

Clinical Features of and Chemotherapy for Cancer of the Small Intestine

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Abstract. *Background:* Cancer of the small intestine is a rare disease, and its clinical features have not been clearly elucidated. Techniques such as double balloon endoscopy and capsule endoscopy allow the preoperative diagnosis of cancer of the small intestine, but this cancer is often detected at an advanced state and in many cases postoperative chemotherapy is required. This study evaluated the pre- and postoperative clinical course of cancer of the small intestine and the effectiveness of chemotherapy. *Patients and Methods:* Patients who underwent surgery for cancer of the small intestine in this Department from July 1985 to December 2008 were included in this study. Duodenal cancer has vastly different origins, methods of diagnosis, and surgical procedures, so this form of cancer was excluded. There were 8 cases of jejunal or ileal cancer treated during the study period. The pre- and postoperative course of these cases was reviewed, as well as the effectiveness of chemotherapy in cases of recurrence. *Results:* The male:female ratio of the 8 patients was 6:2, the mean age at surgery was 59.7 ± 15.9 (35-76) years, and the mean postoperative follow-up was 41.1 ± 48.0 (7-152) months. Six patients underwent a partial resection of the small intestine, and a right hemicolectomy, and a bypass were performed in one case each. The tumor type according to Borrmann's classification indicated that 5 tumors were type 2, 2 were type 3, and 1 was type 5; the mean tumor size was 6.3 ± 5.3 (2.5-18.0) cm. TNM staging indicated that 3 tumors were stage II, 1 was stage III, and 4 were stage IV. Six patients underwent postoperative chemotherapy. One patient underwent adjuvant chemotherapy of, and 5 patients with recurring or advanced

cancer underwent therapeutic chemotherapy of. The course of chemotherapy for the 5 patients with recurring or advanced cancer resulted in 4 patients with progressive disease (PD) and 1 with stable disease (SD). Three out of the four patients with PD died. *Conclusion:* The basic treatment for cancer of the small intestine is surgical resection. Palliative surgery and chemotherapy are considered in cases where resection is not possible or the cancer recurs. Nevertheless, there is no established regimen for such chemotherapy. Cancer of the small intestine is currently being treated with chemotherapy based on the treatment strategies for colon cancer, but there are few reports of its success. Chemotherapy was unsuccessful in treating any of the patients with recurring or advanced cancer reviewed in this report. The diagnosis must therefore be improved and postoperative chemotherapy will be needed to treat cancer of the small intestine given its increasing incidence, and therefore physicians are working as quickly as possible to establish an optimal treatment regimen. Compiling and studying such cases are crucial to accomplishing that goal.

Cancer of the small intestine is a rare disease with few specific symptoms. There are no simple tests to screen for the disease, so its early detection is difficult and it is consequently often detected in an advanced state. The basic treatment is surgical resection, but chemotherapy is considered in cases where a resection is not possible or the cancer recurs. However, there is no established regimen for this chemotherapy. Cancer of the small intestine is currently being treated with chemotherapy in line with treatment strategies for colon cancer, but there are few reports of its success. This study examined the pre- and postoperative course of cancer of the small intestine and ascertained the course of chemotherapy in cases of recurrence.

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Patients and Methods

The small intestine consists of the duodenum, jejunum, and ileum and runs from the pylorus to the ileocecal valve. Duodenal cancer

Table I. Breakdown of gastrointestinal cancer by year (of patients seen by this Department 7/1985-12/2008).

Site of cancer	1985-89	1990-94	1995-99	2000-04	2005-08	Total	(%)
Esophagus	24	57	79	46	35	241	(6.0)
Stomach	238	456	460	440	325	1919	(47.8)
Duodenum	1	2	4	1	3	11	(0.3)
Small intestine	0	0	1	0	7	8	(0.2)
Large intestine	139	381	408	462	446	1836	(45.7)
						4015	

includes cancer that originates from the pancreas and biliary tract and involves vastly different methods of diagnosis and surgical procedures, so it is often classified separately. Therefore, this study excluded duodenal cancer and instead examined jejunal and ileal cancer. A breakdown of 4,015 cases of gastrointestinal cancer treated by surgery in this Department from July 1985 to December 2008 indicated that 8 (0.2%) were cases of cancer of the small intestine (Table I). These cases were the subject of the current study.

