Primary Gastric Lymphoma

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Gastric lymphoma may be treated with a variety of therapeutic approaches.

Background: Gastric lymphoma is a common presentation of non-Hodgkin's lymphoma. Controversy reigns about many aspects of its classification and management, especially regarding roles for surgical resection. Methods: The authors review the clinical features, staging, pathology, prognosis, and management issues with an emphasis on the role of surgical resection. Results: Staging usually can be completed using noninvasive techniques. Those with a low-grade B-cell MALT type lymphoma with Helicobacter pylori infection may be treated with antibiotics and close follow-up. Patients with stage I or II disease may be treated with chemotherapy and radiation. Surgery is indicated for those with perforation or uncontrolled bleeding. Conclusions: Gastric lymphoma, primarily a B-cell tumor, can be diagnosed and managed effectively with various approaches. Few prospective, randomized trials of alternative approaches have been performed.

Introduction

Lymphoma is generally classified as Hodgkin's disease or, for a lack of better term, a non-Hodgkin's type. The latter occurs more often and may be nodal or extranodal in origin. Primary extranodal lymphoma constitutes 25% of the non-Hodgkin's lymphoma cases in North America and up to 50% in parts of Europe and the Far East. The most common site of extranodal non-Hodgkin's lymphoma is the stomach, which represents approximately 24% of all primary extranodal lymphoma in the End Results Groups Cancer Registries in the United States. Compared with carcinoma incidence, non-Hodgkin's lymphoma is rare, representing 2% to 8% of all gastrointestinal malignancies, but its incidence is increasing. At least 60% of gastrointestinal lymphomas arise in the stomach. In the literature, almost every aspect of this entity is controversial, including its definition. Neither the staging system nor the histologic classification is uniform, and there are many types and subtypes with varying degrees of malignancy. The major controversy centers on the therapeutic options, and treatment continues to differ among major institutions.

Definition

In 1961, criteria proposed by Dawson et al to define intestinal lymphoma were subsequently applied to gastric lymphoma as well. Gastric lymphomas are considered primary when the stomach is predominantly involved, and the intra-abdominal lymphadenopathy, if present, corresponds to the expected lymphatic drainage of the stomach. Patients with palpable subcutaneous nodes, mediastinal lymphadenopathy, or abnormal leukocytes on peripheral blood smear or bone marrow aspirate are excluded. The criteria also exclude those with splenic or liver involvement. These strict criteria exclude many advanced cases, which can result in an underestimate of the frequency of the disease. Other series have included patients with predominant gastric involvement in whom the stomach appears to be the primary site on clinical judgment, thus including nodal lymphomas that have spread to the stomach. The definition of the Danish lymphoma group is predicated on the assumption that patients with primary gastric lymphoma have more than 75% of their disease volume in the stomach, based on clinical and radiological staging.

Clinical Features

Most patients are older than 50 years, with disease being most common in the sixth decade. Men are affected more often than women, and it is more common in whites than blacks. Table 1 summarizes the incidence of different clinical features in three series. Many patients experience symptoms, which are vague and nonspecific, for four to 10 months prior to diagnosis. Symptoms are mostly referable to the upper gastrointestinal tract and resemble peptic ulcer disease or gastritis. All patients in the series by Brooks and Enterline and by Rackner et al were symptomatic, and in the gastrointestinal lymphoma series reported by Contreary et al, only 2.7% were asymptomatic. Unlike nodal lymphoma, night sweat is not a common feature. The most common complaints are epigastric pain, weight loss, nausea, and vomiting. Occasionally, an abdominal mass is palpable. Lymphadenopathy is rare, and patients often have no physical signs. Perforation, bleeding, or obstruction are uncommon. Generally, the clinical features are no different from those of adenocarcinoma of the stomach.
Staging

The goals of staging are to provide an insight into prognosis and a sound basis for planning therapy. A combination of clinical, radiological, and surgical procedures may be required to define accurately the stage of each patient. Invasive procedures, however, are performed only if they are likely to change the management. Improvements in computed tomography (CT), lymphangiography, and percutaneous biopsy techniques have reduced the need for laparotomy to stage lymphoma. Laparoscopy is less invasive than conventional laparotomy and has been reported to detect liver involvement in 20% of patients with non-Hodgkin's disease. It has a complementary role to noninvasive investigations if findings are likely to alter the management.

