Non-Hodgkin's Lymphoma of the Stomach: Treatment Outcomes for 57 Patients Over a 20-Year Period

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Background: Gastric non-Hodgkin's lymphoma (NHL) is a rare subtype of malignancy, for which no consensus exists about treatment. In this study, the treatment outcomes of gastric NHL in 57 patients were retrospectively evaluated for a period of 20 years at a single institute.

Methods: Clinical stages were classified according to the Ann Arbor staging system: 29 patients were stage I, 17 stage II, two stage III, and nine stage IV. The 46 stage I/II patients received aggressive, multimodal therapy: 24 of these (group A) were treated with surgery-based management, which included surgery alone (n = 6), surgery + chemotherapy (CT; n = 14), surgery + radiotherapy (RT; n = 2), and surgery + CT + RT (n = 2); 22 patients (group B) did not receive surgery, but received CT alone (n = 11), CT + RT (n = 5), or, in patients with low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, an oral anti-*Helicobacter pylori* regimen (n = 6). The 11 stage III/IV patients received CT and/or RT with regimens similar to those for stage I/II patients.

Results: Except for 1 patient with an initial surgical diagnosis, 56 patients underwent gastric endoscopic examination, which proved that 42 had NHL. The rate of diagnostic accuracy by gastroscopy was 75%. After multimodal treatment (n = 46) and a median follow-up of 54 months (range, 1–210 months), the 5-year survival rate was 40.3%. The 5-year survival rates for stage I, II and III/IV patients were 57.2%, 47% and 0%, respectively ($p < 0.005$). Of the 24 surgical patients (group A) who received sequential CT, with or without RT, 12 remained disease-free after a median follow-up of 98 months (range, 1–210 months); three patients died because of postoperative complications. Of the 22 non-surgical patients (group B) who received CT, alone or combined with RT, 14 remained disease-free after a median follow-up of 40 months (range, 4–189 months); one patient died because of massive gastric hemorrhage after CT. All stage III and IV patients died after a median survival of 4 months (range, 1–8 months).

Conclusion: Clinical stage is the most important factor predicting the long-term survival of patients with gastric NHL. Surgery may still be necessary in cases of failed gastroscopic diagnosis. In early-stage gastric NHL, non-surgical treatment seems able to achieve the aims of improved long-term survival and, in some instances, cure. [*J Chin Med Assoc* 2005;68(1):11–15]

Key Words: chemotherapy, gastroscopy, non-Hodgkin's lymphoma, radiotherapy, surgery

Introduction

The stomach is the most common site of primary extranodal non-Hodgkin's lymphoma (NHL).[1–3] Survival associated with lymphoma at this site is better than that for adenocarcinoma of the stomach,[4–6] but there are many controversial issues about the best treatment, which is based on surgery, chemotherapy (CT) and radiotherapy (RT).[7,8] Traditionally, gastrectomy has been advocated as the first therapeutic

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step for patients with primary lymphoma of the stomach.[9–12] This was because of diagnostic accuracy for large tumors and the ability to prevent life-threatening complications of CT such as gastric perforation and tumor bleeding.[13,14] However, with improved medical technology, diagnosis can be achieved by direct gastroscopy.[15,16] Recent treatment has therefore focused mainly on CT, which can be used instead of surgery in the early management of gastric lymphoma.[14,17]

We carried out a retrospective review of our clinical experience in the treatment of gastric lymphomas. We aimed to compare the results of surgery-based or CT-based treatment programs. Clinicopathologic features of disease and overall survival were evaluated.

Table 1. Aggressive, multimodal treatment programs for 46 patients with stage I–II non-Hodgkin's lymphoma

	n (%)
Surgery-based treatment	24 (52.2)
Surgery alone	6 (13.0)
Surgery + CT	14 (30.4)
Surgery + RT	2 (4.3)
Surgery + CT + RT	2 (4.3)
Non-surgical treatment	22 (47.8)
CT alone	11 (23.9)
CT + RT	5 (10.9)
Oral triple therapy for MALT lymphoma	6 (13.0)

CT = chemotherapy; RT = radiotherapy; MALT = mucosa-associated lymphoid tissue.

