ORIGINAL ARTICLES

Stage IIIA and IIIB Non-Small Cell Lung Cancer: Results of Chemotherapy Combined With Radiation Therapy and Analysis of Prognostic Factors

Julio Sánchez de Cos Escuín,[a] Isabel Utrabo Delgado,[a] Joaquín Cabrera Rodríguez,[b] Marcelo Jiménez López,[c] Carlos Disdier Vicente,[a] and J. Antonio Riesco Miranda[a]

[a]Sección de Neumología, Hospital San Pedro de Alcántara, Cáceres, Spain
[b]Servicio de Radioterapia, Clínica San Francisco, Cáceres, Spain
[c]Servicio de Cirugía Torácica, Hospital Clínico Universitario, Salamanca, Spain

OBJECTIVE: Most patients with stage III non-small cell lung cancer (NSCLC) are not candidates for surgery but can benefit from chemotherapy combined with radiation therapy. The objective of the present study was to analyze the results of sequential chemotherapy and radiation therapy and the prognostic value of initial clinical and laboratory variables.

PATIENTS AND METHODS: We carried out a retrospective study of 92 patients with stage III NSCLC treated with a sequential regimen of chemotherapy (carboplatin–etoposide, carboplatin–gemcitabine, and carboplatin–paclitaxel), and radiation therapy (6000 cGy in daily doses of 200 cGy, 5 d/wk). Response to therapy, overall survival, and the prognostic value of epidemiological, clinical, and laboratory variables were evaluated using univariate and multivariate analyses.

RESULTS: Median survival time was 14 months, with a 3-year survival rate of 16.1%. Poor performance status (score of 2 on the Eastern Cooperative Oncologic Group [ECOG] scale), anemia, and elevated serum concentrations of carcinoembryonic antigen were predictive of poorer survival in the multivariate analysis. In the univariate analysis, weight loss and diagnosis before the year 2000 were also associated with poorer prognosis (*P*<.01). TNM stage was not significantly correlated (*P*=.08). Toxicity was low, with 1 death and few cases of grade 3 or 4 toxicity according to World Health Organization criteria.

CONCLUSIONS: The use of chemotherapy combined with radiation therapy should be considered contraindicated in cases of poor performance status (ECOG scale score of 2). Weight loss, an elevated serum concentration of carcinoembryonic antigen, and a hemoglobin concentration of less than 12 g/dL carry a poor prognosis.

Key words: *Non-small cell lung cancer. Stage III. Chemotherapy. Radiation therapy. Prognostic factors.*

Carcinoma de pulmón no microcítico. Estadios IIIA y B. Resultados del tratamiento combinado (quimioterapia y radioterapia) y análisis de factores pronósticos

OBJETIVO: La mayoría de los pacientes con carcinoma de pulmón no microcítico y estadio III no son candidatos a cirugía y pueden beneficiarse del tratamiento combinado con quimioterapia (QT) y radioterapia (RT). En este trabajo se han analizado los resultados de una pauta combinada secuencial y el valor pronóstico de variables clínicas y analíticas iniciales.

PACIENTES Y MÉTODOS: Se ha realizado un estudio retrospectivo de 92 pacientes con carcinoma de pulmón no microcítico y estadio III tratados con una pauta secuencial combinada de QT (3 combinaciones diferentes de carboplatino: con etopósido, con gencitabina y con paclitaxel) y RT (6.000 cGy: 200 cGy diarios, 5 días/semana). Se evaluaron la respuesta, la supervivencia global y el valor pronóstico de variables epidemiológicas, clínicas y analíticas mediante análisis univariante y multivariante.

RESULTADOS: La supervivencia mediana fue de 14 meses, con una supervivencia a los 3 años del 16,1%. El mal estado general –grado 2 de la escala del Eastern Cooperative Oncological Group (ECOG)–, la anemia y las concentraciones séricas elevadas de antígeno carcinoembrionario fueron predictivos de peor supervivencia en el modelo multivariante. Además, en el análisis univariante la pérdida de peso y los diagnosticados antes del año 2000 también se asociaron a peor pronóstico (p < 0,01). El grado TNM no alcanzó la significación estadística (p = 0,08). La toxicidad fue escasa; hubo una muerte y pocos casos de grados III y IV de la Organización Mundial de la Salud.

CONCLUSIONES: Un mal estado general (ECOG 2) debe considerarse una contraindicación para el uso de pautas combinadas de QT y RT. La pérdida de peso, las concentraciones séricas elevadas de antígeno carcinoembrionario y una cifra de hemoglobina igual o inferior a 12 g/dl conllevan peor pronóstico.

