Primary Lymphoma of the Gastrointestinal Tract

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Primary gastrointestinal lymphoma represents approximately 1% of all gastrointestinal neoplasms. Gastric involvement is more common than small or large intestine and carries a better prognosis. Abdominal pain and weight loss may be the only manifestations and may be present for months or years before the diagnosis is made. Perforation and obstruction occur infrequently. Multiple tumors constitute 8% of cases. Although barium studies and endoscopy reveal the lesion in a high percentage of cases, exploratory celiotomy is not infrequently required for diagnosis. Only one-third of lymphomas are confined to the bowel at laparotomy. Histologically one-third are reticulum cell sarcomas and the remainder lymphosarcoma or lymphocytic lymphoma. Five year survival overall was 38%. Curative resections yielded a survival of 60% regardless of site while palliative resections offered only a 17% chance of cure. As expected, survival was inversely proportional to extent of nodal spread. Postoperative radiotherapy is recommended for residual disease.

WHEREAS GASTROINTESTINAL involvement by malignant lymphoma is found not infrequently in disseminated lymphoma, both Hodgkin's and non-Hodgkin's, primary tumors of the gastrointestinal tract are distinctly less common representing approximately 1% of alimentary tract neoplasms. To survey our experience a retrospective study of five New Orleans hospitals* from 1948 to 1979 was undertaken.

Materials and Methods

Our review yielded a total of 112 cases of primary gastrointestinal lymphoma. In accordance with the criteria proposed by Dawson et al.,[5] lesions were considered primary to the GI tract only if there were no palpable superficial nodes or roentgenographic evidence of mediastinal disease; the peripheral blood smear revealed no leukemic or lymphomatous abnormalities; and, if at laparotomy, all intra-abdominal lymphadenopathy corresponded to accepted lymphatic drainage routes such that the adenopathy could be considered to represent secondary spread from the tumor primary. Patients with hepatic or splenic involvement, except by extension of contiguous disease, were excluded from this study.

In accordance with the nomenclature before Rappaport by which most of these lesions were classified, the histologic diagnoses of lymphocytic lymphoma, giant follicular lymphoma, lymphosarcoma, reticulum cell sarcoma, and Hodgkin's disease were used. The presence or absence of nodulation was an inconsistently reported characteristic and therefore further subclassification into nodular or diffuse lesions was not possible.

Results

The 112 primary gastrointestinal lymphomas were composed of 67 (60%) gastric, 24 (22%) small intestine, and 18 (15%) colorectal tumors. In addition there were three lesions of the appendix (3%).

Patients ranged in age from four to 89 years with a mean of 56 years. Seventy-five per cent of the patients were over 50 years of age. Age did not affect the histologic distribution or GI tract site. There was a slight male predominance, 1.2:1 and a black–white ratio of 1.0:2.3.

As seen in Table 1, only 2.7% of these lymphomas were entirely asymptomatic and discovered on routine examination. Abdominal pain, weakness, and weight loss were the most common complaints of 70, 30 and 47% of patients respectively. Nausea and vomiting were frequent complaints of patients with gastric lymphoma but not of patients with lesions in the small bowel or colon. Gastrointestinal bleeding was encountered in 26 patients, 16 of whom had gastric, four of whom had small bowel, and six of whom had colorectal tumors. No patient related a history compatible with a malabsorption syndrome.

Presented at the Annual Meeting of the Southern Surgical Association, December 3–5, 1979, Hot Springs, Virginia.

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Submitted for publication: December 7, 1979.

