

A clinicopathological study of 152 surgically treated primary gastric lymphomas with survival analysis of 109 high grade tumours

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Aims: To describe the clinicopathological features of a large number of surgically treated and followed up primary gastric lymphomas and thereby gain a better understanding of their biology, with particular reference to the prognostic factors of high grade tumours.

Methods: A retrospective study of 152 patients.

Results: High grade gastric lymphomas, both pure and with a residual low grade component, differed from low grade mucosa associated lymphoid tissue (MALT)-type lymphomas in that they were more frequently large, ulcerated, at an advanced stage, and highly proliferating. In addition, patients were older and had a worse outcome. The prognosis of high grade lymphomas was influenced by patient age, tumour stage, depth of infiltration in the gastric wall, and the invasion of adjacent organs. Adjuvant postsurgical treatment prolonged survival only in patients with advanced stage and deep neoplastic infiltration.

Conclusions: There is a sharp distinction between low grade MALT-type lymphomas and tumours with a high grade component, justifying their different treatment approach. The postsurgical management of high grade lymphomas should be based on the accurate evaluation of the neoplastic extension.

Primary gastric lymphomas represent about 25% of all extranodal lymphomas and 3–5% of all gastric tumours. Most are B cell lymphomas arising from acquired mucosa associated lymphoid tissue (MALT) of the stomach and often remaining localised for a long time.^{1 2}

Although primary gastric lymphoma has been investigated extensively,^{3–30} its optimal histological classification, the most accurate staging system, and the exact role of the different therapeutic options are still debated. Surgical resection has been the traditional treatment, alone or in association with chemotherapy and/or radiotherapy. However, the treatment of low grade MALT-type lymphomas has been revolutionised by the recognition of an aetiological link with *Helicobacter pylori* infection.³¹ Eradication of the bacterium correlates with morphological regression of the lymphoma in a large proportion of cases.^{10 11 14 32} Discrepant remission rates (41–100%) reported in the literature mostly depend on the *H pylori* infection status and tumour characteristics.³³ Different treatment, such as chemotherapy/radiotherapy or surgery, is required in patients with low grade disease when deep infiltration in the gastric wall and lymph node involvement are both assessed by endoscopic ultrasonography, and when histology reveals a high grade component. The optimal management of high grade lymphomas remains a matter of debate: the prognostic and therapeutic value of surgery is widely accepted, although conservative strategies, such as chemotherapy and/or radiotherapy have recently been used with success.^{26 34}

“The treatment of low grade MALT-type lymphomas has been revolutionised by the recognition of an aetiological link with *Helicobacter pylori* infection”

Our present retrospective study of 152 patients with surgically resected primary gastric lymphomas was undertaken with a view to contributing to the knowledge of this disease. In particular, we analysed the prognostic impact of several clinicopathological parameters in high grade lymphomas, including the effect of adjuvant postoperative treatment.

MATERIAL AND METHODS

All the gastrectomy specimens diagnosed as lymphoma from 1976 to 1996 were retrieved from the archives of the institute of pathology of Ancona University (Italy) and reviewed. Clinical data and information regarding staging procedures, treatment before or after surgery, and follow up were obtained from medical charts and from clinicians. Only primary gastric lymphomas were considered. Cases with advanced tumour stage were included only when gastric involvement constituted the bulk of the disease. Stage was defined according to Musshoff's modification³⁵ of the Ann Arbor staging system.

Formalin fixed and paraffin wax embedded sections from gastric specimens were stained with haematoxylin and eosin and Giemsa. Sections immunostained with antibodies against CD20 (clone L26; Dako, Copenhagen, Denmark), CD3 (polyclonal; Dako), CD5 (clone 4C7; Novocastra, Newcastle, UK), CD10 (clone 56C6; Novocastra), and immunoglobulin light chains (polyclonal; Dako) allowed us to classify each case according to the REAL/WHO system.³⁶ Twenty nine tumours were low grade marginal zone derived MALT-type lymphomas (LG), 70 showed a low grade component mixed with variable proportions of confluent sheets of blastic cells outside the follicles (LG + HG), whereas 53 were classified as pure diffuse large cell lymphomas (DLCL). Three cases of mantle cell lymphoma, three cases of peripheral T cell lymphoma, and one case of Burkitt's-like lymphoma were also observed. Depth of infiltration in the gastric wall, status of surgical margins, extension to lymph nodes, and invasion of other structures and organs were evaluated. Sections from other specimens collected at diagnosis (bone marrow, spleen, and liver), or during follow up (bone marrow, gastric stump, colon, and