Methods

Fifty-seven patients with gastric NHL were treated at Tri-Service General Hospital, Taipei, Taiwan, between September 1984 and September 2003. All patients initially presented with gastrointestinal symptoms and then received direct gastroscopy or surgery, as clinically indicated for diagnosis or treatment. Medical records for these patients were retrospectively reviewed, including clinicopathologic characteristics, computed tomography, surgical records, and follow-up information. In all patients, a complete diagnostic evaluation was performed, including blood-chemistry profile, chest X-ray, and bone-marrow biopsy. Histologic classification was done according to World Health Organization criteria[18] and modified according to a recent publication:[19] low-grade B-cell lymphomas, comprising marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type (MALT lymphoma), follicular lymphoma, and mantle-cell lymphoma; high-grade B-cell lymphoma, comprising diffuse, large B-cell lymphoma (DLBL), Burkitt's lymphoma, or lymphoblastic lymphoma; and T-cell lymphoma.

Clinical stages were classified according to the Ann Arbor staging system. Forty-six patients with stage I and II NHL received an aggressive multimodal treatment program (Table 1), and were divided into group A (n = 24; mean age, 66 years) and group B (n = 22; mean age, 62 years). Group A patients received surgery-based management, which included surgery alone (n = 6), surgery + CT (n = 14), surgery + RT (n = 2), and surgery + CT + RT (n = 2). Gastrectomy was performed in 24 patients: subtotal gastrectomy in 13, total gastrectomy in 3, and radical total gastrectomy in 8. Group B patients did not receive surgery, but received CT alone (n = 11), CT + RT (n = 5), or, in patients with MALT lymphoma, an oral anti-*Helicobacter pylori* regimen (n = 6). The CHOP regimen was the principal CT protocol: cyclophosphamide 500 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) on day 1, oral prednisolone 60 mg/m^2 on days 1–5; a total of 6–8 cycles were administered at a treatment interval of 21–28 days. For elderly patients with other chronic conditions, the COP regimen of cyclophosphamide, vincristine and prednisolone was used. Patients with evidence of *H. pylori*-associated MALT lymphoma received oral antibiotic treatment with metronidazole, clarithromycin and omeprazole for 10 days.

Eleven patients with stage III–IV disease received RT, which was given as an abdominal bath with a total dosage of 20–30 Gy (variable fractionation), and a boost to the primary site. These patients received CT and/or RT with regimens similar to those for stage I–II patients.

Statistical analyses were performed using the Statistical Package for the Social Sciences version 10.0 (SPSS Inc, Chicago, IL, USA). Survival time was analyzed by the Kaplan-Meier method and calculated from the time of primary diagnosis to the last follow-up or death. Statistical significance was evaluated by the log-rank test and indicated by a p value of < 0.05.

Results

Clinical features

In the 57 patients with gastric NHL (37 males, 20 females), median age was 64 years (range, 14–83 years). Twenty-nine patients had stage I disease, 17

Table 2. Clinicopathologic characteristics in 57 patients with gastric non-Hodgkin's lymphoma

	n (%)
Gender	
Male	37 (65)
Female	20 (35)
Age (yr), median (range)	64 (14–83)
Stage	
I	29 (50.9)
II	17 (29.8)
III	2 (3.5)
IV	9 (15.8)
Clinical symptom	
Abdominal pain	36 (63.2)
Hematemesis	21 (36.8)
Poor appetite	7 (12.3)
Postprandial fullness	6 (10.5)
Vomiting	7 (12.3)
Weight loss	7 (12.3)
Diarrhea	2 (3.5)
Dysphagia	1 (1.8)
Dizziness	2 (3.5)
Dyspnea	2 (3.5)
Histologic subtype	
Low-grade B-cell lymphoma	16 (28.1)
Marginal zone B-cell lymphoma of MALT type	14 (24.6)
Mantle-cell lymphoma	1 (1.8)
Follicular lymphoma	1 (1.8)
High-grade B-cell lymphoma	40 (70.2)
Diffuse large-cell lymphoma	35 (61.4)
Burkitt's lymphoma	2 (3.5)
Lymphoblastic lymphoma	3 (5.3)
T-cell lymphoma	1 (1.8)
Result of gastric biopsy	
Positive biopsy for lymphoma	42 (73.7)
Misdiagnosed as ulceration/gastritis	11 (19.3)
Misdiagnosed as adenocarcinoma	2 (3.5)
Misdiagnosed as leiomyoma	1 (1.8)
Biopsy not done	1 (1.8)

MALT = mucosa-associated lymphoid tissue.

stage II, 2 stage III, and 9 stage IV disease (Table 2). The major symptoms were pain (63.2% of patients), hematemesis (36.8%), and poor appetite (12.3%). The most common pathologic subtype was diffuse, large-cell lymphoma (61.4%).