Palabras clave: *Carcinoma de pulmón no microcítico. Estadio III. Quimioterapia. Radioterapia. Factores pronósticos.*

Introduction

Stage III (IIIA and IIIB) non-small cell lung cancer (NSCLC) is considered to be nonresectable in the majority of patients. The role of surgery—with or without chemotherapy or radiation therapy—has been placed under scrutiny in recent trials, and it seems to offer no clear advantages in terms of survival,[1,2] although some patients in certain very specific circumstances might benefit from it. These patients, however, represent a very small proportion of the total number of patients diagnosed clinical stage III (before any treatment is undertaken) NSCLC. Once surgery has been ruled out, the best treatment currently available is chemotherapy combined with radiation therapy. The superiority of this combination over radiation therapy alone was demonstrated several years ago.[3-5] Such combined-modality regimens can only be applied in the absence of pleural effusion, significant comorbidity, or poor performance status. The most recent randomized trials studying the integration of chemotherapy and radiation therapy have shown improved survival with concurrent chemotherapy and radiation therapy regimens.[6,7] However, in view of the greater toxicity and the practical difficulties associated with such regimens, there still remain some doubts about the conditions necessary for their use.[8] This greater toxicity may require that we be more selective in enrolling patients in such concurrent protocols.

In the present study we analyzed survival and the adverse effects of sequential combined-modality therapy in patients with stage III NSCLC diagnosed in our hospital. We also examined the prognostic value of various epidemiological, clinical, and laboratory variables. This may help us to select those patients who may be candidates for more aggressive regimens more effectively.

Patients and Methods

We carried out a retrospective study of patients diagnosed with NSCLC treated with a combined-modality regimen of chemotherapy and radiation therapy at our hospital between January 1996 and December 2004. Practically all of the patients were diagnosed in the pneumology department. The majority of the variables analyzed were recorded at the moment of diagnosis, as these same data had been used for studies of another nature.

Patients with a cytologic or histologic diagnosis of Stage III (IIIA or IIIB) NSCLC treated only with chemotherapy and radiation therapy were included in the study. Those patients who underwent surgical resection at any point in the process were excluded. The study period was from 1996 and 2004 and only those patients who had been followed for a minimum of 18 months by the end of the study were included.

Inclusion criteria for the combined-modality protocol were as follows: *a)* absence of malignant pleural effusion; *b)* performance status grade 2 or lower on the Eastern Cooperative Oncological Group (ECOG) scale; *c)* absence of comorbidity (severe chronic obstructive pulmonary disease; significant heart, kidney or liver failure; etc) sufficiently severe for the attending physician to consider combined-modality therapy to be contraindicated; and *d)* informed consent signed from the patient and a family member.

Diagnostic Procedures and Staging

In addition to standard procedures (medical history, physical examination, routine laboratory workup, and chest x-ray), patients underwent chest and upper abdominal computed tomography (CT) as well as spirometry and electrocardiogram. Diagnosis was confirmed by cytology or histology on samples obtained by fiberoptic bronchoscopy or by other procedures (needle aspiration of lymph nodes, transthoracic needle aspiration, or mediastinoscopy). If the patient appeared to be a candidate for surgery or combined-modality therapy, CT or magnetic resonance imaging (MRI) was performed to rule out silent metastases. Other tests (bone scintigraphy, bone radiography, or organ biopsy) were performed according to symptoms.

For staging, a cytology or histology sample was obtained in 52.2% of the patients. Samples were obtained by mediastinoscopy in 33 patients, by transcarinal or transtracheal needle biopsy of lymph nodes in 9 patients, and by supraclavicular lymph node needle biopsy in 6 patients. In 14 patients (15.22%) there was clinical evidence (7 patients with recurring paralysis, 4 patients with tracheal invasion or compression, and 3 patients with superior vena cava syndrome) of mediastinal or T4 involvement.

In the 30 remaining patients (32.6%) the stage was classified by radiologic methods (chest x-ray and CT, with large and clearly diseased lymph nodes) alone. The TNM subgroups are presented below.

Treatment Regimens

– Chemotherapy. Three different regimens were applied during the study period: *a)* intravenous carboplatin —area under the curve (AUC) of 6—on day 1 and 120 mg/m^2 of etoposide administered intravenously on day 1 and orally on days 2 and 3, every 21 days; *b)* paclitaxel, at a dose of 200 mg/m^2 ,and intravenous carboplatin (AUC of 6) on day 1, every 21 days; and *c)* 1500 mg/m^2 of intravenous gemcitabine on days 1 and 8, and intravenous carboplatin (AUC of 5) on day 1, every 21 days. During the first 4 years, from 3 to 6 treatment cycles were scheduled, depending on the regimen applied and the patient's tolerance of chemotherapy. From the year 2000 on, the number of treatment cycles was reduced to 3 or 4. Patients received a course of antiemetic prophylaxis with corticosteroids and antiserotonergic drugs before the beginning of each cycle.

– Radiation therapy. Radiation therapy was scheduled between 20 and 40 days after the last chemotherapy cycle. All patients received a dose fraction of 200 cGy 5 days a week, up to a total dose of 5000 cGy to the areas at risk for subclinical disease and 6000 cGy to the macroscopic tumor volume (primary tumor and lymph node). The total dose to the spinal cord was 4500 cGy or more. The volumes treated and the radiation techniques used underwent modifications during the 8 years of the study.

Between 1996 and 2000 radiation therapy was planned using a conventional 2-dimensional simulator. Most treatments initially targeted macroscopic mediastinal and pulmonary lesions visible on radiographs, the ipsilateral pulmonary hilum, mediastinal stations 2 through 7 for cancers of the upper lobes and 2 through 9 for cancers of the middle or lower lobes, and the supraclavicular fossae in all cases. The volume for the double exposure image consisted of the macroscopic lesion plus an additional margin. Multiple portals were used with cobalt-60 beams and 18-MV linear accelerator photons. Lead-alloy blocks (made of bismuth, lead, tin, and cadmium) were used to shield organs.

