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REVIEW

Prognostic factors in lung cancer: Tables and Comments

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ABSTRACT: Prognostic factors (PF) have a pivotal role in Clinical Oncology. They are helpful in the selection of treatment, provide insights into the disease process and the therapeutic response, and are fundamental in the design of clinical trials or in the interpretation of data from the literature. The number of possibly useful PFs in lung cancer is large (certainly more than one hundred). This paper attempts to provide a comprehensive listing of PFs and other variables potentially associated with outcome of lung cancer. This is achieved using tables, where studies relevant to each PF are referenced in relationship to their results, statistical power, type of analysis, number of variables incorporated in multivariate tests, and cell type. Tables include the outcome of an extensive retrieval of the literature and indicate visually where much of the evidence resides for the contribution of a variable to prognosis. Each table is briefly discussed and systematically comprises one group of PFs.

Among the many pinpointed, the best predictive models still belong to studies based on clinical and routine laboratory data. Recent researches have clarified the role of new PFs (such as the biological factors); others (*e.g.* quality of life measures, the serum content of acute phase reaction proteins or the pathological evidence of tumour neoangiogenesis) might be recognized as important in the future. Like infinity, the fate of the individual patient will never become a completely measurable entity. However, as the discovery of new PFs proceeds, the assessment of the future prospects for patients is becoming more reliable.

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The recognition of prognostic factors (PFs) in lung cancer (LC) has several aims including the following: 1. individual prognostic counselling; 2. selecting treatment -when therapeutic options depend on the baseline clinical characteristics of the subject-; 3. adjusting for inhomogeneities in comparing groups of patients from different locations and studies; 4. defining the eligibility criteria for new clinical trials and stratifying patients by risk subgroups; 5. understanding - certain factors may provide insights into the disease process and provide direction for further studies.

Although some of these reasons may appear rather theoretical, they do have practical relevance. As for many other solid tumours, the variability in prognosis among LC patients is more substantial than improvements in prognosis due to therapy [1], and the failure to appreciate the importance of PFs adequately may contribute to the design of inefficient studies, the erroneous interpretation of results, and the development of inconsistent literature.

Traditionally, a number of baseline clinical characteristics have been used to predict the outcome of patients with LC [1–6]. More recently, simple biochemical tests were thought to be part of the minimal "core" set of important factors [7–9]. At present, newer tests, mostly based on the experimental evidence arising in the laboratory at the cellular and molecular level [10], are being proposed. Unfortunately, the interpretation of relevant literature is not easy. Apart from the magnitude of such literature, there is a remarkable inhomogeneity among studies. Major differences concern:

1. Study populations - patients may be considered if they have lung cancer of any cell type, resected non-small cell lung cancer (NSCLC), inoperable NSCLC, or a tumour of a specific cell type, either surgically or non-surgically treated;
2. Diagnostic criteria and treatment modalities;
3. Statistical analysis (*e.g.*, univariate log-rank test, Kaplan-Meyer and Breslow-Gehan statistics, or multivariate Cox' logistic regression and recursive partitioning and amalgamation algorithms (RPPA). A number of recent papers have discussed these methods in detail [11–13]);
4. The mix of variables which are taken into consideration (a very important source of variability, since the selection of significant covariates in multivariate models depends mainly on what is being tested);
5. The inclusion of post-treatment factors such as response to treatment. These factors need specific corrections, including the landmark and transient state analyses [5], which have not always been performed;

Table 1. – Tumour biology characteristics*

	Nonsignificant**				Significant**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	>200 pts	≤200 pts	>200 pts and/or ≤6 variables	≤200 pts and >6 variables	≤200 pts	>200pts	≤200 pts and/or ≤6 variables	>200 pts and >6 variables
Neural cells adhesion molecule						[14]		
Neuronendocrine features					[15] (16)			
Oncogene abnormalities					[17–20]	[21]	[18]	
Oncogene products		[22]			[23]		[23]	
Growth factors and their receptors					[24, 25]			
Blood-group antigen expression					[26]		[26]	
Thymidine labelling index		[27]			[28]		[27, 28]	
Flow cytometry					[29–40] (41–43)	[44]	[30, 32–34, 36, 38, 40]	
Cell line establishment *in vitro*					[45, 46] (47, 48)		[45] (47, 48)	

For explanation of table layout see text below. * Reference numbers in square brackets refer to studies of [NSCLC/any cell type tumours], numbers in parentheses refer to studies of (pure SCLCs). ** according to definitions in the various studies. NSCLC: non-small cell lung carcinoma; SCLC: small cell lung carcinoma.

6. The end-points themselves (*e.g.*, the entire survival curve or survival at particular times, usually survival rates at 5 to 10 yrs).

With such an abundance and heterogeneity of data, how can a physician determine which pretreatment test, or group of tests, best predicts an adverse outcome? So far, two approaches have been followed. The first is constituted by the classic review, in which the author intending to review a topic describes, comments on, and criticizes a selection of original papers. Accepted limits to this approach are the subjectivity of each of the above mentioned passages, and the absence of quantitative evaluations. The alternative approach is to try to have a quantitative estimate of the performance of each variable. A meta-analysis study of the risk-ratios for mortality, found in populations with different expression of a particular prognostic factor, could be the appropriate method for this quantitative evaluation. This means, however, a new investigation for each PF, with the persistent problem of integrating information from various studies.

