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Original paper

Surgery Plus Chemotherapy or Chemotherapy Alone for Primary Intermediate- and High-grade Gastric Non-Hodgkin's Lymphoma: The Royal Marsden Hospital Experience

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Primary gastric lymphomas (PGL) have traditionally been treated with surgery followed by chemotherapy or radiotherapy. Surgery was thought to improve staging, optimise local disease control and reduce risk of perforation or bleeding, but recent studies question its role. In this study, patients with intermediate- or high-grade PGL who received chemotherapy from 1985 to 1996 at the Royal Marsden Hospital were identified using a prospectively accrued database. A total of 37 patients (6 with low-grade mucosa-associated lymphoid tissue lymphoma (MALT-L), 9 with high-grade MALT-L, 20 with diffuse large B-cell (DLBC) lymphoma and 2 other histologies), 17 of whom had localised disease, were treated with either surgery plus chemotherapy or chemotherapy alone. 5-year overall survival for localised and advanced PGL was 94 and 50%, respectively, with no differences between the two treatments over a 53 months median follow-up. No perforations or serious bleeding occurred. Surgery is associated with important morbidity and we detected no benefit of surgery prior to chemotherapy in this limited series of patients. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

PRIMARY GASTRIC lymphoma (PGL) accounts for up to 5% of all malignant tumours of the stomach, and an increasing incidence has recently been postulated [1]. It represents more than half of all primary gastrointestinal lymphomas in the Western world, but there is marked geographical variation in its incidence and histological types, which probably reflects different aetiologies and pathogeneses. Since the demonstration that a newly recognised PGL subtype, mucosa-associated lymphoid tissue (MALT) lymphoma, is overwhelmingly associated with *Helicobacter pylori* infection [2], and that *H. pylori* is essential in the early stages of MALT lymphoma pathogenesis as an antigenic driving agent [3] whose eradication may lead to regression and possibly cure [4, 5], a surge in interest in this rare but fascinating disease has occurred.

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The use of routine endoscopy as an initial staging tool has recently demonstrated that the stomach is involved in up to one fourth of patients presenting with a typical nodal Non-Hodgkin's lymphoma (NHL) [6]. Thus, endoscopy may be important for staging in patients where radiotherapy is planned as the only treatment modality. However, approximately 30–50% of primary extranodal lymphomas arise in the gastrointestinal tract (GIT) [7, 8], and the distinction between a lymphoma arising in the stomach as a primary site and secondary gastric involvement with a nodal lymphoma is important, since PGL in its early stages may represent truly localised disease with a different natural history and requiring different therapeutic approaches.

The initial criteria for PGL laid down by Dawson [9]—requiring the lymphoma to be limited to the GIT and its adjacent lymph nodes, with no involvement of liver or spleen other than by contiguous invasion were too strict, and led to an underestimation of PGL incidence. Herrmann [10] and Lewin [11] widened the definition to include lymphomas

whose initial presenting symptoms were due to histologically proven involvement of the GIT, and which had a main alimentary tract lesion. MALT lymphomas represent a distinct clinical entity, with pathological features that can be confidently recognised in histological material irrespective of the distribution of the disease. In addition to MALT lymphomas of low- or high-grade, PGL encompasses all other types of low- or high-grade lymphoma of B or T cell type, corresponding to their peripheral lymph node equivalents, and accounting for the greater number of patients presenting with this disease.

Since early stage PGL is thought to be a localised disease, surgery has traditionally been considered to be the cornerstone of treatment, and published series of patients followed up after partial or total gastrectomy reported impressive treatment results, with long disease-free survival (DFS) and overall survival (OS), especially in patients with low-grade NHL [12–17]. Radical resection predicted for longer survival in some reports [17–21] where surgery was the only treatment modality. Further advantages claimed for surgery have included more reliable histological diagnosis given larger tissue samples [13, 22] and more accurate staging and assessment of prognostic factors including depth of invasion [10, 23, 24]. In addition, surgery was claimed to prevent complications like perforation or bleeding which have been associated with chemotherapy or radiotherapy and are attributed to rapid tumour necrosis [19]. More recently the role of surgery has been questioned given the procedure's associated morbidity and mortality, particularly in earlier series [14, 25], and the fact that in some surgical series resectability of tumours can be as low as 66% [26].