Results

The tumor origin was in the jejunum in 6 patients and in the ileum in 2. The male: female ratio of patients was 6:2, and mean age at surgery was 59.7±15.9 (35-76) years. The initial symptoms were principally signs of bowel obstruction such as abdominal pain and nausea, but one patient was found to have anemia. The shortest period from the initial symptoms to surgery was 1 month and the longest was 1 year, with a mean of 4.9 months (Table II). Cancer of the small intestine was diagnosed by fluoroscopy of the small intestine, enteroscopy, or biopsy. The details from Case 2 in Table II are as follows. A barium examination of the small bowel first revealed displacement in the ileocecal region, and the location of the tumor was confirmed. Double balloon endoscopy revealed a tumor lesion along the total circumference of the intestine running 410 cm distally from the ligament of Treitz, and subsequent surgical findings indicated that it was located 20 cm from the ileocecal valve (Figure 1). A biopsy at that time led to a diagnosis of a well-differentiated adenocarcinoma, and surgery was performed. Similar steps resulted in a definitive preoperative diagnosis of cancer of the small intestine in 7 out of 8 patients.

Preoperative computed tomography (CT) revealed a massive intra-abdominal tumor in Case 6 in Table II (Figure 2). Bowel obstruction was extensive, hence it was not possible to perform an endoscopy of the small intestine nor a biopsy preoperatively. Malignant lymphoma was suspected, and surgery was begun. A rapid perioperative pathological diagnosis led to a diagnosis of cancer of the small intestine.

Six patients underwent a partial resection of the small intestine and one patient each underwent a right hemicolectomy and a bypass (Table III). Three out of the

Table II. Initial symptoms.

Case	Gender	Age (years)	Initial symptoms	Time from initial symptoms to surgery (months)
1	M	71	Anemia/abdominal pain/nausea	12
2	M	74	Abdominal pain/nausea (repetitively)	3
3	M	37	Abdominal pain/nausea	6
4	F	35	Nausea/vomitting	4
5	M	63	Epigastralgia/nausea	1
6	M	59	Abdominal pain/palpable mass	7
7	F	75	Epigastralgia/nausea	4
8	M	67	Abdominal fullness	2

F: female; M: male.

seven patients who underwent a partial resection of the small intestine or a right hemicolectomy were found to have peritoneal dissemination and underwent non-curative surgery. Borrmann’s classification indicated that 5 were type 2 tumors, 2 were type 3, and 1 was a type 5. Types 2 and 3 were prevalent, which is also seen in colon cancer. The mean tumor size was 6.3 (2.5-18.0) cm. The histology revealed that 6 patients had tumors ranging from well to moderately differentiated adenocarcinoma and 2 had poorly differentiated adenocarcinoma; the 2 with poorly differentiated adenocarcinoma also had mucinous carcinoma or signet-ring cell carcinoma. Cancer was not detected in its early state, and the TNM classification was stage II for 3 patients, stage III for 1, and stage IV for 4 (Table IV). The mean postoperative follow-up was 41.1±48.0 months (7-152).

Six patients underwent postoperative chemotherapy. One was given chemotherapy prophylactically, one was given chemotherapy therapeutically since the patient did not undergo a resection, and four were given chemotherapy therapeutically to treat recurrence or metastasis. S-1 (tegafur, gimeracil, oteracil) and UFT (tegafur, uracil) were used for prophylactic chemotherapy, and recurrence was not noted 10 months postoperatively. Therapeutic chemotherapy was FOLFOX

