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Predictive value of quantitative metabolic tumor volume and metabolic index analysis in lung cancer stereotactic radiotherapy with F-18 FDG PET/CT

F. ARAS[1], A. OLMEZOGLU[2]

[1]Department of Nuclear Medicine, [2]Department of Radiation Oncology, School of Medicine, Celal Bayar University, Manisa, Turkey

Abstract. – OBJECTIVE: The objective of this study was to investigate predictive value of quantitative metabolic tumor volume and metabolic index analysis in lung cancer stereotactic radiotherapy with F-18 FDG PET/CT.

PATIENTS AND METHODS: Overall, 94 early-stage non-small cell lung cancer (NSCLC) patients who were administered stereotactic radiotherapy were included in the study.

RESULTS: Most of the study patients were male (91.5%). Mean age of the patients was 68.5 ± 9.0 years. The primary lung tumor was located centrally and peripherally in 25 (26.6%) and 69 (73.4%) of the patients, respectively. The median gross tumor volume (GTV) was 16.2 cc [interquartile range (IQR): 7.1-32.9]. Whereas all patients who had peripheral tumors survived, 17 patients with central tumors (70.8%) died during the study period ($p = 0.001$). Biologically effective dose (BED_{10}) values were significantly higher in patients who had peripheral tumors compared with patients with central tumors ($p = 0.001$). Significantly more patients died in patients who had BED values below 100 Gy compared to patients who had BED values over 100 Gy ($p = 0.001$). The survival distributions for the two groups were significantly different ($p < 0.001$). Only GTV and Pretreatment SUVmean appeared as significant predictors of mortality. BED_{10} values showed a significant and strong positive correlation with total radiation dose, whereas it showed a significant strong negative correlation with number of fractions.

CONCLUSIONS: The use of repeated 18F-FDG PET to assess survival early during stereotactic radiotherapy is possible in patients with early-stage non-small cell lung cancer. A decrease in GTV and pretreatment SUVmean according to F-18 FDG PET/CT uptake by the primary tumor correlates with survival.

Key Words:

Non-small cell lung cancer, Stereotactic radiotherapy, F-18 FDG PET, Metabolic tumor volume, Metabolic index.

Introduction

Although surgery is the best treatment option in the early period in non-small cell lung cancers (NSCLC), which accounts for 80% of lung cancers, only 30% of patients have a chance for curative surgery[1,2]. The treatment options for the patient group with lower survival expectancy are neoadjuvant and adjuvant chemotherapy (CT) or chemoradiotherapy (CRT). Targeted therapies have also been tried in recent years. Stereotactic ablative radiotherapy (SABR) is an emerging therapeutic approach that involves the use of focused ablative radiation doses with a higher biological effect compared with conventional radiotherapy (RT) in lung cancer[3].

Early and most accurate evaluation of treatment efficacy is decisive in identifying effective treatment on a patient basis and in terms of survival in this patient group with limited survival[4]. It is common to evaluate the change in lesion size on CT with standardized criteria, such as WHO and RECIST criteria in determining the treatment response in patient groups undergoing conventional chemotherapy/CRT. However, the role of FDG-PET/CT in evaluating response to treatment in patients with NSCLC has been the main focus of research in recent years, since dimensional evaluation on CT is insufficient to distinguish areas of atelectasis around the tumor and especially in lymph node evaluation[5].

In the studies in the literature, there are two criteria most frequently used for the standardization of the evaluation of treatment response with FDG-PET in solid tumors. While the RECIST criterias take into account the change in standard uptake values (SUV), which is a

Corresponding Author: Feray Aras, MD, e-mail: feray.aras@cbu.edu.tr

semi-quantitative parameter of glucose metabolism in tissues, the PERCIST criteria determined in 2009 combine the RECIST criteria used in anatomical imaging with the change in SUV (SUL) ratios corrected for lean body mass[1-3]. In addition to SUV values, parameters that take into account tumor volume, such as total lesion glycolysis (TLG) or metabolic tumor volume (MTV), are also used in studies evaluating treatment response. Tumor control seems to be strictly related to a biologically equivalent dose (BED) of at least 100 Gy with an alpha/beta ratio of 10 (100 Gy10), resulting in a high rate of cell killing owing to several biological effects. Fludeoxyglucose F-18 positron emission tomography integrated with computed tomography (18FDG-PET/CT) is often adopted in the setting of lung metastases as an effective tool in staging and to monitor the response after systemic therapies[3,6].

