PROGNOSTIC FACTORS

From the Cuneo Lung Cancer Study Group (www.culcasg.org), at the Unit of Respiratory Medicine, "S. Croce e Carle" Hospitals, Cuneo, Italy (*)

Authors:

1. Gianfranco Buccheri, M.D. (*) S.C. Pneumologia Ospedale "A Carle" Azienda Ospedaliera "S. Croce e Carle" Cuneo, I-12100, Italy Tel. 0039.0171.616733 Fax. 0039.0171.616724 e-mail: buccheri@culcasg.org	**2. Domenico Ferrigno, M.D. (*)** S.C. Pneumologia Ospedale "A. Carle" Azienda Ospedaliera "S. Croce e Carle" Cuneo, I-12100, Italy Tel. 0039.0171.616733 Fax. 0039.0171.616724 e-mail: ferrigno@culcasg.org

Correspondence to: Gianfranco Buccheri, MD

Key words: Lung cancer; adenocarcinoma; squamous cell carcinoma; prognostic factors; clinical factors; tumor biology; histopathology; tumor markers; coagulation abnormalities; traditional lab tests; quality of life; prognosis; survival

Text pages: 21
Tables: 3

Synopsis

Prognostic factors continue to play a critical role in explaining the outcome of patients with lung cancer. They are vital in many clinical tasks including individual advising, choosing among different treatment options, stratifying for groups of comparable risks -while designing new studies and interpreting the literature-, understanding the biological nature of the disease.

Traditionally, the anatomical extent of disease, the patient's performance status, and few other anthropometric variables are assumed all is needed for a reliable prognostic assessment. Especially in small cell lung cancer, but also in the advanced stages of non-small cell lung cancer, the use of simple biochemical tests is considered an additional valuable option. For years, serum tumor markers have been used to monitor the clinical course of lung cancer and their prognostic capability appears quite certain. More recently, newer biologic prognostic determinants have recalled the attention of researchers. Intriguing patient-related factors, such as a mental state of depression, might be recognized important in the future. Another factor of this group, the quality of life as a whole, is already supported by clear and indubitable evidence.

The life span of each individual patient will never be calculated mathematically as a physical unit, but, as new portions of the universe of prognostic factors are being explored, the approximation becomes increasingly satisfactorily.

Introduction

Lung cancer remains one of the most dreadful human tumors. Treatment is only marginally effective, and prognostic factors continue to play a critical role in explaining the outcome of patients. Failure to

appreciate the importance of prognostic factors may contribute to the design of inefficient studies, the wrong interpretation of results, and the development of an inconsistent literature. Prognostic factors are helpful in individual advising, treatment decision (especially when treatment options depend on the baseline characteristics of the subject), and disease understanding (certain factors provide insights into the disease process and directions for further studies).

A recent development of the research on prognostic factors is technical. Data-recording systems based on microcomputers are now widely available. Single institutions are capable to analyze their own data or to cumulate them into large multi-institutional files, simply by exchanging magnetic support media. As a result, the number of studies dealing with both newer and more traditional prognostic factors is proliferating. For example, the publications indexed in the Medline under the search items "lung, cancer, prognostic, factors" were 18 in 1980, 53 in 1985, 119 in 1990, 160 in 1995 and 275 in 2000! …

Unfortunately, the interpretation of this vast and continuously growing literature is not easy. (1) Attempts to analyze in a semi-quantitative manner the published data has been made by ourselves (2;3) and, more recently, by Brundage and colleagues. (1) Traditionally, the anatomical extent of disease, the patient's performance status, and few other anthropometric variables are believed to be all is needed for a reliable prognostic assessment. (4) Especially in small cell lung cancer, the use of simple biochemical tests is an additional option. (5;6) For years, serum tumor markers have been used to monitor the clinical course of lung cancer and their prognostic capability unequivocally proved. (7) Finally, newer tests, based on the experimental evidence arising in the laboratory at the cellular and molecular level, appear attracting (8;9).

In this review, we will list the principal prognostic factors for the advanced or metastatic non-small cell lung cancer (NSCLC), describing and commenting a few of the relevant studies. Table 1 shows a working classification of prognostic factors that will be used in this review.

Tumor-related factors of prognosis

Biological Factors

Evidence concerning biological factors is mostly limited to resected non-small cell lung cancer. However, data on patients with advanced stages of disease is obtainable from studies that reported patients in stage IIIa/IIIb at the time of operation. Biological prognostic factors are listed in Table 2. Mutation of the p53 tumor suppressor gene may be considered an established marker of poor survival among patients with NSCLC. Data from the literature is somewhat conflicting, (10) but at least three systematic reviews have confirmed the prognostic value of p53 alteration. (11-13) In one meta-analysis, (12) 43 articles were reviewed. Combined survival differences at 5 years were -9.1% ($p = 0.0091$) and -22.0% ($p = 0.0026$) in studies with, respectively, protein over-expression and gene mutation. However, the negative prognostic effect of p53 alteration was not significant in patients with squamous cell carcinoma. The authors concluded that, while p53 alteration is a significant marker of poor prognosis in patients with pulmonary adenocarcinoma, such alteration does not automatically provide information that can alter treatment decisions. (12)

Activation of K-ras gene by point mutations, a common finding in lung adenocarcinomas, may also decrease patient survival. In a classic study, (17) 19 of 69 tumors were found to harbor a point mutation in codon 12 of the K-ras oncogene. Tumors positive for K-ras point mutations tended to be

smaller and less differentiated than those without mutations. The K-ras codon-12 point mutation was a strong (and unfavorable) prognostic factor: 12 of the 19 patients with K-ras point-mutation-positive tumors died during the follow-up period, as compared with 16 of the 50 patients with no mutation in the K-ras oncogene ($p = 0.002$).

DNA content abnormalities have been described as a heterogeneous spectrum of impaired tumor cell DNA histogram patterns. They are merged into the common term of aneuploidy, probably reflecting a high genotypic instability. A meta-analysis of published studies identified 35 trials in the literature. (21) Among the 4033 cases reviewed, 2626 had aneuploid DNA content. Patients suffering from a nearly diploid tumor benefited from a significant reduction in risk of death. Patients who had surgical resection of a cancer with aneuploid DNA content had a higher risk of death.(21)

Histological, pathological and anatomical factors

Histological, pathological and anatomical factors of prognostic significance in the advanced NSCLC are listed in Table 2.

