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Brain metastases at the time of presentation of non-small cell lung cancer: a multi-centric AERIO* analysis of prognostic factors

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Summary A multi-centre retrospective study involving 4 French university institutions has been conducted in order to identify routine pre-therapeutic prognostic factors of survival in patients with previously untreated non-small cell lung cancer and brain metastases at the time of presentation. A total of 231 patients were recorded regarding their clinical, radiological and biological characteristics at presentation. The accrual period was January 1991 to December 1998. Prognosis was analysed using both univariate and multivariate (Cox model) statistics. The median survival of the whole population was 28 weeks. Univariate analysis (log-rank), showed that patients affected by one of the following characteristics proved to have a shorter survival in comparison with the opposite status of each variable: male gender, age over 63 years, poor performance status, neurological symptoms, serum neuron-specific enolase (NSE) level higher than 12.5 ng ml^{-1}, high serum alkaline phosphatase level, high serum LDH level and serum sodium level below 132 mmol l^{-1}. In the Cox's model, the following variables were independent determinants of a poor outcome: male gender: hazard ratio (95% confidence interval): 2.29 (1.26–4.16), poor performance status: 1.73 (1.15–2.62), age: 1.02 (1.003–1.043), a high serum NSE level: 1.72 (1.11–2.68), neurological symptoms: 1.63 (1.05–2.54), and a low serum sodium level: 2.99 (1.17–7.62). Apart from 4 prognostic factors shared in common with other stage IV NSCLC patients, whatever the metastatic site (namely sex, age, gender, performance status and serum sodium level) this study discloses 2 determinants specifically resulting from brain metastasis: i.e. the presence of neurological symptoms and a high serum NSE level. The latter factor could be in relationship with the extent of normal brain tissue damage caused by the tumour as has been demonstrated after strokes. Additionally, the observation of a high NSE level as a prognostic determinant in NSCLC might reflect tumour heterogeneity and understimated neuroendocrine differentiation. © 2001 Cancer Research Campaign http://www.bjcancer.com

Keywords: brain metastases; non-small cell lung cancer; neuron-specific enolase; prognosis

Patients with lung cancer frequently suffer from brain metastases at the time of presentation. This condition affects approximately 10% of non-small cell lung cancer (NSCLC) patients (Newman and Hansen, 1974; Sorensen et al, 1988). Surgery is feasible only for a small proportion of these patients. Whole brain radiotherapy has been, hitherto, the generally recommended treatment in inoperable patients. The survival of NSCLC patients with brain metastases is poor, reported to be between 3 to 6 months in patients treated with medical therapies, either radiotherapy or chemotherapy (compared to 6–10 months in other advanced NSCLC (Paesmans et al, 1995; Shepherd, 1999)). Furthermore, brain metastases at the time of presentation of lung cancer seems to be a worse prognosis (Sorensen et al, 1988) than metachronous brain metastases.

New therapeutic strategies are needed to improve the outcome of these patients. The knowledge of prognostic determinants might be important in both clinical trials and routine practice (Komaki et al, 1993; Charloux et al, 1997; Paesmans et al, 1997; Merrill et al, 1999). In the former setting, prognostic co-variables must be taken into account in survival analyses; by way of illustration, in a given randomized trial, the statement that a difference in survival is related to the effects of the treatment must be supported by a proportional hazards model demonstrating that this effect does not depend on well-known prognostic determinants (Depierre et al, 1999; Furuse et al, 1999). In the second setting, a therapeutic decision might be influenced by the state of prognostic variables (Komaki et al, 1993).

Here we especially take a look at the prognostic significance of 2 specific serum markers, CYFRA 21-1 and neuron-specific enolase (NSE). The prognostic value of CYFRA 21-1 (a fragment of cytokeratin subunit 19) in this disease has been suggested (Pujol et al, 1993; Wieskopf et al, 1995; Brechot et al, 1997). NSE, the γ-subunit of enolase, has been widely investigated as a marker of small cell lung cancer (SCLC; Jorgensen et al, 1989). Although only a small proportion of NSCLC presented with a high NSE level, this marker might indirectly reflect; i) a neuroendocrine component of the disease in favour of tumour heterogeneity; ii) a

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marker of brain damage. In order to evaluate prognostic variables in NSCLC patients with brain metastases at the time of presentation, we conducted a retrospective study.