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0003-4932/80/0500/0593 $00.80

TABLE 1. *Symptoms by Site*

	Overall (%)	Stomach (%)	Small Intestine (%)	Colorectum (%)
Abdominal pain	70	65	79	72
Weight loss	47	60	29	27
Weakness	30	37	16	16
Nausea–Vomiting	27	33	18	11
Bleeding	23	15	18	33
Fever	8	6	8	16
Constipation	8	6	16	5
Diarrhea	4	3	8	5

Physical examination was unremarkable in 27% of patients, In only 30% could a mass be palpated and there was usually some mild associated tenderness in the area. Hepatosplenomegaly was appreciated in only three patients and in these subsequent laparotomy did not confirm the expected organ involvement. Ascites was present in one patient and jaundice in another. Abdominal distension was more likely to be found in small bowel (25%) or colorectal (22%) lesions. Generalized abdominal tenderness with rebound necessitating emergent surgical exploration occurred in five patients with perforated lymphoma: one gastric, two small bowel, and two colonic tumors.

Preoperative laboratory evaluation was unremarkable except for mild anemia, the hematocrit being less than 35 in 40% of patients. White blood cell count and differential were normal except in those patients presenting with severe dehydration or peritonitis. Liver function tests were infrequently requested and were usually normal except for a low serum protein. Malabsorption studies were not done.

The most profitable roentgenologic examination was the UGI series which was abnormal in 55 of the 56 patients with gastric lymphoma in which it was performed. Four of six small intestinal tumors were demonstrated by an upper gastrointestinal study with small bowel follow through. Barium enema disclosed the tumor in ten of 12 patients so studied with colorectal lesions. Liver spleen scans were of no diagnostic value, being abnormal in 5 of 26 (20%) in whom this modality was used: all were subsequently shown to have normal livers at celiotomy. Gallium scans were abnormal in 4 of 9 patients so studied. Gastroscopy visualized the lymphoma in 23 of 25 patients with gastroduodenal lesions.

Eighty-seven per cent of the patients were explored with 55 (58%) of these undergoing resection for cure and 31 (32%) receiving a palliative procedure. The remainder underwent laparotomy with biopsy only. The diagnosis of lymphoma was made at autopsy in nine patients. The percentage of tumors amenable to curative resection was independent of site of origin, being 58, 50, and 49% in gastric, small bowel, and colorectal lesions respectively. Resection with primary anastomosis was most commonly accomplished (97%). Resection with enterostomy and simple bypass were each performed in one patient. Operative mortality, defined as death within thirty days of surgery, was 9%.

Secondary nonlymphomatous malignancies were present in four patients, two of whom had synchronous colonic adenocarcinoma which proved fatal. A third patient died two and a half years after curative resection of a left colon lymphoma with metastatic pancreatic adenocarcinoma. The fourth patient died 16 years after curative resection of a gastric reticulum cell sarcoma of an intracerebral malignancy.

Ninety-eight of the 112 lymphomas were single tumors, eight were multiple, and 6 diffuse (all stomach). The multiple tumors occurred more often in the stomach (4) than in the small bowel (3). In one patient tumors occurred simultaneously in the jejunum and colon. Tumors formed the lead point for intussusception of three small bowel lesions and one cecal lesion. Nine patients had perforated lesions, four gastric, four small bowel, and one colonic. Obstruction was the presenting finding in 13 patients with four gastric, seven small bowel, and three colonic tumors.

Tumors were subdivided into three classes for staging purposes as follows: *Class I*: Lymphoma confined to the bowel without extraintestinal involvement (no spread); *Class II*: Mesenteric nodes only (local spread), and *Class III*: Para-aortic node involvement or extension by contiguity to adjacent viscera (regional spread). Table 2 outlines the findings at surgery. Overall, 50% of all lymphomas were Class III indicating surgically incurable disease although many remained potentially curable with postoperative radiation therapy. It is noteworthy that almost one-half of gastric tumors were Class I (no evidence of spread) at diagnosis. Colorectal lesions were most likely to present at an advanced stage with 66% being Class III at laparotomy. Table 3 illustrates the histologic breakdown of the tumors. Only two cases of Hodgkin's lymphoma were found in this review (one gastric and one ileal). A

