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Original Article

Prognostic Factors in Non-Small Cell Lung Cancer Less Than 3 Centimeters: Actuarial Analysis, Accumulative Incidence and Risk Groups☆

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ABSTRACT

Introduction: In TNM classification, factors determining the tumor (T) component in non-small cell lung cancer have scarcely changed over time and are still based solely on anatomical features. Our objective was to study the influence of these and other morphopathological factors on survival.
Methods: A total of 263 patients undergoing lung resection due to stage I non-small cell lung cancer ≤3 cm in diameter were studied. A survival analysis and competing-risk estimate study was made on the basis of clinical, surgical, and pathological variables using actuarial analysis and accumulative incidence methods, respectively. A risk model was then generated from the results.
Results: Survival at 5 and 10 years was 79.8 and 74.3%, respectively. The best prognostic factors were presence of symptoms, smoking habit and FEV1>60%, number of resected nodes>7, squamous histology, absence of vascular invasion, absence of visceral pleural invasion and presence of invasion more proximal than the lobar bronchus. All these were statistically significant according to the actuarial method. The factor "age<50 years" was close to the margin of statistical significance. Pleural invasion and vascular invasion were entered in the multivariate analysis. The competing-risk analysis showed a probability of death due to cancer of 14.3 and 35.1% at 5 and 10 years, respectively. Significant variables in the univariate and multivariate analyses were similar, with the exception of FEV1>60%.
Conclusions: Pleural invasion and vascular invasion determine survival or risk of death due to non-small cell lung cancer ≤3 cm and can be used for generating a predictive risk model.

Factores pronóstico en el carcinoma bronquial no microcítico menor de 3 centímetros (análisis actuarial, incidencia acumulativa y grupos de riesgo)

Palabras clave:
Carcinoma pulmonar no microcítico
Cirugía
Supervivencia
Incidencia acumulativa
Grupos de riesgo

RESUMEN

Introducción: En la clasificación TNM, los factores determinantes del factor T en el carcinoma pulmonar no microcítico apenas han variado con el tiempo y todavía se basan únicamente en características anatómicas. Nuestro objetivo fue estudiar la influencia en la supervivencia de estos y otros factores de tipo morfopatológico.
Métodos: Se incluyeron 263 pacientes sometidos a resección pulmonar por carcinoma pulmonar no microcítico en estadio I patológico y diámetro ≤3 cm. Se realizó un estudio de supervivencia y de

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estimación del riesgo competitivo observando variables clínicas, quirúrgicas y patológicas, siguiendo los métodos de análisis actuarial y de incidencia acumulativa, respectivamente. Posteriormente, se creó un modelo de riesgo de acuerdo con los resultados.
Resultados: La supervivencia fue de 79,8 y 74,3% a los 5 y 10 años, respectivamente. Los factores con mejor pronóstico, estadísticamente significativo según el método actuarial fueron: presencia de síntomas, hábito tabáquico, FEV1 > 60%, número de ganglios resecados > 7, tipo histológico escamoso, ausencia de invasión vascular, ausencia de invasión pleural visceral y presencia de invasión bronquial lobar proximal. La edad < 50 años rozó la significación estadística. En el análisis multivariante entraron en regresión la invasión pleural visceral y la invasión vascular. El estudio de riesgo competitivo mostró una probabilidad de muerte por cáncer de 14,3 y 35,1% en 5 y 10 años, respectivamente. Las variables significativas en los análisis univariante y multivariante fueron similares excepto el FEV1 > 60%.
Conclusiones: La presencia de invasión pleural visceral y la invasión vascular determina la supervivencia o el riesgo de muerte por carcinoma pulmonar no microcítico ≤ 3 cm y permiten elaborar un modelo predictivo de riesgo.

Introduction

The T component of the TNM non-small cell lung cancer (NSCLC) classification system developed by the AJCC and the UICC remained practically the same from 1974 to 2009. One of the changes made in the latest, 7th edition of the classification system undertaken by the IASLC concerns the redefinition of the T factor in stage I. Stage IA is still reserved for tumors ≤3 cm with no visceral pleural invasion (VPI) or with no evidence of invasion more proximal than the lobar bronchus (ILB), atelectasis or pneumonitis. However, the introduction of a new 2 cm threshold has created 2 new subgroups, T1aN0M0 for tumors ≤2 cm, and T1bN0M0 for those measuring between 2.1 and 3 cm. Stage IB has also changed in accordance with tumor size: T2aN0M0 now includes tumors measuring ≤3 cm with VPI or ILB, or atelectasis or pneumonitis, and also those measuring between 3.1 and 5 cm. Tumors measuring between 5.1 and 7 cm are reclassified as T2bN0M0, and tumors >7 cm as T3N0M0, and included in stage IIB.[1,2]