PATIENTS AND METHODS

Patient selection

This is a multi-centre retrospective study involving 4 French university institutions (Montpellier university hospital, Institut Gustave Roussy, Strasbourg university hospital and Besançon university hospital). In the past, these institutions were involved in numerous cancer trials and therefore they possess comprehensive patient databases. Case reports extracted from these databases were selected on the following criteria: histologically proven NSCLC, brain metastasis at the time of presentation as demonstrated either by computed tomography (CT) or magnetic resonance imaging (MRI), no prior anti-cancer therapy. The accrual period was January 1991 to December 1998. Histological sub-classification was done according to the WHO classification (World Health Organization, 1982). Staging was carried out by exhaustive procedures according to the 4th edition of the Union Internationale Contre le Cancer (UICC) tumour node metastases (TNM) classification (Sobin et al, 1987) and the American Thoracic Society map of regional pulmonary nodes (Tisi et al, 1982). By definition, all patients belonged to stage IV of the new Mountain's stage grouping (Mountain, 1997)

Data collection

For each patient, the following pre-treatment characteristics were recorded: age, sex, performance status (estimated according to the Eastern Cooperative Oncology Group (Zubrod et al, 1960)), percentage of weight loss during the previous 4 months, tumour and nodal status, histology, clinical symptoms belonging to brain metastases (i.e. intra-cranial hypertension, seizure, focal neurological symptoms), other metastatic sites involved (i.e. liver, adrenal glands, bone metastases), serum CYFRA 21-1 level (upper limit of normal values: 3.6 ng ml^{-1}), serum NSE level (upper limit of normal values: 12.5 ng ml^{-1}), serum alkaline phosphatase and lactate dehydrogenase (LDH) levels (either normal or elevated, depending on the institution's upper normal values), serum sodium level (lower normal limit 132 mmol l^{-1}), white blood cell count, serum albumin level, number and location of brain metastases on CT or MRI and finally, treatment modalities.

Statistics

Survival data were updated on February 1 1999. Survival was defined as the time from histological diagnosis to the date of death. Death related to the disease whichever the progression site, or related to its treatment was analysed as an event. Deaths from other causes were treated as censored observations (myocardial infarctions or pulmonary embolisms). Survival was estimated by the Kaplan–Meier method (Kaplan and Meier, 1958). Single variable survival analyses were done by means of log-rank tests.

Coding methods for the different variables depended on their nature. Some of the variables have been extensively described in the literature therefore the threshold has been defined from previous publications. Performance status has been analysed according to 2 classical modalities: PS 0–1 and PS greater or equal to 2 (Zubrod et al, 1960). The effect of nodal status on prognosis was tested according to the presence or the absence of mediastinal lymph node involvement. The same coding regarding tumour status has been adopted according to the new Mountain's stage grouping (Mountain, 1997). Regarding biological variables, including tumour markers we used previously published thresholds: 3.6 ng ml^{-1} for CYFRA 21-1 (Pujol et al, 1993). The threshold values for serum NSE levels to be used in clinical studies have been defined from publications describing this neuroendocrine marker (Cooper and Splinter, 1987; Jorgensen et al, 1989). The treatment modality was not tested as a prognostic variable inasmuch as treatment was decided according to each institution's procedure and was based upon the different pre-treatment variables.

Multivariate regression was done with the Cox model (Cox, 1972; Andersen, 1991). The forward selection of variable procedure has been used. The selection of variables to be tested in the Cox model was made using the results of univariate analysis i.e. variables reaching at least a P level less than 15%. This model was written after a binary coding of the significant variables (except for age which was analysed as a continuous variable): categorical variables (such as performance status) were transformed into binary variables (0: negative or 1: positive). The number of levels of a categorical variable needed to describe a predictive factor is one less than the categories of that factor inasmuch as its baseline level is defined by setting the value of each of the categorical variables at zero. The significance of the effect of a given factor was assessed by determining whether or not the coefficient assigned to one or more of its categories was sufficiently different from zero. The proportional hazard assumption for each of the selected variables retained in the final model was originally checked by plotting the log cumulative baseline hazard ratio. A P level of less than 0.05 was considered significant. SAS software package was used.

According to the above-mentioned procedure, 14 variables were selected as putative prognostic determinants to be tested in the Cox regression hazard model. They represented less than 10% of the total of observed events (207 deaths) and therefore complied with the current recommendation (Harrell et al, 1985).

