Primary gastrointestinal non-Hodgkin's lymphoma in a population-based registry

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Summary In a population-based registry of 580 patients with non-Hodgkin's lymphoma (NHL) 54 patients had a primary gastric lymphoma, 42 an intestinal, 113 a primary extranodal lymphoma localised elsewhere than in the gastrointestinal tract and 371 a primary nodal NHL. Histological specimens were reviewed by a panel of pathologists and classified according to the Kiel classification and the International Working Formulation. The 4-year survival rates for primary gastric, intestinal, other extranodal and nodal NHL ranged from 50 to 60%; the 4-year recurrence-free survival rates were 50%, 35%, 19% and 19%, respectively. Among patients with localised intermediate-grade disease survival for those with gastric NHL was better than for those with intestinal lymphoma. Because it is population-based, our study cohort was not subjected to exclusion due to age, performance scale, etc. and therefore provides a more realistic picture of the occurrence and presentation of as well as prognosis for lymphoma in the population.

In the Netherlands an estimated 1000 new cases of non-Hodgkin's lymphoma (NHL) are diagnosed every year (SOOZ, 1985), 400 of which are primary extranodal lymphomas (Haak et al., 1986) while 100–200 are primary gastrointestinal NHLs (Brady & Asbell, 1980; Freeman et al., 1972; Haber & Mayer, 1988).

Most previous data on primary gastrointestinal lymphoma were obtained from retrospective studies based on patient records in a given hospital over a period of many decades (Brooks & Enterline, 1983; Economopoulos et al., 1985; Haber & Mayer, 1988; Shiu et al., 1986; Thorling, 1984). A variety of histological classification systems led to controversial conclusions with regard to the association between histological type and prognosis (Dworkin et al., 1982; Weingrad et al., 1982). In contrast to these hospital studies we analysed the clinical and histological presentation as well as the survival data recorded in a population-based registry. The advantage of such a registry is that both bias due to hospital referral policy and selection of patients are avoided. In the Netherlands, eight comprehensive Cancer Centres (CCC) cover the entire country geographically. In 1981, the regional NHL Study Group of CCC West (1.58 million inhabitants) started a population-based registry, as defined by MacCennan et al. (1978), of all new NHL cases. The primary gastric and intestinal lymphomas in the registry were investigated and compared with two other categories: other primary extranodal lymphomas and nodal lymphomas. The present paper reports the results of this analysis of the four categories of lymphoma in the population-based registry with special attention directed to gastric and intestinal NHLs.

Materials and methods

A population-based registry of all new cases of NHL within the region of the CCCW was started on 1 June 1981, and is still ongoing. However, for this study, data entry of new cases ended on 1 September 1986, while entry of follow-up data ended on 31 December 1987. All hospitals (15) and pathological laboratories (9) in the region participated through the NHL Study Group, which consists of 45 specialists. Collection of data and quality controls were performed by the NHL registrars of the CCCW. Included were all newly diagnosed patients with NHL except those with

mycosis fungoides, acute lymphoblastic leukaemia, classical chronic lymphocytic leukaemia and multiple myeloma and those first diagnosed post-mortem.

In this study the data were divided into four groups on the basis of the primary involved site coded according to the International Classification of Diseases for Oncology (ICD-O, 1976). A distinction was made between primary extranodal lymphomas and primary nodal NHL; primary extranodal NHL was further subdivided into primary gastric, intestinal and other primary extranodal lymphoma (primary gastrointestinal NHL excluded). The NHL was considered a primary extranodal lymphoma when at initial clinical examination the patient's symptoms were caused mainly by extranodal NHL involvement. When an organ localisation was diagnosed during staging procedures or later in the course of the disease, the lymphoma was not subsequently considered a *primary* extranodal lymphoma. Patients with primary gastrointestinal lymphoma were defined according to Lewin et al. (1978). The initial diagnosis and histological classification of all cases were made by local pathologists. A panel of four pathologists reviewed all newly diagnosed cases weekly. All NHLs were registered, but the tumours were only classified if material was available for additional immunological and enzyme-histochemical studies (Haak et al., 1986). In most other cases, in particular large cell tumours, the character of the lymphoma was confirmed by immunostaining for CD_{45}-leukocyte common antigen on paraffin slides (Warnke et al., 1983). The NHLs were classified according to the Kiel system (Lennert, 1978) with some modifications for intermediate lymphocytic lymphoma and true histiocytic lymphoma (Haak et al., 1986) which were considered additional entities. Lymphomas were graded as low, intermediate and high-grade malignancy according to the International Working Formulation (National Cancer Institute, 1982). Intermediate lymphocytic lymphoma was considered as intermediate-grade, true histiocytic lymphoma as high-grade malignancy.

