Is an Aggressive Surgical Approach to the Patient with Gastric Lymphoma Warranted?

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At the Mayo Clinic, from 1970 through 1979, 84 patients (52 males and 32 females) had abdominal exploration for primary gastric lymphoma. All patients were observed a minimum of 5 years or until death. The histologic findings for all 84 patients were reviewed. Forty-four patients had "curative resection," and 40 patients had either biopsy alone or a palliative procedure. The probability of surviving 5 years was 75% for patients after potentially curative resection and 32% for patients after biopsy and palliation ($p < 0.001$). The operative mortality rate was 5% overall and 2% after potentially curative resection. Increased tumor size ($p < 0.02$), increased tumor penetration ($p < 0.01$), and lymph node involvement ($p < 0.02$) decreased the probability of survival, whereas histologic classification did not affect survival. Radiation therapy after surgery did not significantly affect the survival rate for the entire group or the survival rate for patients who had potentially curative resection. Resectability was associated with increased patient survival—independent of other prognostic factors—when our experience was analyzed by the Cox proportional-hazards model ($p < 0.005$). It was concluded that an aggressive surgical attitude in the treatment of primary gastric lymphoma is warranted. The role of radiotherapy remains in question.

PRIMARY GASTRIC LYMPHOMA is a relatively rare tumor that constitutes 2–5% of malignant gastric lesions. Because of its rarity, few institutions have been able to accumulate a sufficient number of patients to allow meaningful analysis and to determine an optimal approach to treatment. At our institution, experience with primary gastric lymphoma was last reported by Burgess et al.[1] in 1971. Since then, institutional philosophy has been that patients with primary gastric lymphoma should be treated by aggressive resection followed by adjuvant radiotherapy. Worldwide, however, the relative radiosensitivity of malignant lymphoma, coupled with its reputation for systemic dissemination, has led to a conservative attitude toward surgery. Primary radiotherapy alone and palliative resection with adjuvant radiotherapy have been advocated as treatments of choice.[2–4] Various factors have been identified as prognostic determinants, yet few studies have addressed their relative significance—that is, which factors are most important. Our goals were to determine what factors affect prognosis and whether an attempt at potentially curative resection is indicated.

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Methods

The histories of all patients who presented with lymphoma of the stomach at the Mayo Clinic from 1970 through 1979 were reviewed. Only patients with primary gastric lymphoma confirmed by abdominal exploration were included. Patients with secondary involvement of the stomach by non-Hodgkin's lymphoma, Hodgkin's disease, or pseudolymphoma or a history of a myeloproliferative disorder were excluded. Tumor location, size, depth of penetration, and lymph node status were obtained from operative and surgical pathology reports. Tumor histologic characteristics were rereviewed for every patient by one of us (L.E.W.) and were described according to the Rappaport, Kiel, and Working Formulation classifications.[5] Patients were considered to have died from lymphoma unless there was an obvious alternative cause in the absence of clinically persistent or recurrent lymphoma. The probability of surviving with lymphoma was calculated by the Kaplan-Meier method,[6] and survival curves were compared

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with the use of the log–rank test.[7] Independence of prognostic factors and the affect of continuous variation on survival were assessed with the use of the Cox proportional-hazards model.[8]

From 1970 through 1979, 84 patients had abdominal exploration for primary gastric lymphoma. Of the 84 patients, 52 (62%) were men and 32 (38%) were women, with a mean (±SD) age of 65 ± 11 years. Follow-up data were available on all patients for at least 5 years or until death.

Results

Pathologic Findings

The most frequent site for tumor origin was the distal portion of the stomach (44%). Twenty-one per cent of the tumors arose in the proximal portion, and 12% arose in the body of the stomach. Twenty-three per cent of the tumors either showed diffuse gastric infiltration or involved more than two-thirds of the stomach such that the location of origin could not be determined. The mean (±SD) maximal tumor dimension was 9.5 ± 5.2 cm (range: 3–30 cm). Twenty-six tumors were confined to the muscularis propria, and 10 involved the serosa. Forty-six patients had tumor invasion beyond the stomach to adjacent tissues, and seven of these patients had distant intra-abdominal involvement, presumably from intraperitoneal spread. Information regarding depth of penetration was unavailable for two patients. Forty-seven patients (56%) had regional lymph nodal involvement.

Forty-one patients had bone marrow biopsy during the perioperative period, but only one patient had bone marrow involvement. Twenty-four patients had splenectomy as part of the operative procedure. The spleen was involved by direct extension in four patients and was normal on pathologic study in the other 20 patients. Three patients had involvement of the liver by direct extension. Twenty-one patients had either needle or wedge biopsy of normal-appearing liver, and all specimens were free of lymphoma.