RESULTS

Patient's characteristics are summarized in Table 1. Most of the main characteristics of NSCLC were retrieved particularly a median age of 59 years (range, 32–85 years). 85 patients (37%) did not have symptoms related to the brain metastases and the disease was disclosed by a pre-treatment staging procedure including CT scan. 134 patients suffered from neurological symptoms, consisting of intra-cranial hypertension symptoms (33 patients), seizure, epilepsy or muscle weakness (101 patients) or an association of these different symptoms. There were 6 deaths related neither to the disease nor to the treatment. These observations have been censored. At the time of analysis, 207 deaths had been reported and 24 (10%) patients were still alive. In the whole patient population, median survival was 28 weeks (95% confidence interval [CI], 24 to 34 weeks). The 1- and 2-year survival rates were 25% (95% CI, 19–31%) and 8% (95% CI, 4–11%), respectively (Figure 1).

Univariate analysis

Univariate analysis (Table 2) showed that patients affected by one of the following characteristics proved to have a shorter survival in

Table 1 Patients' characteristics

Variables		No. of patients (%)
Total		231
Age (years)	Median ± SD	59 ± 11
	< 40	13 (6)
	40–49	49 (21)
	50–59	65 (28)
	60–69	70 (30)
	70 and over	34 (15)
Male gender	Male	194 (84)
ECOG performance status	0	44 (19)
	1	92 (40)
	2	60 (26)
	3	26 (11)
	4	9 (4)
Tumour status	1–2	107 (47)
	3–4	122 (53)
Nodal status	0–1	64 (28)
	2–3	165 (71)
Histology	Squamous cell carcinoma	95 (41)
	Adenocarcinoma	86 (37)
	Large cell carcinoma	50 (22)
Weight loss (%)	< 5% /≥ 5%	119 (52)/88 (38)
	Unknown	24 (10)
Serum Cyfra 21–1 level	< 3.6 /≥ 3.6	58 (25)/88 (38)
	Unknown	85 (37)
Serum NSE level	≤ 12.5 /> 12.5	142 (61)/57 (25)
	Unknown	32 (14)
Serum albumin level	<32 g l^{-1} /≥ 32 g l^{-1}	159 (69)/27 (12)
	Unknown	45 (19)
Serum sodium level	<132 mmol l^{-1} /≥ 132 mmol l^{-1}	219 (95)/10 (4)
	Unknown	2 (1)
Alkaline phosphatase	Normal/elevated	180 (78)/41 (18)
	Unknown	10 (4)
Lactate dehydrogenase level	Normal/elevated	133 (58)/78 (34)
	Unknown	20 (9)
Blood leucocyte count	≤ 10 000 μl^{-1}> 10 000 µl	108 (47)/120 (52)
	Unknown	3 (1)
Adrenal gland metastases	Yes/No	34 (15)/197 (85)
Bone metastases	Yes/No	47 (20)/184 (80)
Liver metastases	Yes/No	24 (10)/207 (90)
No. of brain metastases	Unique/Multiples	89 (39)/125 (54)
	Unknown	17 (7)
Site of brain metastases	Supra/Infra-tentorial	144 (62) / 19 (8)
	Mixed	49 (21)
	Unknown	19 (8)
Neurologic symptoms	No/Yes	85 (37)/134 (58)
Treatment modalities	Best Supportive Care	19 (8%)
	Radiotherapy	13 (6%)
	Chemotherapy	41 (18%)
	Surgery	0
	Surgery + Chemotherapy	2 (1%)
	Surgery + Radiotherapy	2 (1%)
	Surgery + Chemo. + Radio.	3 (1%)
	Radiotherapy + Chemotherapy	150 (65%)
Brain response to treatment	Yes/No	93 (40)/107 (46)
	Unknown	31 (13)

comparison with the opposite status of each variable: male gender, age over 63 years, performance status equal to or worse than 2, neurological symptoms (Figure 2), serum NSE level higher than 12.5 ng ml^{-1} (Figure 3), high serum alkaline phosphatase level, high serum LDH level and serum sodium level lower than 132 mmol l^{-1}.

