The Impact of Additional Prognostic Factors on Survival and their Relationship with the Anatomical Extent of Disease Expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the Proposals for the 7th Edition

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Purpose: To identify, in the international staging database of the International Association for the Study of Lung Cancer, those prognostic factors that were significant and independent of clinical stage.

Material and Methods: From the data submitted to the staging data base concerning 100,869 patients, cases were selected for which all the following variables were available: clinical stage, age, gender, performance status (PS), and histologic cell types. For non-small cell lung cancer (NSCLC), 12,428 patients were assessable, and for SCLC, 6609 patients were available for this study. Methods used were Cox regression analyses and recursive partitioning and amalgamation analyses.

Results: PS appeared to be a very important prognostic factor for survival in addition to clinical stage. Age and gender were other independent significant variables; For NSCLC and SCLC separately, recursive partitioning and amalgamation allowed the identification of four groups of patients with differing prognoses. In advanced NSCLC (stage IIIB / IV), some routine laboratory tests (mainly white blood cells and hypercalcaemia) were also found to be significant prognostic variables. In SCLC, albumin was an independent biologic prognostic factor.

Conclusion: In addition to stage, PS and, to a lesser extent, age and gender seem to be important prognostic factors for survival in lung cancer. Although this data was obtained from the largest series ever used for such an analysis in lung cancer, these prognostic factors and models require confirmation in the prospective study already planned by the International Association for the Study of Lung Cancer Lung Cancer Staging Project.

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The International Association for the Study of Lung Cancer (IASLC) International Staging Committee (ISC) has submitted proposals for revision of the tumor, node, metastasis (TNM) descriptors[1–4] and stage groupings[5] for lung cancer in the forthcoming (7th) edition of the International Union Against Cancer and American Joint Committee on Cancer TNM Classification of Malignant Tumors. The suggestions are based on survival analyses that show better discrimination is achieved by these changes to the TNM descriptors and stage groupings. These proposals were developed using a very large database that was specifically collected from individual databases for that purpose.[1] The prognostic factors subcommittee of the ISC analyzed in the retrospective ISC database the role of additional prognostic factors for survival, whether related to the tumor or patient characteristics.

METHODS

We describe here the methods specifically used for the purpose of the present study, which is the identification of significant independent prognostic factors for survival in addition to the anatomic extent of disease, expressed by TNM. The general methodology of the IASLC Lung Cancer Staging Project and the major proposals have already been published.[1–6]

Population

The total number of patients submitted to the staging data basis was 100,869 of whom 81,015 remained eligible for

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TABLE 1. Potentially Useful Prognostic Variables for Lung Cancer Survival

Tumor characteristics: localization of metastatic sites: brain, liver, adrenals, bone, lung; number of metastatic sites; pleural effusion; type of lesions (assessable, measurable); tumor size and volume; histology: non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC); squamous cell carcinoma versus adenocarcinoma versus large cell carcinoma . . .; neuroendocrine tumors; tumor differentiation and grade; lymphatic and blood vessel invasion; symptoms; fluorodeoxyglucose positron emission tomography (FDG-PET) scan findings

Patients characteristics: age; gender; performance status (PS); weight loss; smoking history; race; comorbidities (Charslon's index, Colinet's simplified comorbidity score)

Laboratory parameters: serum bilirubin; serum calcium; serum sodium; serum creatinine; hemoglobinemia; leucocytosis; neutrophilia; platelets; serum alkaline phosphatases; sGOT; sGPT; serum albumin; serum CEA; serum LDH; serum NSE; serum CYFRA

Tumor biology: individual markers (p53; bcl-2; microvascular density; VEGF; EGFR; c-erbB-2; Ki-67; Ras; COX2; TTF1; aneuploidy), genetic signatures

analysis after exclusion of cases outside the study period (1990–2000), those with unknown cell type, those not newly diagnosed at the point of entry and those with inadequate information on stage, treatment or follow-up. Of the eligible patients there were 67,725 cases of non-small cell lung cancer (NSCLC) and 13,290 with SCLC.

Among the potentially useful prognostic variables for lung cancer survival (Table 1), data for many were not available in the IASLC staging project database, such as those related to tumor biology or the role of fluorodeoxyglucose position emission tomography (FDG-PET) scanning. For this reason, we had to restrict our analysis to those variables for which we had enough information in a significant number of patients. These included clinical stage, expressed as TNM for NSCLC and limited disease (LD) versus extensive disease (ED) for SCLC (defined by the local institution), age, gender, performance status (PS), and histologic cell type. For NSCLC, 12,428 patients with stage I–IV were assessable and for SCLC, 6609 (3739 with ED and 2870 with LD). For smaller subsets of SCLC and advanced stage NSCLC, we had laboratory values: serum calcium, serum albumin, serum sodium, hemoglobin, and white blood cell count (WBC).

Statistical Analysis

Survival was measured from the date of entry (date of diagnosis for registries, date of registration for trials) for clinically staged data and was calculated by the Kaplan-Meier method. Prognostic groups were assessed by Cox regression analysis, using the SAS system for windows version 9.0 PHREG procedure.