This paper intends to use an intermediate approach, between the merely qualitative method of the classic review and the quantitative estimation of meta-analysis. It is based on a systematic overview of the results of quite a large number of original studies, presented in nine tables and briefly commented on. Practically, the studies relevant to each PF are referenced in relationship to their result (significant or nonsignificant, according to the authors' definitions), statistical power (including up to 200 patients or more), type of analysis (univariate and/or multivariate), number of variables incorporated in multivariate tests (up to 6 or more), and cell type (small cell lung cancer (SCLC) only or NSCLC and mixed histologies). In order to provide an immediate appreciation of the importance of each PF, references are ordered in columns, located from the left to the right side in correlation with the strength of positiveness of their findings. A right crowding of references indicates an important prognostic factor, while the left locations mean a negligible one. The end-point used for study selection was overall survival; while particular survival rates, such as rates at 5 or 10 years, were not considered. In the same way, treatment and post-treatment variables were not considered. However, since post-treatment factors may influence results, their possible inclusion in multivariate models has been noted.

Tumour biology characteristics (table 1)

The biological characteristics of tumours, which have been shown to possess some prognostic relevance in lung cancer, include neuronal and neuroendocrine features, oncogene abnormalities and their products, growth factors and their receptors, blood-group antigen expression, thymidine labelling index, deoxyribonucleic acid (DNA) content and fraction of S,G2,M-phase tumour cells, and, finally, their ability to obtain and expand *in vitro* cell lines from tumour specimens. Table 1 provides the relevant references. Common characteristics of this group of PFs are their recent or very recent discovery, the relatively small size of studies (only three series had more than 200 patients), the absence of multivariate analyses with large sets of cofactors (which means difficulty in the judgement of their relative value), the near absence of negative studies (which makes these PFs quite interesting and worthy of further evaluation), and scarce

representation of studies specialized in SCLCs. The main difference among the factors lies in the degree of complexity of their determination (oncogenes, for example, can be studied only in well equipped laboratories). Another difference lies in the degree of supporting evidence, which is very high for DNA measurements, but more often needs further evaluation.

In the past, DNA content in tumour cells was measured by a variety of techniques, the most widespread of them being the static cytophotometry [49]. The introduction of flow cytometry has permitted the rapid and quantitative determination of diverse individual cellular characteristics, including the abnormalities in DNA and growth kinetic. Since 1985, at least 16 studies, which in total include more than 1,500 patients, have clearly demonstrated the important correlation existing between DNA content and LC survival probability (table 1). This correlation persisted when a few other strong survival predictors (generally, extent of disease and performance status) were taken into consideration. However, because of the necessity of obtaining large samples of tumour, more than 90% of the total evidence is due to resected NSCLCs. This implies that the prognostic significance of DNA patterns in advanced NSCLC and in SCLC is not yet definitively ascertained.

Oncogene-related anomalies comprise a heterogeneous group including abnormalities of c-ras-HA, c-myb, c-myc, l-myc, c-raf-1 genes in NSCLC [17, 19, 21], and, in adenocarcinomas, p185(neu) protein expression of HER2/neu protooncogene [23], K-ras activation [18], and ras family mutation [43]. Based on the available data, it is quite clear that the presence of gene anomalies is well correlated with the survival duration of NSCLC patients. Their value, however, remains more speculative than practical. Similar considerations apply to the ability of establishing cell lines *in vitro,* a prognostic factor which has proved equally important in NSCLCs and SCLCs [45–48]. As previously stated, convincing evidence for other biological characteristics is generally scarce.

Histopathology (table 2)

The attempt to correlate simple morphological aspects of malignant cells and tissues with the biological behaviour of the tumour and its clinical course is of practical interest as it has had scant result so far. Histopathological features, claimed to be potentially effective, include tumour cell types and subtypes (as defined by the World Health Organisation (WHO) [50]), grading of histological differentiation and ultrastructural differentiation, histological heterogeneity, tumour neovascularization, and peritumour lymphoid infiltration. References for these histopathology factors are listed in table 2. The common feature of this group is the inconsistency of results, as demonstrated by the roughly equal number of studies, where significant differences in prognosis of tumours with different histopathological patterns were found. Unlike any other factor of this group, the prognostic significance of the major cell types has been assessed through many studies, most of which account for multiple cofactors (table 2).

