Eur J Cancer Clin Oncol, Vol. 23, No. 11, pp. 1589–1599, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00

Prognostic Factors in Small Cell Lung Cancer: A Simple Prognostic Index is Better Than Conventional Staging

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Abstract—*Conventional staging in small cell lung cancer (SCLC) is only of limited prognostic value and is often based on elaborate investigations. We have carried out univariate and multivariate analysis of possible prognostic factors at presentation in 333 consecutive patients with SCLC. Fifteen parameters were found to have individual prognostic significance, of which the most powerful were serum albumin, bone marrow aspirate, disease extent and performance status (all* $P < 0.00005$*). Factors which were not of prognostic significance included age, sex, SVC obstruction, and pleural involvement. Multivariate analysis excluded many factors including bone marrow aspirate as not being independently variable, and a simple combination of clinical performance status, serum albumin and alanine transaminase could be used to define 3 groups (good; medium; poor) of better prognostic significance (survival at 1 year 50% vs. 27% vs. 3%) than conventional limited/extensive disease staging (1 year survival 48% vs. 18%). Other simple combinations of biochemical parameters including plasma sodium and alkaline phosphatase achieved almost as good prognostic groupings. We suggest that consideration should be given to replacing the conventional limited/extensive disease staging system with a simpler system along the lines we have described.*

INTRODUCTION

SMALL cell lung carcinoma (SCLC) is conventionally staged by disease extent as 'limited' or 'extensive' [1] and these parameters have well-established prognostic significance [1–3]. However, the investigations used to define these stages are often elaborate and costly, and even then the predictive power of the system is poor. For example, the median survival for limited disease is longer than for extensive disease only by a few months (5 months in our series, Fig. 1), and the 2 year for limited disease is only 15%, compared with 5% for extensive disease (Fig. 1). Other large series report very similar data [4, 5].

It would be very helpful in planning management to have a combination of parameters which gave a better separation of prognostic subgroups, or to have an equally effective, but simpler, staging system which did not require elaborate initial investigations. It has been suggested that a simple series of biochemical tests might be useful as prognostic factors, albeit based on a relatively small number of patients [6]. More recently 2 larger studies have suggested that the combination of clinical performance status with a few simple biochemical tests can provide better prognostic sub-groupings than conventional staging by disease extent [7, 8].

We have similarly investigated this problem by analysing retrospectively data in 333 consecutive patients with SCLC referred to our Unit. All had a full clinical examination with basic plasma biochemistry and chest X-ray at presentation; in addition most also had a detailed series of initial staging investigations to determine disease extent. Our aims have been (1) to establish by univariate analysis the prognostic significance and ranking of each of these parameters at presentation; (2) to investigate by multivariate analysis whether any combination of these parameters could be identified which define prognosis more sharply than conventional staging by disease extent; (3) to establish whether claims that a simple system of clinical assessment and blood tests are as effective a prognostic indicator as disease extent can be confirmed.

Accepted 24 November 1986.

MATERIALS AND METHODS

Patients and staging investigations

Between 1978 and 1985, 333 patients with histologically or cytologically-proven SCLC were

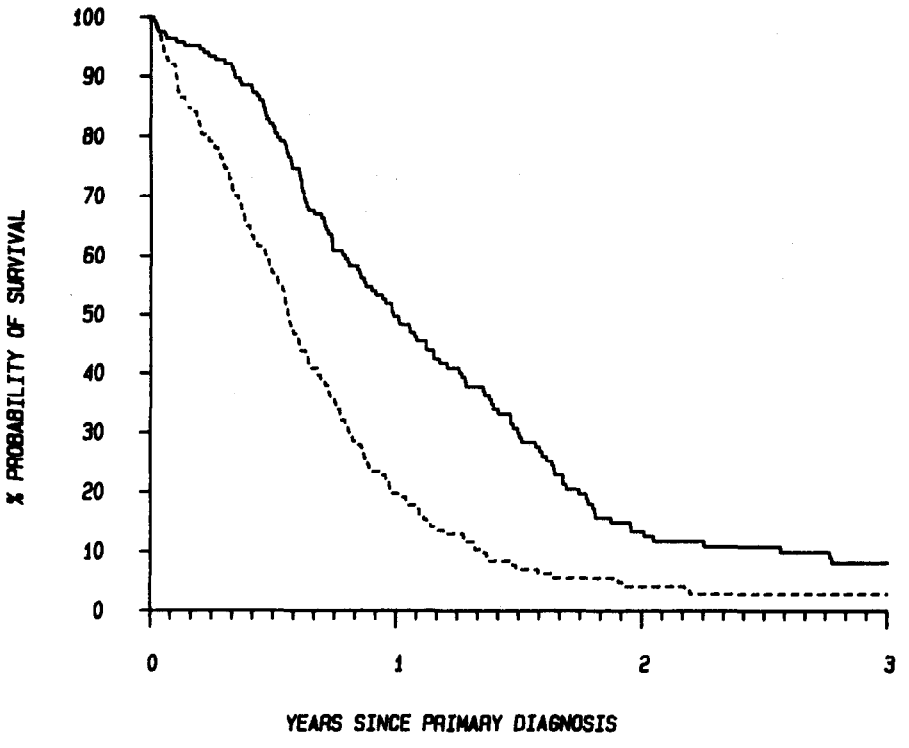

Fig. 1. Survival. Limited (····) vs. extensive (-----) disease. All patients (——).

