Case Analysis

Clinical Analysis and Surgical Results of Primary Colorectal Sarcoma

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Key Words
Sarcoma;
Colorectal neoplasm

Abbreviations
CRS, colorectal sarcoma;
CRC, colorectal cancer

Purpose. Colorectal sarcomas are rare and their treatment remains controversial. This study describes the clinical features of colorectal sarcoma.
Methods. Data were obtained from a retrospective database of all colorectal malignancies at Taipei Veterans General Hospital. From 1998-2008, 873 sarcoma cases and 5594 colorectal malignant tumors were diagnosed. Eleven patients with colorectal sarcoma were identified.
Results. The 11 patients (five males, six females, mean age of 61.7 years) presented primary tumors in the rectum (n = 7) and colon (n = 4). Surgical intervention in 10 patients (one patient was initially diagnosed with lung metastasis and did not undergo surgical intervention) was uneventful. The mean tumor size was 9.6 cm (range, 4-30 cm). Histological findings were leiomyosarcoma in seven cases and sarcomatoid carcinoma, liposarcoma, synovial sarcoma and embryonal rhabdomyosarcoma each in one case. Five of the seven leiomyosarcoma patients (71.4%) developed recurrences during the follow-up period. Recurrence sites included local recurrence (n = 2) and liver metastasis (n = 3). The overall and disease-free survival periods of the leiomyosarcoma patients were 52.8 months and 44.7 months, respectively.
Conclusions. In our experience, sarcoma is a rare tumor in colorectal neoplasm and leiomyosarcoma is the most common histological type. Despite radical surgical intervention and no lymph node metastasis at time of treatment, leiomyosarcoma has a high recurrence rate. The absences of a reliable tumor marker and useful adjuvant chemotherapy make close image follow-up mandatory in the disease management.
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Colorectal sarcoma (CRS) is a rare entity, accounting for 0.1% of colorectal cancer.[1] Surgery is the preferred mode of therapy, and neither radiation therapy nor chemotherapy has any proven efficacy as an adjuvant therapy.[2] Because of the rarity of these lesions and the availability in the literature of only a few large studies with long-term follow-up data, the prognostic factors related to tumor progression and survival of patients are not well-known, and the types of surgical approaches used also remain controversial. In this retrospective study, colorectal sarcomas treated at our hospital were reviewed to evaluate our experience with these rare tumors.

Patients and Methods

There were 5,594 patients newly diagnosed with

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colorectal cancer at Taipei Veterans General Hospital between January 1998 and December 2008. During the same period, there were 873 sarcomas recorded in the database of pathology department and 23 gastrointestinal sarcomas were identified. Eleven of these gastrointestinal sarcomas were finally diagnosed as colorectal sarcoma (Fig. 1). One gastrointestinal histopathologist (Dr. Liang) without prior knowledge of the clinical outcomes retrospectively re-examined all histological slides of the tumors. All of the colorectal sarcomas must appear to have arisen from the muscularis propria layer of the colon or rectum. By means of immunohistochemical staining, all of the colorectal sarcomas were been confirmed with their mesenchymal origin. Gastrointestinal stromal tumors (GISTs) with positive expression of CD117 or CD 34 were excluded from this study. Tumor differentiation of leiomyosarcoma was especially sub-grouped on a two-grade scale (high-grade and low-grade) based on the number of mitoses of tumor cells. High-grade leiomyosarcoma was reported as the number of mitotic cells above 10 in high-power fields of the histology slides; when < 10, low-grade leiomyosarcoma was reported. Clinical data were recorded prospectively and stored in computer files. The database included name, sex, age, family history, and major medical problems; and location, size, gross appearance, stage, differentiation, and other important pathologic prognostic features of the tumor. In these 11 patients, the presurgical events consisted of a physical examination, complete blood count (CBC), chemical profile, chest radiography, and a computed tomography (CT) scan. Post-operatively, all patients were followed-up at 3 month intervals for the first 2 years, 6 month intervals from years 3-5, and annually thereafter. All data were recorded using a standard data form and analyzed using SPSS 15.0 (SPSS, Chicago, IL). For comparison of categorical data, the Chi-square test was applied. P values < 0.05 was considered to indicate statistical significance.

