Primary Gastric Lymphoma
A Review of 50 Cases

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The records of 50 patients with localized primary gastric lymphoma were reviewed and clinical and prognostic factors characterized. Pathologic material was reclassified according to Rappaport's, Lukes-Collins, and Lennert's Kiel classifications. Factors with the greatest prognostic significance included initial stage as determined by surgery and pathology, absolute tumor size, degree of penetration through the stomach wall, and histologic grade of the lymphoma.

After surgical resection for cure, the overall 5-year disease-free survival was 47%. For stage I disease, this was 78% vs 29% for stage II (P = 0.006). Patients with lymphomas less than 5 cm in diameter had 58% 5-year disease-free survival vs 32% for those with tumors greater than 10 cm (P = 0.06). Full-thickness penetration decreased 5-year survival from 75% to 38% (P = 0.06). Patients with histologically low-grade lymphomas had a better prognosis than those with high-grade lymphomas. The most significant correlation of histology to survival was seen with the Kiel classification with a 5-year survival of 39% for centroblastic polymorphous lymphoma vs 66% for LP immunocytoma.

When lymphoma recurred it developed outside the abdomen in a majority of patients. The addition of abdominal radiation therapy to surgical resection made no significant impact on survival for either stage I or II disease.

Gastric lymphoma is an uncommon neoplasm accounting for less than 2% of primary stomach cancers (1). Because of this low frequency, most large institutions see only two to eight cases per year (2). However, it remains an important diagnostic consideration in all patients presenting with gastric ulcerations, masses, or enlarged folds. The stomach is the most frequent site of primary extranodal lymphoma, and the survival associated with lymphoma at this site is better than for adenocarcinoma of the stomach (3). In order to address this question, records of 51 patients with primary gastric lymphoma seen at Memorial Sloan-Kettering Cancer Center between 1949 and 1978 were reviewed.

METHODS

All cases of gastric lymphoma were carefully screened to be certain that the primary site was indeed the stomach. Those with diffuse abdominal involvement, or significant extraabdominal disease at the time of presentation were eliminated if the origin of the tumor was not clearly gastric, even if the stomach was involved with the disease. The histopathology of all cases available was reviewed and reclassified according to the Rappaport (4), Lukes-Collins (5), and Lennert's Kiel (6) classifications. One case was eliminated as review of the pathology revealed adenocarcinoma. Data covering 46 of the remaining 50 cases was then analyzed by computer, and survival curves were obtained using life-table analysis (7). Statistical evaluation was performed by Wilcoxon (8) and log rank techniques (9).
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TABLE 1. INITIAL SYMPTOMS OF 50 PATIENTS WITH PRIMARY GASTRIC LYMPHOMA

| Symptom                  | Percentage |
|--------------------------|------------|
| Abdominal pain           | 84%        |
| Weight loss              | 71%        |
| Anorexia                 | 41%        |
| Vomiting                 | 33%        |
| Melena                   | 24%        |
| Change in bowel movement | 14%        |
| Hematemesis              | 6%         |

RESULTS

The median age at presentation was 58 years, with a range of 21–82 years. For males the average age was 61, and for females 56 years. All of the patients were Caucasian except for one Black and one Hispanic. Males predominated with a ratio of 1.6:1. The mean length of follow-up was 51 months, with the range from one month to 25 years.

Abdominal pain (84%) and weight loss (71%) were the most common presenting symptoms, and abdominal mass (31%) and tenderness (35%) were the most common signs (Tables 1 and 2). Gastrointestinal bleeding with melena occurred in 24% and hematemesis in 6% of patients, respectively. Anemia, defined as a hemacrit of less than 35% or hemoglobin of less than 12 g, was seen in 41%. An upper gastrointestinal x-ray series revealed an abnormality at some time prior to surgery in all 49 patients tested, with 71% showing filling defects or masses, 39% ulcerations, and 20% infiltration or large folds. The diagnosis of malignancy was made in 79% of cases based on the contrast x-rays.