Other T descriptor components, such as VPI, ILB, or radiological appearance of the tumor remain unchanged, and the prognostic implications of these elements will be studied in a future review of the classification.[3,4]

Likewise, other mainly morphological and molecular prognostic factors that could affect survival have been ignored in the TNM classification. Factors such as histologic type, degree of tumor differentiation, vascular invasion (VI), presence of necrosis, etc.,[5,6] or molecular factors[7] are of interest in establishing prognosis and determining adjuvant therapy options.[5,7–9]

The purpose of this study is to validate the new approach to staging NSCLC tumors measuring up to 3 cm in diameter classified as stage I, and to identify other clinical and morphological prognostic factors not included in the current TNM system. On this basis, we aim to create a risk model for these patients.

Materials and Methods

The study was conducted from 1 January 1990 to 31 December 2009. The clinical and surgical data from 268 consecutive NSCLC patients with tumor size up to 3 cm, classified as TNM stage I, were included prospectively. All patients had undergone anatomical pulmonary resection (lobectomy, bilobectomy or pneumonectomy) with curative intent at the same hospital. Patients undergoing sublobar resection were excluded. For the purpose of this study, samples were analyzed by a single histopathologist.

Five patients that died in the perioperative period were excluded, as the aim of the study was to evaluate the prognostic factors for long-term survival. The remaining 263 patients were followed up for at least 12 months (mean 5.31 years [0.23–21.46]). Follow-up was finalized on 31 December 2010, and the study concluded on 1 January 2011.

Clinical Variables

Demographic variables such as age and sex were analyzed. Age was treated as a continuous variable and dichotomized at 3 cut-off points of 50, 60 and 70 years. The clinical variables included the different symptoms presented at the time of diagnosis, the patient's comorbidity, and their classification according to the Charlson index score.[10] Smoking habit was also considered, and patients were classified as smokers, never smokers, and former smokers. Preoperative variables were FEV1 and FVC, expressed as a percentage of predicted value, FEV1/FVC ratio, abnormal ECG findings, and location of the tumor on radiological imaging (right or left lung, lobar, central or peripheral). Fiberoptic bronchoscopy was used to visualize the tumor in the bronchus and the extent of main bronchus involvement.

Surgical variables included the extent of surgical resection, extension to adjacent structures, and the need for angioplasty or bronchoplasty. The number of lymph nodes removed during resection was also analyzed.

Histopathological Variables

Tumors were classified histologically and graded according to the WHO 2004 system into 3 groups: high, moderate, or low differentiation. In the case of squamous cell carcinoma, the level of keratinization and the presence of intercell bridges were also assessed. Adenocarcinomas were assessed on the basis of conventional criteria: tumor architecture and atypical cells.

Tumors were measured by their maximum diameter; this parameter was treated as a continuous variable and grouped according to cut-off points of 1 and 2 cm. The degree of visceral pleural invasion was assessed according to the system proposed by the IASLC,[4] based on the work of Hammar.[11] The presence or absence of VI, lymphatic invasion, perineural invasion and tumor necrosis was also determined.

Statistical Analysis

The study variables were computerized and processed statistically using the RStudio v0.97.320 programming language and environment and the maxstat v0.7-17, survival v2.37-2, Design 2.3-0, prodlim v1.3.7, and cmprsk v2.2-6 packages.

Survival was calculated using Kaplan–Meier actuarial analyses, and results were compared between groups using the log-rank test. Uncensored events were death due to cancer or unknown cause; the latter was assumed to be cancer. Statistical significance was set

at $P<.05$. Variables with a significance level of $P<.10$ were included in the multivariate time-to-event analysis using the Cox proportional hazard model (incomplete observations).

Individual risk was calculated using the regression coefficients of variables selected in the multivariate analysis. On this basis, patients were allocated to different risk groups according to the presence or absence of prognostic variables. The actuarial curves for these groups were plotted using the Kaplan–Meier method and compared using trend testing. If the results were significant, the survival curves were paired and compared using the log-rank test.

Table 1
Descriptive Analysis of Study Patients.