The TNM staging system has been applied to patients with primary gastric lymphoma. However, according to the American Joint Committee on Cancer, the TNM staging system is ineffective for lymphoma in general. The most popular staging classification is a modification of the Ann Arbor system used for Hodgkin's lymphoma (Table 2). However, this system was challenged at the Fifth International Conference on Malignant Lymphoma in 1993, and a new proposal has been recommended (Table 3).

Pathology

The primary lesion is submucosal, originating from the lymphoid tissue in the lamina propria. It usually invades outward through the serosa, and the mucosa is involved later in the disease process. Lymph node involvement usually precedes distant metastases. The most frequent site is the distal portion of the stomach, although the pylorus is usually spared. The whole stomach or more than one site may be involved in 5% to 23% of cases. The appearance varies from small mucosal ulcerations to large fungating polypoidal masses. Occasionally, the tumor is a diffuse infiltrative process that resembles linitis plastica.

An analysis of 27 cases of gastric lymphoma and 1,471 cases of adenocarcinoma revealed that the site of the lesion was similar in both, with the most common being in the middle and distal third of the stomach. The level of invasion was most frequently to the subserosa (30% in each), followed by the submucosa in lymphoma (26%) and the serosa in adenocarcinoma (20%). Lesions in lymphoma tended to be larger than in adenocarcinoma, with approximately 30% of lymphoma lesions being larger than 10 cm compared with 9.5% of carcinoma lesions being larger than 10 cm. Nodal metastases occurred in 63% and 46% of lymphoma and carcinoma cases, respectively, with a more frequent distant level of lymph node metastases in the former. The incidence of adjacent organ infiltration ranges between 7% and 29% in different reports, with the most common sites being the pancreas, omentum, and spleen. The colon is occasionally involved, and the literature describes five case reports of gastrocolic fistulae secondary to primary gastric lymphoma. Most cases develop in patients with a history of gastric damage. In a report by Brooks and Enterline, the most common associated lesions were chronic gastritis and pseudolymphomatous lesions.

The histologic classification of lymphoid neoplasms has been frustrating for both clinicians and pathologists. Many classification systems evolved as the understanding of the biology and immunohistology of the disease improved. By the late 1970s, more than six divergent classification schemes were described. To unify the classification systems, the National Cancer Institute sponsored an international panel of pathologists and generated a working formulation in 1982 that was based on morphologic characteristics of the cells (Table 4). As more advances were made in immunopathology and monoclonal antibody reactions, several new clinical entities were recognized. In April 1993, a system to classify lymphoid neoplasms was developed -- the Revised European-American Lymphoma (REAL) classification (Table 5).
Isaacson and Spencer\textsuperscript{31} introduced the concept of mucosa-associated lymphoid tissue tumor (MALT) in 1983 and described this lesion in the gastrointestinal tract, thyroid, salivary glands, and lungs. The lesion is predominantly of the B-cell lymphoma type. The hallmark of the tumor is the presence of lymphoepithelial lesions with lymphoid follicles and infiltration of plasma cells. The characteristic cells resemble the centrocytes and have small, dense, granular nuclei with clear cytoplasm and irregular borders. Because the mucosa does not contain lymphoid tissue, it has been presumed that the lesion is preceded by chronic inflammation and immunostimulation, probably by the antigenic \textit{Helicobacter pylori}\.\textsuperscript{32} The lymphocytes will proliferate in a polyclonal fashion until one clone emerges that acquires malignant characteristics and develops into frank lymphoma. Histologically, they are divided into low-grade B-cell lymphoma, low-grade B-cell lymphoma with focal high-grade component, and high-grade B-cell lymphoma.\textsuperscript{3}

**Investigation**

In addition to blood cell count and blood chemistry, chest radiographs and bone marrow aspirates should be used to rule out metastatic disease. Barium meal will suggest a potentially malignant lesion in approximately 75\% of cases, with the most common finding being enlarged configured gastric folds.\textsuperscript{4,33} It is nonspecific, and the diagnosis is usually made on endoscopic biopsy. The endoscopic findings are a diffuse infiltrative process with thick, rigid folds that are indistensible on air insufflation, superficial confluent ulceration, or a polypoidal mass protruding into the lumen.\textsuperscript{34} The diagnosis is difficult to establish because the lesion is submucosal and may be inaccessible to biopsy. Lesions will often exfoliate necrotic cells that are difficult to interpret, or they may be small in number and size and thus indistinguishable from anaplastic carcinoma.