TABLE 2. *Extent of Spread*

	Overall (%)	Stomach (%)	Small Bowel (%)	Colon (%)
No spread (Class I)	37	47	26	22
Local spread (Class II)	13	8	26	12
Regional spread (Class III)	50	45	48	66

single case of gastric plasmacytoma with 30-year postoperative survival is reported. Two cases of giant follicular lymphoma were identified (one ileal and one appendiceal). Lymphocytic lymphoma and reticulum cell sarcoma occurred with almost equal frequency, 38% and 37% respectively overall; but the latter comprised 50% of all gastric lesions. On the other hand, reticulum cell sarcomas were infrequent in the colon, comprising only 18% of the colorectal lesions. Lymphosarcoma, which appeared infrequently in the stomach, was responsible for 44% of colorectal tumors. Small bowel lymphomas were fairly evenly divided among the three categories with reticulum cell sarcoma accounting for two of four jejunal lesions and four of eighteen ileal lesions as well as the single duodenal tumor. In no case was a composite lymphoma reported and no patient was noted to have disease with site-variable histology. Distribution of tumors within the gastrointestinal tract was as follows: Stomach—17 fundus, 48 antrum, and two combined tumors; Small intestine—one duodenum, 4 jejunum, 18 ileum, and one case with tumors in both the jejunum and the ileum; Colon—11 cecum, one ascending colon, one transverse colon, two descending colon, three rectum, and three appendix.

Postoperative treatment varied greatly as would be expected in a multicentered study. Early medical records were incomplete in many instances such that some patients were noted to have received chemotherapy or radiotherapy but the particulars of drug type or radiation dose were unavailable for critical review. Overall, 36% of patients received postoperative radiotherapy to involved areas, 15% received chemotherapeutic agents (usually MOPP), and 11% were treated by combined chemotherapy and radiation.

Follow-up data are available on all but four of the 112 patients in this study. Average and five-year survivals are listed in Table 4. As illustrated the overall five-year survival of all GI lymphomas subjected to surgical intervention was 38%. Gastric lymphoma had a slightly better prognosis (42% five-year survival) than either small bowel (27%) or colon (37%). When comparing curative versus palliative procedures, significant differences were noted with an overall 64% five year survival for curative resections while the results of palliative resections were dismal (23%, 0%, and 0% for stomach, small bowel, and large intestine respectively). Curative resection of appendiceal lymphoma yielded good results.

When data were collated according to extent of disease, survival worsened in relation to tumor spread. Overall five-year figures were once again better for gastric lesions. A marked increase in mortality was evident when the disease had progressed from local (Class II) nodal involvement to regional (Class III) spread (72 versus 23%, respectively). This relationship proved true for tumors in all sites (Table 5).

Survival data were also examined to determine if there was any effect of postoperative irradiation or chemotherapy. Although no statistically significant figures are obtainable, nevertheless, there appears to have been some benefit of radiation therapy, especially for gastric lesions where involved nodes and residual tumor were likely to be included in irradiated fields. In examining curative resections only, it was found that postoperative radiation therapy yielded 80 and 83% five-year survival in gastric and small bowel lesions respectively as compared to five-year figures of 44 and 16% without postsurgical radiation treatment (Table 6). No statement can be made regarding chemotherapy since the total number of patients so treated was small and specifics of drug administration are unavailable.

TABLE 3. *Histology*

	Overall (%)	Stomach (%)	Small Intestine (%)	Colorectum (%)
Lymphocytic lymphoma	32	32	40	30
Lymphosarcoma	24	16	30	45
Reticulum cell sarcoma	40	50	22	20
Hodgkin's disease	2	2	4	—
Giant follicular lymphoma	2	—	4	5

TABLE 4. *Postoperative Survival*

	Survival (Total) Average—5 year	Surgical (curative resections) Average—5 year	Survival (palliative resections) Average—5 year
Overall	49 months (38)	85 months (64)	21 months (17)
Stomach	26 months (42)	98 months (62)	35 months (23)
Small Intestine	36 months (27)	84 months (62)	8 months (0)
Colorectum*	53 months (37)	103 months (50)	9 months (0)

* Including Appendix.
Numbers in parentheses indicate per cent.