Since 2001 simulations have been carried out using helicoidal CT and treatments have been planned using 3D dosimetry according to the guidelines outlined in Report 50 of the International Commission on Radiation Units and
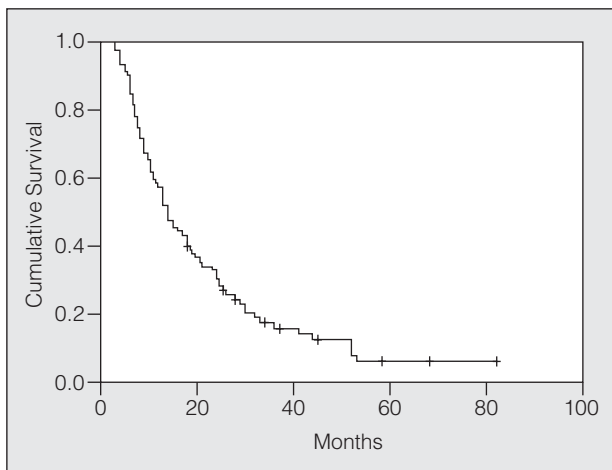
Figure 1. Overall survival in the series. Median survival time, 14 months. Survival rates at 1, 2, and 3 years were 57.6%, 30.1%, and 16.1%, respectively.

Measurements.[9] In addition to spinal cord tolerance dose, lung tolerance dose (risk of pneumonitis), and V20[10] (lung volume receiving a dose ≥20 Gy) were considered in planning treatment. The treatment volume is generally restricted to the macroscopic tumor and lymph node lesions (all diseased lymph nodes ≥1 cm), without an explicit attempt to consider elective radiation to uninvolved lymph node stations.[11-14] Occasionally, however, some patients received elective mediastinal or supraclavicular radiation based on the judgment of the clinician. Treatment was carried out with a linear electron accelerator, using multiple isocentric 15-MV photon beams and multi-leaf collimation.

Response Criteria

In order to evaluate objective response, radiologic tests (chest x-ray and/or CT) were repeated between 20 and 30 days after the end of treatment. We used the RECIST (Response Evaluation Criteria in Solid Tumors) criteria,[15] based on a change in length of one of the diameters of the measurable lesions. The usual criteria were used to classify response as complete or partial remission, stabilization, or progression.

Survival times were calculated from the date of initiation of treatment until death or the last check-up, if the patient was alive.

Treatment toxicity was evaluated according to the criteria of the World Health Organization (WHO).[16]

Statisical Analysis

Survival curves were plotted using the Kaplan–Meier method. The log-rank test was used for between-groups comparisons. Once the univariate analysis had been performed with each of the variables, those that had achieved statistical significance were selected to be entered into the multivariate Cox proportional hazards model using a sequential elimination procedure. Correlations were assessed using the Pearson correlation coefficient. Statistical analyses were performed using the SPSS statistical package, version 8 (Chicago, Illinois, USA).

TABLE 1
Patient Characteristics*

	N	%
Sex		
Men	90	97.8
Women	2	2.2
Age, y†		
40-49	10	10.9
50-59	25	27.2
60-69	37	40.2
70-79	20	21.7
ECOG		
Grade 0	21	22.8
Grade 1	63	68.4
Grade 2	8	8.7
Weight loss		
No	58	69.0
≤10% of body weight	21	25.0
>10% of body weight	5	6.0
No data available	8	-
Histology		
Squamous cell	51	55.4
Adenocarcinoma	24	26.1
Other	17	18.5
TNM stage		
IIIA	27	29.3
T1 N2	2	
T2 N2	16	
T3 N	27	
T <4N2	2	
IIIB	65	70.7
T2 N3	9	
T3 N3	2	
T4 N0	16	
T4 N2	21	
T4 N3	11	
T4 NX	6	

*ECOG indicates Eastern Cooperative Oncology Group performance status scale
†Mean age, 62.3 years (range, 43-77 years).

TABLE 2
Response to Therapy

	N	%
Not evaluable	10	10.9
Evaluable	82	89.1
Complete remission	7	8.5*
Partial remission	37	45.1*
Stabilization	34	41.5*
Progression	4	4.9*

*Percentages calculated as percent of total number of evaluable patients.

Results

From January 1996 to December 2004, 116 patients with NSCLC who had not undergone surgery were enrolled in the combined-modality therapy protocol. Twenty-four patients were excluded from the study: 12 of these patients had TNM stage I or II tumors, and 4 had stage IV tumors; 2 received concurrent chemotherapy and radiation therapy;

for the remaining 6 patients, duration of follow-up was not long enough to meet the inclusion criteria. Characteristics of the 92 patients who were finally included, with TNM subgroups within each group (IIIA or IIIB), are shown in Table 1.

Adherence to Treatment Plan

Six patients (6.5%) received fewer than 3 cycles (only 2 cycles) of chemotherapy. Seventy-nine patients (86%) received the planned 6000 cGy of radiation, with occasional delays due to technical difficulties. The remaining 13 patients received between 2000 cGy and 5000 cGy.

