

Original article

Clinical Outcome of Stage one and Two-E Primary Gastric non-Hodgkin Lymphoma Treated with Surgery Followed by Chemotherapy or Chemotherapy Alone

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Purpose: to evaluate the impact of chemotherapy alone or after surgery in the management of early primary gastric lymphoma as regards the overall and events free survivals.

Patients and Methods: Forty four patients with stage I & II primary gastric lymphoma were enrolled in the study during the period from November 2005 to December 2009. The patients were randomly divided into two groups: the first group of patients received chemotherapy alone and the second group of patients received chemotherapy after they had radical surgery. All patients received chemotherapy in the form of CHOP regimen.

Results: Events-free survival at three years was 64% in the group of patients who received chemotherapy alone and 77% in the group of patients who received chemotherapy after surgery ($p=0.38$). Overall survival at three years was 69% in the group of patients who received chemotherapy alone and 82% in the group of patients who received chemotherapy after surgery ($p=0.35$). Statistically insignificant differences were observed as regards leucopenia, anaemia and fever in both groups.

Conclusion: Events-free and overall survivals were higher in patients with primary gastric lymphoma treated by surgery followed by chemotherapy than in patients who received chemotherapy alone but the differences were statistically insignificant. Large studies are needed that involve a large number of cases, multi-institutional trials and adding anti CD20 in the era of targeted therapy to obtain survival benefit.

Key words: Gastric lymphoma, gastric tumor, extranodal lymphoma, non Hodgkin's lymphoma

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INTRODUCTION

Primary gastric lymphoma (PGL) is an uncommon tumor, accounting for less than 15% of gastric malignancies and about 2% of all non-Hodgkin lymphomas (NHL) but this incidence is increasing. However, PGL is the most commonly extranodal site involvement, representing 30%-40% of all extranodal lymphomas and 60%-75% of all gastrointestinal lymphomas¹. 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 stomach².

Any histological subtype can arise in the stomach, but the main two histological subtypes (more than 90% of cases) are diffuse large B-cell (DLBC) NHL and mucosa-associated lymphoid tissue tumor (MALT) NHL. *Helicobacter pylori* infection is the most common suspects in gastric carcinogenesis. It has been implicated in the pathogenesis of MALT-NHL, but its role in gastric DLBC-NHL is controversial³. As the primary chemotherapy treatment was given either alone or followed by radiation therapy, the role of surgical resection of the primary tumor needs to be clearly defined and justified⁴.

Earlier studies claimed that surgery was the first-line treatment of choice for patients with localized gastric lymphoma⁵. However, because the success of surgical management of primary gastric lymphoma depends on tumor size, the depth of its penetration into gastric tissue and the involvement of regional lymph nodes⁶, chemotherapy has been used to control the tumors and prevent the postoperative morbidities of gastrectomy⁷. In the present study, we try to evaluate the impact of chemotherapy alone or after surgery in the management of early primary gastric lymphoma as regards the overall and events free survivals.

PATIENTS AND METHODS

Forty four patients with stage I and II primary gastric lymphoma who presented to the Clinical Oncology and Nuclear Medicine department and Surgical Gastroenterology center, Mansoura University Hospitals, were enrolled in the study during the period from November 2005 to December 2009. This is the available convenient sample during research time period.

The inclusion Criteria: Patients aged from 30 to 72 years with pathologically proven malignant lymphoma that considered originating from the stomach, were staged according to Musshoff modification of Ann Arbor to be of stage IE or IIE. In stage IE the tumor remains confined within the stomach; in stage IIE1 the perigastric nodal involvement was positive; while in stage IIE2 more distant nodal involvement was found up to the region below the diaphragm⁸. Patients were entered in this prospective, randomized study and they did not receive prior chemotherapy or radiotherapy. Randomization was done using the block randomization method. Patients with MALT lymphoma were excluded.

The eligibility criteria for patient entry included no active second malignancy and an Eastern Cooperative Oncology Group performance status of 0–1, adequate hematological function, defined as leukocyte count of at least 4000 /mm³, platelet count of at least 100,000 /mm³ and hemoglobin level greater than 11 g/dL, adequate liver function, adequate cardiac function and adequate renal function with serum creatinine level of less than 1.5 mg/dL. Patients consent and approval of ethical committee were obtained.