Endoscopic biopsies have become more accurate as histologic and endoscopic techniques have improved. In a report by Maor et al.,\textsuperscript{35} 21 (88\%) of 24 patients had positive biopsy results, and Seifert et al.\textsuperscript{34} reported an accuracy of 98.5\% on 66 patients when repeated endoscopies and multiple biopsies were used. Earlier studies showed disappointing results with cytology, but subsequent reports indicate an accuracy rate of over 90\%.\textsuperscript{34} CT scan of the abdomen can show the extent of the lesion and can rule out other metastatic disease, but it cannot differentiate reliably between metastatic lymphadenopathy and reactive lymphoid hyperplasia. In a report by Doyle and Dixon\textsuperscript{36} describing the CT features of 19 patients with primary gastric lymphoma, the most common and interesting findings were clefts and tracks that have been suggested to be specific and peculiar to these lesions. These were seen in nine scans, while other features included diffuse wall thickening (7), lymphadenopathy (5) rugal prominence (4), and intraluminal mass (3).

Endoscopic ultrasound is fairly accurate in detecting the depth of invasion and the presence of perigastric lymphadenopathy. It is operator-dependent, and Caletti et al.\textsuperscript{33} describe sensitivity and specificity of 89\% and 97\%, respectively, for 44 patients with gastric lymphoma. They report that the transmural pattern of spread and some specific echogenic patterns will allow lymphoma to be distinguished from other neoplastic lesions. The accuracy for depth of invasion and perigastric lymphadenopathy was 92\% and 77\%, respectively, in their series.

**Prognosis**

The prognosis of gastric lymphoma is more optimistic than that of gastric carcinoma or intestinal lymphoma.\textsuperscript{8,37,38} MALT-type lymphoma has a better prognosis because it tends to be localized for a long period of time.\textsuperscript{27} This has been attributed to its homing phenomenon in which the neoplastic cell tends to return to its original mucosal site rather than disseminate elsewhere.\textsuperscript{31}
for five years. Depth of invasion and serosal penetration are other adverse variables.3,38-41 In a report by Lim et al,38 five-year survival rate for T1, T2, and T3 disease was 82%, 65%, and 24%, respectively. Also, younger patients may fare better than older patients with the same stage of disease.11,15 T-cell lymphoma is less common but more aggressive than its B-cell counterpart.3,31 Superficial spreading and nodular types have better prognoses than other types.16,39 Lymphocytic lymphoma has a better survival rate than histiocytic lymphoma.11,41 Lesions with a higher index of cell proliferation as measured by monoclonal antibody Ki-67 or MIB1 are more aggressive.3,42 Patients with aneuploid lymphoma have a poorer survival and disease-free survival than those with diploid tumors.43

**Treatment**

The optimal role of each anticancer modality for treatment of primary gastric lymphoma is not well defined. A review of the literature regarding treatment approaches is difficult for several reasons. A single institution does not accumulate a sufficient number of cases to draw meaningful conclusions with good statistical power. Also, most of the earlier reports included cases of pseudolymphoma, sarcoma, and lymphosarcoma, which influence the results. Many authors address the issue as gastrointestinal lymphoma rather than specifically gastric lymphoma, although the two entities have different biologic behaviors and natural histories.3 The concept of MALT tumors has not been considered in many reports. Neither the staging nor the histologic classification is uniform across reports, and the infrequency of the disease, the widely variable therapeutic options, and the several histologic types and different grades of gastric lymphoma have made it difficult to conduct prospectively controlled, randomized studies.

