Arch Bronconeumol. 2016;52(4):183–188

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

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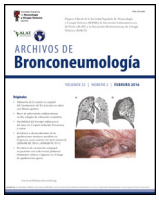

Original Article

Disease Recurrence and Second Tumors in Long-term Survivors of Lung Cancer☆

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ARTICLE INFO

Article history:
Received 1 June 2015
Accepted 22 July 2015
Available online 2 March 2016

Keywords:
Lung cancer
Relapse
Second primary tumors

ABSTRACT

Introduction and objectives: As cancer survival improves, the appearance of multiple tumors in a single patient is becoming more common. The aim of this study was to analyze long-term evolution, focusing particularly on disease recurrence and second primary tumors, in patients with lung cancer (LC) and ≥3 years overall survival.
Materials and methods: Retrospective study of 1769 patients with LC. A total of 218 (136 treated with surgery and 82 with other treatments), followed up for between 5 and 23 years were enrolled. LC progress and intercurrent diseases were recorded.
Results: A total of 65 patients presented tumor relapse, of which 60.9% occurred in the first 3 years; 26 patients developed secondary primary tumors (84.6% after 5 years) and 24 developed 2 or more second extrapulmonary tumors (66.6% after 5 years), most of which were smoking-related. The incidence of second primaries was greater than the expected incidence of cancer in the general population matched for age and sex.
Conclusion: The multiple carcinogenic effect of smoking persists and manifests in various organs, more than 5 years after the diagnosis of LC, even in patients with long survival. After 5 years, a second tumor is more likely than a relapse of the primary disease, and the lung is the most common site of development of a second tumor.

Recidivas y segundos tumores en el cáncer de pulmón de larga supervivencia

Palabras clave:
Cáncer de pulmón
Recidivas
Segundos tumores primarios

RESUMEN

Introducción y objetivos: Al mejorar la supervivencia del cáncer, la presencia de tumores múltiples en un paciente es cada vez más frecuente. El objetivo del estudio ha sido analizar la evolución a largo plazo, especialmente las posibles recidivas y segundos tumores primarios, en pacientes con cáncer de pulmón (CP) y supervivencia ≥3 años.
Material y métodos: Estudio retrospectivo de 1.769 pacientes con CP. Se incluyen 218 (136 tratados con cirugía y 82 con otros tratamientos) con supervivencia global ≥3 años, de cualquier estirpe y seguidos durante un período entre 5 y 23 años. Se registró la evolución del CP y las enfermedades intercurrentes.
Resultados: Un total de 65 presentaron recidiva del tumor, de los cuales el 60,9% apareció en los 3 primeros años; 26 desarrollaron segundos primarios pulmonares (84,6% después de 5 años) y 24, 2 o más segundos extrapulmonares (66,6% después de 5 años), la mayoría relacionados con el tabaco. La incidencia de segundos primarios fue superior a la incidencia esperable de cáncer en población general de similar edad y género.

☆ Please cite this article as: Sánchez de Cos Escuín J, Rodríguez López DP, Utrabo Delgado I, Gallego Domínguez R, Sojo González MA, Hernández Valle M. Recidivas y segundos tumores en el cáncer de pulmón de larga supervivencia. Arch Bronconeumol. 2016;52:183–188.

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1579-2129/

Conclusión: El efecto carcinogénico múltiple del tabaco persiste y se manifiesta en diversos órganos después de pasados 5 años tras el diagnóstico de CP, incluso en pacientes que han tenido una larga supervivencia. Después de 5 años, un segundo tumor es más probable que una recidiva del primero y el pulmón es el órgano con mayor probabilidad de desarrollar un segundo tumor.

Introduction

Of all malignant neoplasms, lung cancer (LC) causes the greatest number of deaths worldwide. Prognosis is poor, with 5-year survival rates of between 10% and 20% in most countries.[1,2] For many years, the possibility of long-term survival was limited almost exclusively to patients who were candidates for complete surgical resection.[3] However, in the last 25 years, new chemotherapy (CT) regimens combined with various thoracic radiotherapy (TRT) programs have been introduced, increasing favorable responses in patients with advanced locoregional disease, some of whom have achieved long-term survival.[4–6] More recently, new drugs aimed at specific molecular targets have been developed for the treatment of selected LC subgroups with certain molecular and genetic features. These compounds have provided favorable and enduring outcomes in some stage IV patients,[7] although there is still very little data available on 5-year life expectancy.

Late disease recurrence and second primary tumors (SPT) are relatively common among the small proportion of patients who achieve prolonged survival. Reports have been published on this topic in resected patients,[8–12] but few have focused on the evolution of long-term LC survivors who did not receive surgery.[13–15]

In this study, we analyzed the evolution of our LC patients with ≥3 years' survival, in order to determine the rate of recurrence and second tumors, and the times to these events.