All NHL patients were staged according to the Ann Arbor Classification system (Carbone et al., 1971); staging was considered adequate only when physical examination (Waldeyer's ring included), surgical and/or endoscopy reports and additional examinations such as bone marrow biopsy, X-rays (at least chest X-ray), CT-scan of the abdomen or lymphangiography and isotope scans of the liver and spleen were performed. All stage II$_E$ primary gastrointestinal lymphomas were further subdivided according to Musshoff (1977) into stages II$_{1E}$ and II$_{2E}$. We considered gastric NHL

with direct extension into adjacent organs (pancreas, liver) as stage IV$_E$ disease, in accordance with the findings of Weingrad et al. (1982).

Although the NHL Study Group reached a general consensus on various treatment modalities at the start of the registry (Table I), no special protocol for the type of surgery for patients with primary gastrointestinal lymphoma was followed. Usually a partial gastrectomy was performed when the lymphoma was localised in the stomach. Surgical procedures for intestinal localisations were total resection of the involved site when cure was considered possible or partial resection. Lymphoblastic lymphomas were treated as acute lymphoblastic leukaemia with an induction, consolidation and maintenance drug scheme. Response to treatment was assessed according to standard criteria.

Survival time and recurrence-free survival time were calculated from the date of diagnosis. Death with tumour was considered the endpoint for survival and recurrence of disease or death the endpoint for recurrence-free survival. Comparison of survival curves was performed with the log rank (Matthews & Farewell, 1985). Comparison of survival rates at specific time points was done using Greenwood's equation for the standard error of the survival rate. Contingency tables were analysed with the χ^2 test.

Results

Out of 640 new cases of NHL registered from 1 June 1981, to 1 September 1986, 580 were evaluable; the registration forms of 60 patients were incomplete, 30 of whom were lost to follow-up.

Gastric and intestinal vs other extranodal vs nodal NHL

Table II lists some patients' characteristics for the two main groups: primary extranodal and primary nodal lymphoma. The extranodal group is further subdivided into primary gastric, intestinal and other extranodal NHLs. Among the 580 evaluable patients, 209 had primary extranodal lymphoma, 54 of which were primary gastric and 42 primary intestinal lymphoma. Thirteen of the intestinal NHLs were localised in the small intestine, 16 in the large bowel and rectum, three at multiple intestinal sites and 10 in the mesentery. The mesenterial localisations (10 patients) were considered to be primary intestinal lymphomas in accordance with the literature (Dragosics et al., 1985; Haber & Mayer, 1988; Weingrad et al., 1982). Because the numbers of patients per subsite were too small, we analysed these patients with intestinal NHL as one group, although it is a very heterogeneous group.

Sex and age

Sex distribution differed between the four groups ($\chi^2 = 12.9$; d.f. $= 3$; $P = 0.05$). Adjusted for age and sex for the regional population there was no difference in sex distribution within a group. Although the median ages for the four groups were similar, 10 patients of the 42 patients with primary intestinal NHL were younger than 20 years of age.

Histology

The histological subtypes are summarised in Table III. Twenty-four per cent of all NHLs were not classified due to the lack of frozen material, in particular those diagnosed on the basis of endoscopic biopsy specimens; histological diagnosis was established on endoscopic biopsy alone in 21 out of 54 gastric lymphoma and four out of 42 intestinal lymphoma. Among the classified lymphomas, high-grade malignancy was encountered more often in primary gastrointestinal lymphomas ($n = 22$ out of the 68, 32%) – in particular the intestinal ($n = 14$ out of the 33, 43%) – than in the group with other extranodal NHL (15%) or primary nodal NHL (13%) ($\chi^2 = 16.9$; d.f. $= 4$; $P = 0.002$). Taking the Kiel classification into consideration the type distribution of the gastric lymphoma was different compared to the other groups, with a predominance of diffuse centroblastic lym-

phoma (45%). Half of the mesenterial lymphomas were of the follicular type; this type was very infrequent in the stomach.

