24. Yang CS. Research on esophageal cancer in China: a review. *Cancer Res* 1980, **40**, 2633–2644.
25. Johnson LS, Nickerson RJ, Esterday CL, Stuart RS, Heritig AT. Epidemiologic evidence for the spectrum of change from dysplasia through carcinoma in situ to invasive cancer. *Cancer* 1968, **22**, 901–914.
26. Böhm N, Sandritter W. DNA in human tumors. A cytophotometric study. *Curr Top Pathol* 1975, **60**, 151–219.
27. Jakobsen A, Kristensen PB, Poulsen HK. Flow cytometric classification of biopsy specimens from cervical intraepithelial neoplasia. *Cytometry* 1983, **4**, 166–169.
28. Hanselaar AGJM, Vooijs GP, Oud PS, Pahlplatz MMM, Beck JLM. DNA ploidy patterns in cervical intraepithelial neoplasia grade III, with and without synchronous invasive squamous cell carcinoma. *Cancer* 1988, **62**, 2537–2545.
29. Rubio CA, Auer GU, Kato Y, Liu F. DNA profiles in dysplasia and carcinoma of the human esophagus. *Anal Quant Cytol* 1988, **10**, 207–210.

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A Numerical Prognostic Index for Clinical Use in Identification of Poor-risk Patients with Hodgkin's Disease at Diagnosis

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The aim of this study was to assess the feasibility of using objective data obtained at diagnosis of Hodgkin's disease to predict those patients who were likely to die of progressive disease within 4 years of diagnosis. 92 consecutive patients from one centre (Newcastle upon Tyne) were used to construct a numerical index based on disease stage (Ann Arbor), age, haemoglobin and absolute lymphocyte count. Weight was assigned according to a predictive value in univariate and multivariate analyses based on survival. The index produced was then validated on a separate patient set (455) from other centres within the Scotland and Newcastle Lymphoma Group (SNLG) on whom the same prospective information was available. The index produced provided a useful separation of those patients destined to die of disease. Of 101 patients with index higher than 0.5, 62 (61.4%) were dead at 4 years, whereas with index lower than 0.5, 61 (18%) of 336 patients were dead at 4 years. The index includes Ann Arbor stage but possesses additional practical prognostic value which allows identification of patients with early stage destined to die of disease. Of 149 patients with stage IA and IIA disease 15 patients had index higher than 0.5, and 10 (60%) have died, whereas the remaining patients had survival of 90% and 85% respectively. This numerical index is applicable to all patients at diagnosis and in the SNLG population gives better predictive survival at 4 years than stage alone, and provides a basis for selecting patients for more aggressive therapy.
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INTRODUCTION

PROGRESS IN Hodgkin's disease therapy has been substantial over the last 15–20 years, with 60% of patients surviving disease-free at 10 years. However 30% of patients will die within 4 years of presentation of progressive disease [1–3]. It is possible to recognise a number of those at risk of progressive disease on the basis of clinical observations alone, such as advanced stage [4], older age group [5] and patients with bulky mediastinal disease [3]. In addition to these simple clinical parameters, a substantial literature now exists relating to haematological and biochemical factors which are associated with poor prognosis, a subject reviewed recently by Hagemeister [6]. In the recent past several groups have undertaken reviews of their patient populations and analysed the results of survival relative to various prognostic indicators. In 1985 the British National Lymphoma Investigation (BNLI) produced a prognostic index on patients with stage I and stage II disease [5]. The Manchester Group reviewed patients with advanced disease in stage III and IV [3]. Both these studies applied an index to specific Ann Arbor staging

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groups and did not include stage as part of their index. Gobbi *et al.* [7] in a study of 586 patients used stage as a factor rather than preselecting for this item and produced an index which was validated on a group of patients other than those on whom it was developed.

