Lymphoma of the Gastrointestinal Tract:

Prognostic Guides Based on 162 Cases

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MALIGNANT lymphoid tumors may involve the gastrointestinal tract either as a primary growth or as a manifestation of generalized lymphomatous disease. The nomenclature of these tumors varies because of differences in interpretation of cell types, cell maturity, and the practical difficulty of distinguishing early neoplastic changes from hyperplastic changes.

Dawson [12] defined clinical criteria for establishing the diagnosis of a primary lymphoma of the gastrointestinal tract: a lymphomatous bowel lesion with lymph node involvement of that segment of bowel only, normal white count and absence of enlarged peripheral or mediastinal lymph nodes.

For purposes of prognosis, lymphomas can be classified on the basis of clinical staging, extent of involvement, extent of operation required, and histological appearance and type.[2, 3, 17, 19, 24, 26, 32, 34]

We adopted a guide to prognosis by grading these tumors into four stages, taking into consideration the extent of the primary tumor, the presence of lymph node involvement, invasion of adjacent structures or the presence of perforation, and distant metastases.

The following classification was used:

Stage I. A tumor confined to a single focus in the G.I. tract without node involvement.

Stage II. A tumor confined to a single focus in the G.I. tract with node involvement without perforation or peritonitis.

Stage III. A tumor in the G.I. tract invading adjacent structures such as pancreas, with or without free perforation or peritonitis.

Stage IV. A tumor arising in the G.I. tract with distant metastases.

This paper is based on the use of this classification in a detailed follow-up evaluation of results of treatment of 162 patients with lymphomas of the gastrointestinal tract who were admitted to the surgical service of the Mount Sinai Hospital from 1935 through 1965. Twenty-eight additional cases have not been included because of incomplete data.

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TABLE 1. *Histological Classification of 190 Cases of G.I. Lymphoma*

Cell Type	Gastric		Small Bowel		Large Bowel	
	All Cases	Cases with Complete Follow-Up Data	All Cases	Cases with Complete Follow-Up Data	All Cases	Cases with Complete Follow-Up Data
Small cell lymphosarcoma	88	76	36	31	14	11
Reticulum cell lymphosarcoma	23	19	12	10	4	3
Hodgkin's disease	2	2	8	7	—	—
Giant follicular lymphoma	3	3	—	—	—	—
	116	100	56	48	18	14

Total number of cases—190; cases with complete follow-up—162.

Pathology

A lymphoma [41] is a malignant tumor arising from lymphoid tissue, characterized by proliferation and abnormal growth with local invasion and destruction and a propensity to widespread distant metastases and to multifocal involvement. The tumor may arise in almost any organ and may spread to any part of the body. Primary lymphomas originate in the gastrointestinal tract in approximately 10–20 per cent of reported cases.

The histological classification follows that suggested by Otani [27] and is similar to that of Faulkner and Dockerty.[13]

A) Small cell lymphosarcoma.

B) Reticulum cell lymphosarcoma or large round cell lymphosarcoma.

C) Hodgkin's disease (Granuloma).*

D) Giant follicular lymphoma.

Other more detailed classifications have been described by Gall and Mallory [16] and Jackson and Parker.[18]

* Some pathologists consider this to be non-neoplastic inflammatory lymph node reaction.[27]

Clinical Material

A. Gastric Lymphoma

One hundred out of 116 records of patients with gastric lymphoma have been reviewed. Seventy-six were diagnosed histologically as lymphosarcoma, 19 as reticulum cell sarcoma, three as giant follicular lymphoma, and two as Hodgkin's Disease (Table 1).

Clinical Features (Table 2)

There were 55 men and 45 women, ranging in age from 26 to 76 years, with the largest number in their 6th decade. The duration of symptoms varied from 2 weeks to 13 years, with an average of 8 months in lymphosarcoma and 3 months in reticulum cell sarcoma.

The most common clinical features were epigastric pain and weight loss. Pain usually increased with eating and was generally not relieved by antacids. Nausea and vomiting were frequent. Almost 90% of patients had lost weight and a moderate anemia was present in about 30%. Fourteen patients had hematemasis and three had massive gastrointestinal bleeding. In

30%, an epigastric mass was palpable; hepatomegaly was noted in 10% and splenomegaly in 3%. Three patients had associated duodenal ulcers for which they had received treatment for many years until a few months before admission when, following weight loss and intensification of symptoms, the new diagnosis was made. A small number (8%) had fever ranging from 100° to 102° on admission. Histamine-fast achlorohydria was present in 9%, but not all patients had gastric analyses. Four patients had dysphagia; in these, the tumor was situated in the cardia.

