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A Multivariate Analysis of Factors Affecting Survival in Patients with High-grade Histology non-Hodgkin's Lymphoma

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Abstract—*One hundred and eleven patients with advanced-stage, high-grade histology non-Hodgkin's lymphoma were studied over a 7-yr period and were treated with one form of chemotherapy and radiotherapy. Multivariate analyses were carried out to identify factors which could predict a favourable prognosis. A complete response, low serum LDH and absence of clinical evidence of liver involvement were associated with long-term survival. The presence of 'B' symptoms, bone marrow involvement, low serum albumin and male sex predicted a reduced chance of achieving a complete remission. For those patients who achieved a complete response, the subdivision of histologies, particularly according to the Kiel classification, was the only significant factor predictive of prolonged relapse-free and overall survival. This confirms the importance of identifying different histological subgroups of lymphoma when considering treatment planning.*

INTRODUCTION

WITH appropriate treatment, patients with non-Hodgkin's lymphoma of high-grade pathology can achieve a complete remission and a significant proportion will have long-term survival [1–4]. Pathological stages I and II disease are now associated with 5-yr relapse-free survivals in excess of 70% [5–7], with long-term survival being achieved in more than 40% of patients with advanced disease [8–10]. Most studies have analysed data using the Rappaport classification and there is evidence that the diffuse histiocytic subtype is associated with prolonged relapse-free survival using combination chemotherapy.

There are several factors, apart from histology, which may influence remission status and survival. Tumour bulk, low haemoglobin, liver involvement, raised serum LDH and gastro-intestinal involvement have been reported to be associated with poor prognosis [2, 11, 12]. These studies have been based on groups of patients who received combination chemotherapy, but of several different kinds within each study. Between 1975 and 1982 the Manchester Lymphoma Group used one regimen of intensive remission induction in patients with advanced high-grade non-Hodgkin's lymphoma, followed by radiotherapy to the sites of previous bulky disease and 2 yr oral maintenance chemotherapy.

This is a report of the results of a multivariate analysis of factors affecting remission and survival of 111 patients receiving this standard treatment regimen. The importance of identifying high- and low-risk subgroups will be discussed with reference to the development of new treatment protocols.

MATERIALS AND METHODS

One hundred and fifteen patients with stages II (abdominal), III and IV disease were treated using the VAP protocol by members of the Manchester Lymphoma Group between 1975 and 1982. All patients originally had a biopsy-proven diagnosis of high-grade pathology non-Hodgkin's lymphoma using the modified Rappaport classification [13]. At the time the patients were referred, pathological specimens were reviewed at the Christie Hospital, and those patients with malignant lymphomas of diffuse histiocytic,

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diffuse poorly differentiated lymphocytic, diffuse mixed or diffuse undifferentiated subtypes were accepted for inclusion in the trial. The histology has since been reviewed again by one of the authors (MH) and is also grouped according to the Kiel classification (with the addition of a 'true histiocytic' category). The histological review was conducted using the file sections which were stained with haematoxylin and eosin. In some cases reticulin and methyl green pyronin stains were also available and in cases where a diagnosis of true histiocytic lymphoma was entertained immunoperoxidase stains for alpha-1 anti-trypsin and muramidase were done if material was available [14, 15]. Material was unavailable for re-analysis in 16 cases, and in four cases the histology was felt not to resemble that of a lymphoma. This latter group was excluded from analysis, leaving 111 patients analysable in the trial. The distribution of patients by age, sex and stage is shown in Table 1 and by histology in Table 2.

The patients were staged using the Ann Arbor classification. Laparotomy was performed to establish the diagnosis of lymphoma in 43 patients but was not routinely used as a staging investigation. A clinician's assessment was made as to whether the liver was involved with lymphoma and took into account both physical examination and the results of radiological and biochemical investigations (the elevation of two or more enzymes was taken as being significantly abnormal). It was appreciated that in several cases such an assessment may not have accurately reflected involvement of the liver with lymphoma. Confirmation of a clinical impression of involvement was obtained by histological proof in several instances and in only four cases was the patient said to have stage IV disease on the basis of a clinical assessment of liver involvement alone.