Surgical Results

Forty-four patients had potentially curative resection —all known tumor was believed to have been removed by the surgeon at the time of operation. Thirty-two patients had distal subtotal gastrectomy, 11 patients had total gastrectomy, and one patient had proximal subtotal gastrectomy. One patient died within 30 days of operation (after total gastrectomy), for an operative mortality rate of 2.3%. A potentially curative resection could not be accomplished for the remaining 40 patients. Twenty-two of these patients had biopsies alone, while 18 had various palliative procedures. In this group, there were three deaths within 30 days of operation, for an operative mortality rate of 7.5%.

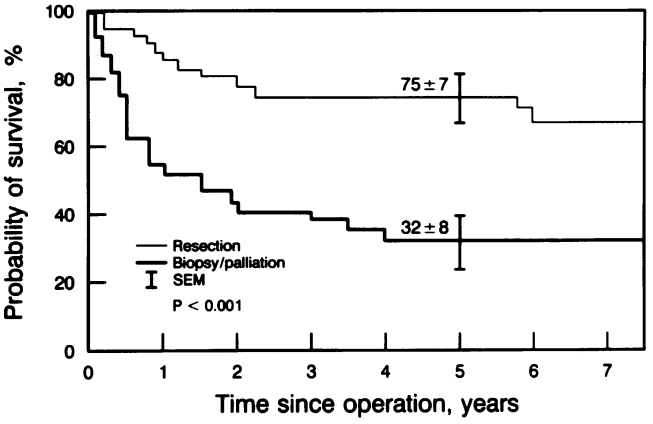

FIG. 1. Survival rate of patients with gastric lymphoma according to type of operation. Five-year survival rates (±SEM) are indicated.

Survival

The probability of surviving for 5 years after potentially curative resection was 75%, compared with 32% after biopsy with or without palliation ($p < 0.001$) (Fig. 1).

Tumors were grouped according to their largest single dimension. Although there was no significant difference in the probability of survival between the patients in either group, patients with larger tumors tended to have decreased survival (Fig. 2). When analyzed as a continuous variable, however, increased tumor size was associated with a poorer survival rate ($p < 0.02$).

Survival rate differed significantly ($p < 0.01$) with the extent of tumor penetration. Patients with tumors that were confined to the stomach had a higher probability of survival than did patients with tumors that had ex-

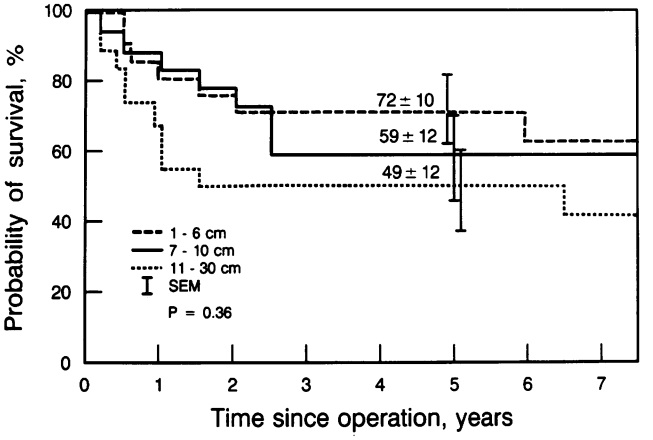

FIG. 2. Survival rate of patients with gastric lymphoma according to tumor size. Five-year survival rates (±SEM) are indicated.

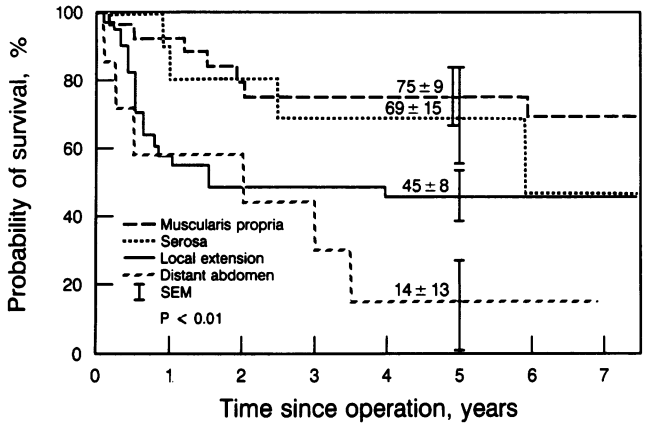

FIG. 3. Survival rate of patients with gastric lymphoma according to tumor penetration. Five-year survival rates (±SEM) are indicated.

tended to adjacent organs or spread to distant abdominal sites (Fig. 3).

