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Original Paper

Primary Gastric Non-Hodgkin's Lymphoma Stage IE and IIE

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The aim of this study was to evaluate retrospectively the different treatment approaches and outcome of patients with stage IE and IIE gastric non-Hodgkin's lymphoma in a cancer registry. Between 1982 and 1992, the Comprehensive Cancer Centre South (CCCS), Eastern Section, The Netherlands, registered, in a population of 1 million people, a total of 81 cases of gastric lymphoma stage IE and IIE (43 men and 38 women). Median age was 69.7 years (range 30.4–88.1). According to the Working Formulation, the malignancy grade was: 9 low, 55 intermediate and 14 high. According to the MALT classification, the malignancy grade was: 38 low and 40 high. Grade was unknown in 3 patients. Patients received the following treatment modalities: surgery alone (n = 22), locoregional radiotherapy without (n = 12) or with (n = 13) surgery; or systemic chemotherapy alone (n = 10) or with radiotherapy and/or surgery (n = 18). No treatment was given or recorded in 6 patients. For stage IE, 5-year actuarial survival and relapse-free survival rates were, respectively, 76 and 64% in 18 patients who received only surgery; 70 and 67% in 17 patients given locoregional treatment (radiotherapy with or without surgery), and 76 and 62% in 13 patients given systemic treatment (chemotherapy alone or with radiotherapy and/or surgery). Radiotherapy as sole treatment seemed to be as effective as other treatment modalities in achieving local and abdominal control. For stage IIE, none of the 4 patients who were treated with surgery alone survived 5 years. The 5-year actuarial survival and relapse-free survival rates of 8 patients who received radiotherapy with or without surgery were, respectively, 25 and 17% and 49 and 33%, for 14 patients given systemic therapy (chemotherapy alone and/or radiotherapy/surgery). In stage IIE, local, abdominal as well as distant relapse were more common, irrespective of treatment modality. In the multivariate analyses, stage (P = 0.002), grade (P = 0.02), age (P = 0.04) and gender (P = 0.04) were significant prognostic factors. This report on a limited number of patients shows that the outcome of patients with stage IIE gastric lymphoma is much worse than for patients with stage IE. Grade, age, gender and particularly stage are much stronger indicators for survival than different modes of treatment. Systemic therapy might improve outcome for stage IIE, but not for stage IE, for which radiotherapy alone seems a good option.

Key words: gastric lymphoma, stage IE and IIE, surgery, radiotherapy, chemotherapy, population based

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INTRODUCTION

THE STOMACH is the single most common site of a primary extranodal lymphoma [1, 2]. Of gastric malignancies, approximately 3% are of lymphomatous origin [3], and, with appropriate treatment, these lymphomas have a better prognosis than gastric carcinoma. Many clinicopathological studies have focused on the impact of certain treatment approaches and on the epidemiology of gastric lymphoma, but only a few have investigated the impact of different treatment strategies within a defined geographical popu-

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lation. Therefore, we performed this study in the Comprehensive Cancer Centre South (CCCS), Eastern Section. The CCCS is located in South-East Netherlands. The region has a population of 1 million inhabitants. Only a few patients are referred for treatment outside the CCCS. There are 10 community hospitals referring to one regional, non-academic radiotherapy department. The CCCS registry is population-based. It has been complete and reliable since the 1970s, covering more than 99% of the cancer incidence [4].

MATERIALS AND METHODS

In the period 1982–1992, a total of 81 patients (43 men, 38 women) with a stage IE or IIE gastric lymphoma were identified by the CCCS cancer registry. All these patients were registered non-selectively. With consent of all involved physicians, all patient records were retrieved and details recorded by one author (ML). Cases were defined as lymphoma of the stomach based on the same criteria as described by d'Amore and coworkers [5], considering the stomach being either the sole site of involvement or the clinically dominant one, i.e. representing >75% of the total tumour volume, as estimated by clinical staging, and/or causing the patient's primary symptoms.

Clinical assessment

Routine clinical staging for all cases included a thorough clinical history and physical examination with particular attention to all lymphoid regions; a biopsy from involved tissue, a bone marrow aspirate and biopsy; ear, nose and throat examination; and computed tomographic scans of the abdomen and thorax. Cases were defined as stage IE when the tumour was confined to the stomach without any sign of dissemination. Additional involvement limited to confluent locoregional lymph nodes (gastric, mesenteric, omentum, para-aortal) was defined as stage IIE. In general, information concerning involvement of the spleen was lacking and could not be considered for staging purposes.