In addition to the last internationally adopted staging classification (60), it is clear that each single parameter that contains a measure of the anatomical burden of disease (e.g., the T and N factors, or the presence, type and number of metastatic sites) reflects prognosis. (2;61) Still today, the accurate assessment of the anatomical spread of disease remains the best and most reliable way to predict the patient's outcome.

Tumor histopathology classification provides the foundation for tumor diagnosis and patient therapy and a critical basis for epidemiological and clinical studies. The newly updated classification was developed with the aim to adhere to the principles of reproducibility, clinical significance, and simplicity.(62) However, although several tumor histotypes (e.g., the large cell neuroendocrine

carcinoma or the basaloid carcinoma) may be associated to a dismal prognosis, (62) the simple histologic classification does not appear to provide valuable and reproducible prognostic information. (2)

The evidence concerning the other prognostic factors of this group arises, again, from surgical series of patients who were postoperatively classified in stage IIIa/IIIb. The growth of newly formed vessels, or neoangiogenesis, represents an important step in both physiological and pathological situations: in particular, tumor growth and metastasis require angiogenesis. Microvessel optical count, the commonest measure of tumor angiogenesis, was evaluated in a series of 195 patients with stage I-IIIA non-small cell lung cancer (NSCLC). (36) In multivariate analysis, microvessel count was found to be the most powerful independent prognostic factor, with a relative hazard of 6.61 ($p < 0.00001$). (36) To assess the prognostic value of microvessel count, a systematic review of the literature was performed by the European Lung Cancer Working Party and recently reported.(37) Published studies were identified by an electronic search in order to aggregate survival results, after a methodological assessment that used a quality scale designed by the authors themselves. The study that reviewed several thousands of patient records confirmed that a high microvessel count in the primitive lung tumor is a statistically significant poor prognostic factor.(37)

The prognostic value of major blood vessel invasion was studied in 593 patients who had curative resection for NSCLC. (38) Histologic type, T and N status, peritumor lung tissue invasion, tumor stroma, necrosis, mitotic rate, and blo od vessel invasion were evaluated. Among such factors, only blood vessel invasion and, less significantly, T stage and lymph node metastasis were independent prognostic factors. (38) In a similar study, (41)other 96 surgical patients were considered for the prevalence of both blood and lymphatic vessel invasion. In univariate analysis, only the lymphatic

invasion was associated with a poor survival ($p = 0.0001$, estimated relative risk of death = 3.2). In multivariate analysis, lymphatic invasion and pTNM were additional predictors for poor disease free and overall survival.(41)

Serological factors (tumor markers)

Standard tumor markers (STM) are a group of substances that "mark" the presence of tumor, providing important information on its anatomical extension and biological aggressiveness. STM are easily, inexpensively and serially measurable in the lab from the sera (or other body fluids) of patients. STM consists of a variety of substances, including oncofetal proteins, structural proteins and their fragments, enzymes, membrane antigens, peptide and non-peptide hormones. Although they are the expression of particular tumor features, standard tumor markers are usually treated apart from the other biologic factors, privileging their characteristic of simple lab tests and their traditional classification. Table 2 lists a few STM, which appear to be the most important from the prognostic point of view.

Cytokeratins are well known structural proteins whose degradation gives rise to soluble fragments, measurable in the blood of patients and capable of cancer marking. Among them, Tissue Polypeptide Antigen (TPA), Tissue Polypeptide-Specific Antigen (TPS) and Cytokeratin-19-Fragments (Cyfra 21-1) are the most commonly studied CK fragments' complexes. The biological characteristics and clinical properties of these substances have been recently reviewed.(63) A clinical study designed to compare TPA and CA 125 tumor associated antigen in 384 lung cancer patients was recently reported.(45) Both TPA and CA 125 were strongly predictive of the patients' outcome, as assessed by the univariate analysis of survival (log-rank test: 37.24 and 29.01) and several Cox' proportional hazards regression models. (63) In another study, (49) the value of TPS and Cyfra 21-1 was compared, with reference

to diagnosis, staging, prognosis, and monitoring of 94 patients with NSCLC. Multivariate analysis of survival identified TPS and Cyfra 21-1 as significant predictors of survival, with relative risks of 2.57 ($p = 0.001$) and 2.05 ($p = 0.01$). The authors suggested that the combined use of these cytokeratin markers may provide additional information for prognosis.(49) Cyfra 21-1 and neuron specific enolase (NSE), the gamma-subunit of enolase, were evaluated as prognostic factors in a large French study, including 621 histologically proven and previously untreated NSCLC patients. (47) The authors reported the following variables to be independent determinants of poor outcome: low performance status, advanced nodal status, metastatic disease, Cyfra 21-1, advanced tumor status (T). When the survival analysis was restricted to 274 patients affected by a NSCLC in metastatic stage, NSE was an additional independent prognostic determinant.(47)

Carcinoembryonic antigen (CEA) is an oncofetal protein normally found in the embryonic and fetal gut and sometimes produced by malignant cells. It was discovered in 1965 by Gold and Freedman in patients with adenocarcinoma of the colon (64). In NSCLC, the prognostic value of CEA was first sanctioned by a consensus conference held at the National Institute of Health in 1980. (64) In 1994, 14 studies looking at CEA in NSCLC were reviewed. (2) Nine of the 14 studies proved CEA to have some prognostic significance. This prognostic capability was almost certain (thousands of patients and seven large studies provided information on the antigen), rather weak (not confirmed in any study with great statistical power), and no or minimally independent (no study including more than 6 prognostic factors found CEA significant within a multivariate approach).