Gastrointestinal x-rays were regarded as normal in only three patients. Twenty had gastroscopic examinations and five of these had positive gastroscopic biopsies. In 10 patients (half of those so examined), the gastroscopist's diagnosis was carcinoma of the stomach.

In 55 of 100 patients, a final preoperative diagnosis of gastric malignant tumor was made. Of these, only 15 were diagnosed and gastric lymphoma before operation.

Treatment

All patients underwent surgical exploration. In 90 resections were performed with a variety of surgical procedures depending on the extent of the tumor (Table 3).

The tumor was most commonly in the prepyloric region. Ten patients had diffuse involvement. In 13 the site was not clearly specified. The tumor was not resected in seven patients with widespread mestastases, and in three patients diagnosis was not established until open gastric biopsy.

The overall operative mortality was 18%. The majority of deaths occurred before 1950.

Of 74 patients who survived operation, 55 received postoperative irradiation. Chemotherapy was administered to four patients.

TABLE 2. *Signs and Symptoms in 100 Cases of Gastric Lymphoma*

Sign or Symptom	Number
Epigastric pain	90
Weight loss	90
Nausea and vomiting	60
Anorexia	30
Anemia	30
Gastrointestinal bleeding	17
Epigastric mass	30
Hepatomegaly	11
Splenomegaly	3
Associated duodenal ulcer	3
Fever	8
Dysphagia	4
Previous exploration	4
Achlorhydria	9

Results of Treatment

Twenty-nine (29%) patients survived 5 years or more. Of these, 24 were in Stage I or II and 5 were in Stage III or IV. The proportion of each histological type in each stage was approximately the same (Table 4). Survival figures therefore for each histological type depends more on the stage of the disease than on histological type. Within each stage the histological type appears to determine survival rate.

B. Small Intestine

There were 48 instances of small intestinal lymphomas (45 treated); 31 of lymphosarcoma, ten of reticulum cell sarcoma and seven of Hodgkin's Disease. There were no instances of giant follicular lymphoma (Table 1).

Age and Sex

Ages ranged from 17 to 78 years, with the highest incidence in the 6th decade. There were 27 men and 21 women—in contrast to other series which report a male to female ratio of 2 to 1.[22, 25, 36]

TABLE 3. *Operative Procedures for Gastric Lymphoma*

Subtotal gastric resection	58
Subtotal gastrectomy, partial pancreatectomy	2
Subtotal gastrectomy, cholecystectomy and small bowel resection	1
Subtotal gastrectomy with segmental colon resection	2
Esophagogastrectomy	11
Total gastric resection	8
Esophagogastrectomy and splenectomy	3
Esophagogastrectomy, partial pancreatectomy and splenectomy	3
Esophagogastrectomy with partial hepatectomy	2 2
Exploratory laparotomy and biopsy	10
Total:	100

Clinical Features

Thirty-eight per cent of the patients complained of crampy pain associated with nausea and vomiting. Weight loss and anemia were common features. Sixteen per cent of the patients were admitted with intestinal obstruction. In 4% a small intestinal intussusception was found, the apex being the tumor. Eighteen per cent had tumors which perforated into the sigmoid colon. Six per cent were operated upon because of massive gastrointestinal hemorrhage.

One patient had regional ileitis discovered at operation and, in addition, a concomitant lymphomatous tumor in the upper jejunum was found and resected. In another patient, being treated as a case of regional ileitis, perforation occurred while on steroid therapy and was found to be lymphosarcoma. Three patients had preoperative diagnoses of tropical sprue. An abdominal mass was palpable in 20% of patients.

The average duration of symptoms was 10 to 30 weeks, which is a shorter time than in lymphosarcomas of the stomach. One patient had intermittent symptoms for 10 years and another for 2½ years before diagnosis was made.

Treatment

Forty-five of 48 patients were treated. Two died during the course of investigation from perforations and peritonitis and in a third lymphoma was found at autopsy. Thirty-seven of the remaining 45 patients were treated surgically and eight were treated with radiotherapy or chemotherapy or both.

Of the 37 patients undergoing operation, three had diffuse involvement of the small bowel, one involvement of the entire small bowel and stomach, and one had a lesion invading the cecum. One patient had sigmoid colonic invasion; another had uterine involvement in addition to a primary ileal lesion.

Segmental small bowel resections were performed in 27 patients and additional subtotal gastrectomies in two. Bypass operations were performed in four patients. In the remainder, no resection was performed. Patients treated with radiotherapy and chemotherapy alone were proven by biopsy at previous laparotomies.