Response was assessed by standard criteria, a complete remission being defined as the disappearance of all known disease (after all previously abnormal investigations had been repeated) and a partial remission as a 50% or more decrease in the sum of the products of perpendicular diameters of measurable lesions, lasting for more than 4 weeks. Progression of disease was defined as the appearance of new lesions or an increase of greater than 25% in the sum of the products of perpendicular diameters of measurable lesions lasting more than 4 weeks. Static disease amounted to neither a 25% increase nor a 50% decrease in the size of measurable lesions.

No patient had received prior chemotherapy, but 12 patients had been given a course of radiotherapy to a single lymph node area before entry into the study. The treatment involved remission induction over 6 weeks with vincristine 2 mg weekly, adriamycin 50 mg/m^2 every 2 weeks and prednisolone 40 mg daily. Patients who achieved a complete remission then received radiotherapy to the site(s) of previous bulky disease (single tumour mass $\geqslant$5 cm), using a small margin and giving 2500 cGy fractionated over 8 days on a 4 MV linear accelerator. In those patients who still had evidence of residual tumour at the sites of previous bulk disease, but who otherwise were in remission after the induction chemotherapy, radiotherapy was given, with more generous margins, over a 3-week period to a

Table 1. Patient characteristics

	No.	%
Total	111	100
Sex		
Male	58	52
Female	53	48
Age (yr)		
<45	30	27
45–65	72	65
66+	9	8
Stage		
II abdomen	26	23
III	18	16
IV	67	61
G.I. involved	23	21

*Table 2. Histology—Rappaport and Kiel classifications (after review)**

Rappaport Histology	No.	Kiel Histology	No.
Nodular poorly differentiated lymphocytic	3	Centrocytic	9
Nodular mixed	7	Follicular centroblastic/centrocytic	1
Nodular histiocytic	1	Follicular and diffuse centroblastic/centrocytic	9
Diffuse poorly differentiated lymphocytic	33	Diffuse centroblastic/centrocytic	18
Lymphoblastic	2	Centroblastic	12
Diffuse histiocytic	45	Lymphoblastic	13
Diffuse unclassified	4	Immunoblastic	10
		Diffuse unclassified	14
		True histiocytic	9

*Material unavailable for review in 16 patients.

dose of 3000–3500 cGy in 16 fractions. Patients who achieved a remission were subsequently given oral maintenance chemotherapy for 2 yr with 6-mercaptopurine (50 mg/m^2 daily), cyclophosphamide (200 mg/m^2 weekly) and methotrexate (20 mg/m^2 weekly) [9]. Reinduction with VAP was attempted in those patients who relapsed. Further relapse treatment was left to the discretion of the clinician. The patients were followed up at regular intervals in the clinic and the median follow-up for the total patient group was 73 months (range 3–107 months).

Statistical methods

Several variables were considered in the following analyses and included age, sex, stage, histology (Kiel and Rappaport), bone marrow, liver and gastrointestinal involvement, individual liver enzymes, serum albumin and LDH, haemoglobin, lymphocyte count and ESR, bulky disease, B symptoms, performance status and remission achieved. Survival curves were calculated according to the method of Kaplan and Meier [16] and tests for differences in survival distributions were based on the log-rank test [17]. Cox's proportional hazards model [18] was used to determine the most significant variables that were related to survival.

A stepwise logistic regression procedure was used to determine combinations of patient characteristics important in predicting complete remission. Survival curves and Cox's models were also applied to the patients achieving a complete remission to see which factors were associated with prolonged relapse-free survival and overall survival. In these analyses time was measured from the date of documentation of complete remission when all previously abnormal staging procedures had been repeated.

RESULTS

Overall survival of patient population

The overall survival of the patient group (as measured from the first day of chemotherapy) is shown in Fig. 1. The median survival was 20 months and the survival rate at 5 yr was 37%. The majority of deaths (44/67) occurred within the first year of diagnosis and the majority of patients who died had failed to achieve a complete remission (39/67). Survival curves were plotted and compared, using the log-rank method, for factors which were of possible prognostic importance, and the most significant of these was whether a complete remission was obtained ($P < 0.0001$). The median survival of the group of 64 complete responders had not been reached at 7 yr. In contrast, the median survival of the 31 patients achieving a partial remission was only 10 months, and only one of 16 unresponsive patients survived beyond 1 yr (Fig. 2). Stage was also important ($P = 0.003$), and early stage was associated with a particularly good prognosis (Fig. 3). Of patients with stage II disease confined to the abdomen (12/26 with G.I. involvement) 72% were alive at 5 yr.