referred to the Lung Unit at the Royal Marsden Hospital and are all included in the analysis. Staging investigations included full clinical assessment, chest X-ray, full blood count and plasma biochemistry, bone marrow aspirate or trephine, isotopic bone scan, skeletal X-rays where clinically or radiologically indicated, and isotopic liver scan or liver ultrasound. Some of the more elaborate investigations were omitted in elderly or very ill patients. Unfortunately, serum albumin was routinely assessed in only 177 patients, since the possible prognostic significance of this was not initially appreciated. In general these were patients more recently referred to the Unit, and they did not differ significantly from the rest of the group in any other way. Simple clinical and radiological parameters, readily assessable by any clinician without access to more specialised investigations, have also been included in this analysis, in an attempt to identify their relevance to a more simplified staging system. These include clinical performance status (PS) (defined according to the WHO classification) [9] and the presence or absence of supraclavicular lymphadenopathy, SVC obstruction and radiological evidence of pleural and/or mediastinal involvement. Patients were staged on the basis of their investigations as having limited or extensive disease according to standard criteria [1]. Patients were treated according to a series of different chemotherapy protocols which ran consecutively during this period.

Statistical methods

The pretreatment variables chosen for analysis are described above and in Table 1. Each variable was used to divide the patients into 2 or more groups in order to determine its prognostic significance (Table 1). The cut-offs used for haematological and biochemical variables were the normal limits of that variable, or if very few patients lay outside the normal limits, the median value was used.

(*a*) *Univariate analysis*

Survival was first investigated with respect to each variate separately by means of the Life Table method [10] and the log-rank test [11]. For performance status, haemoglobin, and plasma albumin, where progressively worse survival could be seen across the groups, a test for trend was used to assess significance [12].

(*b*) *Multivariate analysis*

The proportional hazards model [13] was used to test the pretreatment variables. A step-up procedure was used and significance was assessed by the method of likelihood ratios. This provided information on independent prognostic significance of the variables as well as a determination of the relative risks of death between patient groups.

Estimation of the hazard function for each group and the hazard ratio between groups, i.e. relative risk of death, provided strong evidence of a hazard

Table 1. Pretreatment variables included in the analysis

	Group 1	Group 2	Group 3
Age	> 65	< 65	
Sex	Male	Female	
WHO performance status	0/1	2	3/4
Signs			
SVC obstruction	Present	Absent	
Blood count			
Haemoglobin	> 13	11–13	< 11
WBC	> 8	< 8	
Platelets	> 300	< 300	
Plasma biochemistry			
Calcium	< 2.43	> 2.43	
Sodium	> 137 (median)	≤ 137	
Bilirubin	≤ 17	> 17	
Alanine transaminase	Normal	Elevated	
Alkaline phosphatase	≤ 2 × N	> 2N	
Gamma GT	1–2 × N	> 2 × N	
Albumin	≥ 36	30–35	< 30
Investigations			
Liver US or isotope scan*	Normal	Malignant	
Bone scan/X-ray*	Normal	Malignant	
Bone marrow (aspirate or trephine)	Normal	Malignant	
Sites of disease			
Pleura	Involved	Not involved	
Supraclavicular nodes	Involved	Not involved	
Mediastinum	Involved	Not involved	
Contralateral lung	Involved	Not involved	

*Uncertain scans are included in the normal group as they were prognostically equivalent (data not shown).
Each variable was used to separate the patients into 2 or 3 subgroups for determination of its prognostic significance.

ratio that varied over time. For each variable the relative risk tended towards unity (data not shown). Because of the poor fit that this implies for the proportional hazards model, we subsequently confirmed the independent effect of the prognostic variables using the stratified log-rank test. However, it should be noted that none of the presentation variables analysed has any predictive capacity for survival beyond 1 year, once that has been attained.

RESULTS

Univariate analysis

Prognosis was first investigated with respect to each variable in Table 1 separately. The analysis leads to a ranking of the variables in order of their usefulness as prognostic indicators. In assessing the relative importance of albumin as a prognostic variable we have assumed that those patients having albumin measurements are representative of the whole group. Table 2 shows this ranking together with the survival quartiles for each group. The variables which are not prognostic are also listed in Table 2.

Figures 1 and 2 confirm the prognostic significance of disease extent and PS on survival in this series. The prognostic significance of serum albumin is shown in Fig. 3, confirming other studies [6, 7]. Low serum albumin (< 36 g/l) was positively correlated with the number of sites of disease ($P < 0.005$), liver involvement ($P = 0.001$) and a serum sodium of 137 mmol/l or less ($P = 0.003$).

Multivariate analysis

The results of the multivariate proportional hazards analysis incorporating all the pretreatment variables are shown in Table 3. Initially, that variable which contributed most prognostic information (plasma albumin) was included in the model. Subsequently the model was fitted with albumin plus each of the other variables in turn to determine which one added most additional prognostic information, and this was added to the model. The *P*-value for inclusion of variables is shown in column 1 of Table 3. These were determined by the likelihood ratio test. The procedure continued until no significant (5% level) further

Table 2. Pretreatment variables ranked according to their prognostic significance