In the Scotland and Newcastle Lymphoma Group (SNLG) we have taken a similar view to that of Gobbi *et al.* [7], i.e. that an index which is designed to be used to dictate therapy should include clinical stage and be applicable, at diagnosis, to all cases of Hodgkin's disease, irrespective of stage. Our aim was to produce an index based on survival data collected prospectively on patients diagnosed between 1979 and 1986 and we used univariate and multivariate analyses to settle on the final index applicable to our data. Survival alone rather than disease-free survival was used, as the intention was to define the group destined to die of progressive Hodgkin's disease within 4 years of diagnosis despite optimal therapy.

This paper gives details of how the index was derived and subsequently validated. It includes discussion on the application of the index to all patients with Hodgkin's disease at diagnosis to identify the majority of those patients who are destined not to respond to conventional chemo/radiotherapy, and who can therefore be offered more radical treatment.

PATIENTS AND METHODS

The SNLG was established in 1979 with the intention of studying Hodgkin's disease and the non-Hodgkin lymphomas (NHL) in Scotland and the Northern Region of England. Data collection (initially) covered the east of Scotland and northern region of England (population 7 million). Identical data collection forms were used from 1979 by all participating centres. Each centre kept their own data and whole group data was lodged in Edinburgh. The prospectively collected data have allowed evolution of the index described in this paper. From December 1979 to December 1986, 723 patients with Hodgkin's disease were registered and details of clinical and laboratory features were collected and computerised.

Patients' therapy 1979–1986

During the early years of the Group, formal trials in Hodgkin's disease were not conducted. Therapy guidelines were introduced in 1980 which followed those used in major UK centres. Stage IA and IIA patients received regional radiotherapy alone. At all other stages patients received chemotherapy [chlorambucil, vinblastine, prednisone, procarbazine (CLVPP) or mustine, vinblastine, prednisone, procarbazine (MVPP)] plus radiotherapy to bulk disease.

Patients receiving chemotherapy were given treatment to complete remission (CR) plus three further treatments. In Newcastle radiotherapy was also used to involve field areas, even in patients who had not had bulky disease.

Staging included standard haematological and biochemical parameters and routine radiology. 40% of this cohort of patients had staging laparotomy and 73% bone marrow aspirates and trephines. Computed tomography (CT) was not available during the initial period, but lymphangiograms were performed on 80% of patients prior to introduction of CT facilities. The 20% having no lymphangiogram had staging laparotomy. As CT became available laparotomy became less frequent. 39% of patients had CT.

When the term clinical stage is used in this paper, it refers to the final stage designated by the physician in charge, though in 40% this would conform to a classical definition of pathological staging. 57% of patients received chemotherapy as part of their primary treatment using CLVPP or MVPP. The overall survival curves for patients receiving chemotherapy in clinical stages IIB-IV is shown in Fig. 1A and survival curves for stage IA and IIA are shown in Fig. 1B. These curves demonstrate that the groups have similar survival characteristics to other large series, and they were sufficiently uniform between centres in the SNLG to allow development of a valid prognostic index based on survival. Of the overall cohort of 547 patients, 92 were used for index development in Newcastle and 455 for index validation from the rest of the Group. The remaining 176 could not be used because insufficient information was available.