Stage

Stage I disease was found in 30–40% of the cases of extranodal NHL and only 14% of those with nodal lymphoma. In parallel, 68% of the nodal NHLs were stage IV compared to 20 to 50% of the extranodal lymphomas.

The three patients with gastric lymphoma stage III$_E$ had NHL of the cardia and pathological regional lymph nodes just above and below the diaphragm near the cardia. Sixteen patients with gastric lymphoma had stage IV$_E$ disease: 10 because of a positive bone marrow biopsy without NHL involvement other than the stomach and six because of additional solitary extranodal involvement without lymph node involvement. Eight patients with intestinal NHL had stage IV$_E$ disease as indicated by multiple gastrointestinal localisations ($n = 3$), a solitary cervical lymph node ($n = 3$) and a positive bone marrow biopsy without lymph node involvement ($n = 2$).

Adequate staging procedures as defined by the NHL Study Group were performed in an equal percentage of the cases of primary gastric, intestinal lymphoma and nodal NHL (74%, 67% and 69%, respectively; Table II) and in 59% of the cases of other primary extranodal lymphomas.

Survival and recurrence-free survival

The survival and recurrence-free survival times for patients with gastric and intestinal lymphoma in relation to other extranodal and nodal NHL are shown in Figure 1. No important differences in survival were present between the four groups. Up to 42 months the intestinal group had the poorest survival. The survival rate at 48 months, however, was similar for the four groups. The recurrence-free survival results were markedly influenced by the large number of patients who never achieved complete remission. At 48 months the gastric lymphoma group, in particular, had a better prognosis compared to patients with other extranodal or nodal NHL (Greenwood's equation; $P < 0.05$; Figure 1b). In the next section, our analysis of gastric and intestinal lymphomas is presented.

Table I Radiotherapeutic and chemotherapeutic protocols for NHL patients, listed according to stage and grade of malignancy

Stage	Working formulation		
	Low	Intermediate	High
I	wait and see radiotherapy (35–40 Gy)/ chlorambucil	radiotherapy (35–40 Gy)	CHOP
II$_1$	see stage I	CHOP	CHOP
II$_2$–IV	CVP	CHOP	CHOP

CVP: cyclophosphamide 300 mg m^{-2} orally on days 1–5, vincristine 1.4 mg m^{-2} (max. 2 mg) i.v. on day 1, prednisone 60 mg orally on days 1–5. CHOP: cyclophosphamide 750 mg m^{-2} i.v. on day 1, adriamycine 50 mg m^{-2} i.v. on day 1, vincristine 1.4 mg m^{-2} (max. 2 mg) i.v. on day 1, prednisone 60 mg orally on days 1–5.

Table II Characteristics of patients with NHL ($n = 580$)

Characteristics	Primary extranodal NHL			Nodal NHL
	Stomach	Intestine	Other	
Number of patients	54	42	113	371
Sex: M/F	33/21	22/20	39/74	186/185
Age:				
Median in years	65	65	66	64
Range	20–87	0–95	4–94	0–91
Stage*				
I	21 (15)	12 (7)	35 (17)	51 (34)
II			20 (16)	67 (53)
II$_1$	6 (4)	10 (8)		
II$_2$	8 (7)	12 (8)		
III	3 (3)	0 (0)	1 (1)	82 (52)
IV	16 (11)	8 (5)	57 (33)	171 (118)
Total	54 (40)	42 (28)	113 (67)	371 (257)

*The number of patients adequately staged is given in parentheses.