In NSCLC resected for cure, squamous cell carcinoma should do consistently better than adenocarcinoma and large cell carcinoma [1]. However, in some studies, adenocarcinomas did better than any other histotype [64–68], and in others no difference was observed [52]. Similar

Table 2. – Histopathologic aspects*

	Nonsignificant**				Significant**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	>200 pts	≤200 pts	>200 pts and/or ≤6 variables	≤200 pts and >6 variables	≤200 pts	>200pts	≤200 pts and/or ≤6 variables	>200 pts and >6 variables
Major cell types	[51–55]	[56–59]	[30, 51, 52, 55, 60–63]	[56–59]	[27, 30, 64, 65]	[60, 66–73]	[27, 65, 68]	[69, 70, 72]
Adenosquamous cell type					[74]		[74]	
SCLC subtyping	(75–77)	(78)			(79, 80)	(81)		
Adenocarcinoma subtyping	[82]		[82]			[83]	[84]	
Ultrastructural LC differentiation		[85]						
Ultrastructural BA differentiation		[86]						
Histologic heterogeneity			[62]					
Peritumour lymphoid infiltration					[87]		[87]	
Tumour neovascularization					[88]		[88]	
Tumour grading of differentiation	[82, 89]	[90]	[82, 89]	[90]		[91]	[91]	

* Reference numbers in square brackets refer to studies of [NSCLC/any cell type tumours]; numbers in parentheses refer to studies of (pure SCLCs) ** according to definitions in the various studies. LC: large cell; BA: bronchioloalveolar. For further definitions see legend to table 1.

Table 3. – Paraneoplastic syndromes*

	Nonsignificant**				Significant**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	>200 pts	≤200 pts	>200 pts and/or ≤6 variables	≤200 pts and >6 variables	≤200 pts	>200pts	≤200 pts and/or ≤6 variables	>200 pts and >6 variables
SIADH	(94)		(94)					
Overall	[52, 72]		[52, 72]		(95, 96)		(96)	
Clubbing	[69]		[69]					
Cushing's syndrome					(97)			

* Reference numbers in square brackets refer to studies of [NSCLC/any cell type tumours]; numbers in parentheses refer to studies of (pure SCLCs) ** according to definitions in the various studies. SIADH: inappropriate secretion of antidiuretic hormone. For further definitions see legend to table 1.

inconsistencies can be observed in advanced NSCLCs (table 2). Thus, if the different non-small cell histologies have some prognostic impact, this would be rather modest.

In 1988, the Pathology Committee of the International Association for the Study of Lung Cancer recommended abandoning the WHO subclassification of SCLC [50], and adopting the three new subtypes of small cell, mixed small/large cell, and combined small cell carcinomas [92] This proposal was an attempt to make the subtypes of SCLC more relevant clinically. Prior studies had shown that mixed small/large cell cancers could be associated with worse prognoses than pure SCLCs [79, 81]. But, again, any clinical relevance of the morphological approach was rejected by two following larger studies [76, 77].

As far as the remaining histopathological aspects are concerned, the data are negative or insufficient. However, the lymphoid peritumour infiltration, measured morphometrically in randomized microscopic fields from 30 NSCLC [87], and the tumour neoangiogenesis, measured by the number and density of tumour microvessels from 87 T1N0M0 resected NSCLCs [88], are stimulating possibilities for further pathological research. Indeed, the growth of a tumour beyond a certain size requires angiogenesis [93].

Paraneoplastic syndromes (table 3)

It is stimulating to contemplate the fact that tumours manifesting paraneoplastic syndromes may be associated with worse clinical outcomes. The possibility of a different outcome has been verified at least for the following syndromes: inappropriate secretion of antidiuretic hormone (SIADH); Cushing's syndrome; digital clubbing; and all the paraneoplastic syndromes together. Appropriate references are given in table 3. As shown,

Table 4. – Immune factors*

	Nonsignificant**				Significant**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	>200 pts	≤200 pts	>200 pts and/or ≤6 variables	≤200 pts and >6 variables	≤200 pts	>200pts	≤200 pts and/or ≤6 variables	>200 pts and >6 variables
Delayed skin hypersensitivity	[52, 69, 72]	[98]	[52, 69, 72]		(99)		(99)	
Interleukin-2					[100]			
Soluble interleukin-2 receptors					[101]			
Lymphocyte tumour-killing activity					[102]			
Serum amyloid A protein					[103]			
Concanavalin A response					[103]			
3rd component of complement		[65]	[70]	[65]		[70]		
Immunoglobulins	[70, 104]		[70, 104]	[65]	[65]			
Immunocomplexes				[65]	[65]			

* Reference numbers in square brackets refer to studies of [NSCLC/any cell type tumours]; numbers in parentheses refer to (pure SCLCs) ** according to definitions in the various studies. For further definitions see legend to table 1.

the data are scanty, probably because of the comparative rarity of this type of clinical manifestation, and more often negative. According to a British study on 337 operated patients [69], clubbing is not an important PF in NSCLC. Likewise, SIADH did not influence the overall survival of 350 patients with SCLC [94]. On the contrary, a very recent study at the MD Anderson Cancer Centre, comparing 11 SCLC patients with paraneoplastic Cushing's syndrome, who died within 90 days of the initial administration of chemotherapy, and 90 fully comparable control subjects, concluded that the syndrome did have adverse prognostic significance [97]. Inconsistent results were obtained when the survival of patients with no paraneoplastic syndrome was compared with the survival of patients who manifested syndromes of any type (table 3).

