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Malignant Small Bowel Neoplasms

Histopathologic Determinants of Recurrence and Survival

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Introduction
Small bowel neoplasms account for only a small percentage of gastrointestinal tumors, but their prognosis is one of the worst.

Purpose
This study examines the histopathology, treatment, recurrence, and overall survival of a group of patients with primary small bowel tumors.

Methods
From 1970 to 1991, a retrospective review identified 73 patients with primary small bowel tumors. Four histologic groups were identified: 1) group 1, adenocarcinoma, 29 patients; group 2, lymphoma, 18 patients; group 3, sarcoma, 8 patients; and group 4, carcinoid, 18 patients. There were 44 men and 29 women. The median age was 57 years (range, 26 to 90). Median follow-up was 15 months. Survival analysis was by the Mantel–Cox and Breslow methods.

Results
The most common, by type, was group 1, duodenum; group 2, jejunum; group 3, jejunum; and group 4, ileum. The preoperative diagnosis was made in only 14 patients. The median survival for adenocarcinomas and lymphomas was 13 months, 18 months for sarcomas, and 36 months for carcinoids. Curative resection could be achieved in 48 (65%) of 73 patients, and the median survival was significantly longer for this group (26 months *vs.* 11 months, $p < 0.05$). Of the 48 curative resections, 20 patients (42%) recurred: group 1, 8/19 (42%); group 2, 4/12 (33%); group 3, 4/13 (31%); group 4, 4/4 (100%). The median time to recurrence was 17 months, and the median survival after recurrence was 20 months. Adjuvant chemotherapy–radiation therapy did not alter survival in any group.

Conclusions
The preoperative diagnosis of small bowel tumors rarely is made because symptoms are vague and nonspecific. Surgical resection for cure results in improved survival. Recurrence is common and survival after recurrence is poor. Other treatment methods have no role in the management of these patients.

Table 1. THE MOST COMMON LOCATION OF EACH HISTOLOGIC TUMOR AND THE MOST COMMON HISTOLOGIC TUMOR BY LOCATION IN THE SMALL INTESTINE

	Duodenum	Jejunum	Ileum	Total
Adenocarcinoma	13	10	6	29 (40%)
Carcinoid	1	4	13	18 (25%)
Lymphoma	2	9	7	18 (25%)
Sarcoma	2	4	2	8 (10%)
Total	18 (25%)	27 (37%)	28 (38%)	73 (100%)

It is estimated that there are only 1200 primary, malignant small bowel tumors diagnosed in the United States each year. This breaks down to an incidence of 1 per 10,000 hospital admissions or 1 per 2000 general surgical procedures.[1,2] Therefore, there is little information available about the natural history, presentation, and management of patients with primary small bowel tumors. This study reviews the diagnosis, management, recurrence, and survival of 73 patients with malignant small bowel tumors treated at the Mount Sinai Medical Center in New York.

METHODS

From 1970 to 1991, 73 patients were identified who had treatment for their malignant small intestinal tumor at the Mount Sinai Medical Center. We excluded all periampullary tumors, patients not initially treated at Mount Sinai, and all benign lesions. Medical records and office charts were reviewed for presenting symptoms, physical findings, diagnostic workup, surgical procedure, pathologic diagnosis, and survival data. Recurrence was defined as biopsy-proven tumor or radiologic evidence of obvious local or distant recurrence. Survival was calculated using the Mantel–Cox and Breslow methods and was calculated from the time of surgery and from the time of recurrence.

Four distinct histologic types of tumors were identified: 1) group 1, 29 patients with adenocarcinoma; 2) group 2, 18 patients with lymphoma; 3) group 3, 8 patients with sarcoma; and 4) group 4, 18 patients with carcinoid. Staging of patients was by the American Joint Committee on Cancer guidelines established in the fourth edition.[3] For adenocarcinomas, the following four stages were identified: 1) stage I, tumor confined to the laminal propria, submucosa, or muscularis propria; 2) stage II, tumor extending beyond the muscularis propria or invading adjacent structures; 3) stage III, tumors with any bowel wall extension and positive lymph nodes; and 4) stage IV, tumors with any degree of bowel wall invasion, with or without lymph node metastases, and with distant disease.