Abbreviations: DLCL, diffuse large cell lymphoma; LG, low grade marginal zone derived MALT-type lymphoma; LG + HG, low grade mixed with variable proportions of confluent sheets of blastic cells outside the follicles; MALT, mucosa associated lymphoid tissue

Table 1 Clinical and morphological features of primary gastric lymphomas

	LG	LG+HG	DLCL	Total	Mantle cell	T cell	Burkitt's like
Number of cases	29	70	53	152	3	3	1
Age range (mean) in years	31–81 (60.06)	43–89 (64.31)	33–86 (66.39)		57–78 (68.66)	62–70 (66.6)	72
Adjuvant therapy (%)	9 (32.1)	32 (49.2)	32 (72.7)	73	2	2	–
Location (%)							
Antrum	8 (27.6)	21 (30)	17 (32.1)	46	1	2	1
Body	8 (27.6)	15 (21.4)	13 (24.5)	36	–	1	–
Fundus	1 (3.4)	6 (8.6)	3 (5.6)	10	–	–	–
Diffuse	12 (41.4)	28 (40)	20 (37.7)	60	2	–	–
Macroscopic type (%)							
Ulcerated	12 (41.4)	46 (66.6)	37 (69.8)	95	2	3	–
Polypoid	5 (17.2)	12 (17.4)	11 (20.7)	28	–	–	1
Flat	12 (41.4)	11 (15.9)	5 (9.4)	28	1	–	–
Size range (mean) in cm	2–12 (6.6)	1–17 (7.7)	2.3–17 (8.2)		5–10 (8.3)	5–7 (6.2)	8
Depth of infiltration (%)							
Mucosa	3 (10.3)	1 (1.4)	1 (1.9)	5	1	–	–
Submucosa	13 (44.8)	21 (30)	2 (3.8)	36	–	1	–
Muscularis	5 (17.2)	13 (18.6)	6 (11.3)	24	–	–	–
Serosa	8 (27.6)	35 (50)	44 (83)	87	2	2	1
Stage (%)							
IE1	7 (24.1)	18 (25.7)	2 (3.8)	27	–	–	–
IE2	1 (3.4)	14 (20)	13 (24.5)	28	–	1	–
IIE1	17 (58.6)	21 (30)	27 (50.9)	65	–	–	–
IIE2	2 (6.9)	8 (11.4)	3 (5.7)	13	1	2	–
IIIE	–	–	–	–	1	–	–
IIIES	–	2 (2.9)	1 (1.9)	3	–	–	–
IVE	2 (6.9)	7 (10)	7 (13.2)	16	1	–	1
MIB-1 range (mean) in % of positive nuclei	0.5–28.9 (8.5)	16.1–96.4 (49.7)	14.1–90.6 (53.3)		5.4–33 (15.6)	35.4–72.2 (48.59)	

skin) were also reviewed. Proliferative activity was evaluated on sections immunostained for the Ki67 antigen (clone MIB-1; Dako). It was expressed as percentage of cells with nuclear staining, selecting at low magnification the areas with the highest degree of positivity and counting at least 1000 cells.

Data were coded and entered into an IBM personal computer. Statistical analysis was performed with the SPSS software. The Student's *t* test and the χ^2 test were applied to identify significant differences between two or more groups of data. Survival analysis was performed on the LG + HG and DLCL samples only. Thirteen patients who died from postsurgical complications were excluded, in addition to the cases in which the cause or the date of death were not known. One hundred and nine cases remained available. Survival curves were calculated according to the Kaplan-Meier method, and the log rank test was used to evaluate differences between the curves. All the variables with prognostic value were included in Cox's multiple regression survival analysis to identify the most useful prognostic factors.

