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Postoperative Chemotherapy Increases the Disease-free Survival Rate in Primary Gastric Lymphomas Stage IE and IIE

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We describe 53 patients with primary gastric non-Hodgkin's lymphoma (38 stage IE,15 stage IIE) treated with surgery as a primary procedure. According to the Working Formulation, 13 cases had low, 21 had intermediate and 19 had high grade malignancy. 34 patients considered at high risk received postoperative polychemotherapy. The overall 10-year disease-related survival is 91%. Median follow-up is 52 months. 7 patients relapsed (13%). The 10-year disease-free survival rate of the 19 patients initially treated with surgery alone is 60%, as compared with 92% in the patients who also received chemotherapy ($P = 0.004$). However, overall survival did not differ between the two groups, since two-thirds of the patients who relapsed after surgery alone were rescued with chemotherapy. Stage, age, sex and histology did not correlate with survival. In our experience, surgery was an adequate first step procedure; the addition of chemotherapy significantly reduced relapses and increased the disease-free survival rate in patients with unfavourable prognostic factors.
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INTRODUCTION

PRIMARY EXTRANODAL non-Hodgkin's lymphomas (NHL) account for 10–30% of all NHL [1]. The most common site of extranodal lymphomas is the stomach where they represent approximately 5% of malignant tumours. Lacking randomised studies, the best treatment for primary gastric lymphomas (PGL) has not yet been defined. Some reports suggest that surgical resection may be sufficient treatment in stage IE and that surgical debulking significantly influences survival [2]. However, given that up to 60% of patients with stage IIE ultimately relapse when treated with surgery alone [3–6], there is general concern that surgery is not sufficient. The addition of radiotherapy can improve the local control [1], but recurrences were documented outside the irradiation field of up to 68% [3, 7].

In some studies postoperative chemotherapy alone or combined with radiotherapy enhanced the survival rate [4, 8–14]. Recent reports suggest that chemotherapy alone might be sufficient treatment, without major complications.

The aim of this study is to retrospectively evaluate the outcome of PGL, and the roles of surgery and postoperative chemotherapy.

PATIENTS AND METHODS

Between 1975 and December 1990, 56 consecutive patients with PGL stages IE and IIE were referred to our department. Preoperative gastroscopy, with multiple biopsies, was performed in 52 patients. In 44 cases the procedure was diagnostic for

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lymphoma. 53 of these patients (32 males and 21 females aged 27 to 77 years, median 57) were treated with radical surgery and are included in this study. The remaining 3 patients were found inoperable at laparotomy and, therefore, were not considered.

The histological diagnosis was performed or reviewed according to the Working Formulation published in 1982 (Table 1). The initial evaluation included complete history, physical examination (including Waldeyer's ring examination), routine blood tests, bone marrow aspiration and trephine biopsy, chest X-ray, echography and computed axial tomography (before 1978 hepatic and splenic scintigraphy and bipedal lymphography).

The 53 evaluable patients underwent surgery as initial treatment: 29 patients had a total gastrectomy (in 3 patients resection margins were positive) and 24 had a subtotal gastrectomy (in 2 patients resection margins were positive). 38 patients (72%) were staged as IE and 15 (28%) as IIE.

All 53 patients were evaluable for the follow-up and analysis. Median follow-up was 52 months (range 7–197).

After surgery, patients were considered at high risk of recurrence if they had a high grade malignant lymphoma (HM) or intermediate malignancy (IM) with at least one of the following conditions: stage IIE, positive margins, invasion of serosa, a tumour mass larger than 5 cm. 37 patients were considered at risk, and all but 3 received chemotherapy: 2 HM refused chemotherapy, and 1 (a 69-year-old woman with diffuse large cell lymphoma, still in complete remission after 45 months) was not considered suitable for chemotherapy because of cardiac and metabolic problems. A 27-year-old woman, though presenting a low grade malignant lymphoma (LM), had chemotherapy because of her young age.