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RESULTS

For the entire group, there were 44 men and 29 women for a ratio of 1.5:1. The median age at the time of presentation was 57 years with a range of 26 to 90 years. A comparison of the type and location of the tumors showed that location predicted for histologic type of tumor (Table 1). Adenocarcinomas were located most commonly in the duodenum and proximal jejunum and 13 of 18 duodenal tumors were adenocarcinoma. Tumors located in the jejunum were most likely adenocarcinomas or lymphomas. Roughly half of the ileal tumors were carcinoids, and this represented the majority of all carcinoids. Lymphomas and sarcomas were located most commonly in the jejunum or ileum.

For the entire group, the most common presenting symptom was pain. Table 2 lists the presenting symptoms by the histologic type of tumor. Other symptoms included nausea, vomiting, weight loss, anemia, gastrointestinal (GI) bleeding, or the carcinoid syndrome. Because of the nonspecific nature of the presentation, most patients underwent a number of diagnostic tests before surgical exploration. The preoperative diagnosis was made in only 14 patients (19%) with 6 adenocarcinomas being diagnosed by upper endoscopy (EGD), 7 patients had the carcinoid syndrome on presentation, and 1 lymphoma was diagnosed before surgery (Table 3). Two thirds of all patients presented with stage III or IV disease (Table 4). Curative resection resulted in a significant survival advantage when compared to noncurative management (Fig. 1).

Adenocarcinoma

There were 29 patients who presented with adenocarcinoma of the small intestine. The most common presenting

Table 2. THE PRESENTING SYMPTOMS BY HISTOLOGIC TYPE OF SMALL INTESTINAL TUMOR

	Adenocarcinoma	Carcinoid	Lymphoma	Sarcoma
Pain	14	3	10	2
Nausea/vomiting	9	2	2	0
Weight loss	6	0	3	0
Gastrointestinal bleed	2	4	0	4
Anemia	4	0	2	0
Fever	1	1	3	1
Acute abdomen	1	0	1	1
Carcinoid syndrome	0	7	0	0

Table 3. THE DIAGNOSTIC TESTS USED TO EVALUATE PATIENTS WITH SMALL INTESTINAL TUMORS

	Adenocarcinoma	Carcinoid	Lymphoma	Sarcoma
UGI/SBFT	19	9	7	2
Upper endoscopy	9	1	1	1
Computed tomography	8	4	7	2
Ultrasound	6	2	3	5
Barium enema	5	4	2	2
Colonoscopy	6	4	1	0
Preoperative diagnosis	6	7	1	0

UGI/SBFT = upper gastrointestinal series with small bowel follow through.

symptom was pain followed by nausea–vomiting, weight loss, and GI bleeding. The majority of patients with adenocarcinoma had an upper GI series with small bowel follow through (UGI/SBFT) and EGD. Computed tomography (CT), ultrasound, and lower endoscopy were used less commonly. The preoperative diagnosis of adenocarcinoma was made in 6 (21%) of 29 patients. The majority of adenocarcinomas were located in the duodenum or proximal jejunum (23/29, 79%). All six adenocarcinomas in the ileum arose in the setting of Crohn's disease. Thirteen (43%) patients presented with distant metastatic disease, whereas 7 patients presented in each stage II and stage III. Only two patients presented with stage I disease.

The median survival for all adenocarcinomas was 13 months, and the 5-year survival was 30% (Fig. 2). Curative resection could be performed in 19 (66%) of 29 cases. A significant survival advantage was noted for patients able to undergo a curative resection compared to noncurative treatment (23 months *vs.* 7 months; $p = 0.01$). Of the 29 patients, 11 patients received chemotherapy, and their median survival was 9.5 months compared to 26 months for the 18 patients not receiving chemotherapy. Postoperative chemotherapy was given at the discretion of the primary physician. There are an inadequate number of patients to compare survivals for patients who had a curative resection with or without adjuvant therapy. Of the 19 curative resections, 8 recurred with a median time to recurrence of 24 months. Only two of those recurrences remain alive.