In 1996, the risk of death was analyzed in 108 NSCLC patients with respect of TNM stage, histological type and CEA, CA125 antigen and squamous cell carcinoma antigen (SCC). (66) Multivariate analyses indicated that TNM stage and histological type had the best predictive power,

but serum CA125 and serum CEA contained additional, independent prognostic information. (66) A few years before, the same authors had assessed the prognostic value of pretreatment serum NSE in 84 NSCLC patients, as compared to 40 healthy controls, and 20 patients with benign pulmonary diseases. (58) Patients with a preoperative NSE level < 15 ng/ml had significantly longer 24-month survival than those whose initial levels were > 15 ng/ml (70 vs. 47%; $p < 0.05$), and this was confirmed after stratifying by TNM stage. (58)

Host related factors

Clinical, psychological and relational factors

The Karnofsky's index of performance status (KPS) (67)and the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) (68) are widely used methods of assessing the functional status of cancer patients. Whatever the scale, there is no doubt that performance status is one of the most efficient prognostic factors, also in NSCLC (Table 3).

Seventy-seven prognostic factors were considered in a classic report by the Veterans Administration Lung Group. (106) More than 5,000 patients with inoperable bronchogenic carcinoma of the lung, entered on the group protocols 9-15 (1968-78), were studied. Fifty prognostic factors for survival were identified, and their relative contributions to patient survival were considered. The three most important prognostic factors affecting survival were the Karnofsky initial performance status score, extent of disease, and weight loss in the previous 6 months. (106) In the mid-nineties, over 21 clinical studies were reviewed, in which performance status was consistently the second (after stage of disease) or the first significant co-factor of a multivariate equation of survival. (2) More recently, the

predictive validity of the two scales of performance status was compared. (69) Five hundred thirty-six consecutive lung cancer patients were assigned both KPS and ECOG PS scores before, during and after treatment (in all, 1656 assignments). It was found that KPS and ECOG performance status assignments were strongly related to each other (Spearman R = -0.869). Both univariate and multivariate analyses of survival documented the predictive validity of the two scales. However, KPS showed less ability than ECOG PS to discriminate patients with different prognosis. It was concluded that ECOG PS should be preferred to KPS, but a consensus on the scale to use would be important to avoid problems of conversion, which is not always easy and free of errors. (69)

Several studies have reported on the important role of symptoms of disease and quality of life (QL) scoring in predicting the survival of patients with lung carcinoma (Table 3). In this setting, a few specific components of QL (e.g., depressed mood) have been investigated more in depth (Table 3). QL scores (EORTC QLQ-C30) and symptom scores were obtained in a group of 198 patients treated with radiotherapy. (107) In a multivariate model of survival, global QL was the strongest prognostic factor, while performance status lost its significance. (107) The relationship between survival and QL, as measured by two distinct questionnaires, was examined within another group of 206 patients with advanced NSCLC, treated in a randomized clinical trial conducted by the Cancer and Leukemia Group B (CALGB). Univariate analyses showed that several patient-reported EORTC subscales, overall QL, and physical functioning predicted significantly survival. (108) In another study of 128 patients, (109) stage of disease, difficulty at work or doing the housework, weight loss, performance status, difficulty relaxing, having been felt unsure, and tumor cell type have been all found to be associated with prognosis. QL variables correlated well with each other, but poorly with clinical and

demographic variables, explaining why QL variables maintained their significance in multivariate analyses. (109)

In 133 patients with a newly diagnosed lung cancer, a depression index was calculated using the Self-rating Depression Scale (SDS), while 19 other prognostically important variables were recorded and available for evaluation. (73) The survival of patients with a depressed SDS index was significantly shorter (p=0.048). Diverse SDS subscales were correlated with survival, in either univariate or multivariate analysis. A multivariate model of survival, constructed using only SDS data, had a global Chi-squared value of 29.78, and a p-value of 0.00023. (73)

Body weight loss (WL) prior to the diagnosis has a clear and important impact on prognosis. For example, 7 of 10 univariate tests and 6 of 12 multivariate analyses were counted significant in a review of the literature. (2) A problem with WL arises from the various definitions currently in use. To address this issue, several different WL definitions were prospectively compared in 388 new consecutive lung cancer patients. (87) In univariate analysis, all WL variables were prognostically significant. Among them, total WL (the percent difference between the weight at diagnosis and the last weight recorded while in good health, dichotomized by the median level of 11%) was the most significant factor (log-rank: 29.65, p=0.0000). The best Cox's model for survival prediction was constructed using all the available clinical information and included, in order of importance, the following three factors: stage of disease classification, performance status and total WL. (87)

Gender has emerged as a discriminating factor in NSCLC outcome. The female sex appears to be a favorable, weak, and marginally independent prognostic determinant. In 1994, the evidence of female sex being a protective factor in NSCLC was reviewed. (2) Seven of 19 studies with univariate analysis, and 9 of 23 studies with multivariate analysis were significant. (2) More recently, a gender-

balanced sample of 152 cases was randomly selected for review from a tumor registry population of 368 NSCLC patients. (85) Study parameters were age, race, tobacco and alcohol history, gender, weight-loss pattern, histology, TNM stage, ECOG performance status, and therapy. Overall, median survival after diagnosis was significantly shorter for men than for women with the disease (40 vs. 78 weeks, $p = 0.001$). In multivariate analysis, the strongest independent predictors of NSCLC patient survival were stage of disease, initial weight-loss rate, and gender (all $p < 0.0001$). (85)

Hematological, biochemical and instrumental factors

Lactate dehydrogenase is certainly the strongest prognostic determinant of this group, whether considered alone or in combination with other prognostic factors (Table 3). In ten NSCLC studies (in all, 9 positive univariate tests and 6 positive multivariate analyses), the enzyme was found significantly or highly significantly survival-related. (2) A further effective and independent routine lab test is the determination of serum albumin concentration, which was significant in 8 of the12 studies reviewed (both in univariate and multivariate analysis).(2) Equally important factors, but only when evaluated on their own, are the plasmatic level of hemoglobin (6 significant univariate tests out of 7) and the white blood cell (WBC) count (4 significant univariate tests of 7). (2) An additional study of 1,052 patients with advanced non-small-cell lung cancer, registered onto one of seven trials conducted by the European Lung Cancer Working Party, (91)analyzed WBC counts, along with other 21 variables. In a first Cox regression model, the selected explanatory variables were disease extent, Karnofsky performance status, WBC and neutrophil counts, metastatic involvement of skin, serum calcium level, age, and sex; these results were confirmed then by application of recursive partitioning and amalgamation algorithms. (91)