Recurrent lymphoma developed in 20 patients after initial attempt at curative resection. The median time from initial diagnosis to recurrence was 12 months, with a range from 1 to 71 months. Most recurrences (85%) occurred within 24 months. Only 10 of the recurrences were biopsy proven. The other 10 were suspected clinically, based on abnormal x-rays or physical findings. Of those with recurrence, 80% eventually died with lymphoma. Two patients had biopsy-proven recurrence in cervical lymph nodes treated with radiation and died without tumor 41 months and 62 months later of unrelated causes. One patient had a soft tissue mass in the left thorax treated with radiation therapy two months after surgery, with resolution. No biopsy was taken, and he is alive at 280 months. The fourth patient had an abnormal upper gastrointestinal series 4 months after surgery, suggesting recurrent lymphoma. This was treated with radiation therapy, and his subsequent gastrointestinal series became normal. He is well at 206 months. Of those patients who died with lymphoma following recurrence, the mean survival was 6 months with a range of 1–31 months. Treatment in this group varied from no therapy to radiation or chemotherapy alone or in combination, with generally poor results. Initial recurrence was in extraabdominal lymph nodes in seven patients and intraabdominal sites in 5 patients. At the time of death, 11 of 16 patients had evidence of extraabdominal lymphoma, including positive lymph nodes. One patient had intraabdominal tumor only, and in four patients, the extent of involvement was unknown.

Second tumors were present in 20% of patients (Table 3). Skin malignancies were most common. One patient developed adenocarcinoma of the stomach 16 years following gastric resection and radiation therapy for lymphoma.

Thirty-eight cases were available for survival analysis. Overall disease-free survival was 57% at 2 years and 47% at 5 years. Absolute survival was 60% at 2 years and 52% at 5 years. Five-year survival for males was 37%, and for females 62% ($P = 0.09$). This relationship was independent of stage at presentation and histology, which were similar for both sexes. Five-year disease-free survival was 57% for patients less than 45 years old, 50% for those from 45 to 65, and 32% for those over age 65 ($P = 0.5$).

For tumors less than 5 cm at surgery, 2-year disease-free survival was 87%; for tumors between 5 and 10 cm, 50%; and for tumors more than 10 cm, 47% ($P = 0.06$). At five years, the survival was

| Second Malignancies*                        | Count |
|--------------------------------------------|-------|
| Basal cell or squamous skin                | 4     |
| Melanoma                                   | 1     |
| Breast                                     | 2     |
| Testicle                                   | 1     |
| Cervix                                     | 1     |
| Prostate                                   | 2     |
| Larynx                                     | 1     |
| Orbital sarcoma                            | 1     |
| Acute myelogenous leukemia                  | 1     |
| Gastric adenocarcinoma                      | 1     |

*Present in 10 of 50 cases (20%).

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58%, 50%, and 32%, respectively. Analysis of the effect of full-thickness penetration on survival revealed 5-year disease-free survival of 38% for tumors with penetration vs 75% for those without (P = 0.06) (Figure 1). Antral lesions did slightly better with a 5-year disease-free survival of 58%, compared to 50% for lesions of the cardia and fundus and 41% for diffuse lesions (P = 0.57).

Forty-five cases were restaged retrospectively from a review of surgical and pathological reports using the Ann Arbor system and employing Musshoff’s suggested modification for stage II cases (10). Stage I included involvement of the stomach and contiguous tissues only (20 cases). Stage II included involvement of the stomach and one or more intraabdominal lymph node regions (24 cases). Stage II was further subdivided into positive regional contiguous lymph nodes, II1E (17 cases), and positive noncontiguous nodes such as paraaortic or celiac axis involvement, II2E (7 cases) (Table 4).

Stage I patients had disease-free 2-year survival of 86% and 5-year survival of 78%. Stage II patients had 2-year survival of 41% and 5-year survival of 29% (P = 0.006) (Figure 2). Two-year disease-free survival was 54% for II1E and 27% for II2E (P = 0.10). Five-year disease-free survival was 35% for stage II1E, but could not be analyzed for stage II2E due to small sample size, but all cases in whom follow-up was available have died with recurrent lymphoma.

The effect of treatment on survival could be analyzed for surgery alone vs surgery with radiation therapy. Only initial therapy was considered. Surgery was either total or subtotal gastrectomy with intent to cure. Chemotherapeutic regimens varied widely in content and time of administration, which precluded proper evaluation. One patient underwent surgical staging without resection and was excluded. Four postoperative deaths were also deleted from analysis.