		Survival (days) 25%	50%	75%	Significance *P*
Albumin	⩾ 36	504	311	221	<.00005*
	30–35	294	200	105	
	< 30	166	122	69	
Marrow aspirate	Normal	504	301	185	<.00005
	Malignant	260	174	101	
Disease extent	Limited	601	359	221	<.00005
	Extensive	323	205	111	
Performance status	0–1	538	311	190	<.00005*
	2	318	210	93	
	3–4	235	125	30	
Bilirubin	⩽ 17 (normal)	482	220	158	<.0001
	> 17	220	140	40	
Liver ultrasound or isotope scan	Normal	496	300	173	<.0001
	Malignant	290	199	105	
Plasma sodium	> 137 (median)	583	308	199	.0002
	⩽ 137	386	223	126	
Gamma GT	⩽ 2 × N	540	270	183	.0011
	> 2 × N	356	231	93	
Alanine Transaminase	Normal	496	300	190	.0027
	Elevated	383	208	111	
Alkaline Phosphatase	⩽ 2N	497	269	189	.007
	> 2N		176	96	
Bone scan/X-ray	Normal	507	300	185	.007
	Malignant	304	204	88	
Supraclavicular lymphadenopathy	Not involved	500	275	154	.011
	Ipsilateral	308	205	185	
	Contralateral	300	195	76	
Haemoglobin	> 13	500	293	162	.022*
	11–13	430	253	140	
	< 11	335	209	80	
Mediastinum	Involved	400	218	122	.042
	Not involved	504	282	200	
Contralateral Lung	Involved	352	140	39	.05
	Not involved	469	266	162	
WBC, Platelets, Calcium, Age, Sex, SVC obstruction, Pleural involvement	Unrelated to prognosis at the 5% level				

*Significance assessed by the test for trend across groups.

information could be obtained from the addition of more variables.

Since any variable included in the model may become redundant by the addition of later variables, a check is finally made to see whether any variable may be excluded. The *P*-values for removing each variable are shown in the second column of Table 3.

The final model included all variables which were significant at the 5% level. These were plasma albumin, the liver scans (ultrasound or isotope), alanine transminase and performance status. For each of these variables the estimates of the RR of dying for the groups defined in Table 1 are shown in the final columns of Table 3. These relative risks (which are multiplicative when taken together) were used to define 3 prognostic groups.

Good prognosis. Albumin ⩾ 36 g/l, normal liver scan. Normal alanine transaminase, PS = 0/1 (52 patients).

Medium prognosis. Up to 2 of albumin = 30–35 g/l, PS = 2, elevated alanine transaminase, abnormal liver scans (74 patients).

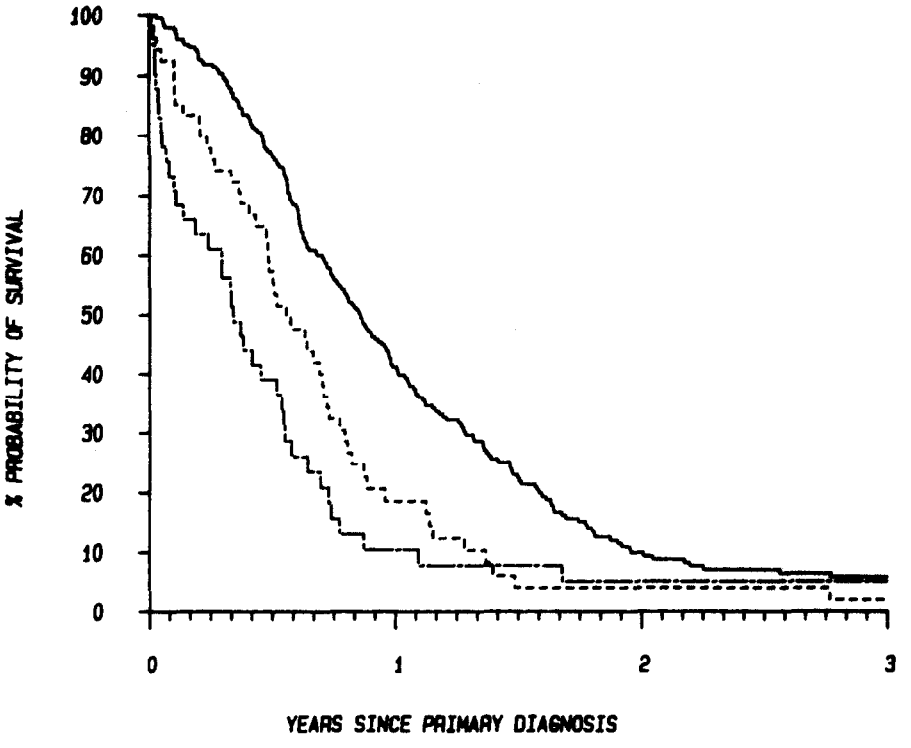

Fig. 2. Survival by performance status. 0–1 (——), 2 (·····), 3–4 (-----).