The probability of surviving 5 years was 68% when the lymph nodes were not involved with tumor, compared with 43% when the lymph nodes were involved with tumor at the time of operation ($p < 0.02$) (Fig. 4).

The survival rate was calculated in relation to tumor classification by the Rappaport, Kiel, and Working Formulation methods (Table 1). Although patients with well-differentiated lymphocytic, plasmacytic, and centrocytic lymphomas tended to do better than those with poorly differentiated immunoblastic lymphomas (Kiel method), the survival rate could not be correlated with lymphoma classification.

There was no significant difference in the survival rate between patients who received radiotherapy after surgery and those who did not (Fig. 5). Also, there was no significant difference in the survival rate between patients who received radiotherapy after potentially curative resection and those who only had potentially curative resection (Fig. 6).

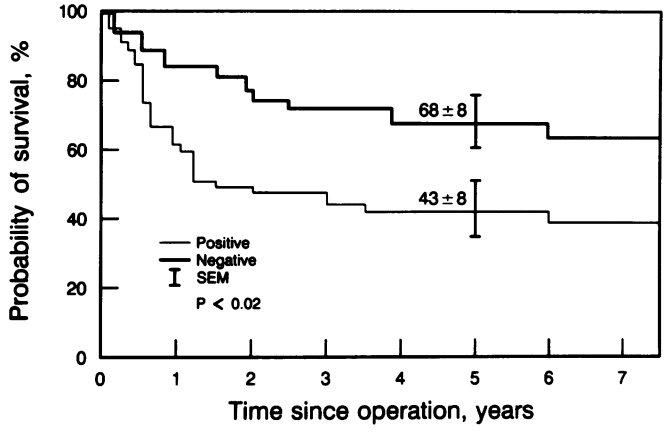

FIG. 4. Survival rate of patients with gastric lymphoma according to lymph node status. Five-year survival rates (±SEM) are indicated.

TABLE 1. *Survival of 84 Patients with Gastric Lymphoma According to Classification of the Lymphoma*

Classification	No. of Patients	Five-Year Survival Rate (% ± SEM)
Rappaport classification		
Well-differentiated lymphocytic	3	100
Diffuse poorly differentiated lymphocytic	1	100
Diffuse mixed histiocytic/lymphocytic	27	44 ± 10
Diffuse histiocytic	53	40 ± 7
Kiel classification		
Lymphocytic	2	100
Plasmacytic	1	100
Centrocytic	1	100
Diffuse centroblastic/centrocytic	27	44 ± 10
Centroblastic	49	41 ± 7
Immunoblastic	4	25 ± 22
Working Formulation		
Small lymphocytic	3	100
Diffuse small cleaved	1	100
Diffuse mixed small cleaved and large cell	27	44 ± 10
Diffuse large cell	49	41 ± 7
Immunoblastic large cell	4	25 ± 22

The Cox proportional-hazards model was used to identify factors that were independently associated with patient survival. The factors analyzed included tumor histologic characteristics, tumor penetration, lymph node status, tumor size, tumor resectability, and radiotherapy. Only tumor resectability affected the patient survival rate, independent of the other factors ($p < 0.005$). When analysis was done for the 44 patients who had potentially curative resection, only tumor size had an independent effect on the patient survival rate ($p < 0.01$).

Discussion

Multiple factors have been identified as prognostic determinants for patients with primary gastric lymphoma. We found that larger tumor size, increased depth of tumor penetration, and involvement of regional lymph nodes tended to be associated with a decreased survival rate. These associations compare favorably with the experiences of others. Joseph and Lattes[9] found a 5-year survival rate for nine of nine (100%) patients with tumors smaller than 5 cm, eight of 11 patients (73%) with tumors 5–10 cm, and only nine of 25 (36%) patients with tumors larger than 10 cm. Dworkin et al.[10] noted 5-year survival rates of 58%, 50%, and 32% for the same groups, respectively. Lim et al.,[11] however, did not find an association between tumor size and the patient survival rate.

Although others[2,10–12] have reported a decreased survival rate when there was full-thickness penetration, we

found a decrease in the survival rate only when the tumor had extended locally beyond the stomach to invade adjacent tissues. However, only Shiu et al.[12] identified the number of lesions with full-thickness involvement that had spread to adjacent tissues. Of their 24 patients with adjacent tissue involvement, only five survived free of disease for 5–24 years after operation.

