

Management of Primary Gastric Lymphoma

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A retrospective study of 51 patients treated for primary gastric lymphoma was made to evaluate the influence of clinicopathologic features and the method of treatment on survival. The lymphocytic type of tumor showed a higher survival rate than the histiocytic type. Tumors that involved only the gastric wall resulted in a five-year survival rate of 62%, as compared with 50% for tumors that involved also the adjacent gastric lymph nodes, and 25% for those involving the distant gastric lymph nodes. Treatment by subtotal, total, or extended forms of gastric resection without postoperative radiation gave a five-year survival rate of 33%. Resection followed by radiation yielded a higher survival rate of 67%. The best results were obtained in 13 patients who received higher doses of radiation: 11 (85%) survived five or more years. One-third of the patients developed manifestations of systemic malignant lymphoma after curative therapy. These observations suggest a planned multimodal therapeutic program for this disease.

PRIMARY GASTRIC LYMPHOMA represents 1 to 5% of all gastric cancers¹⁻³ and is anatomically the most common type of extranodal lymphoma.^{4,5} Prior to the popular use of fiberoptic gastroscopy, most of these tumors were treated with a presumed diagnosis of carcinoma until pathologic examination of the resected tumor. Today, endoscopic biopsy and cytologic or histopathologic examination can reveal the diagnosis before surgical intervention in most cases. This permits a planned approach to treatment that is different from that of gastric adenocarcinoma and may include surgical resection, radiation therapy, and chemotherapy. The individual roles of these modalities of therapy are, however, often debated. There is much disagreement and controversy regarding the efficacy of surgical resection alone, the optimal extent of resection and the curative value of radiotherapy and chemotherapy. The relative rarity of the condition and its confusion with pseudolymphoma^{6,7} during the earlier part of the century have prevented a detailed understanding of its natural history, making it difficult to render intelligent recommendations on treatment. We report here a retrospective study of 51 patients treated over a 27-year period at Memorial Sloan-Kettering Cancer Center.

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Observations were made on the natural history of this disease as influenced by various clinicopathologic factors and by different types of therapy. Suggestions are made for the future management of gastric lymphoma in the light of these observations.

Clinical Material

From 1949 to 1976, 112 patients with a recorded diagnosis of primary gastric lymphoma were seen at Memorial Sloan-Kettering Cancer Center. The clinical charts and histopathologic slides of these patients were reviewed to select appropriate cases for the study. The following criteria were used: (1) no lymphoma disease was revealed outside of the stomach and its vicinity at the time of initial therapy as determined by physical examination, chest roentgenography, bone marrow biopsy, and other diagnostic tests, (2) the tumor involved mainly the stomach, with or without secondary involvement of contiguous organs or adjacent lymph nodes, and (3) review of histopathologic tissue slides confirmed the presence of lymphoma in a portion of the stomach. Only 51 patients satisfied these criteria. The remaining cases were rejected because of the following reasons: tissue slides not available to confirm the diagnosis (40 patients); tissue slides showed lymphoma in a small biopsy with no assurance it came from a part of the stomach (12 patients); a diagnosis other than lymphoma was found (3 patients); and, there was already generalized lymphoma disease (6 patients).

Results

Sex and Age of Patients

The 51 patients consisted of 32 men and 19 women (male to female ratio 1.7 to 1). The age ranged from 21 to 82, with a median of 59 years. Sex did not seem to have influenced prognosis, but age did. None of the five youngest patients, aged 21 to 40 years, died of the

disease, whereas the five-year death rates for patients aged 41–60 and 61–90 were 52% and 48% respectively. No significant difference was noted among these age groups with respect to the extent of tumor involvement, the frequency of the histopathologic types of lymphoma, and the method of treatment. The reason for the favorable outcome of the young patients in this study is not clear.

Clinical Features

The symptoms and signs of these patients with primary gastric lymphoma resembled those of peptic ulcer disease and gastric carcinoma. Epigastric pain (28 patients), melena (10 patients), and hematemesis (5 patients) were among the most common presenting complaints. Six patients had been treated with antacids for presumed uncomplicated peptic ulcers, with some degree of improvement over one to three years, before distressing symptoms or radiologic examination of the stomach led to a change in management and the ultimate diagnosis of gastric lymphoma. Weight loss of 2–15 kg of body weight was reported by 15 patients. The discovery of a palpable abdominal mass by four patients proved to be an ominous feature: all four patients died of tumor. No prognostic significance was observed with the presence or absence of the other symptoms.