For the total group, 2-year disease-free survival for surgery alone was 59% and for surgery with radiation therapy 58%. Five-year survivals were 59% and 40%, respectively (P = 0.32).

If staging of the tumor was also taken into account, the 2-year disease-free survival for stage I disease was 88% for surgery alone and 83% for surgery with radiation. Five-year survival was 88% and 65%. For stage II surgically staged disease, there was a 28% 2- and 28% 5-year disease-free survival with surgery alone, and 48% 2-year, and 31% 5-year survival for surgery with radiation therapy. Small numbers precluded meaningful analysis of the substages of stage II with regard to therapy, but survival curves for stage II1E showed 2-year disease-free survival of 33% for surgery alone and 62% for surgery with radiation therapy (P = 0.41). Five-year survivals were 33% for surgery alone and 36% for surgery with radiation therapy (P = 0.58).

The histology of 43 cases was available for review and reclassified according to the Rappaport, Kiel, and Lukes-Collins classifications. The histologic type was found to be independent of sex.

| Table 4. Gastric Lymphoma Staging |
|-----------------------------------|
| Stage | No. of patients | % of total | 2 yr | 5 yr |
|--------|----------------|------------|------|------|
| Stage I | 20 | 44 | 86 | 78* |
| Stage II (total) | 24 | 53 | 41 | 29* |
| Substage II1E | 17 | 38 | 54 | 35 |
| Substage II2E | 7 | 15 | 27 | |
| Stage IV | 1 | 3 | 0 | |

45 patients

*P = 0.006.
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![Graph](Fig 2. Life-table analysis of the effect of initial stage on disease-free survival.)

Stage did tend to correlate with histology. Applying Rappaport’s classification, 21 cases were diffuse histiocytic lymphoma (49%), with 7 stage I and 14 stage II. Ten patients had diffuse well-differentiated lymphoma (23%), with 6 stage I and 4 stage II. When the Kiel classification was applied, 10 cases were centroblastic polymorphous (23%) with 3 stage I and 7 stage II. Twelve cases were lymphoplasmacytic lymphoplasmacytoid immunocytoma (LP immunocytoma) (28%), with 8 stage I and 4 stage II. In the Lukes-Collins classification, the most common types were plasmacytoid lymphocyte—12 cases (28%), with 8 stage I and 4 stage II. There were 12 cases of immunoblastic sarcoma (28%) with 4 stage I and 8 stage II (Table 5).

By Rappaport’s classification, 2-year disease-free survival for diffuse histiocytic lymphoma was 44% and for diffuse well-differentiated lymphoma was 88%. Five-year survival was 44% and 61%, respectively ($P = 0.13$). By the Kiel classification the 2-year disease-free survival for centroblastic polymorphous was 39% and for lymphoplasmacytoid immunocytoma, 90%. Five-year survivals were 39% and 66%, respectively ($P = 0.05$) (Figure 3). The Lukes-Collins classification revealed 2-year survivals of 89% for plasmacytoid lymphocyte and 44% for immunoblastic sarcoma. Five-year survivals were 61% and 44%, respectively ($P = 0.13$).

DISCUSSION

Primary gastric lymphoma is relatively rare, but important, since treatment and prognosis vary considerably from the more common gastric adenocarcinoma (2, 3). In our series, as in others, the diagnosis was not specifically suggested by the clinical presentation (1, 2). Abdominal pain and weight loss were the most frequent presenting complaints. The median duration of symptoms prior to treatment was 10.3 months. An abdominal mass or anemia were present in less than half the cases. Barium upper-gastrointestinal contrast studies were abnormal in all of our cases, with malignancy suspected in 79%, but lymphoma in less than 20%. Transpyloric extension of tumor into the duodenum, as noted by Meyers, was not reported in our patients (11).

