PRIMARY MALIGNANT LYMPHOMA OF THE GASTRO-INTESTINAL TRACT*

ARTHUR W. ALLEN, M.D., GORDON DONALDSON, M.D.,
RONALD C. SNIFFEN, M.D. AND FAIRFIELD GOODALE, JR., M.D.

BOSTON, MASSACHUSETTS

FROM THE SURGICAL AND PATHOLOGICAL SERVICES OF THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASSACHUSETTS

INTRODUCTION

ALTHOUGH MALIGNANT lymphoma is usually a generalized disease, it does have localized forms or stages as evidenced by cures following local surgery.[1] Localization is found in all types of lymphoma, and 11 per cent of the 618 cases studied by Gall and Mallory[6] were confined to one structure at the time of initial examination (Table I). It is of practical interest that one-half of the isolated tumors in their series were found to occur in the gastro-intestinal tract, bone and skin. It is entirely possible that these tumors have a focal origin and, from such a nidus, invade and destroy the organ in which they arise and metastasize first to lymph nodes of that area. Thus, lymphoma may closely resemble carcinoma in its behavior, and so is theoretically susceptible to cure by extirpation.[24]

The present report reviews the 79 cases of lymphoma, all apparently primary in the gastro-intestinal tract, which have been resected at the Massachusetts General Hospital over the 40-year period, 1913 to 1953 (Table II). Tumors arising in the mesenteric and retroperitoneal areas are not included. All patients were subjected to radical excision of the lesion following the accepted principles of cancer surgery in vogue at the time. Approximately two-thirds of the patients were given postoperative roentgen-ray therapy to the involved area after resection. At the time of writing (December, 1953) follow-up studies are complete on all patients.

INCIDENCE

The relative incidence of malignant lymphoma to all other malignant neoplasms of the gastro-intestinal tract seen at the Massachusetts General Hospital is shown in Figure 1. Carcinoma is far more frequent than lymphoma in the oesophagus, stomach and large bowel, but in the small intestine, lymphoma more nearly equals carcinoma in frequency.

Many previous reports have referred to malignant lymphoma of the stomach only, which is understandable since this organ is involved as a localized process more frequently than the rest of the gastro-intestinal tract. The first report appears to be that of Cruveilhier[3] in 1871. Forni[5] (1914) presented 33 cases, and Taylor[25] in 1937, collected 152 reported cases and added five of his own. In 1952, Snoddy[20] collected from the literature 474 instances and added 34 from his clinic. In the same year, Crile, Hazard and Allen[2] added 19 cases. All of these are of the stomach, and the term applied to the lesion was lymphosarcoma.[9, 10, 12, 17]

Marcuse and Stout[11] in 1950, collected 192 instances of this disease in the small bowel, and added 13 from the Presbyterian Hospital in New York. Singleton and Moore,[19] in 1949, made a combined report on the entire gastro-intestinal tract, finding 569 cases, adding six of their own. In 1954, Sperling[22] reported an additional 14 instances of malignant lymphoma of the gastro-intestinal tract.

* Presented before the American Surgical Association, Cleveland, Ohio, April 29, 1954.

TABLE I. *Incidence of General and Local Forms of Malignant Lymphoma.*

Massachusetts General Hospital	General 618 cases (Gall & Mallory) 1937 Per cent	Local 70 cases (Gall & Mallory 1937 Per cent	Gastro-Intest. 79 cases (Present series 1954 Per cent
Stem cell	9	16	11
Clasmatocytic	12	30	35
Lymphoblastic	13	14	30
Lymphocytic	22	19	7.5
Hodgkin's Lymphoma	31	14	6
Hodgkin's Sarcoma	6	1	7.5
Follicular	7	6	3

TABLE II. *Solitary Gastro-Intestinal Malignant Lymphoma.*

Massachusetts General Hospital 1913–1953 79 Resections	Stomach	Small Bowel	Colon & Rectum	Total
Stem cell	5	2	2	9
Clasmatocytic	15	9	2	26
Lymphoblastic	13	7	4	24
Lymphocytic	4	2	0	6
Hodgkin's Lymphoma	3	2	0	5
Hodgkin's Sarcoma	4	1	1	6
Follicular	0	2	0	2
Total	44	25	9	78
Oesophagus—1 Lymphoblastic Lymphoma				1
				79

Since terminology for these tumors is not standardized[8] and some of the reported cases may not have been primary in any specific organ, it is probable that any attempt at an accurate numerical total would be open to question. There are doubtless thousands of cases of isolated malignant lymphoma of the various parts of the gastro-intestinal tract unreported to date. It is obvious, however, from interim results already recorded that the lesion is favorable for surgery with or without postoperative radiation, particularly in the stomach and small bowel.