**Surgical Therapy**

Historically, surgical excision has been the mainstay of treatment. Several reports show superior outcome with surgical resection in the early stages of disease (Table 6). Lim and associates41 described 36 patients who had curative resection with five-year survival rates of 88% and 32% in stage I and stage II, respectively. However, 16 of them had postoperative adjuvant radiotherapy. Conversely, of 12 patients who had no resection, 11 died within one year, and the remaining patient died four years later. Paulson and colleagues44 performed curative resection in 18 patients with stage I and stage II disease; 15 survived and three died of the disease during a follow-up ranging from 12 to 72 months. In a report by Rosen et al,24 44 patients who had complete resections had five-year survival rates of 75% compared with 32% for 40 patients with palliative resection or bypass and biopsy. Talamonti and colleagues11 reported on 18 patients with gastrointestinal lymphoma who were treated with resection followed by adjuvant therapy. Their five-year survival rate was 82% compared with 16% in 24 patients treated with nonsurgical therapy. Rackner et al19 showed that resection was an independent variable affecting survival in patients with gastric lymphoma, and they reported a five-year survival rate of 80% in 15 patients with stage I and stage II tumors who underwent resections. In another series,27 145 patients with gastric lymphoma -- including 71 of the favorable MALT-type -- had resection with additional adjuvant therapy, and their five- and 10-year survival rates were 76% and 58%, respectively. Another report26 demonstrated a 79% five-year survival for 20 patients who had resections compared with nine patients who had incomplete resection and died within five years. The largest series3 involving 161 patients reported 10-year survival rates of 87% and 60% for stage I and stage II disease, respectively, following resections.

### Table 6.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Patients</th>
<th>Stage I</th>
<th>Stage II</th>
</tr>
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<tbody>
<tr>
<td>Lim et al</td>
<td>1977</td>
<td>36</td>
<td>80%</td>
</tr>
<tr>
<td>Paulson et al</td>
<td>1983</td>
<td>13</td>
<td>100%</td>
</tr>
<tr>
<td>Rosen et al</td>
<td>1987</td>
<td>44</td>
<td>100%</td>
</tr>
<tr>
<td>Talamonti et al</td>
<td>1990</td>
<td>11</td>
<td>82%</td>
</tr>
<tr>
<td>Rackner et al</td>
<td>1991</td>
<td>15</td>
<td>85%</td>
</tr>
<tr>
<td>Doglioni et al</td>
<td>1991</td>
<td>145</td>
<td>87%</td>
</tr>
<tr>
<td>Iyengar et al</td>
<td>1993</td>
<td>20</td>
<td>79%</td>
</tr>
<tr>
<td>Nakamura et al</td>
<td>1995</td>
<td>161</td>
<td>94%</td>
</tr>
<tr>
<td>Kitamura et al</td>
<td>1996</td>
<td>302</td>
<td>95%</td>
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The concept of early gastric lymphoma has been introduced in Japan and defined as disease limited to the mucosa or submucosa, irrespective of lymph node status.45 Kitamura et al45 described 10 cases and reviewed another 202 patients from the literature with this entity. They reported a five-year survival rate of 95% following resection.

Stage I and stage II disease is usually amenable to curative resection, but the resectability rate in all patients regardless of stage ranges from between 52% to 76%.24,26,35,37,41 Nonresectability is usually due to metastatic disease or coexistent morbid conditions. The aim of surgery is to excise all the tumor with negative margins, but this goal must be balanced against the morbidity of the operation and the resulting quality of life. Thus, subtotal gastrectomy is preferable to total gastrectomy or more radical operations when the gross margins are negative. Positive microscopic margins can be controlled later with adjuvant therapy.12,13 In a prospectively randomized multicentric study from France, the incomplete resection status did not influence survival, relapse, or disease-free survival because all patients received adjuvant chemotherapy.46