Details concerning the history and physical examination, echocardiography, complete blood count, liver and kidney function tests and biochemical serum tests including lactate dehydrogenase (LDH) were used to interpret the epidemiological, clinical and laboratory features of patients. Staging procedures included computed tomography of the neck, chest, abdomen and pelvis, barium study, endoscopic ultrasound (EUS) and bone marrow biopsy. Indirect laryngoscopy was performed for excluding Waldeyer's ring involvement.

Upper gastrointestinal (GI) endoscopy with multiple⁸⁻¹⁰ biopsies, one from each quadrant of the lesions was done. Biopsies were taken from the edge of an ulcer rather than the base. Brush cytology of these lesions was used to complement the pathological examination.

The patients were randomly divided into two groups: the first group of patients received chemotherapy alone and the second group of patients received chemotherapy after they had radical surgery. Twenty two patients underwent radical gastrectomy: subtotal gastrectomy was performed in 13 patients, seven patients had total gastrectomy and two patients underwent partial gastrectomy according to the extension of the tumor.

All patients received chemotherapy in the form of CHOP regimen which consisted of intravenous injection of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m² and vincristine 1.4 mg/m² (maximum 2 mg) on day one

and prednisone 60 mg/m² orally on days 1-5. The cycles were repeated every three weeks. All patients received premedication with a 5-hydroxytryptamine-3-receptor antagonist and dexamethasone, given as a 30 min drip infusion before chemotherapy.

The patients were followed up every 2-3 cycles of chemotherapy clinically and using abdominal computed tomography and endoscopic examination and biopsy in order to confirm response, treatment failures or relapse. Grading of treatment toxicity as well as tumor response was evaluated according to the criteria defined by the World Health Organization⁹. Complete response (CR) was defined as the disappearance of all evidence of tumor(s) for a duration of at least 4 weeks. Partial response (PR) was defined as > 50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions in radiographic images, with the reduction lasting at least 4 weeks. Stable disease (SD) was defined as < 50% reduction or < 25% increase in the sum of the products of the longest perpendicular diameters of all measurable lesions, lasting > 4 weeks. Progressive disease (PD) was defined as the appearance of new lesions or > 25% increase in the area(s) of original measurable disease.

Overall survival (OS) was calculated from the date of diagnosis to the date of death due to any cause or the date of last follow-up in the survivors. Event-free survival (EFS) was measured from the date of diagnosis to the date of treatment failure, relapse, evidence of disease progression or death due to any cause or the date of last follow-up if no relapse or death occurred.

Statistical analysis:

Statistical analysis was done by using SPSS (Statistical Package for Social Science) program version 15. Chi square test or Fisher's exact test was used when appropriate to examine relationship between qualitative variables. Primary endpoints of our analysis were OS and EFS. The survival endpoints were analyzed using Kaplan Meier method and log-rank tests were used to compare the two survival curves¹⁰. Differences were considered statistically significant when $p \leq 0.05$.

RESULTS

From November 2005 to December 2009, 44 eligible patients with pathologically proved stage I & II primary gastric lymphoma were enrolled into this study. Twenty two patients were randomly assigned to receive chemotherapy alone and 22 patients were assigned to have surgery followed by chemotherapy. The treatment groups were well balanced in terms of age, sex and tumor stage Table (1).

Total chemotherapy cycles delivered during the study were 249 cycles (137 cycles in the group I and 112 cycles in the group II) with a median of 6 cycles for each patient. Delay cycles occurred in 20 cycles (14.5%) in the group I and in 15 cycles (13.4%) in the group II. The delay was done due to mostly hematological toxicities.

