

## Chemotherapy and Survival in Advanced Non-Small Cell Lung Carcinoma: Is Pneumologists' Skepticism Justified?

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**OBJECTIVE:** Few studies have assessed whether the advantage chemotherapy has been shown to have in treating advanced non-small lung carcinoma in clinical trials is transferrable to normal health care activity. This could explain the skepticism of a large number of pneumologists towards this treatment. The objective of our study was to analyze prognostic factors related to survival and to see whether cytostatic treatment was an independent predictor.

**PATIENTS AND METHODS:** Patients enrolled in the study had been diagnosed with non-small cell carcinoma in stages IV or IIIB with pleural or N2-N3 involvement and with [a performance status of 2 or below according to the Eastern Cooperative Oncology Group (ECOG). Survival was analyzed with regard to the following variables: age, sex, comorbidity, weight loss, laboratory test results, histological type, ECOG score, TNM staging, and treatment. The Student *t* test, the  $\chi^2$  test, the Kaplan-Meier method, the log-rank test, and Cox regression analysis were used in the statistical analysis.

**RESULTS:** We enrolled 190 patients (157 men and 33 women) with a mean (SD) age of 61.75 (10.85) years (range, 33-85 years). Of these patients, 144 received cytostatic treatment and 46 palliative treatment. The median survival was 31 weeks and was related to absence of weight loss (hazard ratio [HR], 1.73; 95% confidence interval [CI], 1.26-2.39;  $P=0.001$ ), cytostatic treatment (HR, 1.85; 95% CI, 1.25-2.76;  $P=0.002$ ), and ECOG score of 0 to 1 (HR, 2.84; 95% CI, 1.62-5.00;  $P=0.0001$ ). In patients with ECOG scores of 0 to 1, weight loss and treatment were significant prognostic factors. Survival in the ECOG 2 group was 15 weeks for patients undergoing cytostatic treatment and 11 weeks for patients with symptomatic treatment.

**CONCLUSIONS:** In normal clinical practice, chemotherapy significantly prolongs survival in patients with performance status of less than 2, more time being gained if there is no associated weight loss. We conclude that the reluctance shown by many pneumologists toward using this treatment is not entirely justified.

**Key words:** *Non-small lung carcinoma. Advanced stages. Chemotherapy. Survival.*

Quimioterapia y supervivencia en el carcinoma broncogénico no microcítico en estadios avanzados: ¿está justificado el nihilismo de los neumólogos?

**OBJETIVO:** Pocas series han valorado si el beneficio que en los ensayos clínicos muestra la quimioterapia en el carcinoma broncogénico no microcítico en estadios avanzados es trasladable a la actividad asistencial habitual, lo que podría explicar el escepticismo de gran parte de los neumólogos. En este contexto, el objetivo de nuestro trabajo es analizar factores pronósticos relacionados con la supervivencia y si el tratamiento citostático influye de manera independiente.

**PACIENTES Y MÉTODOS:** Se incluyó a pacientes diagnosticados de carcinoma no microcítico en estadios IV y IIIB con afectación pleural o N2-N3 y grado de actividad, según el Eastern Cooperative Oncology Group (ECOG), menor o igual a 2. Se relacionaron con la supervivencia las siguientes variables: edad, sexo, comorbilidad, pérdida de peso, parámetros analíticos, tipo histológico, ECOG, TNM y tratamiento. Para el análisis estadístico se emplearon las pruebas de la *t* de Student, de la  $\chi^2$ , el método de Kaplan-Meier, el test de rangos logarítmicos y el modelo de regresión de Cox.