Histological assessment

The period 1982–1992 was selected in order to have complete information concerning the pathology. All reports were revised and reclassified by one author (LV) according to the National Cancer Institute Working Formulation for Clinical Usage (WF) [6] and according to the MALT classification [7–11], as there is increasing agreement that a separate classification is required reflecting the peculiarity of the gastrointestinal tract. Classification according to the WF classification was: 9 low, 55 intermediate and 14 high, according to the MALT classification: 38 low and 40 high. The grade was unknown in 3 patients.

In this retrospective study, no reliable information was available about the presence of *Helicobacter pylori*.

Patient and treatment characteristics

Of the 81 patients, 52 had a stage IE and 28 had stage IIE gastric lymphoma. The stage was unknown in 1 patient. Median age was 69.7 years (range 30.4–88.1).

Treatment was not formally standardised as it was performed in 10 community hospitals. However, there are informal guidelines as there is a periodic decentral consultants system in all participating hospitals. Radiotherapy was performed in one centre with radiotherapists being senior consultants in all referring hospitals.

6 patients received no treatment, of whom 1 died before surgical intervention, and 5 elderly patients were considered too frail for therapy. Treatment was local (surgery only) in 22 patients; locoregional: radiotherapy without surgery ($n = 12$) or with surgery ($n = 13$); or systemic: chemotherapy alone ($n = 10$) or with radiotherapy and/or surgery ($n = 18$).

A total of 46 patients had surgery, which in 38 cases was a partial gastrectomy and in 8 cases a total gastrectomy. There were 4 deaths in the postoperative period. 6 additional patients underwent a laparotomy for biopsy and are not considered as surgically treated.

Radiotherapy always involved the entire region of the stomach, taking into account the barium meal pictures in the treatment position, and the para-aortic lymph node region. The left kidney was partly included in this volume and not shielded, but the right kidney remained outside the treated volume. No attempt was made to include the spleen. Mean total tumour dose was 40 Gy midline (range 10–50), given by means of two parallel opposed fields. A total abdominal irradiation was never given. The radiotherapy was generally well tolerated and no cases of gastric perforation were observed.

Of the patients receiving chemotherapy (28 patients), the vast majority received chemotherapy consisting of CHOP or CHOP-like regimens. Among the latter, the most common variant was CNOP, identical to CHOP, but with mitoxantrone 10 mg/m^2 i.v. on day 1 instead of hydroxydaunorubicin. 3 patients received CVP; all other patients received CHOP ($n = 6$), CNOP ($n = 3$), CHVmP ($n = 5$) or later generation schedules: Promace-MOPP ($n = 4$), BACOP ($n = 1$) and other ($n = 4$). The majority of these patients received a total of six courses, although there was a large variation (1–8) in the total number of courses.

Follow-up

At the time of analysis (end of 1994), the median follow-up was 80 months (range 20–151). Patients were monitored at the 10 referring hospitals with an interval of approximately 3 months up to 2 years, every 6 months from 2 to 5 years, and once a year up to 10 years. At each follow-up examination, the minimum requirement was a physical examination and additionally, on indication, blood analysis, chest X-rays, computed tomographic scans and/or ultrasonography.

Statistical analysis

Demographic data were obtained from the CCCS, Eastern Section. Response to treatment was assessed according to standard criteria. Survival was calculated from the date of conclusive histological diagnosis to the date of last follow-up, death or 1 April 1994 if that was later. Any death occurring within 30 days after surgery was defined as a postoperative death. For the purpose of cause specific survival analysis, only deaths attributable to lymphoma were considered as this study included an aged patient population with a high incidence of intercurrent death. Therefore, in patients without evidence of lymphoma, deaths due to other causes were censored at the time of death. Time to relapse was calculated from the date of achievement of first com-

Table 1. Five-year actuarial survival (S) and recurrence free survival (RFS) for stage IE and IIE gastric lymphoma according to treatment modality

	Local treatment	Locoregional treatment	Systemic treatment*
IE S	76%	70%	76%
RFS	64%	67%	62%
Number of patients	18	17	13
IIE S	—	25%	49%
RFS	—	17%	33%
Number of patients	4	8	14

*One patient, for whom stage was unknown and 6 patients, who received no treatment, were excluded from this analysis.

plete remission. Curves describing survival and time to relapse were calculated by the method of Kaplan and Meier [12]. Independent factors of prognostic value for survival were subsequently identified by a Cox regression analysis [13].