CLASSIFICATION

In this study the classification of malignant lymphoma, as outlined by Gall and Mallory[6] in 1942, has been used. They divided these tumors into the following categories:

1. Stem cell lymphoma. } Reticulum
2. Clasmatocytic lymphoma. } cell sarcoma
3. Lymphoblastic lymphoma. } Lympho-
4. Lymphocytic lymphoma. } sarcoma
5. Hodgkin's lymphoma.
6. Hodgkin's sarcoma.
7. Follicular lymphoma.

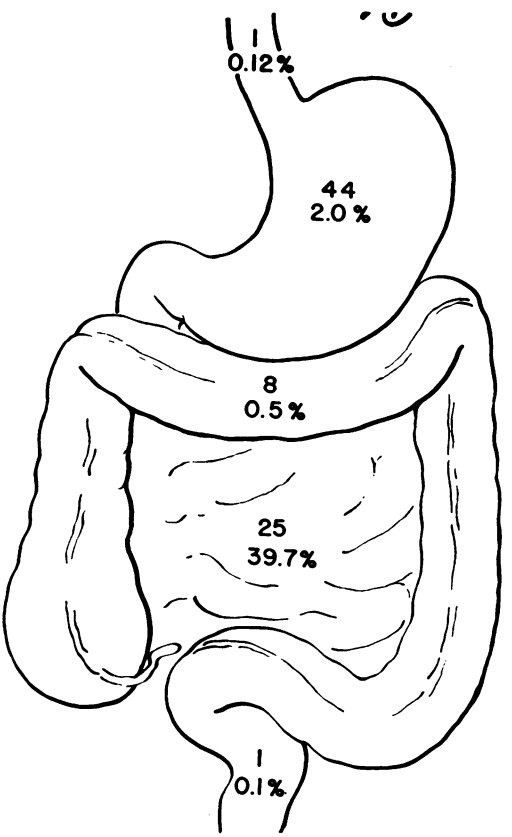

FIG. 1. Relative incidence of malignant lymphoma to all malignant tumors of the gastro-intestinal tract (Massachusetts General Hospital 1913–1953).