In patients with NSCLC, thrombocytosis is well correlated with survival (Table 3). In a specifically designed study, (100) the prevalence of thrombocytosis was analyzed in a large cohort of patients with primary lung cancer (1,115 consecutive patients). The overall prevalence of thrombocytosis (> 400,000/mm^3) in patients with lung cancer was 32%. Platelet counts were significantly higher in advanced stage of disease (stage I and II: 23% vs stage III and IV: 37%; $p < 0.0001$). Patients with thrombocytosis had a significantly poorer survival than patients with normal platelet counts ($p < 0.0001$). In a multivariate survival analysis (Cox model), thrombocytosis continued to correlate strongly with poor survival even when adjusted for histological type, sex, age, and TNM stage ($p < 0.001$). Thrombocytosis was not associated with an increased incidence of thromboembolism. (100) An elevated plasma D-dimer level indicates activation of coagulation and fibrinolysis. Activation of the extrinsic coagulation system and the fibrinolytic cascade is frequent in cancer patients and is thought to be related with tumor growth, invasion and metastasis. (110) The largest evidence on the relationship between D-dimer and lung cancer prognosis arises from a study recently concluded and not yet published (93) In this study, 826 untreated lung cancer patients, seen over a 10-year period (1992-2001), were reviewed. For each patient, 31 variables were available for analysis. D-dimer was capable to separate patients with different outcomes: for patients with abnormal plasmatic levels of D-dimer, the median survival was 154 days (95% CI: 122-189), while for patients with normal levels it was 308 days (95% CI: 227-409, log-rank statistic: 26.56, $p<0.01$). The difference was greater in patients with adenocarcinoma or in subjects presenting with a less advanced disease, especially in pathologically staged Ia patients. The best multivariate survival model selected ten significant covariates, including D-dimer. (93)

Conclusions

The best predictive models of today can predict no more than 50% of the natural variability of the disease, in spite of the sophisticated mathematical analyses and the dozens of variables assessed. Clearly, a universe of still unknown prognostic factors remains to be discovered. In analogy with the measureless of the infinity, the fate of the individual patient will never be calculated mathematically. However, as the discovery of new prognostic factors goes on, the prediction of the outcome of patients becomes more reliable. Recent researches have introduced new groups of prognostic factors (e.g., molecular genetic markers and the sub-clinical activation of coagulation-fibrinolysis); other intriguing factors might be recognized to be important in the near future (e.g., a state of mental depression); while some others (e.g., tumor neoangiogenesis and quality of life) are already supported by a large evidence. A new small portion of the universe has been explored.

References

(1) Brundage MD, Davies D, Mackillop WJ. Prognostic Factors in Non-small Cell Lung Cancer(*) : A Decade of Progress. Chest 2002; 122(3):1037-1057.

(2) Buccheri G, Ferrigno D. Prognostic factors in lung cancer: tables and comments. Eur Respir J 1994; 7(7):1350-1364.

(3) Buccheri G. New prognostic factors in lung cancer. Monaldi Arch Chest Dis 1997; 52(6):535-539.

(4) Minna JD, Higgins GA, Glatstein EJ. Cancer of the lung. In: De Vita VT, Jr., Hellman S, Rosemberg SA, editors. Cancer. Principles and practice of oncology. Philadelphia: J.B. Lippincott Co., 1985: 507-597.

(5) Cohen MH, Makuch R, Johnston-Early A, Ihde DC, Bunn PAJr, Fossieck BEJr et al. Laboratory parameters as an alternative to performance status in prognostic stratification of patients with small cell lung cancer. Cancer Treat Rep 1981; 65:187-195.

(6) Vincent MD, Ashley SE, Smith IE. Prognostic factors in small cell lung cancer: a simple prognostic index is better than conventional staging. Eur J Cancer Clin Oncol 1987; 23:1589-1599.

(7) Ferrigno D, Buccheri G, Biggi A. Serum tumour markers in lung cancer: history, biology and clinical applications. Eur Respir J 1994; 7(1):186-197.

(8) Mountain CF. New prognostic factors in lung cancer: Biologic prophets of cancer cell aggression. Chest 1995; 108:246-254.

(9) Smit EF, Groen HJM, Splinter TAW, Ebels T, Postmus PE. New prognostic factors in resectable non-small cell lung cancer. Thorax 1996; 51:638-646.

(10) Schiller JH, Adak S, Feins RH, Keller SM, Fry WA, Livingston RB et al. Lack of Prognostic Significance of p53 and K-ras Mutations in Primary Resected Non-Small-Cell Lung Cancer on E4592: A Laboratory Ancillary Study on an Eastern Cooperative Oncology Group Prospective Randomized Trial of Postoperative Adjuvant Therapy. J Clin Oncol 2001; 19(2):448-457.

(11) Steels E, Paesmans M, Berghmans T, Branle F, Lemaitre F, Mascaux C et al. Role of p53 as a prognostic factor for survival in lung cancer: a systematic review of the literature with a meta-analysis. Eur Respir J 2001; 18(4):705-719.

(12) Mitsudomi T, Hamajima N, Ogawa M, Takahashi T. Prognostic significance of p53 alterations in patients with non-small cell lung cancer: a meta-analysis. Clin Cancer Res 2000 Oct ;6 (10):4055 -63 2000; 6:4055-4063.

(13) Huncharek M, Kupelnick B, Geschwind JF, Caubet JF. Prognostic significance of p53 mutations in non-small cell lung cancer: a meta-analysis of 829 cases from eight published studies. Cancer Lett 2000 May 29 ;153 (1-2):219 -26 2000; 153:219-226.

(14) Huang CL, Taki T, Adachi M, Konishi T, Higashiyama M, Kinoshita M et al. Mutations of p53 and K-ras genes as prognostic factors for non-small cell lung cancer. Int J Oncol 1998; 12(3):553-563.

(15) Fujino M, Dosaka-Akita H, Harada M, Hiroumi H, Kinoshita I, Akie K et al. Prognostic significance of p53 and *ras* p21 expression in nonsmall cell lung cancer. Cancer 1995; 76:2457-2463.