Recursive partitioning and amalgamation (RPA) analyses were performed to generate tree-based models by stage plus the key prognostic factors; age, gender, PS, and, for NSCLC only, cell type. The analyses were performed on a randomly selected training set comprising two-thirds of the available cases, reserving the remaining cases for later validation. Separate training and validation sets were established for NSCLC and SCLC. The random selection processes were stratified by type of database submission (clinical trials, registries, consortia/surgical series) and time period of case entry (1990–1995 versus 1995–2000).

The RPA analysis generated tree-based models for the survival data using logrank test statistics for recursive partitioning, for selection of the important groupings and bootstrap resampling to correct for the adaptive nature of the splitting algorithm. The terminal nodes were then grouped according to similar hazards and the newly formed groups were in each case evaluated using the remaining one-third of the data.

Laboratory values were first checked for consistency of the units used by laboratories across the contributing databases, and queries or corrections were made where necessary. When viewing survival prognosis for each laboratory measure as a continuous variable in a running logrank test, we found that the best split point for the data for prognosis was consistently at the defined upper or lower limits of normal. Therefore each result was defined dichotomously based on the known normal range for each laboratory measurement. Using these cutpoints, the laboratory measurements were analyzed for prognosis univariately using Kaplan Meier, and multivariately in conjunction with other factors with Cox proportional hazards regression.

Because of the multiple tests performed on the database, the level of significance for p was chosen as <0.01.

RESULTS

Non-small Cell Lung Cancer

Analyses of Survival Using General Characteristics

Cox Models

The following variables were considered: clinical TNM stage as proposed by the IASLC Lung Cancer Project, age, gender, histologic cell type (adenocarcinoma versus squamous cell carcinoma versus other types), and performance status (PS) using the Zubrod scale.[7] The results of the Cox proportional hazards regression model performed on the whole population (12,426 patients) is shown in Table 2. Older age, more advanced stage, male gender, poorer PS and nonsquamous cell histology were found to be significantly associated with decreased survival. The R^2 value for the full model with clinical stage (as proposed by IASLC) and the full set of prognostic factors is 36.2. For a model with just clinical stage and without the other factors, the R^2 value is 32.9. Thus, removing the prognostic factors from the model does not substantially effect the hazard ratios on the clinical stage parameters.

The same prognostic factors were found to be important when the multivariate analysis was performed using the 6th edition of the TNM Classification of Malignant Tumors[8,9] to determine clinical stage (Table 3).

When prognostic factors were analyzed by clinical stage, as proposed by the IASLC staging project (Table 4), histology cell type was a significant prognostic factor for survival only in patients with stage IIIA, whereas PS, gender, and age were significant in all stages, but with a lower limit for age in advanced stages.

TABLE 2. Multivariate Analysis of Prognostic Factors for Survival in NSCLC, Using General Characteristic Variables (Clinical TNM Stage as Proposed by IASLC Staging Project, Age, Gender, PS, Histological Cell Type)

Variable	*n*/*N* (%)	HR (95% CI)	*P*
Stage II	1531/12426 (12%)	1.80 (1.65, 1.97)	<0.001
Stage IIIA	2048/12426 (16%)	2.71 (2.49, 2.95)	<0.001
Stage IIIB/IV	7280/12426 (59%)	5.34 (4.95, 5.76)	<0.001
Age (continuous)	*N* = 12426	1.01 (1.00, 1.01)	<0.001
Squamous cell type	5304/12426 (43%)	0.93 (0.89, 0.97)	<0.001
Male gender	9764/12426 (79%)	1.17 (1.11, 1.23)	<0.001
PS 1 (vs.0)	6294/12426 (51%)	1.38 (1.32, 1.44)	<0.001
PS 2 (vs. 0)	1423/12426 (11%)	2.09 (1.95, 2.23)	<0.001
PS 3–4 (vs. 0)	579/12426 (5%)	3.48 (3.17, 3.83)	<0.001

R2 = 36.2%.

NSCLC, non-small cell lung cancer; IASLC, International Association for the Study of Lung Cancer; TNM, tumor, node, metastasis; PS, performance status; HR, hazard ratio; 95% CI, 95% confidence interval; *p* value from Wald χ^2 Test in Cox Regression; R2: R-squared using method by O'Quigley and Xu.