Carcinoid

Carcinoid was the primary diagnosis in 18 patients, and 7 of these patients presented with the carcinoid syndrome. Other common symptoms included GI bleeding in four patients, pain in three patients, and nausea and vomiting in two patients. More than half of the patients with carcinoids had a UGI/SBFT, whereas CT, ultrasound, barium enema, EGD, and colonoscopy were used less frequently. The preoperative diagnosis was made in the seven patients with the carcinoid syndrome, all of whom had liver metastases. Carcinoids were most common in the ileum followed by the jejunum, and only one was found in the duodenum. The stage at presentation included 12 patients with stage IV disease, 4 patients with stage III disease, and 2 patients with stage I disease.

The median survival for all carcinoids was 36 months (Fig. 2). Survival was improved for the 12 patients (67%) who were able to undergo curative resection compared to those patients not able to undergo a curative resection (81 months *vs.* 18 months, $p = 0.007$). There was no survival benefit for the patients treated with chemotherapy after surgery. Of the four recurrences after curative resection, two remain without evidence of disease.

Lymphoma

Eighteen patients presented with primary small intestinal lymphoma, and the most common reported symptom, abdominal pain, was present in 10 patients. Less-common symptoms included fever in three patients, weight loss in three patients, anemia in two patients, and nausea and vomiting in two patients. One patient presented with an acute abdomen and was found to have a small bowel obstruction. A UGI/SBFT and an abdominal–pelvic CT were performed in seven patients each. Less-common diagnostic tests included EGD, ultrasound, barium enema, and colonoscopy. The preoperative diagnosis was made in the one patient with EGD who had a duodenal lymphoma. The jejunum and ileum accounted for 16 of the 18 lymphomas.

The median survival for patients with lymphoma was 13 months (Fig. 2). Curative surgical resection could be accomplished in 12 (67%) of 18 patients. Final pathologic staging showed seven patients with stage I disease, three patients with stage II disease, two patients with stage III disease, and six patients with stage IV disease. Median survival was improved by curative resection with those

Table 4. THE STAGE OF PRESENTATION FOR EACH HISTOLOGIC TYPES OF TUMOR

Stage	Adenocarcinoma	Carcinoid	Lymphoma	Sarcoma
I	2	2	7	2
II	7	0	3	1
III	7	4	2	0
IV	13	12	6	5

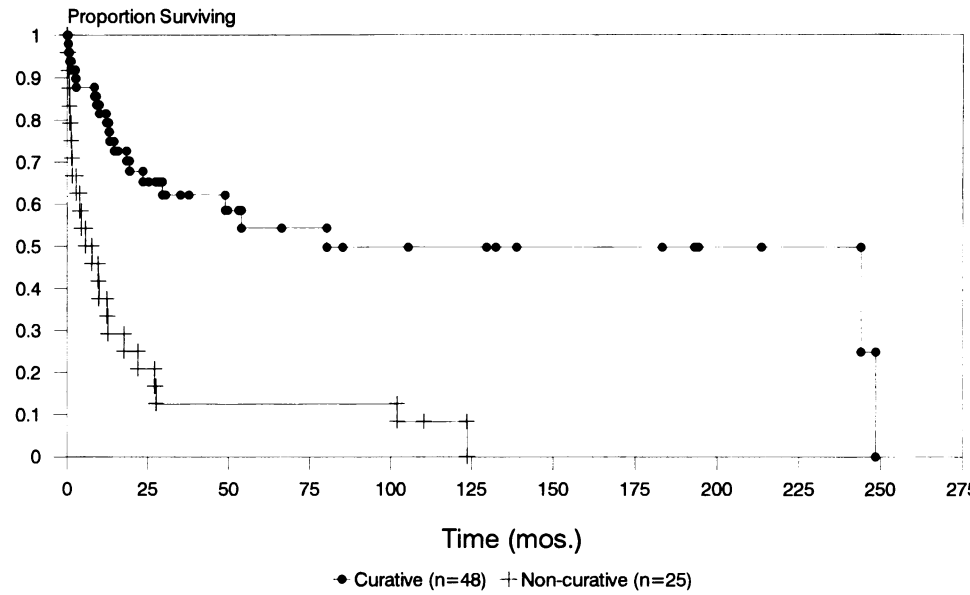

Figure 1. Survival curve showing improved survival for patients who are able to undergo curative resection of their small bowel primary tumor compared to those who can not.