RESULTS

Clinical features

None of the patients received neoadjuvant (preoperative) chemotherapy. Four patients were treated with antibiotics to eradicate *H pylori* before undergoing surgery because of persistence of the tumour. All patients underwent resection of the stomach: there were 90 total and 69 partial gastrectomies. Sixty three patients also received postoperative chemotherapy, two received radiotherapy, and three received both. Chemotherapy protocols were not uniform. They followed the conventional protocol for low grade or high grade lymphoma. Low grade lymphomas were treated with CP (chlorambucil and prednisone) or CVP (cyclophosphamide, vincristine, and prednisone). High grade lymphomas were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), or

PROMACE/MOPP (cyclophosphamide, doxorubicin, etoposide, prednisone, vincristine, nitrogen mustard, procarbazine methotrexate, and leucovorin).

Descriptive statistical analysis

Table 1 summarises the clinical and morphological features of each histological type of gastric lymphoma. Because of the small numbers, the cases of mantle cell, T cell, and Burkitt's-like lymphoma were not considered in the following analysis.

Age showed a normal distribution. Patients with LG lymphoma were significantly younger than those with DLCL (Student's *t* test, $p = 0.019$).

Postoperative adjuvant treatment was given more often for DLCL than for both LG and LG + HG lymphomas (χ^2 test, $p = 0.004$ and 0.002 , respectively).

The location of the tumour in the stomach was not related to the histological type (χ^2 test, $p = 0.93$). Nonetheless, the histological type was related to macroscopic appearance and size: LG lymphomas were more frequently flat and small, whereas LG + HG and DLCL tumours were more frequently ulcerated (χ^2 test, $p = 0.008$) and large (Student's *t* test, $p = 0.03$).

Deep infiltration through the gastric wall to the subserosal fat tissue was seen in significantly more DLCL tumours (44 of 70 cases) than both LG + HG and LG lymphomas (χ^2 test, $p = 0.0005$ and 0.0006 , respectively). LG tumours were more frequently limited to the mucosa than were the other types.

The three groups were significantly different with regard to pathological stage. Patients with DLCL were very rarely found in stage IE1, and patients with LG + HG and DLCL were more frequently at an advanced stage (χ^2 test, $p = 0.016$).

The proportion of nuclei positive for MIB-1 dramatically increased from LG to LG + HG (Student's *t* test, $p = 0.0001$). There was no difference between LG + HG and DLCL ($p = 0.36$), based on the fact that MIB-1 was counted in selected areas with higher positivity.

After a mean follow up period of 52.2 months (range, 0.3–176), 104 patients were alive; 33 patients died of the tumour

Table 2 Patients with postsurgical recurrence of primary gastric lymphoma

Case	Histological grade of primary tumour	Stage of primary tumour	Surgical edges	Histological grade of recurrent tumour	Total follow up (months)	Time of recurrence (months)	Status	Type of gastric resection	Site of recurrence
1	LG	IIIE1	Free	LG	50	18	Alive	Total	Bone marrow
2	LG	IVE	Free	DLCL	98	98	Alive	Total	Colon
3	LG+HG	IE2	Free	LG+HG	48	16	Alive	Partial	Gastric stump
4	LG+HG	IE1	Involved	LG+HG	74	31	Alive	Partial	Gastric stump
5	LG+HG	IE2	Free	LG+HG	73	67	DOD	Partial	Gastric stump
6	DLCL	IIIE1	Free	DLCL	20	15	DOD	Partial	Bone marrow and skin

DLCL, diffuse large cell lymphoma; DOD, died of disease; LG, low grade marginal zone derived MALT-type lymphoma; LG+HG, low grade mixed with variable proportions of confluent sheets of blastic cells outside the follicles.