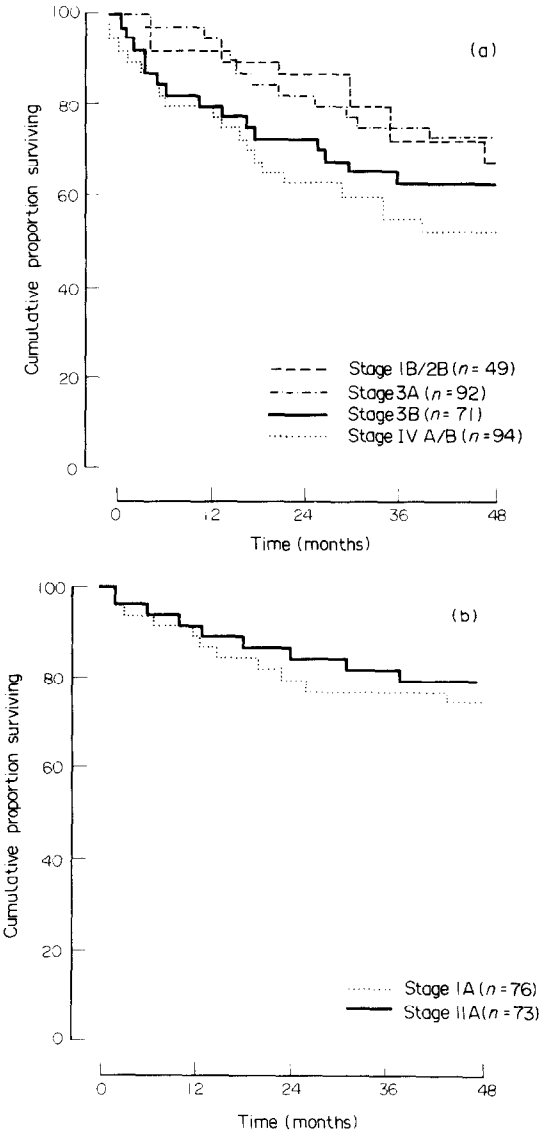

Fig. 1. Hodgkin's disease-survival by stage over study period. (a) stage IB/IIB–IV; (b) stage IA-IIA.

Therapy on relapse and therapy in the elderly

From 1979 to 1986 therapy for relapsed patients depended on the time of relapse. If relapse occurred more than 1 year post treatment or in radiotherapy treated patients, then chemotherapy with MVPP or CLVPP was reintroduced. Patients with progressive disease, or early relapse, received doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) until 1985. From 1985–1988 second line therapy was with lomustine, vinde-

sine and bleomycin (LVB) on an SNLG protocol. This same schedule was also used for some patients as third line therapy. Stage I and II patients who died during the study period all had progressive disease and were predominantly elderly patients. Staging procedures for older patients were less rigorous in that fewer laparotomies were undertaken, but in all other respects, e.g. scans and lymphangiograms there was no difference between the older and younger population.

In the over 65 age group there were 109 patients of whom 57 (52%) completed planned first line chemotherapy and 35% completed planned radiotherapy for early stage disease; i.e. only 13% did not complete planned primary therapy.

Development of the index

We were fortunate to have available the indices of the BNLI [5] and Manchester [3] Lymphoma Study Groups when we began to formulate our index. Application of the BNLI index to SNLG data found a moderately satisfactory fit.

Our intention was to produce an index including clinical stage as a factor so that the index could be applied to all cases at diagnosis. It was decided that the index should be developed on 100 consecutive cases from a single clinic in Newcastle, and subsequently validated on a large number of cases for whom complete prospective data for the same time period was available. Of the 100 consecutive cases seen at a single clinic in Newcastle, 4 patients had died of causes other than Hodgkin's disease, and 4 additional cases had insufficient available information. Therefore the basic index was designed on 92 cases. The details assessed were haemoglobin, absolute lymphocyte count, clinical stage (Ann Arbor), erythrocyte sedimentation rate (ESR), sex, age, pathological grade (all cases were regarded according to BNLI guidelines) and mediastinal involvement. Unfortunately it was not possible to use bulk mediastinal disease as a factor because information was not available prospectively for the whole SNLG, and in the Newcastle series there were insufficient numbers of patients to make this a meaningful exercise. The ESR was available in only 80 of the 92 patients. The details and the relationship to survival are shown in Table 1.

