Predictive and Prognostic Factors in Small Cell Lung Carcinoma (SCLC) – Analysis from Routine Clinical Practice

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Abstract. *Background: Prognostic and predictive factors of routine clinical practice among patients with small cell lung carcinoma (SCLC) were evaluated. Patients and Methods: Data from 106 patients with SCLC treated by first-line adriamycin, cyclophosphamide and etoposide (ACE) chemotherapy were analyzed. Multivariate analysis was performed. Results: The median overall survival (mOS) of patients was 9.36 months with mOS of 31%, 8% and 3% after 1, 2 and 5 years, respectively. Using multivariate analysis ECOG performance status (p=0.008) and white blood count (WBC) (p=0.022) were independent prognostic factors for mOS. With both, three groups of outcome (good, intermediate, poor) resulting in mOS of 15.8 months, 6.87 months and 3.35 months (p<0.0001) could be established, respectively. The absence of brain metastases (p=0.002), dose reduction (p=0.002) and LDH value (p=0.017) were independent predictive markers. Additionally, female gender was predictive (p=0.025) for complete response (CR). Conclusion: Patients with a poor prediction profil might not benefit from ACE chemotherapy. As a consequence, prognostic/predictive factors should be included as stratification criteria in prospective clinical studies.*

Small cell lung carcinomas (SCLC) have a rapid and extensive proliferation rate. Therefore, they are highly malignant and spread early to distant sites. In the literature, in cases where no specific therapy was given, median survival times of 11-14 weeks and 5-7 weeks were reported for limited and extensive disease, respectively (1). In contrast to non-small cell lung carcinoma (NSCLC), chemotherapy is nowadays an integrative aspect of all SCLC stages. Most of the patients with SCLC will not only improve by a reduction in tumour size, but benefit in clinical aspects, especially dyspnoea and cough. Therefore, all patients with limited disease and even most of the patients with extensive disease are treated by chemotherapy.

The primary aim of chemotherapy, especially in cases of limited stage disease, is response with a complete remission at best, leading to an improved survival and even, in some cases, to a cure. In general, a combination therapy is used consisting of two or three substances, which have been shown to be effective in monotherapy. Most often protocols are used, which combine cisplatin and etoposide (EP) or include anthracyclins, like adriamycin, cyclophosphamide and vincristine (ACO) or adriamycin, cyclophosphamide and etoposide (ACE). The later was first described by Aisner *et al.* in 1982 (2) and is still a standard protocol, especially in studies of the EORTC (3).

However, there has been a discrepancy between inclusion criteria of different studies. According to the inclusion and exclusion criteria applied, frequently a selection bias of patients towards a good performance state and less advanced disease can be observed. Therefore, the parameters of each study do not necessarily reflect the situation in routine clinical practice. As most of the predictive and prognostic markers have been observed from patients included in chemotherapy studies, this might also lead to discrepancy from routine clinical practice.

The aim of this study was to evaluate the use of clinicopathological parameters as predictive and prognostic

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Table I. *Main patient characteristics (n=106).*

Variable	No. (%) of patients	
Gender		
male	77	(72.6)
female	29	(27.4)
Age (years)		
<60	43	(40.5)
≥60	63	(59.5)
ECOG performance status		
0	48	(45.3)
1	34	(32.1)
2	21	(19.8)
3	3	(2.8)
Loss of body weight (%)		
no loss	30	(28.3)
<10	54	(50.9)
≥10	19	(17.9)
not assessed	3	(2.9)
Disease extent		
limited	28	(26.4)
extensive	78	(73.6)
Stage according to UICC		
I	3	(2.8)
II	6	(5.7)
III	20	(18.9)
IV	77	(72.6)

Table II. *Laboratory parameters prior to chemotherapy (n=106).*

Variable	No. (%) of patients	
White blood count (WBC)		
<10 /nl	69	(65.1)
≥10 /nl	37	(34.9)
Hemoglobin level		
≥12 g/100 ml	64	(60.4)
<12 g/100 ml	42	(39.6)
Platelet count		
inside (150-400) /nl	85	(80.2)
outside (150-400) /nl	21	(19.8)
Serum LDH		
≤248 mU/ml	43	(47.8)
>248 mU/ml	47	(52.2)
not assessed	16	
Sodium		
≥ 135 mmol/l	89	(84.0)
<135 mmol/l	17	(16.0)
γ-Glutamyl transferase		
normal	42	(43.3)
elevated	55	(56.7)
not assessed	9	

criteria and compare them with data from the literature. Therefore, a retrospective approach including all SCLC patients treated at our department with ACE chemotherapy, not included in clinical studies, from 1989 to 2004, was undertaken.