Radiologic examination of the stomach using barium contrast was the most important diagnostic procedure employed in patients treated prior to 1970. The barium roentgenographs revealed ulcerating, polypoid, or constricting lesions of the stomach. These appearances, when combined with the presence of large, fixed mucosal folds, were often characteristic though not diagnostic of gastric lymphoma. Fiberoptic gastroscopy with biopsy was employed in the diagnostic work-up of most of the patients after 1970. This yielded a pathologic diagnosis of lymphoma in six of eight patients in this study; of the remaining two patients, the biopsy was non-diagnostic in one and interpreted as undifferentiated malignancy in the other. Bone marrow biopsy, pedal lymphangiography, and other diagnostic procedures were also performed, but these tests were, by definition, negative.

Location of Tumor in Stomach

Seventeen of the tumors presented in the distal third of the stomach, which was the most common site. The middle and proximal thirds gave rise to eight and seven tumors respectively. Another eight tumors occupied the distal two-thirds, and four the proximal two-thirds of the stomach. In three patients, the neoplasm involved the entire viscus from the cardiac to the pyloric end. The anatomic site of four remaining tumors was not

clearly recorded. The small numbers of tumors occupying a single segment of the stomach did not permit meaningful comparison of the relationship between site and outcome. However, tumors that invaded only a single gastric segment showed a lower death rate at five years of 36%, as compared with 75% for tumors that involved two adjacent segments. On the other hand, all of the three patients whose tumor involved the entire three segments of the stomach survived free of disease at 7, 10, and 24 years respectively after therapy. All three patients had diffuse histiocytic lymphoma involving the gastric wall and perigastric lymph nodes. Two of these three patients were relatively young, aged 21 and 34 respectively. Except for this possibly favorable clinical feature, the apparent long-term cure of these three patients seemed incongruous with the generally poor outcome of patients who had extensive involvement of the stomach.

Gross Pathologic Characteristics

The tumors varied in appearance from small mucosal ulcerations to massive fungating lesions that invaded large areas of stomach, with or without penetration into adjacent organs. The larger tumors characteristically displayed multiple sessile polypoid protrusions into the gastric lumen, giving the radiologic appearance of giant rigid rugae.

The size of the tumor ranged from 1 cm to over 25 cm in diameter (median 10 cm), and appeared to have had a bearing on survival. Thus, considering only those patients who underwent curative therapy and had a minimum of five years' follow-up, four of six treated for small tumors not greater than 5 cm in diameter survived, while only ten of 19 treated for larger tumors remained alive.

The depth of invasion of the tumor into the stomach wall was studied in 47 patients whose records and histopathologic material were adequate for such retrospective evaluation. Five tumors were limited to the mucosa and submucosa, 12 invaded the musculature and reached the subserosa, 11 penetrated the serosa without invading contiguous structures, and 19 invaded adjacent organs, the diaphragm, or the greater omentum. The depth of tumor involvement appeared to have influenced prognosis in that only one of five patients died when lymphoma involved only the mucosa and submucosa, whereas almost one-half of the patients succumbed to disease when the tumor involved a deeper plane.

Direct Invasion of Extragastric Organs and Structures

Nineteen patients' tumor directly invaded an adjacent organ such as liver, spleen, pancreas, or colon (15

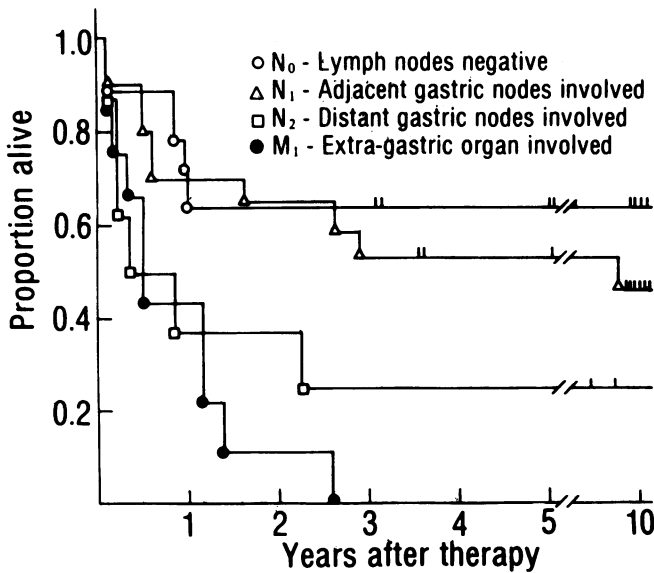


FIG. 1. Survival curves of patients after treatment according to extent of disease. At five years the survival rates were: 62% for tumors that involved the gastric wall only (N₀), 50% for tumors involving the stomach and the immediately adjacent gastric lymph nodes (N₁), and 25% for tumors involving also the more distant gastric lymph nodes (N₂). With involvement of unresectable extra-gastric organ structures, the median survival time was five months.