Immune factors (table 4)

It is well-known that host immune response plays a critical role in defending the organism against tumour cells. Various immune factors can predict the clinical outcome of LC, including: delayed skin hypersensitivity testing; serum concentration of interleukin-2 and its soluble receptors; serum concentration of the amyloid A protein; 3rd component of the complement (C3), immunoglobulins, and immunocomplexes; lymphocyte tumour-killing activity, and response to Concanavalin A. Table 4 summarizes the results of studies, in which the above factors were evaluated.

Delayed cutaneous hypersensitivity is the simplest and the most common way of evaluating cellular immunocompetence. It has been exploited throughout the last 2 or 3 decades, as it was anecdotally believed to be a possible PF. However, the most recent and internationally widespread evidence appears rather negative in this regard, at least for surgically treated NSCLCs [52, 69, 72, 98]. The only positive experience comes from the NCI-VA Medical Oncology Branch, which in 1983 tested prospectively 154 SCLC patients with the following 5 antigens: purified protein derivative (PPD), mumps, candida, streptokines/streptodornase, and histoplasmin [99].

Other negative findings concern the serum concentration of immunoglobulins, immunocomplexes, and C3. Data on the remaining factors are quite sporadic and need confirmation (table 4).

Tumour markers (table 5)

This chapter comprises many different substances, from the hormones of historical significance to the continuously growing family of tumour-associated antigens.

In addition to prognostication, tumour markers can be helpful in screening and early diagnosis of cancer, in the initial assessment of the extent of the disease, and in monitoring tumour growth (or tumour reduction), once the diagnosis of cancer has been established and the treatment started [105]. Tumour markers have been measured in any body fluid and, immunohistochemically, in

Table 5. – Tumour markers*

	Nonsignificant**				Significant**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	>200 pts	≤200 pts	>200 pts and/or ≤6 variables	≤200 pts and >6 variables	≤200 pts	>200pts	≤200 pts and/or ≤6 variables	>200 pts and >6 variables
Carcinoembryonic antigen	[70, 72]	[65, 90, 106] (96, 107)	[70, 72, 89, 108] (109)	[57, 65, 90] (96, 110)	[57, 108, 111–114] (110, 115–118)	[89, 119, 120] (109)	(116, 117)	
Neuron specific enolase		(121)		(110)	(107, 110, 115, 122–125)		(122)	
Tissue polypeptide antigen		(107)		[57]	[57, 106, 111] (110)	[61, 89, 126]	(110, 121)	[61, 89]
Squamous cell antigen	[119]					[127]		
Creatine kinase BB					(115)			
Thimidine kinase				(110)	(110, 118)		(121)	
CA 19-9		[106]						
CA 125					[128, 129]			
ACTH		[65]					[65]	
HCG		[111]			[65]		[65]	
Calcitonin	[72]	[65]	[72]				[65]	
Alpha-fetoprotein					[65]		[65]	

* Reference numbers in square brackets refer to studies of [NSCLC/any cell type tumours]; numbers in parentheses refer to (pure SCLCs) ** according to definitions in the various studies. CA: carcinoantigen; ACTH: adrenocorticotropin hormone; HCG: human chorionic gonadotropic hormone. For further definitions see legend to table 1.

tumour tissues [105]. The attention, however, is usually centred on pre-treatment serum measurements, as they are the most common source of clinical information. Table 5 provides summarizing data on carcinoembryonic antigen (CEA), neuron specific enolase (NSE), tissue polypeptide antigen (TPA), squamous cell carcinoma antigen (SCCA), antigens CA19-9 and CA125, thymidine kinase, creatine kinase isoenzyme BB (CPK-BB), adrenocorticotropin hormone (ACTH), beta-subunit of the chorionic gonadotropic hormone (b-HCG), calcitonin, and alpha-fetoprotein. As a group, tumour markers share no common characteristic. There is a large diversity of supporting evidence and possible conclusions. At least one of these substances, the TPA, shows features of the ideal PF (effectiveness, simplicity, independence from other PFs).

Six out of 8 SCLC and 9 out of 14 NSCLC studies have proved that CEA possesses some prognostic relevance. This prognostic significance appears either: certain (thousands of patients and six large studies provide information on the antigen), rather weak (not confirmed in any study with great statistical power), slightly weaker in NSCLC than in SCLC (more negative studies in the first group), and hardly independent (no statistical significance within multivariate analyses containing more than six factors).

In SCLC, a great many studies suggest that NSE is an effective prognostic indicator, on its own; but data on its possible independence from the other PFs are few and rather inconsistent (table 5).

TPA seems to be effective in any cell type of LC. Eight studies with several hundred patients have clearly shown that this marker is well correlated with the prognosis of LC, and this correlation persists when numerous other PFs are taken into account. However, it is necessary to wait for other studies, for the simple reason that most of the evidence was provided by a single research group (table 5).

Preliminary data would suggest that thymidine kinase in SCLC and CA 125 in NSCLC might be useful, while results concerning hormones and other markers are negative or absolutely inconsistent (table 5).