Disease course was evaluated in all but 1 patient, for whom follow-up was interrupted due to change of residence
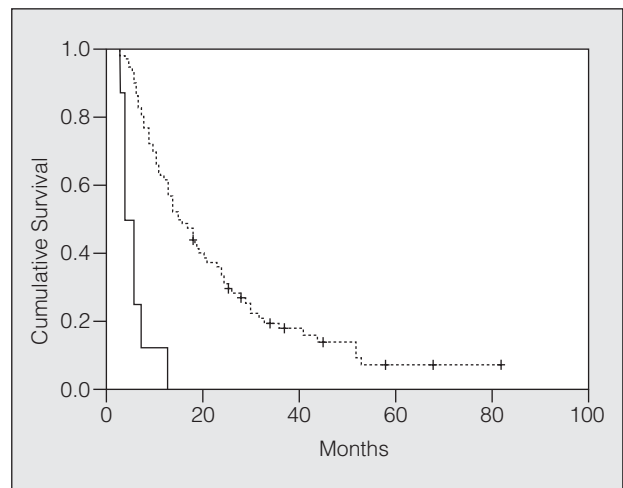

Figure 2. Survival according to the Eastern Cooperative Oncology Group (ECOG) performance status scale score. The dotted line indicates ECOG scores of 0 and 1; the solid line, ECOG grade 2.

TABLE 3
Prognostic Variables. Univariate Analysis*

	No.	Median Survival Time, Months (95% CI)	P
Age, y			.58
< 50	10	15 (0.5-31.3)	
51-70	67	14 (10.6-17.4)	
> 70	15	13 (3.5-22.4)	
ECOG grade			<.0001
0 and 1	84	15 (10.9-19.1)	
2	8	4 (2.3-5.7)	
COPD			.37
No	50	15 (10.0-19.9)	
Yes	30	16 (9.7-22.3)	
Weight loss			.0004
No	58	19.5 (12.5-26.5)	
Yes	26	9.6 (4.6-13.4)	
Histology			.37
Squamous cell	51	16 (9-23)	
Adenocarcinoma	24	13 (8.2-17.8)	
Other	17	13 (6.5-19.5)	
TNM stage			.08
IIIA	27	18 (11.2-24.8)	
IIIB	65	13 (9.9-16.1)	
Period in which diagnosed			.007
1996-1999	48	13 (10.6-15.9)	
2000-2004	44	23 (11-35.0)	
Chemotherapy regimen			.47
CPT + VP-16	12	7.5 (3-12.0)	
CPT + GEN	14	12 (9.3-14.7)	
CPT + paclitaxel	66	17 (12.1-21.9)	
Anemia			<.0001
Hemoglobin <12 g/dL	6	5 (0.2-9.8)	
Hemoglobin ≥12 g/dL	79	18 (13.4-22.6)	
Serum CEA, ng/mL			.0007
≤5	45	20.5 (14.4-26.6)	
>5	28	10.0 (6.9-13.1)	
Serum NSE, ng/mL			.22
≤15	52	14 (9.3-18.7)	
>15	17	20.5 (9.4-31.6)	
Serum SCCAg, ng/mL			.22
≤2	40	15 (10.0-19.9)	
>2	28	14 (5.7-22.3)	

*CEA indicates carcinoembryonic antigen; CPT, carboplatin; ECOG, Eastern Cooperative Oncology Group performance status scale; COPD, chronic obstructive pulmonary disease; GEN, gemcitabine; CI, confidence interval; NSE, neuron-specific enolase; SCCAg, squamous cell antigen; VP-16, etoposide.
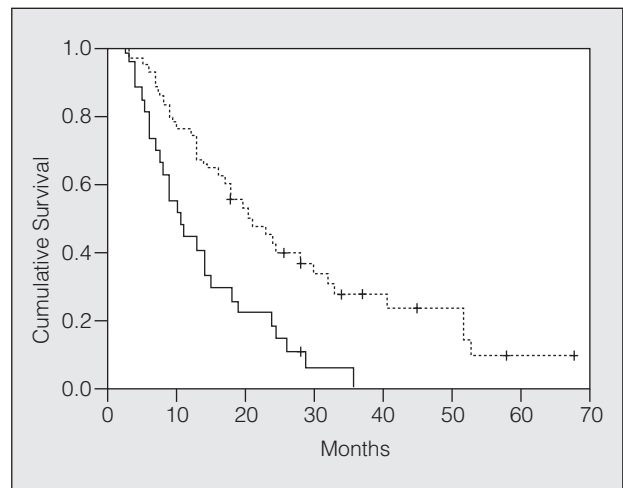