![Table](Table 5. Histopathologic Subclassification of 43 Cases of Gastric Lymphoma according to Rappaport, Lukes-Collins, and Kiel Systems)

| Type                        | No. of patients | Percent |
|-----------------------------|-----------------|---------|
| **Rappaport**               |                 |         |
| Diffuse histiocytic         | 21              | 49      |
| Diffuse well-differentiated  | 10              | 23      |
| Diffuse mixed               | 6               | 14      |
| Nodular mixed               | 1               | 2       |
| Diffuse poorly differentiated| 1               | 2       |
| Unclassified                | 4               | 9       |
| **Lukes-Collins**           |                 |         |
| Plasmacytoid lymphocyte     | 12              | 28      |
| Immunoblastic sarcoma       | 12              | 28      |
| FCC large cleaved, diffuse  | 5               | 12      |
| FCC large cleaved, follicular, and diffuse | 1 | 2 |
| Unclassified                | 12              | 28      |
| **Kiel (Lennert)**          |                 |         |
| Low grade                   |                 |         |
| LP immunocytoma             | 12              | 28      |
| Centroblastic, centrocytic-diffuse | 5 | 12|
| Centroblastic, centrocytic-follicular, and diffuse | 1 | 2|
| Plasmacytic                 | 1               | 2       |
| High grade                  |                 |         |
| Centroblastic polymorphous  | 10              | 23      |
| Centroblastic               | 1               | 2       |
| Immunoblastic               | 1               | 2       |
| Unclassified                | 12              | 28      |

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Endoscopy with biopsy and cytology provides a high incidence of specific diagnoses (12). Reports of positive material obtained on gastroscopy have ranged from 67 to 96% in gastric lymphoma (2, 12–15). In a previous study from Memorial Hospital a definitive diagnosis of lymphoma was made in 10 out of 14 cases (71%) using a combination of biopsy and brush cytology (14). Lavage cytology was positive in only 4 cases, all of which also had either positive biopsies or brush cytology. We consider biopsy and brush cytology complementary procedures to be done in all patients.

Histopathologic classification on non-Hodgkin’s lymphoma has undergone frequent reassessment and modification (4–6, 16–19). The histology of our cases was reviewed and classified according to three separate systems (4–6). Currently, the most frequently used system in the United States is the Rappaport classification, which is based on the architecture of involved nodes and cellular morphology (4, 20). In 43 of our cases reviewed and reclassified according to Rappaport, there were 21 (49%) that were diffuse histiocytic (DH) and 10 (23%) that were diffuse well-differentiated (DWDL), the latter often with plasmacytic features and not associated with chronic lymphocytic leukemia. This is a higher rate of DWDL than usually reported, with others finding a higher percentage of diffuse poorly differentiated lymphoma (DPDL) (21, 22).

Under the Lukes-Collins classification, the most common histologic types were plasmacytoid lymphocyte (28%) and immunoblastic sarcoma (28%). By Kiel classification, the most common types were lymphoplasmacytic lymphoplasmacytoid immunocytoma (28%) and centroblastic polymorphous (23%).

An unexpected finding was a 20% incidence of second or third malignancies in our cases, with 15 additional cancers occurring in 10 patients (Table 3). In contrast, Lewin found only three second malignancies in 117 cases of gastrointestinal lymphoma (21). In our patients, the skin was the most common second primary site, including four epidermoid carcinomas and one melanoma. Only one of the skin cancers developed in a previously irradiated site. One patient developed adenocarcinoma of the stomach 16 years after resection and radiotherapy for primary gastric lymphoma, and another similar case has been reported (23). Gastric adenocarcinoma seems to occur with increased frequency in patients with a long-standing gastrojejunostomy (24).

Recurrent disease after surgical excision of the primary gastric lymphoma usually was evident within 2 years and was often seen in extraabdominal sites, most commonly peripheral lymph nodes. This suggests that the disease is probably “multifocal” in some instances, even when presenting as an isolated gastric lesion. Late recurrences, beyond 2 years, occurred in only three of our patients, but others have stressed that recurrence may occur up to 14 years after initial presentation (22, 25, 26). Survival in our patients averaged less than one year following documented recurrence. However, four of our patients with postsurgical recurrent lymphoma (two biopsy–proven) were treated with local radiotherapy, and subsequently did well. A similar experience has also been reported (27).