TABLE 3. Multivariate Analysis of Prognostic Factors for Survival in NSCLC, Using the 6th Edition of TNM (R2 = 35.4%)

Variable	*n*/*N* (%)	HR (95% CI)	*P*
Age	*N* = 12426	1.01 (1.01, 1.01)	<0.001
6th Ed TNM II	1119/12426 (9%)	1.86 (1.70, 2.03)	<0.001
6th Ed TNM IIIA	1925/12426 (15%)	2.54 (2.35, 2.75)	<0.001
6th Ed TNM IIIB & IV	7401/12426 (60%)	4.79 (4.48, 5.12)	<0.001
Male	9764/12426 (79%)	1.16 (1.11, 1.22)	<0.001
PS 1	6294/12426 (51%)	1.38 (1.32, 1.45)	<0.001
PS 2	1423/12426 (11%)	2.11 (1.97, 2.25)	<0.001
PS 3–4	579/12426 (5%)	3.50 (3.18, 3.85)	<0.001
Squamous cell	5304/12426 (43%)	0.92 (0.88, 0.96)	<0.001

NSCLC, non-small cell lung cancer; TNM, tumor, node, metastasis; PS, performance status; HR, hazard ratio; 95% CI, 95% confidence interval; *p* value from Wald χ^2 Test in Cox Regression; R2: R-squared using method by O'Quigley and Xu.

RPA Analysis

A recursive positioning and amalgamation analysis was performed on the patient population, randomly divided for that purpose in to a learning set (66% = 8199 cases) and a validation set (34% = 4227 cases). The following factors were used to obtain the tree shown in Figure 1: PS (ordered), IASLC stage (ordered with IIIB-IV combined), age (continuous), squamous cell type (yes/no), and gender. The resulting, pruned survival tree showed significant split points for stage, age and PS; cell type did not appear as important as those variables. The numbers at the terminal nodes (Figure 1) represent the parameter estimates (log-hazard ratio) and the number of cases for each terminal node group. The reference group with best prognosis is circled in blue at the far left of the figure. The colored circles encompass those groups with similar prognoses. Four groups with significantly different prognosis were identified: Group 1 (blue) with stage IA–IIA (any age and any PS); Group 2 (red) with stage IIB/IIIA and PS 0–1 (any age); Group 3 (green) with stage IIB/IIIA and PS 2 (any age) or with stage IIIB/IV and PS 0 (any age) or with stage IIIB/IV, age <81 years and PS 1; Group 4 (orange) with stage IIB/IIIA and PS 3–4 (any age) or with stage IIIB/IV and PS 2–4 (any age) or with stage IIIB/IV, PS 1 and age >80 years. The resulting amalgamated categories were applied to a survival analysis on the validation set of patients (Figure 2). Median survival times were, respectively, 53 months for group 1, 16 months for group 2, 8 months for group 3, and 3 months for group 4.

TABLE 4. Multivariate Analysis of Prognostic Factors for Survival Within Clinical Stages in NSCLC (as proposed by the IASLC for the 7th Ed of TNM), Using General Characteristic Variables (Age, Gender, PS, Histological Cell Type)

Variable	*n*/*N* (%)	HR (95% CI)	*P*
Stage I–II			
Male	2628/3098 (85%)	1.22 (1.06, 1.40)	0.006
Squamous	1747/3098 (56%)	0.99 (0.90, 1.09)	0.840
Age	*N* = 3098	1.02 (1.01, 1.02)	<0.001
PS 1	1852/3098 (60%)	1.32 (1.19, 1.46)	<0.001
PS 2	117/3098 (4%)	2.60 (2.07, 3.27)	<0.001
PS 3–4	25/3098 (1%)	7.19 (4.64, 11.14)	<0.001
Stage IIIA			
Age	*N* = 2048	1.01 (1.00, 1.01)	0.002
Male	1635/2048 (80%)	1.21 (1.07, 1.38)	0.003
Squamous	1072/2048 (52%)	0.86 (0.78, 0.95)	0.003
PS 1	871/2048 (43%)	1.33 (1.20, 1.48)	<0.001
PS 2	155/2048 (8%)	1.93 (1.60, 2.33)	<0.001
PS 3–4	37/2048 (2%)	3.94 (2.74, 5.69)	<0.001
Stage IIIB/IV			
Age	*N* = 7280	1.00 (1.00, 1.01)	0.011
Squamous	2485/7280 (34%)	0.95 (0.90, 1.00)	0.042
Male	5501/7280 (76%)	1.15 (1.09, 1.22)	<0.001
PS 1	3571/7280 (49%)	1.41 (1.34, 1.50)	<0.001
PS 2	1151/7280 (16%)	2.13 (1.97, 2.30)	<0.001
PS 3–4	517/7280 (7%)	3.45 (3.11, 3.83)	<0.001

NSCLC, non-small cell lung cancer; IASLC, International Association for the Study of Lung Cancer; TNM, tumor, node, metastasis; PS, performance status; HR, hazard ratio; 95% CI, 95% confidence interval; *p* value from Wald χ^2 Test in Cox Regression.

Analyses of Survival Using Laboratory Values in Advanced Stage IIIB/IV

A total of 7280 cases with advanced NSCLC in the database had data on at least one of the following laboratory values in addition to the other prognostic factors (age, gender, PS): calcium (1316 cases), albumin (1887 cases), sodium (1708 cases), hemoglobin (1564 cases), and WBC (2126 cases). A Cox model was performed with each individual laboratory value and the other prognostic factors (Table 5). The laboratory variables in advanced NSCLC seemed to be strong prognostic factors in a magnitude similar to PS, whereas age and gender were weaker. In 537 patients, data was available on all of the five laboratory values. A multivariate model (Table 6) identified as strong significant prognostic factors ($p < 0.001$) PS and WBC, followed by calcium ($p = 0.0077$), albumin ($p = 0.013$), and age ≥75 years ($p = 0.0415$).