Table 1. The variables examined for possible effects upon survival (log rank test)

Variable	Level	Nos of patients (totals)	% Alive	P
Haemoglobin	<10.0	9	44	0.0001
	10.0–12.0	22	75	
	12.1–14.0	37	84	
	>14.0	24 (92)	100	
Lymphocyte count × 10^9 l	<1000	22	59	0.019
	1000–1500	23	83	
	1500–2000	17	94	
	>2000	29 (91)		
Clinical stage (Ann Arbor)	IA, IIA, IIIA	49	94	0.001
	IIB	8	100	
	IIIB	15	53	
	IVA, IVB	20 (92)	65	
Erythrocyte sedimentation rate	0–9	19	95	0.048
	10–39	24	88	
	40+	37 (80)	70	
Sex	Male	56	88	0.185
	Female	36 (92)	72	
Age (yr)	15–19	15	80	0.072
	20–29	34	85	
	30–49	19	95	
	50+	24 (92)	67	
Pathology Grade	LP, NSI	53	83	0.398
	MC, LD, NSII	39 (92)	79	
Mediastinal Involvement	Yes	36	78	0.200
	No	55 (91)	84	

NSI = BNLI nodular sclerosing favourable group; NSII = BNLI nodular sclerosing unfavorable group.
Insufficient patients in this series had bulk mediastinal disease to include this variable in the index – this will be included subsequently as an evolution of the index. Note the pathological subtypes did not reach statistical significance.

STATISTICAL METHODS

As an initial stage of analysis, survival curves were plotted according to the levels of possible "explanatory" or prognostic variables, and log rank tests were performed (Table 1). Subsequently, alternative multivariate methods were used to derive possible prognostic indices. The methods used were the Cox survival models and linear logistic regression, and were calculated using the package BMDP [8]. The latter method was based on a binary outcome variable of survival or death at the time of analysis. The clinical variables were categorised before analysis, as shown in Table 1. The categories were chosen on the basis of clinical experience in preference to the raw figures, to avoid undue effects on the models of outlying values. Stage was grouped according to the system shown in Table 1 to avoid categories with small numbers and to obtain a ranking corresponding to change in prognosis.

Within the logistic regression analysis, the method of Copas [9] was used to examine whether the effects of the explanatory variables were linear. This showed that the effect of age was described better by a quadratic rather than a linear relationship. Subsequently the index based on logistic regression was obtained by considering all possible subsets of the explanatory variables, and adopting Mallow's Cp criterion to determine the best subset. This method is preferable for the application to the usual stepwise approaches, as a stepwise procedure may exclude variable which do not quite achieve statistical significance at conventional levels, but which may nevertheless be of clinical importance in prediction.

Having developed the best-fit index on the basis of Newcastle data the index was carried forward and tested on a completely separate population of patients (455) whose data had been collected over the same period of time on identical data collection forms.

RESULTS

On a univariate analysis, haemoglobin, clinical stage, absolute lymphocyte count and ESR were found to have statistically significant effects on survival time, at the 5% level (Table 1). Age reached statistical significance at the 10% level. We were unable to confirm the BNLI predicted levels for different pathological grades on our data and therefore could not use nodular sclerosing type 1 and 2 in our index. Sex and mediastinal involvement were not significant. As mentioned previously bulk disease had not been recorded prospectively in our data collection system.

The logistic regression led to a model involving haemoglobin,

Table 2. Calculation of the prognostic index for Hodgkin's disease

To calculate the index, patient's age, clinical stage, absolute lymphocyte count and haemoglobin are required.

$$\text{The index (I)} = 1.5858 - 0.0363\,\text{Age} + 0.005\,\text{Age}^2 + 0.0683\,\text{CS} - 0.086\,\text{LC} - 0.0587\,\text{Hb}.$$

Age is entered as an absolute figure in the equation.

Clinical stage entered according to the key (Ann Arbor classification)

IA, IIA, IIA	= 1
IB, IIB	= 2
IIIB	= 3
IV	= 4.

Absolute lymphocyte count is entered as a score

$<1.0 \times 10^9$/l	= 1
$1.0–1.5 \times 10^9$/l	= 2
$>1.5–2.0 \times 10^9$/l	= 3
$<2.0 \times 10^9$/l	= 4.

Haemoglobin (Hb) in g/dl is entered as an absolute figure in the equation.

The equation looks complicated, but is easily entered on a computer or programmable calculator. The index can then be generated for any patient within minutes. The major strength is that with the exception of stage, which is a composite clinical parameter, all other data are absolute values. Details for entry on IBM compatible computer available from S.J.P.