Table 2 showed the toxicity of treatment (grade 3 or 4) according to the WHO criteria. Leucopenia, anaemia and fever were more frequent in the group of patients who received chemotherapy alone (Group I) than in the group of patients who received chemotherapy after surgery (Group II) but the difference was statistically insignificant. Leucopenia occurred in six patients and three patients in group I and group II, respectively, anaemia occurred in three patients and two patients in Group I and Group II, respectively, fever was observed in two patients in group I and one patient in group II. Thrombocytopenia occurred in one patient in the group II. Four patients in group I suffered from nausea and vomiting while 6 patients in group II suffered from them. Neurotoxicity occurred in two patients in group I and

one patient in group II. Both upper GIT bleeding and perforation developed in one patient in group I while one patient suffered from anastomotic leakage after surgery (Group II). No cardiotoxicity was diagnosed in the patients during the follow up period.

We evaluated the response to chemotherapy in the patients who received chemotherapy alone (Group I), complete response was observed in 18 out of 22 patients (81.8%) and partial response was found in two patients (9.1%). The patients in group II underwent gastrectomy before receiving chemotherapy. Relapse occurred in 6 patients and 4 patients in group I and group II, respectively during the follow up period.

The median follow up period was 41.5 months (range from 2 to 60 months) in the group I and 44 months (range from 4 to 60 months) in the group II. Events-free survival at three years was 64% in the group I and 77 % in the group II, ($p=0.38$) (Figure 1). Overall survival at three years was 69% in the group I and 82% in the group II ($p=0.35$) (Figure 2).

Table 1: Baseline patients characteristics in both chemotherapy alone and surgery plus chemotherapy groups.

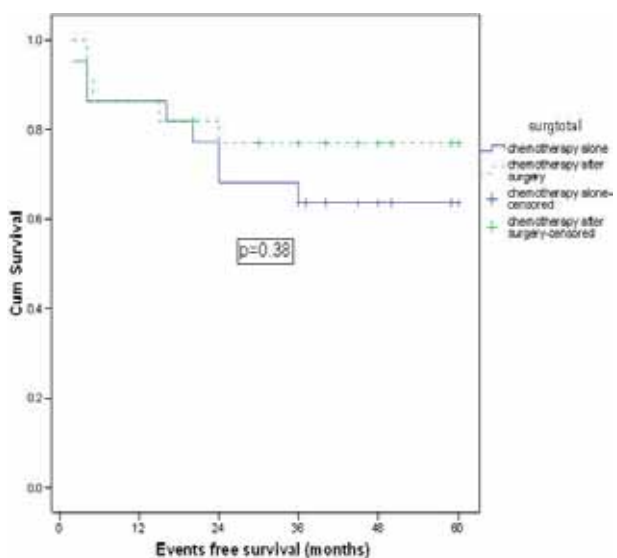
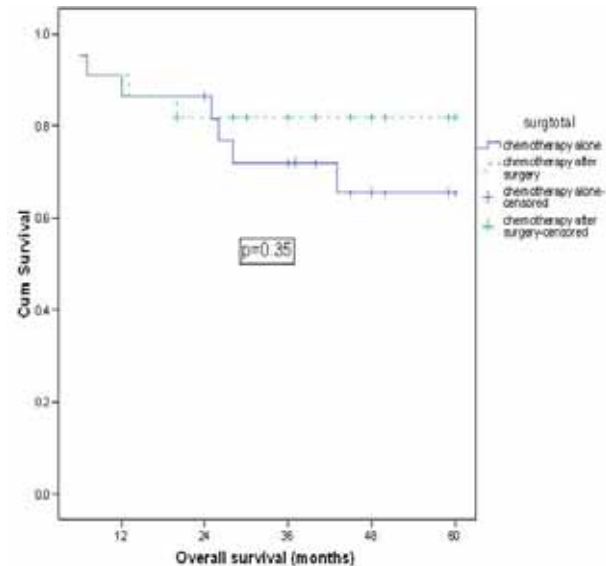
Characteristics	Chemotherapy alone (n =22)		Surgery plus Chemotherapy (n =22)		p value
	No. of Patients	%	No. of Patients	%	
Age(years)					
Median	50		48.5		0.24
Range	30-72		32-70		
Sex					
Male	13	59.1	10	45.5	0.37
Female	9	40.9	12	54.5	
Tumor stage					
I E	14	63.6	12	54.5	0.82
II E1	5	22.7	6	27.3	
II E2	3	13.7	4	18.2	
ECOG score					
0	18	81.8	17	77.3	0.71
1	4	18.2	5	22.7	
B symptoms	3	13.6	2	9.1	0.50
LDH					
Normal	14	63.6	16	72.7	0.52
Elevated	8	36.4	6	27.3	
IPI					
0	8	36.4	11	50.0	0.47
1	11	50.0	7	31.8	
2	3	13.6	4	18.2	

ECOG score: Eastern Cooperative Oncology Group performance status.