		n	%	×	δ
Sex	Men	226	85.9		
	Women	37	14.1		
Age (years)				62.5	8.8
Symptomatology	Asymptomatic	151	57.4		
	Symptomatic	112	42.6		
Smoking history	Active smoker	121	46.0		
	Former smoker	108	41.1		
	Never smoker	34	12.9		
Comorbidity	Diabetes mellitus	20	10.6		
	Hypertension	79	30.0		
	Heart disease	33	16.7		
	Peripheral artery disease	37	14.1		
	COPD	33	12.5		
	Cancer	47	17.9		
	Chronic kidney failure	4	1.5		
	Liver failure	19	7.2		
Charlson index	0	90	34.2		
	1	71	27.0		
	2	63	24.0		
	3	20	7.6		
	4	12	4.6		
	5	5	1.9		
	6	2	0.8		
Spirometry	FEV1/FVC<0.7	33	12.5		
	FEV1<0.6	27	10.2		
ECG	Normal	233	88.6		
	Abnormal	30	11.4		
Lobe	Right main bronchus	2	0.8		
	Right upper lobe	89	33.8		
	Bronchus intermedius	4	1.5		
	Middle lobe	13	4.9		
	Right lower lobe	36	13.7		
	Left main bronchus	10	3.8		
	Left upper lobe	79	30.1		
	Left lower lobe	30	11.4		
Thoracotomy	Right side	144	54.8		
	Left side	119	45.2		
Extent of resection	Lobectomy	228	86.7		
	Bilobectomy	11	4.2		
	Pneumonectomy	24	9.1		
Typical/atypical	Typical	256	97.3		
	Extended to lobar segment	3	1.1		
	Bronchoplasty	3	1.1		
	Angioplasty	1	0.4		
Histology	Epidermoid	115	43.7		
	Adenocarcinoma	134	50.9		
	Anaplastic large-cell	14	5.3		
Tumor size (cm)				2.2	0.7
Tumor differentiation	G1	123	46.8		
	G2	92	35.0		
	G3	48	18.2		
Lymphatic invasion	Yes	56	21.3		
	No	207	78.7		
Perineural invasion	Yes	33	12.5		
	No	230	87.5		
Necrosis	Yes	182	69.2		
	No	81	30.8		
Vascular invasion	Yes	60	22.8		
	No	203	77.2		
Pleural invasion	p10	229	87.1		
	p11	32	12.1		
	p12	2	0.8		
T1	T1a	72	27.4		
	T1b	105	39.9		
T2a	Bronchial	42	16		
	VPI	34	12.9		
	Fissure	10	3.8		

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity: VPI: visceral pleural invasion.

The Kaplan–Meier estimator is the most widely used non-parametric method for calculating survival without the need for the analyzed event to have occurred in all cases (incomplete observation). However, models that take into account risks that compete with the analyzed event, in this case mortality due to causes other than LC, give a more accurate estimate of survival, and can also estimate risk of death from other causes. The cumulative incidence method (competitive risk analysis) meets these requirements, and was therefore chosen to analyze survival in this study.[12]

For the purpose of cumulative incidence analysis, competing events were death from other causes, including death from a second, metachronous lung tumor. Statistical significance was set at $P<.05$. Variables with a significance of $P<.10$ were included in the multivariate analysis performed using the Fine and Gray cumulative incidence model.[13]

Results

The descriptive analysis of patient characteristics and clinical data is shown in Table 1. At the end of the study, 43.7% of patients had survived, 49 (18.6%) had died from causes related to their malignancy, and 6 from unknown causes. In 93 (35.3%) patients, the cause of death was disease other than LC, and in 23 patients, the cause was a second, metachronous tumor. None of the study patients were lost to follow-up (Table 2).

Table 2
Causes of Death.

Local recurrence	5	1.9
Locoregional recurrence	8	3
Distant recurrence		
Central nervous system	12	4.5
Several levels	11	4.1
Bone	7	2.6
Lung	4	1.5
Liver	1	0.3
Suprarenal	1	0.3
Unknown	6	2.3
Cardiovascular		
Acute myocardial infarction	13	5.3
Stroke	7	2.6
Aortic aneurysm	3	1.1
Heart failure	3	1.1
Cor pulmonale	1	0.3
Pulmonary thromboembolism	1	0.3
Intestinal ischemia	1	0.3
Respiratory		
Pneumonia	10	3.8
COPD	6	2.2
Others		
Traffic accident	2	0.7
Urinary sepsis	1	0.3
Terminal kidney failure	1	0.3
Cancer		
Bladder	5	1.9
Bowel	2	0.7
Larynx	2	0.7
Prostate	2	0.7
Amygdala	1	0.3
Hypopharyngeal	1	0.3
Esophageal	1	0.3
Stomach	1	0.3
Tracheal	1	0.3
Liver	1	0.3
Melanoma	1	0.3
Hematologic	2	0.7
Second metachronous LC	23	8.7

COPD: chronic obstructive pulmonary disease; LC: lung cancer.