TABLE 5. *Survival by Extent of Spread*

	No Spread (Class I) Average—5 year	Local (Class II) Average—5 year	Regional (Class III) Average—5 year
Overall	77 months (59)	108 months (72)	18 months (24)
Stomach	89 months (60)	103 months (80)	26 months (39)
Small Intestine	45 months (40)	89 months (75)	14 months (12)
Colorectum*	50 months (50)	36 months (50)	11 months (12)

* Including Appendix.
Numbers in parentheses indicate per cent.

TABLE 6. *Survival by Adjuvant Therapy*

	No Treatment (26 pts) Average—5 year	Radiation (40 pts) Average—5 year	Chemotherapy (18 pts) Average—5 year
Overall	26 months (30)	95 months (50)	30 months (33)
Stomach	32 months (35)	105 months (60)	43 months (33)
(curative) only	50 months (44) (9 patients)	130 months (78) (14 patients)	
Small and Large Intestine	32 months (22)	73 months (37)	24 months (33)
(curative) only	45 months (16)	140 months (83)	

Numbers in parentheses indicate per cent.

Survival of patients receiving chemotherapy was no better than those receiving no postoperative treatment at all. Table 7 reveals the survival data for the lymphomas by histologic type. In general, lymphocytic lymphoma had the best prognosis (56% survival at five years) and lymphosarcoma the worst (25%), except in the large intestine where lymphosarcoma was associated with the longest survivals. Patients who had reticulum cell sarcoma had a moderately favorable prognosis for gastric and small bowel lesions (40% at five years) but had poorer results if colorectal disease (25% five-year survival) was present. Combining the figures for lymphosarcoma and lymphocytic lymphoma allows comparison between reticulum cell sarcoma (histiocytic or large cell lymphoma) and lymphocytic lymphoma (small cell lymphoma). Average and five-year survivals are comparable in all sites. Recurrence rates were computed for all curative resections prior to 1975. Table 7 shows that recurrences were similar in all sites (*i.e.*, approximately 25% at five years for curative resections).

Discussion

Whereas gastrointestinal involvement is common in the terminal stages of malignant lymphoma, primary gastrointestinal lymphoma is much less frequently encountered, variously reported as representing 1–2.2% of all GI tumors,[9,12,19] with gastric lymphomas representing 50–60% of the total.[3,14] The earlier published reports presented a rather pessimistic evaluation and five-year survivors were scarce. However in the last 4–20 years, several series[1,4,7,10,11,14,15,20] have been published which demonstrate a more favorable outcome. It would appear that primary gastrointestinal lymphoma offers as good as, or better, prognosis than adenocarcinoma.

This study corroborates the recent literature in most respects.[9,12] Gastric lymphoma represents about two-thirds of all gastrointestinal lymphoma with small and large intestine almost equally dividing the remainder. Symptoms were nonspecific but complaints of vague abdominal pain and weight loss or fatigue should alert the physician to the possibility of malignancy. Physical examination revealed a mass in less than one third of patients and routine laboratory studies are usually normal. If the tumor is demonstrated preoperatively it will be mainly endoscopic or contrast roentgenologic means. Grossly the disease presented as a single tumor in most instances, but multiple lesions were found in 8%. The lymphomas may present acutely with perforation (9%), obstruction (13%), on intussusception (4%).

For purposes of this report cases were divided into three classes representing degree of tumor spread: Class I—no nodal disease or extension; Class II—mesenteric nodes only, and Class III—regional nodes or extension to adjacent viscera. Tumors were further classified according to histologic type into three main categories: lymphocytic lymphoma, lymphosarcoma, and reticulum cell sarcoma. In addition there were two cases of Hodgkin's disease and two cases of giant follicular lymphoma. These terms have since been replaced in most centers by the Rappaport groupings

TABLE 7. *Survival by Histologic Type*

	Lymphoma Average— 5 year	Lympho-sarcoma Average— 5 year	Reticulum Cell Sarcoma Average— 5 year
Overall	101 months (56) 63 months (36)	42 months (25)	45 months (35)
Stomach	115 months (67) 65 months (40)	24 months (18)	50 months (40)
Small Intestine	89 months (50) 53 months (30)	22 months (14)	20 months (40)
Colorectum	25 months (16) 86 months (36)	87 months (40)	41 months (25)

Numbers in parentheses indicate per cent.