Several trends were identified that indicated decreased risk of developing recurrent disease after surgical removal of the primary gastric lymphoma. Longer survival was correlated with female sex, younger age, smaller tumor size, less penetration of the primary tumor through the gastric wall, localized stage, and well-differentiated or low-grade histology.
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In spite of the relatively small numbers of patients in subgroups, the initial stage of the tumor, determined by surgery, achieved statistical significance as a prognostic factor. A modified Ann Arbor staging system was used: stage I, primary lymphoma arising in the stomach with or without penetration into adjacent tissues; and stage II, associated lymph node involvement on the same side of the diaphragm. Stage II was further subdivided into immediate perigastric lymph node involvement (II₁E), and involvement of intraabdominal noncontiguous lymph node groups (II₂E). The major finding was a 5-year disease-free survival after resection of 78% for stage I compared with only 29% for stage II (P = 0.006). There was a trend for stage II₁E disease toward a longer survival than stage II₂E, but this did not reach a statistically significant level. Others have also found that both the presence and location of lymph node metastases has a marked effect on survival (22, 26, 28, 29).

Aside from initial stage, the best correlations with survival were seen with tumor size and penetration. For gastric tumors less than 5 cm in diameter, 5-year disease-free survival was 58% compared to 32% for those greater than 10 cm (P = 0.06). Five-year disease-free survival was 75% for lesions without full-thickness gastric wall penetration and 38% for those penetrating through the serosa (P = 0.06). Full-thickness penetration was usually accompanied by involvement of adjacent tissues. The study of Lim et al, using TMN staging system, also found that full-thickness penetration decreased 5-year survival from 88% to 24% (28). However, they did not find that the size of the tumor related to prognosis. The site of the lymphoma in the stomach was not a significant prognostic factor in our series, although antral lesions did slightly better than diffusely infiltrating disease. Conners et al concluded from their experience that diffuse gastric involvement with lymphoma did not preclude cure and had a better prognosis than the linitis plastica disease due to gastric adenocarcinoma (30).

Patients with low-grade malignant lymphomas tended to present at an earlier stage and to show improved survival in all three of the classifications. This was most pronounced in our analysis using the Kiel classification. The 5-year disease-free survival for lymphoplasmacytic lymphoplasmacytoid immunocytoma was 66% and for malignant lymphoma, centroblastic polymorphous type, 39% (P = 0.05). Bugat et al, using Lennert's classification, also found a survival difference between those tumors with low-grade versus high-grade malignancy (31). Under the Rappaport system, the 5-year survival was 44% for diffuse histiocytic lymphoma and 61% for diffuse well-differentiated lymphoma (P = 0.13). The Lukes-Collins classification likewise showed only a borderline survival difference between plasmacytoid lymphocytic lymphoma and immunoblastic sarcoma. Other reports have similarly found a weak correlation between histologic type and prognosis (1, 2, 21, 32).

The best treatment approaches for primary gastric lymphoma have not been resolved in the literature, particularly regarding the addition of abdominal radiation therapy to surgical excision (2, 21, 26, 29, 33–38). Most lymphomas are radiosensitive, and radiation therapy has been used successfully as the primary treatment modality in selected patients with primary gastric lymphoma (22). In our series, therapy could be evaluated for those receiving surgery alone or surgery plus adjuvant radiation. For the total group, there were no statistical differences in disease-free survival at 2 and 5 years between these two treatment regimens. Therapy was not controlled, however, and patient selection may have been a factor. Separate analysis of either stage I or stage II patients again revealed no obvious survival benefit in those receiving irradiation. Selecting out the stage II₁E group, there was a trend toward improved 2-year disease-free survival in the radiation group, which did not hold up at the 5-year mark. These subgroups were really too small for creditable analysis, and all the stage II₂E patients did poorly regardless of therapy, although most received irradiation. This subgroup should probably be treated systemically with chemotherapy as well as surgery and possibly radiation therapy.

Since the most frequent site of recurrent disease in patients with stage I and II₁E involved extraabdominal lymph nodes, there is a suggestion that adjuvant chemotherapy may be beneficial after "curative" surgery. This may be particularly relevant where prognostic factors indicate a high risk of recurrence, such as a stage I patient with high-grade lymphoma or involvement of adjacent structures or organs. Extraabdominal sites may harbor multifocal subclinical lymphoma, even when the disease appears to be confined to the stomach. There has been marked improvement in combination chemotherapy for lymphoma in recent years (39, 40). Controlled trials using adjuvant chemotherapy in carefully staged primary gastric lymphoma patients are needed.
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