The index values <0, 0–0.3, 0.3–0.5, <0.5 were selected to give an indication of which numerical band related to particularly poor prognosis.

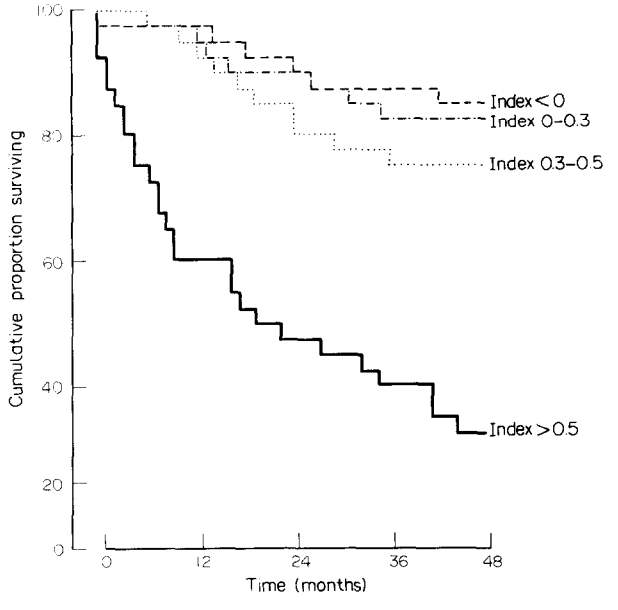

Fig. 2. Survival according to index subgroups including all clinical stages. Note that almost 50% of the deaths (index >0.5 patients) occur in less than 12 months. This is largely an age related phenomenon, but even after this the curve remains steep. Patients with index >0.5 are presently being allocated to alternative treatment in prospective studies.

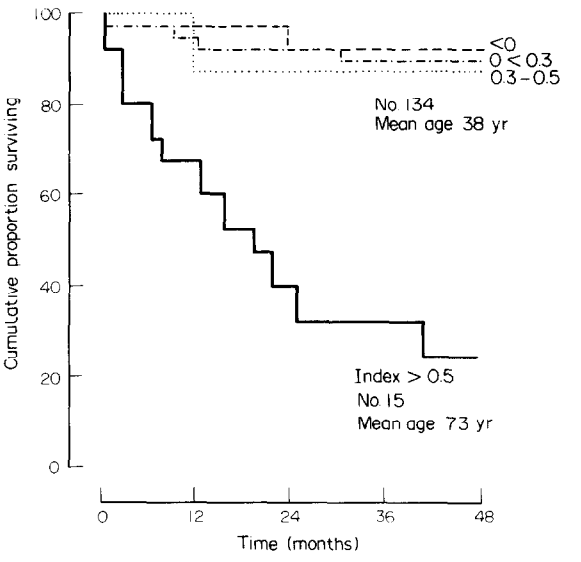

Fig. 3. Stage IA and IIA patients: survival according to index groups. The index has validity in picking out that group of individuals destined to die of Hodgkin's disease even though they are within category stage IA and IIA on the Ann Arbor classification. Note: though this is a slightly age-related phenomenon, young patients are represented in this group. Categories 0–0.5 relate to index subgroups.

age (as a quadratic term), lymphocyte count and clinical stage. Emphasis was given to factors identified by clinicians as objective and easily measured parameters. ESR was excluded as it added little in comparison to haemoglobin and absolute lymphocyte count and many laboratories now measure plasma viscosity instead.