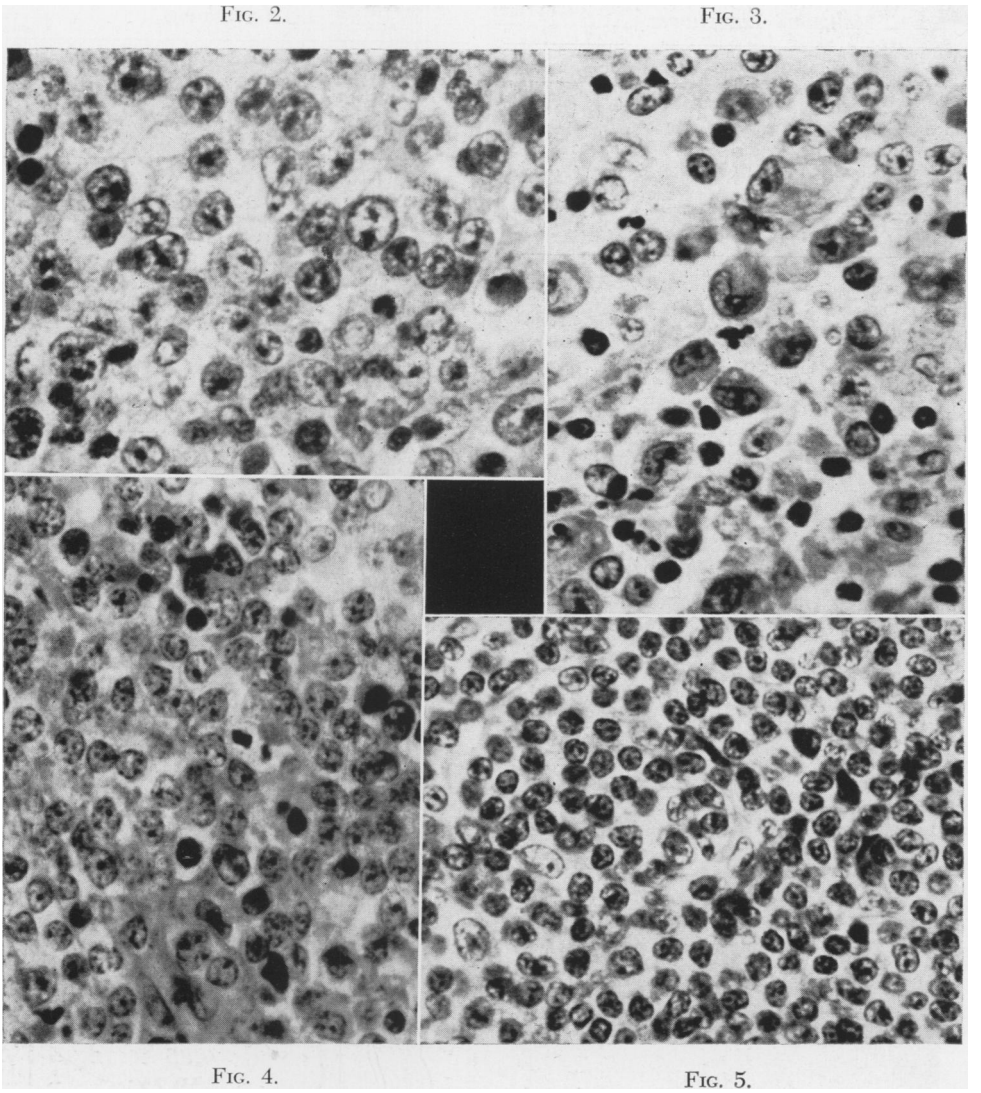

FIG. 2. FIG. 3. FIG. 4. FIG. 5.

FIG. 2. Stem cell lymphoma. The stem cell is defined as a pluripotential undifferentiated cell with a large, pale, poorly outlined cytoplasm, sometimes seemingly forming a syncytium with its neighbors. The nucleus is large, round, distinctly outlined and has a prominent nucleolus.

FIG. 3. Clasmatocytic lymphoma. The clasmatocyte, a phagocytic cell morphologically similar to the monocyte, is smaller than the stem cell but larger than the lymphocyte. It has distinctly outlined abundant eosinophilic cytoplasm of irregular outline, suggesting ameboid properties. The nucleus is often eccentric and may be round, oval or reniform.

FIG. 4. Lymphoblastic lymphoma. The lymphoblast, slightly larger than the mature lymphocyte, is a round cell with a thin rim of basophilic cytoplasm, which, like the clasmatocyte, may show pseudopodial projections. The sharply outlined nucleus is centrally placed, round or slightly indented and vesicular. Mitoses are often numerous.

FIG. 5. Lymphocytic lymphoma. In the lymphocytic type the predominating cell cannot be differentiated from a normal lymphocyte.

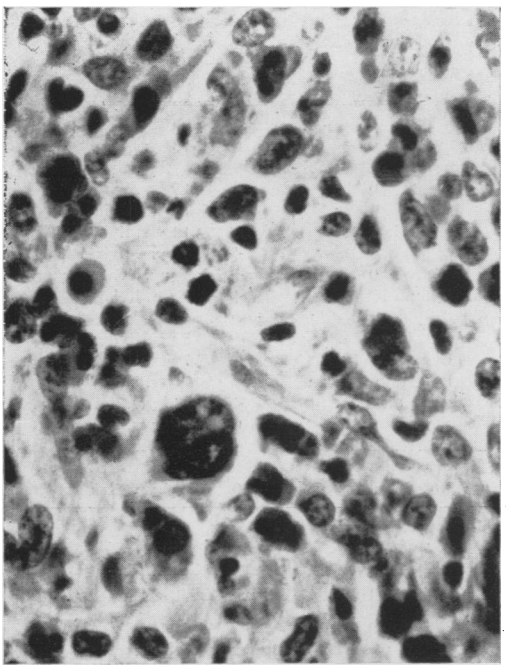

FIG. 6. Hodgkin's lymphoma. Classical Hodgkin's lymphoma, because of its polycellularity, is readily distinguished from the other types. The lesion shows a background of lymphocytes, plasma cells, clasmatocytes and collagen production which increases with age. The histologic hallmark of the disease is the mononucleated or multinucleated Sternberg-Reed cell.

