Int J Clin Exp Med 2019;12(7):8929-8935
www.ijcem.com /ISSN:1940-5901/IJCEM0091061

Original Article

The expression levels of procalcitonin-20 and E-cadherin in lung cancer and their correlations with prognosis

Guang Zheng[1], Tingting Han[2], Jue Wang[3], Yin Xiao[1]

[1]Department of Medical Oncology, The Third Affiliated Hospital of Qiqihar Medical College, Qiqihar, Heilongjiang, China; [2]Department of Obstetrics and Gynecology, Qiqihar Second Hospital, Qiqihar, Heilongjiang, China; [3]Department of Oncology, The Third Affiliated Hospital of Qiqihar Medical College, Qiqihar, Heilongjiang, China

Received January 9, 2019; Accepted April 11, 2019; Epub July 15, 2019; Published July 30, 2019

Abstract: Lung cancer metastasis is correlated with prognosis. Epithelial E-cadherin (EC) inhibits tumor invasion, and EC deficiency facilitates tumor metastasis. Protocadherin-20 (PCDH20) plays important roles in intracellular signal transduction and inhibits the growth and clonal formation potency of non-small cell lung cancer (NSCLC). This study measured PCDH20 and EC expressions in lung cancer tissues to investigate their relationship with prognosis. A total of 68 NSCLC patients were recruited during the period January 2013 to June 2015. Immunohistochemical (IHC) staining was used to measure PCDH20 and EC protein expressions to analyze their correlations with the cohort's clinical/pathological features. The Kaplan-Meier approach plotted survival curves, and the Cox ratio risk model was employed to conduct a multi-variate survival analysis. NSCLC tissues had 20.59% and 44.12% positive rates of PCDH20 and EC expression respectively, which were significantly lower than in adjacent tissues (58.82% and 61.76%, $p<0.05$). Protein expressions were correlated with TNM stage and lymph node metastasis ($p<0.05$) but not with the pathology subtype or tumor size. A Kaplan-Meier curve revealed 12.0 months of median survival time in the PCDH20-negative groups, as compared to the PCDH20-positive rate (20.0 months). The EC-negative patients also showed a shorter median survival span than the EC-positive groups (14.0 months vs. 23.0 months, $p<0.05$). The Cox regression analysis identified the TNM stage, differentiation grade, PCDH20/EC protein expression, and lymph node metastasis as independent prognostic factors for NSCLC ($p<0.05$). PCDH20 and EC may play important roles in NSCLC progression and might work as reference points for prognostic evaluation.

Keywords: Lung cancer, E-cadherin, protocadherin-20, prognosis

Introduction

Primary lung cancer is a common malignant tumor in clinics, with a relatively high incidence and mortality. Based on its differential histopathological features, it can be subdivided into small cell lung cancer and non-small cell lung cancer (NSCLC), the latter of which occupies 80-85% of total lung cancer cases. The treatment strategies and prognostic evaluation of lung cancer are correlated with early diagnosis and histology subtype [1, 2]. Lung cancer metastasis is correlated with prognosis, involving multiple genes and factors, such as the vascular angiogenesis factor, extracellular matrix metalloproteinase (MMP) and adhesion molecules. During the invasion and metastasis of malignant tumors, both the epithelial-mesenchymal transition (EMT) and depressed cell adhesion play important roles [3, 4]. EMT can potentiate cell invasion or metastasis potency, and epithelial EC can inhibit tumor metastasis by regulating cell adhesion. EC knockdown or deficiency may facilitate tumor cell infiltration and metastasis [5, 6]. Protocadherin-20 (PCDH20) plays important roles in the formation of intracellular signal transduction. The PCDH20 gene is located on chromosome 13q-21, and promoter methylation or cell mutation may lead to the inactivation of gene expression. In the NSCLC cell line, PCDH20 is downregulated. The down-regulation of PCDH-PC in prostate cancer tissues is correlated with the methylation level in the promoter region, and PCDH20 overexpression can inhibit prostate cancer cell growth [7, 8]. Previous studies showed that the PCDH20 promoter methylation level is correlated with prognosis, and PCDH20 can inhibit the