**Adjuvant Therapy**

The indications for adjuvant therapy are not clear. However, most authors suggest the use of radiotherapy for residual disease, especially of the low-grade type. Adjuvant chemotherapy is indicated postoperatively for cases in which metastatic disease occurred in the lymph nodes or elsewhere, as well as for cases of high-grade tumors in which the incidence of subclinical metastases is likely to be high and the tumor cells are more sensitive to chemotherapy. Herrmann et al43 reported a better five-year survival rate and longer disease-free survival when radiotherapy was used after resection than in the resected group only -- 75% vs 25%, respectively. In a retrospective study by Shiu et al,28 the five-year survival rates for patients who had surgery only and those who had surgery with adjuvant radiotherapy were 33% and 67%, respectively. Radiotherapy was used mainly for adjacent organ involvement; in 13 patients who had higher radiotherapy doses of at least 30 Gy, the five-year survival rate was 85%. Shim et al49 found that radiotherapy did not affect overall survival, but in a subgroup of patients with poor prognostic factors (e.g., involved margins, nodes, or deep lesions), survival improved from 25% to 38% with radiotherapy. Similarly, Weingrad and colleagues13 reported a benefit from adjuvant radiotherapy in stage II but not in stage I disease. In their review of the literature, Bozzetti et al47 concluded that no benefit is derived by adding radiotherapy for stage I patients, provided that clear surgical margins are achieved. However, in stage II patients, the addition of radiation increased the approximately 50% five-year survival rate to 60%–70%. Some investigators have reported differences in survival when adding radiotherapy and/or chemotherapy, but their data were incongruent since some
patients had distant metastases on presentation. In another prospective study of 36 patients with poorly differentiated and high-grade lymphomas of the gastrointestinal tract, chemotherapy produced a response rate of 75% but a five-year survival rate of only 36%. In a prospectively randomized study, 25 patients were treated with surgery only, 29 received postoperative adjuvant chemotherapy, and 21 patients received preoperative radiotherapy followed by surgery and chemotherapy. The two-year survival rates were 51%, 79%, and 100%, respectively. Muller and colleagues have also shown that patients receiving combined modality therapy had significantly improved survival over those treated with single modality. They recommend adjuvant radiotherapy for stage I disease and adjuvant radiotherapy and chemotherapy for stage II disease. Another report describing 26 patients with stage I and stage II gastrointestinal lymphomas treated with chemotherapy following resection showed a projected five-year survival rate of 72%.

**Surgery or Chemoradiation as Primary Treatment**

Currently, the most controversial issue is whether chemotherapy and/or radiotherapy can be used to replace surgical resection as the primary modality treatment. Advocates of surgery argue that excision is necessary for accurate staging and histologic classification as the pathologist is given the whole specimen for examination rather than a small endoscopic biopsy specimen. However, it seems that the advances and expertise in endoscopic biopsy techniques and in immunohistopathology have allowed for acceptably more accurate histologic classification. The noninvasive radiologic investigations are providing fairly accurate clinical staging. The main concern with nonsurgical treatment is that chemotherapy and radiotherapy can lead to necrosis of the tumor with resultant gastric perforation or bleeding. Gastric perforation with peritonitis is a life-threatening complication with a nearly 100% mortality rate in the immunosuppressed patient. The incidence of chemotherapy-induced complications is variable and has been reported to be as high as 13% to 25%. However, other series indicate no perforation in their chemotherapy-treated patients. In a review of the literature involving 188 patients, Gobbi et al reported an incidence of 3.2% and 2.7% for perforation and bleeding, respectively. In another review of 17 articles, Mittal and colleagues found three instances of gastric perforation in 75 patients after receiving radiotherapy and 25 instances in 626 patients who did not receive radiotherapy and had perforation on presentation. Due to similar risk in both groups, it appears that risk is inherent and is not increased by medical treatment.

It has been suggested that surgery be used for large tumors that are unlikely to regress on medical treatment; however, tumors that are too large to respond to medical treatment may be unresectable as well. Thus, although early limited disease may be cured with surgery, chemotherapy and radiotherapy may be as effective and less morbid.