In our experience, involvement of regional lymph nodes decreased the 5-year survival rate from 68 to 43%. Our experience is similar to that reported by others. In other studies, involvement of regional lymph nodes decreased the 5-year survival rate from 72 to 22%,[9] from 81 to 33%,[2] and from 60 to 21%.[13]

Some authors[3,9–12] have suggested that patients with well-differentiated lymphomas fare better than patients with poorly differentiated lymphomas. Others,[2,14] however, have not found a relationship between survival and histologic characteristics. We identified a few patients with a favorable prognosis. Four patients whose lymphomas were classified as well-differentiated lymphocytic or diffuse poorly differentiated lymphocytic by the Rappaport classification; as lymphocytic, plasmacytic, or centrocytic by the Kiel classification; or as small lymphocytic or diffuse small cleaved cell by the Working Formulation had a 5-year survival rate of 100%. However, we did not find a significant difference in the survival rate among the other subtypes, regardless of which method was used for classification.

The role of radiotherapy in the treatment of primary gastric lymphoma is highly controversial. Dworkin et al.[10] reported no difference in the disease-free survival rate between patients who had operations with radiotherapy and patients who had operations alone. However, Shiu et al.,[12] from the same institution, reported an increased survival rate in a group of patients treated with radiotherapy. Fleming et al.[15] reported a poor survival rate for 15 patients who had primary chemotherapy or radiotherapy (or both)—one of 15 patients was alive at 20 months. Furthermore, four of five patients who had aggressive chemotherapy without resection had massive upper gastrointestinal hemorrhage that required emergent operation. Weingrad et al.[16] reported their experience with all primary gastrointestinal lymphomas. They found no difference in the disease-free survival rate among patients who had operation alone, operation with radiotherapy, or primary radiotherapy. However, their complication rate attributable to radiotherapy was 12% after resection, compared with 22% without resection. Only Herrmann et al.[3] advocated primary radiotherapy. In their experience involving 71 patients with primary gastrointestinal lymphoma, they found that tumor size, degree of local extension, and the type of operative procedure had no prognostic importance.

Our study showed a tendency toward an increased survival rate for patients who had radiotherapy, but there was no statistically significant difference for either the group as a whole or the group that had potentially curative resection. Furthermore, we found that radiotherapy had less of an effect on the survival rate than did surgical resectability or tumor size.

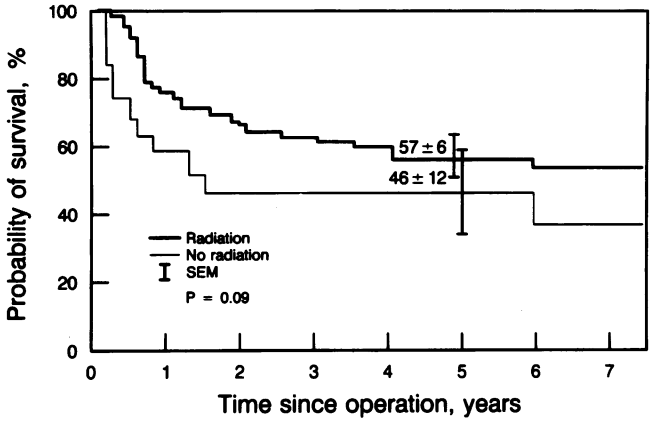

FIG. 5. Survival rate of patients with gastric lymphoma according to adjuvant radiotherapy. Five-year survival rates (±SEM) are indicated.

The generally accepted treatment for primary gastric lymphoma has been surgical resection when feasible. Most reports have advocated resection as the primary therapy.[1,10,11,15–17] Previously, Burgess et al.,[1] from our institution, reported a 5-year survival rate of 50% for patients with primary gastric lymphoma overall and a 5-year survival rate of 64% for those who had resection. Lim et al.[11] found a 5-year survival rate of 67% in patients after resection. However, others have found no benefit from resection.[3,4] Herrmann et al.[3] reported that resectability was not associated with the survival rate for patients with Stage I and II disease (all gastrointestinal lymphomas). Furthermore, they reported no difference in the disease-free survival rate between patients who

