Prognostic Value of ^{18}F-Fluorodeoxyglucose Uptake of Bone Marrow on PET/CT in Patients with Limited Disease Small Cell Lung Cancer

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ABSTRACT

Small cell lung cancer (SCLC) is a malignancy from the neuroendocrine tumor family, which has a poor prognosis and presents with metastases at the time of the diagnosis. The present study investigated the relationship between bone marrow fluorodeoxy-D-glucose (FDG) uptake and survival to evaluate prognosis in limited-stage SCLC. This single-center retrospective study examined a total of 220 patients diagnosed with limited-stage SCLC between January 2010 and June 2019. Bone marrow FDG uptake, serum inflammatory markers, and other factors used to determine the prognosis, as well as overall survival (OS) and progression-free survival (PFS), were recorded and retrospectively analyzed. Within physiological limits, bone marrow standardized uptake value (SUV) mean of > 1.95 was identified as a good prognostic factor for PFS (p= 0.03). The multivariate analysis of OS and PFS revealed that the Eastern Cooperative Oncology Group (ECOG) performance scale (p= 0.001) was a common independent prognostic factor. Stages of the disease, albumin levels and bone marrow-to-liver ratio (BLR) [one of the positron emission tomography/computed tomography (PET/CT) parameters] of < 0.8 were prognostic factors for OS. The bone marrow SUV mean was positively correlated with the primary tumor SUV max and SUV mean. The bone marrow SUV mean is a parameter that can be used to predict PFS in limited-stage SCLC. For OS, in turn, the BLR was identified as an independent factor.

Keywords: Small cell lung cancer, Prognostic factors, Limited stage, Bone marrow FDG uptake

INTRODUCTION

Small cell lung cancer (SCLC) is a malignancy of the lungs with a poor prognosis and accounts for 15% of all lung cancers. The 5-year survival rate is less than 5%.[1-4]. SCLC is an aggressive disease with rapid growth and early distant metastases. About 60-65% of the patients present with metastases at the time of the diagnosis.[5,6] It is closely associated with smoking since 95% of all SCLC patients have a history of intensive tobacco use.[7] In 1958, a two-stage classification scheme developed by the Veterans Administration Lung Study Group (VALSG) divided SCLC into limited and extensive stages. Treatment options include radical therapies such as surgery and concomitant chemoradiotherapy in limited-stage disease, while the options are more limited in extensive-stage disease based on the performance status of the patient. The mean survival is 18 months in early-stage disease despite radical treatment options and decreases down to 6 months in extensive-stage disease.[5] Specific prognostic factors are used to predict survival in SCLC. Performance status, weight loss, disease stage, and lactate dehydrogenase (LDH) are the factors associated with prognosis.

An Eastern Cooperative Oncology Group (ECOG) performance status of[3-4], cachexia, advanced age, presence of multiple metastases, and high LDH levels have been associated with poor prognosis.[5]

Positron emission tomography (PET) is an imaging method widely used to diagnose, stage, and determine the treatment response in lung cancer; however, the experience in SCLC is limited.[8] In SCLC, PET is used in limited-stage disease and patients evaluated for operability. Increased fluorodeoxy-D-glucose (FDG) uptake on positron emission tomography/computed tomography (PET/CT) is an indicator of inflammation and the use of PET parameters as a tool to predict prognosis in various malignancies is currently the subject of many studies.

There is a need for analytical parameters that can be used to predict the prognosis in SCLC. Bone marrow FDG uptake is considered a potential parameter that indicates inflammation. This study aimed to evaluate the association of bone marrow FDG uptake with overall survival (OS) and progression-free survival (PFS) in limited-stage SCLC.

MATERIALS AND METHODS

Selection of the Study Population

This single-center retrospective study analyzed patients diagnosed with SCLC at the SBU Izmir Dr. Suat Seren Pulmonary Diseases and Surgery SUAM (Health Application and Research Center) between 01.01.2010 and 31.06.2019.