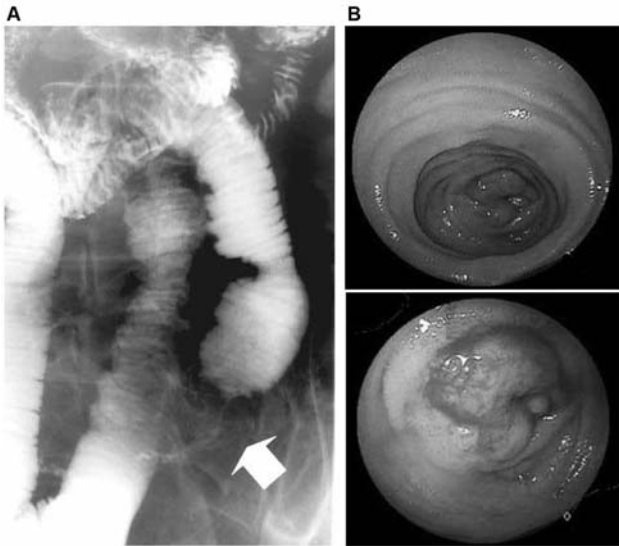


Figure 1. A: Barium examination of the small bowel revealing stenosis in the terminal ileum. B: Double balloon endoscopy revealing a tumor lesion spanning the total circumference of the intestine 410 cm from the ligament of Treitz.

(oxaliplatin/leucovorin/5-FU) therapy in 3 cases, IRIS (S-1/irinotecan) therapy in 3, BV (bevacizumab) therapy in 2, and S-1 therapy in 1 (some patients received multiple regimen). The results were all poor: 1 out of 5 patients had stable disease (SD) and 4 had progressive disease (PD); and 3 out of the latter 4 patients died (Table V).

Discussion

The small intestine is the longest portion of the gastrointestinal tract and is an organ that seldom receives attention, despite its functionally crucial role. Cancer of the small intestine can readily be overlooked by routine gastrointestinal tests because of the anatomical features of the small intestine and is an extremely rare disease. Reports indicate that it accounts for about 0.1-3.0% of all carcinomas of the gastrointestinal tract (1-4). Peak onset is in the fifth to sixth decade, the disease is somewhat more prevalent in men, and it is more prevalent in the jejunum than in the ileum (5, 6). In addition, a report that tallied cases of cancer of the small intestine in Japan reported that about 70% of jejunal carcinomas develop within 49 cm of the ligament of Treitz and about 70% of ileal carcinomas develop within 49 cm of the ileocecal valve (7). Similarly, cancer had developed within 49 cm of the ligament of Treitz or the ileocecal valve in 6 out of 8 patients in the current study (Table III). However, the frequency with which cancer of the small intestine is detected and sites where it is detected may vary

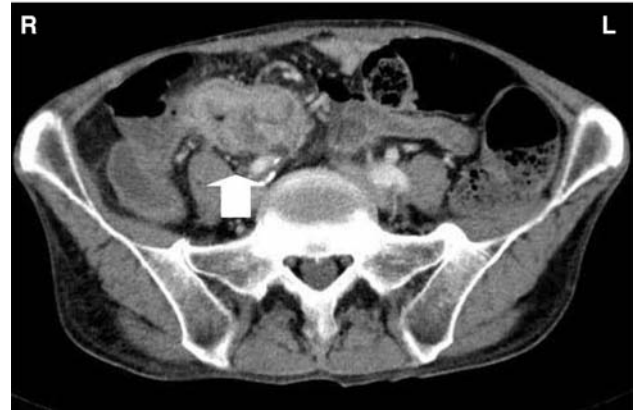


Figure 2. Computed tomography revealing a huge mass in the right lower abdomen.

Table III. Tumor site and operative procedure.

Case	Site	Distance (cm)*	Operative procedure
1	Jejunum	20	Partial resection of jejunum
2	Ileum	20	Partial resection of ileum
3	Jejunum	160	Partial resection of jejunum
4	Jejunum	15	Partial resection of jejunum
5	Jejunum	30	Partial resection of jejunum
6	Ileum	10	Right hemicolectomy
7	Jejunum	25	Partial resection of jejunum
8	Jejunum	180	Gastrojejunostomy

*For jejunal cancer, the distance from the ligament of Treitz, for ileal cancer, the distance from the ileocecal valve.

widely from those previously reported as a result of the prevalence of new methods of examination such as double balloon endoscopy and capsule endoscopy (8, 9).