Figure 3. Survival according to a cutoff of serum carcinoembryonic antigen (CEA) concentration of 5 ng/mL. The dotted line indicates survival for patients with a CEA concentration <5 ng/mL; the solid line, survival for patients with a CEA concentration ≥5 ng/mL (*P*=.0007).
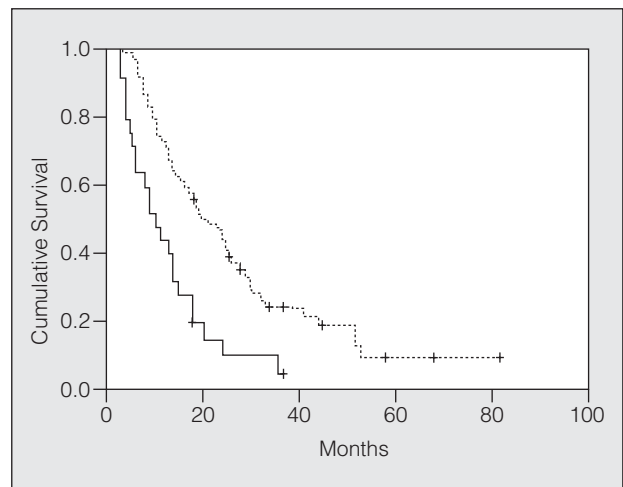

Figure 4. Survival according to weight loss (*P*=.0005). The dotted line indicates without weight loss; the solid line, with weight loss
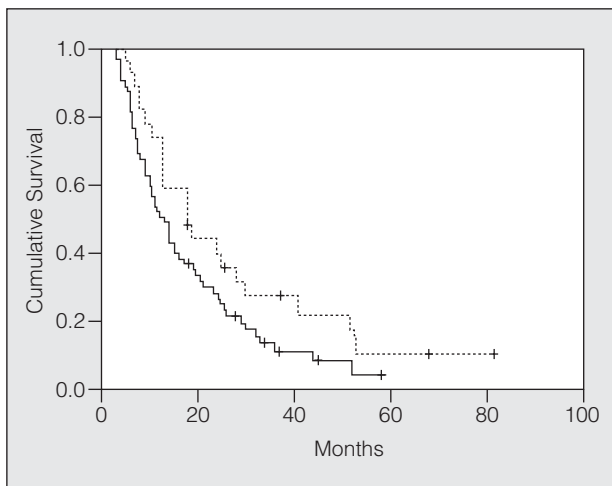
Figure 5. Survival according to TNM stage (*P*=.08). The dotted line indicates stage IIIA; the solid line, stage IIIB.
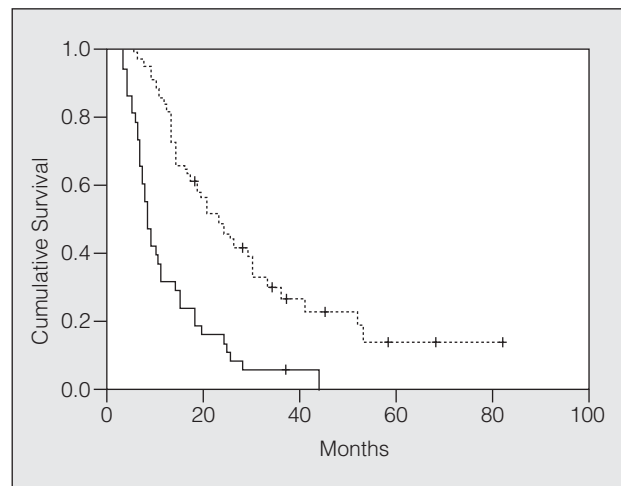

Figure 6. Survival according to response to therapy (*P*>.0001). The dotted line indicates complete or partial remission; the solid line, stabilization, or progression.

to an unknown location. At the close of the study, 13 patients were still alive. Mean duration of follow-up for these patients was 28 months (minimum duration, 18 months; maximum duration, 83 months).

The group labeled *other* under histology in Table 1 included 14 classified as non-small cell tumors, with no further specification; 2 classified as undifferentiated large cell tumors; and 1 classified as a mixed adenosquamous

TABLE 4
Prognostic Variables. Multivariate Analysis*

	β	SE	Exp. (β)	*P*
ECOG score	2.34	0.54	10.4	<.0001
Serum CEA	0.96	0.28	2.6	.001
Anemia	2.09	0.50	8.1	.0001
Global significance of the model (c=59.15)				<.0001

*Variables of the model are categorized according to Table 3.
CEA indicates carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group performance status scale.

TABLE 5
Adverse Effects of Therapy*

Toxic Deaths	1 Patient		
Other Toxic Effects	**WHO Toxicity Grade**		
	Grades 1 and 2, %	Grade 3, %	Grade 4, %
Anemia	10.0	3.8	–
Neutropenia	2.5	2.5	1.3
Thrombopenia	–	–	1.3
Nausea, vomiting	27.5	1.3	–
Paresthesia, paresis	50.0	5.0	–
Joint pain	21.3	–	–
Fever, low-grade fever	7.5	–	–
Pruritus	2.5	–	–
Hair loss	23.8	58.7	–
Esophagitis	5.0	2.5	–
Pneumonitis	–	3.8	–

*WHO indicates World Health Organization.

cell tumor. The level of response to therapy (according to RECIST[15] criteria) is shown in Table 2. Figure 1 shows the survival curve for the entire group. Median survival time was 14 months (95% confidence interval [CI], 11-17 months) and the 3-year survival rate was 16.1% Table 3 shows the univariate analysis of the prognostic factors determined at diagnosis. For some variables, the total number of patients is fewer than 92 because data could not be collected for all of them. Poor performance status (ECOG score of 2), the presence of anemia or weight loss, and an elevated serum concentration of carcinoembryonic antigen (CEA) were significantly associated with poor prognosis. Diagnosis and treatment during the first part of the study period (1996-1999) had a similar association. Patients with stage IIIA tumors had a better prognosis than those with stage IIIB tumors, although the difference was not significant. Figures 2-5 show survival curves according to the values of some of the above-mentioned prognostic factors. When significant variables (*P*<.05) were entered into the multivariate analysis (Cox model), the results shown in Table 4 were obtained. Weight loss, which had considerable prognostic value in the univariate analysis, did not enter the final model due to its close correlation with ECOG scale score (Pearson correlation coefficient, *r*=0.372; *P*<.01). Figure 6 shows that a favorable objective response (complete or partial remission) was associated with significantly longer survival time.