Patients who were pathologically/cytopathologically diagnosed with SCLC, who were scheduled for surgery and concomitant chemoradiotherapy, chemotherapy, or curative radiotherapy were included in the study. The patients were classified as having limited and extensive stage disease according to the classification recommended by the VALSG. "Limited disease" (Stage I, II, III according to TNM) was defined as disease confined to one hemithorax with ipsilateral or contralateral hilar, mediastinal, and supraclavicular lymph node metastasis, and ipsilateral pleural effusion (with negative cytology) and "extensive disease" as tumors outside the definition of limited disease (Stage IV according to TNM).[9]

Since OS is 6 months in extensive disease compared to 18 months in limited-stage disease and vertebral bone metastases in patients with the extensive-stage disease may negatively affect the SUV measurements, patients with the extensive disease were excluded from the study.

Patients with missing pretreatment PET/CT, who were diagnosed with extensive-stage SCLC, who were included in the palliative support group without a treatment plan, who had secondary hematological and/or solid organ malignancies, patients with a time interval longer than 30 days between PET/CT and treatment and laboratory data, patients under 18 and above 90 years of age, pregnant patients and patients with inadequate clinical data in the patient follow-up system were excluded from the study (Figure 1).

Demographic data of the cases with limited-stage SCLC were reviewed. Age, sex, smoking, comorbidities, and factors for survival (weight loss, performance status of the patient, disease stage) were recorded. Primary tumor SUV max and SUV mean, and bone marrow SUV mean and bone/liver ratio on PET/CT were retrospectively analyzed. The association of bone marrow FDG uptake and BLR with survival was evaluated.

PET/CT Imaging

PET/CT images were acquired by PHILIPS GEMINI TF 16-Slice PET/CT scanner. The patients with a blood glucose level of < 200 mg/dl following at least 6 hours of fasting were intravenously administered 7-10 mCi of Fluorine-18 Fluorodeoxyglucose (F-18 FDG). Approximately 60 minutes after the injection, first CT (140 kV, 100 mAs, 5-mm slice thickness) and then PET images (1.5 min/bed) were acquired. The attenuation was corrected using the data from CT.

A three-dimensional region of interest was drawn over the primary tumor and the SUV max and SUV mean of this region were measured.

Image Analysis

Spheroid regions of interest were drawn on the right and left lobes of the liver, and the four thoracolumbar vertebrae (often thoracic 11, 12, and lumbar 3,4