RESULTS

Survival (S) and recurrence-free survival (RFS)

The overall 5-year actuarial survival (S) for the whole group of 81 patients was 57%. As the exact stage was unknown in 1 case, and 6 patients did not receive treatment, the 5-year actuarial S and recurrence-free survival (RFS) of the remaining 74 patients are presented in Table 1. The patient groups were subdivided according to stage (IE and IIE) and according to treatment modality (local, locoregional or systemic). The patient of whom the exact stage was unknown received systemic therapy.

For stage IE 5-year actuarial S and RFS rates were 76 and 64%, respectively ($n = 18$) with surgery alone; 70 and 67% ($n = 17$) with locoregional treatment (radiotherapy with or without surgery) and 76 and 62% ($n = 13$) with systemic treatment (chemotherapy alone or with radiotherapy and/or surgery). The difference between the different treatment modalities concerning S and RFS was small. This is also clearly shown in Figure 1. Surgery alone (18 patients) and radiotherapy alone (11 patients) resulted in a similar 5-year actuarial survival of 76 and 73%, respectively (Figure 2).

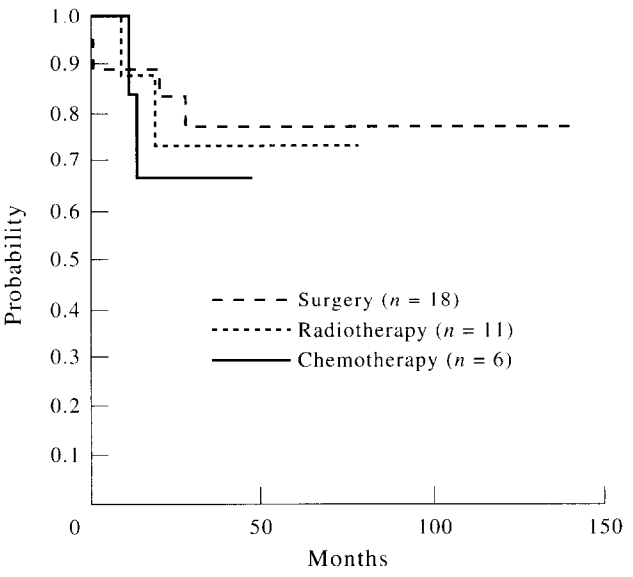

Figure 2. Survival for stage IE gastric lymphoma treated with surgery alone, radiotherapy alone or chemotherapy alone.

For stage IIE, the difference between the different treatment modalities was larger and in favour of systemic treatment (Figure 3; Table 1). None of the 4 patients who were treated with surgery alone survived 5 years. The 5-year actuarial S and RFS with locoregional treatment

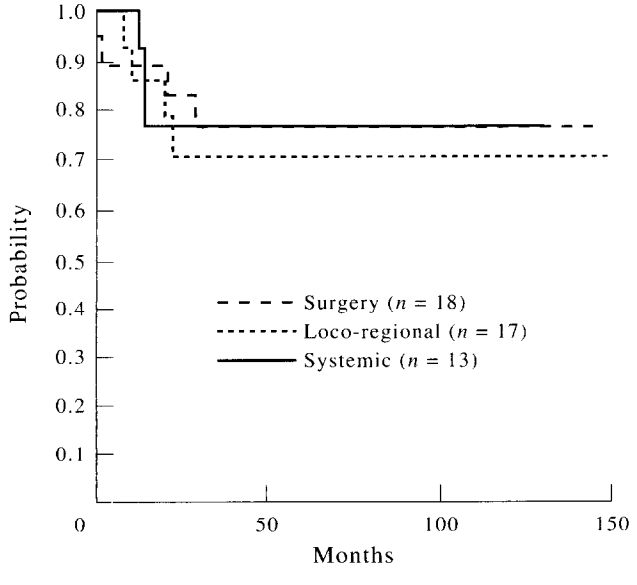

Figure 1. Survival for stage IE gastric lymphoma according to the different treatment modalities.

