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Original Article

Comparative Survival Study Between the Old and New Bronchogenic Carcinoma Classification[☆]

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Introduction: A new classification of bronchogenic carcinoma has been made by the International Association for the study of lung cancer (IASLC) and published by Frank C. Detterbeck et al. in the journal *Chest* (2009). The Thoracic Surgery Department of the Girona (Spain) University Hospital has re-staged a series of patients with bronchogenic carcinoma who had attempted curative surgery, with the aim of comparing the survival (survival for T, survival for M, and survival by disease staging) between the old and new classification, and also to determine whether these changes in survival are statistically significant. Another one of the objectives of the study is to see whether there is agreement between the current survival of our surgical series and that published by the IASLC.

Patients and methods: Data on 855 patients who had attempted bronchogenic carcinoma curative surgery were entered into a data base. They were radiologically, clinically, and histologically staged according to the new and old staging. Survival was calculated according to the T, M, N, and histology stages. A statistical analysis was performed using the SPSS program and the changes in survival between both classifications were analysed.

Results: No statistically significant changes were observed in survival ($P=.58$) with the new classification in stage IIA, but there were statistically significant changes in survival ($P=.0001$) in stage IIIB.

Discussion: The study confirms that the current TNM classification is useful, since it shows changes in survival in 2 histological stages (one of them statistically significant). The survival data of our series now fits better with those provided by the IASLC.

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Estudio comparativo de supervivencias entre la actual y la antigua clasificación del carcinoma broncogénico

RESUMEN

Palabras clave:

Estudio comparativo supervivencias
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Introducción: La nueva clasificación del carcinoma broncogénico ha sido realizada por la Association for the Study of Lung Cancer (IASLC) y publicada por Frank C. Detterbeck et al en la revista *Chest* (2009). En el Servicio de Cirugía Torácica del Hospital Universitario de Gerona se ha re-estadificado la serie quirúrgica de pacientes intervenidos de carcinoma broncogénico con intención curativa con el objetivo de comparar la supervivencia (supervivencia por T, supervivencia por M y supervivencia por estadios patológicos) entre la antigua y la actual clasificación y además objetivar si estos cambios de supervivencia son estadísticamente significativos. Otro de los objetivos del trabajo es el de establecer la concordancia entre la supervivencia actual de nuestra serie quirúrgica y la publicada por la IASLC.

Pacientes y métodos: Se introdujeron en una base de datos 855 pacientes intervenidos con intención curativa de carcinoma broncogénico. Fueron estadificados radiológica, clínica y patológicamente según la antigua y la nueva estadificación. Se calculó la supervivencia según la T, la N, la M y los estadios patológicos. Se realizó un estudio estadístico con el programa SPSS, con el que se analizaron los cambios de supervivencia entre ambas clasificaciones.

Resultados: Se objetivaron cambios de supervivencia no estadísticamente significativos ($P = 0,58$) con la nueva estadificación en el estadio IIA y cambios de supervivencia estadísticamente significativos ($P = 0,001$) en el estadio IIIB.

Discusión: El estudio confirma que la actual clasificación TNM es útil ya que muestra cambios de supervivencia en 2 estadios patológicos (uno de ellos estadísticamente significativo). Actualmente, los datos de supervivencia de nuestra serie se adecuan mejor a los que aporta la IASLC.

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Introduction

The 7th edition of the lung cancer staging classification was done by the International Association for the Study of Lung Cancer (IASLC) and published by Frank C. Detterbeck et al. in the journal *Chest*, in July 2009.¹⁻⁵

The aim of this review, as well as that for any neoplastic disease, is to provide greater specificity in identifying patient groups with similar prognosis and treatment options.^{1,2,6}

The latest TNM classification retrospectively included 100 869 patients diagnosed between 1997 and 2000, who were followed for 5 years. Patients received various treatment modalities, and so it was a clinical and surgical cohort. The patients came from 45 sources over 20 countries and several continents.^{1,2} The findings of this study suggested changes to the T and M and were validated internally (by geographic region and database type) and externally with patients registered in the US Surveillance, Epidemiology and End Results (SEER).^{1,2,7}

The variations in T and M resulted in changes in survival, which were statistically significant for pathological T and M. Changes in survival were also observed for clinical and pathological stages, although the current TNM

publication does not indicate whether they are statistically significant.^{1,8}

The Thoracic Surgery Department of the Dr. Josep Trueta University Hospital, Gerona (Spain) re-staged the surgical cohort of patients intervened for lung cancer with curative intent. The aim of this study was to compare the survival (for T, M and by pathological stages) between the old and current classifications, and to establish if these changes were statistically significant. An additional objective of the study was to establish a correlation between the current survival in our surgical cohort and that published by the IASLC.