(16) Lee JS, Yoon A, Kalapurakal SK, Ro JY, Lee JJ, Tu N et al. Expression of p53 oncoprotein in non-small-cell lung cancer: A favorable prognostic factor. J Clin Oncol 1995; 13:1893-1903.

(17) Slebos RJC, Kibbellaar RE, Dalesio O, Kooistra A, Stam J, Meijer GJL et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N Engl J Med 1990; 323:561-565.

(18) Nemunaitis J, Klemow S, Tong A, Courtney A, Johnston W, Mack M et al. Prognostic value of K-ras mutations, ras oncoprotein, and c-erb B-2 oncoprotein expression in adenocarcinoma of the lung. Am J Clin Oncol 1998; 21(2):155-160.

(19) Miyamoto H, Harada M, Isobe H, Akita HD, Haneda H, Yamaguchi E et al. Prognostic value of nuclear DNA content and expression of the ras oncogene product in lung cancer. Cancer Res 1991; 51(23 Pt 1):6346-6350.

(20) Meert AP, Martin B, Delmotte P, Berghmans T, Lafitte JJ, Mascaux C et al. The role of EGF-R expression on patient survival in lung cancer: a systematic review with meta-analysis. Eur Respir J 2002 Oct ;20 (4):975 -81 2002; 20:975-981.

(21) Choma D, Daures JP, Quantin X, Pujol JL. Aneuploidy and prognosis of non-small-cell lung cancer: a meta-analysis of published data. Br J Cancer 2001 Jul 2001;14-22.

(22) Dazzi H, Thatcher N, Hasleton PS, Swindell R. DNA analysis by flow cytometry in nonsmall cell lung cancer: relationship to epidermal growth factor receptor,histology,tumour stage and survival. Respir Med 1990; 84:217-223.

(23) Isobe H, Miyamoto H, Shimizu T, Haneda H, Hashimoto M, Inoue K et al. Prognostic and therapeutic significance of the flow cytometric nuclear DNA content in non-small cell lung cancer. Cancer 1990; 65:1391-1395.

(24) Shi D, He G, Cao S, Pan W, Zhang HZ, Yu D et al. Overexpression of the c-erbB-2/neu-encoded p185 protein in primary lung cancer. Mol Carcinog 1992; 5(3):213-218.

(25) Kern JA, Schwartz DA, Nordberg JE, altro1, altro2, altro3 et al. p185 (neu) Expression in human lung adenocarcinomas predicts shortened survival. Cancer Res 1990; 56:5184-5191.

(26) Yi ES, Harclerode D, Gondo M, Stephenson M, Brown RW, Younes M et al. High c-erbB-3 protein expression is associated with shorter survival in advanced non-small cell lung carcinomas. Mod Pathol 1997; 10(2):142-148.

(27) Pezzella F, Turley H, Kuzu I, Tungekar MF, Dunnill MS, Pierce CB et al. bcl-2 protein in non-small-cell lung carcinoma. N Engl J Med 1993; 329(10):690-694.

(28) Hirata S, Kubo Y, Kokubo T, Kitada M, Nosaka T. [Expression of major histocompatibility complex of advanced non-small cell lung cancer (NSCLC)]. Nippon Kyobu Geka Gakkai Zasshi 1996; 44(2):138-143.

(29) Yuan A, Yu CJ, Chen WJ, Lin FY, Kuo SH, Luh KT et al. Correlation of total VEGF mRNA and protein expression with histologic type, tumor angiogenesis, patient survival and timing of relapse in non-small-cell lung cancer. Int J Cancer 2000; 89(6):475-483.

(30) O'Byrne KJ, Koukourakis MI, Giatromanolaki A, Cox G, Turley H, Steward WP et al. Vascular endothelial growth factor, platelet-derived endothelial cell growth factor and angiogenesis in non-small-cell lung cancer. Br J Cancer 2000; 82(8):1427-1432.

(31) Pence JC, Kerns BJ, Dodge RK, Iglehart JD. Prognostic significance of the proliferation index in surgically resected non-small-cell lung cancer. Arch Surg 1993; 128(12):1382-1390.

(32) Buccheri G, Marino P, Preatoni A, Ferrigno D, Moroni GA. Soluble interleukin 2 receptor in lung cancer. An indirect marker of tumor activity? Chest 1991; 99:1433-1437.

(33) Lee JS, Ro JY, Sahin AA, Hong WK, Brown BW, Mountain CF et al. Expression of blood-group antigen A. A favorable prognostic factor in non-small-cell lung cancer. N Engl J Med 1991; 324:1084-1090.

(34) Ulger AF, Keklik T, Kumbasar OO, Arbak P, Demirkazyk A, Gungor A et al. Prognostic significance of blood group antigen expression of tumor tissue in lung cancer patients. Tumori 2002 Sep -Oct ;88 (5):395 -9 2002; 88:395-399.

(35) Fontanini G, Bigini D, Vignati S, Basolo F, Mussi A, Lucchi M et al. Microvessel count predicts metastatic disease and survival in non-small cell lung cancer. J Pathol 1995; 177(1):57-63.

(36) Fontanini G, De Laurentiis M, Vignati S, Chine S, Lucchi M, Silvestri V et al. Evaluation of epidermal growth factor-related growth factors and receptors and of neoangiogenesis in completely resected stage I-IIIA non-small-cell lung cancer: amphiregulin and microvessel count are independent prognostic indicators of survival. Clin Cancer Res 1998; 4(1):241-249.

(37) Meert AP, Paesmans M, Martin B, Delmotte P, Berghmans T, Verdebout JM et al. The role of microvessel density on the survival of patients with lung cancer: a systematic review of the literature with meta-analysis. Br J Cancer 2002 Sep 23;87 (7):694 -701 2002; 87:694-701.

(38) Kessler R, Gasser B, Massard G, Roeslin N, Meyer P, Wihlm JM et al. Blood vessel invasion is a major prognostic factor in resected non-small cell lung cancer. Ann Thorac Surg 1996; 62(5):1489-1493.

(39) Matsuyama K, Chiba Y, Sasaki M, Tanaka H, Muraoka R, Tanigawa N. Tumor angiogenesis as a prognostic marker in operable non- small cell lung cancer. Ann Thorac Surg 1998; 65:1405-1409.

