Adenocarcinoma and Lymphoma of the Small Intestine

Distribution and Etiologic Associations

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Malignant small-bowel tumors in 171 patients over 64 years included 68 with adenocarcinomas, 41 with primary lymphomas, 50 with carcinoids, and 12 with sarcomas. The distribution of the carcinomas showed ~80% preponderance in the duodenum and proximal jejunum. A similar distribution in the upper small bowel in small-bowel carcinomas induced in Fischer and Sprague–Dawley rats by azoxymethane (90–160 mg/kg) suggests defense mechanisms within ileal mucosa. The clinical series from 1958 to 1976 included two Crohn's carcinomas (jejunum, defunctioned ileum), two jejunal cancers (lymphoma, carcinoma) associated with celiac disease, two duodenal carcinomas arising in villous adenomas, and one jejunal lymphoma following exposure to irradiation. Multiple primary malignancies were found in 20 to 25% of enteric cancers. Hemorrhage was more common with carcinoma than lymphoma, but lymphomas predominated considering perforation or a palpable mass. Both carcinoma and lymphoma had 75 to 80% resectability rates and 14 to 15% five-year postoperative survival rates. The prognosis was least poor for carcinoma of the jejunum, one third of patients with "curative" resections surviving five years.

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SIMILAR RATES of cell renewal in the small intestine and large intestine[1] should make these organs equally sensitive to carcinogens, which are potentiated in proportion to the degree of proliferative activity.[2] In fact, adenocarcinomas of the small bowel are 100 to 160 times less prevalent than either colorectal cancers or cancers of the stomach, another viscus with a rapid turnover of its epithelial lining.[3,4] A mere 1 to 2% of all primary gastrointestinal malignancies arise in the small bowel,[5–7] which composes nearly 90% of the luminal surface between cardia and anus.[8] Adenocarcinoma is the most common type of small-bowel cancer, constituting 32 to 54% of all malignant enteric tumors or 41 to 70% if carcinoids are excluded[7,9–14]; lymphoma is the next most frequent, then leiomyosarcoma.

The infrequency of correct preoperative diagnosis and the advanced stage of the neoplasm when ultimately discovered[15,16] were underlined in the account of small-bowel tumors from this hospital in 1959.[17] The authors now assess the cumulative experience of 121 patients with carcinoma, lymphoma, or sarcoma of the small bowel, with particular emphasis on factors that could explain the differential susceptibility of adjacent portions of the gut.

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Materials and Methods

In the 64 years from 1913 through 1976, 121 patients with nonendocrine cancers of the small intestine were seen here. Those with carcinoids or carcinomas invading the duodenum from without have been reviewed elsewhere.[18,19] Through 1957, 82 malignancies comprised 38 adenocarcinomas, 33 lymphomas, ten leiomyosarcomas, and one fibrosarcoma.[17] Discovery of 90% of these tumors was made (or confirmed) at laparotomy. Of an additional 44 patients seen through 1976 and followed for five years or until death, five with periampullary cancers have been excluded because of residual uncertainty about the tissue of origin. Data from the entire series have been used to compare the distribution, and major presenting features of carcinoma and lymphoma. Details of the clinical, pathologic, and radiologic diagnosis of each group and of their etiologic associations are confined to the period 1958 to 1976.

Results

Population

Of 39 new cases with unequivocal primary cancer, 30 were adenocarcinomas, eight were lymphomas and one was a leiomyosarcoma. The mean (and median) age of these patients with carcinoma was 61 years (range 35–

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81), and with lymphoma it was 69 years (range 56–83) ($p = 0.10$, 2-tailed Mann–Whitney U test). The sex distribution was about equal in each group. All patients were symptomatic, but in three cases the definitive diagnosis was not obtained before death. The median duration of symptoms was four months (range one week–three years) for adenocarcinoma and three months (range three days–six months) for lymphoma ($p = 0.19$, Mann–Whitney U test).