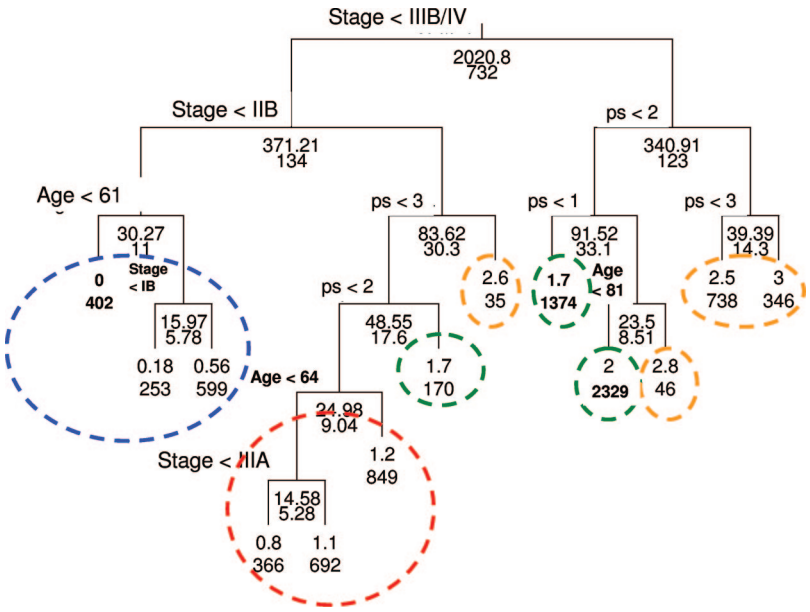

FIGURE 1. Survival tree of the recursive partitioning and amalgamation analysis, performed on a learning set of 8199 non-small cell lung cancer cases.

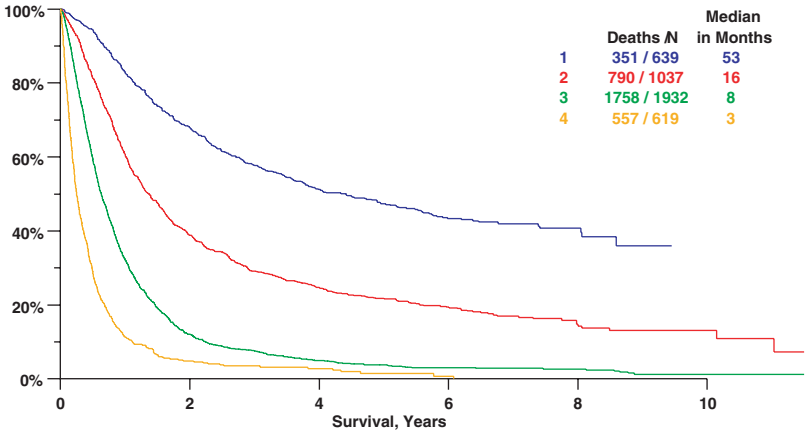

FIGURE 2. Survival obtained for the amalgamated groups in the validation set of 4227 non-small cell lung cancer patients.

TABLE 5. Analyses Using Laboratory Values in Advanced NSCLC Disease (Stages IIIB/IV): Results of Models with Individual Laboratory Variables

		Age ≥75 yr		Gender: Male		PS (ordered)		Laboratory Variable	
Laboratory Variable	**No. of Cases**	***p***	**HR**	***P***	**HR**	***P***	**HR**	***P***	**HR**
Calcium >10.4 mg/dl	1316	0.2248	1.19	0.0356	1.16	<0.0001	1.35	0.0010	1.55
Albumin <3.2 g/dl	1887	0.0116	1.28	0.1875	1.07	<0.0001	1.47	<0.0001	1.45
Sodium <135 mmol/l	1708	0.0674	1.27	0.0016	1.21	<0.0001	1.35	<0.0001	1.35
WBC >10,000 cells/ml	2126	0.0006	1.50	0.0277	1.13	<0.0001	1.42	<0.0001	1.43
Hemoglobin <12 g/dl for females, <13 g/dl for males	1564	0.0725	1.26	0.1746	1.09	<0.0001	1.34	0.0003	1.21

NSCLC, non-small cell lung cancer; PS, performance status; WBC, white blood cells.