Other uncommon laboratory tests (table 6)

There is a variety of other non-routine laboratory tests, claimed to be prognostically important. The majority of these appear to have little practical value. Some may be considered a simple cognitive curiosity, but at least two or three components of this group may warrant further evaluation. The list of these uncommon laboratory tests includes the following determinations: a few specific serum proteins, such as prealbumin, $alpha_1$-acid glycoprotein, $beta_2$-microglobulin, $alpha_1$-antitrypsin, haptoglobin, transferrin, and ferritin; protein-bound carbohydrates; urine polyamines and modified ribonucleosides; and, finally, the angiotensin-converting enzyme. Relevant references for this category are presented in table 6.

The iron-storage protein, ferritin, has been inconsistently shown to possess prognostic relevance. In two NSCLC studies, similar by cell type distribution and size, ferritin

Table 6. – Uncommon laboratory tests*

	Nonsignificant**				Significant**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	>200 pts	≤200 pts	>200 pts and/or ≤6 variables	≤200 pts and >6 variables	≤200 pts	>200pts	≤200 pts and/or ≤6 variables	>200 pts and >6 variables
Ferritin	[70]		[70]	[57]	[57] (130)			
Transferrin						[104]		[104]
Protein-bound carbohydrates					(131)			
Angiotensin-converting enzyme					[132]			
Urine modified ribonucleosides					(133)			
Urinary polyamines					(134)			
C-reactive protein	[70]		[70]		[108, 114]		[108]	
$Alpha_1$-acid glycoprotein			[104, 108]		[108, 114]	[70, 104]		[70]
$Beta_2$-microglobulin	[70]		[70]					
Retinol binding protein			[70]			[70]		
Haptoglobin			[104]			[104]		
Prealbumin	[70]		[70]					
$Alpha_1$-antitrypsin		[65]			[135]	[104]	[65]	[104]

* Reference numbers in square brackets refer to studies of [NSCLC/any cell type tumours]; numbers in parentheses refer to studies of (pure SCLCs) ** according to definitions in the various studies.

Table 7. – Traditional laboratory tests*

	Nonsignificant**				Significant**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	>200 pts	≤200 pts	>200 pts and/or ≤6 variables	≤200 pts and >6 variables	≤200 pts	>200pts	≤200 pts and/or ≤6 variables	>200 pts and >6 variables
Lactate dehydrogenase	[72]		[72, 136] (7)	[137] (110, 138)	[57, 111, 137, 139] (7, 110, 118, 140)	[51, 82, 136] (109, 141–144)	[57, 59, 139] (121, 140)	[51, 82, 145] (9, 109, 141–146)
Albumin	[104]		[104, 108] (142)	[137] (110)	[90, 108, 114, 137, 147] (7, 110)	(8, 142)	[59, 90] (7, 138)	[145] (8, 9)
SGOT	[82] (142, 144)	[65]	(142, 144)	[57, 65]	[57]		(138)	[82] (9)
SGPT		[57, 65]	(9)	[57, 65] (138)		(8)		(8)
Alkaline phosphatase	[72, 82]	(96)	[72, 82, 136] (8, 109, 142, 144)	[57, 139] (96, 138)	[57, 139]	[136] (8, 109, 141, 142, 144)		(9, 141)
Sodium	(142)	[57] (110)	(8, 109, 142)	[57] (96)	(96)	(8, 109, 141, 142, 144)		(9, 141)
Uric acid		[57]		[57]			(138)	
Haemoglobin	(142, 144)	[57] (96)	[72, 82, 136] (8, 9, 142, 144)	[57, 59, 139, 148] (96, 138)	[137, 139] (7)	[72, 82, 136, 149] (8)	[137] (7)	
Total protein	[104]	[57] (7, 96)	[104] (7, 9)	[57, 59] (96)				
Protein electrophoresis		[65]	(7)		(7)			
Serum bicarbonate						(141)		(9, 141)
Bilirubin	(144)		(8, 144)	(138)		(8)		
Gamma GT		(96)	(8, 9, 142)	[139] (96)	[139]	(8, 142)		(9)
WBC	[72] (8)	[57, 65]	[72] (8, 9, 109)	[57, 139] (138)	[139]	[52, 82, 149] (109, 142)	[65]	[52, 63, 82] (142, 145)
Calcium	[136] (8, 144)		[72, 136] (8, 9, 144)	(138)		[72]		[63]
Platelets	[72, 82] (8, 142, 144)	[57]	[72, 82] (8, 9, 142, 144)	[57] (138)	[139]	[149] (109)	[139]	(109)
Urea or creatinine	[72]	[57]	[72]	[57]				[145] (9, 146)
ESR	(142)	[57]	[52, 69] (9, 142)	[57]	[139] (96)	[52, 69, 149]	[139] (96)	

* Reference numbers in square brackets refer to studies of [NSCLC/any cell type tumours]; numbers in parenthesis refer to studies of (pure SCLCs) ** according to definitions in the various studies. SGOT: serum glutamic oxalacetic transaminase; SGPT: serum glutamic pyruvic transaminase; Gamma GT: gamma glutamyl transpeptidase; WBC: white blood cell; ESR: erythrocyte sedimentation rate.

was found either an insignificant factor of prognosis (the series with more operable patients [70]), or a hardly significant one (the series with more advanced stages of disease [57]). Another SCLC study, on 39 patients only, added little, further, positive evidence [130].