Patients and Methods

This was a retrospective study, in which we reviewed the clinical records of 1769 patients with LC diagnosed between 1991 and 2009 (both inclusive): 310 underwent resection with or without neoadjuvant or adjuvant treatment; 1009 received CT, TRT, or combined CT and TRT, and 450 received palliative care only.

In total, 218 patients with a cytohistological diagnosis of LC and overall survival ≥3 years (12.3% of those examined) were included, irrespective of treatment received. The following data recorded at the time of diagnosis were collected: age, sex, smoking habit, histologic type, TNM stage (IASCL 2009 classification), and treatment modality. In the follow-up period, patients with a diagnosis of LC were examined at least 3 times a year during the first 2 years and once a year after the third year. Patients who had received CT or TRT were seen more frequently during the first 2 years. Patients diagnosed before the end of 2009 were included, and the study was closed in December 2014, so the minimum follow-up period for survivors was 5 years. Intercurrent diseases occurring during this period were recorded, and in many cases the incidence of extrapulmonary cancers was retrieved from the records and electronic documentation held in other departments and specialist units, and from biopsy reports relating to other organs.

To differentiate between recurrence of the primary tumor and second primary pulmonary tumor (SPPT), we used the criteria of Martini and Melamed, with the interval proposed by Detterbeck,[16,17] defining second primary tumor as: (1) different histologic type; (b) different lung site, in the absence of mediastinal node involvement; or (c) time to occurrence >4 years.[17]

The rate of recurrence and pulmonary and extrapulmonary SPTs are expressed in number of cases/100 person-years, for which the sum of the follow-up times until the last contact with each patient was computed. To evaluate their magnitude, these rates were compared with incidence rates of LC in the general population in our setting,[18,19] thus providing an estimated relative risk. With regard to SPT rates, comparisons were made with figures from any Spanish region for which protocolized cancer population registries are available[20] (to date, no such registries are available in our region). In view of the small number of women in our series, all comparisons were made with male populations only.

Statistical analysis: means were compared using the Student *t*-test. For comparison of percentages, the χ^2 test was used.

Ethics committee approval: although this was an observational study, authorization was requested and obtained from the Ethics Committee of our hospital.

Results

Demographic characteristics, smoking habit and histologic type of the 218 patients included with survival ≥3 years are shown in Table 1. Table 2 shows the distribution of TNM stages by therapeutic strategy: (1) surgery or (2) other treatment, namely: 20 patients

Table 1
General Characteristics of Lung Cancer Patients with Survival ≥3 Years.

	Men *n* (%)	Women *n* (%)	Total *n* (%)
Total cases	204 (93.5)	14 (6.5)	218 (100.0)
Age in years			
Mean (range)	62.4 (39–85)	57.6 (42–78)	62.1 (39–85)
Age distribution			
<50 years	21 (10.3)	5 (35.7)	26 (11.9)
51–69 years	109 (53.4)	7 (50.0)	116 (53.2)
≥70 years	74 (36.3)	2 (14.3)	76 (34.9)
Smoking habit			
Smokers	130 (60.7)	4 (28.6)	134 (61.4)
Former smokers	74 (39.3)	3 (21.4)	77 (35.4)
Non-smokers	– (0.0)	7 (60.0)	7 (3.2)
Histologic type			
Epidermoid	117 (57.3)	1 (7.1)	118 (54.1)
Adenocarcinoma	38 (18.6)	12 (85.8)	50 (22.9)
Large cell	7 (3.4)	– (0.0)	7 (3.2)
Non-small cell[a]	15 (7.3)	– (0.0)	15 (6.9)
Small cell	22 (10.8)	– (0.0)	22 (10.1)
Other[b]	5 (2.4)	1 (7.1)	5 (2.3)

[a] Non-small cell, with no further specification.
[b] Adenosquamous, mucoepidermoid.

Table 2
TNM Staging by Therapeutic Modality Applied.

TNM	Surgery[a] *n* (%)	Medical Treatment[b] *n* (%)	Total *n* (%)
I	94 (69.1)	5 (6.1)	101 (46.3)
II	25 (18.4)	5 (6.1)	30 (13.8)
IIIa	15 (11.0)	30 (36.6)	45 (20.6)
IIIb	1 (0.7)	40 (48.8)	41 (18.8)
IV	1 (0.7)	2 (12.2)	3 (1.4)
Total	136 (100.0)	82 (100.0)	218 (100.0)

[a] Surgery with or without neoadjuvant or adjuvant treatment.
[b] Chemotherapy alone (20); thoracic radiotherapy alone (3); chemotherapy and thoracic radiotherapy (55); palliative medication only (4).