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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☆

Juan C. Peñalver Cuesta,[a,*] Carlos Jordá Aragón,[b] Nuria Mancheño Franch,[c] José A. Cerón Navarro,[b] Karol de Aguiar Quevedo,[a] Miguel Arrarás Martínez,[a] Francisco J. Vera Sempere,[c] Jose D. Padilla Alarcón[a]

[a] Servicio de Cirugía Torácica, Fundación Instituto Valenciano de Oncología (FIVO), Valencia, Spain
[b] Servicio de Cirugía Torácica, Hospital Universitario y Politécnico La Fe, Valencia, Spain
[c] Servicio de Anatomía Patológica, Hospital Universitario y Politécnico La Fe, Valencia, Spain

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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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* Corresponding author.
E-mail address: jpenalve@ono.com (J.C. Peñalver Cuesta).

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