In a development similar to the one in nodal lymphomas, where good results from chemotherapy led to the abandonment of a local treatment strategy alone, radiotherapy (RT), in favour of chemotherapy or a combination of chemotherapy and RT, the role of systemic treatment has been investigated in PGL. Anthracycline-containing chemotherapy is mostly well tolerated, given on an outpatient basis, and has few long-term side-effects. The Royal Marsden Hospital (RMH) lymphoma unit established a policy of conservative treatment with chemotherapy only for intermediate and high grade PGL patients in the late 1970s. In addition, patients referred following surgery for consideration of chemotherapy from a large area of southwest London were followed. We reviewed a prospective database and the records of all patients with PGL treated in the lymphoma unit with chemotherapy alone or surgery followed by chemotherapy between 1985 and 1996 and report on presentation and long-term outcome of these two treatments.

PATIENTS AND METHODS

Data on lymphoma patients is recorded prospectively on the lymphoma database at first and each subsequent visit to the RMH, and the computerised hospital information system contains comprehensive histological and radiological data. The records of all the patients with a histological diagnosis of intermediate or high-grade NHL according to the Working Formulation (WF) involving the stomach, seen between 1985 and 1996 at the RMH were identified. Patients referred for a second opinion (including histological review) or who received radiotherapy but no chemotherapy treatment at the RMH were not included in this series. Patient records and notes were reviewed for the criteria for PGL as defined by Herrmann [10] and Lewin [11], and patients in whom lymphoma diagnosis predated demonstration of gastric involvement or where the bulk of the disease and its manifestations was extra-abdominal, nodal, hepatic or splenic were considered to have secondary involvement of the stomach and were excluded from analysis following discussion of each case among the authors. Patients unequivocally satisfying the criteria for PGL who were treated with chemotherapy at the RMH were included in this study.

All the original histology slides were reviewed by a single pathologist, and where appropriate new slides were cut and analysed. Patients' histologies were reclassified according to the revised European–American lymphoma (REAL) classification, as detailed in Table 1, together with a reappraisal of the original Kiel and WF diagnosis.

Staging procedures for each patient included clinical examination with inspection of Waldeyer's ring, full blood count and chemistry, computer tomography (CT) scans of chest, abdomen and pelvis or chest X-ray and CT of abdomen and pelvis, bone marrow aspirate and trephine. Where appropriate, endoscopies with biopsies were performed to confirm remission status. Patients were staged according to the Ann Arbor system as modified by Musshoff for lymphomas of the GIT [27], with stage II_1 indicating local nodal involvement, and II_2 more distant intra-abdominal lymph node involvement, and retrospectively according to the staging system agreed upon in the Lugano PGL meeting [28].

Chemotherapy was given as outpatient treatment, except for the first course during which patients were often admitted if there was thought to exist a risk of perforation or bleeding. Patients were treated where appropriate within ongoing randomised clinical studies, presupposing informed consent.

Demographic and presentation data, histology, staging, treatment, side-effects, response and follow-up were recorded on a prospective lymphoma database. Categorical data were examined using the chi-squared test, with Fisher's exact test used where appropriate. Survival analysis was performed using the methods of Kaplan and Meier. The log rank test was used to examine differences in survival curves.

RESULTS

Patient characteristics

A total of 72 patients with intermediate or high-grade lymphoma involving the stomach were identified from January 1985 to October 1996. 12 of these patients were seen for second opinions only and were not treated or followed up at the RMH. 18 patients did not satisfy criteria for primary PGL: 13 of them had had a prior diagnosis of lymphoma, with the stomach involved following progression or relapse, and 5 had the bulk of disease outside of the alimentary tract. 4 patients had localised PGL but received no chemotherapy treatment. 2 of them were referred for radiotherapy only following surgery, and the remaining 2 were observed following eradication of *H. Pylori*. 38 patients satisfying the Herrman and Lewin criteria for PGL were referred and treated with chemotherapy at the RMH for intermediate or high grade NHL. On histology review, 1 patient had Hodgkin's disease, and was excluded from the analysis. The demographic data, presenting symptoms and treatments of the remaining 37 patients are listed in Table 1.