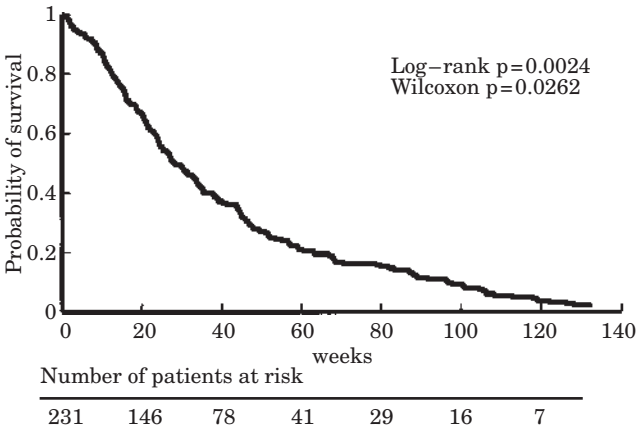

Figure 1 Kaplan–Meier estimation of overall survival in the whole population of non-small cell lung cancer patients suffering from brain metastases at the time of presentation

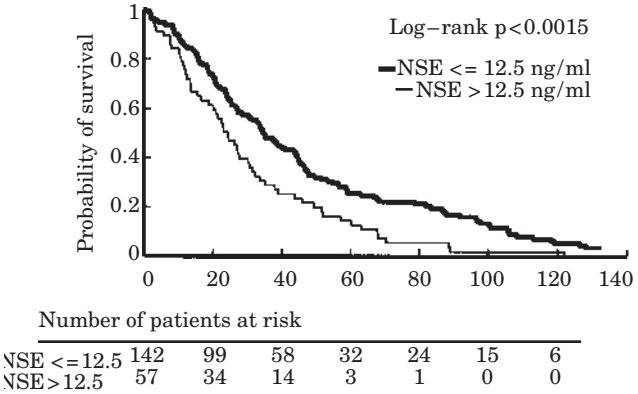

Figure 2 Probability of survival of non-small cell lung cancer patients with or without neurological symptoms

Multivariate analysis

According to the above-mentioned procedure, 14 variables were selected as putative prognostic determinants to be tested in the Cox regression hazard model (sex, age, performance status, histology, serum NSE level, serum CYFRA 21-1 level, serum albumin, alkaline phosphatases, LDH, serum sodium, blood leucocyte count, presence of bone metastases, presence of liver metastases, neurological symptoms). They represented less than 10% of the total observed events (207 deaths) and therefore complied with the current recommendation (Harrell et al, 1985).

The following variables were independent determinants of a poor outcome: male gender: hazard ratio (95% confidence interval): 2.29 (1.26–4.16), poor performance status: 1.73 (1.15–2.62), age: 1.02 (1.003–1.043), a high serum NSE level: 1.72 (1.11–2.68), neurological symptoms: 1.63 (1.05–2.54), and a low serum sodium level: 2.99 (1.17–7.62) (Table 3).

Finally, patients have been coded according to the presence or absence of a major metastatic site (i.e. presence of at least one of the following metastatic sites: liver or adrenal or bone). This variable did not modify the results of the Cox model.

DISCUSSION

Brain metastases at the time of presentation of NSCLC are a frequent clinical problem. Classically, treatment consists of whole brain radiotherapy. Surgery is usually proposed to the small subset of patients presenting with a single brain metastasis and for whom primary site can be controlled. The role of chemotherapy in the management of NSCLC with brain involvement remains controversial. Short life expectancy is generally considered as a deterrent to curative intent. However, recent studies indicate that chemotherapy is active on brain metastases of NSCLC (Ellis et al, 1998; Kelly and Bunn, 1998; Postmus and Smit, 1999). In addition, new therapies such as radiosurgery and combined chemotherapy-radiotherapy are being developed for these patients. Therefore, the appraisal of the prognostic factor is mandatory.

We report herein a survival analysis of a homogeneous population of NSCLC patients with brain metastases at the time of presentation. 4 prognostic factors elicited from this study are classical survival determinants reported to be shared in common by all NSCLC whatever the metastatic site (Zimm et al, 1981; Diener-West et al, 1989; Komarnicky et al, 1991; Lonjon et al, 1994; Ryan et al, 1995; Ando et al, 1996; Auchter et al, 1996; Gaspar et al, 1997; Hsiung et al, 1998; Agboola et al, 1998; Lagerwaard et al, 1999), or by brain metastases whatever the primary tumour (Zimm et al, 1981; Diener-West et al, 1989; Komarnicky et al, 1991; Lonjon et al, 1994; Auchter et al, 1996; Gaspar et al, 1997; Agboola et al, 1998; Lagerwaard et al, 1999). These factors are gender, performance status, age and serum sodium level.