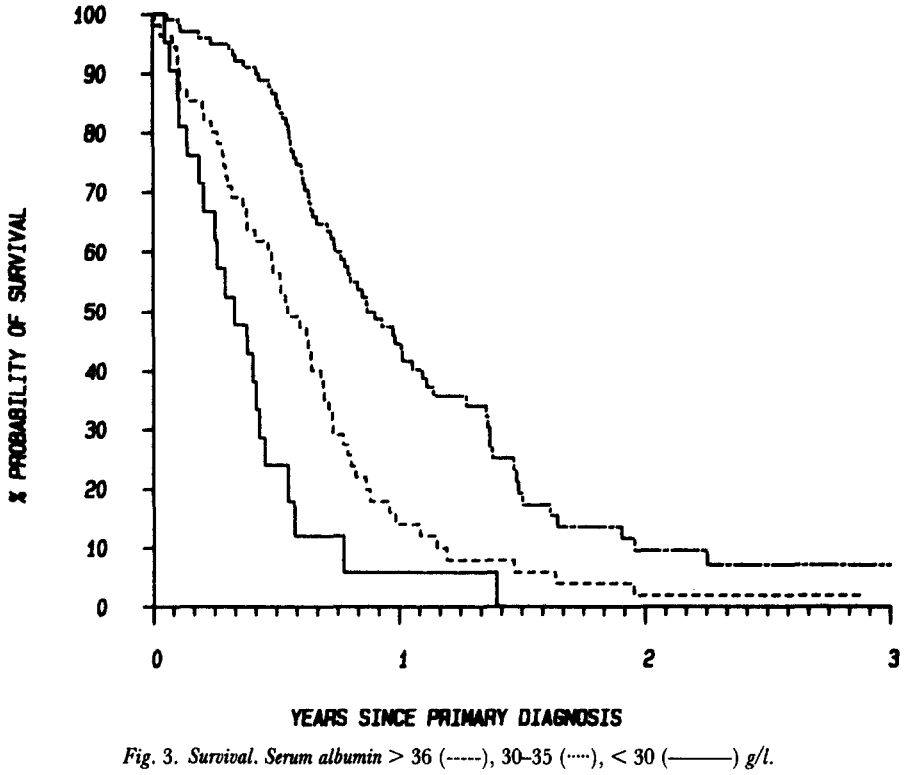

Fig. 3. Survival. Serum albumin > 36 (-----), 30–35 (·····), < 30 (———) *g/l.*

Poor prognosis. The rest (51 patients). The survival of the 3 groups is shown in Fig. 4.

We then repeated the multivariate analysis excluding the elaborate liver scan/ultrasound investigation to see whether a simple system of clinical assessment and blood tests could provide as good a guide to prognosis. (Bone marrow aspirate and bone scan, despite their significance in univariate analysis, were already excluded as having no independent prognostic significance.) In this analysis,

Table 3. Significance levels for the addition/removal of variables to/from the multivariate proportional hazards model based all pretreatment parameters

	P to enter	*P* to remove	Risk relative to Gp 1 Gp 2	Gp 3
Albumin	<.00001	<.00001	1.9	4.1
Liver scan	<.00001	.001	2.0	NA
Alanine transaminase	.0036	.002	1.7	NA
PS	.04	.04	1.3	2.1
Age, sex mediastinal involvement, SVC obstruction, pleural involvement, supraclavicular nodes, plasma sodium, bilirubin, alk.phos., GT, bone scan, marrow investigation haemoglobin, WBC, platelets.			N.S. at the 0.05 level (or redundant).	

Estimates of the relative risk of dying of the groups as defined in Table 1 are given in the final columns.

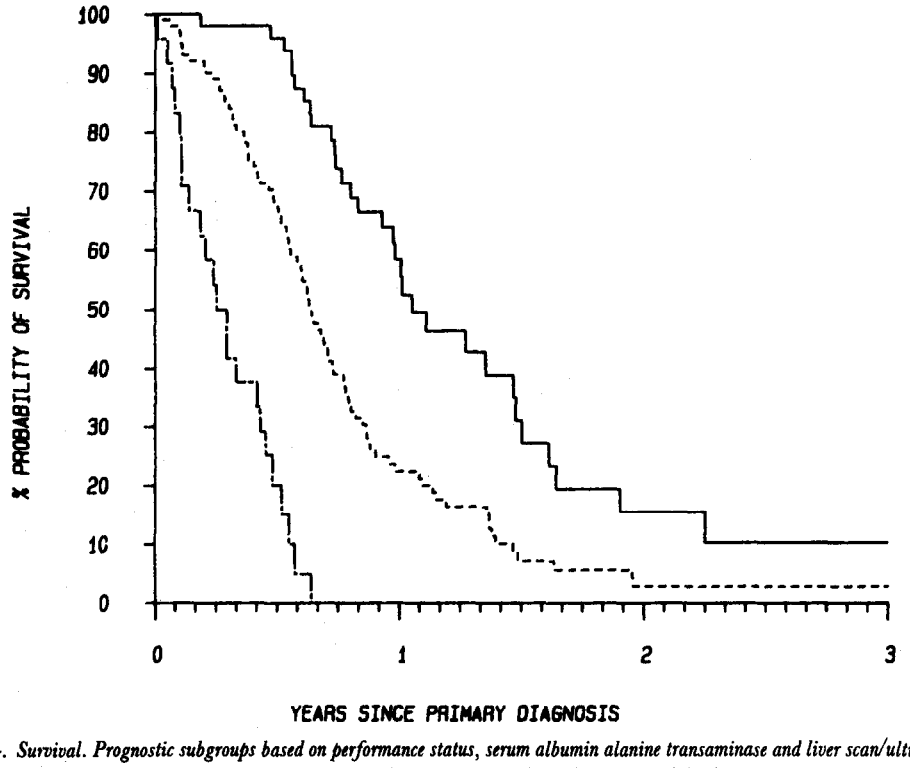

Fig. 4. Survival. Prognostic subgroups based on performance status, serum albumin alanine transaminase and liver scan/ultrasound as described in text. 'Good' (———), 'medium' (-----), 'poor' (·--·).

the final model included only plasma albumin, alanine transaminase and performance status (Table 4). The 3 prognostic groups were defined by:

Good prognosis. Albumin ≥ 36 g/l, normal alanine transaminase, PS = 0/1 (65 patients).

Medium prognosis. Up to 2 of albumin = 30–35 g/l, elevated alanine transaminase, PS = 2 (73 patients).