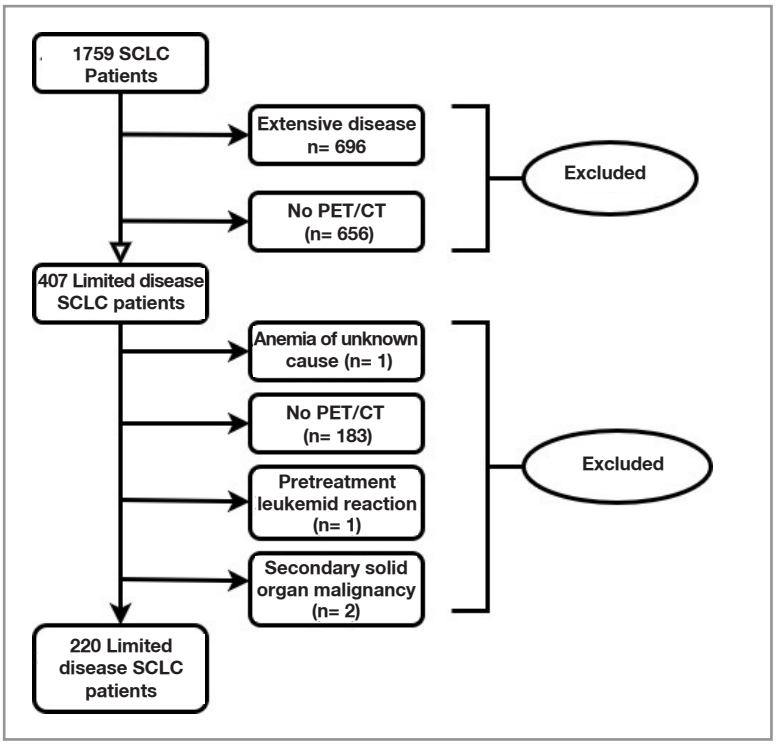

Figure 1. Patient disposition chart

vertebrae) and SUV mean values were recorded. No measurement was performed on the areas with osteoarthritic changes, hemangioma, compression fractures, and postoperative findings. The SUV mean values obtained from the liver lobes and vertebrae were considered liver SUV mean and bone marrow SUV mean. The SUV mean values obtained from the vertebrae and liver were used to calculate the bone marrow-to-liver ratio (BLR).

The study protocol was approved by the İzmir Dr. Suat Seren of the Chest Diseases and Surgery Training Hospital Ethical Committee (date and number: 22.07.2020, No: 6)

Statistical Analysis

The study data were entered into the database created in SPSS (Statistical Package For Social Sciences) 18.0 and statistically analyzed using the SPSS and MedCalc software. The normality of the continuous variables was tested. A Receiver Operating Characteristic (ROC) analysis was performed for independent variables affecting OS and PFS and the optimum cut-off point was determined using Youden's index. OS and PFS were compared between the groups, which were created based on this cut-off point, using Kaplan-Meier and Log-rank tests. In addition, Hazard Ratios were calculated using the same cut-off point. These variables were also analyzed using the Cox regression analysis and the hazard ratios were calculated using the backward step method according to the Wald value.

For all statistical comparison tests, the type I error was set at $\alpha = 0.05$ and tested as two-tailed. Intergroup difference was considered statistically significant when the "p" value was below 0.05.

RESULTS

Characteristic Features

A total of 220 patients were examined, 181 (82.3%) of the patients were male and the mean age was 62.5 ± 8.10 years. Of all patients, 167 patients (75.9%) had mediastinal and/or supraclavicular lymph node metastases. Curative surgical resection was performed on 19 patients (8.6%). Chemotherapy was given to 215 patients (97.7%), whereas radiotherapy was given to 192 patients

(87.3%). The bone marrow SUV mean value in all patients' was 1.69 ± 0.54. Of the 220 enrolled patients, 150 (68.2%) experienced disease progression and 163 (74.1%) died during the clinical follow-up. The mean PFS and OS were 14.5 months and 22.5 months, respectively. Demographical data of 220 study patients diagnosed with SCLC were summarized in Table 1.

The Association between Bone Marrow FDG Uptake and Clinical Factors

Bone marrow SUV mean was calculated as 1.95 by ROC curve analysis (AUC: 0.521). The Kaplan-Meier analysis of bone marrow FDG uptake revealed that PFS was 20.05 months at a SUV mean of > 1.95 (95% Cl: 8.96-31.14) (p= 0.003) (Figure 2). There was no statistically significant result for OS. The bone marrow SUV mean was positively correlated with the primary tumor SUV max (r= 0.502, p= 0.01) and SUV mean (r= 0.520, p= 0.01).

The Association between Bone/Liver Ratio and Clinical Factors

BLR SUV mean cut-off was calculated as 0.8 by ROC curve analysis for OS (AUC:0.541, 95% CI: 0.472-0.608). The OS of patients with BLR above 0.8 (n= 108) on PET/CT was 17.76 months (95% Cl: 13.89-21.62), while the OS of patients with BLR 0.8 and below (n= 112) was 21.73 months (95% Cl: 17.61-25.84, p= 0.154). The multivariate analysis demonstrated that BLR was a statistically significant variable to predict OS (p= 0.016).