Patients and Methods

In the Thoracic Surgery Department of the Dr. Josep Trueta University Hospital, 855 patients who underwent surgery for bronchogenic carcinoma with curative intent between 1997 and 2009 were entered onto a database. This database was updated periodically via outpatient visits or by phone.

A series of data were collected from the patients: year of presentation of lung cancer, patient name, file number, telephone number, origin, sex, smoking, Karnofsky performance score, medical history, date and type of first symptom,

Table 1 – Stages by Old Staging.

Stage	No.	%
IA	164	19.2
IB	218	25.5
IIA	39	4.6
IIB	92	10.8
IIIA	216	25.3
IIIB	83	9.7
IV	43	5

Table 2 – Stages by Current Staging.

Stage	No.	%
IA	174	20.5
IB	151	17.8
IIA	145	17.1
IIB	105	12.4
IIIA	223	26.3
IIIB	20	2.4
IV	29	3.4
Lost	8	0.9

type of lesion on the chest radiography and CT, whether bronchoscopy was performed or not, diagnosis method, preoperative histology, date of first pathological diagnosis, spirometry, lymph node involvement, presence of metastasis, whether mediastinoscopy was performed or not, date and type of surgery, postoperative histology, whether chemotherapy, neoadjuvant or adjuvant radiotherapy were used or not, and patient outcome (type and date of first recurrence, patient's health at the last control, cause of death, if occurred).

The 855 patients were radiologically, clinically, and pathologically staged according to the old classification (in force during the relevant study period) and the new staging. Survival was calculated according to T, N, M, and the different pathological stages of the old and new bronchogenic carcinoma classification.

Statistical analysis was performed with the SPSS program by the Epidemiology Department, Dr. Josep Trueta University Hospital, which analysed changes in survival between the two classifications. Agreement in survival was established.

One of the limitations of this study was that it covered a period of 13 years, during which there were 3 different bronchogenic carcinoma classifications (the 5th, 6th, and 7th).

Results

The re-staging for the surgical cohort carried out by the Thoracic Surgery Department of Dr. Josep Trueta University Hospital, involved changes to the number of patients included at each stage, as well as to their percentage over the total 855 patients undergoing surgery for bronchogenic carcinoma with curative intent.

According to the former classification, stage IA had 164 patients (19.2%), stage IB had 218 patients (25.5%), stage IIA had 39 patients (4.6%), stage IIB had 92 patients (10.8%), stage IIIA had 216 patients (25.3%), stage IIIB had 83 patients (9.7%) and stage IV had 43 patients (5%) (see Table 1).

According to the current classification, stage IA has 174 patients (20.5%), stage IB has 151 patients (17.8%), stage IIA has 145 patients (17.1%), stage IIB has 105 patients (12.4%), stage IIIA has 223 patients (26.3%), stage IIIB has 20 patients (2.4%) and stage IV has 29 patients (3.4%). A total of 8 patients (0.9%) were lost to follow-up (Table 2).

The most significant changes were observed in stage IB, which lost 67 patients (7.8%), stage IIA, which gained 106 patients (12.4%), and stage IIB, which lost 63 patients (7.4%).

The flow of patients was 2-way between stages, with some going to higher and others going to lower stages (Table 3).

This change in the number of patients by stage led to changes in survival. The changes undergone by T alone were not statistically significant: (a) T1 in the old classification had a 62% survival at 5 years, compared with 64.5% for T1a and 58% for T1b in the new classification; (b) The old T2 had a 43% survival at 5 years, compared with 45% for T2a and 37% for T2b

Table 3 – Old Staging vs. Current Staging.

	Current staging							Total
	IA	IB	IIA	IIB	IIIA	IIIB	IV	
Old staging								
IA	160*	2			1			163
IB	12	148*	37	19				216
IIA			38*					38
IIB			62	21*	9			92
IIIA	2		8	54	150*			214
IIIB		1		11	51	18*		81
IV					12	2	29*	43
Total	174	151	145	105	223	20	29	847

* Patients who remained in the same pathological stage.