Patients and Methods

Patients. All the eligible patients with a SCLC diagnosed at our university hospital between 1989 and 2004 were included. The histological diagnosis was made in all cases by the local pathologist according to the WHO classification. Initial staging was performed following the WHO guidelines with CT scans of the thorax and upper abdomen, bronchoscopy and bone scintigraphy. CT scans of the brain were performed at initial diagnosis in the case of limited disease or if clinical examination was suggestive of brain metastases. Additionally, the disease extent was divided into limited (LD) and extensive stage disease (ED).

Chemotherapy. A total of 166 patients was diagnosed with SCLC during the study period; of those, 133 received first-line chemotherapy. ACE chemotherapy was delivered to 106 patients and those patients were included in this study. Standard ACE chemotherapy, as described by Aisner *et al.* (2) consists of cyclophosphamide 1,000 mg/m^2 on day 1, adriamycin (doxorubicin) 45 mg/m^2 on day 1, and etoposide 100 mg/m^2 on days 1 to 5 given intravenously every 3 weeks for three cycles. Following a response evaluated according to WHO criteria using CT scans and bronchoscopy, chemotherapy was continued for three further cycles if tumour control was possible. Chemotherapy was discontinued earlier in the case of progressive disease, treatment failure, patient refusal or unacceptable toxicity. Dose adjustments were made on the basis of day-1 blood count and white blood count (WBC) and/or PLT nadir with delay of application and/or dose reduction according to common toxicity criteria (CTC).

Further treatment prior to chemotherapy. Whole brain irradiation (doses between 10x3 Gy or 20x2 Gy) was performed before chemotherapy in 17 ED patients; radiation was given to the mediastinum (doses between 45-55 Gy) in five ED and two LD patients. The latter had adjuvant radiation after complete (R0) resection of the upper and the lower lobe, respectively. Additionally, an isolated brain filia (n=5), a cervical lymph node (n=1) and a metastasis to the parotis (n=1) were resected in ED patients before chemotherapy.

Statistics. The statistical analysis was performed with SPSS Version 13.0. The clinical and biological variables were categorised into normal and pathological values according to standard norms.

For univariate analysis, logistic regression models with one co-variate were used when looking at categorical outcomes; the survival curves were estimated using the Kaplan and Meier method, and compared according to one factor by the log-rank test. For the estimation of multivariate models, all parameters which were significant at the univariate analysis ($p<0.05$) were fitted to a Cox regression model using a backward-forward stepwise method for the selection of co-variates. Confidence intervals (CI) at 95% for hazard rates (HR) were calculated. All the probabilities that were calculated were two-tailed.

Table III. *Univariate analysis of response (CR and PR) (n=106).*

Variable	No. (%) of responders		No. (%) of Non-responders		*p*-value
Gender					
male	43	(55.8)	34	(44.2)	0.951
female	16	(55.2)	13	(44.8)	
Age					
<60 years	24	(55.8)	19	(44.2)	0.979
>60 years	35	(55.6)	28	(44.4)	
ECOG-PS					
0	34	(70.8)	14	(29.2)	0.036
1	14	(41.2)	20	(58.8)	
2	10	(47.6)	11	(52.4)	
3	1	(33.3)	2	(66.7)	
Disease extent					
limited	19	(67.9)	9	(32.1)	0.130
extended	40	(51.3)	38	(48.7)	
Malignant pleural effusion					
yes	14	(43.8)	18	(56.3)	0.105
no	45	(60.8)	29	(39.2)	
Brain metastases					
yes	6	(23.1)	20	(76.9)	<0.001
no	53	(66.3)	27	(33.7)	
Metastatic sites					
1	18	(48.6)	19	(51.4)	0.225
>1	21	(52.5)	19	(47.5)	
Dose reduction					
yes	31	(75.6)	10	(24.4)	0.001
no	27	(42.1)	37	(57.9)	
White blood count (WBC)					
normal	46	(66.7)	23	(33.3)	0.003
elevated	13	(35.1)	24	(64.9)	
Hemoglobin level					
normal	39	(60.9)	25	(39.1)	0.254
decreased	20	(47.6)	22	(52.4)	
Platelets					
inside	50	(58.8)	35	(41.2)	0.330
outside	9	(42.8)	12	(57.2)	
LDH					
normal	32	(74.4)	11	(25.6)	0.001
elevated	19	(40.4)	28	(59.6)	
Sodium					
normal	50	(56.2)	39	(43.8)	0.866
decreased	9	(52.9)	8	(47.1)	
γ-Glutamyl transferase					
normal	27	(64.3)	15	(35.7)	0.095
elevated	26	(47.3)	29	(52.7)	

CR: complete response, PR: partial response, WBC: white blood count.

