VAN TIP DERGİSİ Medical Journal

KLİNİK ÇALIŞMA / CLINICAL RESEARCH

Van Tıp Derg 28(1): 38-43, 2021
DOI: 10.5505/vtd.2021.21549

Comparison of Suvmax Values Obtained From F-18 Fdg Pet/Ct and Ykl-40 Levels Measured From Serum In The Evaluation of Lung Lesions

Akciğer Lezyonlarının Değerlendirilmesinde FDG PET/CT ile Ölçülen SUVmax ile Serum YKL-40 Düzeylerinin Karşılaştırılması

Ebru Örsal İbişoğlu[1*], Engin Şebin[2]

[1]Medeniyet Üniversitesi Göztepe Eğitim ve Araştırma Hastanesi, Nükleer Tıp AD, İstanbul, Turkey
[2]Sağlık Bilimleri Üniversitesi, Erzurum Bölge Eğitim ve Araştırma Hastanesi, Tıbbi Biokimya AD, Erzurum, Turkey

ABSTRACT

Objective: Fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) is a trusted method for the evaluation of cancer patients. In this study, we aimed to calculate the SUVmax values for semi-quantitative evaluation in patients with pulmonary lesions undergoing diagnostic PET / CT study and to investigate serum YKL-40 and ischemia modified albumin (IMA) levels.

Materials and Methods: We performed a prospective case-control during July 2012-July 2013. Patients referred to the nuclear medicine clinics with suspected pulmonary lesions were enrolled in the study prospectively. In this study we analyzed 85 patients who underwent routine PET/CT imaging for suspicious lung masses. Of the included patients, 20 (23.5%) had BLD, while 65 (76.5%) had lung cancer (LC) in the pathological examination of the lesions. Additionally, 35 participants from the patient relatives were enrolled as healthy controls. SUVmax were calculated in patients who underwent PET / CT study, and serum samples of YKL 40, IMA, carcinoembryonic antigen (CEA) and lactate dehydrogenase (LDH) values were measured.

Results: Patients with LC had higher mean SUVmax values compared to the BLD group (9.49±2.27 vs. 3.13±1.15) (p<0.001). Serum YKL-40 (71,42±7,65ng/L and102.03±12.22 ng/L vs. 31,79±7,52 ng/L), IMA (0,90±0,16 and 0,84±0.09 vs. 0,70±0,08), LDH (268,00±63,30 U/L and 261.03±65,02 U/L vs. 165,08,00±52,62 U/L), and CEA (4,60±1,10 ng/mL and 2,47±0.81 ng/mL vs. 1,9±0,41 ng/mL) measurements remained greater in patients having LC and BLD than the healthy participants (p<0.001).

Conclusion: In this study we concluded that SUVmax and serum YKL-40 levels were increased in LC cases. SUVmax may be an efficient variable to distinguish LC from BLD.

Key Words: Lung cancer, non-small cell lung cancer, small cell lung cancer, PET/CT, Maximum standardized uptake value, YKL40, ischemia modified albumin

ÖZET

Amaç: Florin-18-florodeoksiglukoz kullanılan pozitron emisyon tomografisi (PET) ile birlikte bilgisayarlı tomografi (BT) kanserli hastaların tanı ve evrelemesi için kullanılan bir yöntemdir. Bu çalışmada akciğer lezyonu saptanan tanı amaçlı PET/ BT çalışması uygulanan hastalarda semi-kantitatif değerlendirme amaçlı SUVmax değerlerini hesaplamak ve serum YKL-40 ve iskemi modifiye albümin (IMA) düzeylerini araştırmayı amaçladık.

Gereç ve Yöntem: Temmuz 2012-Temmuz 2013 tarihleri arasında prospektif bir vaka kontrol çalışması yapıldı. Akciğer lezyonlarından şüphelenilen, nükleer tıp kliniğine başvuran hastalar prospektif olarak çalışmaya dahil edildi. Bu çalışmada akciğerlerde şüpheli kitleler için rutin PET/BT görüntülemesi uygulanan 85 hastayı analiz edildi. Lezyonların patolojik muayenesinde hastaların 20'sinde (%23,5) iyi huylu akciğer hastalığı, 65'inde (%76,5) AK mevcuttu. Ayrıca hasta yakınlarından 35 katılımcı sağlıklı kontrol grubu olarak kaydedildi. PET/ BT çalışması uygulanan hastalarda maksimum standartlaştırılmış alım değerleri (SUVmax) hesaplandı ve serum örneklerinde YKL-40, iskemi modifiye albümin (IMA), karsinoembriyonik antijen (CEA) ve laktat dehidrojenaz (LDH) değerleri ölçüldü.