tumors), or an adjacent structure such as the anterior abdominal wall, diaphragm, and omentum. These tumors were very bulky in all instances. Palliative treatment by partial excision with or without radiation therapy was given to eight of these patients who survived from one to 16 months. Curative treatment by gastrectomy with en bloc removal of the involved organ or anatomic structure was given to the other 11 patients, nine of whom also received radiotherapy after operation.

Two of the patients died after operation of anastomotic leakage, pancreatic fistula, and subphrenic abscess, four succumbed to disease at six to 32 months, while only five survived free of disease for five to 24 years. Direct invasion of adjacent organ structures, therefore, portended a generally poor outcome.

Extent of Nodal Involvement

The records and histopathologic materials of 42 patients provided sufficient information for classification of the extent of lymph node involvement. Fifteen showed no nodal involvement (N₀), 19 showed nodal involvement limited to lymph nodes along the lesser or greater curvature immediately adjacent to the gastric lesion (N₁), and eight showed more extensive nodal involvement (N₂), including those lymph nodes along the left gastric, splenic, hepatic, and celiac axis arteries, as well as the upper para-aortic chain. According to the Ann Arbor classification of malignant lymphoma,⁸

these tumors can also be categorized as follows: extra-nodal lymphoma Stage IE, showing absence of nodal involvement, and Stage IIE, with nodal involvement. The extent of nodal involvement was found to be an important prognostic determinant. At five years after treatment, the survival rates for patients with N₀, N₁, and N₂ tumors, excluding postoperative deaths, were 62%, 50%, and 25% respectively (Fig. 1).

Histologic Types of Gastric Lymphoma

Table 1 records the frequency of the various histologic types of lymphoma according to Rappaport's classification. The histiocytic, diffuse type accounted for 51% of the tumors and was the most common, followed by the well-differentiated lymphocytic, diffuse type (22%). A striking difference in the five-year survival rate was noted between these two varieties of gastric lymphoma: only five of 26 patients who had the histiocytic type survived, whereas eight of 11 patients treated for the well-differentiated lymphocytic type remained alive.

Method of Treatment

During the 25 years of this retrospective study period, several changes in the clinical management of primary gastric lymphoma evolved at Memorial Sloan-Kettering Cancer Center. In the first ten years of this period (1949-1959), a preoperative diagnosis of lymphoma was rarely suspected and most of the neoplasms were resected under the presumed diagnosis of adenocarcinoma. Radical surgical resections were performed in accordance with this diagnosis by subtotal gastrectomy in 18 patients and extended total gastrectomy in 12 (40%). Radiation therapy was administered after operation in 18 patients (60%), using cobalt-60 teletherapy or 250 kilovolt peak x-rays. The radiation portals were generally small, often limited to a small portion of the left upper abdomen, e.g., 18 × 18 cm, and the radiation dose was relatively low. In the second ten years (1960-1969), more of the patients were treated by subtotal gastrectomy and fewer by the more extensive forms of resection. A similar proportion of the patients received postoperative radiation using supervoltage machines, but a trend towards higher radiation doses of up to 4,000 rads over five to six weeks and the use of larger portals became evident.

In the most recent period (1970-1976), three further distinct changes developed. First, a preoperative diagnosis of gastric lymphoma was made by biopsy or brush cytology in almost all patients subjected to fiberoptic gastroscopic examination. Second, all of the 11 patients who underwent gastric resection had subtotal gastrectomy. Review of the operative records indicated that

TABLE 1. *Histopathologic Classification (Rappaport) of Primary Malignant Lymphoma of Stomach and Five-year Survival After Curative or Palliative Therapy*

	Total No. of Patients	Status At Five Years			
		Alive NED	Dead of Lymphoma	Deaths After Operation	Dead of Other Causes
Histiocytic, diffuse	26	5	16	2	3
Well-differentiated lymphocytic, diffuse	11	8	1	1	1
Mixed cell type, diffuse	7	3	3		1
Poorly differentiated lymphocytic, diffuse	1	1			
Mixed cell type, nodular	1	1			
Unclassified	5	1	3	1	
Total	51	19	23	4	5

there was an obvious attempt to avoid extensive gastric resection procedures such as total or extended total gastrectomy that might have been applicable if the tumors were adenocarcinomas. As a result, much less postoperative morbidity was encountered. Third, radiation therapy was given to a higher proportion of patients (70%), using higher doses and larger portals. Four of the most recently treated patients received total abdominal radiation to 2,500 rads in three weeks followed by bolster doses of 1,000–1,500 rads over 1½–2 weeks to the stomach bed, para-aortic nodal area and the porta hepatis. Chemotherapy was not administered to any of the patients in the study unless there was evidence of systemic or recurrent lymphoma disease.

