal sarcoma patients. This paper will review the available data.

## Epidemiology

Colorectal sarcomas are a heterogeneous group of tumors of mesenchymal origin with multiple subtypes: leiomyosarcoma, histiocytomas, and desmoplastic small round cell tumors. Leiomyosarcomas are the most common, comprising over 90% of the primary colorectal sarcomas (1,3). Most patients presented in the 6th through 7th decades (3). In the largest review, the mean age of presentation was 59 years; additionally, 23% of cases presented prior to age 50. Of the sarcomas in colon and rectum, the majority are located in the colon (70.7%), with 25.4% found in the rectum and 3.9% in the rectosigmoid region. The histological grade reported as 40.4% high, 21.0% low and 38.6% unknown (1). Node positive disease is rare, with less than 10% of patients found to have node positive disease after resection (3).

## Colorectal sarcoma vs. GIST

Although originally considered the same entity, primary colorectal sarcomas do not include GISTs. GISTs originate from the interstitial cells of Cajal, as opposed to

mesenchymal smooth muscle cells that are thought to give rise to leiomyosarcoma, the most common type of primary colonic sarcoma. GISTs express CD34 and by 1998 the gain of function protooncogene was discovered in the GIST by Hirota *et al.* (7). GIST can be characterized by over expression of the tyrosine kinase receptor cKIT and this receptor remains the main target for imatinib and other TKI therapies (8). It is estimated that 55% of GISTs arise in the stomach, 30% in the small bowel, 6% in the colon and rectum, and 1% in the esophagus (9). Primary colorectal sarcoma, like leiomyosarcomas elsewhere, remains a relative chemotherapy-resistant malignancy without clear molecular targets.

Primary colonic sarcoma and colonic GIST both represent sarcomas. Despite their classification as distinct entities, there are some similarities in the clinical behaviors and treatment of GISTs and primary colorectal sarcomas. Both tumors can be clinically indolent or aggressive. Colorectal sarcomas have been reported to be symptomatic more frequently which is associated with malignant potential (10). Malignant potential is currently poorly predicted, but tumor size and mitosis rates have been described as the most reliable criteria to assess risk of aggressive behavior as they are for sarcomas in other locations (8). Non-gastric GISTs also have a worse prognosis relative to other GISTs, with colorectal GISTs having a particularly poor recurrence free survival (11,12). For both cancers, regional or distant metastasis represent the most frequent pattern of treatment failure, with the liver and peritoneum as the usual sites of relapse. Surgical resection is the cornerstone of treatment for both cancers, although in the case of GIST, due to effective molecular therapies many additional life-extending therapies exist. Extensive lymphadenectomy or mesorectal excision is not necessary for either sarcoma given the low risk of node positive disease. Therapeutic goals for patients with either malignancy focus on a margin-negative resection (4). While Imatinib, and other TKIs, have proven efficacy for GIST tumors, and its use has changed surgical management of many GISTs, there have not been any targeted therapies for colorectal sarcoma. Adjuvant chemotherapy and radiation have also been used for colorectal sarcoma, their effectiveness is less conclusive (1,2,13).

It is because of the availability of effective adjuvant therapies for GIST that great care must be exercised to be sure that a sarcoma diagnosed as a primary colonic sarcoma does not actually represent a GIST. cKIT staining alone is likely insufficient to assure this. Additional molecular sequencing of tumors for KIT and PGDF expression

should be performed as low KIT-expressing GISTs may still respond to TKI therapy (14,15).

## Outcomes

In 2017, Thiels *et al.* did the largest review of patients with primary colorectal sarcoma. GISTs were excluded from the review, unlike most of the earlier literature. They reported a 5-year overall survival with primary colorectal sarcomas of 43.8% (1). As expected, patients with high-grade tumors had worse overall 5-year survival compared to patients with low grade tumors (38% *vs.* 61%). This is similar to prior reports of mean overall survival of 30–53 months (2,3). The overall 5-year survival of 40%, but differed based on histological grade, 66% 5-year survival seen in low-grade compared to 22% with high grade histology.

Recurrence rates in the literature ranges from 20–80% (1–2,16–18) A median recurrence interval of 7 months has been reported (1). Locoregional failure is the most common site of recurrence, noted to be as high as 46% (2,3). The liver has been shown to be the most common site of distant recurrence, accounting for approximately 50%, while the peritoneum was the second most common site (3). In patients with low grade tumors, it has been shown that local recurrence was observed as distant as 15 years after resection (3).

## Colorectal sarcoma vs. adenocarcinoma

Thiels *et al.* compared colorectal sarcomas and to colorectal adenocarcinomas from 1998–2012. Their analysis, patients with colorectal sarcoma tended to present slightly younger, with a median age of 65 years compared to 68 years for adenocarcinoma. Both cohorts were similar in other baseline patient demographics such as gender, race and associated comorbidities. There were some differences in tumor characteristics. Colorectal sarcomas were more commonly discovered in the rectum *vs.* adenocarcinoma (25% *vs.* 21%). Sarcomas were more likely to have larger tumor size and higher histological grade, but less likely to present with positive nodes. The 5-year overall survival of sarcoma patients was significantly worse, with 43% of sarcoma patients alive at 5 years compared to 52% of patients with adenocarcinoma.

## Treatment strategies: surgery and chemo XRT

Complete surgical resection has remained the main mode of therapy since the discovery of colorectal sarcomas.

The index operation should focus on complete resection without need for extensive lymphadenectomy. A complete exploration of the abdominal cavity is necessary given high frequency of intra-abdominal metastases (13). There have been small reports of local excision in both small tumors (less than 2 cm) and low-grade tumors (1). In the largest, most recent review, over 80% of 433 patients underwent formal anatomic colon resection (1). Of the other patients, 9.2% had local tumor destruction and 10.6% did not have surgery. Positive margins were found in 12.7% of surgical specimens. Unfortunately, recurrence rates are not captured in the National Cancer Database

Adjuvant chemotherapy with or without radiation has been reported in several case series with inconsistent results (1,2,4). The data is not robust enough to justify its routine use (1,3). In the review of the NCDB, only 15% of patient underwent chemotherapy. Patients who received chemotherapy in this population were younger, (mean age, 54 *vs.* 65 years) more likely to have node positive disease and more likely to not undergo surgical resection. Only 12% of patients in this review received radiation therapy. Patients who received radiation tended to be younger, have a primary tumor location in the rectum and positive margins on final pathology. No difference was noted in survival among patients who received radiation (1). Some authors suggest that administration of adjuvant radiation diminishes local risk patterns and may allow for sphincter preservation in small tumors <5 cm (2).

## Conclusions

Colorectal sarcomas are a rare mixed group of gastrointestinal tumors and are a different entity from the more common tumors of adenocarcinoma and GIST. Compared to colorectal adenocarcinomas, they occur at a younger median age and portend a poorer survival. Surgery remains the mainstay of treatment and there is minimal data advocating for or against the use of adjuvant chemoradiation. Surveillance should be recommended particularly in low grade cancers given the chance of recurrence to occur many years after therapy.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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