Prognostic Factors Affecting Overall Survival and Progression-Free Survival

ECOG performance status, disease stage, serum inflammatory markers (CRP, LDH, and albumin levels) were statistically significant variables for OS in univariate analysis (respectively, p= 0.001; p= 0.02; p= 0.048; p= 0.037; p= 0.003), while ECOG performance status, disease stage, serum inflammatory markers (LDH and albumin levels) were significant variables for PFS (respectively, p= 0.001; p= 0.034; p= 0.026; p= 0.005). ECOG performance status was one of the factor that was found to be relevant to PFS and OS and high ECOG performance status (ECOG score ≥ 2) increased the risk of progression 4.13-fold (95% Cl: 2.866-5.931; p= 0.001), while increased risk of death 6.32-fold (95% Cl: 4.316-9.279; p= 0.001). The PET/CT parameters and clinical variables

Table 1. Clinical characteristics of the 220 patients

Characteristic		n	%	Median (Range)
Age		220		63 (38-83)
Gender	Male	181	82.3	
	Female	39	17.7	
Smoking History (pack/year)		111	98.2	50 (6-135)
ECOG	ECOG 0	63	28.6	
	ECOG 1	65	29.5	
	ECOG 2	92	41.8	
Weight Loss	Yes	31	72.1	
	No	12	27.9	
T stage	T1a	12	5.5	
	T1b	13	6	
	T1c	23	10.5	
	T2a	25	11.4	
	T2b	35	15.9	
	T3	34	15.5	
	T4	78	35.5	
N stage	N0	38	17.3	
	N1	15	6.8	
	N2	108	49.1	
	N3	59	26.8	
Stage	I	24	10.9	
	II	14	6.4	
	III	182	82.7	
Primary Tumor	SUV Max	220	10.75 (2.2-53)	
	SUV Mean	220	6.05 (1.2-21.3)	
T Bone	SUV Mean	220	1.6 (0.7-3.2)	
L Bone	SUV Mean	220	1.6 (0.6-3.1)	
Bone Mean	SUV Mean	220	1.6 (0.7-3.15)	
Hb (g/dL)		220	13.5(9.5-17.7)	
WBC (x10^9 cell /L)		220	8.9 (4-27)	
PLT (x10^9 cell /L)		220	286 (104-925)	
CRP (mg/L)		193	1.36 (0.04-49.9)	
LDH (U/L)		176	209 (97-824)	
Albumin (g/dL)		208	4 (2.3-4.9)	
PFS (month)		220	11 (0.6-102)	
OS (month)		220	18.7 (0.6-126)	

ECOG= Eastern Cooperative Oncology Group, Hb= Hemoglobin, WBC= White Blood Cell, PLT= Trombocyte, CRP= C-Reaktive Protein, LDH= Lactate Dehydrogenase, PFS= Progression Free Survival, OS= Overall Survival

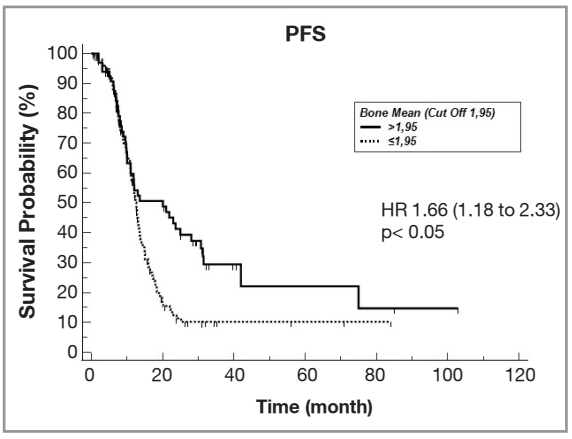

Figure 2. Progression-free survival according to the bone marrow SUVmean cut-off value of 1.95
PFS: Progression free survival

were examined by a univariate analysis, which was summarized in Table 2.

The BLR was an independent prognostic factor for OS in multivariate analysis, while the ECOG performance status were identified as additional prognostic factor for OS in multivariate analysis (respectively, p= 0.016; p= 0.001). It was found that the risk of death increased 1.49-fold with BLR SUV mean levels above 0.8 (95% Cl: 1.076-2.06; p= 0.016) (Table 3).