Bulgular: AK'li hastalarda, iyi huylu akciğer hastalığı grubuna göre ortalama SUVmax değerleri daha yüksekti (9,49±2,27 ve 3,13±1,15) (p<0.001). Serum YKL-40 (71,42±7,65ng/L ve 102,03±12,22 ng/L'ye karşı 31,79±7,52 ng/L), IMA (0,90±0,16 ve 0,84±0.09'a karşı 0,70±0,08), LDH (268,00±63,30 U/L ve 261.03±65,02 U/L'ye karşı 165,08,00±52,62 U/L) ve CEA (4,60±1,10 ng/mL ve 2,47±0.81 ng/mL'ye karşı 1,9±0,41 ng/mL) değerleri AK'li ve iyi huylu akciğer hastalığı olan hastalarda sağlıklı kişilere göre daha yüksekti (p<0.001).

Sonuç: Sonuçlarımız akciğer kanseri olgularında SUVmax ve serum YKL-40 düzeylerinin daha yüksek olduğunu göstermektedir. SUVmax, akciğer kanserlerini iyi huylu akciğer hastalığından ayırmak için yararlı bir ölçüt olabilir.

Anahtar Kelimeler: Akciğer kanseri, küçük hücre dışı akciğer kanseri, küçük hücreli akciğer kanseri, PET/BT, Maksimum standart alım değeri, YKL40, iskemi modifiye albümin

***Sorumlu Yazar:** Ebru Örsal İbişoğlu, Medeniyet Üniversitesi Göztepe Eğitim ve Araştırma Hastanesi, Nükleer Tıp AD, İstanbul, Turkey
E-mail: e.orsal@yahoo.com.tr, Tel: +90 (532) 796 26 73
ORCID ID: Ebru Örsal İbişoğlu: 0000-0002-9132-9092, **Engin Şebin:** 0000-0001-9150-8069
Geliş Tarihi: 28.03.2020, **Kabul Tarihi:** 05.10.2020

Introduction

Fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) /computed tomography (CT) is applied for the diagnosis and staging of various malignancies, and it is a commonly used functional imaging, particularly for patients with pulmonary lesions (1,2). 18F-FDG targets cells which exhibit high glucose metabolism; it is a frequently utilized radiotracer for PET/CT imaging. In this modality, the most strong 18F-FDG uptake in the primary lesion is calculated as the maximum standardized uptake value (SUVmax).

SUVmax measurement is used as a semiquantitative value and is negatively correlated with survival (3). When SUVmax increases, disease-free survival is reported to decrease by 75% (4). However, 18F-FDG as carrier molecule is not particular for malignant tumor cells and can collect nonspecifically in some benign conditions, leading to false-positive results and misdiagnoses (5).

YKL-40 (or Chitinase 3-like 1) is a 40k-Da glycoprotein, having growth factor activity during tissue remodeling processes, which may also be important in the progression of malignant cells (6). Thus YKL-40 may be a new indicator in cancer. It was found that YKL-40 is prominent in many malignancies, such as breast, colon, kidney, lung, glioblastoma, pancreas, and thyroid. Moreover, the relationship between increased serum YKL-40 levels with an unfavorable outcome was detected (6,7).

On the other hand, ischemia modified albumin (IMA) is an oxidative stress marker and a product generated from albumin as a result of hypoxia (8). Serum IMA levels are increased in different types of cancer. Furthermore, serum IMA levels were suggested as a reliable prognostic indicator for malignancies (9).

No reports are published about serum levels of IMA in lung cancer (LC) patients. We hypothesized that there would be significant differences in SUVmax, YKL-40, and IMA values of participants having LC, benign lung disease (BLD), and control participants without any disease. This study aimed to research serum SUVmax, YKL-40, and IMA levels in patients with LC, BLD, and healthy people.