Small Cell Lung Cancer

Analyses of Survival Using General Characteristics

Cox Models

The IASLC database contained data for analysis of prognostic factors for 6609 cases with SCLC. This included 2870 patients with LD and 3739 with ED. For each individual, data was available on PS, age, and gender. Two percent (122 cases) had had surgery. Table 7 shows the results of the multivariate analysis for survival on the whole population. All variables tested (PS, extent of disease, gender, and age) were found to be independent prognostic

TABLE 6. Multivariate Model for Survival Performed in Advanced NSCLC (Stages IIIB/IV) in a Set of 537 Patients for which all 5 Laboratory Variables were Available

Variable	*P*	HR
Age ≥75 yr	0.0415	1.39
Male	0.4761	0.93
PS (ordered: 0, 1, 2, 3–4)	<0.0001	1.44
Calcium >10.4 mg/dl	0.0077	1.77
Albumin <32 g /dl	0.013	1.33
Sodium <135 mmol/l	0.4823	1.09
Hemoglobin <12 g/dl for females, 13 g/dl for males	0.1235	1.16
WBC >10,000 cells/μl	<0.0001	1.60

NSCLC, non-small cell lung cancer; PS, performance status; WBC, white blood cells; HR, hazard ratio.

TABLE 7. Multivariate Analysis of Prognostic Factors for Survival in SCLC, Using General Characteristic Variables (Limited vs. Extensive Stage, Age, Gender, PS)

Variable	*n*/*N* (%)	HR (95% CI)	*P*
Age	*N* = 6609	1.01 (1.01, 1.02)	<0.001
Extensive stage (vs Lim.)	3739/6609 (57%)	2.13 (2.02, 2.25)	<0.001
Male (vs. female)	4368/6609 (66%)	1.25 (1.19, 1.32)	<0.001
PS 1	3161/6609 (48%)	1.36 (1.28, 1.44)	<0.001
PS 2	1060/6609 (16%)	1.93 (1.78, 2.09)	<0.001
PS 3–4	349/6609 (5%)	3.45 (3.05, 3.89)	<0.001

SCLC, small cell lung cancer; PS, performance status; HR, hazard ratio; 95% CI, 95% confidence interval; *p* value from Wald χ^2 Test in Cox Regression.

TABLE 8. Multivariate Analyses of Prognostic Factors for Survival in Limited and Extensive SCLC, Using General Characteristic Variables (Age, Gender, PS)

Variable	*n*/*N* (%)	HR (95% CI)	*P*
Limited stage			
Age	*N* = 2870	1.01 (1.01, 1.02)	<0.001
Male	1838/2870 (64%)	1.21 (1.11, 1.32)	<0.001
PS 1	1338/2870 (47%)	1.42 (1.30, 1.55)	<0.001
PS 2	277/2870 (10%)	1.72 (1.49, 1.98)	<0.001
PS 3–4	129/2870 (4%)	3.68 (3.03, 4.47)	<0.001
Extensive stage			
Age	*N* = 3739	1.01 (1.01, 1.02)	<0.001
Male	2530/3739 (68%)	1.28 (1.20, 1.38)	<0.001
PS 1	1823/3739 (49%)	1.32 (1.21, 1.43)	<0.001
PS 2	783/3739 (21%)	1.98 (1.79, 2.18)	<0.001
PS 3–4	220/3739 (6%)	3.32 (2.84, 3.88)	<0.001

SCLC, small cell lung cancer; PS, performance status; HR, hazard ratio; 95% CI, 95% confidence interval; *p* value from Wald χ^2 Test in Cox Regression.

factors for survival. Table 8 shows the results of the models performed on the subsets of patients with limited or ED. The same independent prognostic factors (PS, gender, and age) were identified as in NSCLC.

RPA Analyses

For the RPA analysis, the population was split in to a learning set (66% of the cases = 4359) and a validation set (34% = 2250). The factors entered in to this analysis were: stage (LD versus ED), PS (0–4) age and gender. The resultant tree (Figure 3) shows that stage and PS are the two most important prognostic factors. The reference group with best prognosis is circled in blue at the far left of the figure. Four groups with differing prognoses were identified: group 1 (blue) with LD, PS 0 and age <60 years or LD, PS 1–2 and age <65 years; group 2 (red) with LD, PS 1–2, age ≥65 years or female with ED, PS 0, and age <65 years; group 3 (green) female with ED, PS0 and age ≥65 years or male with ED, PS 0 or both genders with ED, PS 1, age <70 years; and group 4 (orange) with LD PS 3–4 or with ED, PS 1, age ≥70 years or with ED, PS 2–4. The resulting amalgamated categories were applied to a survival analysis in the validation set (Figure 4). Median survival times were, respectively, 17 months for group 1, 12 months for group 2, 10 months for group 3, and 6 months for group 4.

Analyses of Survival Using Laboratory Values

A total of 6609 cases with SCLC in the database had data on at least one of the following laboratory values in addition to the other prognostic factors (stage, age, gender, PS): calcium (1849 cases), albumin (2773 cases), sodium (2390 cases), hemoglobin (1487 cases), and WBC (1828 cases). A Cox model was performed with each individual laboratory value and the other prognostic factors (Table 9). Two laboratory variables (sodium and albumin) appeared to be very significant prognostic factors in addition to stage, PS, and gender. In 650 patients there was data available on all five laboratory values. A multivariate model (Table 10) identified albumin only, in addition to extent of disease and gender, as significant prognostic factors.