The objective of this study was to investigate predictive value of quantitative metabolic tumor volume and metabolic index analysis in nonsmall cell lung cancer (NSCLC) stereotactic radiotherapy with F-18 FDG PET/CT.

Patients and Methods

Patients

In this study, 94 patients with early stage non-small cell lung cancer (NSCLC) treated with stereotactic radiotherapy were included in the study.

F-18 FDG whole body PET/CT images taken before and after treatment in patients with thoracic mass who underwent stereotactic radiotherapy were reprocessed and calculated on the Philips device analysis computer. After these procedures, SUVmax, SUVmean, metabolic volume (MTV), metabolic index (MI) max and metabolic index mean, and Standard Deviation were calculated. Maximum and mean SUV within the MTV were calculated automatically. MI was calculated by multiplying the MTV by the mean SUV (MI = MTV x SUV).

PET/Computed Tomography

Whole-body and spot F-18 FDG-PET/CT data from all patients were acquired using a Truflight Select PET/CT device (Philips Medical Systems Cleveland, OH, USA). Patients were instructed to fast for at least 6 h before the scan. After confirmation of a normal peripheral blood glucose level (<180 mg/dL), each patient received an intravenous injection of 145 μCi/kg (maximum 200 μCi) of FDG and rested for 60 min before the scan. The FOV was from the base of the skull to the mid-thigh level.

Post-Processing and Analysis of PET/Computed Tomography Images

FDG-PET/CT images were examined (2 mm slices) on whole body maximum intensity projection along with three orthogonal planes (axial, coronal, and sagittal). SUVmax, mean standardized uptake value (SUVmean), mean metabolic index (MImean), and metabolic tumor volume (MTV) values of the lesions were determined automatically by the software after delineation of the ROI on attenuation-corrected PET/CT images.

Statistical Analysis

Descriptive statistics derived from the study data were presented as mean ± standard deviation or median with interquartile range in continuous variables depending on the status of normal distribution. Categorical variables were summarized as number and percentage. Normality check of the numerical variables was performed with the Kolmogorov-Smirnov test.

In independent two group comparisons according to tumor localization, mortality rate and BED10 levels, independent Samples *t*-test was used if the numerical variables distributed normally. When they no normally distributed, Mann Whitney U test was used. In comparison of categorical variables, since observation numbers were below 5, Fisher Exact test was used.

Changes in SUVmax and SUVmean with time were evaluated with the Friedman test. For multiple comparisons, The Durbin-Conover test was used. To determine the factors associated with mortality, a Cox Regression model was constructed. Summary statistics of the model was given as Ratio and 95% confidence intervals.

The log-rank test was performed and Kaplan-Meier survival curve was created to determine any possible difference between the patients who had central and peripheral tumors.

We also investigated the correlation of BED_{10} with several study parameters with Spearman correlation analysis.

Statistical analysis was performed with Jamovi Project (version 1.1.9) and JASP Team (version 0.11.1) software's. A p-value <0.05 was deemed as statistically significant.

Table I. The patient clinic-demographic features, tumor characteristics and radiotherapy parameters of the study participants.

Variables	Mean ± SD	Median [IQR]
Age	68.5 ± 9.0	68.5 [62.2- 76.0]
Gender (%)		
Male	86 (91.5)	
Female	8 (8.5)	
Tumor location (n, %)		
Peripheral	69 (73.4)	
Central	25 (26.6)	
Histopathology (n, %)		
No biopsy	71 (75.5)	
NSCLC	23 (24.5)	
Gross Tumor volume (GTV, baseline), (cc)	23.3 ± 23.7	16.2 [7.1- 32.9]
Number of Fractions	3.5 ± 0.9	3.0 [3.0- 4.0]
Coverage (%)	97.0 ± 2.2	97.0 [95.9- 98.7]
Minimum dose (cGy)	5240.3 ± 1006.6	5222.3 [4676.3- 6288.7]
Maximum dose (cGy)	5054.6 ± 889.6	5067.1 [4493.8- 5670.2]
Mean dose (cGy)	5705.4 ± 961.8	5681.8 [5086.4- 6592.1]
SUVmean pretreatment	13.22 ± 14.29	10.9 [7.22- 14.85]
SUVmean post-treatment 1	4.76 ± 4.37	3.5 [2.7- 5]
SUVmean post-treatment 2	4.44 ± 4.14	3.3 [2.2- 3.9]
SUVmean post-treatment 3	4.61 ± 4.74	3.2 [1.8- 4.9]
MI max1 (SUVxmL)	383.32 ± 786.27	159.11 [52.22- 352.26]
MI max2 (SUVxmL)	70.66 ± 178.15	6.31 [1.11- 36.37]
MI mean1 (SUVxmL)	149.87 ± 292.87	66.04 [30.1- 155.51]
MI mean2 (SUVxmL)	30.13 ± 68.33	5.22 [1.06- 23.19]