**RESULTADOS:** Se incluyó en el estudio a 190 enfermos (157 varones y 33 mujeres), con una edad media ( $\pm$  desviación estándar) de 61,75  $\pm$  10,85 años (rango: 33-85), de los cuales 144 recibieron tratamiento citostático y 46 paliativo. La mediana de supervivencia fue de 31 semanas y se relacionó con: ausencia de pérdida de peso (razón de probabilidad [HR] = 1,73; intervalo de confianza [IC] del 95%, 1,26-2,39;  $p = 0,001$ ), tratamiento citostático (HR = 1,85; IC del 95%, 1,25-2,76;  $p = 0,002$ ) y ECOG 0-1 (HR = 2,84; IC del 95%, 1,62-5,00;  $p = 0,0001$ ). En el grupo ECOG 0-1 mostraban significado pronóstico la pérdida de peso y el tratamiento. La supervivencia en ECOG 2 fue de 15 semanas en los pacientes con tratamiento citostático y de 11 semanas en aquellos con tratamiento sintomático.

**CONCLUSIONES:** En la práctica clínica habitual la quimioterapia prolonga la supervivencia significativamente en los pacientes con grado de actividad inferior a 2 y esta ganancia es mayor si no existe pérdida de peso asociada. Por tanto, creemos que la opinión poco favorable que muestra gran parte de los neumólogos acerca de este tratamiento no parece plenamente justificada.

**Palabras clave:** *Carcinoma de pulmón no microcítico. Estadios avanzados. Quimioterapia. Supervivencia.*

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## Introduction

The most common neoplasms in developed countries are bronchogenic carcinomas. Most are non-small cell cancers, some two thirds of which are at advanced stages on diagnosis and are considered unresectable. Given this situation, several clinical trials have shown that chemotherapy prolongs survival in comparison with purely palliative treatment,<sup>1</sup> for which reason several scientific societies recommend its use in patients with high performance status—Karnofsky performance status over 70% or an Eastern Cooperative Oncology Group (ECOG) score of 2 or less. However, gains are slight and after 6 months of treatment there are no differences with respect to symptomatic treatment.<sup>2,3</sup> This situation has led some authors to question the use of chemotherapy outside clinical trials<sup>4</sup> and appears to justify the skepticism shown by pneumologists towards the advantages of this treatment, although few series have assessed its effects in usual health care contexts.<sup>5,6</sup>

With these aspects in mind, we designed an observational study of all patients with advanced non-small cell bronchogenic carcinoma who were treated at our hospital. The objective was to analyze prognostic factors related to survival and determine whether cytostatic treatment had an independent influence.

## Patients and Methods

Patients with cytohistologic diagnosis of advanced non-small cell bronchogenic carcinoma, defined as those in stages IV and IIIB with pleural effusion or N2-N3 lymph node involvement according to TNM tumor staging, were analyzed retrospectively.<sup>7</sup> The study covered the period from January 1997 through December 2004.

The oncological committee of our hospital (composed of doctors from the oncology, radiotherapeutic oncology, chest surgery, and clinical pneumology departments) assessed all patients to decide on the most appropriate treatment. Patients received purely symptomatic treatment if they themselves refused other treatment proposed or if the committee decided it to be the preferable treatment given the advanced age of the disease or the presence of significant comorbidity (2 or more associated processes).

Patients were excluded from the study if they had ECOG performance status greater than 2, stage IV disease and a single site of metastasis treated surgically, or if they died during diagnosis or from causes unrelated to the neoplastic disease.

The following variables were systematically recorded: age, sex, smoking habit, comorbidity, clinical history, laboratory test results, imaging results, performance status on the ECOG scale, TNM staging, and treatment received.

The following definitions were established: weight loss as a decrease of more than 5% of normal weight in the previous 6 months, cytostatic treatment as at least 2 cycles of chemotherapy with or without associated radiotherapy, symptomatic palliative treatment using pharmacotherapy or radiotherapy as well as endobronchial recanalization using laser resection or stent insertion, and survival as the number of weeks from the time of diagnosis until the last examination or death (cutoff date, April 30, 2005).

## Statistical Analysis

Quantitative variables were expressed as means (SD). Qualitative variables were dichotomous. The Student *t* test was used to compare independent means and the  $\chi^2$  distribution was used for qualitative variables. Correlations were assessed between survival and the following variables: age, sex, comorbidity, weight loss, hemoglobin, total lymphocyte count, albumin serum, lactate dehydrogenase, calcium, histological type, ECOG score, TNM, and treatment.