In the terminology of other authors the stem cell and clasmatocytic types are grouped under "reticulum cell sarcoma," and the lymphoblastic and lymphocytic types are together called "lymphosarcoma." In essence the classification of Gall and Mallory is based on the predominant cell in the tumor. In each type, however, other cell forms are represented, but are present only in relatively small numbers (Figs. 2 to 8).

GROSS PATHOLOGY

The gross appearance of lymphoma involving the stomach and intestine is often indistinguishable from carcinoma. The lesion may be a localized ulceration with irregular heaped-up margins and surrounding induration (Fig. 9), a fungating or an annular growth (Fig. 10). Frequently lymphoma grows in the manner of anaplastic carcinoma, producing a localized or widespread uniform thickening of the wall with superficial ulceration, gradually sloping margins and surrounding induration (Fig. 11). On the other hand, there may be diffuse involvement of the gastric wall with great hypertrophy of the rugae. Gross ulceration in this type may or may not be present (Fig. 12). This type of lesion presents a diagnostic problem to the radiologist and gastroscopist, as it is difficult to distinguish from hypertrophic gastritis, mucosal hypertrophy, and linitis plastica; furthermore, at operation the surgeon cannot always be certain that the resection margins are free from tumor.

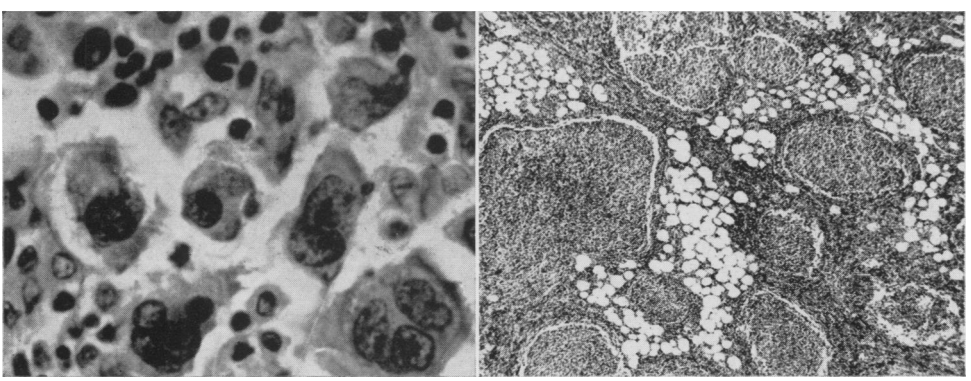

FIG. 7. Hodkin's sarcoma. In Hodgkin's sarcoma there is an overwhelming predominance of Sternberg-Reed cells which are often in mitosis. As in Hodgkin's lymphoma the other cell types are present, but are relatively infrequent. Areas of fibrosis do not develop.

FIG. 8. Follicular lymphoma. Follicular lymphoma is distinguished mainly by its numerous follicle-like nodules which vary in size and approximation. Its predominant cell is the mature lymphocyte.

TABLE III. *Malignant Lymphoma. Long-Term Survival Following Resection of Stomach, 1916–1948.*

#	Age	Sex	Type	Contact Organs Resected	Other Spread	Post op x-ray	Follow-up
1	43	M	Clasmatocytic	0	0	+	22 yrs. living
2	49	M	Clasmatocytic	0	0	0	15 yrs. died coronary thrombosis
3	51	F	Lymphoblastic	0	0	0	15 yrs. living
4	52	M	Lymphoblastic	Liver Edge	0	0	14 yrs. living
5	37	M	Lymphocytic	0	Resection Margin	+	12 yrs. living
6	50	M	Clasmatocytic	0	0	+	11 yrs. living
7	55	F	Stem cell	0	0	+	9 yrs. living
8	63	F	Lymphoblastic	Total Stomach Trans. colon	Lymph Nodes	+	9 yrs. living
9	63	F	Lymphoblastic	0	0	+	8 yrs. living
10	59	F	Hodgkin's Lymphoma	Total Stomach	Lymph Nodes	+	7 yrs. living
11	38	M	Lymphocytic	0	Resection Margin	+	7 yrs. living
12	62	M	Clasmatocytic	Tail of Pancreas	Lymph Nodes	+	5½ yrs. living
13	68	F	Clasmatocytic	0	0	0	5½ yrs. living
14	31	F	Hodgkin's Sarcoma	Total Stomach Tail-Pancreas	Resect. Marg. Lymph Nodes	+	5¼ yrs. living
15	49	M	Hodgkin's Sarcoma	0	Resection Margin	0	5¼ yrs. living