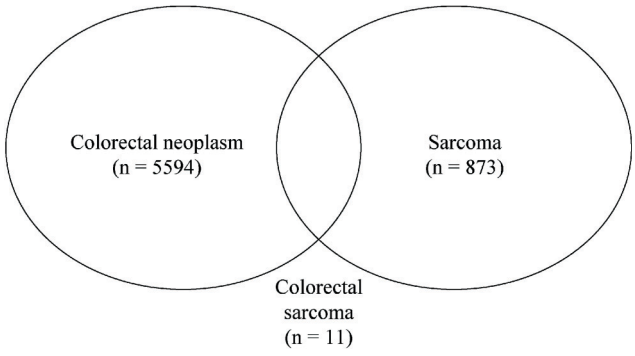

Fig. 1. Colorectal neoplasm and sarcoma in Taipei Veterans General Hospital.

Results

Patients and clinical data

The anatomical sites of gastrointestinal sarcomas are listed in Table 1. Sites of gastrointestinal sarcomas were the stomach (n = 4), small intestine (n = 8), colon (n = 4), rectum (n = 3) and anal canal (n = 4). Colorectal sarcoma comprised about 0.2% (11/5594) of all colorectal malignancies. Of the 11 patients, five (44.4%) were male and six (55.6%) were female (Table 2). The mean age at diagnosis was 61.7 years. The most common sites for cancer occurrence were the anal canal (36.4%) and the rectum (27.2%). The most common symptoms were anal pain (36.4%) and abdominal pain (27.3%). A CT scan was performed preoperatively for staging. One female patient diagnosed as embryonal rhabdomyosarcoma with an initial lung metastasis did not undergo surgical intervention. The final diagnosis for this patient was obtained via CT-guided biopsy. No initial metastasis occurred in the other 10 patients. These patients underwent curative radical surgical resection, including left hemicolectomy, abdominoperineal resection (APR), anterior resection and low anterior resection (LAR). The cut margins in these resected specimens were all free of tumor microscopically. No surgical mortality occurred. The mean size of the resected tumors was 9.6

Table 1. Distribution of gastrointestinal sarcomas

Site	Number (%)
Esophagus	0 (0%)
Stomach	4 (17.4%)
Small intestine	8 (34.8%)
Colon	4 (17.4%)
Rectum	3 (13.0%)
Anal canal	4 (17.4%)
Total	23 (100%)

± 7.6 cm. There were seven leiomyosarcomas and one each of sarcomatoid carcinoma, liposarcoma, synovial sarcoma and embryonal rhabdomyosarcoma (Table 2).

Recurrence and survival

Median follow-up in all patients was 36.3 months (range 17.9-113.2 months) (Table 3). In the leiomyosarcoma group, there were five high-grade tumors and two low-grade tumors. No lymph node metastasis was diagnosed in the resected specimens of all seven leiomyosarcoma patients. However, five of these seven patients (71.4%) developed recurrences (two local recurrences and three liver metastasis) during the follow-up periods (Table 4). Four of these five recurrences were high-grade leiomyosarcoma. The average overall survival and the disease-free survival periods of leiomyosarcoma patients were 52.8 months and 44.7 months respectively. The 1-, 3- and 5-year overall survival rate was 85.7%, 53.6% and 53.6%, respectively. The sarcomatoid carcinoma and liposarcoma patients are still alive without disease and no tumor recurrence. The patient diagnosed with synovial sarcoma developed lung, brain and bone metastasis 5.8 months after abdominoperineal resection. This patient died of the disease with a survival time of 25.3 months. The embryonal rhabdomyosarcoma patient with initial lung metastasis is alive and receives chemotherapy in our oncology department (Table 3).