Consequently, 19 patients were initially treated with surgery alone (2 HM, 5 IM, 12 LM) and 34 patients received chemotherapy after surgery (17 HM, 16 IM, 1 LM) (Table 2).

The planned schedule was six cycles for CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), M-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone) and CVP (cyclophosphamide, vincristine, prednisone). It was reduced in 4 patients because of bad tolerance (2 patients) and refusal (2 patients). 1 patient, suspected of progression after three cycles, received seven cycles of CHOP. 30 patients (88%) received protocols including antracyclines. 28 of these patients were treated with CHOP (mean 5.4 cycles, range 3–7), 1 patient with M-BACOD and 1 with MACOP-B (methotrexate with lencovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin). 4 patients were given CVP.

Table 1. Histology of primary gastric lymphomas

Working formulation	No. of patients	Grade		%
Small lymphocytic	9	A	L	24.5
Follicular, predominantly small cleaved cell	4	B	L	
Follicular, predominantly large cell	2	D	I	
Diffuse, small cleaved cell	1	E	I	
Diffuse, mixed, small and large cell	5	F	I	39.5
Diffuse, large cell	13	G	I	
Immunoblastic/large cell	17	H	H	36
Unclassified	2	K	H	
Total	53			100

L, low malignancy; I, intermediate malignancy; H, high malignancy.

Table 2.

Grade	Stage I	Stage II
Patients treated initially with surgery alone		
Low	8	4
Intermediate	5	
High	2	
Patients treated with combined treatment		
Low	1	
Intermediate	11	5
High	11	6

Survival was calculated from the date of surgery until the last follow-up or date of death. Actuarial curves were prepared using the Kaplan–Meier method and statistical comparison by the log rank test [15]. 3 patients died for causes not related to the tumour: 2 had received chemotherapy after surgery. The survival of these 3 patients was censored at the time of the death.

RESULTS

No major postoperative complications were recorded in this series.

According to the Working Formulation, 13 cases (24.5%) were classified as LM, 21 (39.5%) as IM and 19 (36%) as HM (Table 1). The median overall survival has not yet been reached: at 10 years the overall survival is 91% (Fig. 1). At 10 years the disease-free survival of the group initially treated with surgery alone is 60 versus 92% of the group also receiving chemotherapy (Fig. 2). The difference is statistically significant [χ^2 8.07, degrees of freedom (df) 1, $P = 0.004$] even excluding, in the group treated with surgery alone, those patients with HM (χ^2 4.6, df 1, $P = 0.03$).

So far, 7/53 patients have relapsed (13%). In 4 cases, relapses occurred outside the abdomen. 1 patient out of 34 (3%) relapsed in the group treated with combined therapy and died; 6 out of 19 (32%) relapsed in the group initially treated with surgery alone [$P = 0.006$, odds ratio 15.2, 95% confidence interval (CI) 1.5–94.4]. 4 of these 6 relapsed patients were rescued with chemotherapy, while 2 died of progressive disease (Tables 3, 4).

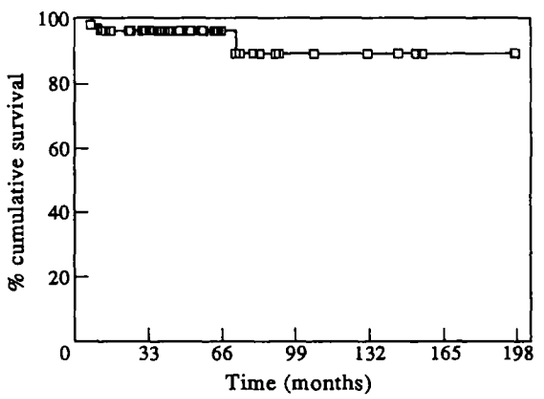

Fig. 1. Survival of all 53 patients.