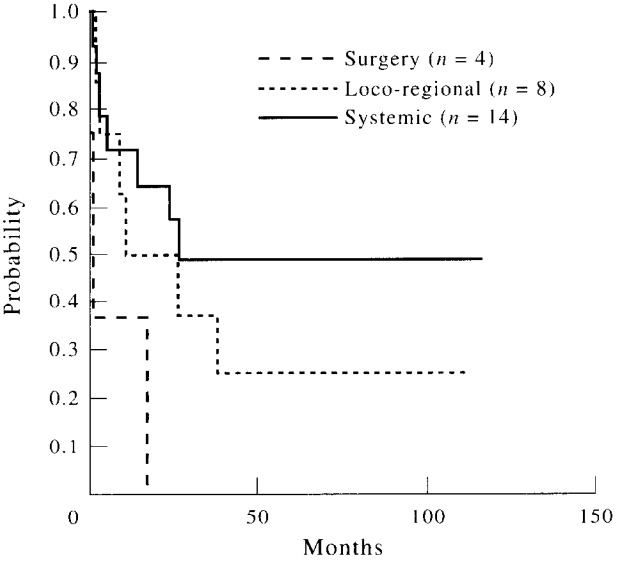

Figure 3. Survival for stage IIE gastric lymphoma according to the different treatment modalities.

Table 2. Location of relapse by stage and therapy

	Total		Local		Locoregional				Systemic			
			S		R		R + S		C		C + S + R	
	Stage IE $n = 48$	Stage IIE $n = 26$	Stage IE $n = 18$	Stage IIE $n = 4$	Stage IE $n = 11$	Stage IIE $n = 1$	Stage IE $n = 6$	Stage IIE $n = 7$	Stage IE $n = 6$	Stage IIE $n = 3$	Stage IE $n = 7$	Stage IIE $n = 11$
No relapse	36	14	13	3	9	1	4	2	4	2	6	6
Relapse												
Local only (1)	3	3	2	0	0	0	1	1	0	0	0	2
Abdominal (2)	1	4	0	1	0	0	0	1	1	0	0	2
Distant (3)	4	4	2	0	2	0	0	3	0	0	0	1
(1) (2) (3)	3	1	0	0	0	0	1	0	1	1	1	0
Unknown	1	—	1	—	0	—	0	—	0	0	0	—
Total	11 (23%)	12 (46%)	4	1	2	0	2	5	2	1	1	5

S, surgery; R, radiotherapy; C, chemotherapy.

(radiotherapy with or without surgery) were 25 and 17%, respectively ($n = 8$), and with systemic treatment (chemotherapy alone or with radiotherapy and/or surgery) 49 and 33%, respectively ($n = 14$).

Location of relapse by stage and therapy

Of the total number of 81 patients, stage was unknown in 1 patient and 6 patients received no treatment. Of the remaining 74 patients, the sites of first relapse were analysed by stage and treatment (Table 2). Relapses were classified as local (stomach region), abdominal (e.g. para-aortal, mesenterial etc.) and/or distant. In stage IE, radiotherapy as sole treatment appeared at least as effective as other treatment modalities in achieving local and abdominal control. Of the distant failures, only two were localised in the ear, nose and throat region.

In stage IIE, local, abdominal as well as distant relapses were common, irrespective of the treatment modality. Two local and two abdominal relapses were observed in a subgroup of 7 patients treated with surgery (3 partial and 1 total gastrectomy) followed by chemotherapy. Of the distant failures, none were localised in the ear, nose and throat region.

Prognostic factors

In the multivariate analyses, the following factors were statistically significant indicators for S: stage ($P = 0.002$), grade ($P = 0.02$), age ($P = 0.04$) and gender ($P = 0.04$), with a survival benefit for women, the 5-year actuarial survival for women being 67%, and 52% for men. Grade was associated with stage, as older patients generally had a higher stage.

DISCUSSION

This study focused on treatment regimens and their outcome for primary gastric lymphoma stage IE and IIE in a multi-institutional setting as registered in a cancer registry (CCCR). This patient population is representative of that seen by the common gastroenterologists in The Netherlands and probably different from that seen in specialist tertiary referral centres.

In the absence of large prospective randomised trials, the optimal management of primary gastric lymphoma has yet to be defined in terms of the exact role of surgery, chemotherapy, radiotherapy, and particularly antibiotics in the low grade lymphoma. While it is claimed that early gastric lymphomas can respond to *H. pylori* eradication therapy [14, 15], it was impossible to verify this retrospectively in our study. Most cases had bulky disease with ulcerating tumours as was also described in the population-based study of Muller and coworkers [16]. So from our series, we do not know if anti-*H. pylori* therapy may result in tumour regression in patients with low grade bulky disease. It is even less likely that patients with high grade disease will benefit. Patients with advanced tumour stages (IIE) or tumours with transition to high grade malignancy did not respond to cure of the *H. pylori* infection in the study of Bayerdorffer and colleagues [14].