Treatment and outcome

Treatments are listed in Table 1. 24 patients had no previous surgical intervention and were treated with chemotherapy

alone; of these 17 (71%) received anthracycline-containing chemotherapy. An average of 10.2 weeks (median of 10 weeks, range 1–20 weeks) chemotherapy were administered. 13 patients had a partial or total gastrectomy prior to referral to the RMH. Of these, 8 had localised disease, and the surgery was thought to be curative in 5 patients by the referring surgeons. 5 patients with more advanced disease had a partial resection: 1 patient presented with perforation and underwent emergency partial gastrectomy. All patients received chemotherapy within 2 months of original surgery, with an average number of 11.8 weeks (median 12 weeks, range 3–18 weeks) of treatment. 10 (77%) received anthracycline containing chemotherapy.

Table 1. *Patient characteristics, treatments and survival*

	Surgery and chemotherapy	Chemotherapy alone
	$n = 13$	$n = 24$
Average age (range)	59 (19–81) years	62 (32–80) years
Gender		
Male	7	16
Female	5	8
Histology		
(WF)		
Interm	13	23
High	0	1
(REAL)		
DLCL	7	13
HG MALT	4	5
LG	2	4
Other	0	2 (1 MCL, 1 Burkitt)
Lugano stage		
I	4	5
II1	4	4
II2	0	1
IIE	2	6
IV	3	8
Presenting features		
Abdominal pain	9	21
Anorexia	9	23
Vomiting	3	5
Weight loss	3	14
Diarrhoea	1	0
Haematemesis	2	2
Melaena	0	6
Anaemia	0	4
Palpable mass	1	9
Perforation	2	2
Resections	13	0
Complete	5	
Chemotherapy		
Stage I+II1	8	9
Single agent	0	2
Combination chemotherapy	8	7
Anthracycline-containing regimens	7	6
Median number of courses (range)	6 (1–10)	6 (6–12)
Stage II2–IV	5	15
Single agent	0	3
Combination chemotherapy	3	12
Anthracycline-containing regimens	3	11
Median number of courses (range)	3 (1–14)	5 (1–20)
5-year survival	60%	67%
Relapse free	85%	62%
Overall		

WF, Working Formulation; interm, intermediate grade; high, high-grade; DLCL, diffuse large cell lymphoma; HG MALT, high-grade MALT; LG MALT, low-grade MALT.

*Stage I—II*1. A total of 17 patients had PGL limited to the stomach or adjacent lymph nodes, by radiological staging criteria; 8 had a partial or total gastrectomy, 5 of whom were deemed to have had a curative resection. 9 patients were treated with chemotherapy alone. Treatment toxicity was as would be anticipated for moderately myelosuppressive chemotherapy. No gastric perforation occurred, and only 1 patient in the chemotherapy alone group had a small episode of GI bleeding on treatment which settled spontaneously. One patient experienced early satiety and had diarrhoea consistent with malabsorption as a consequence of gastrectomy. 2 patients in the chemotherapy group and 1 patient in the surgery plus chemotherapy group also received RT to the stomach bed (30 Gy). 5-year survival was 94% and progression free survival was 76%. 2 patients progressed between the time of surgery and start of chemotherapy, 1 of whom was thought to have had a complete resection by the referring surgeon. Both achieved complete remission following chemotherapy. A patient had progression following chemotherapy alone with CEOP-B and re-attained a complete response (CR) following four courses of etoposide, prednisolone, ifosfamide and cisplatin (EPIC), and a further patient was retreated with chlorambucil for radiologically suspected progression and remains in CR since. No lymphoma-related deaths occurred in either group. 2 patients (aged 74 and 75 years) died of other causes.