Materials and Methods

We conducted a prospective case-control study at Atatürk University Hospital nuclear medicine clinics during July 2012-July 2013. With a staff of 11 people (including 6 specialists and residents of nuclear medicine), the department welcomes yearly around 1855 patients. Written informed consent was taken from all participants, and ethical clearance of the research was received from the Atatürk University Medical Faculty local ethics committee (number: 62; date: 9 July 2012).

This study included participants who were referred to our nuclear medicine clinics with suspected lung lesions in a prospective manner. The study analyzed 85 patients who received routine PET/CT imaging for suspicious masses in the lungs detected with other imaging modalities. Referred patients were also investigated for blood variables. As a result of the investigation, 20 (23.5%) of the 85 participants had some BLD, while 65 had LC in the pathological report. No patients had any connective tissue or other systemic disease or received any treatment pertinent to the lung lesion before PET-CT scanning. Additionally, 35 participants from the patient relatives were enrolled as healthy controls (Figure 1). The healthy controls were examined by a lung specialist and underwent plain chest x-ray examination to rule out any lung pathology.

Data for BLD and LC cases were obtained from the patient files, while the control group participants were analyzed for blood variables.

The FDG-PET protocol: All patients fasted for at least 6 hours, and the serum glucose was analyzed prior to administering 18F-FDG to make sure that the level was less than 150 mg/dL. Participants received intravenous injections of 444–555 MBq (12–15 mCi) 18F-FDG and were asked to rest for 60–90 min after the injection. The PET/CT analysis was done with a Siemens Biograph PET/CT system (Siemens, Knoxville, TN, USA). A low-dose CT scan was taken from the vertex to the thigh. Then, PET images were taken (seven to nine beds, 3min/bed) in the supine position. PET images were configured with iterative reconstruction and attenuation correction. Sagittal, coronal, and transverse images were evaluated. Increased 18F-FDG uptake compared with the background activity was considered as abnormal, and CT images were used for anatomic landmarking. In each case, the region of interest was drawn manually from the PET/CT images that showed the most strong 18F-FDG uptake in the primary lung lesion, and the SUVmax was automatically calculated.

Biochemical analysis: Venous blood was taken; the sera were separated and frozen at -80 °C. YKL-40, IMA, carcinoembryonic antigen (CEA), and LDH values were measured in the sera. Serum levels of YKL-40 were measured using a commercial YKL-40 Quantikine ELISA Kit Cat DC3L10 (R&D Systems, Inc. Minneapolis, MN, USA). Serum samples were diluted 1:50 with assay buffer. IMA levels in the sera

Fig. 1. Study participant flow chart

were analyzed using the albumin cobalt binding test. Results were presented as an absorbance unit (ABSU). Serum CEA levels were measured in a DXI analyzer using the chemiluminescence method (Beckman Coulter, USA). LDH concentrations were measured by the spectrophotometric method using AU 5800 analyzer (Beckman Coulter, Atlanta, Georgia, USA).

The patient files were reviewed by two researchers, who discussed their findings in case of disagreement. External professional service was taken for data analysis.

Post hoc sample size estimation was done based on the primary variable mean YKL-40 levels. A total sample size of 57 participants is required for comparing mean YKL-40 measurements between patients with LC, BLD, and control participants using the one-way ANOVA test with an effect size of 0.45, an alpha error of 0.05, and a power of 80% (10).

The SPSS software program (Version 20.0 for Windows; SPSS, Chicago, Illinois, USA) was used for statistical calculations. All numerical variables were tested for skewness with the Shapiro-Wilk test. Depending on the variable type, the data were represented in means ± standard deviations (SD) or frequency (%). Differences between groups were analyzed using the one-way ANOVA; pairwise associations were assessed with the Tukey analysis. Mean values between two independent variables were compared with the independent samples t-test. Associations among numerical variables were assessed by the Pearson correlation analysis. The threshold of significance was taken as $p < 0.05$.

Results

Data for 120 participants were analyzed. Of the 85 patients who received PET/CT scanning, 20 (23.5%) had some benign lesions, while the remaining 65 (76.5%) were diagnosed as having lung cancer. Of the LC patients, 46 (70.8%) had non-small cell lung cancer (NSCLC), while 19 (29.2%) had squamous cell lung cancer (SCLC).