DISCUSSION

The IASLC staging project allowed an analysis of prognostic factors for survival in a very large population of lung cancer patients: more than 12,000 with NSCLC and more than 6000 with SCLC. In addition to clinical stage, PS appeared to be a very important prognostic factor. Age and gender were other independent significant variables. For NSCLC, histologic cell type was a significant prognostic factor in stage IIIA, with squamous cell lung cancer having a better prognosis in comparison to other cell types. For both NSCLC and SCLC, RPA allowed the identification of four groups of patients with differing prognoses. Finally, in advanced NSCLC, some biologic variables (serum calcium, albumin, and WBC) were found to be prognostic factors in addition to stage, age, and gender. In SCLC, albumin only, in addition to extent of disease and gender, was identified as a significant prognostic biologic factor. Our findings are summarized in Table 11 with a grading as following: ++++ and +++ = factors present in any model; ++ = factors significant in RPA and Cox models; + = factors significant in Cox models (or in a meta-analysis for SUVmax); +§ = biologic factors significant in Cox models not taking into consideration other biologic variables.

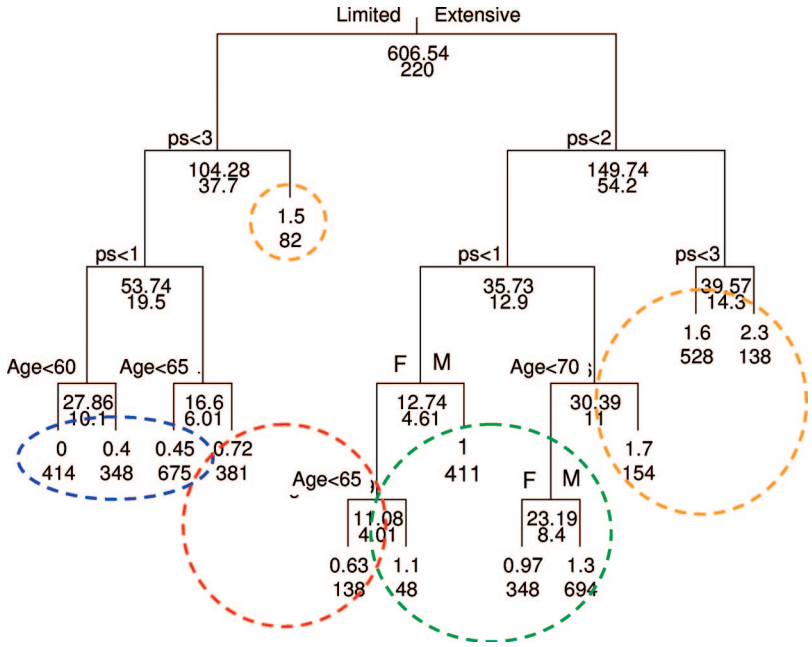

FIGURE 3. Survival tree of the recursive partitioning and amalgamation analysis, performed on a learning set of 4359 small cell lung cancer cases.

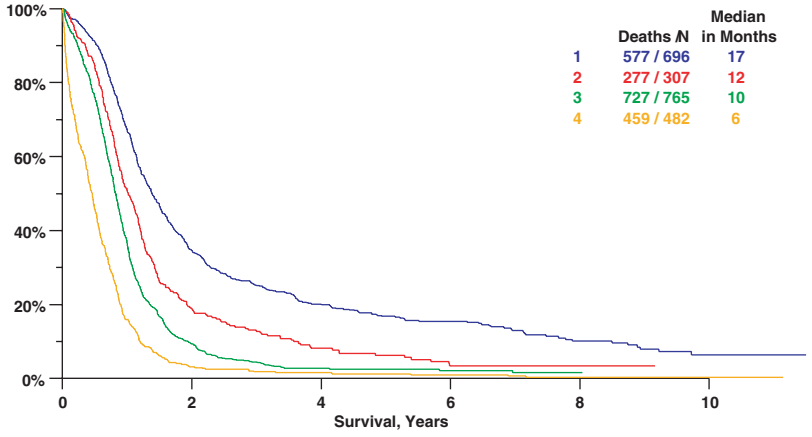

FIGURE 4. Survival obtained for the amalgamated groups in the validation set of 2250 small cell lung cancer patients.

TABLE 9. Analyses Using Laboratory Values in SCLC: Results of Models with Individual Laboratory Variables

		Stage: Extensive		Age ≥75 yr		Gender: Male		PS (ordered)		Laboratory Variable	
Laboratory Variable	**No. of Cases**	***P***	**HR**	***P***	**HR**	***P***	**HR**	***P***	**HR**	***P***	**HR**
Calcium >10.4 mg/dl	1849	<0.0001	1.87	0.8528	1.02	0.0008	1.19	<0.0001	1.5	0.0608	1.28
Albumin <3.2 g/dl	1887	<0.0001	1.79	0.0403	1.21	<0.0001	1.23	<0.0001	1.44	<0.0001	1.31
Sodium <135 mmol/l	2390	<0.0001	1.96	0.6003	1.07	0.0001	1.19	<0.0001	1.48	<0.0001	1.31
WBC >10,000 cells/μl	1828	<0.0001	2.12	0.8544	1.03	<0.001	1.26	<0.0001	1.33	0.2414	1.07
Hemoglobin <12 g/dl for females, <13 g/dl for males	1487	<0.0001	2.25	0.9618	0.99	0.0011	1.21	<0.0001	1.34	0.5040	1.04

SCLC, small cell lung cancer; PS, performance status; HR, hazard ratio; WBC, white blood cells.