Adverse effects, classified according to WHO[16] criteria, are shown in Table 5.

Discussion

Since several randomized trials in patients with Stage III NSCLC showed that combined regimens of chemotherapy and radiation therapy were more effective than the traditional radiation therapy alone,[3-5] various authors have studied multiple combinations of new drugs, new radiation therapy regimens, and new ways

of integrating chemotherapy and radiation therapy.[5,7,18-23] Some of the preliminary results of these trials have been promising, although more time is needed to understand the therapeutic implications of such new regimens.

One of the limitations common to many trials of combined-modality therapy for unresectable stage III tumors is the low level of certainty in tumor staging, which is often based (especially in cases of mediastinal involvement) on radiography alone or on unspecified methods.[6,7,18-24] However, in two thirds of the patients in our series there was either cytologic or histologic confirmation or sufficient clinical evidence (recurrent paralysis, superior vena cava syndrome) of mediastinal involvement. In the rest, although no such confirmation was available, chest CT showed extensive mediastinal lymph node involvement. Systematic intracranial radiography (by CT or MRI) was also performed in order to rule out possible silent metastases, which may be present in an appreciable percentage of patients.[25,26] Unlike other studies that included patients with stage I and II disease,[5,18,19,24] our analysis was limited strictly to patients with stage III disease. Furthermore, while we included some patients with an ECOG scale score of 2 or with weight loss more than 10% of body weight, these characteristics constituted exclusion criteria in several other studies.[5,18-23,27-29] In view of the importance of patient-related prognostic factors, small differences in inclusion criteria may explain the differences in survival observed in these studies, with median survival times ranging from 11 months to 17 months.[5-7,19,20,27,28] Our results (median survival time of 14 months and a 3-year survival rate of 16.1%) were within the predicted range for patients with stage III disease and were very similar to those of another series of patients treated with concurrent regimens whose less favorable prognosis prevented them from participating in other clinical trials with cisplatin. [30]

The analysis of possible prognostic factors showed that TNM stage (IIIA or IIIB) was not statistically significant, although the small size of the stage IIIA group must be borne in mind. This is not surprising, and in other studies, such as that of the Radiation Therapy Oncology Group (RTOG), stage IIIB patients were even found to have a better survival rate than stage IIIA patients.[29] The authors attributed this result to the considerable heterogeneity of patients in both group IIIA and IIIB, as well as to the above-mentioned difficulty in precise staging. In our opinion, even with more exact staging, there are other factors that carry more prognostic weight than TNM subgroup in the context of combined-modality therapy without surgery. As expected, the authors whose series included stages I and II patients did usually find TNM stage to be of high prognostic value. In our opinion, however, such patients, who did not undergo surgery for reasons that were not always explicit, would require separate analysis.

The ability to carry out activities of daily living, including personal care (performance status, usually evaluated on the Karnofsky or ECOG scale) invariably has high prognostic power. Even some authors who

excluded patients with ECOG scale scores of 2 or higher from combined-modality therapy observed significant differences between patients with scores of 0 and 1.[29] In our study we found that only one of the patients with an ECOG scale score of 2 managed to survive more than 1 year (13 months). We therefore conclude that such patients should be candidates for less aggressive therapies and should only exceptionally be considered for radical combination-modality regimens.

The poor prognosis associated with weight loss in the previous 6 months not attributable to other causes such as metabolic disorders (diabetes, etc) or a weight-loss diet[29,30] is well known and was observed in our study. However, the high statistical significance observed in the univariate model was not maintained in the multivariate model due to its close colinearity with a high ECOG scale score, which was already present in the model.

Some trials carried out with combined-modality regimens established an upper age limit, usually 75 years, as an inclusion criterion. The oldest patient in out study was 77, and little information is available on such treatment in patients more than 80 years old. However, age in itself does not seem to have a negative influence on outcomes.[28] In our series we found no differences in survival between patients over 70 years and the rest. Toxicity does seem to be greater in older patients, and this is probably related to the more frequent comorbidity associated with older age.

As in other studies, particularly that of the RTOG,[29] the presence of anemia at baseline was closely associated with a poorer prognosis. Hemoglobin concentration less than 12 g/dL was one of the 3 factors that maintained independent prognostic significance in the multivariate analysis. As this condition can be corrected through the use of transfusions or erythropoietin preparations, the possible use of such support therapies should be considered before anemic patients are excluded from such aggressive treatments, provided they meet the other criteria.[29]

Serum CEA concentration, one of the oldest known molecular markers for cancer in general, has a moderate diagnostic value in NSCLC.[31] Its value for prognosis and follow-up of patients who have undergone surgery has been assessed in several studies,[32] but we found none that evaluated its significance in the particular context of stage III patients receiving combined chemotherapy and radiation therapy. In the present study we observed that a serum CEA concentration higher than the established normal limit (5 ng/mL) was clearly associated with shorter survival and that this discriminating capacity was independent of other factors, as shown in the multivariate analysis. This finding indicates that an elevated serum concentration of CEA may signal more aggressive tumor behavior.