Table III Histological classification

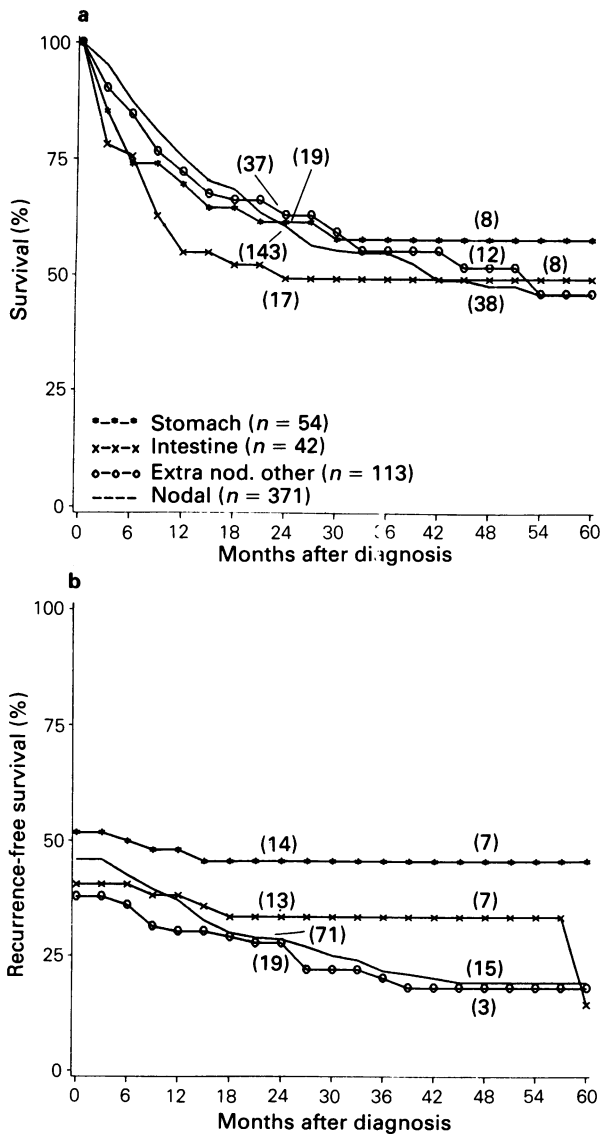|	Primary extranodal NHL			Nodal NHL
	Primary gastrointestinal NHL		Other	
	Stomach	Intestine		
Classified	**35 (100%)**	**33 (100%)**	**73 (100%)**	**300 (100%)**
Low grade	2 (5%)	9 (27%)	20 (27%)	93 (31%)
Lymphocytic	–	–	–	10
Lymphoplasmocytoid immunocytoma	1	1	11	15
Follicular centroblastic/centrocytic	1	8	9	68
Intermediate grade	24 (69%)	9 (27%)	39 (54%)	161 (54%)
Diffuse centroblastic/centrocytic	5	1	6	23
Centrocytic	1	–	2	4
Intermediate lymphocytic	1	–	1	15
Follicular centroblastic	–	–	1	13
Diffuse centroblastic	16	4	23	92
Immunocytoma pleomorphic	1	4	6	14
High grade	8 (23%)	14 (43%)	11 (15%)	40 (13%)
Immunoblastic	6	2	8	17
Lymphoblastic	–	3	–	13
Burkitt's	1	6	–	2
True histiocytic	1	3	3	8
Others	1 (3%)	1 (3%)	3 (4%)	6 (2%)
Lennert's lymphoma	–	–	2	6
T-medium sized lymphoma	1	1	1	–
Non-classified	**19**	**9**	**40**	**71**
Total	**54**	**42**	**113**	**371**

Figure 1 Survival (**a**) and recurrence-free survival (**b**) rates for patients with primary gastric, intestinal, extranodal lymphoma other than gastrointestinal lymphoma and nodal NHL (the number of patients at risk is given in parentheses).

Gastric vs *intestinal NHL, prognostic factors*

Treatment The treatment modalities are listed in Table IV. The majority of the patients with gastric NHL (61%) and nearly all patients with intestinal lymphoma (90%) underwent surgery. In our study, patients with primary gastric NHL stage I_E or stage II_{1E} only achieved complete remission after surgery.

