Arch Bronconeumol. 2011;47(8):397–402

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Original Article

Prognostic Value of Epithelial Growth Factor Receptor, Vascular Endothelial Growth Factor, E-Cadherin, and p120 Catenin in Resected Non-Small Cell Lung Carcinoma☆

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ARTICLE INFO

Article history:
Received 21 November 2010
Accepted 13 April 2011
Available online 4 October 2011

Keywords:
Lung cancer
Non-small cell carcinoma
Epithelial growth factor receptor
Vascular endothelial growth factor
E-cadherin
p120 catenin
Surgery

ABSTRACT

Introduction: Several markers have been investigated to predict the prognosis of lung cancer. In the present study, the prognostic values of epithelial growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), E-cadherin, and p120 catenin expression were investigated by immunohistochemistry in patients with a surgically resected non-small cell lung carcinoma (NSCLC).
Patients and method: EGFR, VEGF, E-cadherin, and p120 catenin expression were prospectively determined in resected specimens from patients with NSCLC who had undergone surgery between 2003 and 2007. Patients' and disease-related general characteristics and survival rate were recorded.
Results: One hundred seventeen patients with a mean age of 61.3 years were included in the study. After a mean follow-up of 27.5 months, the median survival was determined to be 44.0 months and the 5-year survival was 46.2%. The 5-year survival in negative and positive staining groups were as follows; 32% and 66.7% for EGFR (*P*=.02), 37.8%, and 50.7% for VEGF (*P*=.5), 41% and 66% for E-cadherin (*P*=.19), and 46% and 50% for p120 catenin (*P*=.27). The differentiation, N status, stage, and EGFR staining were variables significantly affecting survival (*P*=.001, .006, .03, and .02, respectively). In multivariate Cox analysis, the EGFR staining level and N status were variables those significantly affecting survival (*P*=.021 and *P*=.010).
Conclusions: While negative staining of EGFR was related with poor survival, staining of VEGF, E-cadherin, and p120 catenin were not related with survival in patients with resected NSCLC.

Valor pronóstico del receptor del factor de crecimiento epitelial, factor de crecimiento endotelial vascular, E-cadherina, y p120 catenina en el carcinoma de pulmón no microcítico resecado

Palabras clave:
Cáncer de pulmón
Carcinoma no microcítico
Receptor del factor de crecimiento epitelial
Factor de crecimiento endotelial vascular
E-cadherina
p120 catenina
Cirugía

RESUMEN

Introducción: Para predecir el pronóstico del cáncer de pulmón se han investigado varios marcadores. En el presente estudio, mediante inmunohistoquímica se investigaron los valores pronósticos de la expresión del receptor del factor de crecimiento epitelial (EGFR), factor de crecimiento endotelial vascular (VEGF), E-cadherina y p120 catenina en pacientes con un carcinoma de pulmón no microcítico (CPNM) sometidos a resección quirúrgica.
Pacientes y métodos: Se determinó prospectivamente la expresión de EGFR, VEGF, E-cadherina y p120 catenina en muestras resecadas de pacientes con CPNM que se habían sometido a cirugía entre 2003 y 2007. Se registraron las características generales de los pacientes y relacionadas con la enfermedad y la tasa de supervivencia.
Resultados: En el estudio se incluyeron 170 pacientes con una edad media de 61,3 años. Después de un seguimiento medio de 27,5 meses, se determinó que la supervivencia mediana era de 44,0 meses y la tasa de supervivencia a 5 años era del 46,2%. En los grupos con una tinción negativa y positiva, la tasa de supervivencia a los 5 años fue la siguiente: 32 y 66,7% para la expresión de EGFR (p = 0,02), 37,8 y 50,7%

☆ Please cite this article as: Ucvet A, et al. Valor pronóstico del receptor del factor de crecimiento epitelial, factor de crecimiento endotelial vascular, E-cadherina, y p120 catenina en el carcinoma de pulmón no microcítico resecado. Arch Bronconeumol. 2011;47:397–402.