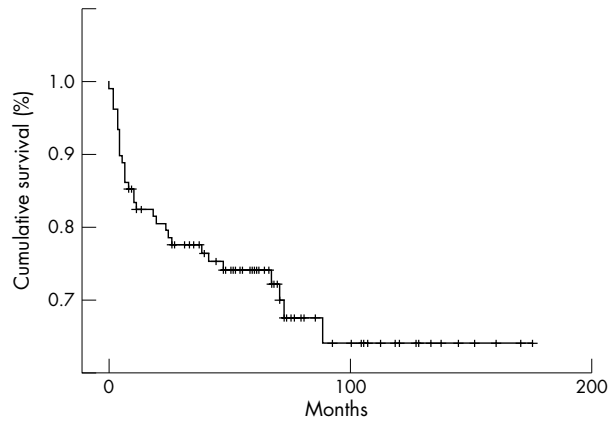


Figure 1 Overall survival curve of patients with LG + HG (low grade mixed with variable proportions of confluent sheets of blastic cells outside the follicles) and DLCL (diffuse large cell lymphoma) lymphomas: 74.1% of patients were alive at five years and 64% at 87 months. The proportion then remained constant.

and 15 of unrelated causes. The cumulative proportion of survival progressively worsened with increasing histological grade, and the difference between LG and DLCL was significant (Kaplan Meier log rank test, $p = 0.017$).

During the follow up period, the histological examination of other tissue specimens documented the recurrence of the tumour in six cases. As shown in table 2, two of these patients subsequently died of disease.

Survival analysis of LG + HG and DLCL

One hundred and nine cases were available for survival analysis. The mean follow up period was 56.4 months, ranging from

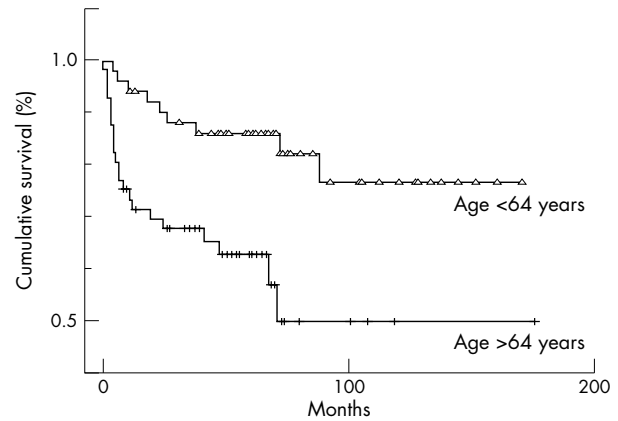


Figure 2 Kaplan-Meier survival analysis with age as selecting variable (cutoff value, 64 years). The difference between the two curves is significant (log rank test, $p = 0.003$).

two to 176 months. Sixty nine patients were alive and 31 had died from the lymphoma. Nine patients, who died from unrelated causes after a follow up period ranging from nine to 119 months, were considered alive in the interval between diagnosis and death.

Figure 1 shows the disease specific overall survival curve. Five year survival was 74.1% and no deaths occurred after 87 months. Table 3 shows the results of the univariate statistical analysis. Patient age (fig 2), tumour stage (fig 3), depth of infiltration (fig 4), and infiltration of adjacent organs (fig 5) all affected outcome in the overall series. These results were confirmed repeating the analysis in the LG + HG and DLCL groups separately, excluding the fact that the age was not

Table 3 Significance level (p value) of the univariate survival analysis (Kaplan-Meier method, log rank test) with the different clinicopathological features used as selecting variable

Selecting variable	All cases (n=109)	LG+HG (n=65)	DLCL (n=44)
Age	0.003	NS (0.14)	0.001
Stage	0.005	0.0005	0.0001
Depth of infiltration	0.005	0.002	0.69
Adjacent organs infiltration	0.0005	0.002	0.004
Size	NS (0.07)	NS (0.1)	NS
Sex	NS	NS	NS
Macroscopic type	NS	NS	NS
Gastric location	NS	NS	NS
Surgical margins	NS (0.1)	NS (0.19)	NS (0.13)
Type of gastric resection	NS	NS (0.08)	NS
Adjuvant therapy	NS	NS (0.1)	NS
MIB-1	NS (0.1)	NS	NS

If not specified in brackets, the significance level of the test between the survival curves is larger than 25%. DLCL, diffuse large cell lymphoma; LG+HG, low grade component mixed with variable proportions of confluent sheets of blastic cells outside the follicles; NS, not significant.