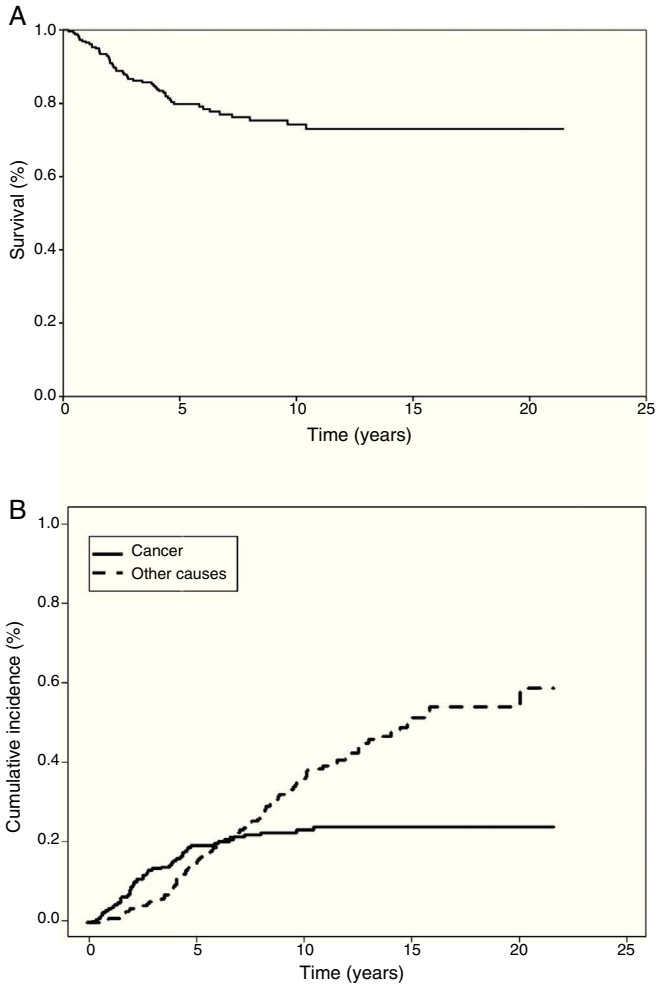

Fig. 1. Survival and competitive risk. (A) Cancer survival curve (Kaplan–Meier actuarial analysis). (B) Competitive risk curves: death from cancer vs no cancer (cumulative incidence method).

In the Kaplan–Meier actuarial analysis, the cancer-specific probability of survival was 79.8% and 74.3% at 5 and 10 years, respectively (Fig. 1). No difference was observed in terms of the 2 cm cut-off point, or in the analysis of the T1 and T2, or T1a, T1b and T2a subgroups. Statistically significant factors for good prognosis were presence of symptoms ($P=.040$), smoking history ($P=.037$), FEV1>60% ($P=.032$) and removal of more than 7 lymph nodes during resection surgery ($P=.035$). Age<50 years was border-line significant ($P=.050$). In terms of histological variables, epidermoid tumor ($P=.042$), absence of VI ($P=.008$), absence of VPI ($P<.001$) and ILB ($P=.004$) were significantly associated with longer survival (Table 3).

In the Cox proportional hazard analysis, only 2 variables entered into the regression model: VPI ($P=.001$) and VI ($P=.023$) (Table 4 and Fig. 2).

Cumulative incidence analysis, meanwhile, estimated risk of death from cancer as 19.4% and 23.2% at 5 and 10 years, respectively (Fig. 1). When death from other causes was analyzed as a competing event, risk of death was 14.3% and 35.1% at 5 and 10 years, respectively. It is interesting to note that the probability of death from cancer and from non-cancer causes at 6.3 years was the same. Thereafter, the risk of death from non-cancer-related causes increased (Fig. 1).

In the analysis of cancer as the cause of death, no differences were observed in terms of tumor size or TNM subgroup, such as T1a, T1b, and T2a. However, presence of symptoms ($P=.038$), history of

Table 3
Kaplan–Meier Univariate Analysis vs Gray's Cumulative Incidence Method.