Poor prognosis. The rest (39 patients).

These 3 groups differed from those defined above only in that they ignored the results of the liver scan; the exclusion of this more elaborate investigation had only a minimal effect on the prognostic power of the 3 groups (Fig. 5).

Figure 6 shows the breakdown of conventionally-staged limited and extensive disease patients between the 3 prognostic groups as defined immediately above. This demonstrates that 8% of so-called

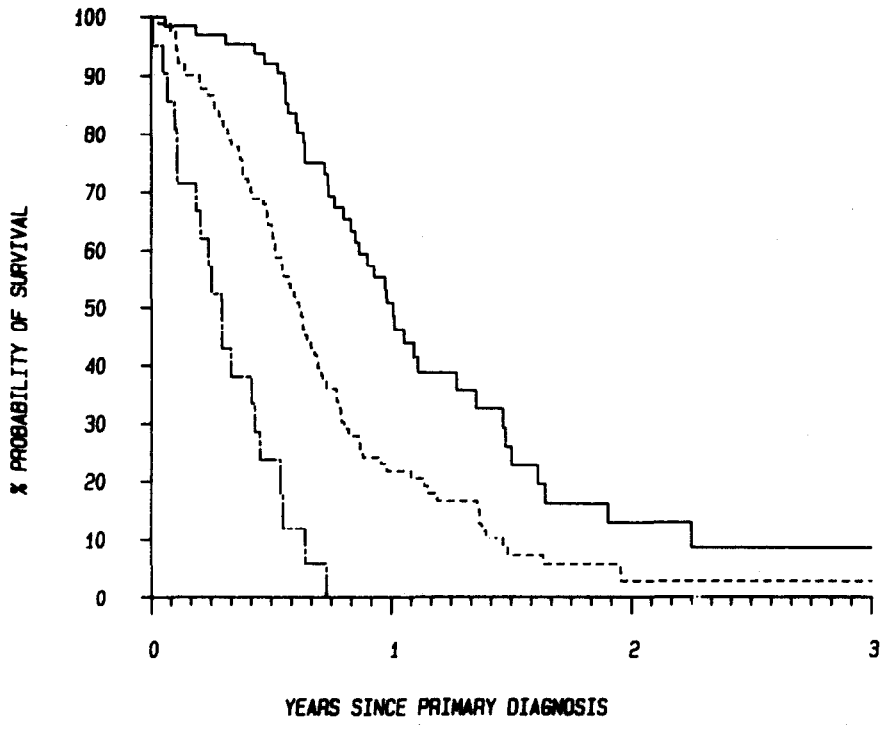

Fig. 5. Survival. Prognostic subgroups based on performance status, serum albumin and alanine transaminase as described in text. 'Good' (———), 'medium' (·····), 'poor' (-·-·-).

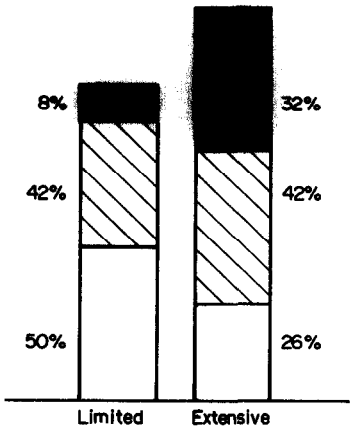

Fig. 6. Survival. Prognostic groups 'good' □, 'medium' ▨, 'poor' ■ based on serum albumin, alanine transaminase and performance status) as a function of disease extent (limited and extensive).

Table 4. The significance levels for the addition/removal of variables to/from the multivariate proportional hazards model based on clinical parameters and blood tests

	P to enter	*P* to remove	Relative risk of death Gp 1	Gp 2	Gp 3
Albumin	<.00001	<.00001	1	1.91	3.53
Alanine transaminase	.0002	.0008	1	1.81	
PS	.020	.007	1	1.45	2.40

The estimate of relative risk of death of the separate groups is shown in columns 4–6.

'good prognosis' LD patients in fact had a poor prognosis arising on new criteria, and Fig. 7 confirms that their prognosis was as bad as patients with extensive disease. Likewise, Fig. 6 shows that 26% of so-called 'poor prognosis' extensive disease patients in fact fell into the good prognosis group by our new criteria: Fig. 8 confirms that their prognosis was similar to patients with limited disease (except perhaps for long-term survival).

Finally, for comparison we have also used the criteria of Souhami *et al.* (1985) [7] for defining prognostic groups on our own set of patients, as follows:

Good. PS = 0/1, albumin ≥ 36 g/l (median value), sodium > 136, alkaline phosphatase < 1.5 × upper limit of normal (54 patients).

Poor. Alkaline phosphatase > 3 × upper limit of normal or PS = 3/4, or albumin < 36 g/l and sodium < 135 mmol/l (73 patients).

Medium. By exclusion (50 patients).