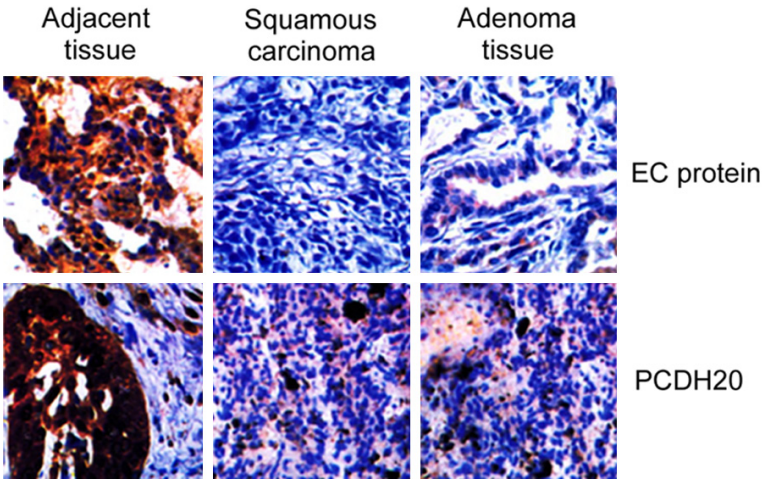

Figure 1. PCDH20 and EC protein expression in lung cancer tissues (×100).

growth or clonal formation of NSCLC cell line A459, thus exerting an antitumor role in NSCLC [9, 10].

Previous studies also showed that the adhesion molecule E-cadherin could induce tumor angiogenesis and plays important roles in tumor vascular formation and distal metastasis. In various tumors such as pancreatic cancer and colorectal carcinoma, E-cadherin expression is downregulated and is closely correlated with lymph node metastasis. As an endogenous negative regulator, E-cadherin at its normal expression level can inhibit cancer cell metastasis. In malignant tumors, the deactivation of the E-cadherin gene is correlated with promoter methylation [11, 12]. However, the exact role and mechanism by which E-cadherin and PCDH20 are involved in the occurrence/progression of lung cancer remains poorly understood. This study measured PCDH20 and EC protein expression levels in lung cancer tissues to evaluate their correlation with prognosis, thus providing evidence for the diagnosis, treatment and prognostic evaluation of lung cancer in clinics.

Materials and methods

General information

A total of 68 NSCLC patients who were admitted from January 2015 to June 2017 and diagnosed by pathology or histology in the Affiliated Cancer Hospital of Zhengzhou University were recruited in this study. None of the patients had received any chemo- or radiotherapy before surgery. Cancer tissues samples were collected from surgical resections and were confirmed by pathology. Tumor adjacent tissues with a distance of >5 cm from the cancer edge were also collected. In the patient cohort, there were 32 males and 36 females, aged between 31 and 76 years (average age = 60.5±6.7 years).

The study protocol was approved by the Research Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University, and all the patients gave their informed consent before the study began.

Inclusive criteria

All the patients received a confirmed diagnosis by histology or pathology, including percutaneous puncture, lymph node biopsy, fiber bronchoscopy biopsy, thoracic cavity fluid cytology assay, or sputum cytology. All recruited patients had their complete clinical information recorded and clear stage determined, and they received systemic post-op treatment (including intravenous chemo-therapy and focal treatment).

Exclusive criteria

Those patients complicated with other primary malignant tumors or who were lost during follow-up were excluded.

Reagent and equipment

PCDH20, EC antibody and SP immunohistochemistry (IHC) staining kits were provided by Boster Bio (China). The secondary antibody was provided by Zhongshan Jinqiao Biotech (China). The inverted microscope was from Olympus (Japan). The tissue embedding equipment was from SAKURA (Japan). The Microtome was from Leica (Germany). The oscillator was from Jinghong Equipment (China). The heat-resistant glass slide rack was from Maixin Biotech, (China). The computer-assisted image analysis system was from HP (United States).

Table 1. PCDH20 and EC protein expressions in lung cancer tissues

Tissue type	PCDH20 (%, n)	EC (%, n)	χ^2 value	*P* value
Tumor tissue	20.59 (14/68)*	44.12 (30/68)*	20.762	0.000
Tumor adjacent tissue	58.82 (40/68)	61.76 (42/68)	4.250	0.032

Note: *, p<0.05 compared to control group.

