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Original Article

# Is there any correlation between levels of serum ostepontin, CEA, and FDG uptake in lung cancer patients with bone metastasis?

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ABSTRACT

*Objective:* In this study, an evaluation was made of the relationship between the serum levels of carcinoembryonic antigen (CEA), osteopontin (OPN), and the semi-quantitative parameters of 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) in lung cancer patients with bone metastasis.
*Material and methods:* The evaluation included 42 non-small cell lung cancer (NSCLC) and 31 small cell lung cancer (SCLC) patients who were referred to our institution for staging by $^{18}$F-FDG PET/CT. The biochemical parameters measured included CEA and OPN serum levels.
*Results:* Serum levels of OPN in NSCLC patients with and without bone metastasis were $21.20 \pm 4.97$ ng/ml and $13.33 \pm 4.53$ ng/ml, respectively ($p < 0.05$). In SCLC patients with and without bone metastasis serum OPN levels were $23.95 \pm 4.78$ ng/ml and $17.30 \pm 3.09$ ng/ml, respectively ($p < 0.05$). Serum levels of CEA in NSCLC patients with and without bone metastasis were $33.79 \pm 6.49$ ng/ml and $11.74 \pm 2.96$ ng/ml, respectively ($p < 0.05$). In SCLC patients with and without bone metastasis serum levels of CEA were $28.93 \pm 4.59$ ng/ml and $13.88 \pm 4.47$ ng/ml, respectively ($p < 0.05$). There were no correlations between primary tumor SUVmax, and serum levels of CEA and OPN.
*Conclusions:* Bone metastasis can be detected in patients with lung cancer by measuring CEA and OPN levels. Increased levels of CEA and OPN levels may be considered an early warning sign in patients needing accurate imaging, as they are at higher risk of bone metastasis.


## ¿Existe correlación entre los niveles de osteopontina en suero sanguíneo, CEA y captación de $^{18}$F-FDG en pacientes con metástasis óseas por cáncer de pulmón?

*Palabras clave:*
Cáncer de pulmón
Metástasis ósea
Tomografía de emisión de positrones
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RESUMEN

*Objetivo:* Evaluar la relación entre los niveles de antígeno carcinoembriionario (CEA), osteopontina (OPN) y los valores semicuantitativos (SUV) de la PET/TC con $^{18}$F-FDG en pacientes con metástasis óseas por cáncer de pulmón.
*Material y método:* Se incluyeron 40 pacientes con cáncer de pulmón de células no pequeñas (NSCLC) y 31 pacientes con cáncer de pulmón de células pequeñas (SCLC) referidos a nuestro centro para la realización de un estudio PET/TC con $^{18}$F-FDG de estadificación. Se analizarón los niveles sanguíneos de OPN y CEA.
*Resultados:* Los niveles de OPN en pacientes con NSCLC con y sin metástasis óseas fueron de $21.20 \pm 4.97$ ng/ml y $13.33 \pm 4.53$ ng/ml, respectivamente ($p < 0.05$). En pacientes con SCLC con y sin metástasis óseas fueron de $23.95 \pm 4.78$ ng/ml y $17.30 \pm 3.09$ ng/ml, respectivamente ($p < 0.05$). Los niveles sanguíneos de CEA en pacientes de NSCLC con y sin metástasis óseas fueron de $33.79 \pm 6.49$ ng/ml y $11.74 \pm 2.96$ ng/ml, respectivamente ($p < 0.05$). En pacientes con SCLC con y sin metástasis óseas fueron de $28.93 \pm 4.59$ ng/ml y $13.88 \pm 4.47$ ng/ml, respectivamente ($p < 0.05$). No hubo correlación entre el SUV máximo del tumor primario, los niveles OPN ni de CEA.
*Conclusiones:* La metástasis ósea puede ser detectada en pacientes con cáncer de pulmón con la determinación de los niveles de OPN y CEA. Los niveles incrementados de CEA y OPN pueden ser considerados como una señal de advertencia temprana en pacientes que necesiten imágenes precisas, porque ellos están en mayor riesgo de metástasis en el hueso.


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## Introduction

Lung cancer is the leading cause of cancer deaths in the world. It is divided into two major types: non-small cell lung cancer (NSCLC) (85%) and the prognostically poorer small cell lung cancer (SCLC) (15%).[1] The skeleton is the most common site for distant metastasis. Clinical presentation of bone metastasis includes severe bone pain, limitation of movement, hypercalcemia and pathologic fractures.[2] Early diagnosis and aggressive treatment of these complications play important roles in improving the patient's quality of life,[3] and accurate staging of patients with lung cancer is critical for appropriate treatment.[4]

In recent years, positron-emission tomography/computed tomography (PET/CT), using the glucose analog 18-fluoro-2-deoxyglucose ($^{18}$F-FDG), has been indicated to provide a more accurate diagnostic approach than the conventional methods.[5] PET/CT has proven to be a very effective imaging modality for the bone metastases of lung cancer.[6] PET/CT has also been recognized for particular value in primary tumor staging and it allows differentiation of tumor tissue from post-obstructive atelectasis.[7]

The molecular mechanisms leading to the development of bone metastasis in lung cancer are still unclear.[8] One of the best known tumor markers in the management of lung cancer is the carcinoembryonic antigen (CEA), and higher CEA concentrations were found in advanced stages.[9] Osteopontin (OPN) mediates biological processes, such as adhesion, migration, invasion, proteolysis, enhanced cell survival, and angiogenesis,[10] and several studies have indicated a correlation between high OPN expression and poor patient outcomes in lung cancer.[11] Additionally, it is known that there is a relationship between the biochemical markers and existence of bone metastases.[12] Reliable blood tests for the early detection and monitoring of progression are a "holy grail" in cancer diagnostics.