The Cox survival model (which is theoretically the most attractive approach) led to the inclusion of sex, stage, lymphocyte count and haemoglobin in the index. The index based on this model was rejected on the grounds that males appeared to have a more favourable prognosis, contrary to experience elsewhere, and its ability to predict survival was no better than the logistic model. Thus, only the index shown in Table 2 was applied to the data from centres other than Newcastle. The survival curves according to the levels of this index are shown in Fig. 2, showing the ability of the index to discriminate a particularly poor prognostic group. Of those with a numerical index value of 0.5 or lower, 68% are dead, those with an index of lower than 0.5 have a four year survival rate of 80% ($P<0.001$). It is of particular importance that the index is able to discriminate those patients with classical Ann Arbor stage IA and IIA disease who are destined to have a poor prognosis. This discrimination occurs predominantly on the basis of age (Fig. 3). In Table 3 (a)–(e) the relationship of the index to overall survival is shown numerically and also the index is related to the various factors within it in a numerical way showing age, stage, haemoglobin and absolute lymphocyte count. It is quite evident that the index is strongly age linked and that a large proportion of the patients with an index 0.5 or lower are aged over 50, but there are also quite large proportions of those under 20 years with an index above 0.5.

We accept that it is unfortunate that bulk disease, particularly of the mediastinum, could not be included. However, we found that in the Newcastle series bulk dsease is frequently associated with low haemoglobin and absolute lymphocyte count at diagnosis and therefore had a bad index anyway. Nevertheless, in the further prospective evolution of this index a modification

Table 3(a). Hodgkin's disease prognostic index—summary table. Survival at 4 years

Index	Total	Dead	Lost	Alive
<0	67	9	0	58
>0≤0.3	182	29	0	153
>0.3≤0.5	87	23	0	64
>0.5	101	62	1	38
Totals	437*	123	1	313

*18 patients survival data unavailable.
These survival data relate to deaths due to Hodgkin's disease demonstrated graphically in Fig. 2. Low index (<0) patients dying of Hodgkin's disease are younger patients with bulk mediastinal disease.
Note: Tables 3(a)–(e) do not include the patients on whom the index was developed initially in Newcastle.

Table 3(b). Hodgkin's disease prognostic index—age

	Index					
Age	<0	>0–≤0.3	>0.3–≤0.5	>0.5		Total
<10	0	0	4	3	(43%)	7
11–20	3	31	23	9	(14%)	66
21–30	29	81	14	6	(5%)	130
31–40	21	26	14	6	(9%)	67
41–50	10	29	8	6	(11%)	53
51–60	7	20	16	13	(23%)	56
61–70	0	4	9	20	(61%)	33
71–80	0	0	3	28	(90%)	31
81–90	0	0	0	11	(100%)	11
91–100	0	0	0	1	(100%)	1
>100	0	0	0	0		0
Total	70	191	91	103		455

This index, along with most others, mirrors the strong quadratic association of survival with age.

Table 3(c). Hodgkin's disease prognostic index—stage

	Index					
Stage	<0	>0–≤0.3	>0.3–≤0.5	>0.5		Total
I–IIIA	63	115	39	24	(10%)	241
IIB	4	26	9	10	(20%)	49
IIIB	2	20	23	26	(37%)	71
IVAB	1	30	20	43	(46%)	94
Total	70	191	91	103		455

The index does not simply mimic Ann Arbor state categories.
Note: more patients in stage IV group have index <0.5 than >0.5.

Table 3(d). Hodgkin's disease prognostic index—effect of haemoglobin

	Index					
Hb g/dl	<0	>0–≤0.3	>0.3–≤0.5	>0.5		Total
≤6	0	0	0	5	(100%)	5
>6–8	0	0	1	9	(90%)	10
>8–10	0	4	15	27	(59%)	46
>10–12	1	42	41	35	(29%)	119
>12	70	191	91	103	(29%)	455

These figures demonstrate the strength of haemoglobin as an important factor in the index.

Table 3(e). Hodgkin's disease prognostic index—effect of lymphocyte count

	Index					
Lymphocyte count × 10^9/l	<0	>0–≤0.3	>0.3–≤0.5	>0.5		Total
≤1000	1	35	33	58	(46%)	127
≤1500	13	54	34	28	(22%)	129
≤2000	16	54	12	6	(7%)	88
>2000	40	48	12	11	(10%)	111
Total	70	191	91	103		455

Lymphocyte count becomes a more striking prognostic factor when linked with haemoglobin.

including an additional weighting for bulk disease is under evaluation.