Management of patients with primary gastric lymphoma varied between localised surgery to a combination of all treatment modalities (surgery, radiotherapy and chemotherapy). In the literature, some advocate chemotherapy solely [17], some surgery alone [18], and others prefer a combination of treatment modalities [19, 20]. The small numbers in each report prevent comparisons.

However, the number of patients was also small in this study, so care is required in the interpretation of the results. Nevertheless, the difference in prognosis between stage IE and IIE was manifest. This was also demonstrated by Burgers and coworkers [21], and, therefore, stage IE and stage IIE were analysed separately.

Our study demonstrates that for stage IE, the various modes of treatment had a similar impact on S and RFS. In patients with stage IE, local and abdominal relapses were low, as were distant relapses, independent of the treatment modality.

Surgery or radiotherapy as single modality therapy had similar survival rates compared with combined treatment modalities. This result was also reported by d'Amore and coworkers [5], who demonstrated that radiotherapy was the most important relapse preventing treatment modality in the multivariate analyses. The surgical debulking of gastric lymphomas is controversial. Arguments in favour of surgery are: larger specimens for histological diagnosis, fast relief of symptoms, debulking, prevention of the risk of bleeding or perforation, and a more accurate staging. Most of these arguments seem to be partially superseded. Pathological diagnosis if obtained by endoscopic biopsy appeared feas-

ible, as grading was impossible in only 3 cases in our study. Moreover, grading was less important than stage as a prognostic factor in the multivariate analyses, and one should also keep in mind that a gastrectomy has some mortality (four cases of postoperative deaths were encountered in this study) and a long-term morbidity. No cases of perforation or bleeding problems were observed. The risk of perforation and bleeding seems to be overestimated, as was also described by Gobbi and coworkers [22]. Staging, performed with non-invasive methods, seems to be safer and adequate, as indicated in the study of d'Amore and coworkers [5] where no significant difference in survival was demonstrated between surgically staged patients and patients who underwent conservative staging with endoscopy, abdominal computed tomographic scans and/or lymphangiography. Hence, we would like to suggest that non-surgical treatment is a good option in localised gastric lymphoma, a reflection which was also made in the study of d'Amore and coworkers [5].

In our study population, radiotherapy was limited to the region of the stomach and adjoining lymph node regions. A total abdominal irradiation was never given. Burgers and coworkers [21] advocate this approach in view of a high risk of intra-abdominal relapse with limited irradiation, and by investigations dealing with the normal flow of intraperitoneal fluid. In our study, the rate of intra-abdominal relapses in stage IE was low, so we cannot support this approach, taking into account the additional toxicity.

For stage IIE gastric NHL, the outcome was much worse than for stage IE. In stage IIE, systemic therapy might improve outcome, as a survival benefit was observed over local or loco-regional treatment modalities. This approach was also advocated by Burgers and colleagues [21]. A benefit concerning RFS was not demonstrated, as local, abdominal as well as distant relapses were common, irrespective of the treatment modality (Table 2).

Some studies suggested that patients with low grade disease have a better prognosis [19, 23, 24]. Grade did have an impact on survival at the multivariate level. Grade was associated with stage, as was also observed in the studies of Muller and coworkers [16] and d'Amore and coworkers [5]. With regard to survival, male gender and increasing age were associated with a statistically significant lower survival rate in the multivariate analyses.

Our study, and other recent studies, seem to indicate that surgery does not improve the final result, provided a thorough non-invasive staging is performed [5, 25, 26]. Definitive studies that prospectively and randomly compare the outcome of different treatment strategies in localised gastric lymphoma have yet to be conducted. Recent results have shown a complete remission in *H. pylori* positive stage IE gastric low-grade MALT lymphomas after bacterial eradication following antibiotic treatment [14, 15, 27].

If confirmed, these data could move, at least in a specific subset of gastric lymphoma, the therapeutic focus from interventional strategies to more conservative ones, being antibiotics, radiotherapy and/or chemotherapy.

From our study, although on a limited number of patients, it seems that for stage IE, surgery and radiotherapy as single modality have equal impact on survival and local control. For stage IIE, having a much worse prognosis than stage IE, additional adjuvant systemic therapy might improve outcome.

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