Table 2. The correlation between PCDH20 and EC protein expression and clinical/pathological features

Item	N	PCDH20 positive rate	EC positive	χ^2 value	*P* value
Sex					
Male	32	6 (18.75)	14 (43.75)	0.125	>0.05
Female	36	8 (22.22)	16 (44.44)	0.033	>0.05
Age					
<60	46	10 (21.74)	18 (39.13)	0.112	>0.05
≥60	22	4 (18.18)	12 (54.54)	1.434	>0.05
Tumor size (cm)					
<5	25	4 (16.00)	10 (40.00)	0.509	>0.05
≥5	43	10 (23.26)	20 (46.51)	1.809	>0.05
Pathology time					
Adenoma	49	11 (22.45)	23 (46.94)	0.417	>0.05
Squamous carcinoma	19	3 (15.79)	7 (36.84)	0.824	>0.05
Differentiation grade					
Low	47	13 (27.66)	25 (53.19)	4.655	<0.05
Moderate to high	21	1 (4.76)	5 (23.81)	5.083	<0.05
Infiltration depth					
No reaching serosa	50	11 (22.00)	26 (52.00)	3.118	>0.05
Penetrating serosa	18	3 (16.67)	4 (22.22)	0.230	>0.05
Lymph node metastasis					
Yes	16	0 (0.00)	1 (6.25)	5.425	<0.05
No	52	14 (26.92)	29 (55.77)	12.169	<0.05
Tumor TNM stage					
I+II	32	10 (31.25)	24 (75.00)	23.382	<0.05
III+IV	36	4 (11.11)	6 (16.67)	4.205	<0.05

Patient follow-ups

The patients received post-op follow-ups by electronic charts and telephone interviews. Progression-free survival (PFS) was evaluated from the time of confirmed diagnosis until the treatment efficacy evaluation revealed any progression of the disease (PD). Overall survival (OS) was deduced from the time of diagnosis until mortality or January 2017, using months as the unit. Till the endpoint of the observation window, the survivors were treated as cut-tail data. The correlation between PCDH20/EC expression and clinical pathology or prognosis was analyzed, along with survival period follow-ups. The Kaplan-Meier approach was used to plot the survival curve, and the Cox ratio-risk model was employed for multi-variant survival analysis.

Experimental approaches

IHC staining was employed to measure PCDH20 and EC expression in lung cancer and adjacent tissues. In brief, the tissues were fixed in formalin, followed by being dehydrated and then immersed in paraffin for tissue embedding. Paraffin-based tissues were cut into sections, which were dried, dehydrated, and processed in heat antigen retrieval. After blocking, normal goat serum (NGS) was added, followed by 1 h room temperature incubation with 50 μl rabbit anti-human monoclonal antibody of PCDH20 or EC (1:100 for both). 50 μl of secondary antibody (1:100) was then added for 10 min incubation, followed by incubation with 50 μl streptavidin-peroxidase for 10 min at room temperature. After development, quenching, counter-staining and differentiation, a computer-assisted imaging system was used to capture the images. Five fields were randomly selected from each slide for recording.

Deduction of positive expression

Positive expression was deduced as brown-yellow granules in the nucleus, cytoplasmic membrane or cytoplasm. The IHC staining results were analyzed in a semi-quantitative manner. Scores were given according to the percentage of positive cells: 0 for no positive cells; 1 for <25% positive cells, 2 for 25%~50% positive cells, 3 for 50%~75% positive cells, and 4 for >75% positive cells. Staining intensity was given for 0, 1, 2, and 3 for no significant stain-

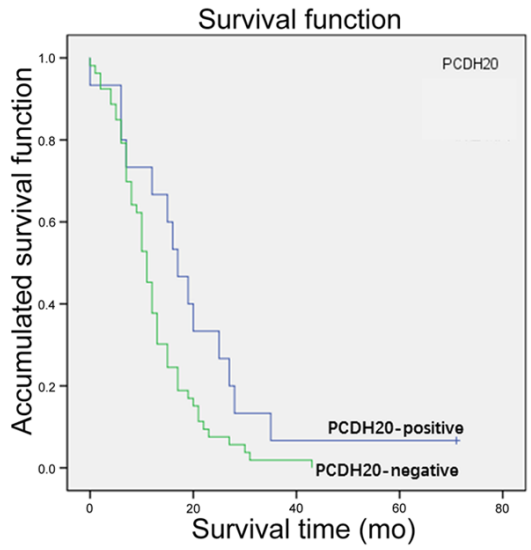

Figure 2. Correlation analysis between PCDH20 protein expression in NSCLC and its prognosis.