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1579-2129/$ – see front matter

para la de VEGF (p = 0,5), 41 y 66% para la de E-cadherina (p = 0,19), 46 y 50% para la de p120 catenina (p = 0,27). El grado de diferenciación del tumor, estado de N, estadio y tinción de EGFR fueron variables que afectaron significativamente a la supervivencia (p = 0,001, 0,006, 0,03 y 0,02, respectivamente). En el análisis multivariante de Cox, el nivel de tinción de EGFR y el estado de N fueron las variables que afectaron significativamente a la supervivencia (p = 0,021 y p = 0,010).
Conclusiones: Aunque la tinción negativa de EGFR se relacionó con una supervivencia desfavorable, la tinción de VEGF, E-cadherina y p120 catenina no se ha relacionado con la supervivencia en pacientes con CPNM resecado.

Introduction

Tumor markers are used to determine organ tumor dissemination, predict prognoses and monitor treatment more than for establishing diagnoses.[1] For lung cancer, no ideal or organ-specific tumor marker has been identified.[2] Currently, numerous tumor markers are being studied for the evaluation of malignant tumors, including lung cancer.

Recently, numerous target molecules have been defined that either affect the course of the malignant tumor or stop it. The epithelial growth factor receptor (EGFR) is a transmembrane glycoprotein with tyrosine kinase activity activated by the surface receptor. EGFR plays a role in motility, adhesion, cell invasion, and tumor angiogenesis.[3–5] Tumor growth depends on neoangiogenesis, which, at the same time, also facilitates tumor progress and metastasis. Therefore, the magnitude of the intratumoral neoangiogenesis is related with prognosis, which is one of the controversial aspects of the research studies that are being carried out. The tumor cells can release numerous positive regulatory factors that contribute to micro-angiogenesis, among which considerable attention has been paid to vascular endothelial growth factor (VEGF).[6–8]

E-cadherin, a calcium-dependent cell adhesion molecule, plays a key role in the maintenance of tissue integrity. In part, the function of this molecule is mediated by the catenins.[9,10]

Our intention is to evaluate the under-researched roles of E-cadherin and catenin together with those of EGFR and VEGF, which have often been researched in non-small cell lung cancer (NSCLC).

In the present study in patients with NSCLC who underwent surgical resection, we determined by means of immunohistochemistry the expression of EGFR, vascular endothelial cell growth factor (VEGF), E-cadherin, and p120 catenin with the objective of revealing their effects on prognosis.

Patients and Methods

Patient Selection

Included for study were those patients who had undergone either lobectomy or pneumonectomy due to NSCLC at the Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital in the Thoracic Surgery Clinic between 2003 and 2007. The anatomic pathologists prospectively evaluated all the surgical samples. Excluded from the studies were those patients who had received neoadjuvant treatment, those who underwent incomplete exeresis, those who had died within the early post-surgery period (first 3 months), those evaluated by another anatomic pathologist, those who underwent a resection of less than a lobectomy, and those who could not be followed-up. The study was approved by the research committee of the Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital. Informed consent was obtained from each patient.

Clinical History of the Patients

All the patients were examined in the pre-operative period with posteroanterior and lateral-projection chest radiography, complete hemogram, serum biochemistry electrocardiogram, thoracic and upper abdominal computed tomography (CT), abdominal ultrasound, and bronchoscopy. Bone gammagraphy and cranial CT were only done in patients with clinical signs or positive lab results. All the surgical material was evaluated histopathologically and classified in accordance with the extension diagnosis system of the TNM classification from 1997.[11] In all patients, we carried out the systematic dissection of the lymph nodes. The post-operative histopathological evaluation followed the recommendations of the WHO.[12]

Patient Follow-up

One month after hospital discharge, the patients were seen every 3 months for the first 2 years, then every 6 months for another 2 years, and then at yearly intervals. At each follow-up visit, both hemogram and chest CT were done systematically. If necessary, detailed blood analyses and radiological exams were ordered. All the patients were followed-up until either the end of the study, or until their death. Lastly, the patient information was updated by evaluating the clinical histories and by contacting either them or their families. The date on which the first metastasis was detected was considered the date of the metastasis. New lesions in the same hemithorax were considered local relapses, and other lesions were considered distant metastases.