Results

Patient characteristics are given in Table I, and laboratory values and cut offs in Table II. In contrast to selected studies there was a rather high percentage of patients with ECOG performance status (PS) stages 2 and 3 (n=24 (22.6 %)), and about two thirds (73.6%) had extensive disease at diagnosis. In all cases but one, extensive disease was scored due to synchronous metastases, which were present at distant organs: liver (n=36; 46% of ED), brain (n=26; 33% of ED), lung (n=23; 29% ED), adrenal gland (n=19; 24% of ED) and bone (n=13; 17% of ED). One organ and > one organ were involved at diagnosis in 48.7% and 51.3% of the ED patients, respectively. A malignant pleural effusion was present in 32 (30.2%) of those patients.

Table IV. *Best fitted multivariate regression model for response to ACE chemotherapy.*

Variable	Coefficient	Standard deviation	HR (95% CI)	*p*-value
Brain metastases	–2.210	0.712	0.11 (0.02-0.44)	0.002
Dose reduction	2.372	0.748	10.72 (2.47-46.48)	0.002
LDH	1.582	0.661	4.86 (1.33-17.78)	0.017

Tumour response. Tumour response was evaluated after 3 and 6 cycles of chemotherapy, and was available for 78 and 42 patients, respectively. Twenty-eight patients had less than 3 cycles of chemotherapy due to: death during or after the first application (n=13), death during or after the second application (n=3), death during the third application (n=1), toxicity (n=5), unknown reason (n=2), or loss of follow-up (n=4). The best response, obtained at any time during therapy (and after at least three cycles of chemotherapy) was classified into two categories: response (n=59), including complete response (CR) and partial response (PR); and non-response (n=47), including stable disease (SD), progressive disease (PD) and patients not available for response evaluation after three cycles of chemotherapy (NA).

In univariate analysis, a good PS ($p=0.036$), a normal LDH ($p=0.001$), a normal WBC ($p=0.003$), absence of brain metastases ($p<0.001$) and a dose reduction ($p=0.001$) were associated with a response (Table III). In multivariate analysis a dose reduction ($p=0.002$, HR 10.7), absence of brain metastases ($p=0.002$, HR 0.110) and a normal LDH ($p=0.017$, HR 4.864) were the best fitting independent predictive factors for response (Table IV).

The ACE chemotherapy resulted in 16 patients in CR. In univariate analysis female gender ($p=0.027$), LD ($p=0.020$), absence of brain metastases ($p=0.013$) and a dose reduction ($p=0.037$) were associated with an improved response. In the multivariate analysis female gender ($p=0.025$, HR 0.219 (95%CI 0.058-0.824)) and dose reduction ($p=0.027$, HR 3.381 (0.895-12.775)) were independent predictive factors for CR (data not shown).

Survival status. Overall, the estimated median survival time was 9.36 months with actual 1-, 2- and 5-year survival rates of 31%, 8% and 3%, respectively. Median 1- and 2-year

Table V. *Univariate survival analysis (n=106).*

Variable	Median survival (months)	*p*-value
Gender		
male	9.36	0.6966
female	9.40	
Age		
<60 years	9.40	0.3825
>60 years	8.71	
ECOG-PS		
0	14.08	<0.0001
1	6.28	
2	5.28	
3	1.08	
Disease extent		
limited disease	12.16	0.0103
extensive disease	8.54	
Malignant pleural effusion		
yes	6.87	0.0960
no	9.66	
Brain metastases		
yes	4.67	<0.0001
no	11.04	
Metastatic sites		
1	14.06	0.0150
>1	9.69	
Dose reduction		
yes	11.04	0.2663
no	8.74	
White blood count (WBC)		
normal	10.45	<0.0001
elevated	4.21	
Hemoglobin level		
normal	9.66	0.5423
decreased	8.71	
Platelets		
inside	9.59	0.9321
outside	6.28	
LDH		
normal	11.43	0.0103
elevated	5.98	
Sodium		
normal	8.84	0.9656
decreased	9.59	
γ-Glutamyl transferase		
normal	12.62	0.0080
elevated	6.87	

survival rates were 45.6% and 23.9% for LD and 30.7% and 7.2% for ED, respectively.

The detailed results of the univariate analysis are shown in Table V. The following factors were identified as favourable prognostic features by the log-rank test: a good PS, LD, a normal WBC, normal LDH, absence of brain metastases and (in ED) only 1 metastatic site (in contrast to >1 sites). After selection of these parameters for a multivariate Cox regression analysis, ECOG-PS, WBC and absence of brain metastases were independent prognostic factors for improved survival (Table VI).