Mean survival was calculated using the Kaplan-Meier method of comparison of the survival curves, the log-rank test. Significant variables were included in the Cox regression model of proportional risk to identify prognostic factors associated with survival.

A *P* value of less than .05 was considered significant.

## Results

### Overall Results

During the study period, 235 patients were diagnosed, of whom 45 fulfilled at least 1 of the exclusion criteria: 28 with ECOG scores greater than 2, 12 in stage IV with a single metastasis treated surgically, and 5 deaths. The study sample was finally composed of 190 patients (157 men and 33 women), with a mean age of 61.75 (10.85) years (range, 33-85 years). A history of smoking was found in 170 (89%) patients and associated comorbidity in 93 (49%). Histological types were distributed in the following way: epidermoid carcinoma was found in 79 patients, adenocarcinoma in 70, and undifferentiated large cell carcinoma in 41. According to TNM staging, 65 patients were classified in stage IIIB and 125 in stage IV.

Treatment was cytostatic for 144 patients (76%) and purely palliative in the remaining 46, of whom 4 patients had refused the proposed cytostatic treatment. The oncological committee decided on palliative treatment for 42 patients, in 16 because of their advanced age (mean age, 78.16 years; range, 73-87) and in 26 because of comorbidity (the diseases found were cardiovascular disease in 16 patients, kidney disease in 9, chronic obstructive pulmonary disease in 7, neurological disease in 5, and liver disease in 3). Table 1 shows patient characteristics according to treatment received.

### Survival Analysis

The median survival was 31 weeks (range, 26-38): 38 weeks with chemotherapy and 17 with palliative treatment (*P*=.0001). In the univariate analysis, the following variables were significantly associated with prolonged survival: ECOG of 0 to 1 (*P*=.00001), cytostatic treatment (*P*=.0001), absence of weight loss (*P*=.001), total lymphocyte count greater than 1500/ $\mu$ L (*P*=.02), and lactate dehydrogenase count less than 460 IU/L (*P*=.02). When these variables were analyzed with the Cox regression model, absence of weight loss, cytostatic treatment, and ECOG score of 0 to 1 remained significant (Table 2).

TABLE 1  
Patient Characteristics by Treatment\*

	Cytostatic (n=144)	Symptomatic (n=46)
Mean age (SD), y	59.79±10.46	67.89±8.43 <sup>†</sup>
Sex		
Men	116 (81%)	41 (89%)
Women	28 (19%)	5 (11%)
Comorbidity	60 (42%)	33 (72%) <sup>†</sup>
ECOG		
0-1	137 (96%)	33 (72%)
2	7 (4%)	13 (28%) <sup>†</sup>
Weight loss	59 (41%)	20 (43%)
Hemoglobin, g/dL		
<11	15 (8%)	9 (20%) <sup>†</sup>
>11	129 (92%)	37 (80%)
Total lymphocytes		
<1500/μL	49 (33%)	16 (35%)
>1500/μL	95 (67%)	30 (65%)
Albumin, g/L		
<3.5	64 (44%)	18 (38%)
>3.5	80 (56%)	28 (62%)
Lactate dehydrogenase, IU/L		
<460	109 (77%)	34 (76%)
>460	35 (23%)	12 (24%)
TNM		
IIIb	55 (38%)	10 (22%)
IV	89 (62%)	36 (78%)

\*ECOG indicates Eastern Cooperative Oncology Group.  
<sup>†</sup>P<.05.