A Cox's multivariate analysis was performed to identify those variables with the most significant effect on the length of survival. Continuous variables were transformed by taking logarithms. The first three patient characteristics ranked in order of importance by the stepwise regression procedure showed that again remission status was

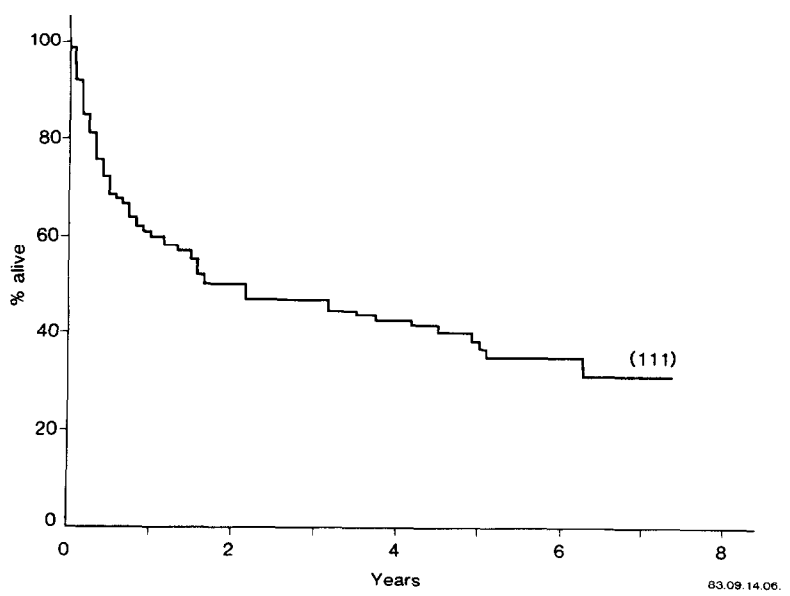

Fig. 1. Overall survival.

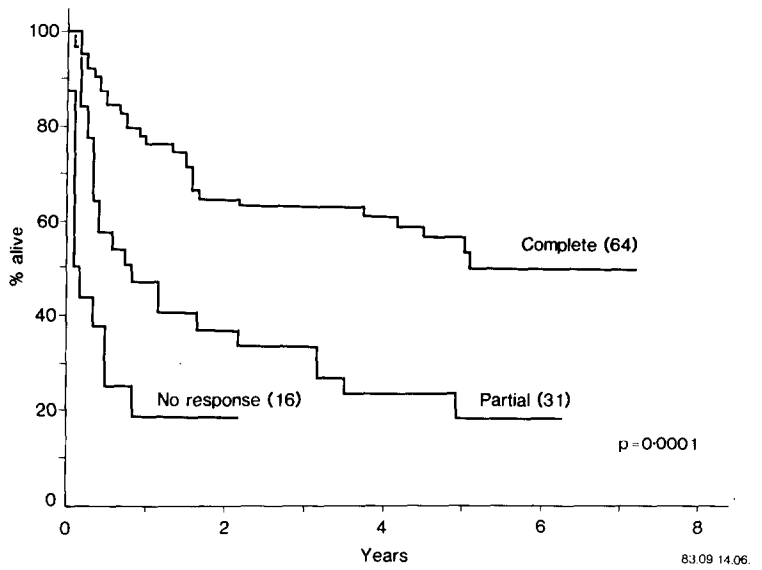

Fig. 2. Overall survival according to response.