patients having complete removal of their tumor surviving a median of 15 months and those having residual disease living a median of 12 months (p = 0.01). The use of adjuvant chemotherapy in 5 of the 18 patients appeared to have no impact on overall survival. Of the 12 curative resections, 4 eventually recurred with a median time to recurrence of 14 months.

Sarcoma

Sarcomas were found in eight patients, most commonly in the jejunum. Half of the patients presented with GI bleeding, whereas two patients presented with pain and one each with fever and an acute abdomen. There was no radiologic test that was diagnostic of sarcoma. More than half of the sarcomas presented with stage IV disease.

Surgical resection for cure was possible in four of eight patients. For those patients who had a curative resection, there was a dramatic improvement in survival compared to those patients who did not, but this failed to reach significance (66 *vs.* 9 months, p = not significant). All four curative resections recurred, and two patients are alive with evidence of disease.

Postoperative chemotherapy was given to 11 patients

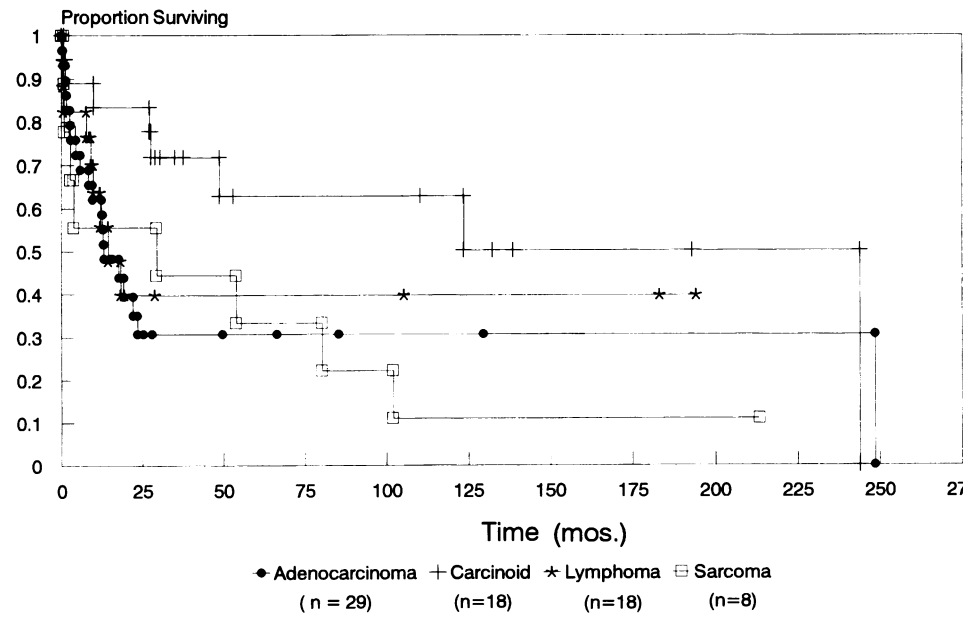

Figure 2. Survival curves for small bowel tumors by histologic type.

in the adenocarcinoma group, 6 patients in the carcinoid group, 5 patients in the lymphoma group, and 2 patients in the sarcoma group. The retrospective nature of this study precludes one from determining why certain patients received chemotherapy and others did not. With this in mind, there appears to be no value in using postoperative chemotherapy in any group of patients.

DISCUSSION

The small bowel accounts for less than 3% of GI malignant tumors despite comprising more than 70% of the length and 90% of the surface area of the GI tract. A number of explanations have been proposed to account for this discrepancy. Reasons include the liquid nature of the intestinal contents, which may be less irritating to the mucosa, the rapid transit time in the small bowel that reduces the exposure to carcinogens, a decreased bacterial population to produce carcinogens, the increased lymphoid tissue, an alkaline pH, and the presence of the enzyme benzyprene hydroxylase, which helps to detoxify potential carcinogens. The explanation for the infrequent finding of small bowel primary tumors is most likely multifactorial and encompasses all of the above theories.