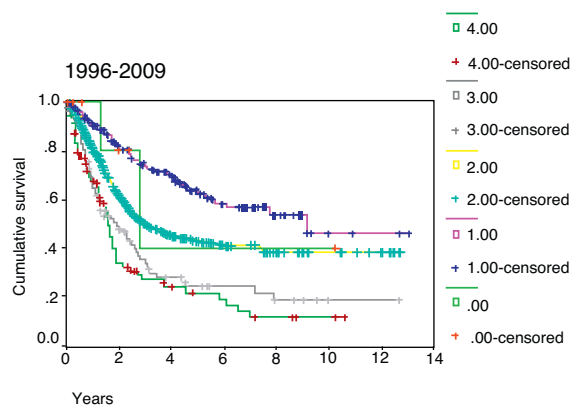


Fig. 1 – Survival curve for T (old staging).

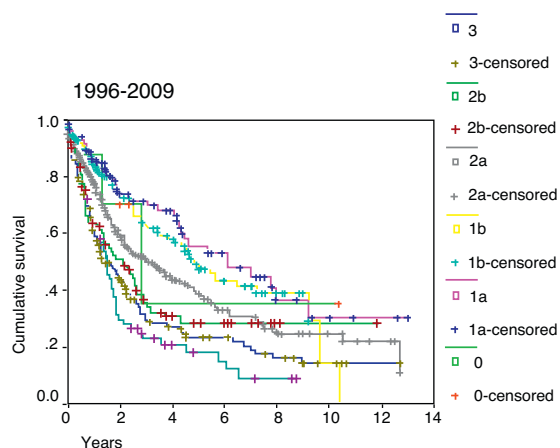


Fig. 2 – Survival curve for T (new staging).

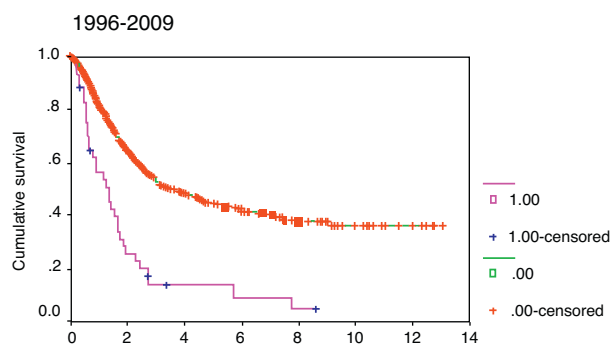


Fig. 3 – Survival curve for M (old staging).

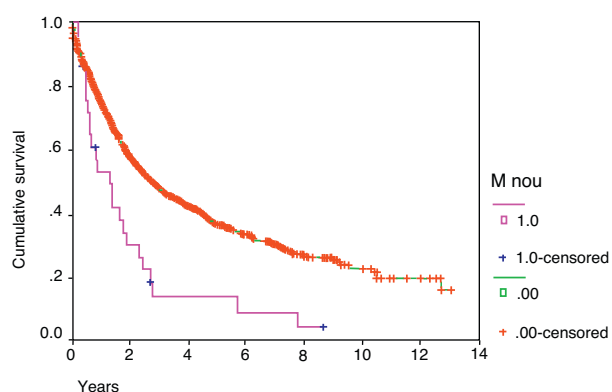


Fig. 4 – Survival curve for M (new staging).

in the current classification; (c) The old classification had a T3 survival at 5 years of 24.5%, compared to 27% currently; (d) The old T4 had a 5-year survival of 21.5%, compared with the current 20% (Figs. 1 and 2).

No changes were seen in N survival, as the current classification is not different from the old one.

Changes in M survival alone were not statistically significant: (a) M0 patients had a 44% survival at 5 years under the old staging, compared with 43.5% in the new classification; (b) M1 patients had a 5-year survival of 13.5% in the old scale, compared with 15% in the new one (Figs. 3 and 4).

Finally, there were significant differences in survival according to the pathological stage, and some are statistically significant (Tables 4 and 5; Figs. 5 and 6). The survival change in the new IIA staging (from 38% to 44%) was not statistically significant ($P=.58$). There were statistically significant survival changes ($P=.0001$) for stage IIIB, which decreased from 25% to 6.5%.