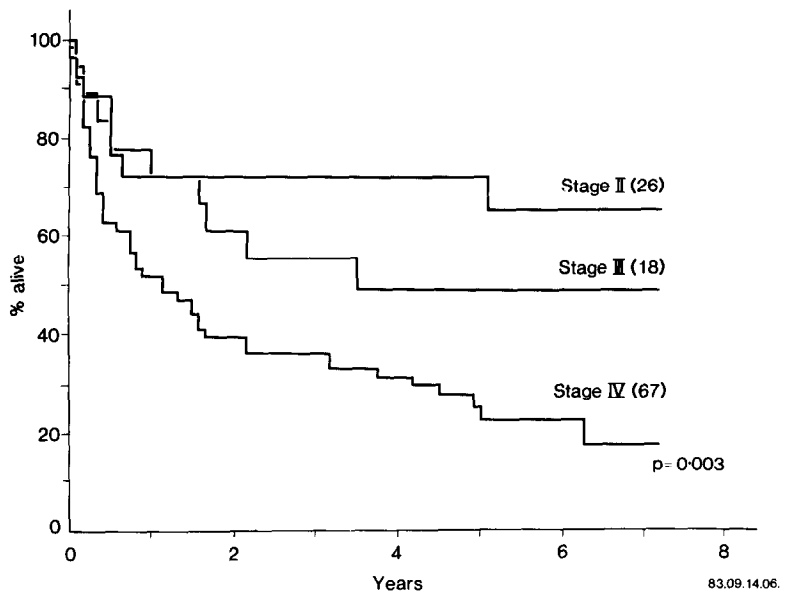

Fig. 3. Overall survival by stage.

important ($P < 0.001$), followed by the serum LDH level (smaller values being associated with a better prognosis) ($P < 0.001$) and a clinician's assessment of whether the liver was involved (worse prognosis if involved with lymphoma) ($P < 0.001$). With these three variables in the model, the other variables did not add significantly to the ability to predict survival.

As the achievement of a complete remission appeared to be of primary importance in obtaining long-term survival, the influence on complete remission of the patient characteristics was examined.

Factors affecting complete remission

A multivariate analysis of factors which could affect the probability of achieving a complete remission was performed using a forward logistic regression analysis. A model including the lack of B symptoms ($P < 0.001$), absence of bone marrow involvement ($P = 0.007$), high serum albumin ($P = 0.018$) and female sex ($P = 0.02$) was the most accurate in predicting an increased likelihood of a patient achieving a complete remission. For each patient a score could be obtained, depending on the number of risk factors present, which could be correlated with the probability of his achieving a complete response (Tables 3 and 4). There was close agreement between the observed probabilities of achieving a complete remission and the probabilities predicted from the logistic regression equation (Table 5). This internal check on the method shows that the equation can separate patients into groups that differ widely in their

likelihood of achieving a complete remission. One would expect, however, the best possible fit because the equation has been applied to the same data from which it was derived, and so the prediction may not fit so closely when applied to another series of patients.

Factors relating to relapse-free survival and survival after complete response

Although the most significant factor predicting survival was the achievement of a complete response, 31/64 (48%) complete remitters have relapsed and 28 (44%) have died. Further analysis was therefore carried out for the complete remission patients only, to identify factors which were associated with relapse. The log-rank analysis of relapse-free survival suggested a significant difference ($P = 0.01$) between the group of patients with diffuse poorly differentiated lymphocytic lymphoma (based on the Rappaport classification) and that with diffuse histiocytic lymphoma, only three deaths occurring after 7 months in the latter (Fig. 4). However, when a Cox multivariate analysis of relapse-free survival was carried out, this showed that the only significant variable was the subdivision of histology according to the Kiel classification ($P = 0.006$), and the subsequent addition into the model of other variables did not significantly improve the likelihood of predicting relapse (Fig. 5). A breakdown of the histologies of the patients achieving a complete remission and their outcome is shown in Table 6.

When a similar analysis of the length of survival of the complete remitters was carried out, the results were the same; again the only significant variable as a predictor for survival of complete remitters was the Kiel classification ($P < 0.001$). Patients with centroblastic lymphoma did particularly well, only one relapsing and dying after achieving a complete response. On the other hand, patients with immunoblastic lymphoma did badly, 5/6 patients dying after documentation of a complete response. Patients with centrocytic and centrocytic/centroblastic diffuse lymphoma formed an intermediate group (Fig. 6).

When a Cox multivariate analysis of patients achieving a complete remission was repeated without including the Kiel classification, the only significant variable predicting survival was the Rappaport classification ($P = 0.008$). Clinical stage became the most significant variable to predict relapse-free survival ($P = 0.008$), and with this in the model, other variables did not add significantly to the ability to predict this.

Table 3. Scoring system derived from logistic regression equation for probability of achieving a complete remission

Risk factor	Score added*
'B' symptoms present	5
Bone marrow involved	3
Male sex	2
Serum albumin (g/l)	
<22	9
22–27	7
28–35	5
36–44	3
≥45	1

*Patient has initial score of zero and added to this are values depending on the risk factors present.