Distribution

The duodenum is traditionally defined as the first 25 cm of small intestine. Suspended freely on its mesentery, the remaining small bowel may be only 3.0–3.5 m long, but a length of 5.0 m has been accepted in view of other much larger estimates. The proximal 40% is designated jejunum and the distal 60% ileum, measured from the ligament of Treitz as the fixed point.

The distribution of the different histologic types of small-bowel cancer is shown in Figure 1, using for comparison previous data for benign tumors and carcinoids from this hospital.[17,18] Lymphoma and sarcoma appeared randomly distributed; in each case the number of tumors in the duodenum, jejunum, and ileum reflected the length of that segment of bowel. Only 10% of carcinoids arose outside the ileum. By contrast, benign tumors were evenly distributed between the three intestinal segments and were therefore most frequent per unit length of duodenum. The proximal concentration was even more pronounced in adenocarcinoma (Fig. 2). Of 68 carcinomas, 29 (42.5%) were duodenal, 31 (45.5%) were jejunal, and eight (12%) were ileal. One ileal carcinoma arose at the site of a Meckel's diverticulum, and another coexisted with synchronous carcinomas of the jejunum and ascending colon.

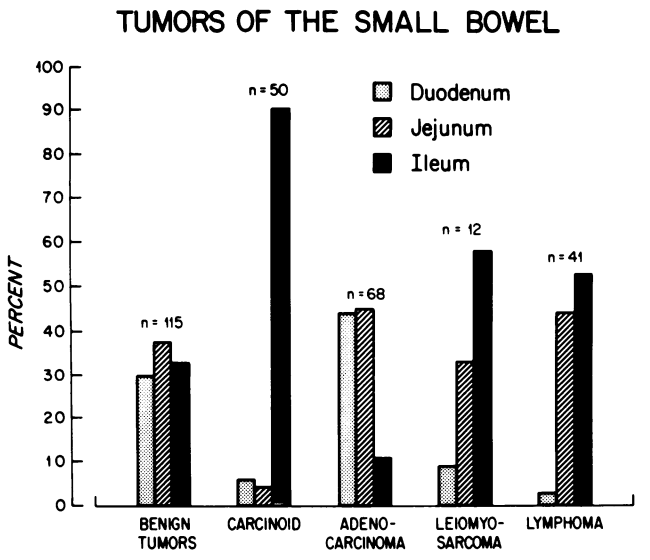

FIG. 1. Distribution of neoplasms in small bowel by type.

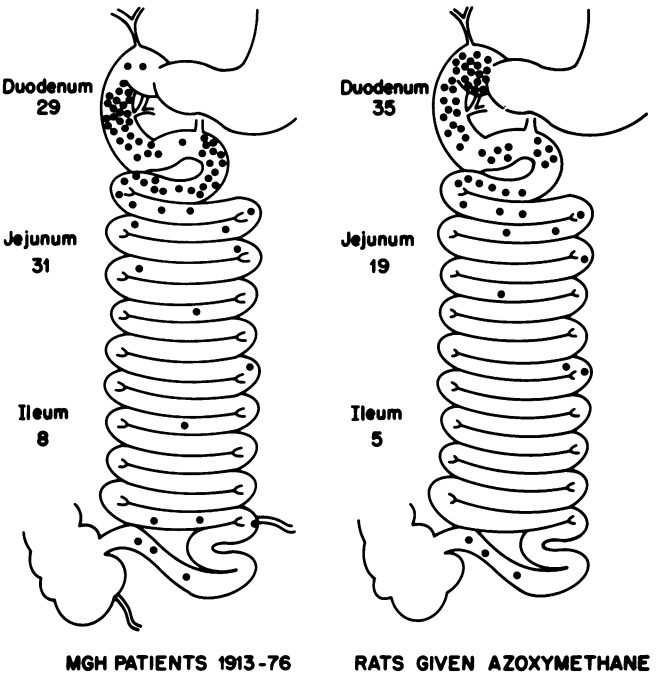

FIG. 2. Distribution of human neoplasms in small bowel by location as compared with those in rats given azoxymethane.