In about 25 per cent of cases lymphoma appears to be multicentric in origin (Figs. 13 and 14). The stomach may contain several isolated, ulcerated tumors, and in the intestine several annular segments of the bowel may be involved. In the intestine, lymphoma sometimes appears to have arisen in the immediately adjacent lymph nodes, with secondary invasion of the intestinal wall.

The cut surface of lymphoma is usually grey to light yellow, homogeneous and glistening, and in these respects it resembles anaplastic carcinoma or sarcoma. There is no great propensity to undergo necrosis or hemorrhage. At the time of operation the regional lymph nodes may be enlarged, but this is no guarantee that they are involved in the neoplastic process. In our experience the gross appearance of enlarged nodes on cut section is deceptive, for a non-specific chronic inflammation may simulate lymphoma or anaplastic carcinoma. Therefore, it is recommended that for purposes of frozen section, or a diagnostic biopsy when the tumor is deemed inoperable, tissue be removed from the primary growth.

LYMPHOMA OF THE STOMACH

The diagnosis of lymphoma of the stomach is rarely made preoperatively by the clinician, roentgenologist or gastroscopist, as it is confused with cancer, ulcer and gastritis, which are much more common. Gastroscopic biopsy may be helpful. The position of the lesion in the stomach is of no diagnostic aid.

In this series the average age of the patients was 53 years, with a spread from 22 to 81 years; the sexes were equally affected.

The duration of symptoms referable to the gastro-intestinal tract varied from one month to seven years. The character of the symptoms was not specific. In 20 per cent of the patients there was obstructive vomit-

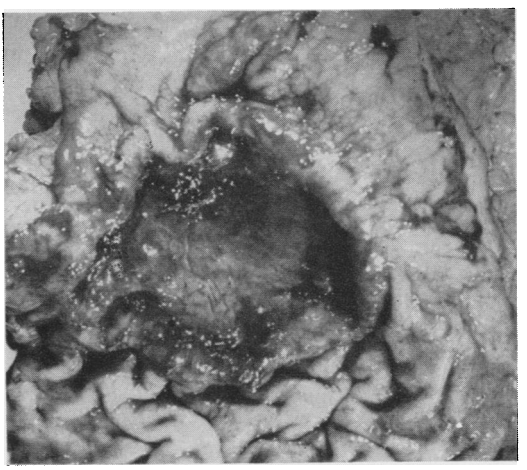

FIG. 9. Stomach. Local ulcerating tumor.

FIG. 10. Small intestine. Annular growth with ulceration.

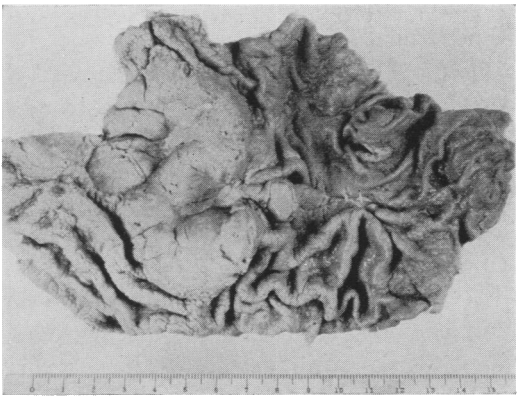

FIG. 11. Stomach. Large tumor mass involving about one-quarter of stomach.

ing. It should be emphasized that ulcer type pain was frequently observed. Massive bleeding occurred in 14 per cent of the cases, 60 per cent had occult blood in the stools, and two-thirds showed a mild to moderate anemia. An abdominal mass was palpable in 20 per cent of the patients.