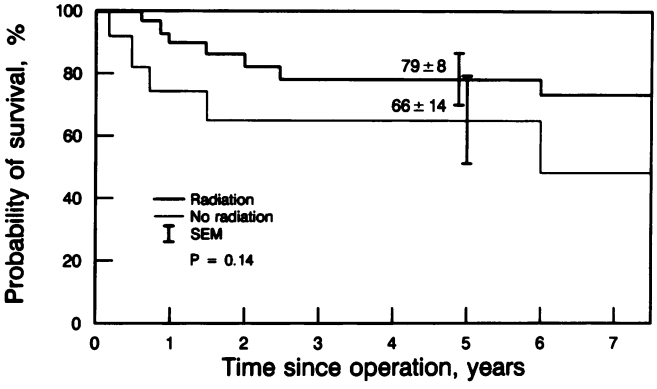

FIG. 6. Survival rate of patients with gastric lymphoma according to adjuvant radiotherapy after potentially curative resection. Five-year survival rates (±SEM) are indicated.

had resection combined with radiotherapy and those who had radiotherapy alone (a 75% survival rate for both treatments at 5 years), and they found a decreased survival rate after resection alone (25% at 5 years).

Our recent experience relates resectability to a more favorable prognosis for patients with primary gastric lymphoma. Herein, we report a 5-year probability of survival of 75% for patients with resectable lesions, compared with 32% for patients with unresectable (or partially resectable) lesions. However, our experience also suggests that tumor size, depth of tumor penetration, regional lymph node involvement, and histologic classification affect prognosis. One may ask whether the patients who had potentially curative resection had an increased survival rate simply because their tumors tended to be less advanced. However, analysis with the use of the Cox proportional-hazards model demonstrates that resectability influenced the patient survival rate independent of the other factors. Because the efficacy of radiotherapy remains to be determined, we propose that an aggressive surgical attitude in the treatment of primary gastric lymphoma is warranted.

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Discussion

Dr. Kirby I. Bland (Gainesville, Florida): I want to congratulate Dr. van Heerden and his associates, and Dr. Adkins, Dr. Scott, and Dr. Sawyers for bringing to the attention of the Association an important and increasingly accepted concept for the critical appraisal of approaches to gastric and intestinal lymphomas. Until recently, little objective data was forthcoming with regard to the biology and the management of this relatively uncommon neoplasm. Indeed, a quick perusal of the literature that has existed since the mid-1960s would suggest that we, perhaps, should discount many of these reports because of the inclusion of what has been termed "pseudolymphoma" of the stomach. In many of the series we have seen, perhaps, in excess of one third of these cases, the pathologist and clinician were confusing gastric lymphomas with the pseudolymphomatous lesion of which there are actually three distinct histologic types: (1) the "inflammatory" variant with accompanying ulceration and fibrosis, (2) the angiofollicular lymphoid hyperplasia, which was mentioned, and (3) nodular lymphoid hyperplasia. When one is in the abdomen, the differentiation grossly of the pseudolymphomatous process from gastric lymphoma is often not possible.

For concomitant diffuse intestinal lesions, the necessity of microscopic differentiation of mitotic rates and nuclear cytology is paramount to exclude the pseudolymphoma. This lesion usually has an earlier onset in life and often has involvement of smaller sites in the gastric mucosa, and many consider the gastric pseudolymphoma to be a premalignant process.

Over the past two decades, however, and as late as 1977, most reports suggest that the pseudolymphoma and reticulum-cell sarcomata classifications are essentially uninterpretable in light of our current knowledge. As Dr. van Heerden's series spanned the era from 1970–1979 in which critical alterations have occurred both in pathology and immunology, one would have to ask if these classifications are going to be preserved. I believe he used the Crile classification in this case, and as we know, the Rappaport and the Lukes' classifications have been used extensively.

In use of these classifiations, were the lymphocytic predominant groups observed to have the worst prognosis? You observed an increase in tumor size, the positive lymph nodes, and depth of tumor penetration as important prognosticators. Have you noted the histologic predominance of the cell type to have an important bearing in these results? Another important aspect is that many of us are now using flow cytometric analysis in which one can differentiate the hypertetraploid or hyperdiploid variant. Did that reflect poorly on the prognosis of these patients?

Our experience is essentially the same as the authors in this study, in that radiation adds little to palliation and perhaps nothing to survival, whereas the duration necessary for delivery of radiation therapy will incur morbidity, which translates into a reduction in the quality of survival.

Although we all consider gastric lymphoma as a multicentric disease, do you currently attempt to resect the lesion for margins and obtain a frozen section? Thereafter, do you clip the bed around this tumor resection and follow this anatomic site with scans to evaluate responses to cytotoxic chemotherapy and/or radiation?

Another fundamental question, since you have looked at the variance of gastric lymphoma, especially the multiple variants with bad histology, *e.g.*, the nodular or the large-cell variants, would you do a