	n	5 a (%)	KM (*P*)	1-KM	5 a (%)	IA (*P*)
Sex						
Men	226	80.8	.370	19.2	18.2	.256
Women	37	73.5		26.5	25.8	
Age (*years*)						
≤50	21	94.4	.050	5.6	5.3	.118
>50	242	78.4		21.6	20.3	
≤60	106	80.1	.754	19.9	19.0	.977
>60	157	79.9		20.1	19.0	
≤70	206	79.7	.703	20.3	19.1	.795
>70	57	80.2		19.8	18.8	
Symptoms						
Asymptomatic	151	77.4	.040	22.6	21.6	.038
Symptomatic	112	83.0		17.0	15.8	
Smoking habit						
Never	34	74.7	.064	25.3	24.9	.034
Smoking history	229	80.6		19.4	18.2	
Never	34	74.7	.037	25.3	24.9	.021
Smoker	121	74.9		25.1	12.9	
Ex-smoker	108	86.3		13.7	22.5	
Charlson index						
0	90	80.4	.641	19.6	18.5	.788
>0	173	79.5		20.5	19.4	
≤2	224	79.0	.723	21.0	20.1	.929
>2	39	85.7		14.3	13.2	
COPD						
FEV1/FVC<70%	33	72.0	.564	28.0	24.9	.692
FEV1/FVC≥70%	230	80.9		19.1	18.2	
FEV1<60%	27	58.0	.032	42.0	36.1	.069
FEV1≥60%	236	82.0		18.0	17.0	
ECG						
Normal	233	80.5	.640	19.5	18.45	.771
Pathological	30	74.5		25.5	23.84	
Extent of resection						
Partial resection	239	78.7	.100	21.3	20.2	.083
Pneumonectomy	24	90.8		9.2	8.5	
Lobectomy	228	78.2	.126	21.8	20.6	.119
Bilobectomy	11	88.9		11.1	11.1	
Pneumonectomy	24	90.8		9.2	8.5	
Lymph nodes						
≤7	212	77.3	.035	22.7	31.3	.033
>7	51	91.9		8.1	8.0	
Histology						
Squamous	115	84.9	.113	15.1	14.5	.103
Adenocarcinoma	134	75.9		24.1	22.6	
Large-cell	14	77.1		22.9	22.1	
Squamous	115	84.9	.042	15.1	14.5	.037
Non-squamous	148	76.1		23.9	22.5	
Adenocarcinoma	134	75.9	.036	24.1	22.6	.040
Non-adenocarcinoma	129	83.9		16.1	15.4	
Tumor size						
≤2 cm	109	77.4	.330	22.6	20.7	.381
>2 cm	154	81.1		18.9	18.1	
≤1 cm	23	80.7	.827	19.3	17.6	.767
>1 cm–≤2 cm	86	78.4		21.6	19.9	
>2 cm	154	80.3		19.7	18.9	
Tumor differentiation						
G1	123	82.4	.986	17.6	16.7	.980
G2	92	77.3		22.7	21.7	
G3	48	77.4		22.6	20.5	
Lymphatic invasion						
No	207	82.0	.115	18.0	17.0	.114
Yes	56	71.9		28.1	26.7	
Perineural invasion						
No	230	80.7	.763	19.3	18.2	.688
Yes	33	74.0		26.0	24.9	
Necrosis						
No	81	81.8	.526	18.2	17.0	.596
Yes	182	79.0		21.0	20.0	

Table 3 (*Continued*)

	n	5 a (%)	KM (*P*)	1-KM	5 a (%)	IA (*P*)
Fissure invasion						
No	253	79.0	.395	21.0	19.8	.427
Yes	10	80.0		20.0	0.0	
Vascular invasion						
No	203	82.4	.008	17.6	16.4	.007
Yes	60	71.3		28.7	27.8	
Pleural invasion						
No	229	83.2	.000	16.8	15.8	.000
Yes	34	56.0		44.0	42.4	
T factor						
T1	177	82.0	.332	18.0	17.0	.296
T2	86	75.4		24.6	23.4	
T1a	72	80.4	.400	19.6	17.9	.402
T1b	105	82.8		17.2	16.4	
T2a	86	75.4		24.6	23.4	
T2 (pleural invasion)	34	56.0	.004	44.0	42.4	.003
T2 (proximal bronchial)	42	84.6		15.4	14.5	

The 1-KM column has been added to facilitate comparison between KM and CI results.
COPD: chronic obstructive pulmonary disease. FVC: forced vital capacity FEV1: forced expiratory volume in 1 s; CI: cumulative incidence; KM: Kaplan–Meier.

smoking (*P*=.034), removal of more than 7 lymph nodes (*P*=.033), epidermoid tumor (*P*=.037), absence of VI (*P*=.007) or VPI (*P*<.001) and ILB (*P*=.003) were protective factors (Table 3).

In the Fine–Gray multivariate analysis, VPI (*P*=.001) and VI (*P*=.020) entered into the regression model (Table 4 and Fig. 3).

A risk model was created that considered absence or presence, together with the product of their β factor, of each of the 2 variables that entered into the regression analysis in the multivariate analysis. This model was applied to the study population, producing 3 groups: a low-risk group where none of the variables are present, a moderate-risk group, where 1 or other of the variables are present, and a third high-risk group where both are concurrently present. All 3 groups showed statistical significance when they were paired and subjected to trend and log-rank analysis. In the first group, probability of survival at 5 and 10 years was estimated to be 84% and 81%, 75% and 59% in the second group, and 38% in the third (*P*<.001), respectively (Fig. 4).

Discussion

The TNM system of tumor grading is currently the gold standard for determining treatment and estimating prognosis in NSCLC. However, the involvement of other, non-anatomical factors that could affect survival remains unchanged. In this study, we found that 2 morphopathological variables, IPV and VI, have an independent effect on survival, and can determine a risk prediction model in ≤3 cm NSCLC.