In one patient, with a tumor of the first portion of the duodenum, the lesion crossed the pylorus and subtotal gastrectomy and partial duodenectomy were performed.

There were 11 patients operated upon for intestinal perforations or small bowel obstructions and three for massive gastrointestinal hemorrhage.

There were six deaths in the postoperative period, an operative mortality of 18 per cent.

TABLE 4. *Stomach*

Stage	No. of Pts.	5 Yr. Surv.	Uncorr. % Surv.	Corr. % Surv.	Pathological Type	No. of Pts.	5 Yr. Surv.	Op. Mort.	F.U. Less than 5 Yrs.	Corr.* % Surv.
I	34	16	47%	64%	S.C. lymphosarcoma	26	13	3	4	68.4%
					R.C. lymphosarcoma	6	2	2	—	50%
					Hodgkin's disease	1	—	—	—	—
					G.F. lymphoma	1	1	—	—	100%
II	30	8	26.6%	42.1%	S.C. lymphosarcoma	21	7	6	2	53.8%
					R.C. lymphosarcoma	6	1	3	—	33.3%
					Hodgkin's disease	1	—	—	—	—
					G.F. lymphoma	2	—	—	—	—
III	26	4	15.3%	17.4%	S.C. lymphosarcoma	21	4	1	1	21%
					R.C. lymphosarcoma	5	—	1	—	—
					Hodgkin's disease	—	—	—	—	—
					G.F. lymphoma	—	—	—	—	—
IV	10	1	10%	12.5%	S.C. lymphosarcoma	8	1	2	—	16.6%
					R.C. lymphosarcoma	2	—	—	—	—
					Hodgkin's disease	—	—	—	—	—
					G.F. lymphoma	—	—	—	—	—

* Excluding operative deaths.

TABLE 5. *Small Intestine*

Stage	No. of Pts.	5 Yr. Surv.	Uncorr. % Surv.	Corr. % Surv.	Pathological Type	No. of Pts.	5 Yr. Surv.	Op. Mort.	F.U. Less than 5 Yrs.	Corr. % Surv.*
I	16	9	56%	75%	S.C. lymphosarcoma	9	6	—	1	75%
					R.C. lymphosarcoma	3	—	2	—	—
					Hodgkin's disease	4	3	1	—	100%
					G.F. lymphoma	—	—	—	—	—
II	8	3	37.5%	50%	S.C. lymphosarcoma	4	2	—	1	66.6%
					R.C. lymphosarcoma	3	1	1	—	50%
					Hodgkin's disease	1	—	—	—	—
					G.F. lymphoma	—	—	—	—	—
III	10	2	20%	28%	S.C. lymphosarcoma	7	2	2	—	40%
					R.C. lymphosarcoma	2	—	—	—	—
					Hodgkin's disease	1	—	—	1	—
					G.F. lymphoma	—	—	—	—	—
IV	11	1	9%	10%	S.C. lymphosarcoma	11	1	—	1	10%
					R.C. lymphosarcoma	—	—	—	—	—
					Hodgkin's disease	—	—	—	—	—
					G.F. lymphoma	—	—	—	—	—

* Excluding operative deaths.

Of 27 patients who survived operation, 15 received postoperative radiotherapy and eight received chemotherapy. Of the four patients who underwent bypass procedures, one died in the postoperative period and the others received postoperative radiation. Nineteen patients had curative procedures with resection of localized tumors not extending beyond the involved segment or its draining lymph nodes. Fourteen patients had palliative procedures including resections and bypass operations. Four were non-resectable. Eight patients were treated with chemotherapy and radiotherapy alone.

Results of Treatment (Table 5)

Fifteen patients survived five years or more (31%). Four patients were followed-up less than 5 years and are alive and well at the time of this report. Average 5-year survival, including operative deaths and non-surgically treated cases, was 36.5 per cent. Of those operated upon, including non-resectable cases and operative mortalities, 5-year survival rate was about 38 per cent. Of eight patients treated with radiation and chemotherapy alone, only one survived 5 years.

In Stage I lesions, nine of 16 patients survived 5 years (corrected percentage: 75% survival). In Stage II, there were three survivors (37.5%), in Stage III two of ten (20%), and in Stage IV, one of eleven (9%). Patients with palliative resections and bypass operations survived as average of 3 years.