DISCUSSION

Classical Ann Arbor staging [10] has been immensely valuable over the last 20 years while investigators have attempted to optimise treatment for Hodgkin's disease. It has, however, been evident that this staging system, which simply relates to anatomical sites of disease, is not completely satisfactory. It was recognised a decade ago that a prognostic index including Ann Arbor stage as a factor was indicated [11]. The most important prognostic factor to emerge in the literature over the last few years, irrespective of clinical stage, is that of age [12–16] and this has been incorporated in all prognostic indices used recently [3, 5, 7]. There is little dispute that the haemoglobin or haematocrit level at diagnosis is also of value [6, 17]. Of the other factors included in our index, only absolute lymphocyte count is not universally accepted as a valuable indicator. However, we have confirmed the observations of Henry *et al.* [18] (Table 3e) and McLennan *et al.* [19] on the prognostic value of absolute lymphocyte count.

The SNLG decided that treatment for many patients was already optimal, and that it is important to identify poor-risk patients for trials of more intensive therapy whilst avoiding overtreatment of good-risk patients which may include many patients with Ann Arbor stages III and IV disease. We also decided that there is little value in continuing to collect information on prognostic factors unless it is used clinically in the

form of an objective predictive index to determine treatment strategies.

In the recent past the BNLI, the Manchester Group and more recently an Italian Group have all produced prognostic indices for clinical use [3, 5, 7]. The BNLI index was produced to look specifically at Ann Arbor stages I and II. The Manchester Group [3] looked at more advanced stage Hodgkin's disease and had a simplified scoring system, but the most essential feature was the emergence of age and presence of bulk as important features. As mentioned previously bulk disease had to be excluded from our index development as the appropriate data had not been collected prospectively. Gobbi *et al.* [7] undertook to incorporate stage in their index, but as all the factors used are binary a large amount of information might be lost, especially for age and stage. In such an approach the start and cutoff points mean that an ESR of 45 in a 44-year-old compared to an ESR of 46 in a 45-year-old results in a difference of a factor of 100 between two patients in expected mean survival time. Nevertheless, the general use of the information in the paper by Gobbi *et al.* [7] is similar to our own in that a prediction of those patients destined to die from Hodgkin's disease on conventional treatment can be obtained.

It seems that there are a number of ways in which indices can be derived by various groups for assessment of prognosis in their patients and this, to a large extent, depends on how information has been prospectively collected. It is encouraging that in a recent paper that Manchester index demonstrated a good fit with the information on patients from St Bartholomew's Hospital [20]. We are particularly pleased with the fact that our index proved to be an extremely valuable predictor of prognosis in those patients with stage I and stage II disease who are destined to have a poor survival on conventional treatment. This effect is demonstrated in a striking way in Fig. 3. We have been sufficiently impressed by the accuracy of our index based on objective data that presently all patients who have an index of 0.5 or above are being allocated to highly aggressive novel therapeutic schedules which include a randomisation to auto-transplantation and high dose chemotherapy for those in this group under 60 years of age. It remains evident, however, that the present index is still missing a proportion of young individuals who are destined to die of Hodgkin's disease. We suspect this might be partially explained by exclusion of those patients with bulk disease who have a normal lymphocyte count and a normal haemoglobin. A modification of the present index which adds an additional weighting factor for bulk disease is currently being assessed in a prospective manner. We consider that the use of indices such as this which are directly applicable at diagnosis will enhance the use of clinical Ann Arbor staging as the predictor and indicator of specific forms of therapy.