Individuals with LC had higher mean SUVmax values compared to the BLD group (Table 1). Additionally, the mean SUVmax values were higher in the NSCLC patients (10.30±2.27) compared to the SCLC patients (8.09±3.19) ($t=3.157$, $p=0.002$).

Serum YKL-40 and IMA levels were higher in patients with LC and BLD compared to healthy subjects. However, post hoc analysis showed that there was no significant difference in the serum YKL-40 measurements among LC and BLD groups.

On the other hand, serum CEA and LDH levels showed significant variations between the groups, too (Table 1).

SUVmax showed no meaningful correlation with serum YKL-40 or other blood analyzes in the LC and BLD groups ($p>0.05$). Nevertheless, an association was seen among YKL-40 and IMA in the BLD group ($r=0.360$, $p<0.001$).

Discussion

This study showed significant differences in PET/CT findings well as the investigated biochemical markers of cancer between patients with BLD, LC, and healthy controls. All the investigated variables (SUVmax, YKL-40, IMA, LDH, and CEA) were higher in patients with LC.

Although this study was prospectively planned, and measures were taken to collect reliable data, there are some drawbacks to be considered in the interpretation of the results. First, despite the relatively long prospective patient enrollment, the total number of cancer cases allowed only for a sample with a large effect size. Additionally, having a control group less than the study group may have decreased the study power to some extent. Lastly, a time gap exists between data collection and publication, which was due to the personal problems of the primary author.

Conventional radiological modalities have been used for the differential diagnosis of lung lesions based on morphological differences for many years. PET/CT is valued in providing molecular imaging of biological function in addition to the morphological changes in

Table 1. Comparison of the outcome variables between the groups

	BLD (n=20)	LC (n=65)	HC (n=35)	t/F	p	Tukey
SUVmax (mean±SD)	3.13±1.15	9.49±2.27	-	12.028	<0.001	
YKL-40 ng/L (mean±SD)	102.03±12.22	71.42±7.65	31.79±7.52			BLD vs. LC: 0.177 BLD vs. HC: 0.001 LC vs. HC: <0.001
IMA (mean±SD)	0.84±0.09	0.90±0.16	0.70±0.08	472.552	<0.001	BLD vs. LC: <0.001 BLD vs. HC: 0.001 LC vs. HC: <0.001
LDH U/L (mean±SD)	261.03±65.02	268.00±63.30	165.08±52.62	34.675	<0.001	BLD vs. LC: 0.894 BLD vs. HC: 0.001 LC vs. HC: <0.001
CEA ng/mL (mean±SD)	2.47±0.81	4.60±1.10	1.9±0.41	115.781	<0.001	BLD vs. LC: <0.001 BLD vs. HC: 0.067 LC vs. HC: <0.001

BLD: Benign lung disease, LC: Lung cancer, HC: Health controls, SUVmax: maximum standardized uptake value, SD: Standard deviation, IMA: ischemia modified albumin, LDH: lactate dehydrogenase, CEA: carcinoembryonic antigen

the lesions (11,12). Compared to conventional radiological techniques, the sensitivity of 18F-FDG PET/CT is greater in diagnosing LC (13). Besides, 18F-FDG PET/CT was found useful for characterizing lung lesions in many reports (2,11,14,15). 18F-FDG PET/CT was also ordered in our research for individuals with a suspicious mass detected in conventional imaging methods.

The most commonly preferred PET/CT radiotracer is 18F-FDG, which has demonstrated benefits in a variety of circumstances (1). SUVmax indicates the concentration of 18F-FDG in the tissue and is useful for assessing changes in metabolism (14). However, elevated SUVmax is not limited to cancer cells. Despite its high sensitivity, false-positive findings may occur with 18F-FDG PET, particularly in inflammatory conditions (5,16).

The prognostic value of increased FDG uptake is variable because there are several reasons of cellular FDG uptake, such as tumor glucose use, increased cellular proliferation, hypoxia, the size of the lesion, as well as the time interval between injection and imaging (17). Also, there are controversial results due to pitfalls in FDG uptake. In some studies, an SUVmax alone was not regarded as sufficiently reliable to differentiate malignant and benign lesions (14). However, it was clinically shown that FDG uptake correlated with proliferative activity in NSCSLC (18). Furthermore, Vansteenkiste et al. showed that survival in NSCLC was higher in patients with a SUV below 7 (19).