In our study, survival at 5 and 10 years was 79.8% and 74.3%, respectively, and echoes the finding of other authors.[5,14–16] Although we were unable to compare the results of our cumulative incidence analysis (19.4% and 23.2% risk of death from cancer at 5 and 10 years) with any other series, this analysis allowed us to identify the non-tumor-related factors that compete with LC on a prognostic level, and how, after 6.3 years, these factors prevail over cancer-related risk factors.

Generally speaking, the new TNM classification has been validated with few exceptions.[17] However, very few studies in N0M0 tumors with a maximum diameter of 3 cm have been published, and the findings so far have been contradictory. Ye et al.[18] and Suzuki et al.,[19] found that tumors classified as T1aN0M0 had a better prognosis than T1bN0M0 tumors. Li et al.,[20] meanwhile, found no differences between these groups or with T2aN0M0 tumors, showing that prognosis was comparable to stage IA. Our results coincide fully with the results of this group, and do not validate the new TNM classification. It is important to note that in our series, 34 tumors that invaded the visceral pleura and therefore classified as T2a had a significantly worse prognosis than 42 other tumors also classified as T2a due to their location in the main bronchus; survival in the latter group was comparable to that of class T1a and T1b tumors.

Interestingly, our study found greater survival in symptomatic patients that were former smokers. The role of smoking as a prognostic factor is unclear, although some studies have also reported improved survival in former smokers.[21] Moreover, our finding of poorer survival in asymptomatic patients may be explained by earlier and mostly asymptomatic detection in the last 10 years of the study, and the change in the predominant tumor type to adenocarcinoma, with a poorer prognosis.

Tumor size has been the focus of innumerable studies of the prognostic significance of this factor. In their systematic review, Nesbitt et al.[22] found considerable variability in the prognosis of stage I tumors measuring ≤3 cm in diameter, and since then several studies have found that prognosis is determined by size.[15,23,24] On this basis, the latest TNM classification system set the cut-off point at 2 cm. Despite this, other studies echo our findings, namely that size has no impact whatsoever on prognosis.[25,26] We did, however, find that it plays a role in competitive risk, since the smaller the

Table 4
Multivariate Analysis: Cox Proportional Hazard Method vs Fine–Gray Method.

	Multivariate (Cox)			Multivariate (Fine–Gray)		
	B	*P*	HR (95% CI)	*β*	*P*	HR (95% CI)
Vascular invasion	0.644	.023	1.90 (1.09–3.32)	0.628	.020	2.33 (1.10–3.18)
Pleural invasion	1.022	.001	2.77 (1.50–5.13)	0.962	.001	3.24 (1.46–4.68)

HR: hazard ratio; CI: confidence interval.

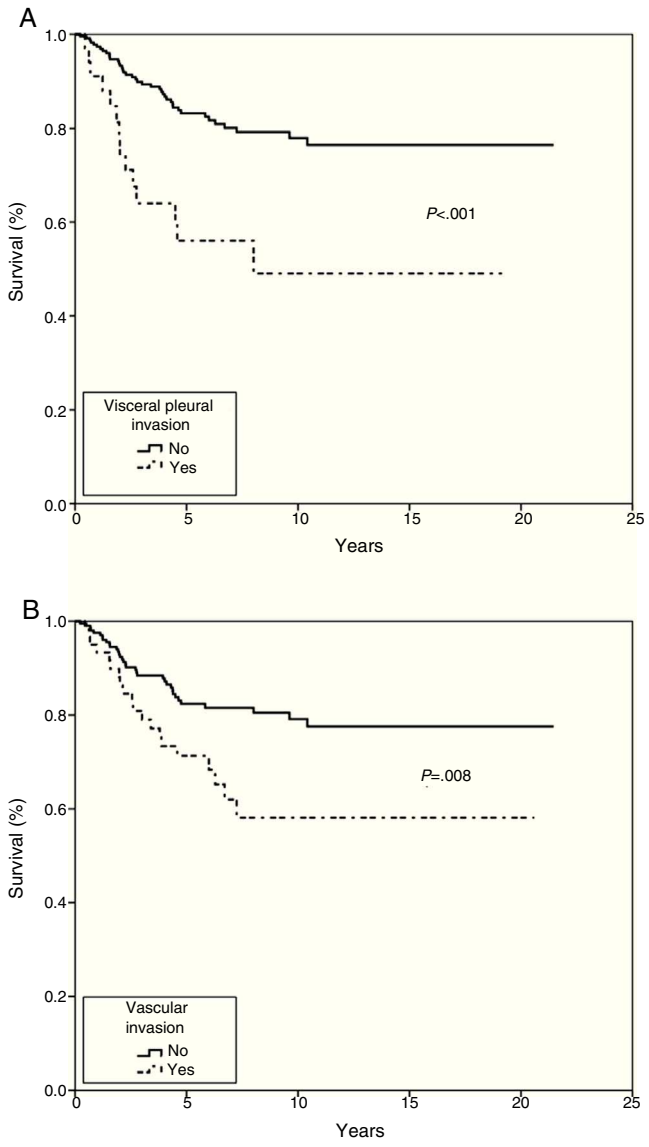

Fig. 2. Kaplan–Meier significant variables. (A) Survival curve based on visceral pleural invasion. (B) Survival curve based on vascular invasion.