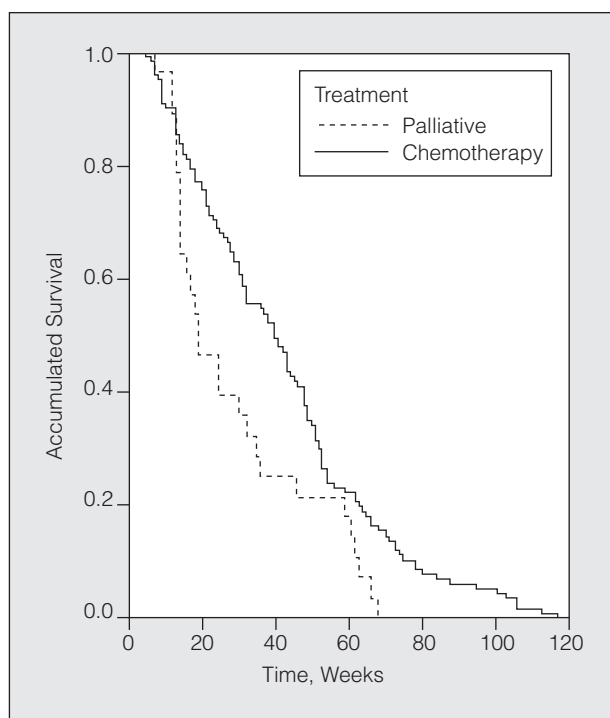


Figure 1. Survival curve for ECOG 0-1 according to treatment received.

TABLE 2  
Cox Regression Model for the Whole Group\*

Variable	HR	95% CI	P
Weight loss	1.73	1.26-2.39	.001
Treatment	1.85	1.25-2.76	.002
ECOG	2.84	1.62-5.00	.0001

\*HR indicates hazard ratio; CI, confidence interval.

TABLE 3  
Cox Regression Model in Patients With Performance Status 0-1\*

Variable	HR	95% CI	P
Weight loss	1.55	1.11-2.20	.01
Treatment	1.85	1.19-2.87	.006

\*HR indicates hazard ratio; CI, confidence interval.

Figure 1 shows the survival curve according to treatment received, in patients with ECOG scores 0 to 1: the median was 40 weeks for patients who received chemotherapy and 21 weeks for patients with symptomatic treatment ( $P=.002$ ). In patients with ECOG 2, the median survival was 15 weeks with chemotherapy and 11 weeks with symptomatic treatment.

In patients with a high performance status (ECOG 0 to 1), an ECOG score of 0 and the rest of the variables mentioned were significantly associated with survival in the univariate analysis but only treatment and weight loss were independently associated in the Cox regression model (Table 3). Figure 2 shows the survival

curve for patients with cytostatic treatment according to weight loss; in patients who lost weight, the median survival was 30 weeks for patients who lost weight and 46 weeks for those who did not ( $P=.02$ ).

## Discussion

Since the first clinical trials showing that chemotherapy prolonged survival in advanced bronchogenic carcinoma patients, the treatment has been applied in usual clinical practice without there appearing many reports of patient series in which possible benefits have been analyzed. We designed a study of prognostic factors, through which we found that cytostatic treatment, performance status, and weight loss were associated with survival. Similar results were obtained in 2 large studies in 1980 and 1991 with 5138 and 2531 patients, respectively.<sup>8,9</sup> Our study added a series of aspects we consider interesting, however:

1. Cytostatic treatment managed to prolong mean survival by approximately 5 months, notably longer than the 2 months obtained in meta-analyses<sup>1,3</sup> or the 3 months observed in a clinical trial recently published.<sup>10</sup> Our nonrandomized design could have affected the results—a possibility we will discuss below. The 8-year duration of the study could also have had an effect as during this time new drugs had been developed, improving palliative treatment and thereby influencing survival, as has been described by other authors.<sup>11</sup>

2. The benefits of chemotherapy are limited to patients with performance status 0 to 1, as recently demonstrated,<sup>12,13</sup> although the study by Spiro et al<sup>10</sup>