Several reports in the literature support this observation. Solidoro et al described complete remission in 16 of 18 patients with stage IV gastric lymphoma treated with chemotherapy. None of the six patients who were explored had gross disease, and one had a focus of microscopic disease. In another report, primary chemotherapy alone destroyed malignant cells in five patients with stage I and stage II gastric lymphomas in their gastrectomy specimens. In a study by the Danish Lymphoma Study Group, involving 66 patients who received chemotherapy and radiotherapy, 94 who had surgery with or without postoperative adjuvant chemotherapy and radiotherapy, and 15 who were untreated, the five-year survival rate was 63%. Surgery had no significant influence on survival in stage I and stage III cases on multivariate analysis. In the Amsterdam experience, radiotherapy alone was used, with chemotherapy added for bulky disease. The five-year survival rate for stage I and stage II patients was 85% and 58%, respectively. Hammel et al used mono-chemotherapy (either chlorambucil or cyclophosphamide) in 17 patients with stage I disease and in seven patients with stage IV disease. They reported complete remission in 18 patients (75%) within a median follow-up of 45 months. They were low-grade MALT tumors. A French study used the LNH-84 chemotherapy regimen in 37 patients with gastric lymphoma and reported a complete response rate of 81% and a four-year survival rate of 61%. However, 15 of these patients had complete resection of their disease prior to the chemotherapy. All patients had high-grade lymphomas, stage II through stage IV, or stage I disease with tumors larger than 10 cm. A study by Maor et al described 34 patients with stage I and stage II disease treated with radiotherapy and chemotherapy in which all patients had endoscopic biopsy or laparotomy and biopsy with no resection. Six deaths were disease related, and two died of treatment complications. Interestingly, two patients required surgery - one for progressive disease and the other for treatment-induced cicatrization and obstruction. The five-year survival rate and disease-free survival rate for the whole group were 73% and 62%, respectively. Another report analyzed 50 patients with gastrointestinal lymphoma, of which 25 were gastric in origin. They were treated with radiotherapy, surgery, or both. The five-year survival rate was equivalent for those treated with radiotherapy alone or in combination with surgery (75%) and was superior to that of the group treated with surgery only.

**Antibiotic Therapy**

Proliferation of low-grade B-cell primary gastric lymphoma is dependent on activation of T cells by *H. pylori*. In a large cohort study, the sera of 33 patients who developed gastric lymphoma were tested for evidence of prior *H. pylori* infection based on an enzyme-linked immunoassortent assay. They were found positive with an odds ratio of 6.3 compared with that of the control group. Using amoxicillin, metronidazole and bismuth, or omeprazole, Roggero and coworkers eradicated *H. pylori* infection in 25 of 26 patients with low-grade MALT lymphoma. Total remission of the lymphoma was achieved in 15 patients. Another report describes six patients with *H. pylori* infection and low-grade gastric B-cell MALT lymphoma treated with ampicillin, metronidazole, and bismuth. *H. pylori* was eradicated in all six, and five showed complete regression with no evidence of lymphoma on follow-up biopsies.

**Conclusions**

Patients with primary gastric lymphoma should be staged properly with noninvasive techniques. Surgical intervention is not indicated for stage III or stage IV disease unless complications or limited residual disease occurs following chemoradiation. Patients should undergo repeated endoscopic biopsies to confirm the diagnosis and accurately define the histology. Patients with a low-grade B-cell MALT-type lymphoma with *H. pylori* infection can receive antibiotics with careful follow-up and reassessment. Those with stage I and stage II disease may be treated with chemotherapy and radiotherapy rather than surgery; however, if resection is performed, it should be conservative since residual disease can be managed with adjuvant therapy.

Surgery is indicated upfront in some cases. Those presenting with perforation or with bleeding that cannot be controlled with nonsurgical treatment should undergo exploration. Obstruction is another complication but may respond to medical treatment, while placement of a jejunostomy feeding tube for nutrition is sometimes required. In patients with gastric lesions and repeated nondiagnostic biopsies, laparotomy is necessary to avoid treating an adenocarcinoma as a lymphoma. Although the risk of perforation does not appear to be related to medical treatment per se, it is more likely to occur in patients with full-thickness lesions. This extent of tumor may be recognized on CT scan or endoscopic ultrasound.
To define more accurately the indications of different therapeutic options in gastric lymphoma, more prospectively randomized studies are needed that involve a large number of cases and multi-institutional trials. Japan has the highest number of cases, but investigations there are refractory to performing prospective, randomized trials. Interestingly, while Europe and the United States report success for medical treatment of gastric lymphoma, a recent report from Japan advocates total gastrectomy for early gastric lymphoma.

References


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