Grade of malignancy (according to the Working Formulation) Too few patients had low-grade gastric lymphoma (Table III). For this reason wer focussed on intermediate-grade and high-grade NHL. Although the survival rates for patients with intermediate-grade gastric NHL and intermediate-grade intestinal lymphoma did not differ significantly within the first 2 years of follow-up (log rank = 2.41; d.f. = 1; P = 0.12) they did at 4 years (Greenwood; $P < 0.05$). There was no difference in survival between high-grade gastric and intestinal lymphoma. (See Figure 2.)

Stage The survival rates for stage I_E and II_{1E} patients with gastric NHL were similar; however, survival for stage II_{2E} patients was as poor as that for stage IV_E disease. For this reason, we compared the survival data for patients with localised lymphoma (stage I_E + stage II_{1E}) with those with more extensive disease (stages II_{2E}, III_E and IV_E). Localised gastric lymphoma tended to have a better survival rate than localised intestinal NHL although the difference was not significant (log-rank = 1.74; d.f. = 1; P = 0.18). Survival rates for patients with extensive disease were equal for those with gastric and intestinal NHL. (See Figure 3.)

Figures 2 and 3 suggest that there might be a difference in survival between localised intermediate-grade gastric and intestinal lymphoma; despite the small numbers of patients ($n = 14$ and $n = 5$), Figure 4 shows a significant difference (log rank = 4.41; d.f. = 1; P = 0.03).

Discussion

In this study we analysed all primary gastrointestinal lymphomas diagnosed in a clearly defined population over a short period of time. Since most studies are based on a hospital registry or clinical investigations instead of a population-based registry, our patients represent a wider age range (0–94 years) than is found in the reports of others (Dragosics *et al.*, 1985; Economopoulos *et al.*, 1985). Moreover, since a

Table IV Treatment modalities related to the stage of the primary gastrointestinal NHL

	Surgery		No surgery	
	$I_E + II_{IE}$	$II_{2E} + III_E + IV_E$	$I_E + II_{IE}$	$II_{2E} + III_E + IV_E$
Stomach				
no additional treatment	8 (8)	1 (0)	–	1 (0)
chemotherapy alone	7 (5)	6 (4)	2 (0)	15 (1)
radiotherapy alone	6 (6)	–	3 (2)	0 (0)
radiotherapy + chemotherapy	1 (1)	4 (0)	–	–
Total	22 (20)	11 (4)	5 (2)	16 (1)
Intestine				
no additional treatment	5 (1)	4 (0)	–	–
chemotherapy alone	16 (7)	9 (4)	–	3 (1)
radiotherapy alone	1 (1)	–	–	–
radiotherapy + chemotherapy		3 (3)	–	1 (0)
Total	22 (9)	16 (7)	–	4 (1)