The distribution of small bowel tumors varies between studies but was similar to the findings in this study with 25% of the tumors in the duodenum, 37% in the jejunum, and 38% in the ileum.[4] There is less variability in numbers when the location and the histology are compared. The most common location of adenocarcinomas is in the duodenum and proximal jejunum, carcinoids in the ileum, and lymphoma and sarcomas in the jejunum. The six adenocarcinomas found in the ileum all were associated with Crohn's disease, which has been reported by others.[5] Overall, there is a slight male predominance for the development of small bowel malignant tumors.[1,6,7]

Malignant tumors of the small bowel present most commonly with symptoms. The most common symptom in our study and in the literature is pain followed by GI bleeding, weight loss, nausea, and vomiting.[1,2,4,6,7] The nonspecific nature of the reported symptoms usually leads to a delay in presentation and diagnostic workup.[1,2,4,6–8] Plain abdominal films rarely are useful, and the diagnostic evaluation is driven by the presenting signs and symptoms. Proximal tumors can be identified by UGI/SBFT, and this was the most common method used in our series. Small bowel enteroclysis is a useful test for evaluating the small bowel distal to the ligament of Trietz. It has the advantages of not using barium in patients who may be obstructed partially, it can be performed in less than an hour, and the test is more sensitive in detecting mucosal lesions than is UGI/SBFT.[9] No patients in our study had enteroclysis most likely because of the nonspecific presentation of their small bowel tumors.

This series extends over 20 years, and CT and flexible EGD were not used routinely until the early 1980s and 1970s, respectively. In this day and age, it is almost impossible for a patient to present to a surgical office for the evaluation of pain or any other abdominal symptom for that matter without a CT scan. Despite the large number of tests ordered for the evaluation of these symptoms, the preoperative diagnosis was made in only 14 patients. Almost half of these were adenocarcinomas, which were diagnosed by EGD. Upper endoscopy is useful in the diagnosis of small bowel tumors that are located in the duodenum or proximal jejunum. Push enteroscopy has not been used routinely to evaluate lesions in the small bowel because this test takes up to 8 hours to perform, it may not visualize the entire small bowel, and only 50% to 70% of the mucosa generally is seen.[10]

The mean duration of symptoms for patients with small bowel tumors is 3 to 12 months, and this often is given as the reason for the late presentation of these tumors.[1,4,11] Almost two thirds of our patients presented with metastatic disease (stage III or stage IV), but it was difficult to ascertain the duration of the symptoms in our retrospective review. The prognosis for patients may be related to late presentation but also may be related to the biology and aggressiveness of this type of tumor. A poor prognosis has been associated with a long duration of symptoms, but if survival was calculated from the time of symptoms, the difference may not be appreciated.[2,6] Therefore, the late stage at presentation for patients with small bowel tumors may be more of a reflection of the disease than a delay in diagnosis.

Adenocarcinomas are the most common small bowel tumor, usually present with pain, bleeding, or nausea and vomiting, and are found most commonly in the duodenum.[1,2,4,6,12,13] The diagnostic test of choice for proximal tumors is the UGI/SBFT, which may show mucosal irregularities, ulceration, or anular constricting lesions. Upper endoscopy subsequently is performed to confirm the x-ray findings and to obtain a tissue diagnosis. Computed tomography currently is indicated to stage the patient by evaluating the local extension of the tumor and to look for metastatic disease.[14] Surgical resection is the treatment option for patients with adenocarcinoma. Lesions located in the proximal duodenum usually require pancreaticoduodenectomy but may be removed with a local resection. Lesions located more distally in the duodenum, in the jejunum, or in the ileum should be resected as wedge resections, including the mesentery. Two thirds of the adenocarcinomas in our study underwent curative resection (no gross disease), and this is comparable to other series.[1,13,15] The correct operation for duodenal lesions has been debated. Some authors have shown no survival