Table 4. Scores for risk factors present and estimated probabilities of achieving a complete remission

Score	Estimated probability of achieving complete remission
≥12	0.00–0.24
10–11	0.25–0.49
7–9	0.50–0.74
≤6	0.75–1.00

DISCUSSION

This study has confirmed the finding of several other workers who have shown that for lymphomas of high-grade histology the achievement of a complete remission is the single most important factor correlated with long-term

Table 5. Observed and predicted probabilities of obtaining a complete remission

Predicted probability of complete remission	No. of complete remission patients	Total	Observed probability of complete remission
0.00–0.24	3	18	0.17
0.25–0.49	7	24	0.29
0.50–0.74	16	24	0.67
0.75–1.00	36	41	0.88

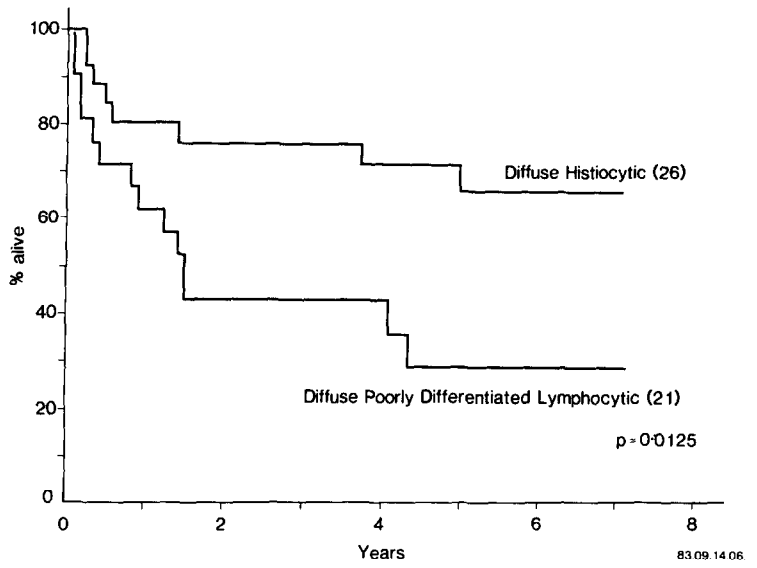

Fig. 4. Relapse-free survival for CR patients with diffuse histiocytic and diffuse poorly differentiated lymphocytic lymphoma.

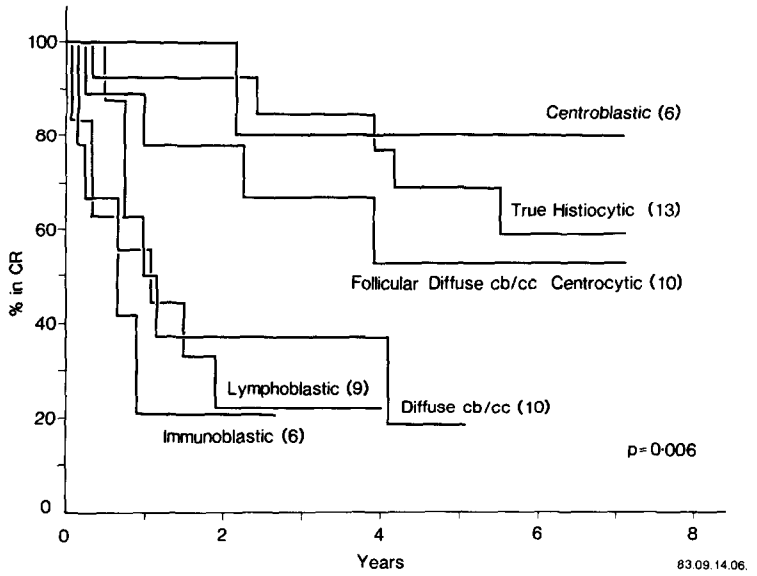

Fig. 5. Relapse-free survival of CR patients according to Kiel classification.

Table 6. Outcome for patients with known Kiel classification achieving a complete remission

Histology	Patients	Deaths	Relapses
Follicular and diffuse centroblastic/centrocytic	5	0	1
Centrocytic	5	3	3
Diffuse centroblastic/centrocytic	10	7	6
Centroblastic	6	1	1
Lymphoblastic	9	7	7
Immunoblastic	6	5	4
True histiocytic	5	1	2
Diffuse unclassified	8	0	3