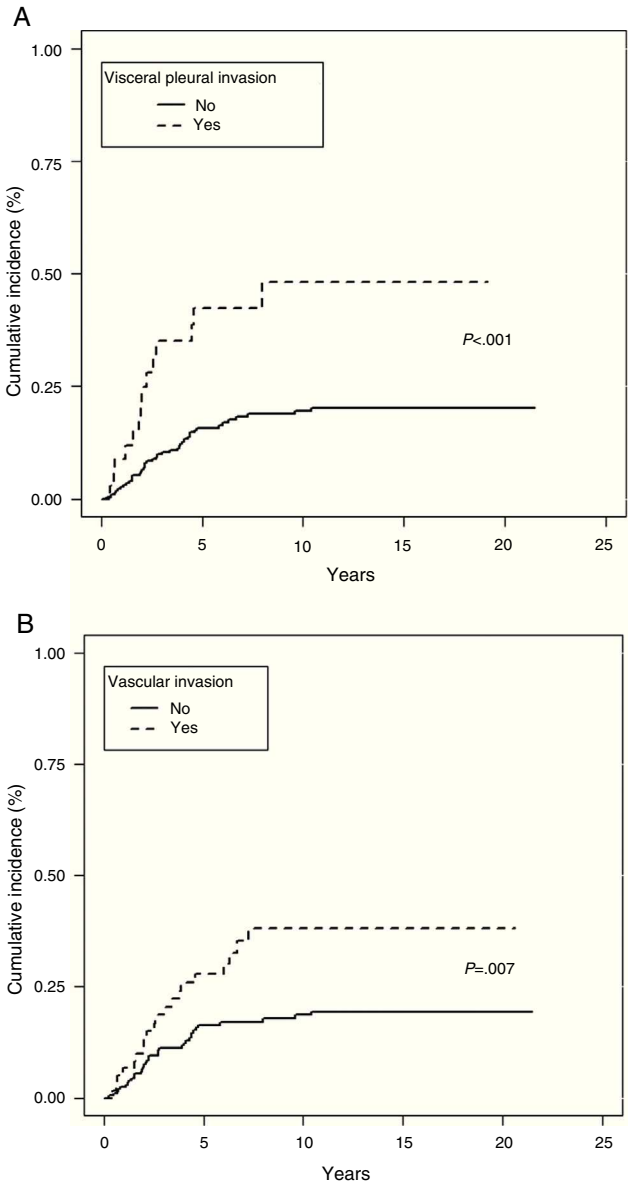

Fig. 3. Cumulative incidence of significant variables. (A) Competitive risk based on visceral pleural invasion. (B) Competitive risk based on vascular invasion.

tumor, the greater the probability of death from causes other than LC.

ILB is still the criterion for classifying the T descriptor as T2a. Very few studies have explored the prognostic significance of ILB,[27,28] and the few references available fail to confirm its impact on survival. This is also confirmed by our results.

The prognostic significance of VPI is controversial, probably due to the lack of a commonly accepted morphological criterion for classifying the extent of the invasion. The IASLC,[4] based on studies published by Hammar,[11] drew up a series of guidelines to improve the accuracy of comparisons and to identify VPI as an independent factor for poor prognosis in LC[9,29,30]; our findings are consistent with this recommendation.

In our analysis, VPI was the first variable to enter into the regression model in the multivariate analysis in both the Fine–Gray and Cox proportional hazard model. VPI was also a competitive factor, insofar as absence of this phenomenon determined a greater likelihood of dying from other causes.

In conclusion, we found that tumor size $\leq$2 cm did not determine survival in either of the stage IA groups. Within the T2aN0M0 group, tumors with VPI have poorer prognosis, with a 5-year survival rate of 56%, while survival in IPB tumors was similar to that of T1aN0M0 tumors (84.6%). Nevertheless, competitive risk analysis showed that risk for non-cancer-related mortality in patients classified as T1 and T2 was higher, in the latter case due to bronchial involvement.

With regard to non-anatomical factors, our study of histopathological variables showed that VI had a significant impact on survival. VI was included in both the univariate and multivariate analysis, and was the second factor to enter into regression as an independent prognosis factor in both the Fine–Gray and Cox proportional hazard model.