Other NSCLC studies evaluated acute-phase reaction proteins, of which the most interesting are $alpha_1$-acid glycoprotein (4 positive studies out of 4 studies), $alpha_1$-antitrypsin (3 positive studies out of 3), and, less, C-reactive protein (2 positive studies out of 3).

Other laboratory tests, such as the determination of protein-bound carbohydrates, polyamines, and modified ribonucleosides, were performed in urine and sera samples from untreated patients with SCLC (maximum 41 subjects), all of which should indicate the clinical outcome [131, 133, 134].

Traditional laboratory tests (table 7)

This, and the following clinical chapter, are the largest sections both in terms of number of PFs evaluated and of relevant studies: there are scores of traditional laboratory test reports and thousands of patients studied. The simple explanation for this phenomenon is the zero cost of obtaining data. Clinical and routine laboratory tests, which are essential for therapeutic management, are available for any patient, wherever seen and treated. The only additional cost is computerized recording (already becoming widespread praxis for easier medical management) and statistical analysis. For many cooperative groups, studies of traditional PFs are the natural consequence of their clinical trials.

The list of commonly used laboratory tests evaluated as possible prognostic determinants comprises the following: serum albumin and total protein concentration; protein electrophoresis; glutamic oxalacetic and glutamic pyruvic transaminases; alkaline phosphatase and gamma glutamyl transpeptidase; lactate dehydrogenase; serum sodium, calcium, and bicarbonates; bilirubin, uric acid, creatinine, and urea serum content; erythrocyte sedimentation rate; and, finally, a number of haematological tests, such as haemoglobin concentration, or erythrocyte, leukocyte, and thrombocyte counts. Table 7 provides the appropriate references for each variable. This is undoubtedly a very "busy" table. Indeed, in order to maintain the previous scheme of presentation, studies reporting analyses of multiple laboratory tests (the majority) are cited repeatedly. In this group, both SCLC and NSCLC studies are well represented, even though, with the exception of erythrocyte sedimentation rate (ESR) and kidney function parameters, laboratory testing was reported more frequently in the former cell type.

Lactate dehydrogenase is the strongest prognostic determinant in this group, whether considered alone or in combination with other PFs. In 7 out of 8 NSCLC and in 9 out of 9 SCLC univariate tests, plus in 6 out of 9 NSCLC and in 10 out of 13 SCLC multivariate tests (for a total of 23 studies), the enzyme was found significantly or highly significantly survival-related. A further effective and independent laboratory test is the determination of serum albumin concentration (13 positive studies out of 14 studies considering either univariate or multivariate tests, and both SCLCs and NSCLCs). Equally important factors, but only when evaluated on their own, seem to be haemoglobin in NSCLC (6 significant univariate tests out of 7) and alkaline phosphatase in SCLC (5 out of 6). Other less important variables are erythrocyte sedimentation rate (4 significant univariate tests out of 5) and white blood cell count (4 out of 7) in NSCLC, as well as serum sodium concentration (6 out of 8) in SCLC.

However, studies are not all equally important; for example, the report of the Subcommittee for the Management of Lung Cancer (UK Coordinating Committee on Cancer Research) merits a special mention. The report, collecting information from 10 different British SCLC studies and nearly 4,000 patients, concluded that the most useful parameters, among the 17 laboratory parameters considered, were alkaline phosphatase, glutamic oxalacetic transaminase, lactate dehydrogenase, and plasma sodium [9]. In the opinion of the Subcommittee, these parameters should be evaluated in any future SCLC study [9]. In extensive-stage NSCLC, the Southwest Oncology Group experience is probably the most important [136]. The group analysed their own database, containing information on the clinical and laboratory pre-treatment characteristics of 2,531 patients, and concluded, from a subset analysis, that haemoglobin and lactate dehydrogenase were the most prognostically prominent laboratory tests, sufficiently capable of defining distinct prognostic subgroups [136].

Clinical and sociodemographic characteristics (table 8)

As previously mentioned, this is another full chapter. It deals with the following: age; sex; weight loss in the months preceding the diagnosis; performance status; stage of disease and other parameters of disease extension, such as tumour dimension, presence of metastasis in lung, brain, bone, and liver, and the number of metastatic sites; complicating lung infections; other associated disorders; plus a myriad of symptoms, physical signs, radiological findings, and other clinical observations. Table 8 is relevant to this group. Among the studies cited, a few large cooperative group reports are worth quoting. They include the Cancer and Leukemia Group B study [151], the already cited British Committee review [9], 2 South West Oncology Group reports [136, 144], and the classic Veteran's Administration Lung Group study [63].