Discussion

The 7th edition of the of bronchogenic carcinoma staging was done by the International Association for the Study of Lung Cancer (IASLC) and published by Detterbeck et al. in the journal *Chest*, in July 2009.¹⁻⁵ The purpose of any TNM review is to group patients with similar prognosis, who can be offered optimal treatment options in the most appropriate manner.¹⁻⁵

The very high number of patients (100 869) entered onto an international database provides internal validity for the classification, and also records non-surgical patients.¹⁻³ This new classification is recommended for both small cell carcinoma and carcinoid tumors.² One of the major limitations of this new classification is that many T descriptors are still included despite the failure to validate them with sufficient statistical significance. This could have been prevented if prospective studies collecting detailed data from the databases had been performed.² The cohort analysed in

Table 4 – Survival According to the Old Staging.

Stage	12 m	24 m	60 m
IA	95	91	75.5
IB	90.5	75	57
IIA	90	71	38
IIB	81	63	40
IIIA	69	46	22
IIIB	67	36	25
IV	56	25	13

m: months.

Table 5 – Survival According to the New Staging.

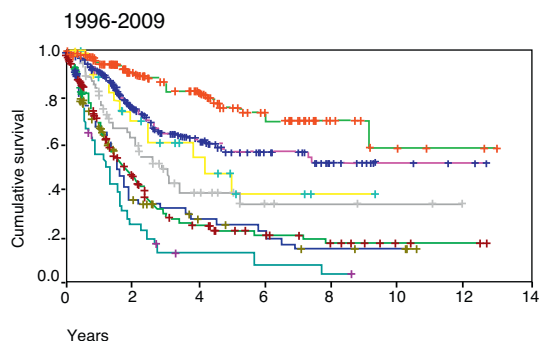
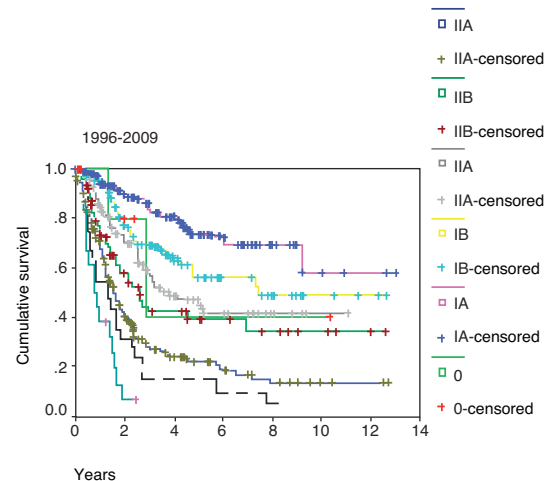
Stage	12 m	24 m	60 m	IASLC 60 m
IA	94	90	74	73
IB	94	76	56	58
IIA	86	71	44	46
IIB	74	59	39	36
IIIA	68	40	23	24
IIIB	39	6.5	6.5	9
IV	55	32	15	13

m: months.

the Department of Thoracic Surgery, University Hospital of Gerona included a smaller number of patients from a single centre, which gives it lesser internal validity. The cohort included only patients undergoing surgery with curative intent and did not take into account small cell or carcinoid tumors, as it was a retrospective study. Finally, the re-staging of this cohort was statistically validated, as all the data in the database was collected. Nevertheless, one of the limitations encountered was the loss of 8 patients in postoperative monitoring and the detection of 12 errors in the old classification that were resolved in the current re-staging.

T (Tumor Size)

The change in T was due to the importance granted in the new edition to tumor size and the fact that nodules in the same

**Fig. 5 – Survival curve for stages (old staging).****Fig. 6 – Survival curve for stages (new staging).**

lung lobe behave as a T3 and not a T4, and that the behaviour of nodules in different lobes of the same lung is more like the behaviour of a T4 tumor than a M1.^{1-3,8}

These were the reasons for the new staging. Thus, T1 is divided into T1a (tumor ≤ 2 cm) and T1b (tumors >2 cm but ≤ 3 cm); T2 was divided into T2a (tumors >3 cm but ≤ 5 cm) and T2b (tumors >5 cm but ≤ 7 cm); T3 is for tumors >7 cm or nodules in the same lung lobe; and finally, T4 is now considered for nodules in different lobes of the same lung.^{1-3,9,10}

Detterbeck et al. found statistically significant survival changes in the pathological T stages and statistically insignificant survival differences in the clinical T stages.¹ Small statistically insignificant changes in survival were found in the surgical cohort reported in our study.