DISCUSSION

Bone marrow FDG uptake on PET/CT may increase due to malignant cell infiltration, benign diseases with immunological, degenerative, and inflammatory processes, and stimulation of the bone marrow by colony-stimulating factors.[10] The use of bone marrow biopsy for disease staging in SCLC was the subject of many studies in the past.[11] Today, however, with the development of imaging methods, noninvasive imaging methods that would replace bone marrow biopsy and produce prognostic results are preferred. PET/CT is widely used in the staging of lung cancer, mostly for screening distant metastases. The present study demonstrated that PFS was better in patients with higher FDG uptake (but within physiological ranges) in limited-stage SCLC.

Malignant cell infiltration was shown to positively correlate with bone marrow FDG uptake in patients who were followed up for hematological or solid organ malignancies.[12,13] Shen et al., on the other hand, found a SUV mean of 1.76 ± 0.24 (1.36-2.37) in healthy individuals in the same vertebral bones as in the present study on the physiological FDG uptake in the bone marrow and established decreased bone marrow FDG uptake with advanced age.[14] This negative correlation between

Table 2. Univariate analyses for overall survival and progression-free survival

	Overall Survival		Progression-Free Survival	
	p value	HR (%95 Cl)	p value	HR (%95 Cl)
Age (> 65 / ≤ 65 years)	0.64	1.35 (0.98-1.87)	0.442	1.14 (0.81-1.61)
Gender (Female/male)	0.45	0.85 (0.57-1.28)	0.98	0.99 (0.66-1.49)
Comorbid Disease (Yes/No)	0.89	1.02 (0.74-1.40)	0.97	0.99 (0.71-1.37)
ECOG performance status (2/0-1)	0.001	6.12 (4.33-8.90)	0.001	4.11 (2.87-5.87)
Stage (III/I-II)	0.02	2.07 (1.30-3.28)	0.034	1.59 (1.03-2.45)
Hemoglobin (≤ 12 / > 12 g/dL)	0.92	1.01 (0.68-1.52)	0.32	1.24 (0.80-1.91)
Leukocyte (>10 / ≤10 x10^9 cell /L)	0.57	0.90 (0.63-1.28)	0.94	0.98 (0.69-1.41)
CRP (> 0.5 / ≤ 0.5 mg/L)	0.048	1.51 (1.00-2.28)	0.565	1.12 (0.75-1.66)
LDH (> 225 / ≤ 225 U/L)	0.037	1.45 (1.02-2.06)	0.026	1.49 (1.04-2.13)
Albumin (≤ 3.5 / > 3.5 g/dL)	0.003	1.79 (1.21-2.66)	0.005	1.87 (1.21-2.90)
Bone/liver ratio (> 0.8 / ≤ 0.8)	0.150	1.25 (0.91-1.70)	0.367	0.80 (0.50-1.28)
Primary Tumor SUV max (> 9.90 / ≤ 9.90)	0.14	1.27 (0.92-1.76)	0.181	1.27 (0.89-1.82)
Bone marrow SUV mean (> 1.45 / ≤ 1.45)	0.47	1.13 (0.81-1.57)	0.016	1.54 (1.08-2.21)

ECOG= Eastern Cooperative Oncology Group, CRP= C-reactive protein, LDH= lactate dehydrogenase