During the second part of the study period (2000-2004), the median survival time (23 months) was significantly longer than during the first part (1996-1999), in which the median survival time was 13 months. Although the most obvious interpretation might be that of a possible effect of experience after an initial learning curve, it is

difficult to rule out other factors closely associated with the second period, such as greater accuracy in staging, the use of more precise radiation therapy planning techniques, or the increased use of paclitaxel and carboplatin in chemotherapy regimens leading to increased survival. Increased survival with this chemotherapy regimen did not achieve statistical significance, but this would be difficult to obtain in view of the small sample size of the other regimens.

The favorable response (complete or partial remission) observed by radiography is difficult to measure and would ideally require independent assessment (not carried out in the present study). It has recently been seen that CT evaluation tends to underestimate the percentage of complete remissions.[33] Despite such limitations, achievement of complete or partial remission according to traditional criteria was a prerequisite for long survival in our patients (Figure 6).

Two recent trials showed concurrent combined-modality therapy to be more effective than sequential therapy.[6,7] Such regimens are also more toxic, particularly in producing more esophagitis and pneumonitis. The rate of severe toxicity (grade 3 or 4 according to WHO criteria) with the sequential regimen was very low in our series and clearly lower than the rates reported in other series.[5-7,18-21,27] This seems to suggest that there is a certain margin for the use of the more aggressive concurrent regimen, as this might at least benefit patients with a favorable prognosis (young patients, those without anemia, those with a low ECOG scale score, etc). Furthermore it is likely that in the immediate future the incorporation of new technological advances (intensity-modulated radiation therapy, respiratory gating, 4D radiation therapy, etc)[34] may make it possible to increase the dose to the tumor by limiting the effects on healthy tissue.

In conclusion, median survival time in our patients with stage IIIA and IIIB NSCLC treated with sequential combined radiation therapy and chemotherapy was 14 months. This result was similar to that found in other studies. Poor performance status (ECOG scale score ≥ 2) should be considered a serious contraindication for the use of such combined-modality therapies. The presence of anemia carries a poor prognosis and it should be corrected, if possible, before aggressive chemotherapy and radiation therapy are undertaken. Other factors, such as weight loss and an elevated serum CEA concentration, also carry a poor prognosis. In view of the relatively low level of toxicity of the regimen analyzed, it is possible that those patients with the most favorable prognosis would benefit from treatments that are somewhat more effective, even if more toxic, such as concurrent chemotherapy and radiation therapy.

REFERENCES

1. van Meerbeeck J, Kramer G, van Schil PE, Legrand C, Smit EF, Schramel FM, et al. EORTC-Lung Cancer Group. A randomized trial of radical surgery (RS) versus thoracic radiotherapy (TRT) in patients with stage IIIA-N2 non-small cell lung cancer (NSCLC) after response to induction chemotherapy (ICT) (EORTC 08941). J Clin Oncol. 2005;23 Suppl 16:7015.

2. Albain KS, Swann RS, Rusch VR, Turrisi AT, Shepherd FA, Smith CJ, et al. North American Lung Cancer Intergroup. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA (pN2) non-small cell lung cancer (NSCLC): outcomes update of North American Intergroup 0139 (RTOG 9309). J Clin Oncol. 2005;23 Suppl 16:7014.

3. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small cell lung cancer. N Engl J Med. 1990;323:940-5.

4. le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non small cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst. 1991;83:417-23.

5. Sause W, Kolesar P, Taylor S, Johnson D, Livingston R, Komaki R, et al. Final results of phase III trial in regionally advanced unresectable non small cell lung cancer. Chest. 2000;117:358-64.

6. Cullen MH, Billingham LJ, Woodroffe AD, Chetiyarawardana AD, Gower NH, Joshi R, et al. Mitomycin, ifosfamide and cisplatin in unresectable non-small cell lung cancer: effects on survival and quality of life. J Clin Oncol. 1999;17:3188-94.

7. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III non small cell lung cancer. J Clin Oncol. 1999;17:2692-9.

8. West H, Albain KS. Current standards and ongoing controversies in the management of locally advanced non small cell lung cancer. Semin Oncol. 2005;32:284-92.

9. International Commission on Radiations Units and Measurements. Prescribing, recording and reporting photon beam therapy. ICRU Report 50. Bethesda: ICRU; 1993.

10. Graham MV, Purdy JA, Emmami B, Harms W, Bosch W, Lockett MA, et al. Clinical DVH analysis for pneumonitis after 3D treatment NSCLC. Int J Radiat Oncol Biol Phys. 1999;45:323-9.

11. Hayman JA, Martel MK, ten Haken RK, Normolle PD, Todd RF III, Littles JF, et al. Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase I trial. J Clin Oncol. 2001;19:127-36.