Symptoms and Signs

Epigastric pain and vomiting suggestive of gastric outlet obstruction were present in ten of 17 patients with duodenal carcinoma seen between 1958 and 1976 (Table 1). Three of these were thought to have duodenal ulceration with pyloric stenosis, and one underwent subtotal gastrectomy before the nature of the duodenal mass was appreciated. Gastrointestinal hemorrhage of some degree was common. In one cancer of the fourth part of the duodenum, the site of bleeding was particularly elusive during three years of repeated investigation. Jaundice was painless and progressive in three and mild or intermittent in another three.

Frank or occult bleeding occurred in seven of ten cases of jejunal carcinoma. Five patients had symptoms of subacute intestinal obstruction, including one in whom the tumor perforated. Peritonitis was the presenting feature of two cases of ileal carcinoma; the third patient with pre-existing Crohn's disease developed subacute obstruction.

Four lymphomas arose in the jejunum, three in the ileum and one in the duodenum, causing jaundice. Abdominal cramps and weight loss were the most common symptoms, but two patients presented with peritonitis following perforation.

TABLE 1. *Symptoms and Signs of Patients with Carcinoma and Lymphoma of the Small Bowel (1958–76)*

	Carcinoma of duodenum	Carcinoma of jejunum	Carcinoma of ileum	Lymphoma (all sites)
Number	17	10	3	8
Cramps and vomiting	10	5	1	7
Bleeding — overt	3	2	0	7
Bleeding — occult	7	5	0	1
Jaundice	6	0	0	1
Weight loss >5kg	10	9	3	5

The clinical features of adenocarcinoma and lymphoma during the entire 64-year experience are summarized in Table 2. Obstruction (71%) and hemorrhage (68%) characterized symptomatic adenocarcinomas. Lymphomas carried a similar incidence of obstructive symptoms (65%), but bleeding was a little less common (49%). Lymphomas were much more likely than carcinomas to present with perforation (27% *vs.* 5%) or a palpable mass (43% *vs.* 21%). Altogether, two patients with jejunal lymphoma and two with jejunal carcinoma had an antecedent history of a sprue-like syndrome.

Associated Diseases

There were two cases of adenocarcinoma arising at the site of long-standing Crohn's enteritis, one in the mid-jejunum and one in a segment of ileum bypassed six years earlier (Table 3). Unlike the jejunal cancer, the ileal lesion was diffuse and had undergone metastasis to the adjacent lymph nodes. In each case there was a long delay (26 years and 27 years) between diagnosis of the original condition and the subsequent cancer.

Two patients developed jejunal cancer as a complication of celiac disease (nontropical sprue), with a latent interval of nine to ten years. One tumor was an adenocarcinoma; the other was a reticulum cell sarcoma, which perforated both initially and when it recurred. In each case the underlying condition had been treated by withdrawal of gluten from the diet and prolonged corticosteroid therapy.

Two adenocarcinomas of the third part of the duodenum arose unmistakably from a villous adenoma. Both patients appear to have been cured by partial pancreaticoduodenectomy. Prolonged irradiation may have contributed to the development of a reticulum cell sarcoma of the jejunum in a woman who had received a course of radiotherapy for chronic tonsillitis 18 years earlier and had subsequently worked in a department of diagnostic radiology.

One patient had three primary carcinomas of the intestinal tract, another had synchronous carcinomas of the jejunum and rectum, and two others developed metachronous carcinomas of the intestine (jejunum, ascending colon), which could have been metastatic. There was one case of several coincident lymphomas in the jejunum. One patient with a jejunal carcinoma and one with an ileal lymphoma subsequently developed primary carcinoma of the thyroid. One patient with a jejunal carcinoma probably had a carcinoma of the bladder.