Table VI. *Best fitted multivariate regression model for survival*

Variable	Coefficient	Standard deviation	HR (95% CI)	*p*-value
ECOG-PS	0.424	0.150	1.53 (1.14-2.05)	0.005
WBC	0.347	0.131	1.42 (1.10-1.83)	0.008
Brain metastases	–0.933	0.265	0.39 (0.23-0.66)	<0.001

WBC: white blood count

Taking the PS and the WBC as a prognostic signature, three highly significant different groups in terms of outcome could be constructed ($p<0.001$): favourable group A, patients with PS 0 and a normal WBC (median survival time 15.8 months); intermediate group B, patients with either PS >0 or WBC > 10/nl (median survival time 6.87 months); and, poor prognosis group C, patients with both PS>0 and WBC >10/nl (median survival time 3.35 months). The Kaplan Meier curves are presented in Figure 1.

Toxicity. Toxicity was documented according to CTC criteria. Overall, 19.8% and 46.2% experienced toxicity CTC 3 and 4, respectively. Most common was leucopoenia, which was evident in 75.2% of the patients, CTC 3/4 was described in 61.3%. Leukopenia led to a dose reduction or to a cessation of chemotherapy in 22.9% and 5.7% of those patients. Leukopenia was significantly associated with increased LDH levels ($p=0.003$). Other grade 3/4 toxicity was as follows: fever 32.7%, thrombopenia 20.6%, anemia 19%, nausea/vomiting 11.4% and diarrhoea 7.7%.

Discussion

As prognosis in SCLC is still dismal and has not substantially changed during the last three decades, it is of the utmost importance, that the majority of the patients should be included in prospective therapy studies. However, in everyday clinical practice, patients with SCLC are often elderly, of a suboptimal PS and frequently present with other diseases related to cigarette smoking, such as severe chronic obstructive pulmonary disease. The majority of these patients will be excluded from clinical studies. Despite the fact, that intensive chemotherapy often proves toxic and difficult to administer, most patients have a strong wish to be treated, at least to relieve their symptoms, such as dyspnoea, hemoptysis or cough. In these patients, a simple predictive and prognostic algorithm would be helpful to weigh the risks and benefits of treatment.

In the past decades a large number of studies aiming to

identify prognostic and predictive aspects of treatment in SCLC patients have been published. With the exception of some congruent findings there is still a lot of discrepancy which might be due to the following reasons: (i) Most of the studies used either data from one prospective clinical study or described parameters of one institution including different studies. Patients who received different agents and regimens and who, therefore, might hardly be comparable were analysed for the same parameters. (ii) Laboratory markers were not analysed in all studies and different cut-off levels were used in the respective studies. (iii) None of the studies had validated their results by an independent test-set cohort or tested their parameters against patients in routine clinical practice. While all publications have reported on prognostic markers of survival, predictive markers of response have been rather uncommon. This is probably due to the fact, that different regimens were used. The present retrospective study has compared clinical and laboratory parameters described in the literature (4-13) (for an overview of parameters from relevant studies in the literature see Table VII) in a cohort of patients from one institution, all treated in routine clinical practice with the same chemotherapy regimen (ACE).

Absence of metastases in the brain at diagnosis, as well as a favourable PS and a normal WBC were the most powerful positive prognostic indicators of survival in the multivariate analysis of our trial. A CT scan of the brain to exclude metastases is not normally recommended as a part of the initial staging in the absence of neurological findings. Therefore, this parameter, though highly significant in the outcome analysis, was excluded from our prognostic model. A two factor classifier consisting of the most important clinical parameter (PS) and a laboratory factor that is a prerequisite prior to chemotherapy (WBC) was strong enough to create a reliable predictor of outcome in routine clinical practice. Best survival was reached when the PS was 0 and the WBC normal (median survival 15.8 months). The outcome was worst, when the PS was >0 and the WBC was increased (median survival 3.35 months). For the patients in the later group, ACE chemotherapy may only result in increased toxicity and loss of quality of life without improvement of survival. In this situation it should, therefore, probably be replaced by an individually tailored palliative supportive treatment or a less toxic regimen, *e.g.* topotecan (14).