MI: Metabolic Index.

Results

Patient Demographics and Baseline Tumor Characteristics

Overall, 94 early-stage non-small cell lung cancer (NSCLC) patients who were administered stereotactic radiotherapy were included in the study. Most of the study patients were male (91.5%). Mean age of the patients was 68.5 ± 9.0 years.

Twenty-three patients had undergone biopsy and had histopathological diagnosis of NSCLC. On the other hand, rest of the patients (75.5%) had not undergone biopsy due to several reasons. The primary lung tumor was located centrally and peripherally in 25 (26.6%) and 69 (73.4%) of the patients, respectively. The median gross tumor volume (GTV) was 16.2 cc (interquartile range (IQR): 7.1- 32.9).

The patient demographics and tumor characteristics of the study participants were summarized in Table I.

Stereotactic Radiotherapy

The median number of radiotherapy fractions was 3 [IQR: 3-4]. The stereotactic radiotherapy treatment covered the mean 97.0 ± 2.2% of the tumor mass. Mean dose of administered radiotherapy was 5705.4 ± 961.8 cGy. The median baseline standardized uptake unit (SUV_{mean}) was 10.9 [IQR: 7.22- 14.85]. The median MI_{mean} and MI_{max} values were 159.11 [IQR: 52.22- 352.26] and 66.04 [IQR: 30.1- 155.51], respectively (Table I).

Tumor Localization

When the patients were compared based on the location of their tumors, there was no sex or age difference between the patients who had centrally or peripherally located tumors. The mean GTV were comparable in both groups ($p = 0.103$). In a similar vein, there was no difference between the groups in terms of the number of fractions. There was a significant difference between the groups in terms of mortality rate. Whereas all patients who had peripheral tumors survived, 17 patients with central tumors (70.8%) died during the study period ($p = 0.001$). Baseline mean SUVmax and SUVmean values were again no different from one another in centrally and peripherally located tumors. Biologically effective dose (BED_{10}) values were significantly higher in patients who had peripheral tumors compared with patients with central tumors ($p = 0.001$) (Table II).

Table II. Comparison of radiation treatment parameters between centrally and peripherally located tumors.

	Tumor Location		*p*
	Peripheral (n=69)	Central (n=25)	
Age	69.5 ± 9.4	65.8 ± 7.5	0.056**
Gender (n, %)			
Male	64 (92.8)	22 (88.0)	0.435*
Female	5 (7.2)	3 (12.0)	
GTV	13.8 [6.8- 24.4]	20.2 [8.6- 42.1]	0.103***
Minimum dose (cGy)	5600.6 ± 790.2	4245.9 ± 868.4	**<0.001****
Maximum dose (cGy)	4938.2 ± 816.4	5375.9 ± 1015.8	0.060**
Mean dose (cGy)	5966.6 ± 827.9	4984.3 ± 951.0	**<0.001****
Number of fractions	3.0 [3.0- 4.0]	3.0 [3.0- 5.0]	0.060
BED_{10}	140.3 ± 36.0	108.4 ± 36.4	**0.001**
SUVmax1 (median [IQR])	11.6 [8.3- 16.5]	12.3 [7.2- 16.7]	0.817***
SUVmax2 (median [IQR])	3.6 [2.9- 5.2]	5.6 [3.3- 13.0]	0.076***
SUVmax3 (median [IQR])	3.1 [2.4- 3.9]	7.4 [4.9- 12.2]	**0.036*****
SUVmax4 (median [IQR])	2.9 [1.7- 4.1]w	7.9 [5.9- 9.9]	0.296***
SUVmean1 (median [IQR])	5.0 [3.9- 6.5]	4.9 [4.0- 6.6]	0.803***
SUVmean2 (median [IQR])	2.9 [2.7- 3.3]	3.2 [2.8- 5.2]	0.098***
SUVmean3 (median [IQR])	2.7 [2.1- 3.0]	3.8 [3.0- 5.7]	**0.042*****
SUVmean4 (median [IQR])	2.4 [1.1- 2.9]	3.9 [3.4- 4.5]	0.192***
Mortality (%)			
Survivor	69 (100)	7 (29.2)	**0.001***
Deceased	0 (0)	17 (70.8)	