Cancer of the small intestine has few symptoms, so it is often discovered in an advanced state. Therefore, the tumor is often large in size and spans the total circumference of the intestine, and stenosis and serosal infiltration are often noted (5, 6, 10). Bowel obstruction resulting from tumor growth, occult blood in the stool, and anemia are often noted as initial symptoms (11). Similarly, the current study found that the initial symptoms were primarily signs of bowel obstruction such as abdominal pain and nausea. There were also cases in which patients repeatedly had mild symptoms of bowel obstruction and symptoms of anemia. Cancer of the small intestine must be suspected when bowel obstruction and symptoms of anemia are noted but their cause cannot be determined by routine gastrointestinal tests. Cancer of the small intestine may involve the existence of an adenoma–carcinoma sequence

Table IV. Cancer progression.

Case	Tumor size (cm)	Microscopic type*	TNM staging				Histologic type
			T	N	M	Stage	
1	3.0	2	3	0	0	II	Well
2	2.5	2	3	0	0	II	Well to moderately differentiated
3	4.0	2	3	0	1	IV	Well to moderately differentiated
4	5.0	2	3	0	0	II	Well to moderately differentiated
5	3.5	3	3	1	1	IV	Well to moderately differentiated
6	18.0	5	4	1	1	IV	Poorly to well differentiated with mucinous components
7	4.5	2	3	1	0	III	Poorly differentiated with signet-ring
8	10.0	3	4	1	1	IV	Moderately differentiated

*Borrmann's classification.

Table V. Postoperative course.

Case	Site of metastasis	Chemotherapy	Outcome of chemotherapy	Follow-up time (months)	Current status
1	–	–		152	Alive
2	–	–		46	Alive
3	Peritoneum	FOLFOX/IRIS/ BV	PD	32	Dead
4	Left ovary	FOLFOX/IRIS/ BV	PD	27	Alive
5	Peritoneum	S-1	PD	7	Dead
6	Peritoneum	IRIS	SD	17	Alive
7*	–	S-1→UFT		10	Alive
8	Peritoneum, Para-aortic lymph node	FOLFOX	PD	11	Dead

*Adjuvant therapy case; PD: progressive disease; SD: stable disease; FOLFOX: oxaliplatin/leucovorin/5-FU; IRIS: S-1/irinotecan; BV: bevacizumab; UFT: tegafur, uracil.

(3, 12-14). This malignancy progresses to local infiltration and leads to lymph node metastasis, hematogenous metastasis, and peritoneal dissemination. It presents with a histology similar to that of colon cancer, although it includes a higher percentage of poorly differentiated adenocarcinomas than does colon cancer (10). Therefore, cancer of the small intestine is currently treated using strategies established for colon cancer, but it has a poorer prognosis and a 5-year survival rate of 6-48% (1, 15, 16). Chemotherapy is considered when a resection is deemed not to be possible. Nevertheless, there are no established regimens for such chemotherapy. Chemotherapy is chosen in line with treatment strategies for colon cancer (17, 18), but there are few reports of cases where it has been effective (19). Similarly, chemotherapy was unsuccessful in treating patients with recurring or advanced cancer in the current study.

The examinations that are most helpful in diagnosing cancer of the small intestine are a barium examination of the small bowel and enteroscopy. A barium examination of the small bowel and endoscopy led to a preoperative diagnosis of cancer of the small intestine in 7 out of the 8 cases in this study. Other examinations of the small intestine include capsule endoscopy and multidetector-row computed tomography (20, 21). However, these examinations are not typically applied, and screening tests have yet to be established. The crucial steps to improving the prognosis for cancer of the small intestine are active screening of small intestine lesions using a variety of methods and diagnosis of the cancer in its early stages (22).

Cancer of the small intestine has a poor prognosis in comparison to other types of cancer of the gastrointestinal tract, such as those of the stomach and large intestine. Advances in diagnosis such as endoscopy of the small

intestine are crucial, as is the compiling of cases to establish effective surgical procedures and chemotherapy regimens following diagnosis.

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