The prognostic model described here is in line with data from the literature. In particular, there is a broad consent about PS. Despite the use of different scoring systems (WHO, ECOG-PS or Karnofsky index), all the studies cited here found PS to be an independent prognostic factor and in all but one this was independent of disease extent (see Table VII). The WBC was found to be a prognostic factor in three out of the seven studies, which included laboratory parameters in their analyses (8-10). However, in the study by Souhami *et al.* (4), who did not find an association with prognosis, the cut-off level of WBC was 7.5/nl. In all other studies and in our analysis, the cut off level was 10/nl.

Interestingly, the extent of the disease (LD *versus* ED) was not found to be of independent prognostic value by us although it was significant in the univariate log-rank analysis. Probably, this was due to the fact, that brain metastases, evident in 33% of the ED cases at the time of diagnosis, were a predominant predictor of poor outcome. Additionally, there was a trend towards significance between the PS and the extent of disease ($p=0.055$) in our study. Data from clinical studies uniformly describe tumour extent as one of the most important prognostic factors with a high relevance for treatment decision making. Indeed, as the data from this study were generated over 15 years, patients with LD are nowadays not treated any more with the ACE regimen, with few exceptions. According to recent study data, patients with LD seem to benefit from combined radiochemotherapy using Cisplatin/Etoposide or may even be surgically resected in UICC stages I and II (15).

Female gender is another commonly described prognostic factor in SCLC. However, some studies have postulated that only females with LD have an increased median overall survival. In the present analysis a different survival outcome related to gender could not be found. However, female gender was an independent predictor of complete response, as in the study by Christodoulou *et al.* (13). Additionally, an independent predictive marker of response to ACE chemotherapy in general, and for complete response in particular, was a dose reduction of the substances in our study. A dose reduction normally became necessary after a patient experienced toxicity CTC 3 or 4 in a previous application. Most often leukopenia, or even febrile leukopenia was the noted toxicity. As a consequence, one might argue, that patients not experiencing a higher toxicity might benefit from a dose escalation. Indeed, this hypothesis is supported by a study assessing high dose cyclophosphamide and doxorubicin as part of a three-weekly CAV regimen (16). The authors have shown, that dose escalation was associated with an increased rate of complete response (22% *versus* 12%, $p=0.045$). However, dose escalation did not provide a survival benefit. A survival benefit has been demonstrated by Arriagada *et al.*(17), who reported a prospective study in 105 patients randomised to higher *versus* lower doses of cyclophosamide and cisplatin in the first cycle of chemotherapy in LD patients. The study was prematurely closed after an interim analysis due to the favourable outcome in the intensified arm (2-year survival rate 26% *versus* 43%, $p=0.02$). However, other studies have not confirmed these results, but only an excess of toxicity (18, 19). As these studies were small and the dose escalation was only moderate, data remain conflicting to date (20). Therefore, any dose escalation should be discussed individually and has to be decided with the patient. Once the decision is made, a close