Antibody Staining Protocol for Immunohistochemistry

The resected materials were processed in accordance with the procedures described further ahead. The biopsy samples were transferred to poly-L-lysine coated microscope slides and were incubated the entire night at 50–60 °C. The slides were treated with xylene for 2×15 min and 2×20 min, then with 96% ethanol for 6×1.5–2 min, and then were later washed 2 or 3 times with distilled water. For the recuperation of the antigen, the sections prepared for VEGF, EGFR, and E-cadherin were incubated with trypsin (Trypsin 4-Pack KIT; BioGenex, San Ramon, California, United States) at 37 °C for 45 min. As the enzymatic treatment was not appropriate for p120, it was warmed in a microwave oven with ethylenediaminotetraacetic acid (EDTA) (pH 8) for 20 min. Afterwards, it was cooled for 15 min and washed 2 or 3 times in distilled water. Each slide was dried individually. The tissue cuts were marked with a circle made with a water-proof marker (Super PAP PEN, Beckman Coulter, Marseille, France) and immediately after having been marked, drops of hydrogen peroxide were poured on. The slide was incubated for 5 min and washed in water. Then, the slide was washed in a phosphate buffered saline (PBS) for 5 min. After applying the solution on the slide, it was incubated for 10 min, the excess was eliminated and rinsed and the slide was put in a wet flask. VEGF (A20, sc-152, 1:100; Santa Cruz Biotechnology, Inc., Santa Cruz, California, United States),

EGFR (AR335-5R, 1:10; BioGenex), E-cadherin (1:10, clone 36; BioGenex), and catenin p120 (15D2, sc-23872, 1:50; Santa Cruz Biotechnology, Inc.) were left at room temperature for 1 h and were used as primary antibodies. The slide was put in a liquid that had PBS, without spilling any, and afterwards it was washed, the excess eliminated and rinsed. The slide was left in PBS for 10 min. The secondary antibody was transferred to the slide and left for 15 min. It was washed with PBS and left for 5 min. Streptavidin (Lab Vision, Fremont, California, United States) was placed on the slide and left for 15 min. It was washed with PBS, which was left for 5 min. After eliminating the excess and rinsing, diaminobenzidine (DAB, BioGenex) was put on the slide, which was left for 10 min, and afterwards the slide was transferred to PBS. After washing in distilled water, the slide was left in hematoxylin for 1 min, and immediately afterwards was washed in water. The slide was treated with 96% ethanol for 1 min and then dried. After leaving it in xylene for 5 min, it was covered with a cover slip. p120 catenin was only studied in 69 of 117 cases due to technical reasons that arose in the anatomic pathology department.

Immunohistochemistry

Negative staining was defined in the following way: absence of stain or stain <10% for EGFR, stain <25% for VEGF, stain <50% for E-cadherin and p120 catenin. The positive stain was accepted as values greater than these mentioned.

Statistical Analysis

The survival rates in the different groups of patients were compared in accordance with the staining characteristics of EGFR, VEGF, p120 catenin, and E-cadherin. Due to the limited number of patients, the variables were grouped in the following way: histologic type as squamous or non-squamous; T status as T1–2 or T3–4; stage as stage I (IA and IB), stage II (IIA and IIB), or stage III (III and more); and N status as N0–1 (N0 and N1) or N2.

The statistical analyses were done with SPSS (Version 9.0; SPSS, Inc., Chicago, Illinois, United States). The comparisons between groups were carried out with the Student's *t*-test for parametric variables and Fisher's exact test or Pearson's χ^2 test for non-parametric variables. For the survival analyses, the Kaplan–Meier method was used. The comparisons between the survival rates were carried out by means of the *log-rank* test using life tables and the Kaplan–Meier method. In the survival rate calculations, mortality related with lung cancer was taken into account. A multivariate analysis was done, using the forward conditional Cox model. A *P* value $\leq$.05 was considered statistically significant.

Results

The mean age of the 117 patients included in the study was 61.3 (range, 42–77). Table 1 presents the general patient characteristics. Adjuvant treatment was administered in 33 patients: 5 received chemotherapy, 18 radiotherapy, and 10 chemoradiotherapy. The indications of the adjuvant treatments were T3 in 3 patients, T4 in 1, N1 in 6, and N2 in 23, while 5 patients with N2 disease could not receive adjuvant treatment due to the unfavorable evaluation of their functional state. The patients were followed for a mean period of 27.5 ± 20.0 months (range, 3–70 months). Median survival was 44.0 months and the 5-year survival rate was 46.2% at the end of the study. In 12 patients, the follow-up was more than 60 months: 6 patients survived disease-free, 5 survived relapses, and 1 died of unrelated causes.