Similar to our results, Prauer et al. (20) showed in pulmonary nodules that SUVmax was significantly higher in malignant lesions than benign lesions. Additionally, we demonstrated higher SUVmax values in patients with NCSLC compared to SCLC. Furthermore, we analyzed SUVmax together with IMA and YKL-40. Combined, these markers may be new biomarkers in cancer patients for differentiating malignant and benign lesions.

In 2010, Choi et al. (21) found that YKL-40 is a potentially efficient prognostic indicator in NSCLC patients. Later, it was confirmed that serum YKL-40 level is essentially higher in patients with SCLC than healthy people, with a 74.4% accuracy for the diagnosis (22). Sakazaki et al. suggested that beyond lung cancer, YKL-40 may play a significant role in detecting pulmonary inflammation (23). In the current study, compared to healthy subjects, we had comparatively higher serum YKL-40 levels in patients with benign or malignant lung disease.

On the other hand, IMA was studied in individuals with gastric cancer (24). Increased levels of IMA were detected in gastric cancer, suggesting its possible use as a diagnostic clue. However, no such association was studied in lung cancer. CEA and LDH, on the other hand, are long-known markers, known with their value in the diagnosis, treatment, and prognosis of many cancer types (25). Their expression and association have also been shown in the targeted therapy of lung cancer (26).

Our results reveal that mean SUVmax levels are higher in LC compared to BLD. Furthermore, serum YKL-40, IMA, LDH, and CEA measurements are higher in lung cancer cases compared to healthy controls. Thus, combined with the other variables, SUVmax may be an effective parameter to differentiate LC from BLD and healthy people. The

methodology and combination of these variables in diagnostic makeup or their potential as prognostic markers must be further studied.