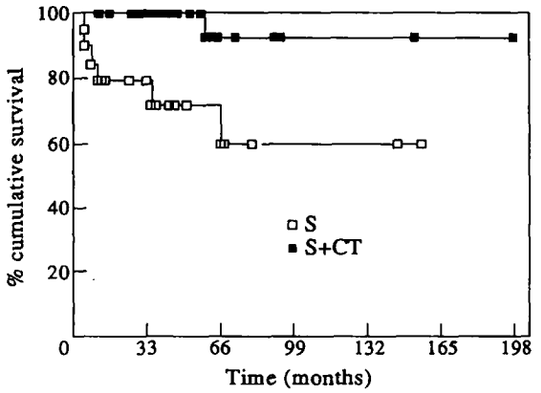

Fig. 2. Comparison of the disease-free survival of patients initially treated with surgery alone (S) and surgery plus chemotherapy (S + CT).

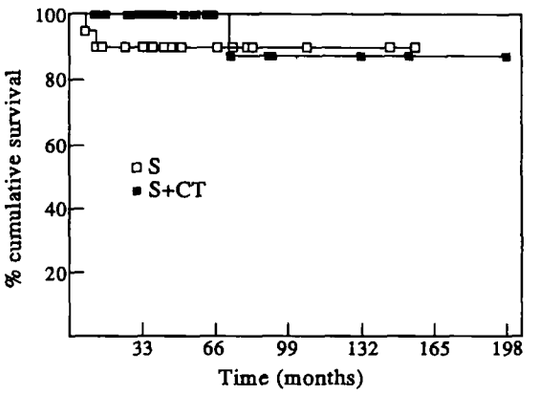

Fig. 3. Comparison of survival of patients initially treated with surgery alone (S) and surgery plus chemotherapy (S + CT).

Table 3.

Treatment	No. of patients	Relapses/grade H	I	L
S	19	2/2	1/5	3/12
S + CT	34	1/17	0/16	0/1
Total	53	3/19	1/21	3/13

S, surgery; CT, chemotherapy; H, high grade; I, intermediate grade; L, low grade.

Consequently, no difference in terms of overall survival was found between the group treated with surgery alone and with combined modality (10-year survival rate: 89 and 87%, respectively, χ^2 1.07, df 1, $P = 0.3$; Fig. 3).

Survival was not affected by stage (χ^2 1.07, df 1, $P = 0.3$), age ≥55 years (χ^2 0.4, df 1, $P = 0.5$), sex (χ^2 0.01, df 1, $P = 0.9$) and histology (χ^2 1.89, df 2, $P = 0.38$). The 10-year survival is 81% in the high grade group compared with 100 and 92% in the intermediate and low grade groups, respectively.

In our series no patients had Waldeyer's ring involvement during the course of the disease.

DISCUSSION

Most authors have recommended surgical resection as first-line treatment for PGL in order to (1) obtain adequate specimens for histological diagnosis, (2) prevent the risk of haemorrhage and perforation, and (3) improve survival [1–3, 7–10, 12, 14, 16–20].

Table 4. *Relapses*

First-line therapy	Months from diagnosis	Outcome after second-line therapy	Stage/grade
S	5	Died	IE/H
S	6	CR (80+)	IE/H
S	68	CR (12+)	IE/I
S	11	Died	IE/L
S	8	CR (25+)	IIE/L
S	35	CR (9+)	IIE/L
S + CT	59	Died	IE/H

S, surgery; CT, chemotherapy; H, high grade; I, intermediate grade; L, low grade; CR, complete remission.

In fact, emergency surgical intervention during chemotherapy or radiotherapy can present a high degree of risk because of leukopenia and thrombocytopenia, whereas elective procedures reduce the rate of complications [14].

On this basis, we considered surgical resection the first step in localised PGL. The incidence of perforation and/or bleeding has been reported between 22 and 55% [7, 8, 16, 20, 21]. However, in more recent reviews [22, 23] it accounted for about 3.5% in localised disease and 10% if advanced patients were included. This risk is considered similar to that of death resulting from surgery (about 7%). On the other hand, recent studies did not report relevant postsurgical complications [9–12, 24, 25], as has been our experience.