Fifty-six patients underwent initial gastroscopy because of their clinical symptoms; abnormal gastric lesions were seen, and endoscopic tissue biopsies were performed by experienced gastroenterologists. A correct histologic diagnosis of NHL was made in 42 patients, whereas other patients were misdiagnosed with ulceration (n = 11), adenocarcinoma (n = 2), and leiomyoma (n = 1); biopsy was not performed in 1 patient. The rate of diagnostic accuracy by gastroscopy was, therefore, 75%.

Treatment survival

After multimodal therapy (n = 46), the 5-year survival rate after a median follow-up of 54 months (range, 1–210 months) was 40.3%. Overall survival relating to disease stages is illustrated in Figure 1. The 5-year survival rates for stage I, II and III–IV patients were 57.2%, 47% and 0%, respectively ($p < 0.005$). All stage III and IV patients died after a median survival of 4 months (range, 1–8 months).

Figure 2 compares the overall survival in surgical (group A) and non-surgical (group B) patients; there was no significant difference between the 2 groups

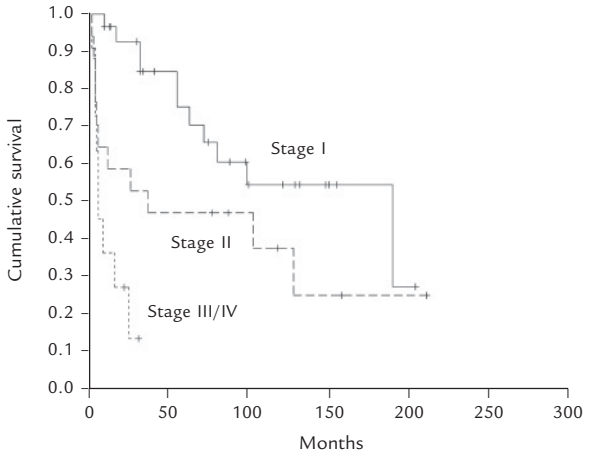

Figure 1. Kaplan-Meier analysis of overall survival relating to disease stage in 57 patients with gastric non-Hodgkin's lymphoma.

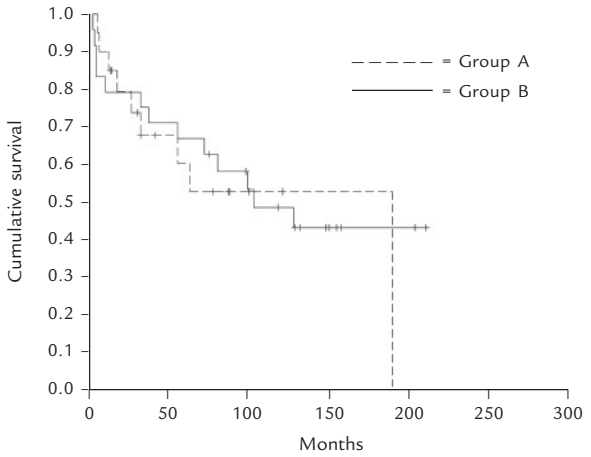

Figure 2. Overall survival in 46 patients with stage I/II gastric non-Hodgkin's lymphoma according to treatment: group A (n = 24) patients received surgery-based treatment; group B (n = 22) patients received non-surgical treatment.