Radiologic Diagnosis

Because of the period of this study, radiologic investigations were more extensively used than endoscopy, which would only have been helpful for duodenal carcinomas in any event. There was a 38% false-negative rate (6/16) with barium meal examinations in the diagnosis of duodenal carcinoma. Only in 44% of instances (7/16) was an unequivocal diagnosis made. On

TABLE 2. *Symptoms of Enteric Carcinomas and Lymphomas Seen Between 1913–1976*

	No.	Symptoms No.	Obstruction No.	Hemorrhage No.	Mass No.	Perforation No.	Icterus No.	Sprue No.	Ascites No.
Carcinoma									
Duodenum	29	27	18	17	2	—	6	—	—
Jejunum	31	28	22	21	9	1	—	2	—
Ileum	8	7	4	4	2	2	—	—	1
All carcinomas	68	62	44	42*	13†	3‡	6	2	1
Lymphoma	41	37	24	18	16	10	1	2	1
Total	109	99	68	60	29	13	7	4	2

Significance *vs.* lymphoma: * $p = 0.06$ (χ^2 test); † $p < 0.025$ (χ^2 test); ‡ $p < 0.005$ (Fisher's exact probability test).

TABLE 3. *Patients with Conditions Predisposing to Enteric Cancer (1958–76)*

Patient (No. and Sex)	Predisposing Disease				Cancer				
	Type	Site	Age at Diagnosis	Treatment	Type	Site	Age at Diagnosis	Resection	Outcome
1. F	Crohn's	jejunum + ileum	40	laparotomy	carcinoma	jejunum	67	+	alive 8 yr
2. M	Crohn's	ileum	21	ileocecal resection, jejunocolostomy	carcinoma	ileum (bypassed)	47	+	died 26 mo
3. M	celiac	jejunum	50	diet, steroids	carcinoma	jejunum	60	+	died 28 mo
4. M	celiac	jejunum	60	diet, steroids	lymphoma	jejunum (perforated)	69	+	died 12 mo
5. F	irradiation	—	—	(15-yr exposure)	lymphoma	jejunum (perforated)	68	+	died 12 mo
6. F	villous adenoma	duodenum	46	—	carcinoma	duodenum	46	+	alive 10 yrs
7. F	villous adenoma	duodenum	59	—	carcinoma	duodenum	59	+	alive 7 yrs

the other hand, the accuracy was 88% (8/9) in jejunal carcinoma. Emergency presentations in ileal carcinoma and lymphoma often precluded detailed radiologic study.

Pathology

The degree of histologic differentation of ten of 17 adenocarcinomas of the duodenum was good or moderate; five were anaplastic, and in two there was a mucinous (colloid) pattern with prominent signet-ring cells. In all but two cases, the carcinoma penetrated the full thickness of the bowel wall, and about half showed invasion of adjacent organs, notably the common bile duct and the pancreas. Lymph-node metastases were confirmed in eight patients; in one of these hepatic metastases were also present at the time of operation.

All ten jejunal adenocarcinomas transgressed the bowel wall, and four showed direct extension into the mesentery. Five poorly differentiated growths had already metastasized to mesenteric lymph nodes, one to the liver, and one to bone. Two ileal carcinomas were anaplastic, showing evidence of transcelomic spread; one was a mucinous adenocarcinoma. The third (Crohn's) carcinoma was moderately differentiated, but diffuse.

Six of eight lymphomas were classified as reticulum cell sarcoma. There was one plasmacytoma of the mid-ileum and one unidentified "malignant lymphoma" of the duodenum. Lymph-node secondaries were present at operation in at least three cases, and peritoneal deposits were also found in two of these.

Treatment

Three duodenal carcinomas were irresectable; in a fourth the diagnosis was only established at autopsy. The remaining 13 cancers were resected, one by local excision of a duodenal polyp, one by a limited removal of the descending duodenum and head of pancreas, and 11 by pancreaticoduodenectomy. All ten jejunal carcinomas were resected. In one patient with metastases to bone, partial gastrectomy was also carried out because of a large benign gastric ulcer. Resection was undertaken for two ileal carcinomas, the third patient dying of untreated intestinal obstruction.

Six of eight enteric lymphomas were resected; in one patient with multiple tumors, several segments of jejunum were removed, and in another the operation was clearly only palliative. In a solitary case of duodenal lymphoma, only a bypass was feasible.