The findings on gastric analysis differed significantly from cancer in that 11 of the 14 patients tested showed free HCl (av. 50 units after histamine), and half of these ranged between 70 and 90 units. This is in agreement with the findings of McSwain and Beal[13] and Warren and Lubenski.[26] In spite of a recent enthusiastic report,[8] in the five instances in this series in which Papanicolau smears were obtained, all were reported negative.

THERAPEUTIC RESULTS

The 44 cases of malignant lymphoma involving the stomach that were resected extend back to 1916. Eight abdominal or transthoracic total gastrectomies and 36 proximal or distal subtotal resections were carried out. In 11 cases, contact organs or portions thereof were removed. The overall operative mortality was 16 per cent, but since 1944 the mortality has been reduced to 3.7 per cent. Twenty-six patients operated on prior to 1949 survived resection, and so can be included in the five-year follow-up. An additional five patients have been followed for three years. The longest survival was 22 years after a subtotal gastrectomy for a 6 cm. flattened clasmatocytic tumor on the lesser curvature. In spite of uninvolved lymph nodes, postoperative radiation therapy was given. At present the patient is well. It is known that untreated cases may run a slow course, and one ten-year survival has been reported.[23] The reticulum cell and lymphoblastic types accounted for 20 of the 26 cases. Fifteen of the 26 patients have sur-

TABLE IV. *Malignant Lymphoma of Small Bowel—Five-Year Survival Following Surgical Resection—1913–1948.*

Age	Sex	Site	Type	Spread	Post-op roentgenray	Follow-up
32	M	Ileum	Lymphocytic	O	0	died 18 yrs.*
55	F	Ileum	Stem	Lymph node	+	living 14 yrs.
59	F	Jejunum	Clasmatocytic	0	+	living 10 yrs.
50	F	Ileum	Follicular	Resect. Edge	0	died 9 yrs.†
46	M	Jejunum	Follicular	Resect. Edge	+	living 7½ yrs.

* Death 18 years later due to carcinoma of pancreas.

† Explored elsewhere six years after resection and recurrence found. Treated by further resection and roentgen ray.

vived for at least five years, a "cure" rate of 58 per cent (Table III).

Of the 44 gastric resections, 15 revealed lymph node involvement, 21 had no tumor spread, and in eight of the cases in the earlier years no report on the lymph nodes was available. Of the 15 cases surviving five years or more, four specimens revealed lymph node involvement. The comparative five and three year salvage in relation to lymph node spread is shown in Figure 15. Of even greater interest was the finding that the resection edge of the stomach was involved by tumor on 11 occasions. In the five year survival group of 15 cases, a resection margin was involved in four instances. Therefore, it may be said that in contrast to carcinoma of the stomach involved regional nodes or submucosal spread to surgical resection edges does not preclude a five-year cure.

FIG. 12

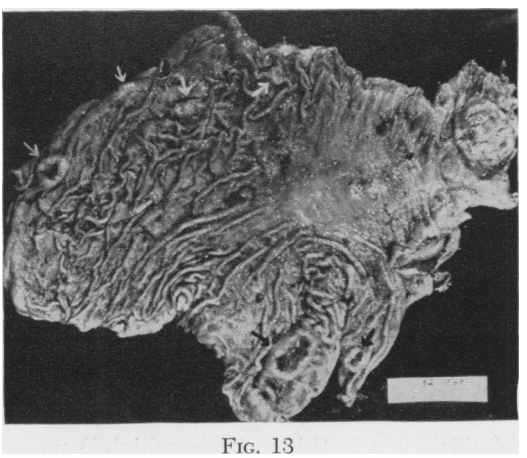

FIG. 13

FIG. 12. Stomach. Greatly thickened rugal folds involved by lymphoma.

FIG. 13. Stomach. Note six separate lesions, three of which have ulcerated.