Stage II2–IV. Advanced disease was present in 20 patients. Palliative resections were performed in 5 patients prior to referral to the RMH, with reduction of tumour perforation risk and relief of gastric outlet obstruction as the main reasons given for surgery. Patients received chemotherapy as detailed in Table 1. No differences in chemotherapy treatment were present in the two groups. The outcome of treatment was as follows: 9 patients are in first complete remission, 7 in the chemotherapy alone and 2 in the surgery plus chemotherapy groups. One of these latter 2 patients had some disease progression between surgery and start of chemotherapy. A further patient progressed both following surgery and shortly after cyclophosphamide, doxorubican, oncovin, prednisolone-methotrexate (CHOP-M), but remains in second CR 11 years after salvage therapy. 10 patients have died, 2 in the surgery plus chemotherapy group. One of them was a 81 year old patient who died of a myocardial infarction 2 months following surgery and start of CHOP chemotherapy, with responding NHL. The other patient was 75 years old and had stage IV diffuse large cell lymphoma (DLCL) with performance status (PS) IV at start chemotherapy and progressed after one course of COP. No salvage chemotherapy was attempted. In the chemotherapy alone group, 8 patients died, of whom two, aged 75 and 84 years, were in CR at last review 3 and 6 years after completion of chemotherapy. One patient had MCL that progressed despite salvage treatment with CHOP; and another had a Burkitt's lymphoma and achieved a 1 month remission after CHOP×6 and was resistant to

DHAP. 4 patients finally had DLCL, which in one of them rapidly progressed in spite of M-BACOD chemotherapy and radiotherapy to abdominal bulk. The other 3 patients with DLCL who died had advanced age and poor PS. One of them received six courses of prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin and oncovin (PAdriaCEBO) and progressed, the other 2 were treated with chlorambucil only. Overall 5-year survival was 50%.

Review of histology showed that 5 patients with localised PGL and 1 patient with stage IV PGL had classical low-grade MALT-L histology. Since this newly recognised entity is thought to carry a better prognosis, an analysis of overall and cause related survival by treatment group and stage (localised versus advanced PGL) was performed only for the 31 patients with more aggressive clinical behaviour and is shown in Figure 1.

No differences between the groups were observed regarding chemotherapy toxicity. However, no patients in the surgically treated group but 4 of 16 patients (25%) in the chemotherapy alone group had bleeding episodes while receiving treatment. Of these, 2 had a priori unresectable tumours as judged by the referring surgeons. In 2 patients bleeding occurred during the first week of chemotherapy. One patient with mantle cell lymphoma had recurrent