Results of Treatment

Forty-two patients underwent curative treatment by complete surgical resection of tumor with or without adjunctive radiation therapy after operation. There were three deaths after operation and three deaths due to causes not related to lymphoma, leaving 36 patients eligible for evaluation of results at five years.

Fifteen patients were treated by radical gastric resection alone without adjunctive radiotherapy; five, or 33%, survived five or more years free of disease; two of the five had tumor that also involved the perigastric lymph nodes. Eleven of the 15 patients underwent radical subtotal gastrectomy with three five-year survivors, while four had extended total gastrectomy with two cures.

Adjunctive radiation therapy was used following radical surgical resection in 21 patients, 14 or 67% of whom survived five or more years free of disease. Twelve of the 21 patients underwent radical subtotal gastrectomy, resulting in eight five-year survivors, while nine had total or extended total gastric resections with six cures. Many of these patients received radiation doses that are

judged today to be inadequate. The low dosage may have been due to limitations of the radiation equipment, but was, in many instances, due to the presence of debilitation and complications after operation.

Very striking results were observed when only patients who had received at least 2,000 rads to the abdomen were considered: there were six patients who received 2,000 to 3,000 rads over three to four weeks, and seven patients who received more than 3,000 rads, mostly through larger portals. Eleven of these 13 patients (85%) survived five or more years after treatment (Fig. 2). These eleven survivors included six who had lymphoma confined to the stomach wall, four with disease involving also the adjacent (N1) gastric lymph nodes, and two the distant gastric lymph nodes (N2). Histopathologically, these tumors were classified as: histiocytic type, diffuse in four patients; well-differentiated lymphocytic type, diffuse in three; mixed cell type, diffuse in one; mixed cell type, nodular in one; and unclassified in one.

Palliative treatment was given to nine patients because of extensive unresectable para-aortic nodal disease, free nodules of tumor in the abdomen, or liver involvement. Treatment in most instances consisted of radiation following resection of the gastric lesion leaving behind extragastric disease. These nine patients lived from one to 32 months (median survival—five months).

Complications of Treatment

There were four deaths related to surgical treatment, three in the 1950s, one in the 1960s, and none after 1969. All except one followed complicated extended gastrectomies with extensive lymph node dissections and removal of the distal pancreas and other adjacent organ structures. Death was due to anastomotic leakage, pancreatic fistula or subphrenic abscess, leading

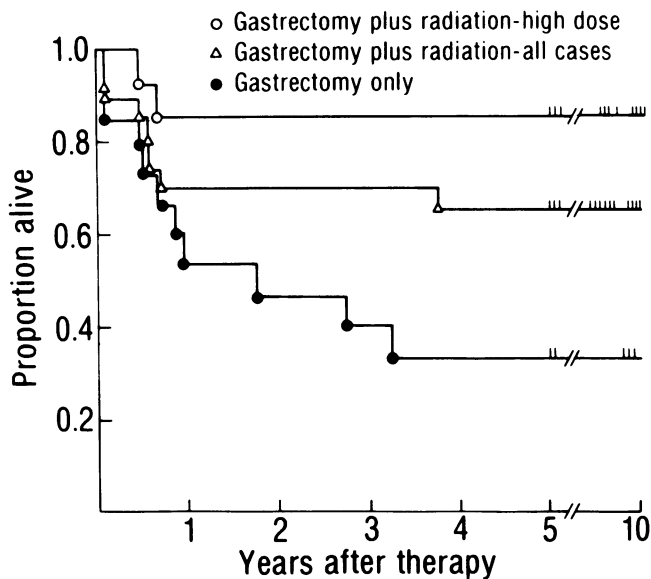


FIG. 2. Survival curves of patients after curative treatment of primary gastric lymphoma according to the method of therapy. At five years the survival rates were: 85% after gastrectomy and postoperative radiation of at least 2,000 rads given in 2½–3 weeks, 67% after gastrectomy and postoperative radiation for all patients so treated, and 33% after gastrectomy alone without postoperative radiation.

to massive bleeding or uncontrolled sepsis. Similar complications and the well-known morbidity associated with the more extensive types of gastric resection also precluded postoperative radiation therapy in many patients, or at least compromised the administration of an otherwise sufficiently high dose of radiation. In the absence of surgical complications, the radiation treatments were generally well tolerated. Two patients who received total abdominal radiation developed chronic diarrhea and malnutrition that responded to diet adjustment and intensive nutritional therapy.