To the best of our knowledge, this is the first study to evaluate bone metastasis in lung cancer using $^{18}$F-FDG PET/CT imaging functional data and its correlation with CEA and OPN. The purpose of this study was to directly compare the results of semi-quantitative analyses by $^{18}$F-FDG PET/CT with biochemical parameters including CEA and OPN.

## Material and methods

### *Patients*

Over 10 months, 42 NSCLC patients (34 males and 8 females) and 31 SCLC patients (26 males and 5 females), referred to our institution for $^{18}$F-FDG PET/CT scanning for staging were included. The diagnoses of the lung cancer patients were confirmed by histological or cytological examinations of specimens taken from bronchoscopy, or by computerized tomography-guided fine needle biopsies. At the time of $^{18}$F-FDG PET/CT, pathologic TNM staging was evaluated according to the criteria of American Joint Committee on Cancer (AJCC).[13] Among the NSCLC patients, 15 cases were in stage I/II, 27 cases were in stage III/IV. Among the SCLC patients 14 cases were in stage I/II and 17 cases were in stage III/IV. The control group consisted of 20 healthy volunteers (11 males and 9 females). Approval was received from the local ethics committee, and each patient signed an informed consent form. Patients with chronic kidney disease, osteoporosis, connective tissue disease, degenerative bone disease, traumatic fracture and history of current medication use affecting bone metabolism were not included in the study. Patients were excluded if they had received chemotherapy, radiotherapy or surgery, a history of extrapulmonary cancer or pregnancy. Histological diagnosis of bronchioloalveolar cell carcinoma subtype were also excluded from the study. All patients were imaged using $^{18}$F-FDG PET/CT.

### *$^{18}$F-FDG PET/CT imaging*

The patients fasted overnight, for at least 12 h. PET/CT whole body imaging was performed after an intravenous injection of approximately 12 mCi (444 MBq) $^{18}$F-FDG; Patients with a fasting blood glucose level above 120 mg/dl were excluded. After a one hour waiting period in a silent room, the patient was imaged using an integrated PET/CT camera, which consisted of a 16-slice CT gantry, integrated with an LSO-based fullring PET scanner (Siemens Biograph 16, Siemens, Knoxville, TN, USA). The CT was performed with 120–200 mAs adjusted to the patient's body weight at a 140 kV and from the base of the skull to the proximal thighs. For attenuation correction and image fusion, the PET images were reconstructed by using an iterative algorithm (ordered-subset expectation maximization: two iterations, eight subsets). The reconstructed PET, CT, and fused images were displayed by commercially available software (e-soft/VSIM, Siemens Medical Solutions) in axial, coronal, and sagittal planes. Maximum intensity projection (MIP) PET images and integrated and co-registered PET/CT images were visually evaluated by two experienced nuclear medicine physicians. The $SUV_{max}$ was determined by drawing region of interest (ROI) around the primary tumor on the transaxial slices, and calculated according to the following formula: measured activity concentration [Bq/ml] × body weight [kg]/injected activity [Bq].

### *Biochemical assessment*

The fasting blood samples taken on the day of the PET/CT scan were centrifuged, and the serum samples were divided into portions and kept at −80 °C until analyses. The biochemical parameters in the serum; aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), Ca, albumin, and total protein were determined using a Beckman Coulter AU 5800 auto analyzer and Beckman reagents within five days of the PET/CT scan for all patients. The serum concentration of CEA was performed at the Clinical Biochemistry Laboratory of our institution using the Beckman Coulter UniCel DxI 800 with Beckman reagents. The OPN serum levels were measured using a Platinum ELISA kit (eBioscience, San Diego, CA, USA).

### *Bone metastasis evaluation*

All patients were evaluated for bone metastasis by $^{18}$F-FDG PET/CT. $^{18}$F-FDG PET/CT results were read by 2 specialists and classified into (1) normal/benign, (2) positive for bone metastases, or (3) equivocal (the image could not be confidently categorized into one of the former two subgroups, requiring additional imaging procedures). When the interpretation differed among specialists the following criteria were used for confirmation. (1) Progression of bone lesion on the follow-up PET/CT; (2) confirmed bone metastasis by simple radiography, bone scintigraphy or magnetic resonance imaging (MRI); (3) concordance between positive initial findings on PET/CT and symptoms and (4) histopathological confirmation.

### *Statistical analysis*

Results were subjected to one-way analysis of variance (ANOVA) using the Statistical Package for the Social Sciences (SPSS version 19.0) software. Differences among the groups were obtained using the Duncan's multiple range test option. For the correlation between primary tumor SUVmax, CEA and, OPN levels. Pearson's correlation coefficients were computed. $p < 0.05$ were considered