The survival of these 3 groups is shown in Fig. 9. The 2 graphs (Figs 4 and 9) may be directly compared since the proportion of patients in the corresponding prognostic groups is the same under the separate schemes. The groups defined using the RMH data give slightly better prognostic information since we have used the same data both to determine the groups and to illustrate them. However, the 3 prognostic groups in Fig. 9 show a

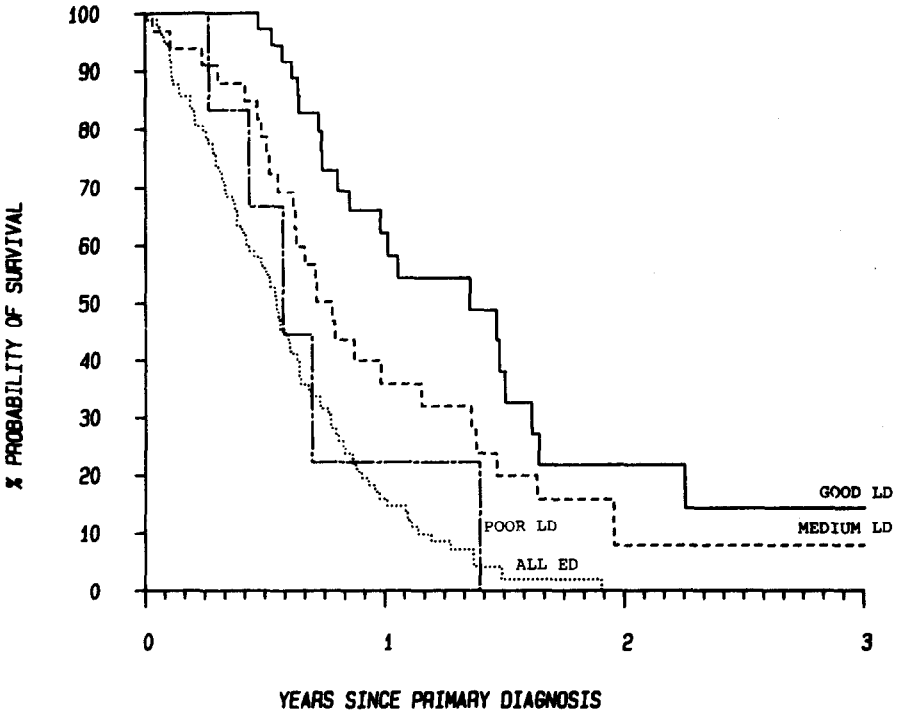

Fig. 7. Survival. Prognostic groups ('good' (———), 'medium' (-----) and 'poor' (-·-·-) based on serum albumin, alanine transaminase and performance status) within the limited disease category vs. all extensive disease patients (·····).

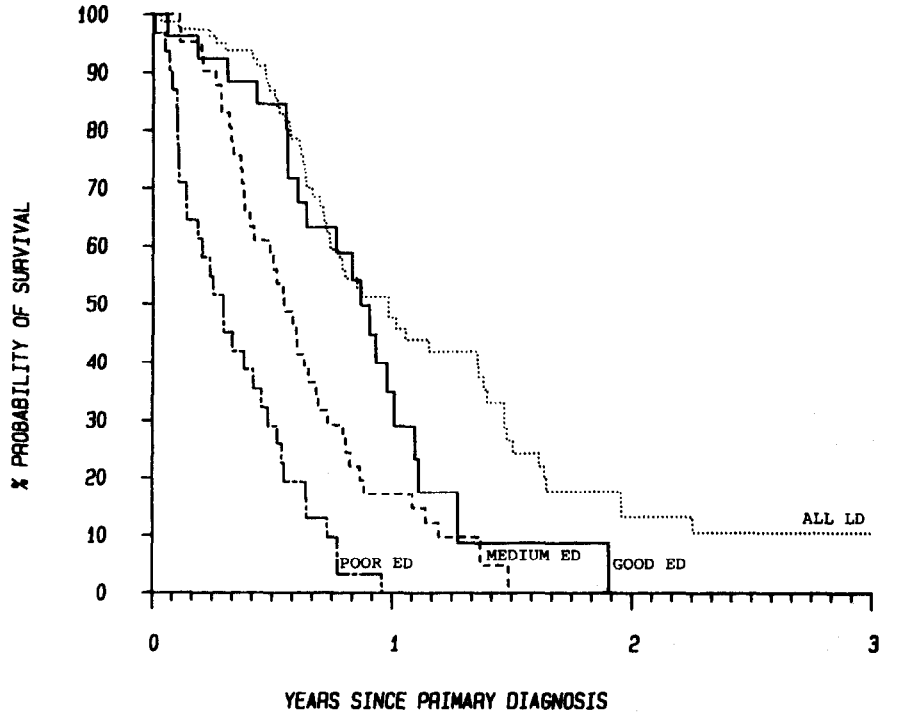

Fig. 8. Survival. Prognostic groups ('good' (———), 'medium' (-----) and 'poor' (-·-·-) based on serum albumin, alanine transaminase and performance status vs. all limited disease patients (·····).

comparable separation, indicating that there are a number of ways in which we could define the groups to give very similar prognostic information.

DISCUSSION

Univariate analysis of our data confirm the very powerful prognostic significance of serum albumin and clinical performance status at presentation for patients with SCLC [6–8, 14–19]. The importance of plasma sodium, liver function tests (bilirubin, alanine transaminase and alkaline phosphatase) and haemoglobin concentration has also been emphasised in our study as in others [6–8]. Lactate dehydrogenase (LDH) has recently been shown to