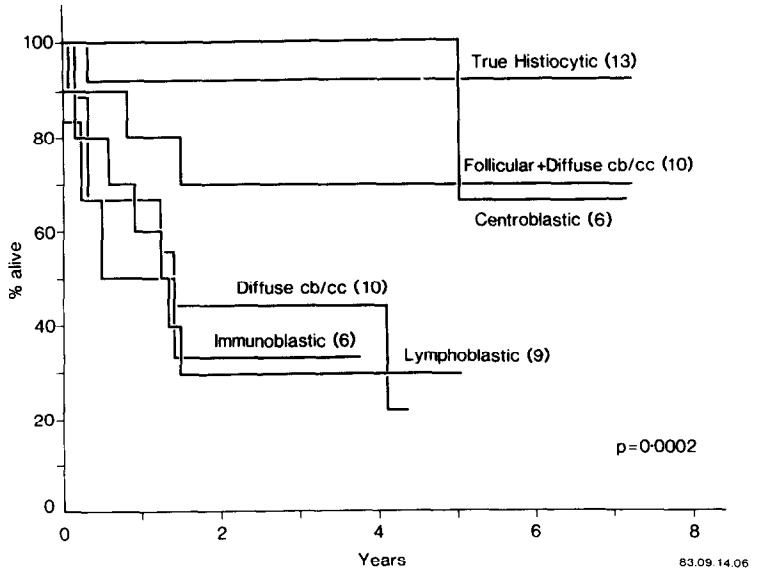

Fig. 6. Survival of CR patients according to Kiel classification.

survival [12, 19, 20]. A 6-week regimen of chemotherapy produced a complete remission in 58% of the patients included in this series (54% of those with stages III and IV disease). Multivariate analysis of factors which may have predicted the likelihood of a patient achieving such a response showed that, with the exception of sex, pre-treatment variables relating primarily to the extent of disease within each individual were of significance for achieving complete remission. In this series patients with stage II disease confined to the abdomen had a particularly good prognosis and the results compare favourably with those of Fisher *et al.* [2], where the median survival of patients with stage II disease in the abdomen was only 2 yr. The presence of bulky disease did not affect remission rates or the duration of relapse-free survival, but in this study patients routinely received radiotherapy to the sites of bulk, and it is therefore possible that this negated any influence of bulky disease on prognosis and may have accounted for the considerably better survival of our group as compared with those of other workers.

It is of note that factors predicting complete remission were different from those predicting survival, and this confirms an earlier report by Cabanillas *et al.* [20]. In particular, response and overall survival were not affected by histological subtype but relapse-free survival and survival of those achieving a complete remission were both primarily influenced by histology. Patients with diffuse histiocytic lymphoma (based on the Rappaport classification) were found to have a significantly longer relapse-free survival than other histological groups in this series. The proportion of patients achieving a complete remission who subsequently relapsed was higher in our series than has been reported in series from North America and this may reflect the greater proportion of patients who have diffuse poorly differentiated lymphocytic lymphoma in Europe. Strauchen *et al.* [21] suggested that the subdivision of the group of patients with large cell lymphoma may produce groups with different prognoses although, as in our series, Fisher *et al.* [2] failed to confirm such a correlation with survival. In our series the pathology was reviewed and subdivided according to the Kiel classification, and a multivariate analysis including this confirmed the value of such a classification when it became the only significant variable to predict survival and relapse-free survival in patients achieving a complete remission.

The histologies of most of the patients were re-analysed by one histopathologist and the Rappaport classification was changed in 15% of the cases. A degree of follicularity was found in 10% of the specimens examined (histology previously reported as diffuse). This figure corresponds with that of the NCI report on the working formulation [22], where a discrepancy of 10% between different pathologists was found in the recognition of nodular or follicular patterns.

This study confirms the data on gastro-intestinal lymphoma from Fisher *et al.* [2], showing that, on multivariate analysis, survival and the probability of achieving a complete response were not adversely affected for this group taking other factors into account. Of the 23 patients with gastro-intestinal lymphoma in this series, 13 (57%) achieved a complete response and the 5-yr survival was 31%. Only two deaths occurred beyond 10 months after treatment.

The results of this series have demonstrated that careful assessment of a small number of pre-treatment variables will give an accurate indication of whether or not a patient is likely to achieve a complete remission using the current therapy. This predictive model must be tested in a further series. New treatment protocols need to be devised for patients with high-risk factors so that a larger proportion can achieve a complete remission. For those patients who achieve a complete response and yet can be identified as likely to relapse using the Kiel classification, improved consolidation therapy is required.

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