References

1. Almuhaideb A, Papathanasiou N, Bomanji J. 18F-FDG PET/CT imaging in oncology. Ann Saudi Med 2011; 31(1): 3-13.
2. Demura Y, Tsuchida T, Ishizaki T, Mizuno S, Totani Y, Ameshima S, Miyamori I, Sasaki M, Yonekura Y. 18F-FDG accumulation with PET for differentiation between benign and malignant lesions in the thorax. J Nucl Med 2003; 44(4): 540-548.
3. Miele E, Spinelli GP, Tomao F, Zullo A, De Marinis F, Pasciuti G, Rossi L, Zoratto F, Tomao S. Positron Emission Tomography (PET) radiotracers in oncology--utility of 18F-Fluoro-deoxy-glucose (FDG)-PET in the management of patients with non-small-cell lung cancer (NSCLC). J Exp Clin Cancer Res 2008; 27: 52.
4. Inoue T, Yutani K, Taguchi T, Tamaki Y, Shiba E, Noguchi S. Preoperative evaluation of prognosis in breast cancer patients by [(18)F]2-Deoxy-2-fluoro-D-glucose-positron emission tomography. J Cancer Res Clin Oncol 2004; 130(5): 273-278.
5. Long NM, Smith CS. Causes and imaging features of false positives and false negatives on F-PET/CT in oncologic imaging. Insights Imaging 2011; 2(6): 679-698.
6. Rusak A, Jablonska K, Dziegiel P. The role of YKL-40 in a cancerous process. Postepy Hig Med Dosw (Online) 2016; 70(0): 1286-1299.
7. Johansen JS, Jensen BV, Roslind A, Nielsen D, Price PA. Serum YKL-40, a new prognostic biomarker in cancer patients? Cancer Epidemiol Biomarkers Prev 2006;15(2): 194-202.
8. Jena I, Nayak SR, Behera S, Singh B, Ray S, Jena D, Singh S, Sahoo SK. Evaluation of ischemia-modified albumin, oxidative stress, and antioxidant status in acute ischemic stroke patients. J Nat Sci Biol Med 2017; 8(1): 110-113.
9. Huang Q-X, Ma J, Wang Y-S. Significance of preoperative ischemia- modified albumin in operable and advanced gastric cancer. Cancer Biomark 2018; 22(3): 477-485.
10. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007.
11. Gallamini A, Zwarthoed C, Borra A. Positron emission tomography (PET) in oncology. Cancers (Basel) 2014; 6(4): 1821-1889.
12. Sun Y, Yu H, Ma J, Lu P. The Role of 18F-FDG PET/CT Integrated Imaging in Distinguishing Malignant from Benign Pleural Effusion. PLoS One 2016; 11(8): e0161764.
13. Fischer BM, Mortensen J, Langer SW, Loft A, Berthelsen AK, Petersen BL, Daugaard G, Lassen U, Hansen HH. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol 2007; 18(2): 338-345.
14. Ambrosini V, Nicolini S, Caroli P, Nanni C, Massaro A, Marzola MC, Rubello D, Fanti S. PET/CT imaging in different types of lung cancer: an overview. Eur J Radiol 2012; 81(5): 988-1001.
15. Halac M, Özhan M, Aksoy SY, Vatankulu B, Aliyev A, Asa S, Atahan E, Sağer MS, Sönmezoğlu K. The role of FDG-PET/CT in detecting unsuspected and unknown distant metastasis in the initial staging of NSCLC. Turkish J Med Sci 2014; 44(6): 1029-1040.
16. Kaseda K, Watanabe K-I, Asakura K, Kazama A, Ozawa Y. Identification of false-negative and false-positive diagnoses of lymph node metastases in non-small cell lung cancer patients staged by integrated (18F-)fluorodeoxyglucose-positron emission tomography/computed tomography: A retrospective cohort study. Thorac cancer 2016; 7(4): 473-480.
17. Farwell MD, Pryma DA, Mankoff DA. PET/CT imaging in cancer: current applications and future directions. Cancer 2014; 120(22): 3433-3445.
18. Vesselle H, Schmidt RA, Pugsley JM, Li M, Kohlmyer SG, Vallieres E, Wood DE. Lung cancer proliferation correlates with [F-18] fluorodeoxyglucose uptake by positron emission tomography. Clin Cancer Res 2000; 6(10): 3837-3844.
19. Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, Verbeken EK, Deneffe GJ, Mortelmans LA, Demedts MG. Prognostic importance of the standardized uptake value on 18F-fluoro-2-deoxy-glucose–positron emission tomography scan in non–small-cell lung cancer: an analysis of 125 cases. J Clin Oncol 1999; 17(10): 3201-3206.
20. Präuer HW, Weber WA, Römer W, Treumann T, Ziegler SI, Schwaiger M. Controlled prospective study of positron emission tomography using the glucose analogue [18f] fluorodeoxyglucose in the evaluation of pulmonary nodules. Br J Surg 1998; 85(11): 1506-1511.
21. Choi IK, Kim YH, Kim JS, Seo JH. High serum YKL-40 is a poor prognostic marker in patients with advanced non-small cell lung cancer. Acta Oncol (Madr) 2010; 49(6): 861-864.
22. Xu C-H, Yu L-K, Hao K-K. Serum YKL-40 level is associated with the chemotherapy response and prognosis of patients with small cell lung cancer. PLoS One 2014; 9(5).
23. Sakazaki Y, Hoshino T, Takei S, Sawada M, Oda H, Takenaka S, Imaoka H, Matsunaga K, Ota T, Abe Y. Overexpression of chitinase 3-like 1/YKL-40 in lung-specific IL-18-transgenic mice,

smokers and COPD. PLoS One 2011; 6(9).

24. Fidan E, Mentese A, Kavgaci H, Orem A, Fidan S, Uzun A, Ozdemir F, Aydin F. Increased ischemia-modified albumin levels in patients with gastric cancer. Neoplasma 2012; 59(4): 393-397.
25. Shrotriya S, Walsh D, Bennani-Baiti N, Thomas S, Lorton C. C-Reactive Protein Is an Important Biomarker for Prognosis Tumor Recurrence and Treatment Response in Adult Solid Tumors: A Systematic Review. PLoS One 2015; 10(12): e0143080.
26. He G, Jiang Z, Xue S, Sun X, Wang W. Expression of LDH and CEA in serum in the process of targeted therapy of lung adenocarcinoma and the association between them and prognosis. Oncol Lett 2019; 17(5): 4550-4556.