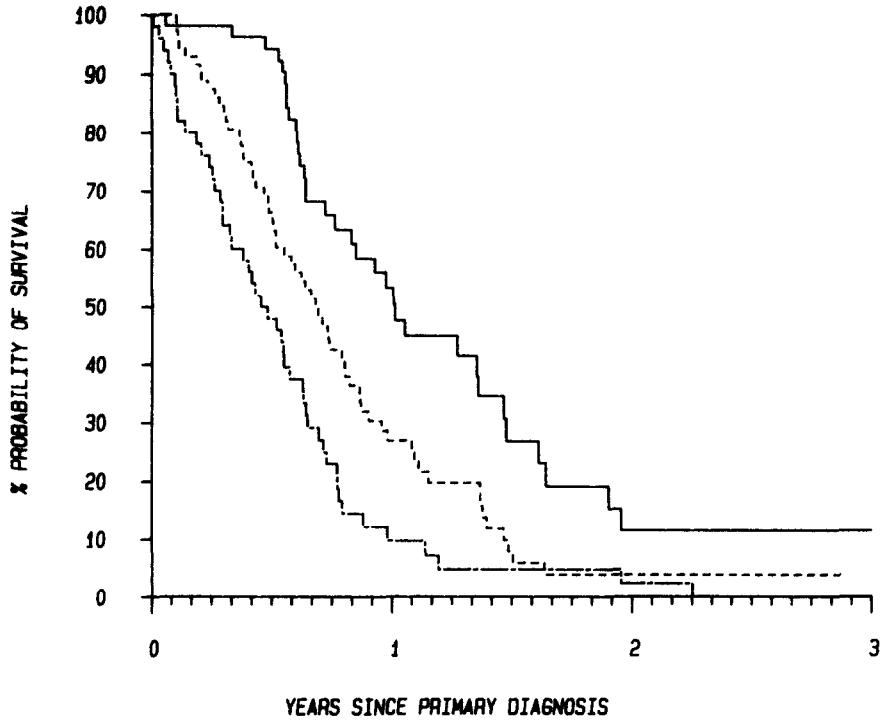

Fig. 9. Survival. Prognositc groups based on serum albumin, sodium, alkaline phosphatase and performance status. 'Good' (——), *'medium'* (-----) *and 'poor'* (-·-·-).

carry high prognostic significance [6, 8, 14, 20], as has hypouricaemia [21] but we have not routinely carried out these tests and are unable to assess them in our system.

Other important prognostic factors included: bone marrow infiltration, confirmed by most [8, 14, 18, 22] but not all other studies [19]; liver infiltration, as defined by an abnormal scan, confirmed by others [8, 14, 17–19]; and mediastinal involvement, again confirmed by others [20, 23–25]. However, it was of interest to us that superior vena caval obstruction (SVCO) did not specifically carry prognostic weight, as another group have also reported [26]. Likewise, we can confirm the lack of prognostic effect of pleural effusions [14, 19, 27]. Our study showed no prognostic impact of either age or sex. This accords with some studies [7, 14, 19] but contradicts others [8, 15, 18, 21].

The main finding of this study comes from multivariate analysis which demonstrates that in our series of patients only serum albumin, alanine transaminase, clinical performance status and isotopic live scans/ultrasound are independently prognostic to a 0.05 significance level. All other parameters become either insignificant or redundant in the face of these 4 items, including bone marrow investigation, despite its prime position in the univariate league. Furthermore it is possible to exclude the relatively sophisticated liver scan/ultrasound investigation and construct a survival table based only on performance status, serum albumin and alanine transaminase which has almost as much prognostic power. This extremely simple system delinates prognostic groups more effectively (50 vs. 27 vs. 3% 1 year survival) than the conventional staging system of limited and extensive disease (48 vs. 18% 1 year survival). Although survival differences within the 3 groups persist at 2 years, it should be noted that we were unable to define any combination of presentation variables which was prognostic for survival beyond 1 year once that had been reached.

Our findings strongly support those of Souhami *et al.* (1985) [7] despite differences in detail. In their study, a prognostic index was based on a combination of clinical performance status, plasma sodium, serum albumin and alkaline phosphatase. It is unlikely that these differences in detail matter; indeed the application of their parameters to our own data gave a prognostic separation almost as effective as that provided by our own multivariate regression model, and the best group of parameters could undoubtedly be determined by pooling data from different centres. What matters is the principle: prognostic assessment for patients with SCLC can be most effectively obtained from a combination of performance status and 2 or 3 simple biochemical tests, without the need for sophisticated, costly, time-consuming and sometimes unpleasant staging procedures to define disease extent.

A possible explanation for this single staging correlated with number of disease sites, and it may system being superior to the conventional one is the inability of the LD/ED stratification to give much

information about tumour bulk. It is known from several studies that the number of metastatic sites is an important prognostic indicator [8, 16, 19] and the size of the primary tumour has been correlated with survival [28]; yet these factors are not accommodated by conventional LD/ED staging. In contrast we have shown that a low serum albumin is well be that this parameter in association with performance status may have some correlation with overall bulk of disease.

Whether or not there are still indications to carry out some of the more elaborate investigations will depend on the aims of clinical management. They might, for example, be relevant in a clinical research context. They might be required for treatment decisions, if, for example, thoracic radiotherapy in addition to chemotherapy were considered appropriate for patients with limited disease. Or it might be considered relevant to look for asymptomatic CNS metastases with a brain CT scan at presentation (our current policy). But for much of the management of patients with SCLC this very simplified system may be all that is required both for assessing prognosis and for planning treatment.

There would be one other important problem in switching to a simplified staging system, and this concerns comparability of data in clinical research. For this reason it remains necesssary at present to continue with the conventional LD/ED system. But there is a case for centres carrying out clinical research in SCLC to come together and devise a new, internationally-agreed staging system based on the simplified lines we have described.