Overloading a review on prognostic factors with a discussion on the importance of the stage of disease and performance status is clearly useless, given the unquestioned acceptance of their supremacy over any other factor believed to be effective in lung cancer [1–6]. Thus, both performance status and stage will not be further discussed, even though for the sake of completeness, they have been included in the table.

Other effective PFs in this group are weight loss in

Table 8. – Clinical parameters*

	Nonsignificant**				Significant**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	>200 pts	≤200 pts	>200 pts and/or ≤6 variables	≤200 pts and >6 variables	≤200 pts	>200pts	≤200 pts and/or ≤6 variables	>200 pts and >6 variables
Age	[51, 52, 54, 63, 69, 82] (8)	[30, 56–58, 65, 90] (80, 96)	[30, 51, 52, 54, 55, 61, 62, 68, 69, 72, 82, 89, 91] (8, 109)	[56–58, 90, 148] (96)	(110, 150)	[53–55, 67, 68, 71, 72, 89, 91, 136] (109, 142, 144)	[59, 65, 136] (110, 150, 151)	[152] (9, 142, 144, 145)
Sex	[52, 53, 69, 72, 82, 89, 91, 153] (8, 142)	[30, 56, 57, 90] (96)	[30, 52, 61, 62, 68, 69, 72, 82, 89] (8, 109, 142)	[57, 59, 65, 90, 148] (96)	[58, 137] (80, 110)	[51, 67, 70, 71, 136] (109, 144)	[56, 58, 71, 91, 136, 137] (48, 110)	[51, 70, 145] (9, 144)
Race	[136, 154]	[56] (80)	[136]	[56]		(144)		(144)
Weight loss	[51, 72]	[56] (96)	[51, 72, 82, 136] (116)	[56, 139] (96)	[57, 65, 137, 139]	[54, 55, 63, 69, 82, 136]	[57, 65, 137]	[54, 55, 61, 63, 69, 89, 104, 152]
Performance status			[108] (7)	[65]	[56–58, 65, 90, 108, 114, 137] (7, 78, 96, 110, 118, 150)	[51, 52, 54, 55, 63, 68, 72, 82, 89, 136] (8, 109, 141, 142, 144)	[56–59, 68, 84, 90, 136, 137] (48, 96, 110, 116, 150, 151)	[51, 52, 54, 55, 61, 63, 72, 82, 89, 104, 145, 152] (8, 9, 109, 141, 142, 144–146)
TNM stage		[58, 65] (96)		[58, 59, 65, 90] (96)	[5, 27, 56, 57, 90, 137, 139]	[51–53, 55, 60, 66, 68, 70, 71, 73, 82, 89, 91]	[28, 30, 38, 56, 57, 62, 68, 84, 91, 137, 139]	[51, 55, 61, 70, 82, 89, 104, 145]
ECOG stage (limited *vs* extensive)			(8)	(150)	(78, 80, 110, 118, 150)	(8, 109, 141, 142, 144)	(48, 96, 110, 116, 150, 151)	(8, 9, 109, 141, 142, 144–146)
Primary tumour dimension		[27] (140)	[63] (140)	[148]		[69]		[69, 72]
Liver metastases	[51]	(96)	[51, 61, 89] (116)	[58] (96, 150)	[58] (150, 155)	[54, 82, 89] (8)	(48)	[54, 82] (8)
Bone metastases		(96, 156)	[51, 61, 82] (8, 116, 142)	[58] (96, 138)	[58] (157, 158)	[51, 54, 82, 89] (8, 142)		[54, 89] (109, 145)
Lung metastases			[61, 89] (8)			[54, 89] (8)		[54]
Brain metastases	[51]	[58]	[51, 61, 82, 89]	[58]		[82, 89]	(48)	[54, 104] (109, 145)
Number of metastases		(96)	[136] (116)	(96)		[51, 136] (109, 144)	(151)	[51, 145] (109, 144)
Other parameters of tumour extension	(142)		[69, 72, 82]	[56, 57]	[56, 57]	[54, 63, 69, 72, 82, 159] (109, 144)		[54, 63, 104, 152] (109, 144)
Associated lung infection					[160]	[72]		[72]
Other associated illness	[52]	[56, 57]	[52, 72, 89]	[56, 57]		[72, 89]		
Other (symptoms, physical & radiological signs, *etc*.	[52, 82]	[57]	[52, 55, 72, 82, 89]	[57, 65]	[65]	[52, 53, 55, 63, 69, 72, 82, 89]		[63, 69] (145)

* Reference numbers in square brackets refer to studies of [NSCLC/any cell type tumours]; numbers in parenthesis refer to studies of (pure SCLCs) ** according to definitions in the various studies. TNM: tumour, node, metastasis; ECOG: eastern cooperative oncology group