The number of patients who achieved complete remission is given in parentheses.
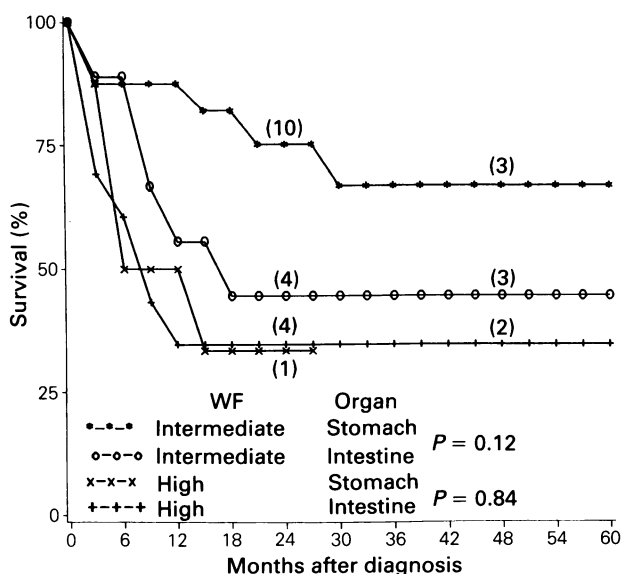
Figure 2 Survival of patients with primary gastric ($n = 54$) and primary intestinal NHL ($n = 42$) subdivided into those wtih intermediate-grade and those with high grade malignancy according to the Working Formulation (the number of patients at risk is given in parentheses).
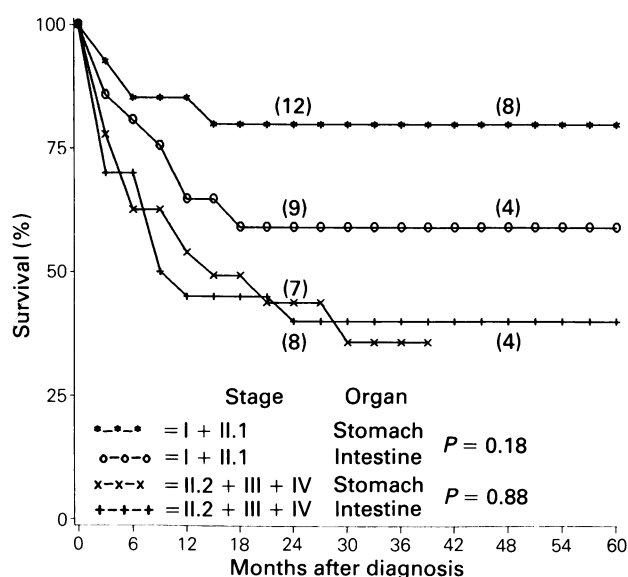
Figure 3 Survival of patients with primary gastric ($n = 54$) ᴗnd primary intestinal NHL ($n = 42$) subdivided into those wtih localised and those with more disseminated disease (the number of patients at risk is given in parentheses).
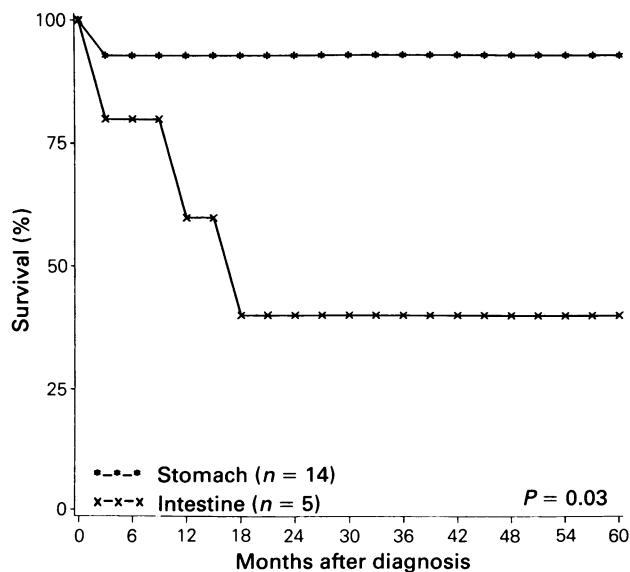

Figure 4 Survival of patients with localised intermediate-grade NHL of the stomach ($n = 14$) and the intestine ($n = 5$).

population-based registry can be studied after a shorter period of registration diagnostic procedures and therapeutic approach are less likely to vary within the study period.

In the majority of series published (Green *et al.*, 1979; Haber & Mayer, 1988; Weingrad *et al.*, 1982), primary gastrointestinal lymphoma exhibits a marked predilection for males. In our registry and other reports (Brady & Asbell, 1980; Dragosics *et al.*, 1985) both sexes were equally represented. The incidence of intestinal NHL varies considerably (Aozasa *et al.*, 1988; Haber & Mayer, 1988; Weingrad *et al.*, 1982), particularly the relative incidence for the small intestine: from 9% (Dragosics *et al.*, 1985) to 59% (Weingrad *et al.*, 1982) of all primary gastrointestinal lymphomas. These differences might be explained by selection of patients: some studies did not include children (Dragosics *et al.*, 1985; Economopoulos *et al.*, 1985; Weingrad *et al.*, 1982), whereas Burkitt's and lymphoblastic lymphomas are relatively more frequent in young people (Haber & Mayer, 1988).

Grading according to the International Working Formulation appeared to be related to survival in our series (Figures 2 and 4). In other studies only a weak (or no) association was found between prognosis and histological type as given by the Rappaport and/or Lukes-Collins classification system (Dragosics *et al.*, 1985; Dworkin *et al.*, 1982; Haber & Mayer, 1988; Thorling, 1984). When the different classification systems were applied to the same histological

material, the Kiel classification system and the International Working Formulation were found to have the better discriminating capabilities (Dragosics et al., 1985; Dworkin et al., 1982).