Although earlier studies on histological factors mention the effect of lymphatic invasion, and not VI, on survival,[31,32] more recent research[33] confirms our findings, namely, that VI is an independent determinant of survival in stage I tumors. These later studies go so far as to suggest including this factor in the T descriptor of TNM.[34] Similar results were reported by other authors who, contrary to our findings, also demonstrated the significance of lymphatic invasion in prognosis.[35–37]

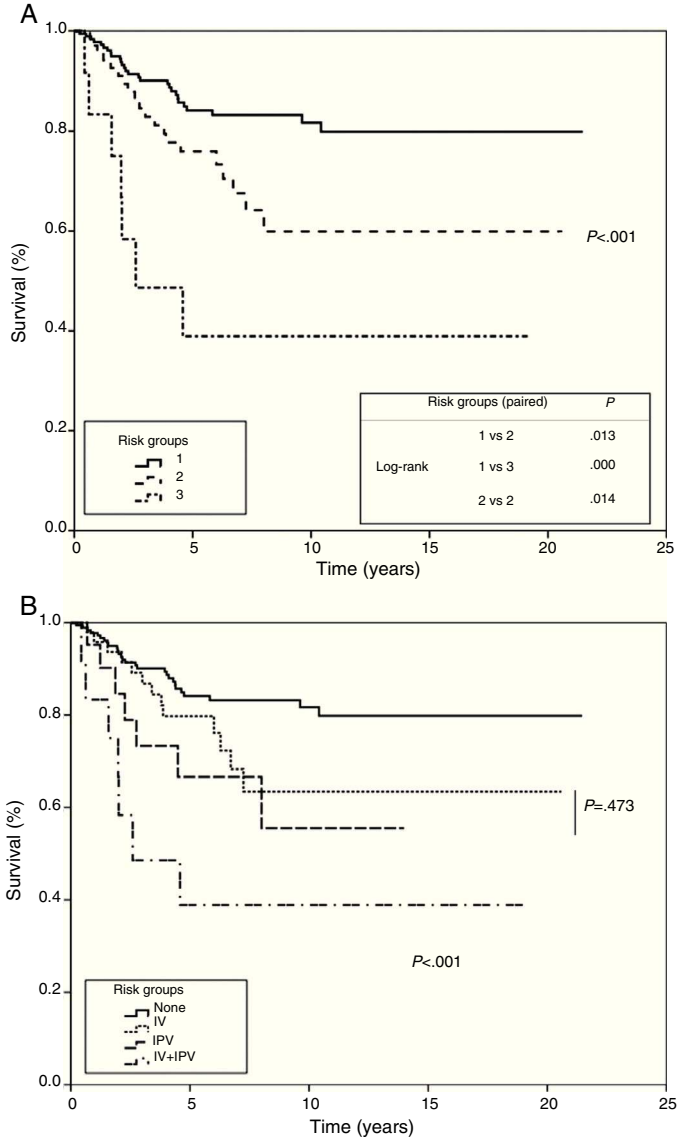

Fig. 4. Risk groups based on multivariate analysis (Cox proportional hazard method). Survival curves by risk group plotted using significant variables for the multivariate analysis. (A) Group 1: no visceral pleural invasion or vascular invasion; group 2: presence of visceral pleural invasion or vascular invasion; group 3: presence of visceral pleural invasion and vascular invasion. Trend test and comparison of paired curves. (B) Analysis of the intermediate risk group by visceral pleural invasion and vascular invasion.

VI, together with VPI and lymphatic involvement, could even determine the disease-free period in stage I LC.[35,38,39]

As we have shown in this study, estimation of survival depends on many different factors, and although TNM is still a valuable therapeutic decision-making tool in NSCLC, it does not adequately stratify patients according to prognosis. For this reason we believe the problem should be approached from a multivariate perspective. Developing risk models based on molecular markers would be complicated,[7,40] mainly because not all groups have access to the advanced technology needed. However, the problem can also be approached from a clinical and pathological perspective.[5,8] Even though our study is limited insofar as we were unable to validate our model in an independent population, we have shown that estimating risk on the basis of VPI extension and VI will identify 3 subgroups of patients with significantly different prognoses. Our findings are largely consistent with those reported by Maeda et al.[5,9] who used multivariate analysis to confirm that VPI and VI, together with the degree of tumor differentiation, determined survival in stage I tumors measuring up to 3 cm in diameter.

Conclusions

We believe that the analysis and consideration of clinical and morphological prognosis factors can be put into practice immediately, irrespective of whether or not they are included in future reviews of the TNM classification system. These factors could form the basis for new lines of research into the need for medical treatment as an adjuvant to surgery in early-stage NSCLC, even in small tumors with no signs of extra-pulmonary involvement.

Conflict of Interest

The authors declare they have no conflict of interest.

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