The patients who stained positive for EGFR, VEGF, E-cadherin, and p120 catenin were characterized by a greater 5-year survival (Fig. 1A–D). In the univariate analysis, the differentiation, N status, stage, and EGFR stain were variables that significantly affected survival (*P*=.001, .006, .03, and .02, respectively) (Table 2).

In addition to the values of EGFR, VEGF, E-cadherin, and p120 catenin, the Cox multivariate analysis for stage, histologic type, differentiation, and T and N status revealed that the EGFR stain level

Table 1
General Patient Characteristics.

Characteristics	*n* (%)
Sex	
Men	111 (94.9)
Women	6 (5.1)
Age, years	
≤60	53 (45.3)
>60	64 (54.7)
Intervention	
Lobectomy	80 (68.4)
Pneumonectomy	37 (31.6)
Histologic grade	
Well-differentiated	29 (24.8)
Moderately differentiated	75 (64.1)
Poorly differentiated	13 (11.1)
Histologic type	
Squamous cell	62 (53.0)
Adenocarcinoma	47 (40.2)
Large-cell	7 (6.0)
Other	1 (0.9)
T state	
1	7 (6.0)
2	84 (71.8)
3	20 (17.1)
4	6 (5.1)
N state	
0	69 (59.0)
1	20 (17.1)
2	6 (5.1)
Anatomic pathology stage	
IA	4 (3.4)
IB	50 (42.7)
IIA	3 (2.6)
IIB	26 (22.2)
IIIA–IIIB	34 (29.1)
EGFR	
Positive	49 (41.9)
Negative	68 (58.1)
VEGF	
Positive	82 (70.1)
Negative	35 (29.9)
E-cadherin	
Positive	29 (24.8)
Negative	88 (75.2)
p120 catenin	
Positive	43 (62.3)
Negative	26 (37.7)
Outcome	
Disease-free survival	30 (25.6)
Survival with continued disease	27 (23.1)
Mortality related with the disease	51 (43.6)
Mortality due to other causes	9 (7.7)
Relapses	
Present	73 (62.4)
Absent	44 (37.6)
Type of relapse	
Local	37 (50.7)
Distant	26 (35.6)
Local + distant	10 (13.7)

EGFR: epithelial growth factor receptor; and VEGF: vascular endothelial growth factor.