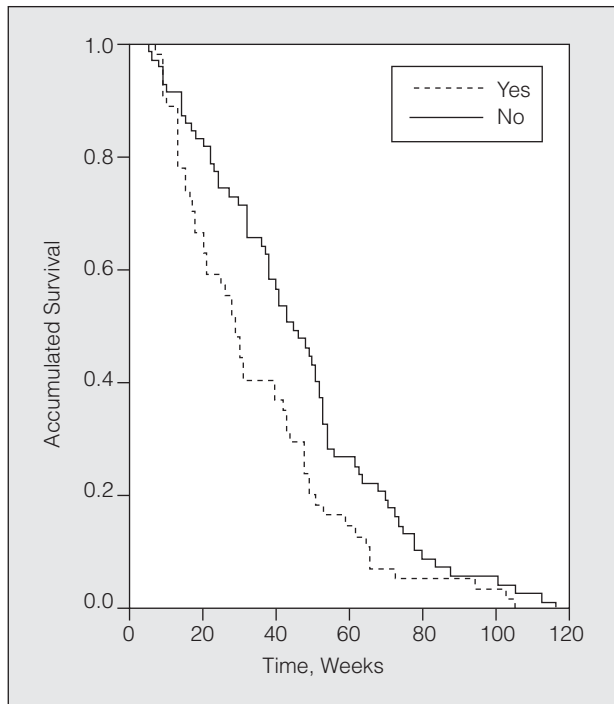


Figure 2. Survival curve for ECOG 0-1 with cytostatic treatment according to weight loss.

found no significant differences with respect to grade 2 performance patients. Given these differences, the groups of patients who could most benefit need to be carefully identified, as in usual clinical practice patients with performance status greater than 1 should not be given chemotherapy. On this point our results must be interpreted with caution, given the small number of patients with grade 2 in our study sample. Accordingly, it is of interest to determine which aspects influence patients with performance status 0 to 1. In our experience, absence of weight loss is associated with a better response to chemotherapy and, while it is not a defining factor, weight loss should be taken into consideration when found in the presence of other factors with poor prognosis, as has been suggested.<sup>14,15</sup>

3. We think that the results obtained in clinical trials are applicable to usual health care practice. Schroen et al,<sup>16</sup> however, observed that only a third of pneumologists believed chemotherapy was beneficial. Likewise, in a recent study which analyzed the opinion of a variety of medical specialists, Jennens et al<sup>17</sup> found that only 16% of pneumologists favored cytostatic treatment in stage IV patients, despite the fact that 56% (a percentage only surpassed by oncologists and radiotherapists) were knowledgeable about response and survival, with and without chemotherapy. This attitude does not seem justified, given our results, even though the increase in survival is slight and may be inadequate. The answer to this question depends on the personal situation of the patient whose perception of this benefit is the one that counts the most.<sup>18</sup>

We should recommend this treatment to our patients, then, with accurate information which weighs the benefits patients could obtain against their expectations, in order to arrive at the most appropriate decision.

It should be remembered that, because this study was retrospective and nonrandomized, there could be bias as the results of Table 1 seem to indicate: the patients who received palliative treatment were older and had greater comorbidity. The bias is difficult to remove as both features are determining factors of the therapy to be used, as agreed by all members of the hospital oncological committee, in line with the tendency against giving cytostatic treatment to these patients,<sup>19,20</sup> despite there being no firm results on the negative prognostic significance of these variables as also shown in our study. It should be noted that the group with performance status of 0 to 1 was more homogenous and that the difference between the 2 treatment groups remained significant, and we believe do this adds validity to our results.

Another limitation was not analyzing quality of life, which is, together with survival, a factor that defines the success of a treatment. However, the main objective of the study was to examine a health care process and to open to debate questions we pose in our daily working life and which are reflected in our work.

We conclude that in normal clinical practice, chemotherapy significantly prolongs survival, although this benefit is restricted to patients with performance status of less than 2 and is greater if there is no associated weight loss, factors which should be taken into account when informing the patient of the most appropriate treatment for him or her. Taking all into account, we do not believe pneumologists' skepticism of this therapy to be justified.

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