(40) Sorensen JB, Hirsch FR, Olsen J. The prognostic implication of histopathologic subtyping of pulmonary adenocarcinoma according to the classification of the World Health Organization. An analysis of 259 consecutive patients with advanced disease. Cancer 1988; 62:361-367.

(41) Brechot JM, Chevret S, Charpentier MC, Appere d, V, Capron F, Prudent J et al. Blood vessel and lymphatic vessel invasion in resected nonsmall cell lung carcinoma. Correlation with TNM stage and disease free and overall survival. Cancer 1996; 78(10):2111-2118.

(42) Fujisawa T, Yamaguchi Y, Saitoh Y, Hiroshima K, Ohwada H. Blood and lymphatic vessel invasion as prognostic factors for patients with primary resected nonsmall cell carcinoma of the lung with intrapulmonary metastases. Cancer 1995; 76:2464-2470.

(43) Lee TK, Horner RD, Silverman JF, Chen YH, Jenny C, Scarantino CW. Morphometric and morphologic evaluations in stage III non-small cell lung cancers. Prognostic significance of quantitative assessment of infiltrating lymphoid cells. Cancer 1989; 63(2):309-316.

(44) Buccheri G. Tumor Markers: Clinical Meaning and Use. In: Brambilla C, Brambilla E, editors. Lung Tumors. New York: Marcel Dekker, Inc., 1999: 435-452.

(45) Buccheri G, Ferrigno D. Lung tumour markers in oncology practice: a study of TPA and CA125. Br J Cancer 2002 Nov 4;87 (10):1112 -8 2002; 87:1112-1118.

(46) Reinmuth N, Brandt B, Semik M, Kunze WP, Achatzy R, Scheld HH et al. Prognostic impact of Cyfra21-1 and other serum markers in completely resected non-small cell lung cancer. Lung Cancer 2002; 36(3):265-270.

(47) Pujol J, Boher J, Grenier J, Quantin X. Cyfra 21-1, neuron specific enolase and prognosis of non-small cell lung cancer: prospective study in 621 patients. Lung Cancer 2001; 31(2-3):221-231.

(48) Bergqvist M, Brattström D, Hesselius P, Wiklund B, Silen A, Wagenius G et al. Cytokeratin 8 and 18 fragments measured in serum and their relation to survival in patients with non-small cell lung cancer. Anticancer Res 1999; 19(3A):1833-1836.

(49) Nisman B, Lafair J, Heching N, Lyass O, Baras M, Peretz T et al. Evaluation of tissue polypeptide specific antigen, CYFRA 21-1, and carcinoembryonic antigen in nonsmall cell lung carcinoma - Does the combined use of cytokeratin markers give any additional information. Cancer 1998; 82:1850-1859.

(50) Ray P, Quantin X, Grenier J, Pujol JL. Predictive factors of tumor response and prognostic factors of survival during lung cancer chemotherapy. Cancer Detect Prev 1998; 22(4):293-304.

(51) Hirashima T, Takada M, Komiya T, Nitta T, Masashi K, Masuda N et al. Prognostic significance of CYFRA 21-1 in non-small cell lung cancer. Anticancer Res 1998; 18(6B):4713-4716.

(52) Pujol JL, Grenier J, Parrat E, Lehmann M, Lafontaine T, Quantin X et al. Cytokeratins as serum markers in lung cancer: a comparison of CYFRA 21- 1 and TPS. Am J Respir Crit Care Med 1996; 154(3 Pt 1):725-733.

(53) Salgia R, Harpole D, Herndon JE, Pisick E, Elias A, Skarin AT. Role of serum tumor markers CA 125 and CEA in non-small cell lung cancer. Anticancer Res 2001; 21(2B):1241-1246.

(54) Sanchez De Cos J, Masa F, De la Cruz JL, Disdier C, Vergara C. Squamous cell carcinoma antigen (SCC Ag) in the diagnosis and prognosis of lung cancer. Chest 1994; 105:773-776.

(55) Díez M, Torres A, Maestro ML, Ortega MD, Gómez A, Pollán M et al. Prediction of survival and recurrence by serum and cytosolic levels of CEA, CA125 and SCC antigens in resectable non- small-cell lung cancer. Br J Cancer 1996; 73:1248-1254.

(56) Diez M, Torres A, Pollán M, Gomez A, Ortega D, Maestro ML et al. Prognostic significance of serum CA 125 antigen assay in patients with non-small cell lung cancer. Cancer 1994; 73:1368-1376.

(57) Pujol J-L, Cooper EH, Lehmann M, Purves DA, Dan-Aouta M, Midander J et al. Clinical evaluation of serum tumour marker CA 242 in non- small cell lung cancer. Br J Cancer 1993; 67:1423-1429.

(58) Diez M, Torres A, Ortega L, Maestro M, Hernando F, Gomez A et al. Value of serum neuron specific enolase in nonsmall cell lung cancer. Oncology 50, 127-131. 1993.
Ref Type: Journal (Full)

(59) Niklinski J, Furman M, Laudanski J, Kozlowski M. Prognostic value of pretreatment CEA, SCC-Ag and CA 19-9 levels in sera of patients with non-small cell lung cancer. Eur J Cancer Prev 1992; 1:401-406.

(60) Mountain CF. Revisions in the International System for Staging Lung Cancer [see comments]. Chest 1997; 111:1710-1717.

(61) Buccheri G, Ferrigno D. Prognostic value of stage grouping and TNM descriptors in lung cancer. The European Respiratory Journal 16 (Supplement 31), 362s. 2000.
Ref Type: Abstract

(62) Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. Eur Respir J 2001; 18(6):1059-1068.

(63) Buccheri G, Ferrigno D. Cytokeratin-derived markers of lung cancer. Expert Rev Mol Diagn 2001; 1(3):315-322.

(64) Gold P, Freedman SO. Demonstration of tumor-specific antigenin in human colonic carcinomata by immunological toleramce and absorption techniques. J Exp Med 1965; 121:439-462.

(65) N.H.I. Carcinoembryonic antigen: its role as a marker in the management of cancer. Br Med J 1981; 1:282-373.