The necessity of surgical intervention has been challenged by some authors claiming that, in localised PGL, initial surgery is not mandatory and patients may be treated only with chemotherapy/radiotherapy without affecting survival [22, 26–29]. Even in the past, complete remissions and long survivors were occasionally reported in unresected patients [3, 5, 10]. In a recent series [26–29], the 4–6-year survival rate of unresected patients ranged between 58 and 83% and perforation/haemorrhage were reported not to be relevant. However, overall mortality has been reported up to 23% [26, 27].

From our experience, surgery is likely to offer the main advantage in patients with localised non-bulky disease because, besides reducing the risk of perforation/haemorrhage, it can be a radical procedure itself [1, 2, 9, 10, 14, 19]. Furthermore, in low grade PGL, chemotherapy and radiotherapy could be an overtreatment. In fact, 13 out of our 19 patients (68%) treated with surgery alone have not relapsed, and of the 6 relapsed patients, 4 were able to be rescued with chemotherapy. The mortality rate in our study (6%) seems lower when compared with the previously quoted series [26, 27] treated without surgery. Moreover, we have not found relevant postoperative complications. Thus, our data support the use of surgery in localised PGL.

The question is still open as to whether lymphomas originating in the gastrointestinal tract are different from lymphomas of the same morphology arising in lymph nodes. Isacson and Spencer [30] have proposed the concept of mucosa-associated lymphoid tissue (MALT) to explain the "homing behaviour" of these lymphomas. The morphology and clinical behaviour of low

grade primary B-cell lymphomas arising in gastrointestinal mucosa are different from those of low grade lymphomas arising in peripheral lymph nodes. Whereas the low grade B-cell lymphomas of peripheral lymph nodes disseminate widely, those of the gastrointestinal tract tend to remain localised. The peculiar clinical behaviour ("homing") of low grade PGL would strongly support the use of surgery alone in this group.

Although many studies have been carried out, it is difficult to assess the role of adjuvant therapy in PGL, the frequency of recurrence varying in different papers.

Favourable results with surgery followed by chemotherapy have been published. Even in series including advanced patients, survival rates ranging from 74 to 94% [9–11, 14, 19] and few or no relapses have been found [23].

Combination chemotherapy following surgery was often recommended for patients with PGL infiltrating the muscolaris or extending beyond the stomach [3, 6, 9, 10, 12, 13].

Our basic policy consisted of the addition of chemotherapy when already identified unfavourable prognostic factors, such as stage IIE, serosa invasion and positive margins [2, 6, 7, 12, 13, 18, 19] were present. As far as tumour size is concerned, we chose the restrictive limit of 5 cm [3, 7, 17, 19] in order to minimise the risk of relapse in patients with intermediate grade malignant lymphoma. The addition of chemotherapy in our series significantly reduced the relapse rate and increased the disease-free survival rate as compared to low risk patients treated with surgery alone. Consistent with the best results reported in the literature, the 10-year survival rate in the high risk group is 87%. Moreover, chemotherapy was effective as salvage therapy in patients who relapsed after surgery.

The majority (78%) of our patients treated with chemotherapy received CHOP. The protocol had tolerable toxicity, could be administered even to older patients and chemotherapy-related deaths did not occur. More intensive protocols have been used in patients with aggressive primary gastrointestinal lymphoma, but non-negligible (10%) treatment-related deaths occurred [28].

We conclude that in our study: (1) localised PGL is a curable disease, (2) radical surgery is a mainstay and may be curative by itself in low risk patients, (3) no postoperative deaths or major complications occurred, and (4) postoperative chemotherapy, mostly the CHOP regimen, was well tolerated and allowed a high cure rate in patients with unfavourable prognostic factors.

Prospective randomised trials would be requested to assess the best treatment for PGL.

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