Treatment Failure

The site of disease recurrence or progression was documented in 15 patients with sufficient detail to permit analysis of the cause of treatment failure. Ten patients developed manifestations of generalized malignant lymphoma in the form of cervical, axillary, inguinal or mediastinal lymphadenopathy, and involvement of liver, lung, and other visceral or nonvisceral sites. The development of generalized lymphoma disease occurred after an interval of two months to six years from the time of initial therapy, the median time being 6½ months. Intra-abdominal tumor recurrences were recorded in three patients, at 10 months, 27 months, and 7 years, respectively, after definitive therapy. Two of these three patients presented with obstructive jaundice due to enlargement of lymph nodes in the porta hepatis or the pancreaticoduodenal area, while the third patient de-

veloped multiple intra-abdominal masses of lymphoma. The two patients who developed obstructive jaundice following gastrectomy had received relatively low radiation doses, and the radiation portals did not include the porta hepatis and biliary passage areas; no radiation was given to the third patient. Both generalized and intra-abdominal recurrent lymphoma developed in two other patients, at 19 and 30 months respectively; neither of these patients had received radiation therapy. Irrespective of whether the treatment failure was regional or systemic, the patients succumbed within months after its manifestation despite further therapy.

Discussion

Malignant lymphoma is usually a generalized disease, but its occasional presentation in localized form as a primary gastric lymphoma has long been recognized,^{10,11} and is attested to by some reports of cure following treatment by surgical resection alone. Compared to gastric adenocarcinoma, primary lymphoma of the stomach is rare. The two conditions often present similar symptoms and radiologic signs. It is important, however, to be aware of the diagnosis of lymphoma, for the biologic behavior, diagnostic work-up, and clinical management of a gastric lymphoma are quite different. The therapeutic results are also better than those of gastric carcinoma in general. An overall five-year survival rate of 50% was achieved after curative treatment in this retrospective study of patients seen over a 27½ year period, and even higher survival rates are possible with modern methods of therapy.

A preoperative diagnosis of gastric lymphoma can be suspected by astute clinicians with any bulky gastric lesion, but radiologic signs such as large rigid mucosal folds or duodenal involvement often prompt the diagnosis. Pathologic examination of endoscopic biopsies or cytologic examination of brush samples of the tumor have in recent years proved to be most helpful in confirming the diagnosis. This has been the experience in the latter part of this study. Such techniques are the only means of identifying the less conspicuous early lesions that often masquerade as benign gastric ulcer or gastric carcinoma. Fiberoptic gastroscopy is, therefore, rightfully regarded as an indispensable step in the diagnostic evaluation of all gastric tumors and ulcerations. Once the diagnosis of gastric lymphoma is established, every effort must be made to rule out the presence of systemic lymphoma disease. Bone marrow examination, pedal lymphangiography, review of chest roentgenographs are in order, and when surgery is performed, biopsies of the liver as well as celiac, mesenteric, para-aortic, and iliac lymph nodes also need to be carried out for proper staging of the disease.

Whereas the mainstay of therapy for gastric adenocarcinoma is radical surgical ablation with extensive resection of the stomach and dissection of the regional lymph nodes,¹²⁻¹⁴ both surgical resection and radiation therapy must be recognized as important yet complementary modalities in the curative treatment of primary gastric lymphoma.

Surgical resection alone by subtotal gastrectomy and extended forms of radical gastrectomy yielded a rather low five-year survival rate of 33% in this study, and similar survival rates have been reported by others with surgical treatment alone.¹⁻² On the other hand, radiation therapy applied as the sole modality of treatment has also been reported in some patients.^{11,15,16} The small number of patients in these series, the possibility that some of the earlier reports may have included gastric pseudolymphomas as pointed out by Smith and Helwig and others,^{6,7} and the generally low survival rates reported for either the surgery or radiation treatment group argue against advising the use of either modality exclusive of the other. In fact, evidence adduced by earlier as well as more recent authors supports the therapeutic superiority of combined resection and postoperative irradiation. Five-year survival rates after combined therapy were reported to be 67% by Burnett and Herbert,¹⁷ 46% by Connors and Wise,¹⁸ and 60% by Joseph and Lattes.¹¹ In the present study, the survival rate was 67%. But when only patients who had received at least 2,000 rads in 2½-3 weeks to the stomach bed were considered, 11 of 13 patients (85%) survived five or more years. Included in the 11 survivors were six patients who had lymphoma that involved both the stomach wall and the regional lymph nodes.