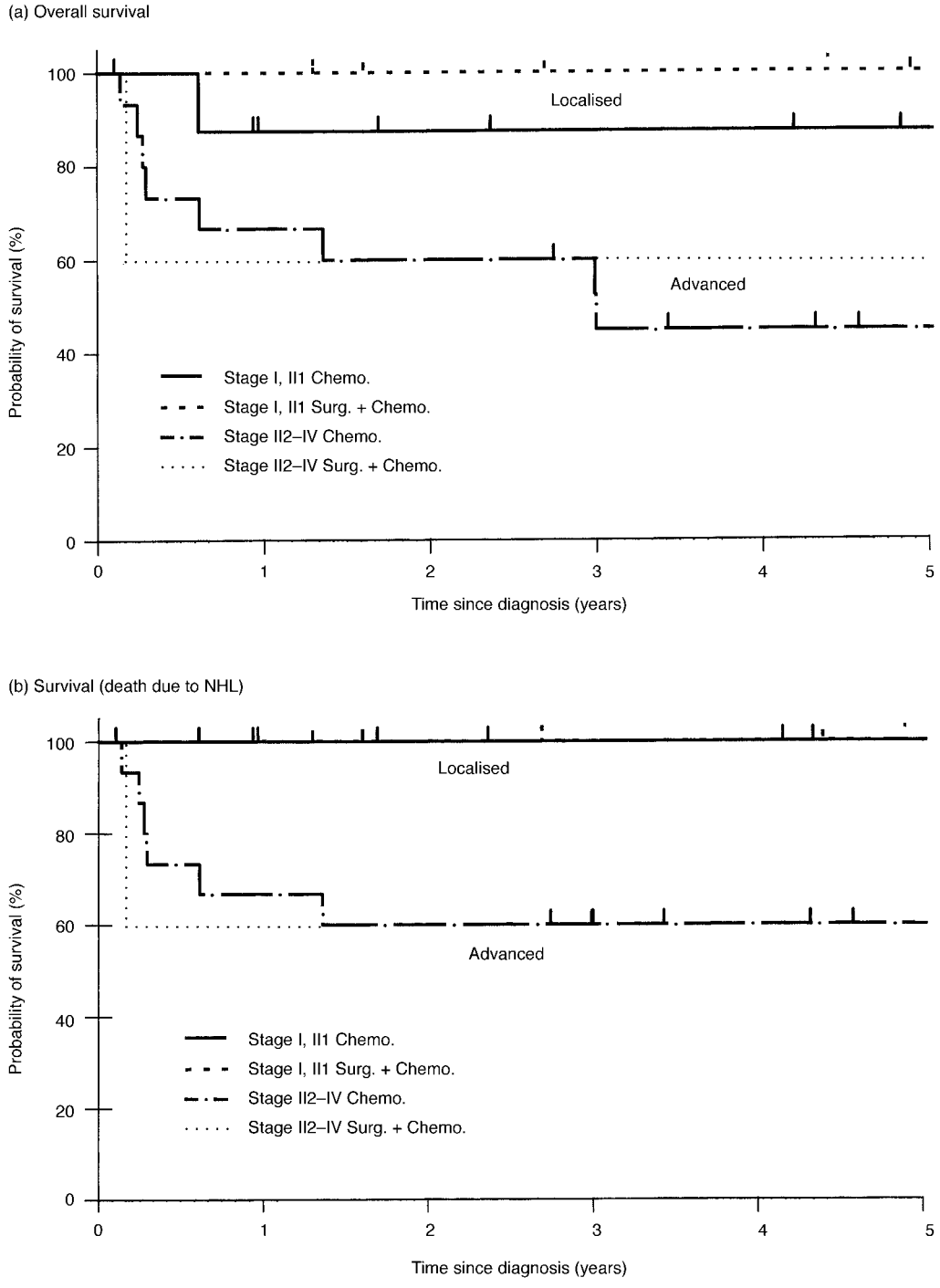

Fig. 1. (a) Overall survival and (b) cause specific by Lugano stage and treatment type. Data is shown for the 31 patients with unfavourable histologies. The 6 patients with low-grade MALT (5 stage I–III, 1 stage IV) are all alive.

melaena and underwent elective gastrectomy. No patient had life threatening GI bleeding.

DISCUSSION

Diagnosis of PGL has been aided by recent improvements in imaging and biopsy techniques. An abnormal mucosal pattern, ulceration/erosion, or polypoid masses are seen in the majority of PGL cases [5, 29–31], and the correct diagnosis is sometimes suspected at endoscopy, although no pathognomonic endoscopic picture exists for PGL. The practice of obtaining multiple endoscopic biopsies has led to a dramatic improvement in diagnostic yields currently of over 90% [29, 30], even in patients with no distinctive endoscopic features. Uniformly high levels of concordance have been reported between pre- and postoperative histological diagnosis in a series of 66 patients where tumour resection was performed in all patients [30]. Multiple biopsies from various areas of the stomach, including endoscopically unremarkable ones, is also required in order not to miss an area of high-grade malignancy.