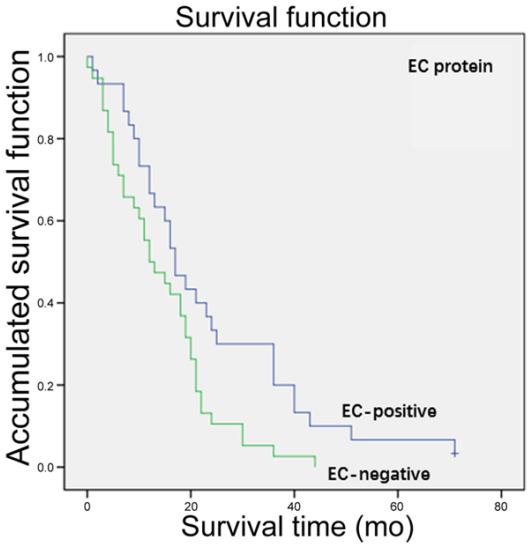

Figure 3. Correlation between EC protein expression and prognosis in NSCLC patients.

ing, light yellow, brown-yellow and dark brown, respectively. The total score was determined by calculating the product of staining intensity score and the positive cell score. The product was deduced as negative (-) for scores of 0~3, weak positive (+) for scores of 4~8, and positive (++) for scores of 9~12.

Data processing

Data were analyzed using SPSS 19.0 software. Enumeration data were processed using a chi-square test. The measurement data were tested for normality using a Kolmogorov-Smirnov test. The biased distribution was described using median ± quadrille (M ± Q). A rank-sum test was used to compare the independent samples. The measurement data that were fitted into a normal distribution were presented as the mean ± standard deviation (SD) and analyzed using an analysis of variance (ANOVA) and Student's *t*-test. The Kaplan-Meier approach was used to plot the survival curve, and the Cox ratio risk model was employed to do a multi-variant survival analysis. Statistical significance was defined as $p<0.05$.

Results

PCDH20 and EC protein expressions in lung cancer tissues

In NSCLC tissues, the positive rates of PCDH20 and EC protein expressions were 20.59% and 44.12%, respectively, which were significantly lower than those in controlled tumor adjacent tissues (58.82% and 61.76%, χ^2=20.762 and 4.250, $p<0.05$). Positive expression of the target protein was shown as light yellow to dark brown colors. PCDH20 positive expression was mainly shown in the nuclei and cytoplasms, but EC protein was mainly expressed in the cytoplasmic plasma and cytoplasms. T-cadherin expression is mainly located on the membranes, and CD34 positive expression exists on the membranes and cytoplasms (**Figure 1**, **Table 1**).

Correlation analysis between PCDH20/EC protein expressions in NSCLC and clinical/pathological features

PCDH20 and EC protein positive expressions were found to be correlated with the tumor differentiation grade, TNM stage and lymph node metastasis ($p<0.05$), but not with tumor size, age, sex, or pathological type. The patients with lymph node metastasis had a lower PCDH20/EC protein positive expression rate compared to those without lymph node metastasis. In the advanced clinical stages, the PCDH20 and EC proteins showed decreased positive expressions (**Table 2**).

PCDH20 and EC expressions in lung cancer tissues and their relationship with prognosis

A total of 68 patients received post-up follow ups until January 2017, with median overall survival (OS) at 15 months (95% CI: 13.716~

Table 3. Cox regression analysis for the adverse factors of prognosis in NSCLC patients

Relevant factors	β	$S^{\bar{x}}$	Wald χ^2	*P* value	OR value	95% CI	
Clinical TNM stage	0.839	0.354	5.610	0.019	2.314	1.156	4.633
PCDH20	0.623	0.292	4.548	0.035	1.865	1.052	3.305
EC	0.677	0.313	4.689	0.034	1.968	1.066	3.632
Tumor differentiation	0.986	0.416	3.782	0.01	2.680	1.186	6.058
Lymph node metastasis	0.864	0.365	3.582	0.01	2.372	1.161	4.848

17.088). Those patients with PCDH20-negative expression showed a significantly shorter survival span than the PCDH20-positive ones (11.0 months vs. 17.0 months, $p<0.05$). The EC-negative patients also showed shorter OS than the EC-positive individuals (12.0 months vs. 18.0 months, $p<0.05$, **Figures 2** and **3**).