Table 4. Recurrence and survival of leiomyosarcoma (n = 7)

Median follow-up (months)	36.3 (months)
Local/distant metastasis	5 (71.4%)
Local recurrence	2 (40%)
Liver metastasis	3 (60%)
Lung metastasis	0 (0%)
Overall survival	52.8 (months)
Disease-free survival	44.7 (months)

Table 2. Clinicopathologic features of colorectal sarcoma

Case	Age/Gender	Primary symptom	Histology type	Location	Tumor size (cm)	Stage[a]	Surgery	Metastases
1	63/F	Anal pain	Sarcomatoid carcinoma	Anal canal	4 cm	II	APR	None
2	55/M	Anal pain	Synovial carcinoma	Anal canal	6.5 cm	II	APR	None
3	17/F	Anal pain	Rhabdomyosarcoma	Anal canal	12 cm	IV	None	Lung
4	27/M	Abdominal mass	Liposarcoma	Colon	30 cm	II	LH	None
5	84/M	Abdominal pain	Leiomyosarcoma	Colon	9 cm	II	LH	None
6	70/F	bowel habit change	Leiomyosarcoma	Rectum	4 cm	II	LAR	None
7	93/M	Abdominal pain	Leiomyosarcoma	Colon	5.5 cm	II	LH	None
8	48/F	Abdominal pain	Leiomyosarcoma	Rectum	5 cm	II	LAR	None
9	70/F	Abdominal mass	Leiomyosarcoma	Colon	15 cm	II	LH	None
10	81/F	Anal pain	Leiomyosarcoma	Anal canal	8 cm	II	APR	None
11	71/M	Rectal bleeding	Leiomyosarcoma	Rectum	7 cm	II	LAR	None

APR: abdominoperineal resection; LAR: low anterior resection; LH: left hemicolectomy.
a. Stage groupings according to the AJCC and UICC system for cancer of the colon and rectum., 6th edition.

Table 3. Recurrence and survival condition of the colorectal sarcomas

Case	Time to recurrence (months)	Site	Survival condition	Survival time (months)
1	None	None	Alive without disease	70.9 months
2	5.8 months	Lung/Brain/Bone	Died of disease	25.3 months
3	X	Lung	Alive with disease	23.4 months
4	None	None	Alive without disease	65.10 months
5	4.4 months	Liver	Died of disease	17.9 months
6	None	None	Alive without disease	74.3 months
7	29.8 months	Local recurrence	Died of disease	36.3 months
8	53.4 months	Local recurrence	Alive without disease	72.5 months
9	6.0 months	Liver	Died of disease	22.6 months
10	100 months	Liver	Alive with disease	113.2 months
11	None	None	Alive without disease	32.5 months

Discussion

Sarcoma is a rare gastrointestinal malignancy. According to our database, gastrointestinal sarcomas account for 2.6% (23/872) of all sarcomas in our hospital. It has been reported that the distribution of anatomical sites of gastrointestinal sarcomas are the stomach (50% of patients), small bowel (30%), colorectum (15%) and esophagus (5%).[3] However, the findings from our hospital indicate that the most common site affected by gastrointestinal sarcoma is the colorectum instead of the stomach (45.4% vs. 18.2%). The explanation could be that most tumors of stomach referred to as leiomyomas and leiomyosarcomas in the older medical literature is actually GISTs.[4] GISTs are a subset of gastrointestinal mesenchymal tumors of varying differentiation. GISTs lack characteristics of smooth muscle tumors on histologic examination. They are often CD34 immunoreactive and express tyrosine kinase c-kit (CD117) receptor activity, in contrast to leiomyosarcomas.[5] In the past, GISTs were misdiagnosed as leiomyosarcomas. With the advent of immunohistochemical staining techniques and ultrastructural evaluation, GISTs are now recognized as a distinct group of mesenchymal tumors. Recent elucidation of their molecular pathogenesis, namely the common presence of activating mutations in the gene encoding KIT, may have significant clinical importance, making it necessary to accurately define and clinically diagnose these tumors and separate them from other mesenchymal tumors of the abdomen. The term GIST is now preferentially used for the tumors that express CD34 and KIT. KIT expression and mutations in the c-kit gene are found only in GISTs, but not in myogenic or neurogenic tumors.[4] Thereafter, GISTs with a positive expression of CD117 or CD 34 were excluded from this study.