12. Rosenzweig KE, Sim SE, Mychalczak B, Braban LE, Schindelheim R, Leibel SA. Elective nodal irradiation in the treatment of non-small-cell lung cancer with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys. 2001;50:681-5.

13. Senan S Burgers JA, Samson MJ, van Klaveren RJ, Osei SS, van Sornsen de Koste J, et al. Can elective nodal irradiation be omitted in stage III non-small cell lung cancer? An analysis of recurrences in a phase II study of induction chemotherapy and "involved-field" radiotherapy. Int J Radiat Oncol Biol Phys. 2002;54:999-1006.

14. Emami B, Mirkovic N, Scott C, Byhardt R, Graham M, James Andras B, et al. Impact of regional nodal radiotherapy (dose/volume) on regional progression and survival in unresectable non-small cell lung cancer: an analysis of RTOG data. Lung Cancer. 2003;41:207-14

15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000;92:205-

16. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting the results of cancer treatment. Cancer. 1981;47:207-14.

17. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer. A meta-analysis using updated data on individual patients from 52 randomised trials. BMJ. 1995;311:899-909.

18. Saunders M, Dische S, Barrett A, Harvey A, Gibson D, Parmar M, et al. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non small cell lung cancer: a randomised trial. Lancet. 1997;350:161-5.

19. Maguire PD, Marks LB, Sibley GS, Herndon JE, Clough RW, Light KL, et al. 73.6 Gy and beyond: hyperfractionated, accelerated radiotherapy for non small cell lung cancer. J Clin Oncol. 2001;19:705-11.

20. Lau D, Leigh B, Gándara D, Edelman M, Morgan R, Israel V, et al. Twice-weekly paclitaxel and weekly carboplatin with concurrent thoracic radiation followed by carboplatin/paclitaxel consolidation for stage III non small cell lung cancer: a California cancer consortium phase II trial. J Clin Oncol. 2001;19:442-7.

21. Socinski MA, Rosenman JG, Halle J, Schell MJ, Lin Y, Russo S, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B non small cell carcinoma. Cancer. 2001;92:1213-23.

22. Jeremic B, Milicic B, Acimovic L, Miliasavljevic S. Concurrent hyperfractionated radiotherapy and low-dose daily carboplatin and paclitaxel in patients with stage III non small cell lung cancer: long-term results of a phase II study. J Clin Oncol. 2005;23:1144-51.

23. Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, et al. Combined chemotherapy regimens of paclitaxel and carboplatin for locally advanced non small cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol. 2005;23:5883-91.

24. Olasolo JJ, Alonso Redondo E, León Jiménez A, Rueda Ramos A. Carcinoma no microcítico de pulmón. Supervivencia y factores pronósticos del tratamiento radioterápico. Arch Bronconeumol. 2003;39:81-6.

25. Schouten LJ, Rutten J, Huveneers HAM, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney and lung and melanoma. Cancer. 2002;94: 2698-705.

26. Mamon HJ, Yeap BY, Jänne PA, Reblando J, Shrager S, Jaklitsch MT, et al. High risk of brain metastases in surgically staged IIIA non small cell lung cancer patients treated with surgery, chemotherapy and radiation. J Clin Oncol. 2005;23:1530-7.

27. Schild SE, Stella PJ, Geyer SM, Bonner JA, Marks RS, McGinnis WL, et al. A phase III trial comparing chemotherapy plus either once a day radiotherapy or twice a day radiotherapy in stage III non small cell lung cancer. Int J Radiat Oncol Biol Phys. 2002;54: 370-8.

28. Schild SE, Stella PJ, Geyer SM, Bonner JA, McGinnis WL, Mailliard JA, et al. The outcome of combined-modality therapy for stage III non small cell lung cancer in the elderly. J Clin Oncol. 2003;21:3201-6.

29. Socinski MA, Zhang C, Herndon JE, Dillman RO, Clamon G, Vokes E. Combined modality trials of the cancer and leukemia group B in stage III non small cell lung cancer: analysis of factors influencing survival and toxicity. Ann Oncol. 2004;15:1033-41.

30. Lau DH, Crowley JJ, Gándara DR, Hazuka MB, Albain KS, Leigh B, et al. Southwest Oncology Group phase II trial of concurrent carboplatin, etoposide, and radiation for poor-risk stage III non small cell lung cancer. J Clin Oncol. 1998;16:3078-81.

31. Sánchez de Cos J. Utilidad clínica de los marcadores tumorales en el cáncer de pulmón [dissertation]. Badajoz: Universidad de Extremadura; 1992.

32. Yoshimasu T, Miyoshi S, Maebeya S, Suzuma T, Besso T, Hirai I, et al. Analysis of the early postoperative serum carcinoembryonic antigen time-course as a prognostic tool for bronchogenic carcinoma. Cancer. 1997;79:1533-40.

33. Milleron B, Westeel V, Quoix E, Moro-Sibilot D, Braun D, Lebeau B, et al. Complete response following preoperative chemotherapy for resectable non small cell lung cancer. Chest. 2005;128: 1442-7.

34. Schild SE, Bogart JA. Innovations in the radiotherapy of non small cell lung cancer. J Thorac Oncol. 2006;1:85-92.