(66) Diez M, Torres A, Maestro ML, Ortega MD, Gomez A, Pollan M et al. Prediction of survival and recurrence by serum and cytosolic levels of CEA, CA125 and SCC antigens in resectable non-small-cell lung cancer. Br J Cancer 1996; 73(10):1248-1254.

(67) Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, editor. Evaluation of chemotherapeutic agents. New York: Columbia University Press, 1949: 199-205.

(68) Zubrod CG, Scheiderman MA, Frei E, Brindley C, Gold LG, Shnider B et al. Appraisal of methods for the study of chemotherapy in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. J Chron Dis 1960; 11:7-33.

(69) Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer 1996; 32A(7):1135-1141.

(70) Nakahara Y, Mochizuki Y, Miyamoto Y, Tanaka A, Kawamura T, Sasaki S et al. Mental state as a possible independent prognostic variable for survival in patients with advanced lung carcinoma. Cancer 2002; 94(11):3006-3015.

(71) Stommel M, Given BA, Given CW. Depression and functional status as predictors of death among cancer patients. Cancer 2002; 94(10):2719-2727.

(72) Faller H, Bülzebruck H, Drings P, Lang H. Coping, distress, and survival among patients with lung cancer. Arch Gen Psychiatry 1999; 56(8):756-762.

(73) Buccheri G. Depressive reactions to lung cancer are common and often followed by a poor outcome. Eur Respir J 1998; 11(1):173-178.

(74) Mizushima Y, Kashii T, Yoshida Y, Sugiyama S, Kobayashi M. Characteristics of lung cancer in the elderly. Anticancer Res 1996; 16:3181-3184.

(75) Buccheri G, Ferrigno D. Delay in specialist referral and clinical presentation in lung cancer: a 14-year study with 1277 patients. Thorax 2003; (submitted).

(76) Montazeri A, Milroy R, Hole D, McEwen J, Gillis CR. Quality of life in lung cancer patients. As an important prognostic factor. Lung Cancer 2001; 31(2-3):233-240.

(77) Langendijk H, Aaronson NK, de Jong JM, ten Velde GP, Muller MJ, Wouters M. The prognostic impact of quality of life assessed with the EORTC QLQ-C30 in inoperable non-small cell lung carcinoma treated with radiotherapy. Radiother Oncol 2000; 55(1):19-25.

(78) Herndon JE, II, Fleishman S, Kornblith AB, Kosty M, Green MR, Holland J. Is quality of life predictive of the survival of patients with advanced nonsmall cell lung carcinoma? Cancer 1999; 85(2):333-340.

(79) Wigren T, Oksanen H, Kellokumpu-Lehtinen P. A practical prognostic index for inoperable non-small-cell lung cancer. J Cancer Res Clin Oncol 1997; 123:259-266.

(80) Buccheri GF, Ferrigno D, Tamburini M, Brunelli C. The patient's perception of his own quality of life might have an adjunctive prognostic significance in lung cancer. Lung Cancer 1995; 12(1-2):45-58.

(81) Ganz PA, Lee JJ, Siau J. Quality of life assessment. An independent prognostic variable for survival in lung cancer. Cancer 1991; 67:3131-3135.

(82) Feinstein AR, Wells CK. A clinical-severity staging system for patients with lung cancer. Medicine 1990; 69:1-33.

(83) Kaasa S, Mastekaasa A, Lund E. Prognostic factors for patients with inoperable non-small cell lung cancer, limited disease. The importance of patients' subjective experience of disease and psychosocial well-being. Radiother Oncol 1989; 15:235-242.

(84) Sorensen JB, Badsberg JH, Olsen J. Prognostic factors in inoperable adenocarcinoma of the lung: a multivariate regression analysis of 259 patients. Cancer Res 1989; 49:5748-5754.

(85) Palomares MR, Sayre JW, Shekar KC, Lillington LM, Chlebowski RT. Gender influence on weight-loss pattern and survival of nonsmall cell lung carcinoma patients. Cancer 1996; 78(10):2119-2126.

(86) Ferrigno D, Buccheri G. Anthropometric measurements in non-small-cell lung cancer. Support Care Cancer 2001 Oct ;9 (7):522 -7 2001; 9:522-527.

(87) Buccheri G, Ferrigno D. Importance of weight loss definition in the prognostic evaluation of non-small-cell lung cancer. Lung Cancer 2001; 34(3):433-440.

(88) Page WF, Kuntz AJ. Racial and socioeconomic factors in cancer survival. A comparison of veterans administration results with selected studies. Cancer 1980; 45:1029-1040.

(89) Naughton MJ, Herndon JE, Shumaker SA, Miller AA, Kornblith AB, Chao D et al. The health-related quality of life and survival of small-cell lung cancer patients: results of a companion study to CALGB 9033. Qual Life Res 2002 May ;11(3):235 -48 2002; 11:235-248.

(90) Gislason T, Nou E. Sedimentation rate, leukocytes, platelet count and haemoglobin in bronchial carcinoma: an epidemiological study. Eur J Resp Dis 1985; 60:141-146.

(91) Paesmans M, Sculier JP, Libert P, Bureau G, Dabouis G, Thiriaux J et al. Prognostic factors for survival in advanced non-small-cell lung cancer: Univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1, 052 patients. J Clin Oncol 1995; 13:1221-1230.

(92) Ferrigno D, Buccheri G, Camilla T. Prognosis and lung cancer: the contribution of plasma proteins. Oncol Rep 1995; 2:637-641.

(93) Buccheri G, Torchio P, Ferrigno D. Plasmatic levels of D-dimer in lung cancer: clinical and prognostic significance. Cancer 2003; (in press).

(94) Pavey SJ, Hawson GA, Marsh NA. Impact of the fibrinolytic enzyme system on prognosis and survival associated with non-small cell lung carcinoma. Blood Coagul Fibrinolysis 2001; 12(1):51-58.

(95) Ferrigno D, Buccheri G, Ricca I. Prognostic significance of blood coagulation tests in lung cancer. Eur Respir J 2001; 17(4):667-673.

(96) Taguchi O, Gabazza EC, Yasui H, Kobayashi T, Yoshida M, Kobayashi H. Prognostic significance of plasma D-dimer levels in patients with lung cancer. Thorax 1997; 52:563-565.