We found a better 1 year survival rate for nodal NHL but a higher 4-year survival rate for patients with primary gastric lymphoma (Figure 1a). Probably, the initially better but later poorer survival of patients with nodal NHL is caused by the higher percentage of low-grade malignancies among patients with nodal NHL compared to those with primary gastric lymphoma (Table III). It is well known that although patients with low-grade NHL can achieve CR by means of therapy, relapse and death with tumour can rarely be avoided (Ciampi et al., 1981).

Our stage distribution for primary gastrointestinal lymphoma is in accordance with observations of some authors (Blackledge et al., 1979; Haber & Mayer, 1988). Notably higher percentages for stage I$_E$ and II$_E$ disease will be found when the definition of primary gastrointestinal lymphoma is based on the more rigid criteria proposed by Dawson et al. (1961), who excluded cases with bone marrow localisation (Dragosics et al., 1985). In our study, 10 out of 16 patients with stage IV gastric NHL and two out of eight with stage IV intestinal NHL would have had stage I$_E$ disease according to physical examination and CT-scan of the abdomen but became stage IV after bone marrow biopsy. Because of the lack of nodal involvement we believe that these patients should nevertheless be included in the primary gastrointestinal lymphoma group. Once more these data emphasise the importance of adequate staging procedures (Come & Chabner, 1979).

Since the Ann Arbor system was not considered suitable for the staging of gastrointestinal lymphomas, other staging systems were set up (Blackledge et al., 1979; Crowther & Rankin, 1983; Musshoff, 1977). In our study the modification of the Ann Arbor system by Musshoff (1977) proved to be useful as a prognostic determinant, which is in accordance with the findings of others (Dawson et al., 1961; Weingrad et al., 1982). Analysis of the relation between stage and prognosis showed that survival was better for patients with localised (stages I and II$_{1E}$) primary gastric lymphoma than for those with extensive disease. Patients with localised gastric lymphoma tended to have a better survival than those with intestinal NHL.

The best treatment for primary gastric lymphoma is a matter of active debate. Many investigators (Dworkin et al., 1982; Gospodarowicz et al., 1983; Haber & Mayer, 1988; Shiu et al., 1986) claim that surgery plus postoperative radiotherapy gives the best chance of survival for those with limited disease. However, in these series, irradiation was consistently given postoperatively, so it is impossible to estimate its impact on survival. More recently, chemotherapy

alone or in combination with surgery and/or radiotherapy has been used for limited as well as more extensive disease (Brooks & Enterline, 1983; Economopoulos et al., 1985; Gospodarowicz et al., 1983; Haber & Mayer, 1988; Maor et al., 1984; Weingrad et al., 1982). In our series chemotherapy alone did not seem to be successful in achieving CR (11%), in contrast to the combination surgery plus chemotherapy with or without radiotherapy (52%). The choice of surgery as treatment modality was apparently not based on the stage of disease (Table IV). Complications such as perforation and gastrointestinal bleeding have been described (List et al., 1988; Sheridan et al., 1985; Weingrad et al., 1982) after chemotherapy. None of our patients receiving chemotherapy developed such complications, nor did those described by Economopoulos (Economopoulos et al., 1985). The possible beneficial effect of curative or debulking surgery before chemotherapy, i.e. to prevent perforation and gastrointestinal bleeding, has not yet been established.

Unlike nodal lymphomas, many primary gastric and intestinal lymphomas are presumed to behave clinically as unifocal tumours presenting in a localised fashion which might, therefore, be curable by local radical treatment (Brooks & Enterline, 1983; Dragosics et al., 1985; Haber & Mayer, 1988). However, the far greater likelihood of systemic rather than isolated recurrence in patients with gastric and intestinal NHL (Haber & Mayer, 1988; Figures 1b, 3 and 4) raises reservations about the lack of dissemination at presentation and therefore the justification for adjuvant local irradiation. Optimal management of patients with primary gastric and intestinal lymphoma can be determined only by multicentre prospective trials.

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