Six patients with carcinoma and five with lymphoma were given radiotherapy. Six with carcinoma and one with lymphoma were treated with cytotoxic drugs.

Outcome

In 13 patients with duodenal carcinoma, the tumor appeared to have been completely excised. Five of these survived for three years (Table 4); three patients are alive and free of symptoms, four, seven, and ten years after operation. Five of eight patients undergoing curative resection for jejunal carcinoma lived for five years after operation (mean survival, 8.5 years). Two ileal carcinomas proved rapidly fatal, the third causing death at 26 months. The longest postoperative survival after resection for lymphoma was only 13 months.

Table 4 shows the fate of 61 patients with carcinoma of the small bowel and 36 patients with lymphoma who came to operation between 1913 and 1976. The crude five-year survival rates are almost identical (15% and 14%). After curative resection six of 18 patients with jejunal carcinoma and three of 18 with duodenal carcinoma survived five years and may be cured.

TABLE 4. *Outcome of Patients with Enteric Carcinoma and Lymphoma Coming to Operation Between 1913–76*

	Patients Operated No.	Curative Resection No.	Five-Year Survival No.	Five-Year Survival Rates: All Operations %	Five-Year Survival Rates: Curative Resections %
Duodenal carcinoma	26	18	3	12	17
Jejunal carcinoma	29	18	6	21	33
Ileal carcinoma	6	4	0	0	0
All carcinomas	61	40	9	15	22.5
Lymphoma	36	28	5	14	18
Total	97	68	14	14	21

Resection is classified as curative if it was macroscopically complete and the patient survived the operation.

Discussion

Distribution

The concentration of small-bowel carcinomas in the duodenum and proximal jejunum suggests either a uniquely high concentration of carcinogen in these areas or local lack of resistance to neoplasia; to the contrary, the paucity of tumors in the ileum suggests either small amounts of carcinogen or high resistance. Results of 1,050 case reports collected by Reiner in 1976 show the same kind of decreasing aboral gradient: 40% duodenal, 38% jejunal, and 22% ileal.[20] Recent reports show a similar pattern of distribution.[21,22] In a comparison of the distribution of small-bowel adenocarcinomas in patients treated here with that found in the studies of clinical carcinogenesis of the bowel, the congruence is remarkable (Fig. 2). Closely resembling human cancers in all aspects these experimental carcinomas were produced in Sprague–Dawley or Fischer rats by weekly subcutaneous injections of azoxymethane at a total dose ranging from 90 to 160 mg/kg.[23–25]

Although azoxymethane is excreted into the bile and is directly carcinogenic to the luminal surface of the intestine, it is also effective when carried by the bloodstream.[2] Internal diversion of the bile before exposure of the animal to azoxymethane does little to reduce yields of duodenal cancers.[23] On these grounds alone, biliary excretion of a carcinogen can scarcely be incriminated as the sole reason for the density of duodenal carcinomas in man and the rat.

The susceptibility of the mucosal surface must be considered. The segment of the gastrointestinal tract that represents its greatest surface area, the ileum, has the lowest incidence of carcinoma. Even a hyperplastic stimulus for the ileum, like proximal small-bowel resection or distal diversion of bile and pancreatic juice, cannot overcome its resistance to azoxymethane-induced carcinogenesis.[2] The greater fluidity of small-bowel contents, their relative sterility, and their rapidity of transit have been imputed to protect against cancer by diluting luminal carcinogens, limiting bacterial production of cocarcinogens and reducing mucosal exposure.[15] Yet paradoxically all these features apply more to the upper small bowel, where carcinoma is comparatively common, than to the ileum, where it is extremely rare. Neither are mucosal enzymes likely to prevent small-bowel carcinoma by providing a metabolic barrier to ingested carcinogens or those elaborated from endogenous precursors, such as bile acids. Enteric concentratons of the enzyme benzpyrene hydroxylase are ten times those encountered in the stomach or colon, but levels in the proximal small bowel exceed those in the distal bowel.[26]