Table 3. Comparison of progression-free survival and overall survival

	Overall Survival (Univariate)		Overall Survival (Multivariate)	
	p value	HR (%95 CI)	p value	HR (%95 CI)
Age (> 65 / ≤ 65 years)	0.64	1.35 (0.98-1.87)		
Gender (Female / male)	0.45	0.85 (0.57-1.28)		
Comorbid Disease (Yes / No)	0.89	1.02 (0.74-1.40)		
ECOG performance status (2 / 0-1)	0.001	6.12 (4.33-8.90)	0.001	6.32 (4.31-9.27)
Stage (III / I-II)	0.02	2.07 (1.30-3.28)	0.052	1.58 (0.99-2.52)
Hemoglobin (≤ 12 / > 12 g/dL)	0.92	1.01 (0.68-1.52)		
Leukocyte (>10 / ≤ 10 x 10^9 cell /L)	0.57	0.90 (0.63-1.28)		
CRP (> 0.5 / ≤ 0.5 mg/L)	0.048	1.51 (1.00-2.28)		
LDH (> 225 / ≤ 225 U/L)	0.037	1.45 (1.02-2.06)		
Albumin (≤ 3.5 / > 3.5 g/dL)	0.003	1.79 (1.21-2.66)	0.087	1.41 (0.95-2.10)
Bone/liver ratio (> 0.8 / ≤ 0.8)	0.150	1.25 (0.91-1.70)	0.016	1.49 (1.07-2.06)
Primary Tumor SUV max (> 9.90 / ≤ 9.90)	0.14	1.27 (0.92-1.76)		
Bone marrow SUV mean (> 1.45 /≤ 1.45)	0.47	1.13 (0.81-1.57)		

ECOG= Eastern Cooperative Oncology Group, CRP= C-reactive protein, LDH= lactate dehydrogenase

bone marrow FDG uptake and age is suggested to be due to the decreased hematopoietic activity by age.[15] In addition, the cytokines (TGF-B1) secreted in malignancies are suggested to increase the bone marrow activity and increase FDG uptake in the absence of malignant infiltration.[16] Bone marrow FDG uptake within physiological ranges is an indicator of an active and healthy hematopoietic system. The longer PFS in patients with FDG uptake was considered a potential indicator of a better response to chemotherapy as a result of an active hematopoietic system.

The study by Lee et al. calculated the cut-off point for bone marrow SUV mean as 1.60 and found better one-year PFS in patients with a SUV mean value of < 1.60.[17] This difference from the present study can be because of the inclusion of the patients with bone and bone marrow metastases in the study since both patients with limited and extensive stage disease were analyzed together.

In their study, Mattonen SA, et al. found that the bone marrow SUVmean value was an effective prognostic marker for overall survival.[18] Lee WJ, et al. on the other hand, identified the BLR as an effective marker for OS and PFS in their study analyzing non-small cell lung cancer patients.[19] Similar to other studies, the present study found the bone marrow SUVmean and BLR values to be potential prognostic markers for survival in SCLC.

In the present study, the bone marrow SUVmean was positively correlated with the primary tumor SUVmax and SUVmean. Likewise, Lee WJ, et al. established a positive correlation between the bone marrow SUVmean and the primary tumor SUVmax.[17] The correlation between the bone marrow SUVmean and the primary tumor SUV value has been attributed to the increased bone marrow activity by the cytokines released in malignancy in the absence of malignant infiltration.[16]

Proven prognostic factors in SCLC include the disease stage, weight loss, performance status, and serum inflammatory factors.[5,20] Consistent with the literature data, the present study identified performance status, stage, and albumin levels as prognostic factors.

The present study has some limitations. First, it had a single-center and retrospective design. Second, micrometastatic bone lesions that could not be detected by PET/CT in patients with bone metastases may affect the bone marrow FDG uptake. Third, misregistration between PET and CT images due to the patient's respiratory motions may affect the measurement of PET/CT parameters. Finally, no

histopathological assessment was performed to establish the association between the bone marrow FDG uptake and the malignant cell differentiation of the bone marrow and to exclude the hematological disorders other than malignant involvement.

Conclusion

The present study found the bone marrow SUVmean to be a parameter that could be used to predict PFS in limited-stage SCLC. In addition, BLR was identified as an independent factor for OS in SCLC. The bone marrow SUVmean was positively correlated with the primary tumor SUVmax and SUVmean. The bone marrow SUVmean and the (BLR) are parameters that can be used to predict the prognosis in limited-stage SCLC.

There is limited experience in using PET/CT to diagnose, stage, and follow-up the disease in SCLC. To the best of our knowledge, the present study has the largest patient series in which PET/CT parameters and bone marrow SUV were assessed in limited-stage SCLC. The findings of the present study may cause PET/CT to become the first option as a noninvasive imaging tool in the diagnosis, staging, and determination of prognosis in SCLC.

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