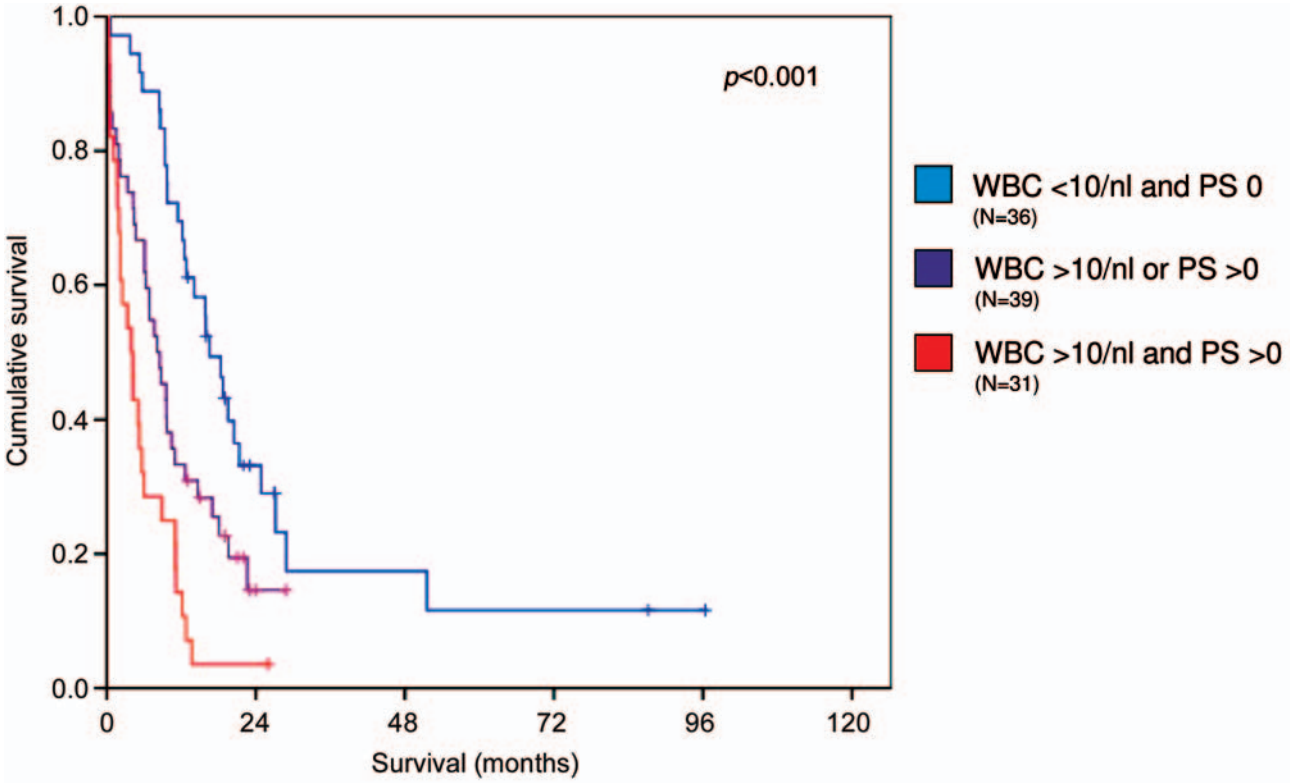
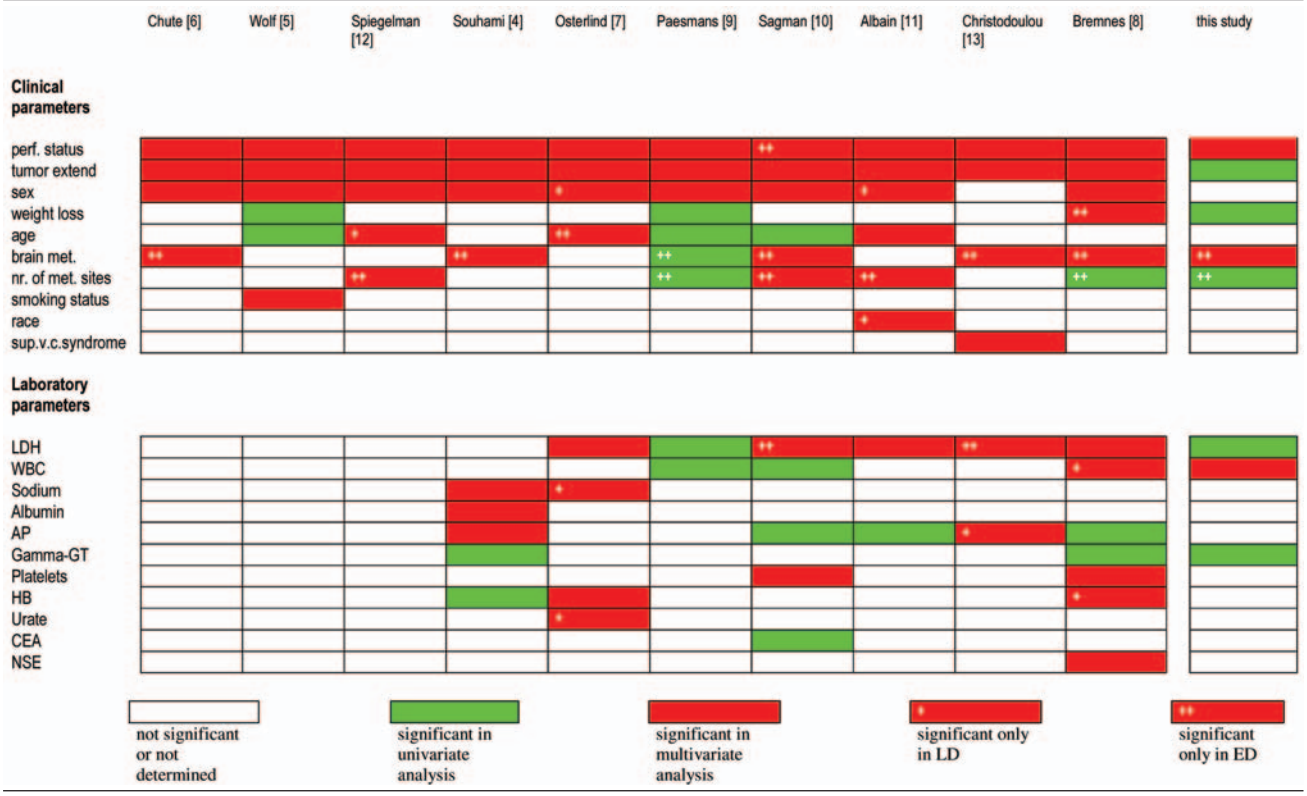