The need for adjunctive radiation therapy after operation, and for adequate radiation doses delivered to a large field cannot be overemphasized. Bush and co-workers¹⁹ have also pointed out that for non-Hodgkin's lymphoma in general, particularly the histiocytic type, tumor doses of 4,000 to 5,000 rads in 20 to 25 fractions are needed to achieve a 75% rate of local disease control. Experience in the present series of intra-abdominal tumor recurrence outside the radiation field, causing obstructive jaundice and intra-abdominal masses, also serves to emphasize the importance of extended radiation portals. The more recently treated patients in the study received total abdominal radiation, with additional boosting doses directed at the stomach bed, para-aortic, splenic, porta hepatis, and pancreaticoduodenal areas. To date, the results of such combined therapy have been encouraging in a small number of patients. Obviously, longer follow-up study of a large number of patients treated in this manner will be necessary to determine its long-term results.

Granted the therapeutic efficacy of radiation therapy

as an adjunctive measure, and its known effectiveness in controlling other varieties of malignant lymphoma,⁴ most clinicians are, nevertheless, unwilling to recommend its use without surgical resection for the treatment of gastric lymphoma. The reason is that bleeding or perforation may develop with tumor lysis consequent to successful radiation therapy.¹⁸⁻²⁰ Emergency attempts to salvage these patients by surgical resection or other measures are often futile as anastomotic disruption or overwhelming intra-abdominal sepsis in a radiated field would usually prove to be fatal. A priori reasoning suggests that such bleeding or perforation would be more likely to occur with bulky, ulcerated, and necrotic tumors and less so with the small, superficial gastric lymphomas that may well be quite suited to primary treatment by radiotherapy. Whether selected patients with gastric lymphoma can be safely and effectively treated with radiation alone is a matter of continuing debate. In the lack of convincing clinical experience it would seem that such a controversy can only be resolved by a prospective clinical trial.

Until such a trial is conducted, however, combined therapy by surgical resection and radiation after operation must be regarded as the optimal method of treatment for the majority of patients with gastric lymphoma.

Surgical resection achieves several important objectives in such a treatment program. Surgical resection alone may be curative. Also, by removing all grossly visible tumor, subsequent complications such as bleeding and perforation are obviated, and, at least on theoretical grounds, further treatment of microscopic or occult residual tumor by radiation or chemotherapy may be rendered more effective. Furthermore, laparotomy permits a more accurate staging of the lymphoma disease by means of biopsies of the liver and intra-abdominal lymph nodes, so that more meaningful prognostication and therapeutic decisions can be made. The complications of treatment can be minimized by avoidance of total gastrectomy and complex forms of extended gastric resection whenever technically possible. While every effort must be made to remove all gross tumor, some compromise is justifiable on the demand for extra wide margins of gastric resection and extensive regional lymphadenectomy, which are usually recommended for gastric adenocarcinoma.¹²⁻¹⁴ Whatever measure of tumor control possibly lost by performing a less extensive or complex resection may well be compensated for by the assured early application of postoperative radiation therapy to adequate dose.

The role of chemotherapy is assuming an ever greater importance in the treatment of malignant lymphoma as more effective drugs and drug combinations become available. Chemotherapy was not used in the primary

therapy of the patients in this series. At least ten of 36 patients who underwent curative therapy developed manifestations of generalized lymphoma disease. It would seem reasonable, therefore, to administer chemotherapy after surgical resection and postoperative radiation therapy, especially when adverse prognostic factors such as nodal involvement and diffuse histiocytic disease would suggest that generalized lymphoma would be likely to develop. The effectiveness of chemotherapy may vary with the histologic type of lymphoma,²¹ and there have been few reports of its use with gastric lymphoma. Further clinical experience and investigative study, such as by cytochemical, immunologic, and ultramicroscopic methods,²¹⁻²² are therefore needed to fully elucidate the biologic behavior of the gastric lymphomas, so that a rational plan of treatment, using individual modalities or combinations of different modalities, can be made for each patient in the future.

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