Perhaps the resistance of ileum to carcinoma may lie in its extraordinarily rich content of lymphoid tissue, characterized by a substantial output of IgA.[27] The hypothesis that intensive immunosurveillance prevents the growth of a malignant clone of enterocytes is supported by the occurrence of small-bowel cancers in immunosuppressed or otherwise anergic patients.[27,28] Moreover, the greater susceptibility of the stomach than the ileum to experimentally-induced lymphoma is abolished by thymectomy or irradiation.[29]

Associated cancers occurred elsewhere in the intestine or at other sites in the body in 20 to 25% of patients with enteric carcinoma or lymphoma. This high incidence of multiple primary malignancies agrees with other series of small-bowel tumors,[3,6,9,30] but contrasts with a much lower incidence (3–6%) for other index cancers.[31] Both the occurrence of three separate intestinal primaries[10,30] and the association of small-bowel and large-bowel carcinoma[9,32] have previously been described. Since the small intestine is normally so resistant to malignant change, it might be anticipated that when its defenses are overcome, other cancers develop both inside and outside the gut.

Potentiating diseases

The two patients with associated Crohn's disease reported here add to the approximately 60 already described.[33,34] Because Crohn's carcinoma usually occurs in the ileum, the segment most often affected by gran-

ulomatous enteritis, the intense hyperplasia of injury could be proposed as a carcinogenic promoter. As in one of these two cases, however, 30 to 40% of the reported enteric cancers have actually arisen in loops of bowel that have been defunctioned and are presumably atrophic.[33–35] Both carcinoma and lymphoma may complicate granulomatous colitis[35,36] and may be preceded by epithelial dysplasia akin to the precancer seen in ulcerative colitis.[37] Crohn's-associated cancers of the small bowel are usually insidious and are followed by a mean survival time of about eight months.[34]

Primary malignant lymphoma of the jejunum is a documented complication of long-standing adult celiac disease,[38,39] that clearly occurred in one of the recent patients and probably in one of the earlier reports. Esophageal cancer may also be more common.[39] Occasionally adenocarcinoma of the duodenum or jejunum may develop in nontropical sprue, especially in those with onset in adulthood[13,38,40,41]; two of the cases show this association.

Villous adenomas of the small intestine have malignant foci in two thirds of cases[22,42]; fortunately, they are rare. In the two cases of the present report, a radical resection was apparently curative. There were no examples of the rare malignant transformation of Peutz–Jeghers hamartomatous polyps[43] nor of duodenal cancer associated with Gardner's syndrome.[44]

Clinical Features

As previously reported, carcinoma of the small intestine is a disease of those aged 50 to 70, affecting both sexes equally.[5,7,14,16] Lymphomas seem to have a shorter latent period before causing symptoms and thus are more frequently the cause of emergency admissions than carcinomas. Almost all malignant tumors are symptomatic, while benign tumors are often occult. Both carcinomas and lymphomas obstruct, but carcinomas tend more frequently to bleed and lymphomas to perforate. Obstruction is a feature of all enteric malignancies, mimicking benign pyloric disease or pancreatic cancer if located in the duodenum and other causes of chronic small-bowel obstruction if lower. Ileal cancer tends to be advanced when discovered. Intussusception is much more commonly associated with benign tumors and lymphomas than with cancer.

The sensitivity of fiberoptic duodenoscopy[45,46] should yield faster and more accurate diagnosis of duodenal cancer than the little-better-than-50% success of barium-contrast roentgenograms in these cases overall. But whether endoscopy will increase the rate of cure is another consideration. Despite a resectability rate of 75 to 80%, the prognosis for both carcinoma and lymphoma of the small bowel is poor, because half the patients have metastases at the time of operation. During the 64 years of this study, the crude five-year survival rate for both carcinoma and lymphoma was about 14%, only slightly better than that of gastric cancer. Nonetheless, survival rates of 25 to 28% are being reported,[13,21,47] especially for nonduodenal carcinoma and lymphoma. The authors are encouraged by the 50% survival rate for seven to 13 years of the ten patients with jejunal carcinoma in the last 19 years of this survey.

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