Figure 1. *Kaplan Meier curves for overall survival of 106 patients with SCLC stratified by PS (0 versus >0) and WBC (<10 /nl versus <10 /nl).*

Table VII. *Prognostic factors for survival in SCLC – data from the literature.*



AP: alkaline phosphatase, HB: haemoglobin, CEA: carcinoembryonic antigen, NSE: neuron-specific enolase.

surveillance of clinical status and laboratory parameters is of utmost importance.

Besides WBC, a normal LDH seems to be another important laboratory marker. It has been shown to be an independent prognostic marker in several studies and even in our analysis it showed significance in the univariate analysis. It did not reach the status of independence because of a high association with WBC ($p<0.001$). Furthermore, LDH levels were inversely associated with leukopenia, the most often described kind of toxicity (75.2%). As a glycolytic enzyme, it is expressed in multiple tissues. Therefore, high serum levels of LDH indicate injury, infarction or necrosis of cells (10). They also seem to correlate with tumour mass and tumour aggressivity. Byhardt *et al.* have successfully stratified SCLC patients according to tumour mass and even to a modified tumor-node-metatasis classification by serum LDH levels (21). Furthermore, it has been shown to be effective for serially monitoring response to therapy with a direct correlation between disease activity and serum LDH (22).

The tumour markers NSE and Cyfra 21-1 are discussed in the literature as being of diagnostic and prognostic value (8, 23, 24). In accordance with the literature, we saw a trend towards a worse prognosis in patients with elevated levels. However, as these markers were not determined in every patient before starting chemotherapy, they were not included in the final calculation.

In summary, routine clinical and laboratory parameters at initial diagnosis of SCLC might be of prognostic and predictive value. In particular, the combination of a reduced performance status and increased serum levels of WBC and LDH might be predictors of non-response, high toxicity and poor survival. Those patients may, at least, not benefit from an ACE based chemotherapy. Additionally, our own and the literature data document the importance of predictive and prognostic markers which should be prospectively tested as stratification criteria in clinical studies.

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References

1 Morstyn G, Ihde DC, Lichter AS, Bunn PA, Carney DN, Glatstein E and Minna JD: Small cell lung cancer 1973-1983: early progress and recent obstacles. Int J Radiat Oncol Biol Phys *10*: 515-539, 1984.

2 Aisner J, Whitacre M, VanEcho DA, Wesley M and Wiernik PH: Doxorubicin, Cyclophosphamide and VP16-213 (ACE) in the treatment of small cell lung cancer. Cancer Chemother Pharmacol *7*: 187-193, 1982.

3 Tjan-Heijnen VC, Caleo S, Postmus PE, Ardizzoni A, Burghouts JT, Buccholz E, Biesma B, Gorlia T, Crott R, Giaccone G, Debruyne C and Manegold C: Economic evaluation of antibiotic prophylaxis in small-cell lung cancer patients receiving chemotherapy: an EORTC double-blind placebo-controlled phase III study (08923). Ann Oncol *14*: 248-257, 2003.

4 Souhami RL, Bradbury I, Geddes DM, Spiro SG, Harper PG and Tobias JS: Prognostic significance of laboratory parameters measured at diagnosis in small cell carcinoma of the lung. Cancer Res *45*: 2878-2882, 1985.

5 Wolf M, Holle R, Hans K, Drings P and Havemann K: Analysis of prognostic factors in 766 patients with small cell lung cancer (SCLC): the role of sex as a predictor for survival. Br J Cancer *63*: 986-992, 1991.

6 Chute JP, Venzon DJ, Hankins L, Okunieff P, Frame JN, Ihde DC and Johnson BE: Outcome of patients with small-cell lung cancer during 20 years of clinical research at the US National Cancer Institute. Mayo Clin Proc *72*: 901-912, 1997.

7 Osterlind K and Andersen PK: Prognostic factors in small cell lung cancer: multivariate model based on 778 patients treated with chemotherapy with or without irradiation. Cancer Res *46*: 4189-4194, 1986.

8 Bremnes RM, Sundstrom S, Aasebo U, Kaasa S, Hatlevoll R and Aamdal S: The value of prognostic factors in small cell lung cancer: results from a randomised multicenter study with minimum 5 year follow-up. Lung Cancer *39*: 303-313, 2003.