The main symptoms and signs reported were abdominal or anal pain. Both symptoms can be caused by a larger tumor partially obstructing the bowel lumen. This was supported with the large average size of the tumor (9.6 cm, range 4-30) in this series. In this study, CT scans could provide clinicians with information about the tumor size, differential diagnosis of tumor origin and the presence of tumor invasion into adjacent organs and metatstatic lesions. Operatively, all of the sarcoma lesions were noted to arise from the colorectum with an intact mucosa layer. With specific immunohistochemical staining, the mesenchymal origin of all of the colorectal sarcomas was confirmed.

At the Oncology Hospital of the National Medical Center from 1986-1996, 1,260 new patients with colorectal neoplasms were treated, and the estimated frequency of colorectal sarcomas was 1.03%. The most common histologies are leiomyosarcoma, fibrosarcoma and malignant fibrous histiocytoma.[6] Leiomyosarcoma is the most common histology of colorectal sarcoma, as reported in the literature and shown in our study (70%, 7/10).

Choice of a wide local excision or radical resection for leiomyosarcoma still remains controversial. Some authors have suggested that wide local resection should be limited to those cases with a smaller tumor confined within the bowel wall, because higher local recurrence rates were found in patients with local excision as compared with radical excision. As with colonic leiomyosarcoma, radical resection is generally the preferred approach. Local excision is liable to be followed by recurrence, even though this may be delayed for some years.[7,8] Luna-Pe´rez and colleagues suggested that in rectal sarcoma, surgery plus radiotherapy may reduce the incidence of local recurrence and, in selected patients, allow for anal sphincter preservation.[6] Chemotherapy with vincristine, cyclophosphamide, actinomycin D and doxorubicin (Adriamycin) has also been advocated. To approach complete resection and avoid local recurrence, we typically performed radical surgical resection. In the leiomyosarcoma group, the cut margins were all free of tumor and no lymph node metastasis was diagnosed in the resected specimens. However, five of seven patients (71.4%) developed recurrences during the follow-up periods. Astarjian and colleagues reported on an attempt to stage the disease as follows: tumor confined to the intestinal wall with no invasion and no ulceration was classed as stage I, submucosal tumor was classed as stage IA and subserosal tumor was classed as stage IB ; tumor extending beyond the wall of the colon with intraluminal ulceration was classed as stage IIA, with infiltration into adjacent extracolonic tissues classed as stage IIB; and tumor with distant metastases classed as stage III.[9] Stage I

and IIA tumors had excellent prognoses and stage IIB had a fair prognosis. Tumors with distant metastasis had a poor prognosis. Previous studies supported the usefulness of counting mitotic figures in predicting the behavior of gastrointestinal smooth muscle tumors.[10,11] In our study, we adopted the AJCC and UICC systems for cancer staging. Predicting factors for recurrence of leiomyosarcoma was further analysis including grade, tumor size and invasion of the tumor into adjacent organs (Table 5). Although there was no statistical difference, high-grade leiomyosarcoma and tumor size > 5 cm seemed to have a higher tendency of tumor recurrence ($p = 0.427$). The prognosis of primary colon leiomayosarcoma in our study was difficult to predict because of the small number of cases. In a review of patients with small-bowel and large-bowel sarcomas treated between 1959 and 1987 at Roswell Park Cancer Institute, after complete resection with negative margins, the overall five-year survival rate was 44% for low-grade tumors and 0% percent for high-grade tumors.[12] In the same study, patients undergoing complete resection had a median survival period of 33.3 months, while patients receiving less than complete resection had a median survival period of 15.4 months. Intra-abdominal spread was the most common pattern of recurrence. By multivariate analysis, significant predictors of survival included tumor size, grade, stage at presentation and invasion of tumor into adjacent organs. Another study found pathologic grade to be the single most important prognostic factor in patients treated for sarcomas of the gastrointestinal tract. For patients treated with a curative resection, the median disease-free survival time for high-grade tumors was approximately 18 months, whereas low-grade tumors had an 80% 10-year disease-free survival rate.[13] Another study reviewed the results of 108 patients treated at the Mayo Clinic from 1950-1974 for primary intestinal leiomyosarcoma. Sixteen patients had tumors limited to the rectum and two patients had tumors arising from the anus. At 1-25 years of follow-up, 31% of the patients had no evidence of disease. The majority of patients who died developed hematogenous metastasis.[14] The authors concluded that the site of the primary neoplasm did not have a significant impact on overall survival. In their analysis, histologic grade was the most significant predictor of outcome. In a study of 40 patients treated for rectal tumors at Taipei, Taiwan, the 5-year disease-free survival was 46%, but 75% were alive at that time.[8] In addition to high histologic grade, a younger age was a significantly poor prognostic factor. Apart from local recurrence, metastasis to the liver and lungs is the most common cause of death. In our experience, although complete tumor resection with free margin, no lymph nodes metastasis and no distant metastasis occurred initially in the leiomyosarcoma group, five cases subsequently developed metastasis. Time to recurrence was 44.7 months. In our follow-up protocol, a chest X-ray and abdominal sonograpgy was arranged at 3 month intervals for the first 2 years, 6 month intervals from years 3-5, and annually thereafter. CT scans were arranged at 6 month intervals. Due to the absence of any reliable tumor marker for follow-up and any effective adjuvant chemotherapy agents, close image follow-up for early detection of recurrence is advised. The inclusion of CT at 6 month intervals may be a reasonable approach.