Thus, corrected survival figures of Stage I and II are considerably better (75% and 50%, respectively) than in Stages III and IV (25% and 10%). Twelve of 15 5-year survivors were in Stage I and II. The histological types in each group were not as good a guide to prognosis as was the staging. For instance, statistics in small cell lymphosarcoma show a decreasing percentage of survivors depending on the stage of disease.

TABLE 6

Path Type	Cecum	Rt. Colon	Tr. Colon	Lt. Colon	Sigmoid	Rectum
1. Lymphosarcoma	2	1	1	1	2	4
2. Reticulum Cell	0	0	0	1	0	2

C. Large Intestine

Fourteen records have been reviewed: two were in the cecum, six in the rectum, and six in the remaining large bowel (Table 7).

Histologically, eleven were lymphosarcomas and three were reticulum cell sarcomas.

The youngest patient was a 14-year-old boy and the oldest was 76 years. The maximum number of patients were between 50 and 70. An equal male-female distribution was found.

Signs and Symptoms

The usual initial symptom was crampy lower abdominal pain. In lesions of the rectum and recto-sigmoid, the chief complaint was bleeding per rectum. A moderate to severe degree of anemia was a feature in many cases. The average duration of symptoms was 4 to 5 months. With rectal tumors, a mass was usually palpable and biopsy established the diagnosis.

Treatment

Six patients had definitive operations. Colectomy was performed, depending upon the site and extent of the lesion in these patients. The tumor was non-resectable in one patient. Rectal and recto-sigmoidal lesions were biopsied and treatment consisted

TABLE 7. *Large Intestine*

Stage	No. of Pts.	5 Yr. Surv.	Uncorr. % Surv.	Corr. % Surv.	Pathological Type	No. of Pts.	5 Yr. Surv.	Op. Mort.	F.U. Less than 5 Yrs	Corr. % Surv.
I	3	2	66%	66%	S.C. lymphosarcoma	3	2	—	—	66.6%
					R.C. lymphosarcoma	—	—	—	—	—
					Hodgkin's disease	—	—	—	—	—
					G.F. lymphoma	—	—	—	—	—
II	5	2	40%	50%	S.C. lymphosarcoma	4	2	—	—	50%
					R.C. lymphosarcoma	1	—	—	1	—
					Hodgkin's disease	—	—	—	—	—
					G.F. lymphoma	—	—	—	—	—
III	4	1	25%	25%	S.C. lymphosarcoma	3	1	—	—	33.3%
					R.C. lymphosarcoma	1	—	—	—	—
					Hodgkin's disease	—	—	—	—	—
					G.F. lymphoma	—	—	—	—	—
IV	2	0	0%	0%	S.C. lymphoma	1	—	—	—	—
					R.C. lymphoma	1	—	—	—	—
					Hodgkin's disease	—	—	—	—	—
					G.F. lymphoma	—	—	—	—	—

of radiation and chemotherapy. No abdominal-perineal procedures were performed.

There were no operative mortalities in the large bowel series. The only postoperative complication was an obstructing volvulus at an ileo-sigmoidostomy site.

Results (Table 7)

Five patients lived 5 years or more (44%); the longest survived 17 years. Among 5 long-term survivors, three were treated by biopsy and radiation and two by operation. There was no appreciable difference in survival rates between patients treated with extirpative operation and those treated with radiotherapy alone.

Stomach

Gastric lymphomas are difficult to diagnose preoperatively. They may have the characteristics of carcinoma, benign ulcer, or gastritis. The position of the lesion in the stomach is of no diagnostic aid, and only biopsy can establish the diagnosis. The malignant nature of gastric lymphomas may not be apparent at operation and palpation of the stomach. Gastrotomy should be performed whenever there is suspicion. Two patients were operated upon and no tumor was palpated in the stomach; following gastrotomy, hypertropic gastric rugae were seen and only biopsy established the diagnosis.

A palpable mass on physical examination does not invariably mean inoperability or non-resectability.

These tumors are prone to penetrate into the pancreas or to perforate into the free peritoneal cavity, a reason for biopsy of the edges of perforated ulcers. In two instances, perforations were closed. In one, biopsy was taken and the diagnosis was established. The other had no biopsy and was treated medically for 6 months for a presumed peptic ulcer. He finally died from

advanced lymphosarcoma of the stomach. Histological diagnosis may not always be accurate. In two patients operated upon elsewhere, only on review of the specimen was lymphosarcoma diagnosed.

Small Intestine

The proportion of jejunal tumors is higher than that reported,[5, 13, 22] as being equally divided between jejunum and ileum. In two instances, the tumor was in the first portion of the duodenum—a rare site. Four patients treated with radiotherapy and chemotherapy perforated during the course of treatment. Presumably, dissolution of radiosensitive tumors by radiotherapy leads to perforation.