($p = 0.12$). Twelve group A patients who received CT, with or without RT, were disease-free after a median follow-up of 98 months (range, 1–210 months). Twelve patients died: 3 from postoperative complications; 1, a long-term survivor, from other causes (adenocarcinoma of the colon with liver metastasis) while tumor-free at 98 months; and 8 from NHL relapse. Fourteen group B patients who received CT, with or without RT, were disease-free after a median follow-up of 40 months (range, 4–189 months). Eight patients died: 1 from another cause (cirrhosis of the liver with esophageal variceal bleeding); 1 from leukopenic septic shock 5 months after starting CT; 1 from massive gastric hemorrhage after CT; and 5 from NHL relapse.

Discussion

Primary gastric NHL is a relatively uncommon gastric neoplasm, which is reported to account for about 5% of gastric malignancies.[18,19] This series of 57 cases comprises 3.1% of all gastric malignant neoplasms seen at our hospital over a 20-year period.

The major presenting symptoms of gastric lymphoma were abdominal pain, fullness, hematemesis, vomiting, and weight loss; these symptoms are similar to those of benign or malignant gastric disorders.[20] Hence, it is difficult to differentiate clinically between gastric lymphoma and other gastric tumors. Nonetheless, the typical picture of lymphoma seen at gastroscopy is a large lesion with extensive gastric wall infiltration and ulceration, and a diagnostic accuracy of up to 90% has been reported in some series.[21,22] Gastroscopy was employed in 56 patients in this series, but the diagnostic accuracy was only 75%. Factors precluding diagnosis by endoscopic biopsy, because they were difficult to interpret, were the lymphoma growing deep into the submucosa, and large, ulcerating lesions exfoliating necrotic materials.[23,24] Thus, regardless of tumor appearance, multiple specimens should be obtained by biopsy, particularly at the edges of ulcerations. Repeated specimens should be taken at the same site to reach the submucosa. Of course, non-diagnostic or negative biopsies in patients with radiologic or endoscopic evidence of gastric lesions require further investigation with either repeat gastroscopy or surgical intervention.[16,25]

Total or partial gastrectomy was previously considered the first, conventional-therapy step for gastric NHL.[9,24] The reasons for this approach were as follows: exploration offering an opportunity to diagnose; disease staging; potential removal of tumor for good local control; and lack of CT or RT complications such as hemorrhage and perforation. However, several studies have shown that improvements in the diagnostic ability of gastroscopy have rendered surgery both an inappropriate primary diagnostic tool and an inappropriate initial treatment choice due to its high operative mortality (up to 16–18%), and because clinical responses and survival did not differ between surgical and non-surgical patients.[3,11] In our study, the operative mortality rate was 12.5%, and overall survival time did not differ significantly between surgery-based and CT-based groups. Although nearly all authors report that gastric resection should remove the risk of bleeding and perforation from tumor necrosis that may occur during CT and RT, such a risk was not seen in our patients.

CT for high-grade gastric lymphoma is similar to that for other high-grade NHL and is based mainly on the CHOP regimen,[14,17] which may be replaced by a COP schedule in elderly patients or in those with poor performance status, to prevent life-threatening complications.[4] The effects of other drug combinations containing bleomycin, methotrexate and cytarabine have also been reported in the literature.[26] As we only had a small number of patients who received RT, the role of such therapy cannot be assessed from our data. Further, RT has been used in only a few series, either as an adjuvant to surgery or as a single treatment. Nonetheless, RT is theoretically an additional effective treatment for controlling local disease.[15]

The most important prognostic factors in gastric lymphoma are clinical stage and cell type. All studies have shown that limited disease carries a better prognosis than extensive disease.[5,13,23–26] However, the Ann Arbor system is not suitable for the classification of gastric lymphoma. Musshoff et al[27] introduced a modification for Ann Arbor stage II disease to differentiate between local nodal involvement (II1) and more distant spread to para-aortic nodes (II2). It is reported that patients with stage II2 disease fare significantly worse than those with stage II1 disease.[27] Due to insufficient data, we could not analyze the survival of stage II patients according to the Musshoff staging system.

Based on our experience and data from the literature, we believe that surgery should not be considered an essential, primary treatment for gastric lymphoma. Improvements in endoscopic technology, with accurate diagnosis made from small biopsy specimens, led us to eliminate gastrectomy as a necessary, initial procedure.[28] As there is survival benefit with CT-based treatment, we recommend that initial CT should be mandatory in the treatment of gastric lymphoma.

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