IPI: International Prognostic Index.

Table 2: Adverse events (grades 3-4) in both chemotherapy alone and surgery plus chemotherapy groups.

Toxicity	Chemotherapy alone (n =22)		Surgery plus Chemotherapy (n =22)		p value
	No.	(%)	No.	(%)	
Hematological					
Leucopenia	6	27.3	3	13.6	0.23
Thrombocytopenia	0	0	1	4.5	0.50
Anemia	3	13.6	2	9.1	0.50
Fever	2	9.1	1	4.5	0.50
Nausea&vomiting	4	18.2	6	27.3	0.36
Neurotoxicity	2	9.1	1	4.5	0.50
Cardiotoxicity	0	0	0	0	0
Upper GIT bleeding	1	4.5	0	0	0.50
Anastomotic leakage	0	0	1	4.5	0.50
Perforation	1	4.5	0	0	0.50

**Figure 1:** Event free survival in both chemotherapy alone and surgery plus chemotherapy groups.**Figure 2:** Overall survival in both chemotherapy alone and surgery plus chemotherapy groups.

DISCUSSION

Traditionally, aggressive surgical resection has been the mainstay treatment of primary gastric non-Hodgkin lymphoma because it can collect definitive tissues for pathologic examination, allow exploration of the abdomen, reduce tumor burden and obviate the concern that gastric hemorrhage or perforation would complicate medical treatment of lymphomas. The aim of surgery was 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. Positive microscopic margins can be controlled later with adjuvant therapy¹¹.

Several reports have shown a superior outcome when surgical resection is undertaken in the early stages of the disease with a 5-year survival rate of 80%-93%¹². In a prospectively randomized multicentric study, the incomplete resection status did not influence survival, relapse, or disease-free survival because all patients received adjuvant chemotherapy¹³. Therefore, aggressive surgery is not indicated due to increased morbidity which is outweighing the benefit gained in terms of survival, also gastrointestinal organ preservation may provide substantial advantage for the quality of life in these patients^{14,15}.

Adjuvant chemotherapy is indicated postoperatively for cases in which metastatic disease occurred in the lymph

nodes, 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. A Chinese study has suggested that chemotherapy plays a role in improving survival rates post-surgical resection¹⁶. Other authors also found surgery alone to be an adequate treatment for stage I with a survival rate of more than 95%, provided staging is performed after radical gastrectomy¹⁷. A prospective study, has found that in stages I E and II E, the complete response, survival rate and disease free survival rates were similar to those who underwent complete resection, partial or no surgery prior to administration of chemotherapy. The survival rates of 60% with surgery alone comparing to 85% if adjuvant chemotherapy was given, were reported¹³.

Both Tondini et al. and Vaillant et al. had shown the superiority of combined surgery and chemotherapy to single mode with survival rates between 86%-94% for stages IE and IIE primary gastric lymphoma. In these series the survival rates were higher for those who had complete resection; resection was the most important variable and major determinant of prolonged complete remission^{18,19}. On the other hand, surgery is advocated as the first option with adequate control of the disease and occasionally with the necessity of wide resection and extensive lymph node dissection, however, adjuvant chemotherapy was indicated to control the local and distant disease^{20,21}.

In Lin et al. and Thieblemont et al., chemotherapy alone compared with surgical resection alone, has shown no significant difference in the matter of survival. The overall 2-year survival was 67% and 81%^{22,23}. In three trials with variable chemotherapy regimens, the survival rates ranged from 82% to 88% in stage IE and IIE, high grade lymphoma with only few and manageable complications were found²⁴⁻²⁶.