Cox regression analysis for the independent prognostic factors of NSCLC

Various factors, including age, sex, clinical stage, pathological type, and PCDH20/EC protein expression were included in the Cox ratio risk model for multi-variate survival analysis, and we found that clinical TNM stage, tumor differentiation grade, PCDH20/EC protein expressions and lymph node metastasis were independent prognostic factors of NSCLC ($p<0.05$, **Table 3**).

Discussion

PCDH is an important member of the cadherin protein family and plays important roles in intracellular signal transduction. Mainly expressed in the nervous system, PCDH has cell adhesion properties. Such extracellular features of transmembrane PCDH20 exerts important roles in cell-to-cell adhesion [13, 14]. PCDH20 is a non-clustered PCDH, and its gene is located on chromosome 13q21.2, with six extracellular cadherin domains. Previous studies showed decreased PCDH20 expressions in the NSCLC cell line, and NSCLC tissues also showed higher a PCDH20 gene methylation rate than normal lung tissues. After treatment with de-methylation drugs, PCDH20 expression is significantly up-regulated. The promoter methylation level of the PCDH20 gene is closely correlated with its expression in NSCLC tissues [15-17]. In epithelial cell adhesion, the epithelial EC protein complex has important roles, and lowly differentiated EC is correlated with tumor cell differentiation. Previous studies have generated inconsistent results regarding the relationship between NSCLC prognosis and EC expression [18, 19]. This study measured PCDH20 and EC expression in lung cancer tissues to investigate their correlation with prognosis. The results showed lower PCDH20 and EC expression in NSCLC tissues, which were higher in tumor tissues compared to the adjacent tissues, indicating that they might be involved in NSCLC onset and progression.

Previous studies showed important roles of tumor cell adhesion lost and separated during the tumor invasion and metastasis process. The EC protein is a major mediator for epithelial cell adhesion and intracellular connections [20, 21]. By transfecting highly invasive tumor cells with the wild type EC gene, tumor invasion or metastasis was inhibited. EC down-expression is correlated with the lymph node metastasis of various malignant tumors. A previous study showed a correlation between PCDH20 methylation levels and unfavorable cancer prognoses [22]. In the present study, we did not reveal a significant correlation between PCDH20/EC protein expression and sex, age, or patients' pathological subtypes. However, tumor differentiation grade, TNM stage, lymph node metastasis, and EC expression affect tumor cell reattachment and de-attachment. During tumor progression, EC down-regulation or deficiency is directly correlated with tumor infiltration and metastasis [23, 24]. This study further proved that PDH20/EC protein down-regulation or deficiency caused decreased cell adhesion potency, making tumor cells detach from primary lesions, thus facilitating tumor infiltration or metastasis. A Kaplan-Meier curve showed that the PCDH20-negative patients had a significantly shorter survival period than the PCDH20-positive patients did, and the EC-negative patients had a shorter survival than the EC-positive ones, indicating possible roles of PCDH20 and EC in NSCLC progression. PCDH20

and EC expression thus might be used as reference points for the prognostic evaluation of NSCLC.

A Cox regression analysis showed that TNM stage, tumor differentiation grade, PCDH20/EC protein expression and lymph node metastasis were independent prognostic factors for NSCLC, suggesting that patient prognosis could be primarily evaluated according to PCDH20 and EC expression, which might be beneficial for the clinical evaluation of NSCLC patient prognosis. Due to the limited sample size included in the present study, a large cohort clinical study should be performed to demonstrate the correlation between PCDH20/EC expression and post-op survival time in NSCLC patients. Moreover, determining the roles and mechanisms of E-cadherin and PCDH20 in lung cancer onset and progression is also worthy of further investigation.