Table 9. – Miscellaneous*

	Nonsignificant**				Significant**			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	>200 pts	≤200 pts	>200 pts and/or ≤6 variables	≤200 pts and >6 variables	≤200 pts	>200pts	≤200 pts and/or ≤6 variables	>200 pts and >6 variables
Quality-of life subjective rating				[161]	[161, 162]	[163]	[162]	[163]
Gallium-76 scintigraphy		[164]			[165]			
Perioperative blood transfusion	[166]	[167]					[148]	
Respiratory function	[69, 72]		[69, 72, 89]			[52, 89]	[59]	[52]
Smoking history	[52, 69, 72, 136] (144)		[52, 69, 72, 136] (144)		(168)	[89, 91]	[91]	[89]
Treatment variables	[51, 166]		[51, 69]	[59]	[58, 108]	[63, 69, 72, 82, 136]	[30, 58, 108, 136, 148]	[55, 63, 72, 82]
		(110)		(110)	(90, 114, 150)		(47, 90, 150)	(144, 146)

* Reference numbers in square brackets refer to studies of [NSCLC/any cell type tumours], numbers in parentheses refer to studies of (pure SCLCs) ** according to definitions in the various studies.

NSCLC, and perhaps the number of metastatic sites. Weight loss has not been sufficiently evaluated in SCLC (only 2 negative studies), while in NSCLC it does have an important prognostic impact (10 significant univariate tests out of 13, plus 11 significant multivariate tests out of 17). In both NSCLC (3 positive out of 3 studies considering either univariate or multivariate tests) and SCLC (3 out of 5), the number of metastatic sites adds a little to the stage of disease, resulting informative also in multivariate tests. To be metastatic to a particular organ or to have any other sign of more widespread tumour involvement usually worsens the prognosis, but normally has no detrimental effect when the stage of disease is already accounted for. Interestingly enough, bacterial lung infections and postoperative infections seem to have an adverse effect on survival, while the other associated diseases, considered all together, have no recognizable effect (table 8).

Both younger and older ages are inconsistently reported to be associated with unfavourable outcomes (table 8). In NSCLC, age is probably a weak factor on its own (10 positive analyses out of 22), and its value disappears completely when other variables are taken into account (only 4 positive tests out of 23). In SCLC, it may be more predictive (5 positive studies out of 8 studies) and independent (6 out of 9).

The female sex appears to be a favourable, weak (7 positive studies out of 19 studies), and marginally independent (9 out of 23) determinant in NSCLC, as well as in SCLC (a total of 6 positive studies out of 10 studies).

With one exception [144], racial differences have never been found important. In a review of male patients treated at the Veteran Administration Hospitals between 1955 and 1964 [154], not only race, but also the income status were not related to the percentage of localized disease or survival.

Miscellaneous (table 9)

In spite of the previous eight chapters, there are still a number of factors, which cannot be classified easily. They are: subjective ratings of quality of life; gallium[67] uptake; perioperative blood transfusion; respiratory function testing; and smoking history. Table 9 contains the relevant references and indicates those studies, where pre-treatment factors were challenged in correlation with therapeutic variables. As already mentioned, the addition of these variables may affect the significance of the pre-treatment factors, on which this review is focused.

Except for two [144, 168], there are no SCLC studies in this group. The only factors that were sufficiently studied (such as respiratory functional testing, and smoking history) appear to be rather weak prognosticators (in all, 6 positive studies out of 14 studies), even if, in two large studies, either respiratory function or smoking habit emerged as significant variables among numerous other cofactors [52, 89]. Other unlikely or noninfluential factors appear to be the intensity of the *in vivo* Gallium[67] uptake and the perioperative execution of blood transfusions. The accumulation of the gallium radioisotope was measured semiquantitatively in a series of 74 diagnostic scintigraphies of NSCLC and claimed to be significantly correlated with the incidence of metastases and host survival [165]; however, a second, specifically designed study was unable to confirm the preliminary evidence [164]. Conflicting reports on the possible detrimental effect of perioperative blood transfusions [148, 166, 167], has only had the effect of advocating new prospective studies, in spite of the recognized difficulties [169].

Perhaps, the most promising variable in this group is the patient's subjective evaluation of his own quality of

life [161, 162]. Self-rated instruments of recording physical and psychosocial well-being might integrate the information of performance status [162].

Summary

The best predictive results, among the many mentioned in this paper, still belong to studies based on clinical and routine laboratory data. This explains the lack of significant progress, in spite of the sophisticated mathematical analyses and the dozens of variables tested.

The myriad of known and unknown prognostic factors of lung cancer bring to mind a universe of constellations already known and constellations yet to be discovered. Like infinity, the fate of individual patients will never become a completely measurable entity. However, as the discovery of new prognostic factors proceeds, the assessment of the future of patients is becoming more reliable. Recent research has clarified the role of new constellations of PFs (*e.g.*, biological factors); other constellations, seen indistinctly today, might be recognized as important in the future (*e.g.*, quality of life measures); while a number of new prognostic factors (*e.g.*, the pathological evidence of tumour neoangiogenesis or the serum content of acute-phase reaction proteins) are beginning to shine in the already known firmament. We hope that this necessarily brief and schematic overview has achieved the goal of offering an up-to-date, unbiased, and 360 degree-open picture of the entire cosmos of PFs of lung cancer.

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