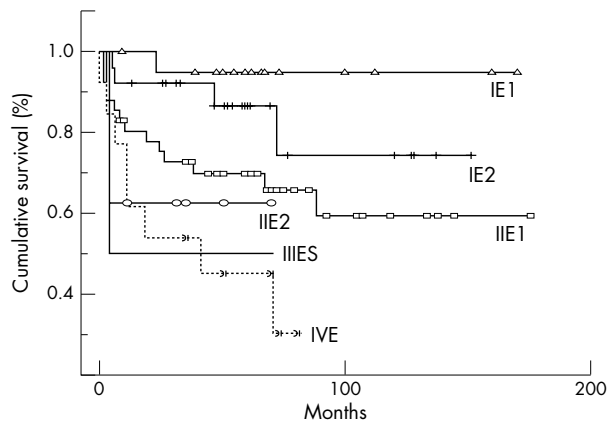


Figure 3 Kaplan-Meier survival analysis with tumour stage as selecting variable. The difference between the curves is significant (log rank test, $p = 0.005$).

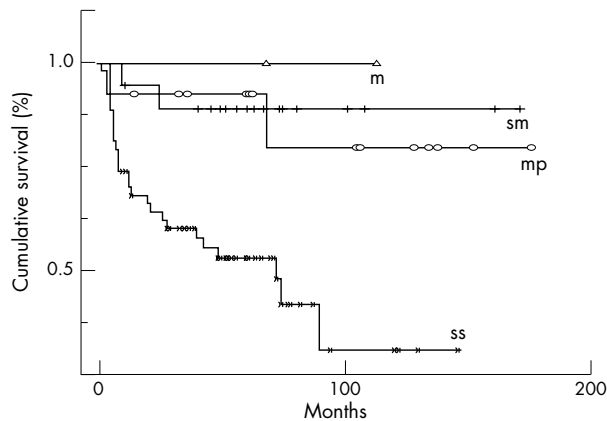


Figure 4 Kaplan-Meier survival analysis with depth of infiltration as selecting variable. The four groups correspond to neoplastic infiltration limited to the mucosa (m), submucosa (sm), muscularis propria (mp), or extended to the serosa (ss). The difference between the curves is significant (log rank test, $p = 0.005$).

important in the LG + HG group and the depth of infiltration did not affect prognosis in patients with DLCL.

With regard to depth of infiltration, no significant differences in survival were found among lymphomas infiltrating the mucosa, the submucosa, or the muscularis propria. They were thus placed in a single group and compared with cases showing infiltration of the serosa (fig 6). Comparable results were obtained performing separate survival analysis for both LG + HG and DLCL.

With reference to tumour stage, patients with stages IIE2, IIIES, and IV showed overlapping survival curves and were grouped together. Moreover, there was no significant difference in survival between stages IE1 and IE2, or between stages IE2 and IIE1; but the corresponding survival curves did not overlap and there was a trend of increasing hazard of mortality going from stage IE1 to IIE1. Therefore, they were not grouped together. The resulting four group classification resulted in a highly significant overall difference in survival (log rank test, $p = 0.001$) and it was used in the Cox analysis. Repeating the analysis separately for LG + HG and DLCL did not yield reliable results because of the small number of cases in each class.

As already stated, there was no significant difference in survival in patients receiving or not receiving postsurgical adjuvant treatment. However, when the patients were stratified by depth of tumour infiltration, an important finding became apparent: adjuvant treatment had little effect