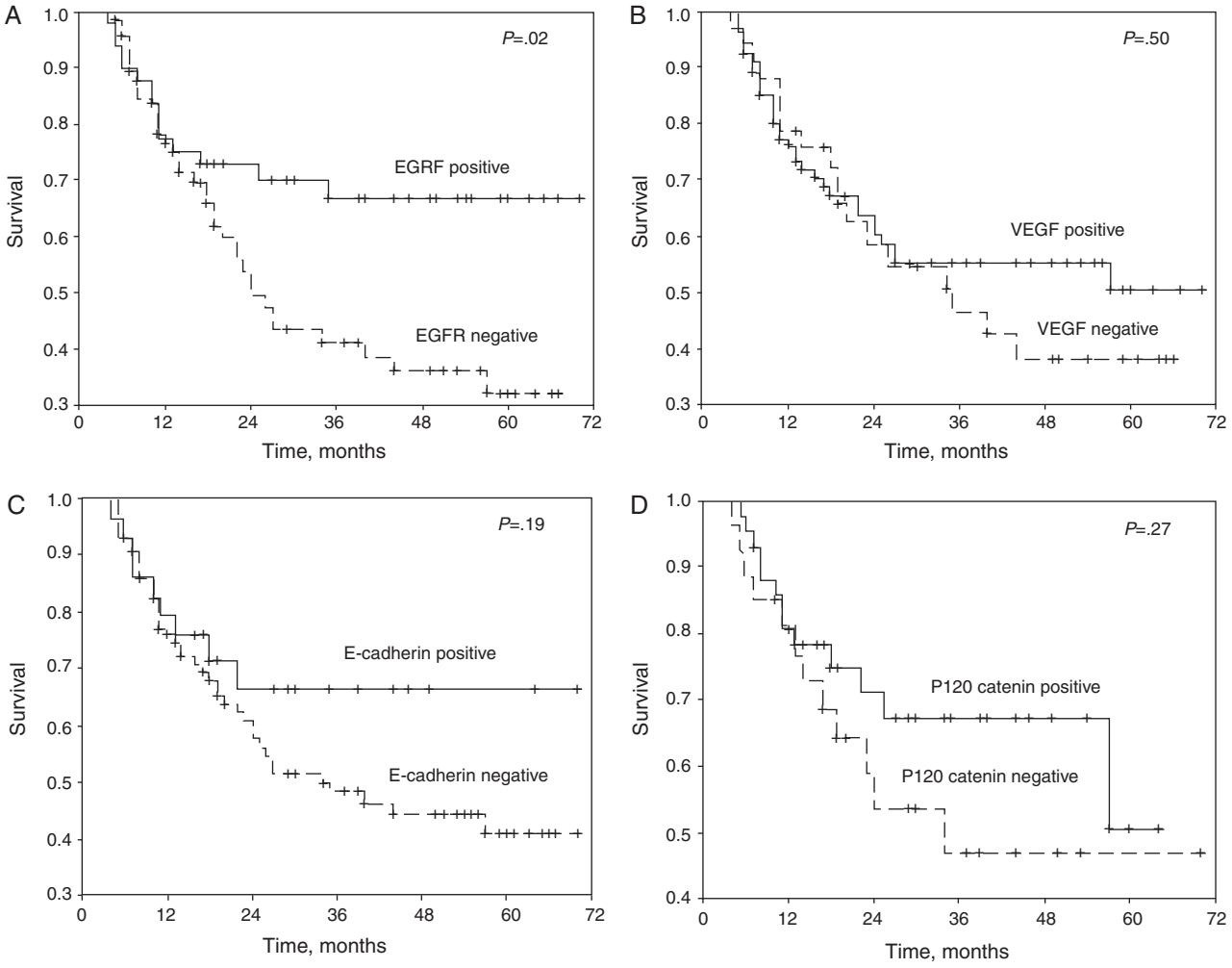

Fig. 1. (A) Survival curve of the patients of the study according to the results of the staining for epithelial growth factor receptor (EGFR). (B) Survival curve of the patients of the study according to the results if the staining for vascular endothelial growth factor (VEGF). (C) Survival curve of the patients of the study according to the results of the staining for E-cadherin. (D) Survival curve of the patients of the study according to the results if the staining for p120 catenin.

and the N status were variables that significantly affected survival (*P*=.021 and *P*=.010) (Table 3).

Discussion

Although it was demonstrated that the weak EGFR stain was related with a less prolonged survival, staining for VEGF, E-cadherin, and p120 catenin was not related with the survival of patients in whom samples were obtained from the exeresis of a NSCLC.

The overexpression of EGFR was related with the disease in advanced stage, development of a metastatic phenotype, reduced survival, and a poor prognosis.[3,13–15] Although in the immunohistochemical studies of post-operative tissues it has been reported that EGFR is a negative prognostic factor in NSCLC,[16] in general it is suggested that, by itself, this marker cannot be a prognostic factor.[15,17,18] In the present study, in patients with negative EGFR samples, the 5-year survival rate was 32%, while in the EGFR-positive group it was 66.7% (*P*=.02). Although it has been suggested that the excessive secretion or the powerful staining characteristics of EGFR give rise to a predictable decrease in survival,[18–20] studies have also been published documenting that it is related with longer survival, as was observed in the present study.[21,22]

Rusch et al.[23] documented that the overexpression of EGFR was present in 70.8% of patients with NSCLC, and that these patients had a longer 5-year survival (*P*=.023). In a study that included a series of 408 patients with complete tumor resection, in the EGFR-positive and EGFR-negative groups the 5-year survival rates were 63% and 61%, respectively.[13] In the present study, no significant differences were identified regarding the staining characteristics of EGFR and the determined stage of the disease. Likewise, nor was a significant difference detected between the positive and negative EGFR groups either for differentiation or metastases.

In some studies, it was found that the high expression of VEGF and the frequency of metastasis to the lymph nodes are related in the tumor tissue of patients with lung cancer without distant metastasis, while in others this relationship has not been reported. In patients without metastasis to the lymph nodes, no relationship has been demonstrated between tumor size and VEGF values.[6,7,24] Although it has been previously suggested that there is an increase in lymph node affectation as VEGF values increase,[6] in the present study this relationship was not detected. Furthermore, while in the VEGF-negative group the 5-year survival rate was 37.8%, in the positive group it was 50.7%. Despite the studies reporting that positive VEGF staining produces negative effects on survival,[8,25] there are also studies available that suggest that they are related with greater survival.[26,27] The results of the present study coincide with this latter group.