There are some methodological problems that may limit the generalization of these results. Firstly, the retrospective nature of the database, that allowed such a very high number of lung cancer patients to be collected, inevitably lead to a lot of missing data on some prognostic factors. This restricted our analysis to a subset of the population for which we had each prognostic factor: clinical stage as proposed by the IASLC staging project,[1] PS, gender, age, and histologic cell type. Pathologically, stage was not considered because in general we did not get much prognostic factor data, particular

TABLE 10. Multivariate Model for Survival Performed in SCLC in a set of 650 Patients for which the 5 Laboratory Variables were Available

Variable	*P*	HR
Stage: ED	<0.0001	1.931
Age ≥75 yr	0.4064	1.146
Male	0.0007	1.336
PS (ordered: 0, 1, 2, 3–4)	<0.0001	1.283
Calcium >10.4 mg/dl	0.9451	1.019
Albumin <32 g/dl	0.0168	1.385
Sodium <135 mmol/l	0.0483	1.221
Hemoglobin <12 g/dl for females, 13 g/dl for males	0.0579	0.833
WBC >10,000 cells/μl	0.7929	1.024

SCLC, small cell lung cancer; ED, extensive disease; PS, performance status; WBC, white blood cells.

TABLE 11. Summary of the Prognostic Factors with a Grading as Following: ++++ and +++ = factors present in any model; ++ = factors significant in RPA and Cox models; + = factors significant in Cox models (or in a meta-analysis for SUVmax); +§ = biological factors significant in Cox models not taking into consideration other biological variables

Variable	NSCLC	SCLC
Clinical extent of disease[a]	++++	++++
Performance status[b]	+++ (≥IIB only)	+++
Age	++ (≥IIIB only)	++
Male gender	+	++
Squamous cell type	+ (IIIA only)	N/A
PET SUV_{max}	+	N/A
Calcium	+[c]	—
Albumin	+[c]	+
Sodium	+§[c]	+§
White blood cells	+[c]	—
Hemoglobin	+§[c]	—

RPA, recursive partitioning and amalgamation; SUV_{max}, standard uptake value maximum; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; PET, position emission tomography; TNM, tumor, node, metastasis; LD, limited disease; ED, extensive disease; N/A, not applicable/not available.

[a] Extent of disease by TNM stage for NSCLC and LD/ED for SCLC.

[b] Performance status by Zubrod scale.

[c] Advanced stage IIIB/IV for NSCLC.

PS, from the surgical database and for those for which we had the data, they are nearly all either P.S. 0 or 1, which is not very interesting for prognostic analysis. For SCLC, we were unable to use TNM stage and limited our analysis to that limited versus ED as defined in the local databases. As biologic variables were mainly available in patients with advanced NSCLC (stage IIIB/IV), the analysis was restricted to those cases for which we also had the other prognostic factors (age, PS, gender). When we wished to study, in a multivariate model, the five biologic variables, data was only available in little more than 500 patients. Secondly, the local databases amalgamated in the staging project were of differing types: clinical trials, surgical series, institution series and registries. Some have been the topic of prognostic analyses that have already been published. Therefore our results are not fully independent of the data already in the literature. Thirdly, the effect of the treatment has not been taken into account because of the great heterogeneity of the various local databases. The prognostic analysis thus reflects not only the natural history of the disease but also the modalities of treatment used according to the local attitudes worldwide. Fourthly, a large number of statistical tests necessitated an increase of the threshold level of significance. Our analysis does not have the strength of a prospective study in which statistical analysis could be based upon a predefined primary end point. For all of these reasons the reported conclusions have to be considered as exploratory, requiring confirmation in a prospective validation study.

Despite these limitations, this study of prognostic factors provides important information. It confirms, in the largest series ever published, the prognostic role of gender and age in addition to PS and clinical stage, whether one uses the 6th edition of the TNM Classification of Malignant Tumors or the IASLC proposals for the forthcoming 7th edition.

Similar general prognostic factors were found to be important for NSCLC and SCLC. The RPA allowed the construction of trees (Figures 1 and 3), which may help in the management of lung cancer patients. For NSCLC, the model developed included all clinical stages, which is a new finding. Indeed the published survival models have so far been limited to retrospective analyses of data bases of clinical trials performed by cooperative groups in advanced disease.[10–13] It should be noted that the number of patients included in those studies ranged form 893 to 2631, which is far less than the 12,428 cases available for our analyses. By taking into consideration the clinical stage in a population with a much broader case-mix, stage seems to be the strongest prognostic factor. PS becomes important only in stage IIB or higher when analyzed with RPA due to the very low frequency of patients with poor PS in the early stage cases (Figures 1 and 2).