1. Sutcliffe SB, Wrigley PFM, Peto J, *et al.* MVPP chemotherapy regimen for advanced Hodgkin's disease. *Br Med J* 1978, **1**, 679–683.
2. DeVita VT, Simon RM, Hubbard SM, *et al.* Curability of advanced Hodgkin's disease with chemotherapy: long term follow-up of MOPP treated patients at the NCI. *Ann Intern Med* 1980, **92**, 587–595.
3. Wagstaff J, Steward W, Jones M, *et al.* Factors affecting remission and survival in patients with advanced Hodgkin's disease treated with MVPP. *Hematol Oncol* 1986, **4**, 135–147.
4. Moore MR, Jones SE, Bull JM, William LA, Rosenberg SA. MOPP chemotherapy for advanced Hodgkin's disease. Prognostic factors in 81 patients. *Cancer* 1973, **32**, 52–60.
5. Haybittle JL, Easterling MJ, Bennett MH, *et al.* Review of British national lymphoma investigation studies of Hodgkin's disease and development of prognostic index. *Lancet* 1985, **i**, 967–972.
6. Hagemeister FB. Prognostic factors in decision making in the clinical management of Hodgkin's disease. *Hematol Oncol* 1988, **6**, 257–269.
7. Gobbi PG, Federico M, Di Prisco UA, *et al.* Hodgkin's disease prognosis: a directly predictive equation. *Lancet* 1988, **i**, 675–679.
8. Dixon WJ, Brown MB, Engleman L, *et al.* BMDP *Statistical Software*. Berkeley, University of California Press, 1983.
9. Copas JB. Plotting p against x. *Appl Statist* 1983, **32**, 25–32.
10. Staging in Hodgkin's disease. Symposium sponsored by the American Cancer Society and the National Cancer Institute, Ann Arbor, Michigan. *Cancer Res* 1971, **31**, 1707–1861.
11. Schilling R. Complexities of classifying patients with Hodgkin's disease: a plea for a prognostic index. *Am J Haematol* 1978, **4**, 93–95.
12. Vaughan Hudson B, MacLennan KA, Easterling MJ, Jelliffe AM, Haybittle JL, Vaughan Hudson G. The prognostic significance of age in Hodgkin's disease: examination of 1500 patients (BNLI report no 23). *Clin Radiol* 1983, **34**, 503–506.
13. Tubiana M, Henry-Amar M, Hayat M, Carde P, Somers R. Prognostic factors in Hodgkin's disease. *Lancet* 1985, **ii**, 165–165.
14. Tubiana M, Henry-Amar M, Van der Werf-Messing B, *et al.* A multivariate analysis of prognostic factors in early stage Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1984, **11**, 23–30.
15. Carde P, Burgers JMV, Henry-Amar M, *et al.* Clinical stages I and II Hodgkin's disease: a specifically tailored therapy according to prognostic factors. *J Clin Oncol* 1988, **6**, 239–252.
16. Wedelin C, Bjorkholm M, Biberfeld, P, Holm G, Johansson B. Prognostic factors in Hodgkin's disease with special reference to age. *Cancer* 1984, **53**, 1202–1208.
17. MacLennan KA, Vaughan Hudson B, Easterling MJ, Jelliffe AM, Vaughan Hudson G, Haybittle JL. The presentation haemoglobin level in 1103 patients with Hodgkin's disease (BNLI Report no 21). *Clin Radiol* 1983, **34**, 491–495.
18. Henry L, Knowelden J, Swan HT. Relationship of the pre-treatment peripheral lymphocyte count to histology in Hodgkin's disease. *Br J Haematol* 1973, **24**, 773–776.
19. MacLennan KA, Vaughan Hudson B, Jelliffe AM, Haybittle JL, Vaughan Hudson G. The pretreatment peripheral blood lymphocyte count in 1100 patients with Hodgkin's disease: the prognostic significance and the relationship to the presence of systemic symptoms (BNLI Report no 19). *Clin Oncol* 1981, **7**, 333–339.
20. Wagstaff J, Gregory WM, Swindell R, Crowther D, Lister TA. Prognostic factors for survival in stage IIIB and IV Hodgkin's disease. A multivariate analysis comparing two specialist treatment centres. *Br J Cancer* 1988, **58**, 487–492.

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