Sulzer et al.[28] described a significant correlation between the expression of E-cadherin and greater survival. There was a

Table 2
General Survival Rates.

Characteristics	5-Year Survival, %	*P* Value
General	46.2	–
Sex		
Men	43.8	.22
Women	83.3	
Age		
≤60	59.7	.55
>60	33.8	
Intervention		
Lobectomy	48.1	.55
Pneumonectomy	42.1	
Histologic grade		
Well-differentiated	57.9	
Moderately differentiated	48.2	.001
Poorly differentiated	0.0	
Histologic type		
Squamous cells	43.0	.97
Non-squamous cells	49.2	
T state		
1–2	48.9	.74
3–4	34.3	
N state		
0–1	50.2	.006
2	34.5	
Anatomic pathology state		
I	55.9	
II	41.1	.03
III	35.8	
EGFR		
Positive	66.6	.02
Negative	32.0	
VEGF		
Positive	50.7	.50
Negative	37.8	
E-cadherin		
Positive	66.0	.19
Negative	41.0	
p120 catenin		
Positive	50.0	.27
Negative	46.0	

EGFR: epithelial growth factor receptor; and VEGF: vascular endothelial growth factor.

significant inverse correlation between the expression of E-cadherin and the stage of the lymph nodes, just like the tumor differentiation. The reduced expression of E-cadherin correlated with the absence of histological tumor differentiation, an increase in lymphogenic metastases, and lower survival. In the present study, no significant difference was detected between the positive (24.1%) and negative (23.9%) E-cadherin groups regarding the frequency of N2. Although it was not statistically significant, in the positive E-cadherin group we observed a tendency towards a higher survival rate compared with the E-cadherin-negative patients in stage III (50% and 30.2%, respectively; *P*=.48).

Table 3
Cox General Multivariate Analysis.

Variable	*P* Value
EGFR (positive/negative)	.021 (OR=0.36)
N state (N2/N0–1)	.010 (OR=3.04)
VEGF	.8684
E-cadherin	.4840
p120 catenin	.1923
Stage	.5574
Histologic type	.1808
T state	.5557
Differentiation	.6872

EGFR: epithelial growth factor receptor; OR: odds ratio; and VEGF: vascular endothelial growth factor.

Among the 331 patients that underwent resection, it was demonstrated that the expression of E-cadherin was preserved in 193 (58%) patients and reduced in 138 (42%) patients. Regarding this E-cadherin expression, the 5-year survival rates related with lung cancer were 66.2% in the group with preserved expression and 56.3% in the group with reduced expression (*P*=.065). Among the cases with reduced expression of E-cadherin as well as β-catenin, a significant, unfavorable prognosis was demonstrated compared with the cases of decreased E-cadherin or β-catenin expression and compared with the cases of preserved expression of the two.[9]

In a study done by Retera et al.[29] in patients with resected NSCLC, the decrease in the expression of catenin was clearly related with metastasis to the lymph nodes and an unfavorable prognosis. The lower expression of E-cadherin and β-catenin were related with shorter survival.

A deficient expression of catenin is related with shorter disease-free periods and survival in patients with adenocarcinoma, NSCLC pT1–2 and pN0.[30] Intense staining of β-catenin correlates with greater survival.[9] In the present study, the 5-year survival rates were similar in the positive and negative groups.

The variations between the results of the study regarding survival rates are probably due to the variations in the evaluation criteria. Although the staining of a cell is considered positive for EGFR in some studies, others consider strong positive a stain >25% and weak negative a stain <25%. This causes a substantial difference in the results.

In the present study, the presence of EGFR negativity and N2 disease was related with an unfavorable prognosis. The variables that affected survival were the degree of EGFR staining and the N status, while the staining for VEGF, E-cadherin, and p120 catenin produced no effects on survival of resected non-small cell lung cancer.

Conflict of Interests

No source of funding or support was received for the completion of this manuscript. The authors declare having no conflict of interests.

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