In our study, we tried to compare the outcome of primary high grade primary gastric non-Hodgkin lymphoma treated with either chemotherapy alone or surgery followed by chemotherapy as regards survivals and toxicities. We evaluated the response to chemotherapy in the patients who received chemotherapy alone, complete response was observed in 81.8 % of patients and partial response was observed in 9.1%. This result was correlated with the results obtained by Chang et al.²⁷ and Sbitti et al.²⁸ in which complete response was achieved in 84.2% and in 87% of patients who received chemotherapy alone in the first trial and in the second trial, respectively. Partial response was found in 15.8% and in 6%, in patients who received chemotherapy alone in the first trial and in the second trial, respectively.

During the period of follow up in our study, relapse occurred in 6 patients in group I and 4 patients in group II, events-free survival and overall survival were higher in patients who had surgery followed by chemotherapy than in patients who received chemotherapy alone but the differences were statistically insignificant, 3-year events-free survival was 64% in the group I and 77 % in the group II. Overall survival at three years was 69% in the group I and 82% in the group II.

This result coincided with that conducted by Chang et al.²⁷. Sbitti et al. suggested that the clinical outcome of localized primary gastric lymphoma treated by chemotherapy alone was comparable to that treated by surgery combined with chemotherapy in terms of disease-free survival and overall survival and they did not suppose doing surgery²⁸. In Koch et al, appear to suggest its diminished role, it might enhance the effect of chemotherapy in stage IE primary gastric lymphoma²⁹. Ruskone-fourmesttraux et al. concluded that combination of radical surgery followed by chemotherapy had been associated with a significantly improved outcome in comparison with chemotherapy alone³⁰. Gobbi et al. revealed that in patients treated with conservative surgery followed by three cycles of chemotherapy had a better 5-year survival rate than patients treated with chemotherapy alone³¹.

Our study showed that the toxicities of treatment (grade 3 or 4) including leucopenia, anaemia and fever were more frequent in the group of patients who received chemotherapy alone but the difference was statistically insignificant, in consistent with both Chang et al.²⁷ and Sbitti et al.²⁸. Both upper GIT bleeding and perforation developed in one patient in the group of patients who received chemotherapy alone while one patient suffered from anastomotic leakage after surgery and there were no other toxicities such as cardiotoxicity, stomatitis and diarrhea in our study. This agreed with the result of Chang et al.²⁷ and Sbitti et al.²⁸. Maor et al showed that the 6-year overall survival of patients treated with chemotherapy alone was 76%. However, for bulky tumors, the advantage of chemotherapy was overshadowed by the potential for tumor bleeding and gastric perforation. Therefore some investigators suggested that debulking surgery followed by chemotherapy might offer better tumor control with reduced complication rates³².

Most studies had revealed a rather low incidence of severe haemorrhage or perforation, accounting for 2.1% and 1.7%, respectively, of those individuals treated with chemotherapy alone and 2.2% and 0.9%, respectively, of surgically-treated individuals^{7,33}. Such evidence suggests that the role of surgery in the treatment of primary gastric lymphoma may be less important than previously

considered, that organ function is better preserved by chemotherapy alone than surgery. Resection of the primary tumor before systemic chemotherapy does not appear to improve the cure rate of patients and could be reserved for those with severe complication (severe bleeding or perforation) after chemotherapy. Stomach conservation and avoidance of postoperative complications such as myocardial infarction, gastrointestinal bleeding, enterocutaneous fistula and malabsorption syndrome were important factors that obviated the choice of chemotherapy.

CONCLUSION

On studying clinical outcome of stage one and two-E primary gastric non-Hodgkin lymphoma treated with surgery followed by chemotherapy or chemotherapy alone we found that events-free survival and overall survival were higher in patients with primary gastric non-Hodgkin lymphoma treated by surgery followed by chemotherapy than in patients who received chemotherapy alone but the differences were statistically insignificant. Large studies are needed that involve a large number of cases, multi-institutional trials and adding anti CD20 in the era of targeted therapy to obtain survival benefit.

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