Descriptive statistics were presented as number and (%) in categorical variables, mean and standard deviation or median and [IQR] in numerical variables. IQR: Interquartile Range. Bold *p*-values were accepted as significant ($p < 0.05$). BED10: Biologically effective dose. *The Fisher Exact test was used. **The Independent Samples *t*-test was used. ***The Mann-Whitney U test was used.

Biologically Effective Dose (BED_{10})

We stratified patients into groups based on BED_{10} values as below and over 100 Gy and below and over 150 Gy (Table III). There were 24 patients whose BED10 was below 100 Gy, whereas 70 patients had BED10 values over 100 Gy. The patient numbers did not change when we grouped patients with a BED10 cutoff of 150 Gy. Significantly more patients died in patients who had BED values below 100 Gy compared to patients who had BED values over 100 Gy ($p = 0.001$). This mortality difference disappeared when patients were stratified as BED10 values below and over 150 Gy. Moreover, Minimum, maximum and median radiotherapy doses were significantly lower in patients who had BED10 value over 150 Gy.

Change in SUV Values During the Course of the Treatment

SUVmax and SUVmean values showed significant decrease with the first treatment. The median SUVmax value reduced from the baseline value of 11.8 [8.1-17.1] to 3.9 [3.0-5.6] at the first post treatment evaluation ($p = 0.007$). It reached value of 3.2 [2.8-7.0] at the second post treatment. Similarly, the mean SUV value decreased from the initial value of 2.8 [2.6-3.8] at the second post treatment evaluation.

Mortality

In total, 17 patients died during the study period (all of them patients with centrally located tumors). The mean ages were comparable between the surviving and deceased patients ($p = 0.585$). Similarly, GTV was not different between the groups. The only significant difference observed was minimum radiotherapy dose; 5158.0 ± 1048.4 cGy in surviving patients and 5647.7 ± 708.1 cGy in deceased patients. The mean biologically effective dose (BED10) was significantly lower in deceased patients compared with surviving patients (111.6 ± 43.1 Gy *vs.* 136.6 ± 36.4 Gy, respectively). The comparisons of treatment parameters were demonstrated in Table IV.

We performed the Log-Rank test to determine to differences, if any, in the survival distribution for

Table III. Comparison of the groups which had below and over BED_{10} cutoff values of 100 and 150 Gy.