Sarcomatoid carcinoma is an extremely rare biphasic tumor characterized by a combination of malignant epithelial and mesenchymal cells. As a result, the natural history of these unusual tumors and the best methods of treatment are uncertain. These tumors occur in various anatomical locations such as the upper aerodigestive tract,[15] small intestine,[16] bladder,[17] prostate[18] and many other sites. A malignant tumor with a mixed phenotype is a controversial field of pathology. The rare sarcomatoid carcinomas of the colon have been described under a variety of names,

Table 5. Predicting factors for recurrence of leiomyosarcoma (n = 7)

	Recurrence	*p* value
Grade		0.427
High grade (> 10/HPF) (n = 5)	4/5 (80%)	
Low grade (< 10/HPF) (n = 2)	1/2 (50%)	
Tumor size		0.427
> 5 cm (n = 5)	4/5 (80%)	
< 5 cm (n = 2)	1/2 (50%)	
Invasion of tumor into adjacent organs		0.495
Yes (n = 1)	1/1 (100%)	
No (n = 6)	0/6 (0%)	

which has caused great uncertainty about their classification and histogenesis.[19-21] The pathogenesis of mesenchymal differentiation in sarcomatoid carcinoma is uncertain. The explanations include the collision theory of independent neoplastic growth from multipotent stem cell origins, epithelial to mesenchymal conversion by epithelial-stromal interaction, and a combination of the two.[17,22] The best predictors of outcome in sarcomatoid carcinoma seem to be tumor location, size, invasion depth, and the clinical stage of the disease.[15,17,18,22] The histologic features, stage, and outcome of the reported cases indicate that this neoplasm generally has a highly aggressive and malignant biological course with rapid growth and wide local infiltration, leading to a poor prognosis.

Synovial sarcoma accounts for 5-10% of soft tissue sarcomas.[23] The majority occur in the deep soft tissue, near the large joints of the extremities in young adults. The pathological variants of synovial sarcoma include biphasic, monophasic epithelial, monophasic fibrous and poorly differentiated types. More than 90% of synovial sarcomas, regardless of histological type, bear the X;18 translocation (p11.2; q11.2), which appears to be specific for this neoplasm. Synovial sarcoma has been reported in several locations, including the head and neck, intrathoracic, vulva, brain, liver, kidney, prostate, bone, peritoneal cavity and retroperitoneum.[23] While the rate of metastasis of synovial sarcoma is 50-70% in most series, gastrointestinal synovial sarcomas may have a better prognosis.

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and occurs most frequently in the head and neck, genitourinary tract, extremity and trunk.[24] A few cases have been reported in the perirectal area.[25,26] Horn and Enterline classified rhabdomyosarcoma into four types: pleomorphic, alveolar, embryonal, and botryoid.[27] Current therapy should include adequate local excision or resection followed by chemotherapy including vincristine, actinomycin D and cyclophosphamide.[25,26] The prognosis is generally poor.