Apart from the above-mentioned factors, our study disclosed 2 determinants which might result from brain metastases: the presence of neurological symptoms and a high serum NSE level. Clinical symptoms related to the brain metastases were the only site-specific factor independently affecting survival. Neither the number nor the location of brain metastases were statistically significant determinants of prognosis. This finding contrasts with some other studies also aimed at prognosticating the outcome of patients suffering from brain metastases (Zimm et al, 1981; Swift et al, 1993; Nussbaum et al, 1996; Sen et al, 1998). However, one can mention that these determinants vary from one study to another (Zimm et al, 1981; Swift et al, 1993; Ando et al, 1996; Nussbaum et al, 1996; Hsiung et al, 1998; Nguyen et al, 1998; Sen et al, 1998). This discrepancy could be in relationship with a possible underestimation of the number of metastases and the tumour burden shown by means of CT scan. Therefore, the case of anatomic characteristics of brain metastases seems of less prognostic importance than the presence of symptoms by themselves. This statement does not minimize the paramount consequence of anatomic characterization of brain disease in treatment decision.

The γγ isomer of the ubiquitous enzyme enolase referred to as NSE is the most widely used neuroendocrine serum marker in SCLC clinical management (Cooper and Splinter, 1987; Jorgensen et al, 1989). In the NSCLC histology, the evaluation of this neuroendocrine marker might seem unexpected. However, the common endodermal origin of all histological types of lung cancer makes it possible to include SCLC and NSCLC in a unique spectrum of differentiation with frequent overlaps (Yesner and Carter, 1982). Early studies using histology (Yesner and Carter, 1982) or electronic microscopy (Gould et al, 1983) have demonstrated that mixed SCLC-NSCLC may be observed in a low proportion of all lung cancers. Patients with mixed SCLC-large cell carcinoma proved to have a shorter survival than those with pure histological

Table 2 Univariate analysis

Variable		Median survival (weeks)	*P* (Log- rank)
Age (year)	≤ 63	33.7	0.0363
	> 63	21.4	
Gender	Female	50.7	0.0004
	Male	26.3	
ECOG performance status	< 2	35.3	0.0003
	≥ 2	20.9	
Tumour status (T)	1–2	30.6	0.2923
	3–4	26.9	
Nodal status (N)	0–1	27.3	0.2247
	2–3	29.6	
Histology	Squamous-cell carcinoma	26.3	0.1075
	Adenocarcinoma	32.7	
	Large cell carcinoma	28.4	
Weight loss	< 5%	28.4	0.4312
	≥ 5%	27.3	
Serum Cyfra 21–1 level	≤ 3.6	33.6	0.1314
	> 3.6	24.6	
Serum NSE level	≤ 12.5	34.4	0.0015
	> 12.5	24.3	
Serum albumin level	< 32 g l^{-1}	20.1	0.1293
	≥ 32 g l^{-1}	31.4	
Serum sodium level	< 132	15.4	0.0141
	≥ 132	30.1	
Serum alkaline phosphatase level	Normal	32.3	0.0080
	Elevated	20.6	
Serum lactate dehydrogenase level	Normal	33.6	0.0358
	Elevated	23.6	
Blood leukocyte count	≤ 10.10^9 l^{-1}	33.6	0.1005
	> 10.10^9 l^{-1}	27	
Adrenal gland metastases	Yes	24.3	0.4637
	No	29.6	
Bone metastases	Yes	23.9	0.0663
	No	30.3	
Liver metastases	Yes	24.1	0.1414
	No	28.4	
No. of brain metastases	Unique	30.6	0.1675
	Multiples	28	
Site of brain metastases	Supra-tentorial	32.3	0.7317
	Infra-tentorial	27.3	
	Mixed	26.9	
Neurologic symptoms	No symptoms	38.7	0.0019
	Neurologic symptoms	24.3	

SCLC suggesting that this heterogeneity has clinical relevance (Radice et al, 1982). Therefore, we decided to evaluate this marker in the particular setting of brain metastasis of NSCLC.