	BED_{10}		*p*	BED_{10}		*p*
	≤100 (n=24)	>100 (n=70)		≤150 (n=24)	>150 (n=70)	
Age	69.0 ± 8.7	68.3 ± 9.2	0.765**	69.4 ± 9.0	67.1 ± 9.1	0.239**
Gender (n, %)						
Male	20 (83.3)	66 (94.3)	0.196*	52 (89.7)	34 (94.4)	0.706*
Female	4 (16.7)	4 (5.7)		6 (10.3)	2 (5.6)	
GTV	16.2 [7.6- 33.3]	16.2 [7.0- 32.6]	0.735***	17.8 [7.8- 33.9]	14.1 [6.0- 19.9]	0.258***
Minimum dose (cGy)	5453.2 ± 958.3	5167.3 ± 1019.1	0.222**	5438.1 ± 940.1	4921.6 ± 1041.1	**0.018****
Maximum dose (cGy)	5352.9 ± 811.8	4952.3 ± 897.4	**0.049****	5202.2 ± 842.6	4816.8 ± 923.1	**0.046****
Mean dose (cGy)	5958.7 ± 877.6	5618.5 ± 979.8	0.119**	5888.1 ± 899.5	5411.0 ± 997.9	**0.022****
Number of fractions	3.5 ± 0.8	3.5 ± 1.0	0.995**	3.5 ± 0.8	3.6 ± 1.0	0.452**
SUVmax1 (median [IQR])	12.7 [5.0- 18.6]	11.7 [8.4- 15.6]	0.913***	9.4 [6.8- 15.5]	12.8 [9.6- 17.8]	0.222***
SUVmax2 (median [IQR])	4.3 [2.9- 5.9]	3.8 [3.0- 5.5]	0.962***	4.3 [3.1- 6.1]	3.5 [2.9- 5.5]	0.733***
SUVmax3 (median [IQR])	5.6 [4.1- 11.7]	3.2 [2.6- 5.8]	0.256***	3.9 [2.8- 8.9]	3.2 [2.8- 4.1]	0.559***
SUVmax4 (median [IQR])	9.9 [5.8- 14.1]	3.7 [2.0- 4.1]	0.794***	3.6 [2.6- 10.9]	3.8 [1.9- 4.3]	0.909***
SUVmean1 (median [IQR])	5.1 [3.3- 6.5]	5.0 [4.2- 6.4]	0.971***	4.9 [3.6- 6.5]	5.1 [4.5- 6.7]	0.352***
SUVmean2 (median [IQR])	2.9 [2.7- 3.5]	3.0 [2.7- 3.6]	0.924***	3.1 [2.7- 3.7]	2.8 [2.7- 3.4]	0.561***
SUVmean3 (median [IQR])	3.5 [3.0- 4.4]	2.8 [2.4- 3.3]	0.292***	3.0 [2.6- 4.3]	2.8 [2.4- 3.0]	0.460***
SUVmean4 (median [IQR])	3.2 [2.1- 4.2]	2.8 [1.8- 2.9]	0.602***	2.8 [2.0- 4.1]	2.8 [1.5- 2.9]	0.569***
Mortalite (%)						
Surviving	14 (58.3)	62 (89.9)	**0.001***	44 (77.2)	32 (88.9)	0.252*
Deceased	10 (41.7)	7 (10.1)		13 (22.8)	4 (11.1)	

Descriptive statistics were presented as number and (%) in categorical variables, mean and standard deviation or median and [IQR] in numerical variables. BED10: Biologically effective dose, IQR: Interquartile Range. Bold *p*-values were accepted as significant ($p < 0.05$). *The Fisher Exact test was used. **The Independent Samples *t*-test was used. ***The Mann-Whitney U test was used.

the patients with the peripheral and the central tumors (Figure 1). The survival distributions for the two groups were significantly different ($p < 0.001$)

Determinants of Mortality

We constructed a Cox regression model to examine the independent predictors of mortality. However, we did not include the "location of the tumor" variable, since there was no deceased patient in the peripheral location group. Age, GTV, Pretreatment SUVmean and SUVmax values and Mean dose were included in the univariate analysis. Only GTV and Pretreatment SUVmean appeared as significant predictors of mortality. In multiple Cox regression model, constructed with the same variables, GTV and SUVmean values remained as the independent predictors of mortality (Table V).

Determinants of Local Control

We defined local control as the difference between $MI_{Max}2$ and $MI_{Max}1$. To determine the significant independent determiners of local control, we created a linear regression model, in which mean radiation dose, number of fractions, GTV and tumor location were involved. There wasn't any statistical difference between the parameters.

Correlation Analysis of BED_{10}

BED_{10} values showed a significant and strong positive correlation with total radiation dose (r: 0.800, $p < 0.001$), whereas it showed a significant strong negative correlation with number of fractions (r: - 0.700, $p < 0.001$). There was not any significant correlation with BED_{10} values and GTV, preSUVMean, postSUV1Mean, postSUV2Mean, and postSUV3Mean.

Discussion

In the present study, we found that the GTV and Pretreatment SUVmean appeared as significant predictors of mortality in patients with non-small cell lung cancer (NSCLC) patients. BED_{10} values showed a significant and strong positive correlation with total radiation dose, whereas it showed a significant strong negative correlation with number of fractions.

Table IV. Comparison of the radiation treatment parameters according to patient mortality status.