Conclusion

PCDH20 and EC may play important roles in NSCLC progression, and their expressions may serve as reference points for evaluating the post-op prognosis of NSCLC.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yin Xiao, Department of Oncology, The Third Affiliated Hospital of Qiqihar Medical College, No. 27, Taishun Street, Tiefeng District, Qiqihar, Heilongjiang, China. Tel: +86-0452-2120197; Fax: +86-0452-2120197; E-mail: kqegomaw2sq@sina.com

References

[1] Birse CE, Lagier RJ, FitzHugh W, Pass HI, Rom WN, Edell ES, Bungum AO, Maldonado F, Jett JR, Mesri M, Sult E, Joseloff E, Li A, Heidbrink J, Dhariwal G, Danis C, Tomic JL, Bruce RJ, Moore PA, He T, Lewis ME and Ruben SM. Blood-based lung cancer biomarkers identified through proteomic discovery in cancer tissues, cell lines and conditioned medium. Clin Proteomics 2015; 12: 18.

[2] Korbakis D, Dimitromanolakis A, Prassas I, Davis GJ, Barber E, Reckamp KL, Blasutig I and Diamandis EP. Serum LAMC2 enhances the prognostic value of a multi-parametric panel in non-small cell lung cancer. Br J Cancer 2015; 113: 484-91.

[3] Romero-Ventosa EY, Blanco-Prieto S, Gonzalez-Pineiro AL, Rodriguez-Berrocal FJ, Pineiro-Corrales G and Paez de la Cadena M. Pretreatment levels of the serum biomarkers CEA, CYFRA 21-1, SCC and the soluble EGFR and its ligands EGF, TGF-alpha, HB-EGF in the prediction of outcome in erlotinib treated non-small-cell lung cancer patients. Springerplus 2015; 4: 171.

[4] Cingelova S, Labudova V, Berkesova D, Dienerova M, Dammak A, Grmanova E, Nadaska O, Vasilenkova I, Najselova E, Skarbova V, Migasova M, Viktorinova Z, Jurga L. [Prognostic markers of advanced non-small cell lung carcinoma - assessing the significance of oncomarkers using data-mining techiques RPA]. Klin Onkol 2014; 27: 347-52.

[5] Liu XL, Zhang XT, Meng J, Zhang HF, Zhao Y, Li C, Sun Y, Mei QB, Zhang F, Zhang T. ING5 knockdown enhances migration and invasion of lung cancer cells by inducing EMT via EGFR/PI3K/Akt and IL-6/STAT3 signaling pathways. Oncotarget 2017; 8: 54265-54276.

[6] Enderle-Ammour K, Bader M, Ahrens TD, Franke K, Timme S, Csanadi A, Hoeppner J, Kulemann B, Maurer J, Reiss P, Schilling O, Keck T, Brabletz T, Stickeler E, Werner M, Wellner UF, Bronsert P. Form follows function: morphological and immunohistological insights into epithelial-mesenchymal transition characteristics of tumor buds. Tumour Biol 2017; 39: 1010428317705501.

[7] Feng J, Zhang X, Zhu H, Wang X, Ni S and Huang J. FoxQ1 overexpression influences poor prognosis in non-small cell lung cancer, associates with the phenomenon of EMT. PLoS One 2012; 7: e39937.

[8] Kinoshita Y, Takasu K, Yuri T, Yoshizawa K, Uehara N, Kimura A, Miki H, Tsubura A, Shikata N. Two cases of malignant peritoneal mesothelioma without asbestos exposure: cytologic and immunohistochemical features. Ann Diagn Pathol 2013; 17: 99-103.

[9] Park J, Yang JS, Jung G, Woo HI, Park HD, Kim JW, Huh W, Ko JW, Kim H, Cho JY, Lee SY. Subunit-specific mass spectrometry method identifies haptoglobin subunit alpha as a diagnostic marker in non-small cell lung cancer. J Proteomics 2013; 94: 302-10.

[10] Li M, Zheng C, Xu H, He W, Ruan Y, Ma J, Zheng J, Ye C, Li W. Inhibition of AMPK-related kinase 5 (ARK5) enhances cisplatin cytotoxicity in non-small cell lung cancer cells through regulation of epithelial-mesenchymal transition. Am J Transl Res 2017; 9: 1708-1719.