Liposarcoma, the most common soft tissue sarcoma, represents 20% of the mesenchymal malignancies, and tends to occur in the retroperitoneum and deep soft tissues of the trunk and extremities.[23,28] It infrequently arises in the gastrointestinal system, and colon liposarcoma is extremely rare. The first case of primary liposarcoma of the colon was reported in 1989.[29] Since then, only four well-documented cases have been reported.[30] From a histopathologic point of view, these neoplasms originate from primitive mesenchymal cells and are rarely encountered in fat-rich areas such as the subserosa of the intestinal tract.[28] In the recent World Health Organization classification, liposarcomas are divided into five major histological subtypes: atypical lipomatous tumor (well-differentiated liposarcoma), myxoid liposarcoma, pleomorphic liposarcoma, dedifferentiated liposarcoma, and mixed type liposarcoma. In general, liposarcoma occurs almost exclusively in adults, with a peak incidence between ages 50 and 70. The protocol for treatment of liposarcoma of the colon has not been well-established. However, the treatment of choice for such tumors is complete wide excision.[29,30] The role of adjuvant or neoadjuvant therapy in colon liposarcoma is, however, still unclear and is a controversial subject. This neoplasm has a remarkable tendency to recur after surgical excision but rarely metastasizes.[23,28] The prognosis of primary colon liposarcoma is difficult to predict because of the small number of reported cases. Well-differentiated tumors have the most favorable outcome, with a 5-year survival rate estimated between 75% and 100%. Round cell and pleomorphic liposarcomas have the worst prognosis with 0-20% survival rate at 5 years.[23] Patients with myxoid liposarcoma who are surgically treated demonstrate good survival even 10 years after surgery. Three parameters have been correlated with poor prognosis: age (> 45 years), the presence of round cells and necrotic areas within the mass; the grade of the neoplasm influences the incidence of metastasis and its recurrence.

Conclusion

Sarcoma is a rare subgroup in colorectal neoplasm and leiomyosarcoma is presently the most common type of colorectal sarcoma. Despite radical surgical intervention and no lymph node metastasis during surgical intervention, leiomyosarcoma has a tendency of recurrence. No reliable tumor markers or useful adjuvant chemotherapy are as yet available, making

close image follow-up a necessity for the management of this disease.

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病例分析

結腸直腸肉瘤的臨床及病理分析

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目的 結腸直腸肉瘤十分罕見，臨床上的治療方式仍無定論。此篇研究是為了分析本院結腸直腸肉瘤病患臨床及病理上的表現。

方法 本研究回溯並收集台北榮民總醫院大腸直腸外科及病理部資料庫，於 1998 至 2008 年間，共有 5594 位診斷為結腸直腸惡性腫瘤的病患及 873 位診斷為肉瘤的病患，其中 11 位病患確定診斷為大腸直腸肉瘤。將這些病人的臨床及病理的資料予以分析。

結果 這 11 位病患分別為 5 位男性及 6 位女性，平均年齡是 61.7 歲。7 位病患的病灶是為於直腸，4 位是位於結腸。有一位病患因診斷時已肺部轉移，沒有接受外科手術治療。其餘 10 位病患接受根除性手術治療。切除下來的病灶平均是 9.6 公分。病理診斷有 7 位是平滑肌肉癌、其餘分別各是 1 位的肉瘤樣癌、惡性脂肪肉瘤、滑囊肉瘤、胚胎型橫紋肌肉瘤。在 7 位平滑肌肉癌病患中，有 5 位在追蹤期間發生復發轉移。有 2 位是局部復發，另外 3 位是肝臟轉移。在平滑肌肉癌病患中，總存活期間及無病存活期間分別是 52.8 及 44.7 個月。

結論 在台北榮民總醫院，結腸直腸肉瘤十分罕見，以平滑肌肉癌為最常見的組織型態。即使接受根除性手術治療及沒有淋巴結轉移，平滑肌肉癌有十分高的傾向會復發。臨床上缺乏可以信賴的腫瘤追蹤指標及有效的輔助化學治療，使得密切的影像學追蹤對於大腸直腸肉瘤的治療是需要的。

關鍵詞 結腸直腸惡性腫瘤、肉瘤。