REFERENCES

1. Zelen M. Keynote address on biostatistics and data retrieval. *Cancer Chemother Rep* 1973, **4**(2), 31–42.
2. Bunn PA, Cohen MH, Ihde DC, Fossieck BE, Matthews MJ, Minna JD. Advances in small cell bronchogenic carcinoma. *Cancer Treat Rep* 1977, **61**, 333–342.
3. Greco FA, Einhorn LH, Richardson RL, Oldham RK. Small cell lung cancer: progress and perspectives. *Semin Oncol* 1978, **5**, 323–335.
4. Hansen HH, Dombernowsky P, Hirsch FR, Hansen M, Rygard J. Prophylactic irradiation in bronchogenic small cell anaplastic carcinoma. A comparative trial of localized versus extensive radiotherapy including prophylactic brain irradiation in patients receiving combination chemotherapy. *Cancer* 1980, **46**, 279–284.
5. Osterlind K, Hansen HH, Rorth M, *et al.* Continuous versus alternating combination chemotherapy for advanced small cell carcinoma of the lung. *Cancer Res* 1983, **43**, 6085–6089.
6. Cohen MH, Makuch R, Johnston-Early A, *et al.* Laboratory parameters as an alternative to performance status in prognostic stratification of patients with small cell lung cancer. *Cancer Treat Rep* 1981, **65**, 1187–1195.
7. Souhami RL, Bradbury I, Geddes DM, Spiro SG, Harper PG, Tobias JS. Prognostic significance of laboratory parameters measured at diagnosis in small cell carcinoma of the lung. *Cancer Res* 1985, **45**, 2878–2882.
8. Osterlind K, Anderson PK. Prognostic factors in small cell lung cancer: multivariate model based on 778 patients treated with chemotherapy with or without irradiation. *Cancer Res* 1986, **46**, 4189–4194.
9. World Health Organization. *WHO Handbook for Reporting Results of Cancer Treatment.* Geneva, WHO Offset Publication No. 48, 1979.
10. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
11. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. Part 2. Analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
12. Tarone RE. Tests for trend in life table analysis. *Biometrika* 1975, **62**, 679–682.
13. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc* 1972, **B34**, 187–220.
14. Feld R, DeBoer G, Evans WK. Prognostic factors in patients with small cell carcinoma of the lung. *Proc Am Assoc Cancer Res* 1983, **24**, 575.
15. Poplin E, Whitacre M, Thompson B, Aisner J. Small cell carcinoma of the lung: influence of age on treatment outcome. *Proc Ann Meet Am Soc Clin Oncol* 1984, **3**, 223.
16. Bunting N, Bonomi P, O'Reilly W, *et al.* Prognostic factors in patients with small cell bronchogenic carcinoma treated on an ECOG phase II trial. *Proc Ann Meet Am Soc Clin Oncol* 1984, **3**, 228.
17. Sagman U, Feld R, DeBoer G, *et al.* Small cell carcinoma of the lung—derivation of a prognostic index. *Proc Am Assoc Cancer Res* 1986, **27**, 189.
    Proc Am Assoc Cancer Res 1986, **27**, 189.
18. Maurer LH, Pajak TF. Prognostic factors in small cell carcinoma of the lung: a cancer and leukemia group B study. *Cancer Treat Rep* 1981, **65**, 767–774.
19. Ihde DC, Makuch RW, Carney DN, *et al.* Prognostic implications of stage of disease and

sites of metastases in patients with small cell carcinoma of the lung treated with intensive combination chemotherapy. *Am Rev Resp Dis* 1981, **123**, 500–507.

20. Sagman U, Feld R, DeBoer G, *et al.* Serum lactate dehydrogenase—prognostic significance and correlation with bone marrow metastasis in small cell lung cancer. *Proc Am Soc Clin Oncol* 1986, **5**, 176.
21. Osterlind K, Hansen HH, Hansen M, Dombernowsky P, Anderson PK. Long-term disease-free survival in small cell carcinoma of the lung. A study of clinical determinants. *J Clin Oncol* 1986, **4**, 1307–1313.
22. Hirsch FR, Hansen HH. Bone marrow involvement in small cell anaplastic carcinoma of the lung: prognostic and therapeutic aspects. *Cancer* 1980, **46**, 206–211.
23. Shepherd FA, Ginsberg R, Evans WK, Haddad R, Feld R, DeBoer G. 'Very limited' small cell lung cancer (SCLC)—results of non-surgical treatment. *Proc Ann Meet Am Soc Clin Oncol* 1984, **3**, 223.
24. Meyer JA, Gullo JJ, Ikins PM, *et al.* Adverse prognostic effect of N2 disease in treated small cell carcinoma of the lung. *J Thoracic Cardiovasc Surg* 1984, **88**, 495–501.
25. Meyer JA. Effect of histologically-verified TNM stage on disease control in treated small cell carcinoma of the lung. *Cancer* 1985, **55**, 1747–1752.
26. Van Houtte P, DeJager R, Lustman-Marechal J, *et al.* Prognostic value of the superior vena caval syndrome as the presenting sign of small cell anaplastic carcinoma of the lung. *Eur J Cancer* 1980, **16**, 1447.
27. Livingstone RB, McCracken JD, Trauth CJ, Chen T. Isolated pleural effusion in small cell carcinoma: favorable prognosis. A review of the Southwest Oncology Group experience. *Chest* 1982, **81**, 208–211.
28. Harper PG, Souhami RL, Spiro SG, *et al.* Tumour size, response rate, and prognosis in small cell carcinoma of the bronchus treated by combination chemotherapy. *Cancer Treat Rep* 1982, **66**, 463–470.