[11] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tu-

mours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.
[12] Lumachi F, Santeufemia DA, Del Conte A, Mazza F, Tozzoli R, Chiara GB, Basso SM. Carboxy-terminal telopeptide (CTX) and amino-terminal propeptide (PINP) of type I collagen as markers of bone metastases in patients with non-small cell lung cancer. Anticancer Res 2013; 33: 2593-6.
[13] Shibuya M, Kogo M, Kurihara T, Shikama Y, Nakajima H, Yoneyama K, Kiuchi Y. [Analysis of the risk factors for severe neutropenia in advanced non-small cell lung cancer after the first course of chemotherapy with third-generation agents]. Yakugaku Zasshi 2013; 133: 703-9.
[14] Kozu Y, Maniwa T, Takahashi S, Isaka M, Ohde Y, Nakajima T. Prognostic significance of postoperative serum carcinoembryonic antigen levels in patients with completely resected pathological-stage I non-small cell lung cancer. J Cardiothorac Surg 2013; 8: 106.
[15] Tanaka K, Hata A, Kaji R, Fujita S, Otoshi T, Fujimoto D, Kawamura T, Tamai K, Takeshita J, Matsumoto T, Monden K, Nagata K, Otsuka K, Nakagawa A, Tachikawa R, Otsuka K, Tomii K and Katakami N. Cytokeratin 19 fragment predicts the efficacy of epidermal growth factor receptor-tyrosine kinase inhibitor in non-small-cell lung cancer harboring EGFR mutation. J Thorac Oncol 2013; 8: 892-8.
[16] Hur J, Lee HJ, Nam JE, Kim YJ, Hong YJ, Kim HY, Kim SK, Chang J, Kim JH, Chung KY, Lee HS and Choi BW. Additional diagnostic value of tumor markers in cytological fluid for diagnosis of non-small-cell lung cancer. BMC Cancer 2012; 12: 392.
[17] Jung M, Kim SH, Hong S, Kang YA, Kim SK, Chang J, Rha SY, Kim JH, Kim DJ and Cho BC. Prognostic and predictive value of carcinoembryonic antigen and cytokeratin-19 fragments levels in advanced non-small cell lung cancer patients treated with gefitinib or erlotinib. Yonsei Med J 2012; 53: 931-9.
[18] Trape J, Montesinos J, Catot S, Buxo J, Franquesa J, Sala M, Domenech M, Sant F, Badal JM and Arnau A. A prognostic score based on clinical factors and biomarkers for advanced non-small cell lung cancer. Int J Biol Markers 2012; 27: e257-62.
[19] Li X, Asmitananda T, Gao L, Gai D, Song Z, Zhang Y, Ren H, Yang T, Chen T and Chen M. Biomarkers in the lung cancer diagnosis: a clinical perspective. Neoplasma 2012; 59: 500-7.
[20] Lee DS, Kim YS, Jung SL, Lee KY, Kang JH, Park S, Kim YK, Yoo Ie R, Choi BO, Jang HS and Yoon SC. The relevance of serum carcinoembryonic antigen as an indicator of brain metastasis detection in advanced non-small cell lung cancer. Tumour Biol 2012; 33: 1065-73.
[21] Cabrera-Alarcon JL, Carrillo-Vico A, Santotoribio JD, Leon-Justel A, Sanchez-Gil R, Gonzalez-Castro A and Guerrero JM, CYFRA 21-1 as a tool for distant metastasis detection in lung cancer. Clin Lab 2011; 57: 1011-4.
[22] Hong YJ, Hur J, Lee HJ, Nam JE, Kim YJ, Kim HS, Kim HY, Kim SK, Chang J, Kim JH, Chung KY, Choi BW and Choe KO. Analysis of tumor markers in the cytological fluid obtained from computed tomography-guided needle aspiration biopsy for the diagnosis of non-small cell lung cancer. J Thorac Oncol 2011; 6: 1330-5.
[23] Jung M, Kim SH, Lee YJ, Hong S, Kang YA, Kim SK, Chang J, Rha SY, Kim JH, Kim DJ and Cho BC, Prognostic and predictive value of CEA and CYFRA 21-1 levels in advanced non-small cell lung cancer patients treated with gefitinib or erlotinib. Exp Ther Med 2011; 2: 685-693.
[24] Hanagiri T, Sugaya M, Takenaka M, Oka S, Baba T, Shigematsu Y, Nagata Y, Shimokawa H, Uramoto H, Takenoyama M, Yasumoto K and Tanaka F. Preoperative CYFRA 21-1 and CEA as prognostic factors in patients with stage I non-small cell lung cancer. Lung Cancer 2011; 74: 112-7.