advantage for pancreaticoduodenectomy compared to local excision, whereas others have found a significant difference in survival.[1,13,15] Although these studies were not randomized, the results most likely reflect the late stage at presentation combined with physician preference at the time of surgery. Regardless of the type of surgery, patients who have a curative resection for adenocarcinoma of the duodenum live longer than those who are unable to undergo curative resection, and our data support this.[1,2,6,11,12] Therefore, the appropriate operation for patients with adenocarcinoma of the small bowel is complete extirpation of the tumor.

Carcinoids are the most common tumor of the distal small intestine and almost all occur within the last 2 ft of the ileum.[1,2,7,8] The vague symptoms associated with carcinoids lead to the use of a myriad of diagnostic tests, which seldom are helpful.[8] Unless the patients present with the carcinoid syndrome, the preoperative diagnosis seldom is made.[8] Computed tomography is useful for patients who present with the carcinoid syndrome to evaluate the liver for metastatic disease and to plan management for these patients.[14]

The risk of lymph node metastases for carcinoid tumors increases with the size of the tumor, and nodes are found in more than half of the patients with tumors larger than 2 cm.[1,8] Thompson et al.[8] found lymph node metastases in 18% of patients with tumors less than 1 cm in size. The optimal management of carcinoid tumors is a wedge resection of the primary tumor, including the small bowel mesentery. At the time of surgery, one must look for other intestinal carcinoids because these tumors can be multiple in up to 25% of cases.[8] Carcinoid tumors have the best prognosis of all small bowel tumors whether the disease is localized or metastatic. Curative resection of localized disease results in close to 100% long-term survival.[1,8] A survival benefit was noted for patients who had a curative resection in our study that included resection of metastatic disease. For metastatic disease in the abdomen or liver, surgical resection is advocated because survival data show an improved survival for surgical resection of metastatic disease.[1,4,8]

Lymphomas are found most commonly in the jejunum and ileum.[1,2,4,6,7] The median age at presentation is in the sixth decade, and the GI tract is the most common extranodal location for non-Hodgkin's lymphoma.[16] Lymphoma can be associated with celiac sprue, parasitic infection, or patients who are immunocompromised.[16–18] The presenting symptoms are nonspecific but may include systemic manifestations of fever and night sweats.[4] The diagnosis rarely is made before surgery, but the GI series may show coarsened, thickened mucosal folds or an intramural lesion with an intact mucosa.

At the time of surgery, lymphomas should be resected completely with a wedge of mesentery.[4,19] A comparison of series in the literature is difficult because of the multiple systems used for histologic staging. Small bowel lymphomas usually present late, but curative resection can be performed in most patients.[4,19] The prognosis is dependent on complete resection of the tumor, and this is the only small bowel tumor where adjuvant therapy appears to play a role.[20,21] Adjuvant therapy is recommended for patients with positive nodes or margins, and a survival advantage is seen for patients treated with postoperative chemotherapy or radiation therapy or both.

Sarcomas of the small bowel are the fourth most common tumor, and they may arise from the intestinal or vascular smooth muscle. There were only eight sarcomas in our series, and the most common site was the jejunum, with one half of the tumors arising there. These lesions usually present with some manifestation of GI hemorrhage, as in this study, because it is common for these tumors to ulcerate the mucosa.[4,22–24] The diagnosis rarely is made before surgery, but a contrast study may show an extraluminal mass with a mucosal defect.[4,22] Sarcomas spread by direct extension into adjacent organs and by the hematogenous route to the liver, lungs, and bone.

The optimal treatment is surgical resection and should include an *en bloc* resection if adjacent structures are involved.[4,22–24] A wide local excision is performed with lymphadenectomy, but sarcomas rarely spread by the lymphatic route.[22] Histologic criteria, number of mitoses per high power field, differentiate benign from malignant lesions. Curative resection predicts for long-term survival, and there is no role for adjuvant therapy.[22–24] Five-year survivals range from 28% to 48%.[4,22–24]

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