SMALL BOWEL

Primary lymphoma of the small bowel is uncommon, but seems to increase in frequency as one approaches the distal intestine. This, presumably, is due to the relative increase in lymphoid tissue in the terminal ileum. As has been stated already, this series is limited to those cases in which the lesion appeared to be primary in the bowel, and in which radical resection was possible. The incidence of malignant lymphoma arising in the mesenteric lymph nodes is approximately twice that of lymphoma primary in the bowel. The frequency of the histologic types is shown in Table II. The average age

TABLE V. *Malignant Lymphoma Gastro-Intestinal Tract—Summary of Five-Year Survivals—1913–1948.*

Location	46 cases surviving resection						
	Resection Alone		Resection + X-ray		Total		
	Number cases	5 years survival	Number cases	5 years survival	Number cases	5 years survival	
Oesophagus	..	..	1	0	1	0	0%
Stomach	10	5	16	10	26	15	58%
Small bowel	6	2	9	3	15	5	33%
Colon and rectum	..	..	4	0	4	0	0%
Total					46	20	43%

of the patients was 48 years, with a span from 22 to 68 years. There were 15 males and ten females. Frequently the symptoms were those of obstruction, accompanied by loss of weight and strength. In half of the cases a mass, usually in the left upper or right lower quadrant, was palpable. In one-third of the cases the mass was tender, and at operation local peritonitis or abscess formation was found. Masses of lymphoma within the abdomen not involving a hollow viscus or revealing any abscess at exploration are often tender on palpation. When stool examinations were made, gross or occult blood was found in about one-half of the cases.

THERAPEUTIC RESULTS

As in the case of the stomach, an attempt was made to remove all tumor-bearing tissue, including the lymphatic drainage area in the mesentery, whenever possible. When the tumor involved the lower ileum, a right colectomy was performed. In this group of 25 patients, it was possible in 16 to resect segments of small bowel varying from 10.5 to 70 cm. in length. On three occasions in which the tumor was found to have perforated, a side-tracking procedure was performed, entero-enterostomy or entero-colostomy, reserving resection until a later date.

There were six postoperative deaths. In four of these the tumor had perforated at the time of laparotomy. The regional lymph nodes were involved in six of the 11 cases in which they were studied. On four occasions the surgical resection margin contained tumor. In this group of patients only five survived five years. In contrast to these cases, only four of the remaining 20 patients lived longer than one year following resection, and the majority died within six months. Postoperative radiation therapy was given to 12 of the 19 patients who survived surgery; three of the five long-term survivors were so treated (Table IV).

COLON

Nine cases of primary malignant lymphoma of the large bowel are included in this series, four in the cecum or right colon, three in the transverse colon, one in the sigmoid and one in the rectum. Although the appendix was involved in several instances, in none of these was it considered to be the primary site of the tumor. In most respects the signs and symptoms simulated the small bowel tumors. Obstruction was frequent, gross bleeding common, and an abdominal mass was palpable in seven of eight colon cases. Perforation was found in three instances.

THERAPEUTIC RESULTS

A radical cancer resection of bowel and regional lymph nodes was performed in all patients. All cases surviving operation received postoperative radiation therapy. The longest survival in this group was two years and four months, and only two other patients lived one year.

ESOPHAGUS

A solitary case of lymphoblastic lymphoma of the esophagus was encountered. The patient died two months following esophagectomy and roentgen ray therapy.

COMMENT

The published reports of others,[2, 13, 15, 16, 19, 20, 21, 23, 25] and this series of cases from the Massachusetts General Hospital, strongly suggest that isolated lymphoma of the stomach and small intestine does not have the pessimistic outlook indicated by Minot and Isaacs[14] 30 years ago. Indeed, the prognosis is considerably better than that of carcinoma of the stomach, and as good as it is in other malignant tumors of the small bowel. Excluding operative deaths, there were 58 per cent five-year cures in the former, and 33 per cent in the latter. There were no five-year survivals in the nine cases of malignant lymphoma involving the large bowel and rectum.

It is difficult to find any definite correlation between cell type and prognosis. In the generalized malignant lymphoma group studied by Gall and Mallory in 1942, the more differentiated cell types (lymphocytic, Hodgkin's, and follicular lymphoma) carried a life expectancy of two to three times that of the other four types. The present series is far too small for statistically significant analysis. It is of interest, however, that although only 17 per cent of the group fall into the lymphocytic, Hodgkin's, or follicular lymphoma classification, 30 per cent of those patients surviving five or more years after resection were of these histologic types. Moreover, of the 20 cases presenting multiple lesions within an organ, the majority were of the more malignant types (clasmatocytic, lymphoblastic, and Hodgkin's sarcoma), and the prognosis in this group was only half that of the entire group, 60 per cent dying within one year of operation.