Table 3 Estimated hazard ratio for significant variables

Variables	Hazard ratio	95% CI	*P*
Male gender	2.29	1.26–4.16	0.006
Poor performance status (2–4)	1.73	1.15–2.62	0.009
Age	1.02	1.003–1.043	0.021
High serum NSE level	1.72	1.11–2.68	0.016
Presence of neurological symptoms	1.63	1.05–2.54	0.026
Low serum sodium level	2.99	1.17–7.62	0.022

In our study patients with a pre-treatment high serum NSE level proved to have a poor outcome. Two hypotheses could explain this finding and they are not mutually exclusive. First, this high NSE level might reflect a neuroendocrine differentiation. This heterotopic antigen expression could be regarded as a consequence of a phenotypic heterogeneity, a unique characteristic of human malignancy thought to be in relationship with genotypic instability and tumour progression (Nicolson, 1987). Alternatively, high serum NSE levels may reflect the extent of the neuronal damage. One piece of evidence which can support this hypothesis is the relationship between the degree of neuronal damage and the serum NSE level following a cerebral stroke (Cunningham et al, 1991, 1996; DeGiorgio et al, 1995, 1999; Fogel et al, 1997; Missler et al, 1997; Martens et al, 1998; Buttner et al, 1999; Schoerkhuber et al, 1999; Wunderlich et al, 1999) or other neuronal brain damage (DeGiorgio et al, 1995, 1999; Fogel et al, 1997; Martens et al,

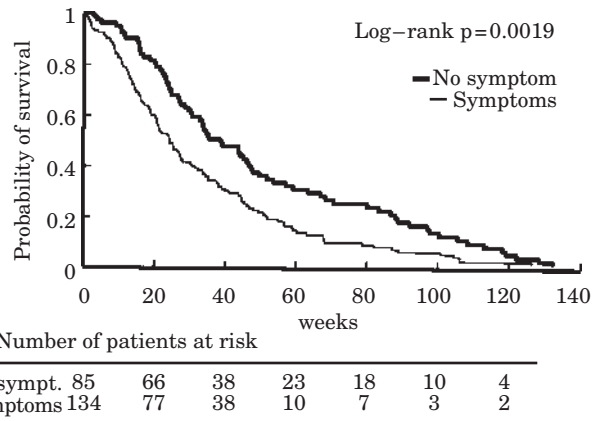

Figure 3 Probability of survival of non-small cell lung cancer patients with normal and elevated pre-treatment serum NSE level

1998; Buttner et al, 1999; Schoerkhuber et al, 1999). In these diseases, the serum NSE level exhibits a prognostic indication inasmuch as studies have found a close relationship between the volume of affected neuronal tissue and the serum NSE level (Cunningham et al, 1991, 1996; Missler et al, 1997; Wunderlich et al, 1999). We hypothesize that the poor outcome of patients with a high NSE level and brain metastasis is due to the severity of normal neuronal tissue damage surrounding metastases. However, the latter explanation and the first hypothesis, i.e. serum NSE as a marker of phenotypic heterogeneity, are not mutually exclusive.

One may hypothesize that, due to the retrospective nature of the herein study, a possible bias was introduced by the treatment heterogeneity (as shown in Table 1). Patients received a combination of chemotherapy or chemo-radiotherapy according to each centre's policy. Each indication was based upon specific variables such as solitary or multiple brain metastases, performance status, etc. This treatment heterogeneity mainly reflects the lack of consensus regarding the management of NSCLC patients affected by brain metastases at time of presentation. There is no clear demonstration in the literature that a given drug combination or a given combined modality could be considered as a standard regimen. In addition, in our population, the distribution of serum NSE levels did not differ according to treatment modality suggesting that the prognostic significance of the marker was not affected by therapy.

The present manuscript reports an exploratory multi-centre study with identification of prognostic determinants taken as the primary endpoint. Therefore, it would be hazardous to draw specific treatment recommendations from our data. According to the classification proposed by Simon and Altman (1994), the study herein could be considered as a type 2 prognostic factor investigation. The findings of the current study deserve further confirmatory investigations in a larger population of patients with homogeneous therapeutic strategies. Such phase III studies are considered as the only means 'to determine which subsets of patients benefit from a given therapy'.

In conclusion, our study confirms age, sex and performance status as prognostic factors of NSCLC with brain metastases at the time of presentation suggesting that this subset of patients shares similar determinants of outcome with the general NSCLC population. In addition, both neurological symptoms and serum NSE levels are site-specific predictors of outcome to be taken into account in new therapeutic approaches in this setting.

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