(97) Buccheri G, Ferrigno D, Ginardi C, Zuliani C. Haemostatic abnormalities in lung cancer: prognostic implications [see comments]. Eur J Cancer 1997; 33(1):50-55.

(98) Seitz R, Rappe N, Kraus M, Immel A, Wolf M, Maasberg M et al. Activation of coagulation and fibrinolysis in patients with lung cancer: relation to tumour stage and prognosis. Blood Coagul Fibrinolysis 1993; 4(2):249-254.

(99) Cox G, Walker RA, Andi A, Steward WP, O'Byrne KJ. Prognostic significance of platelet and microvessel counts in operable non-small cell lung cancer [In Process Citation]. Lung Cancer 2000; 29(3):169-177.

(100) Pedersen LM, Milman N. Prognostic significance of thrombocytosis in patients with primary lung cancer. Eur Resp J 1996; 9:1826-1830.

(101) Ferrigno D, Buccheri G, Camilla T. Serum copper and zinc content in non-small cell lung cancer: abnormalities and clinical correlates. Monaldi Arch Chest Dis 1999; 54(3):204-208.

(102) Ferrigno D, Buccheri G. A comprehensive evaluation of serum ferritin levels in lung cancer patients. Lung Cancer 1992; 8:85-94.

(103) Ahuja V, Coleman RE, Herndon J, Patz EF, Jr. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with nonsmall cell lung carcinoma. Cancer 1998; 83(5):918-924.

(104) Dunagan DP, Chin R, McCain TW, Case LD, Harkness BA, Oaks T et al. Staging by Positron Emission Tomography Predicts Survival in Patients With Non-small Cell Lung Cancer. Chest 2001; 119(2):333-339.

(105) Jeong HJ, Min JJ, Park JM, Chung JK, Kim BT, Jeong JM et al. Determination of the prognostic value of [(18)F]fluorodeoxyglucose uptake by using positron emission tomography in patients with non-small cell lung cancer. Nucl Med Commun 2002 Sep ;23(9):865 -70 2002; 23:865-870.

(106) Stanley KE. Prognostic factors for survival in patients with inoperable lung cancer. J Natl Cancer Inst 1980; 65(1):25-32.

(107) Langendijk H, Aaronson NK, de Jong JM, ten Velde GP, Muller MJ, Wouters M. The prognostic impact of quality of life assessed with the EORTC QLQ-C30 in inoperable non-small cell lung carcinoma treated with radiotherapy. Radiother Oncol 2000; 55(1):19-25.

(108) Herndon JE, II, Fleishman S, Kornblith AB, Kosty M, Green MR, Holland J. Is quality of life predictive of the survival of patients with advanced nonsmall cell lung carcinoma? Cancer 1999; 85(2):333-340.

(109) Buccheri GF, Ferrigno D, Tamburini M, Brunelli C. The patient's perception of his own quality of life might have an adjunctive prognostic significance in lung cancer. Lung Cancer 1995; 12(1-2):45-58.

(110) Falanga A. Mechanism of hypercoagulation in malignancy and during chemotherapy. Haemostasis 1998; 28(Suppl S3):50-60.

Table 1

Prognostic factors in NSCLC patients

Tumor-related factors	Biological

	Histopathological Anatomical Serological
Host-factors	Clinical Psychological and relational Hematological and biochemical Instrumental

Table 2

TUMOR-RELATED FACTORS

Biological Factors

Certain or nearly certain	Probable or fairly probable	Possible
P53 tumor suppressor gene [10-16]	K-ras gene mutation [10;14;17-19]	c-erbB-1 gene or EGF-R overexpression [20]
	DNA ploidy [19;21-23]	c-erbB-2 or HER-2/neu gene amplification [24;25]
		c-erbB-3 gene amplification [26]
		bcl-2 gene amplification [27]
		PCNA [28]
		VEGF [29;30]
		Ki-67 proliferation antigen [31]
		s-IL2r [32]
		Blood-group Antigen A expression [33;34]

Histological, pathological and anatomical factors

Certain or nearly certain	Probable or fairly probable	Possible
Parameters of disease extent [2]	Vessel density [30;35-39]	Adenocarcinoma sub-types [40]
	Vessel invasion [38;41;42]	Peri-tumor lymphoid infiltration [43]

Serological factors (standard tumor markers)

Certain or nearly certain	Probable or fairly probable	Possible
Cytokeratin markers [2;44-52]	CEA [2;44;53]	SCC-Ag [54]
	CA 125 [45;55;56]	CA 242 [57]
	NSE [47;58]	CA 19-9 [59]

Abbreviations:

EGF-R: epidermal growth factor receptor; PCNA: proliferating cell nuclear antigen; VEGF: vascular endothelial growth factor; s-IL2r: soluble interleukin-2 receptors; CEA: carcinoembryonic antigen; SCC-Ag: squamous cell carcinoma antigen; CA: cancer antigen; NSE: neuron specific enolase.

Table 3

HOST-RELATED FACTORS

Clinical, Psychological and Relational Factors		
Certain or nearly certain	**Probable or fairly probable**	**Possibile**
Performance status (2;69)	**Depressed mood** (70-73)	**Age** (2;74)
Symptoms & quality of life (75-84)	**Sex** (2;85)	**Anthropometric measures (body mass)** (86)
Weight loss (2;87)		**Race & socioeconomic status** (88;89)
		Marital status (81)
Hematological, biochemical and instrumental factors		
Certain or nearly certain	**Probable or fairly probable**	**Possible**
LDH (2)	**Hemoglobin blood content** (2) (79)	**ERS** (90)
Albumin (2)	**Leukocyte count** (2;91)	**Total serum proteins** (92)
D-dimer (93-98)	**Platelet count** (95;99;100)	**Cu, Zn serum content** (101)
		Other coagulation factors (95;97)
		Ferritin (102)
		Hypercalcemia (91)
		PET- scanning (103-105)

Abbreviations:

LDH: lactate dehydrogenase; ERS: erythrocyte sedimentation rate; Cu: cupper; Zn: zinc; PET: positron emission tomography.