9 Paesmans M, Sculier JP, Lecomte J, Thiriaux J, Libert P, Sergysels R, Bureau G, Dabouis G, Van Cutsem O, Mommen P, Ninane V and Klastersky J: Prognostic factors for patients with small cell lung carcinoma: analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. Cancer *89*: 523-533, 2000.

10 Sagman U, Feld R, Evans WK, Warr D, Shepherd FA, Payne D, Pringle J, Yeoh J, DeBoer G and Malkin A: The prognostic significance of pretreatment serum lactate dehydrogenase in patients with small-cell lung cancer. J Clin Oncol *9*: 954-961, 1991.

11 Albain KS, Crowley JJ, LeBlanc M and Livingston RB: Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. J Clin Oncol *8*: 1563-1574, 1990.

12 Spiegelman D, Maurer LH, Ware JH, Perry MC, Chahinian AP, Comis R, Eaton W, Zimmer B and Green M: Prognostic factors in small-cell carcinoma of the lung: an analysis of 1,521 patients. J Clin Oncol *7*: 344-354, 1989.

13 Christodoulou C, Pavlidis N, Samantas E, Fountzilas G, Kouvatseas G, Pagdatoglou K, Palamidas F, Nikolaidis C, Angelidou M, Kalofonos HP, Kosmidis P and Skarlos DV: Prognostic factors in Greek patients with small-cell lung cancer (SCLC). A Hellenic Cooperative Oncology Group Study. Anticancer Res *22*: 3749-3758, 2002.

14 Ardizzoni A, Hansen H, Dombernowsky P, Gamucci T, Kaplan S, Postmus P, Giaccone G, Schaefer B, Wanders J and Verweij J: Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. J Clin Oncol *15*: 2090-2096, 1997.

15 Brock MV, Hooker CM, Syphard JE, Westra W, Xu L, Alberg AJ, Mason D, Baylin SB, Herman JG, Yung RC, Brahmer J, Rudin CM, Ettinger DS and Yang SC: Surgical resection of limited disease small cell lung cancer in the new era of platinum chemotherapy: Its time has come. J Thorac Cardiovasc Surg *129*: 64-72, 2005.

16 Johnson DH, Einhorn LH, Birch R, Vollmer R, Perez C, Krauss S, Omura G and Greco FA: A randomized comparison of high-dose *versus* conventional-dose cyclophosphamide, doxorubicin, and vincristine for extensive-stage small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol *5*: 1731-1738, 1987.

17 Arriagada R, Le Chevalier T, Pignon JP, Riviere A, Monnet I, Chomy P, Tuchais C, Tarayre M and Ruffie P: Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. N Engl J Med *329*: 1848-1852, 1993.

18 Ihde DC, Mulshine JL, Kramer BS, Steinberg SM, Linnoila RI, Gazdar AF, Edison M, Phelps RM, Lesar M and Phares JC: Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. J Clin Oncol *12*: 2022-2034, 1994.

19 Humblet Y, Weynants P, Bosly A, Majois F, Duprez P, Francis C, Beauduin M, Machiels J, Gailly C and Delaunois L: Carboplatin in association with etoposide and either adriamycin or epirubicin for untreated small cell lung cancer: a dose escalation study of carboplatin. UCL Clinical Oncology Group. Med Oncol Tumor Pharmacother *6*: 207-212, 1989.

20 Tjan-Heijnen VC, Wagener DJ and Postmus PE: An analysis of chemotherapy dose and dose-intensity in small-cell lung cancer: lessons to be drawn. Ann Oncol *13*: 1519-1530, 2002.

21 Byhardt RW, Hartz A, Libnoch JA, Hansen R and Cox JD: Prognostic influence of TNM staging and LDH levels in small cell carcinoma of the lung (SCCL). Int J Radiat Oncol Biol Phys *12*: 771-777, 1986.

22 Ganz PA, Ma PY, Wang HJ and Elashoff RM: Evaluation of three biochemical markers for serially monitoring the therapy of small-cell lung cancer. J Clin Oncol *5*: 472-479, 1987.

23 Ando S, Suzuki M, Yamamoto N, Iida T and Kimura H: The prognostic value of both neuron-specific enolase (NSE) and Cyfra21-1 in small cell lung cancer. Anticancer Res *24*: 1941-1946, 2004.

24 Molina R, Auge JM, Filella X, Vinolas N, Alicarte J, Domingo JM and Ballesta AM: Pro-gastrin-releasing peptide (proGRP) in patients with benign and malignant diseases: comparison with CEA, SCC, CYFRA 21-1 and NSE in patients with lung cancer. Anticancer Res *25*: 1773-1778, 2005.

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