Accurate staging of gastric lymphomas is more controversial. Whilst the positive predictive value of CT scans is excellent, and they are part of the suggested staging system in PGL [28], determining the exact extent of disease may be difficult. CT examination may show only thickening of the gastric wall, with poor demarcation of surrounding organs, precluding comment on lymphomatous involvement of perigastric lymph nodes or invasion of other organs. Grau showed in a recent study that CT scans failed to identify correctly small involved perigastric nodes [32], comparing radiological stage prior to gastrectomy with the pathological stage after the operation in 15 patients with PGL. In this series, 10 patients were clinically understaffed as Musshoff stage El, whilst at operation they were found to have involved lymph nodes measuring 0.7–1.5 cm, and received additional chemotherapy or radiotherapy. This is important since the absence or presence of involved lymph nodes is the crucial factor differentiating between stage I and II, with important prognostic implications. Endoscopic ultrasonography (EUS) has recently been shown to be a useful tool both in diagnosing and staging gastric lymphomas [33–35]. EUS identifies neoplasms by the changes induced in the normal ultrasonographic layer pattern or thickness of the stomach wall, and allows accurate estimation of the depth of invasion in over 90% of cases when compared with gastrectomy specimens [34, 35]. Sensitivity for enlarged lymph nodes varies between 44 and 100% in different series [34, 35], with specificity being the trade-off. The sensitivity and specificity of EUS is likely to improve further, as higher resolution images and 3-dimensional reconstruction will become available in the near future.

Whilst accurate staging is essential in understanding the pathogenesis of PGL and determining prognostic factors, it may turn out to be a mandatory prerequisite only in patients receiving local therapy, i.e. either surgery or radiotherapy. In the past, staging laparotomy and lymphangiography became obsolete in patients with localised Hodgkin's disease once therapy protocols incorporated chemotherapy in treatment of early stage disease.

Surgery has been advocated by some as the treatment modality of choice in localised PGL, with some small series reporting 5-year survival rates of 95–100% [17, 18, 36, 37] following partial or total gastrectomy. However, these series represent a highly selected population. In the largest of these publications, Bartlett [17] reported the Memorial Sloan-Kettering experience of 12 years: of 106 patients only 34 patients were finally operated and staged IE or IIE1; of these only 15 were selected for surgery alone, while 19 received some additional adjuvant treatment. The 15 patients selected for surgery alone (stage 1 in 13) had a 10 year DFS of 100%. However, an early important paper by Herrmann [10] claimed that extent of resection has no prognostic value and that according to their experience, surgery alone cannot be considered adequate treatment.

The combination of surgery and chemotherapy has been frequently used in both localised PGL [15, 16, 20, 38–42] and in more advanced cases, where it was thought to minimise the risk of bleeding and perforation following rapid necrosis of tumour tissue as a result of chemotherapy or radiotherapy [43, 44] as well as improving response rates [19, 45]. High-grade tumours are more likely to cause complications [31], but recent series have shown that the risk of bleeding and perforation has been overestimated [46], with regard to both incidence and severity. In addition, bleeding and perforation can occur even after resection [47].

Gastric resection is associated with significant operative mortality and postoperative morbidity. Elective partial gastrectomies for gastric ulcers have mortality rates of around 3%, but mortality following resection for gastric cancer is higher. Reported mortality rates in PGL range between 0–16% in various studies [16, 48]; Roukos reported an average 7% mortality in 881 resections reported in the literature [49]. Sequelae of gastrectomy include early satiety and abdominal discomfort, weight loss, afferent loop syndromes following Billroth II operations, dumping syndrome and malabsorption, including B12 deficiency, vitamin D and calcium malabsorption leading to osteomalacia and osteoporosis. Although some of these complications are rare, overall relevant postoperative problems have been estimated to occur in up to 25% of patients. In a disease where high cure rates can be expected, avoidance of treatment-related complications affecting quality of life is preferred, and stomach-conserving therapeutic approaches have been explored.