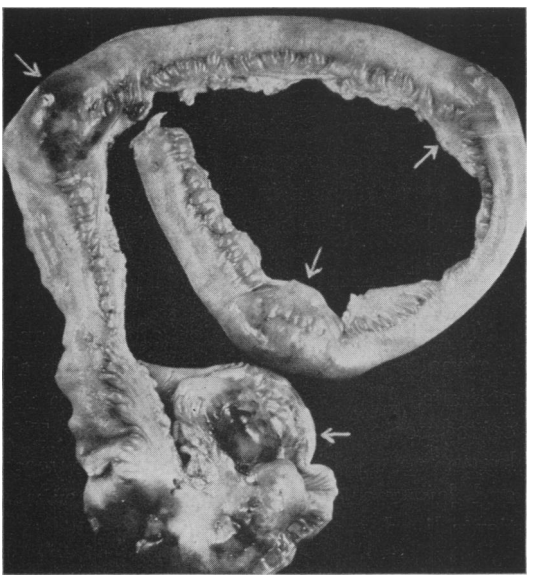

FIG. 14. Small intestine. Multiple involvement by four tumors.

The value of postoperative irradiation therapy is also not entirely proven. At one extreme Yarnis and Colp[27] favor irradiation over total gastrectomy in diffuse gastric lymphoma. On the other hand, some radiologists feel that roentgen therapy should be given only when tumor has been left behind at operation. Holmes, Dresser and Camp[7] warned of the dangers of hemorrhage and

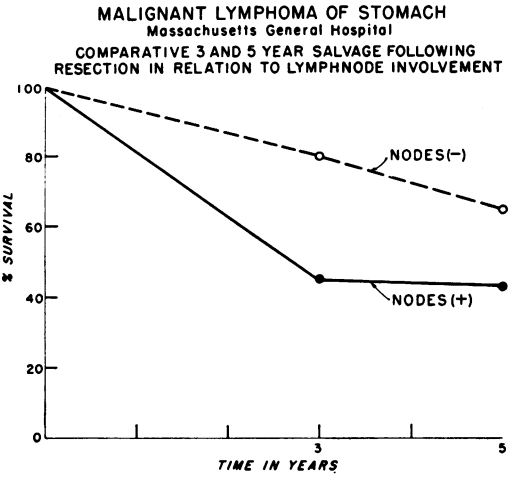

FIG. 15.

perforation following irradiation of a hollow viscus containing a large ulcerating lesion. It is of particular interest that of the 20 five-year survivals, five patients had neoplastic involvement of regional lymph nodes and six patients involvement of the surgical resection margin; and in all but two instances in the latter group, postoperative irradiation therapy was given. Thus, it is obvious that involvement of the lymph nodes and resection margins does not preclude a cure. Therefore, with these facts in mind, it is felt that emphasis should be placed on early diagnosis, wide excision of the involved organ with its mesentery, and, if the nodes or resection margins are found to contain tumor, irradiation therapy should be given postoperatively. This attack appears to offer the patient the maximum therapeutic benefits available at the present time.

In addition to the 79 patients treated by surgical excision there have been 15 other cases of malignant lymphoma apparently arising in the gastro-intestinal tract, encountered during the period covered in this report. Eleven of these were biopsied and

treated by radiation only. One of the six stomach lesions, a lymphoblastic tumor, finally biopsied after many attempts at diagnosis over a period of two years, lived six and a half years after radiation therapy. At postmortem, no active lymphoma was found and death was due to amyloidosis. All of the remaining ten were dead of spread of their original disease within four years. There were two instances each of stomach and of small bowel lymphoma appearing with an acute perforation, to which they succumbed before surgery could be undertaken. All four of these were proved at autopsy to be isolated lesions.

SUMMARY

Seventy-nine cases of resected isolated malignant lymphoma of the gastro-intestinal tract are reported. Of these, 44 involved the stomach, 25 the small bowel, nine the large bowel, and one the esophagus. A radical cancer type operation was performed in each case, usually followed by irradiation therapy. The overall five-year survival rate was 43 per cent, excluding 16 operative deaths. An additional 15 cases, with isolated lesions apparently arising in the gastro-intestinal tract, were not treated by resection, making a total of 94 patients observed during the time covered in this report.

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