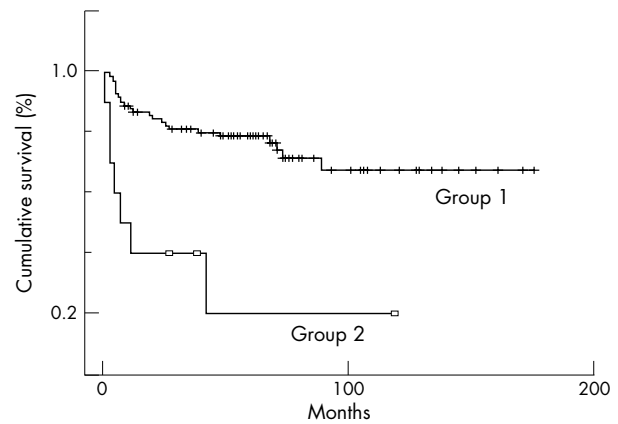


Figure 5 Kaplan-Meier survival analysis of patients without infiltration of adjacent organs (group 1) and with lymphoma invading adjacent organs (group 2). The difference between the curves is highly significant (log rank test, $p = 0.0005$).

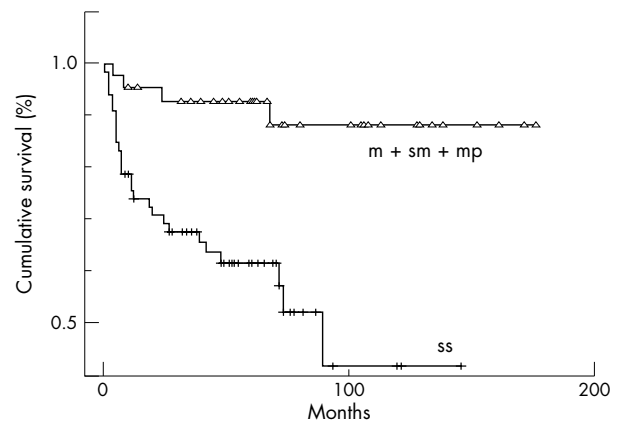


Figure 6 Kaplan-Meier survival analysis of patients stratified by level of infiltration in the gastric wall: cases with invasion of mucosal (m), submucosal (sm), and muscularis propria (mp) layers were compared with patients with invasion of the serosa (ss). The difference between the curves is highly significant (log rank test, $p = 0.00001$).

in patients with the lymphoma limited to the gastric wall (log rank test, $p = 0.92$), but dramatically improved survival when the tumour extended to the subserosal fat tissue ($p = 0.00001$). Repeating the analysis separately for LG + HG and DLCL yielded similar results in both groups. The importance of postsurgical treatment was also checked in the patients stratified by pathological stage. Treatment was more effective in improving survival in advanced stages (IIE1 and the group IIE2 + IIIES + IVE) than in early stages. However, the significance of the test was affected by the small number of cases in each class and by the fact that no patients in stage IE1 were treated.

The variables that were found to affect prognosis were paired in each possible combination and analysed by the χ^2 test to detect a correlation between them. Depth of infiltration correlated with tumour stage ($p = 0.0005$), with infiltration of adjacent organs ($p = 0.0058$), and with tumour size ($p = 0.05$). Tumour size also correlated with tumour stage ($p = 0.0056$).

Cox multivariate analysis provided a very accurate prediction of survival (χ^2 test, $p < 0.00001$) and selected age and depth of neoplastic infiltration as the most significant parameters.

DISCUSSION

In our study we compared the clinicopathological features of primary gastric lymphomas, which were surgically treated, divided into three groups based on the histological grading.

Patients with LG lymphomas differed from the other two groups, being younger in age, having longer survival, and having tumours that were smaller in size, more frequently flat, with a lower proliferative activity, and at an earlier stage. In contrast, there were only minor differences between LG + HG and DLCL, mainly concerning the infiltration of the serosa, which was more frequent in DLCL. We saw no significant differences in survival between the two groups. These findings suggest a distinction between LG lymphomas, which nowadays are treated conservatively as first choice, and LG + HG or DLCL tumours, which show features of disease progression and require more aggressive treatment.^{10 11 14} Therefore, the recognition of a high grade component in preoperative small biopsies has become crucial for the further management of patients with gastric lymphomas.^{9 13} We think that the analysis of proliferative activity can aid the definition of histological grade in small biopsies, where the blastic aspect of the cells can be obscured by artifacts. In our series, MIB-1 immunostaining provided a sharp distinction between LG and the other two groups: values greater than 15–20% were invariably associated with the presence of a high grade component. In contrast, there were no differences in MIB-1 positivity between LG + HG and DLCL tumours because measurements were done in areas with the highest positivity.