Granulomatous lesions have been reported as predisposing to intestinal lymphomas.[38] There were two such instances, one in a 62-year-old man with regional ileitis and another patient with non-tropical sprue. In patients with concomitant ileitis and lymphoma, the tumors were found in non-ileitis segments of the bowel.

The development of lymphatic leukemia should not contraindicate operation. One patient lived eight years following resection of a primary lesion.

It becomes apparent on review that even if a patient has a secondary lesion in the bowel palliative operation should be performed in conjunction with radiation and chemotherapy. Non-resected lesions are prone to perforation.

Large Intestine

The most common site of involvement was the rectum. There was no appreciable difference in prognosis of patients treated by operation as against radiotherapy alone in a small number of patients.

Discussion

Lymphomas of the G.I. tract are infrequent. Treatment and natural history have been periodically reviewed in small series from this and other institutions. Approximately 1,200 cases of gastric lymphomas and 750 intestinal lymphomas have been previously recorded.[1, 4, 5, 9, 10, 12, 13, 19, 21–23, 26, 30, 31, 34, 35, 37, 38, 40]

In this series, the stomach was the most frequent site (61%), more than twice as common as the small intestine (27.5%). The large bowel was the site of the fewest (11.5%). No esophageal lymphomas were encountered.

In general, the tumor was of slight male preponderance and the lesions occurred most commonly in the 6th decade.

Gastrointestinal lymphomas were graded from Stages I to IV on the basis of extent of the tumor. Best results of treatment were in tumors contained locally. For example, in gastric lesions, 5-year survival in Stage I lesions (confined to stomach without nodal involvement) was 64%, while Stage III lesions (invading surrounding structures with or without free perforation) 5-year survival rate was 17.4 per cent.

Overall 5-year survival rates were 29% in gastric lesions (corrected: 38.6% excluding operative death; follow-up less than five years), 33.3% in small intestinal lesions (corrected: 42.8% excluding operative death and follow-up less than five years), and 35.5% in large intestinal lesions (corrected: 38.4%).

Survival statistics also depend on the histological nature of the tumor. Within each stage results were better with Hodgkin's Disease and giant follicular lymphoma than in lymphosarcoma or reticulum cell sarcoma. It is difficult to compare different treatment groups because of the variety and combinations of therapy practiced and difficulty in defining limits of spread from the primary tumor. It seems advisable to remove the tumor and as much of the secondary spread as possible, then to control

the surrounding area by radiotherapeutic or chemotherapeutic means. Radiotherapy and chemotherapy should be administered for leukemic degradation or widespread invasion or distant metastases.

Summary

1. One hundred and sixty-two cases of gastrointestinal lymphomas treated and followed over a 30-year period are reported.

2. The stomach was the most frequent site of these tumors, 61%, more than twice the number in small intestine (27.5%), large bowel was least frequent site (11.5%).

3. Tumors were graded both histologically and on the basis of extent of disease into four stages. Staging offers a valuable prognostic guide and within each stage, histologic type appears to be a further guide to prognosis.

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Book Review

An Introduction to the History of General Surgery. RICHARD HARDAWAY MEADE, M.D. W. B. Saunders Company, 1968, 403 pages. $17.00.

THIS introductory history of general surgery should be of interest to all surgeons regardless of specialty. The beginning chapters of the book contain the story of the evolution from "barbery" to surgery and extends to include modern concepts of surgical training. The management of wounds, of infection and of fractures are traced from the earliest of recorded time to the present. Other chapters recount the developmental history of surgical anatomy, anesthesia, blood transfusions, plastic surgery, etc. The major portion of the book records the progress of surgical history in relation to the surgery of specific organs with their respective pathological entities. Such diverse chapter titles, Surgery of the Breast, Surgery of the Small Intestines, Surgery of the Pancreas, etc., generously illustrated, contain the history of these subjects according to significance of surgical contribution with reference to time and surgeon. This procedural plan provides a valuable source of classified historical material which extends beyond the province of general surgery into the subspecialties. References at the end of each subject title can be useful to authors in the preparation of historical introductions to surgical treatises.

A pleasant surprise awaits the reader as one comes across familiar names of contemporaries involved in the surgical events of our time. All surgeons will appreciate this concise up-to-date history. It should be available in hospital libraries for our younger colleagues, especially surgical residents. B. SHAFIROFF, M.D.