Some investigators have suggested that chemotherapy alone or with radiotherapy may be as effective as surgery in localised PGL [46, 47, 50–54], with no survival advantage conferred by surgical debulking in advanced gastric lymphoma [20, 46, 52]. The discrepancy between these results and those showing a prognostic advantage for resection [19, 45] may be partially explained by patient selection in retrospective surgical series, from which poor anaesthetic risk patients and those with extensive, inoperable lymphomas had been excluded. In an attempt to overcome this limitation, Avilles and colleagues [55] randomised patients with localised PGL irrespective of histological sub-type to chemotherapy only (28 patients) or gastrectomy followed by chemotherapy, with no differences in response rate or survival, but unfortunately 2 toxic deaths occurred in the chemotherapy alone arm. In a review of the British National Lymphoma Investigation Group (BNLI) experience with GI lymphomas, Morton comments on a similarly higher incidence of infection related deaths on chemotherapy [47]. In a study of patients with histologically aggressive lymphomas, Haim and colleagues [53] treated 15 patients with stage I, 7 with stage II and 4 with stage IV PGL with anthracycline containing chemotherapy, followed by RT in those patients with limited disease that achieved CR. Excluding 2 early

deaths, 16 of 24 patients achieved a CR after chemotherapy, and 6 a PR. 2 of these 6 patients were found to have only low-grade component lymphoma on repeat endoscopy and achieved CR after RT. All patients who failed to achieve CR died, but no patient in CR relapsed with a median follow up of 22 months. Patients retained good gastric function.

The data we present here add further support to the view that chemotherapy alone is adequate initial treatment for PGL. There were no differences in patients treated with surgery followed by chemotherapy compared with those receiving chemotherapy alone. Criteria for PGL were applied strictly, minimising the risk of inclusion in this study of nodal lymphomas that secondarily involved the stomach. As well, all histological material was reviewed to reclassify each case in the light of the new REAL classification. This is particularly important since the WF does not recognise the MALT lymphoma entity, which frequently gets assimilated among intermediate grade lymphomas. In most of the series reported in the literature, this group of patients cannot be identified. However, low grade MALT-L of the stomach has been shown to have an indolent nature, with histological regression documented by various groups following antibiotic treatment alone, and overall survival that is substantially better than the one reported for series of similar stage PGL. A recent series of 93 patients with low-grade MALT-L of the stomach (92% stage I or II1) reported a projected overall 5-year survival of 82%, including 49 patients treated with antibiotic *H. pylori* eradication only. Death was due to secondary cancers in all but 1 patient, rather than aggressiveness of the lymphoma itself [56] In our series, 5 localised and one stage IV lymphoma were recognised as low-grade MALT-L. All these patients achieved a CR following chemotherapy (1 CHOP, 3 chlorambucil) or surgery leading to a PR followed by chemotherapy (1 CHOP, 1 M-BACOP) and remain disease free. As well as reporting overall survival data for all patients, we have also presented survival graphs for the remaining 31 patients with less favourable histologies, once this good prognosis group of patients that remain in first CR was removed from analysis. Both for the entire group and for the subset of patients with histologies other than low grade MALT-L, no response or survival benefit from surgery was demonstrated, and no serious bleeding or perforation occurred in patients treated with chemotherapy alone.

Optimal treatment for PGL is still being defined. For low-grade gastric lymphoma, non surgical treatment options are studied in trials such as the current UKLG LY03 study. Patients with endoscopically diagnosed localised low grade gastric lymphoma responsive to *H. pylori* eradication treatment are being followed by repeat endoscopies and randomised between observation and chlorambucil treatment. Data on frequency and length of PGL remissions following *H. pylori* eradication, on the value of added chlorambucil and natural history of low grade lymphoma without surgical resection are being collected. The prognostic importance of high-grade areas in low-grade tumours also needs assessing, particularly in the context of observation alone following eradication of *H. pylori*. Whilst many reports, including the present one, question the value of initial surgery in the modern management of PGL patients, definite evidence can only emerge from a large randomised trial like the German multicentre gastrointestinal lymphoma study, where the role of surgery followed by risk adapted CHOP is prospectively compared to 6 courses of CHOP chemotherapy alone.

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