N (Lymph Nodes)

N has not changed in the current classification, but changes are being considered for the next review, to be published in February 2016.²

The changes being considered involve: (a) the creation of a supraclavicular lymph node area to include supraclavicular, lower cervical and suprasternal fossa lymph nodes; (b) expansion of the subcarinal lymph node area to include all lymph nodes from the tracheal bifurcation to the upper edge of the left lower lobe bronchus and the lower edge of the bronchus intermedius; (c) introducing more precise limits for the hilar region¹⁰; (d) moving the midline of the upper mediastinum from the anatomical midline of the trachea to the left paratracheal margin.²

M (Metastasis)

In the current classification, M has also undergone changes, with a subdivision in M1a (contralateral lung nodules, pleural nodules, pericardial and pleural effusion with positive

cytology, previously considered as T4) and M1B (distant metastases).^{1-3,9,10}

The cohort presented by Detterbeck et al. show statistically significant differences in the prognosis of each group (M1a and M1b), while reporting high internal validity (based on data from different geographical regions) and high external validity (compared with the SEER database).¹ There were no significant changes in survival in the cohort studied by our Thoracic Surgery Department.

TNM (Stages)

There was a reorganisation of TNM stages and, even though there were no new divisions or subdivisions appearing within divisions already present,¹ the changes in T and M have resulted in a 2-way redistribution of patients between stages, including some patients with a better prognosis stage and others with a poorer prognosis.

The changes are as follows: (1) patients with 5-7 cm tumors, initially in stage IB, are now in stage IIA; (2) patients in stage IIB with 3-5 cm tumors and positive hilar lymph nodes are now considered T2aN1 with an improved staging to IIA; (3) Those patients with >7 cm tumors that were in stage IB, are now in stage IIB, according to the new classification; (4) stage IIIB has lost patients, with some going to a better staging: (a) nodules in the same lobe that were previously considered T4 and are now T3 move to stage IIB; (b) T4N0 and T4N1 tumors under the old classification are now under the new classification as IIIA. Moving to stage IV are those stage IIIB patients at a worse stage, who have tumors with a positive cytology for malignancy (formerly T4), which are currently considered M1a. Finally, stage IV has lost patients to: (a) stage IIIA (nodules in a different lobe of one lung, now considered T4), (b) stage IIIB (nodules in a different lobe of one lung with hilar lymph node involvement, i.e. T4N1).

It is not reflected in the study of Detterbeck et al. whether changes in survival by stage are statistically significant or not. However, 2 significant findings were made in the cohort presented by the Department of Thoracic Surgery, Dr. Josep Trueta Hospital: statistically significant survival changes were found in pathological stage IIA, which increased from 38% to 44% ($P=.58$), by statistical analysis using SPSS. This improvement in survival was mainly attributable to stage IIA receiving 37 patients from stage IB (with a theoretically better survival), 62 patients with a better prognosis from stage IIB, and 8 patients from stage IIIA. Another important fact is that statistically significant survival changes ($P=.0001$) were observed in pathological stage IIIB, whose 5-year survival dropped from 25% to 6.5%. This decline is attributable to losing patients with a better prognosis (11 patients were included in stage IIB and 51 in stage IIIA).

The current survival at 5 years in our surgical cohort correlated much better with the IASLC data, and are virtually identical: IA: 74% vs 73%; IB: 56% vs 58%; IIA: 44% vs 46%; IIB: 39% vs 36%; IIIA: 23% vs 24%; IIIB: 6.5% vs 9%; IV: 15% vs 13% in our surgical cohort and the IASLC, respectively.

Nevertheless, there are a number of factors that influence survival in patients with lung cancer, which have not been

included in this review. These include data from genetic, molecular (genomic signatures detected by microarrays) and metabolic factors, which may influence the systemic response to chemotherapy^{5,10}; also age, sex, tumor histology,^{2,4,5} cardiorespiratory status of the patient and associated comorbidity,² which are factors to be taken into account in the next lung cancer TNM review to be published in 2016.

The data from study, which is performed by the Department of Thoracic Surgery of the Hospital of Gerona confirm that the current TNM classification is useful, as we found survival changes in 2 pathological stages (one of which was statistically significant). Moreover, the survival data in our cohort now fit much better with those provided by the IASLC after this re-staging.

Finally, we believe that despite all the therapeutic regimens applied in our cohort and those used by the IASLC, the final survival results by stage are very similar.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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