For SCLC, we also identified that the extent of disease at presentation, classified as ED versus LD, was the most important factor, with PS and age also being important. Gender was found to have a role in deciding prognosis in ED (Figures 3 and 4). Other models, performed on databases of clinical trial cases from cooperative groups, are published in the literature.[14–16] These publications also identify the extent of disease at presentation as the main factor. The number of patients included in those analyses was respectively, 614, 2580, and 763, many fewer than those used in the present study. The large size of our series allowed us to perform a validation analysis in a subset of 2250 patients, which were not used to construct the model.

Other prognostic factors were identified in this study by the analysis of data within different stages of disease. Histologic cell type is a controversial prognostic factor in NSCLC.[17] The data presented in this report (Table 4) revealed that cell type was only a significant prognostic factor for survival in stage IIIA in addition to PS, age and gender, when stage IIIA was defined using the IASLC proposals for the 7th edition of TNM.[5] Squamous cell cancer seemed to have a better prognosis than other histologies. This information suggests one should stratify by histology in trials that include patients with stage IIIA disease.

Routine laboratory variables have been included in many models for advanced disease published in the literature. Because of a lot of missing data, the analysis of these was restricted to assessing their value in advanced (stage IIIB/IV) NSCLC. Adequate data was available on five blood tests: calcium, albumin, sodium, WBC, and hemoglobin. All were found to be significant variables (Table 5). A model with a small number of patients was constructed, which suggested that WBC and calcium might be important prognostic factors, in accordance with other studies.[11,12,18] The same approach in SCLC allowed identifying albumin as a significant independent factor in addition to PS and extent, which is a new information, albumin having not been so far investigated in large series.[19]

Many potentially useful prognostic variables (Table 1) were not investigated because of missing data or missing variables, inevitable in a retrospective database. Some could not be assessed because they had only recently been suggested, such as for those related to molecular biology or to the value of PET scanning. In regard to the role of molecular or biologic markers in lung cancer, more than 5000 articles have been published, often of varying methodological quality. The best evidence available in the literature at present on this subject has come from the meta-analyses summarized in Table 12. The estimate of the prognostic value of these variables reported in these studies is limited by their use of univariate analyses. The independent role of the prognostic factors identified in this study has to be confirmed in prospective studies, using methodology such as that recently proposed by Zhu et al.[20] and the international recommendations REMARK.[21] The prognostic value of the primary tumor SUV max (maximal standard uptake value) measured on FDG-PET has been assessed by a meta-analysis of the literature, undertaken by the European Lung Cancer Working Party evidence-based medicine committee for the IASLC staging project. This showed that SUV max is a strong prognostic factor for survival in a univariate analysis.[22] This should be confirmed by a meta-analysis based on individual patient data allowing multivariate analysis to be performed which takes into account the prognostic factors identified in the present article.

TABLE 12. Meta-Analyses Published on the Prognostic Value of Biological or Genetic Markers for Survival in Lung Cancer

Biological Variable	Prognostic Factor	Reference
Bcl-2	Good	Martin et al., 2003[23]
TTF1	Poor	Berghmans et al., 2006[24]
Cox2	Poor	Mascaux et al., 2006[25]
EGFR	Poor	Nakamura et al., 2006[26]; Meert et al., 2002[27]
ras	Poor	Mascaux et al., 2005[28]; Huncharek et al., 1999[29]
Ki67	Poor	Martin et al., 2004[30]
HER2	Poor	Meert et al., 2003[31]
		Nakamura et al., 2005[32]
VEGF	Poor	Delmotte et al., 2002[33]
Microvascular density	Poor	Meert et al., 2002[34]
p53	Poor	Steels et al., 2001[35]
		Mitsudomi et al., 2000[36]
		Huncharek et al., 2000[37]
Aneuploidy	Poor	Choma et al., 2001[38]

In conclusion, the present analysis of the database of the IASLC staging project identified important prognostic factors for survival in lung cancer patients in addition to clinical stage. Those factors were PS, age, and gender. In stage IIIA NSCLC, histologic cell type seemed to be important. In advanced NSCLC some routine laboratory tests were found to be additional, significant factors. In SCLC, albumin was also found to be an independent prognostic factor. Models were constructed using a RPA method for both NSCLC and SCLC. They allowed the identification of groups of patients with differing prognoses, taking into account clinical stage and PS and, to a lesser extent, age, and gender. Although the results reported in this study were obtained in the largest series ever used for prognostic analysis in lung cancer, the prognostic variables and models found require to be confirmed by a prospective study, such as that already planned by the IASLC Lung Cancer Staging Project. It is our hope that colleagues around the world will continue to support this initiative.

APPENDIX 1

IASLC ISC

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