In most cases we found that the histopathological features of recurrences were similar to those seen in the primary lymphoma (table 2). In the single case of an LG lymphoma recurring as DLCL after a long time period we cannot exclude the possibility of a second malignancy. Moreover, it should be pointed out that stage I tumours showed local recurrence in the gastric stump, whereas distant relapses were seen in patients with higher stage tumours (II and IV). The histopathological examination of the resection margins failed to show lymphomatous involvement in two of the three patients with gastric stump relapse. This finding suggests that undetectable neoplastic foci may exist at a distance from the main tumour, as recently reported.³⁷

“The recognition of a high grade component in preoperative small biopsies has become crucial for the further management of patients with gastric lymphomas”

In our present study, we excluded all LG cases from the survival analysis, because nowadays *Helicobacter pylori* eradication and chemotherapy are the first treatment choice for such cases. In LG + HG and DLCL, which are still treated by surgery, we found that age, stage, depth of infiltration, and invasion of adjacent organs all affected outcome. In agreement with other studies,^{2 15 19 23 25 26} age appeared to be an independent prognostic factor: it was not related to other parameters with prognostic significance, or to differences in the treatment choices that could have been based on patient age. It should be noted that age was found to be most important factor in predicting the outcome of patients with DLCL.

As already claimed by others,^{4 5 7 8 12 17 18 20 22 23 25 26} we believe that stage is of crucial importance for prognostic evaluation. It should be estimated as carefully as possible, including the level of nodal involvement, tumour size, depth of infiltration, and invasion of other organs. All these factors correlated with survival in our present study. The prognosis was unfavourable when regional lymph nodes were involved by lymphoma and it was even worse when the disease extended to more distant lymph nodes and other organs. Depth of infiltration was one of the most important prognostic indicators, particularly in LG + HG lymphomas, which showed a much lower survival rate when the serosa was infiltrated.

Take home messages

- High grade gastric lymphomas (both pure and with a residual low grade component) were more frequently large, ulcerated, at an advanced stage, and highly proliferating than were low grade lymphomas, and patients were usually older with a worse outcome
- These differences appear to justify the different treatment approaches used
- Adjuvant postsurgical treatment prolonged survival only in patients with advanced stage and deep neoplastic infiltration, so that postsurgical management of high grade lymphomas should be based on accurate evaluation of the neoplastic extension

In our study, patients with unfavourable prognostic factors, such as serosal involvement and advanced stage, seemed to benefit from adjuvant postsurgical therapy. This did not occur in the overall series. A similar correlation has been reported in recent papers.^{6 16 19 24 26 28 30} We believe that these findings should be taken into account in the postsurgical management of primary gastric lymphomas.

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ECHO

Screen test



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A large study in the UK concludes that the incidence of complement abnormalities is so low that screening all children after meningococcal disease (MCD) is unnecessary, contradicting the blanket screening advocated in some paediatric textbooks. The researchers also say, though, that testing is warranted when children have had previous suspicious infections, complications of infection, infection with unusual meningococcal serogroups, recurrent infections with *Neisseria*, or have coexisting autoimmune or connective tissue disease.

Out of nearly 300 survivors of MCD tested for classical and alternative complement components, only one child, aged 4 years, showed a deficiency—in C2. She had MCD with a complicated course—septicaemia with Group B meningococcus, disseminated intravascular coagulation, and coexistent bacterial and viral infections—and a made slow recovery. When 4 months old she had had a pneumococcal infection and while convalescing had contracted a respiratory syncytial virus infection. None of her immediate family were prone to recurrent infections or autoimmune disease.

The study was based on an unselected series of 824 children known to the Regional Paediatric Infectious Diseases Unit or the Paediatric Intensive Care Unit Retrieval Service in North East region between 1996 and 1999 with suspected or confirmed MCD. In total, 212 of 352 children with laboratory confirmed MCD and 85 of 96 with clinically diagnosed MCD were tested for components of the classical and alternative complement pathway at a review six to eight weeks after discharge.

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