TABLE 8. *Recurrence after Curative Resection*

Site	Number of Cases	Number of Recurrence	Per Cent Recurrence
Stomach	28	7	25
Small Bowel	8	2	25
Colon	5	1	20
Appendix	3	1	33

but are used here to avoid misrepresentation of our cases since pathologic review was not a part of this study. It may be argued that lymphocytic lymphoma and lymphosarcoma are somewhat overlapping categories and the distinction made in this retrospective review may be arbitrary.

Analysis of our survival figures reveals a reasonably good prognosis for primary gastrointestinal lymphoma. As would be expected, mortality at five years increases in relation to extent of tumor spread with overall survival for Class I lesions at 59% and for Class III lesions at 24%. Two-thirds of our cases had nodal involvement at laparotomy and this agrees with other published reports.[2,5,7] Although some authors[11,13,15] report no difference in five year survival for the various histologic categories, we, as have others,[6,14,16] demonstrated a slightly greater mortality for reticulum cell sarcoma that for the lymphocytic lymphoma. Lymphosarcoma, on the other hand, which in most series carries a prognosis similar to lymphocytic lymphoma, had a distinctly poorer five-year survival in all sites except the colon.

Overall five-year survival following curative resections was about 60% regardless of site of origin. Palliative resections yielded only a 17% survival overall with gastric lesions showing a slightly better 23% five-year statistic. Small bowel tumors carry a higher mortality than either colon or stomach, and this is probably related to the difficulty in diagnosis and late presentation of disease.

No statistically significant evaluation of postoperative radiotherapy or chemotherapy can be made. However we did note an overall five-year survival of 80% in curative resections followed by adjuvant radiotherapy. We therefore agree with most authors[3,6–8,13,15,17,18] that radiotherapy is invaluable in the total management of these tumors.

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Discussion

Dr. William H. ReMine (Rochester, Minnesota): In the recent past, I have had the opportunity to review our experience with malignant lymphoma, particularly of the stomach. For the sake of comparison, I think it would be practical to present our results.

Two hundred-seventy cases of primary noncarcinomatous malignant lesions of the stomach were reviewed. Two hundred-eighteen patients were diagnosed as having malignant lymphoma, manifested clinically by epigastric pain, anorexia, and loss of weight. Anemia and achlorhydria were common, and barium meal x-ray examination usually was thought to demonstrate carcinoma. Fifty-two patients were diagnosed as having leiomyosarcoma, manifested clinically by severe persistent bleeding and an abdominal mass. Anemia and achlorhydria were again common, and the roentgenogram usually was thought to show a benign lesion.

All patients underwent laparotomy, and biopsy proof of the diagnosis was obtained. The lymphosarcomatous lesions were surgically resected when possible, and later the patients were given a course of radiotherapy. The crude five-year survival rate was 50%, and the ten-year survival rate was 32%. For those patients surgically treated with reasonable hope of cure, the five- and ten-year survival rates were 64 and 44%, respectively, Leiomyosarcoma was resected more "locally" and did not require irradiation. The crude five- and ten-year survival rates were 50 and 45%, respectively. If only those patients undergoing resection with hope of cure were included, the five- and ten-year survival rates were 62 and 45%.

Dr. David B. Skinner (Chicago, Illinois): The fact that Dr. Becker's has a 50 to 60% cure rate in this difficult group of patients should lead us all to reconsider the primary role of surgery for this disease.

In many areas now lymphoma is thought to be principally a disease to be treated by radiation therapy and chemotherapy. These modalities, however, can also cause mischief that involves surgical treatment, and I would like to briefly related one case to you which illustrates this point.

(slide) This is a 70-year-old woman who had a reticulum cell sar-