	Mortality		*P*
	Surviving patients (n=76)	Deceased patients (n=17)	
Age	68.1 ± 8.8	69.5 ± 9.9	0.585**
Gross tumor volume (GTV)	15.9 [7.4- 32.9]	16.8 [5.3- 34.2]	0.984***
Minimum dose (cGy)	5158.0 ± 1048.4	5647.7 ± 708.1	**0.026****
Maximum dose (cGy)	5003.1 ± 929.0	5268.5 ± 698.6	0.195**
Mean dose (cGy)	5643.0 ± 983.9	6021.4 ± 830.2	0.113**
Number of fractions	3.5 ± 0.9	3.6 ± 0.9	0.796**
SUVmax1 (median [IQR])	11.9 [8.3- 15.5]	9.4 [6.5- 23.8]	0.755***
SUVmax2 (median [IQR])	3.6 [2.8- 5.2]	7.3 [5.0- 11.7]	**0.022*****
SUVmax3 (median [IQR])	3.2 [2.7- 6.6]	15.8 [10.2- 21.5]	0.102***
SUVmax4 (median [IQR])	3.6 [1.7- 3.9]	18.2 [18.2- 18.2]	0.117***
SUVmean1 (median [IQR])	5.0 [4.2- 6.3]	4.6 [3.6- 7.4]	0.922***
SUVmean2 (median [IQR])	2.9 [2.6- 3.3]	4.2 [3.2- 5.0]	**0.026*****
SUVmean3 (median [IQR])	2.8 [2.6- 3.7]	4.6 [3.9- 5.4]	0.156***
SUVmean4 (median [IQR])	2.8 [1.1- 2.9]	5.3 [5.3- 5.3]	0.117***
BED_{10} (Gy)	136.6 ± 36.4	111.6 ± 43.1	**0.037****

Descriptive statistics were presented as number and (%) in categorical variables, mean and standard deviation or median and [IQR] in numerical variables. IQR: Interquartile Range. Bold *p*-values were accepted as significant ($p < 0.05$). BED10: Biologically effective dose; **The Independent Samples t-test was used; ***The Mann-Whitney U test was used.

PET, which has been widely used in the diagnosis and staging of lung cancer recently, is claimed to be a non-invasive method that can provide information about the prognosis of the tumor[7]. PET imaging using FDG has taken its place in routine clinical use today as an effective, non-invasive imaging method that is increasingly used in the diagnosis, staging, evaluation of treatment response and predicting prognosis of lung cancer[8]. In addition to its superiority in demonstrating metastatic spread, FDG PET provides additional information about the biological activity and prognosis of the disease by showing the metabolic activity in the tumor[9]. It is suggested that FDG uptake (SUV) in PET examination will reflect some biological information such as proliferative activity of the primary tumor, metabolic tumor volume, microvascular density, metabolic index and tumor grade[8]. In our study, we investigated that the predictive value of metabolic index, GTV, SUV, BED and dose values on survival in early stage lung cancer stereotactic radiotherapy with F-18 FDG PET/CT.

Pöttgen et al[10] evaluated 50 locally advanced NSCLC patients with PET/CT 3 times, before treatment, after 3 cycles of induction chemotherapy and following chemoradiotherapy. Thirty-seven patients were considered respectable after chemoradiotherapy, and the operation was performed. In this study, a decrease of 45-62% in tumor FDG uptake in pre-treatment and both follow-up PET/CT examinations was found to correlate with histopathological response[10]. In a study of 56 patients, it was found that there was a close linear relationship between the changes in SUVmax of the lesions observed on F-18 FDG PET after neoadjuvant chemotherapy and the pathological response, and that more accurate predictions were made than the changes observed in the size of the lesions on CT. This study showed that when there is an 80% or greater reduction in SUVmax, the patient has a high probability (with 96% accuracy) of a complete response to treatment, regardless of cell type[11]. Similarly, Vansteenkiste et al[12] conducted with stage IIIa-N2 NSCLC patients; showed that 50% reduction in primary tumor uptake after induction chemotherapy had a better survival prediction than standard WHO criteria[12]. Nahmias et al[13] evaluated the tumor metabolic response of 16 NSCLC patients who had undergone chemotherapy with FDG PET/CT 1 and 3 weeks after the start of treatment. In this study, it has been shown that positive tumor metabolic response can detect patients responding to chemotherapy in the early period and is correlated with long-term survival[13]. In addition, in a prospective study conducted with 47 locally advanced NSCLC patients who underwent neoadjuvant chemotherapy; In the interim FDG PET/CT examination taken after 1 course of chemotherapy, it was determined that 35% and more reduction in

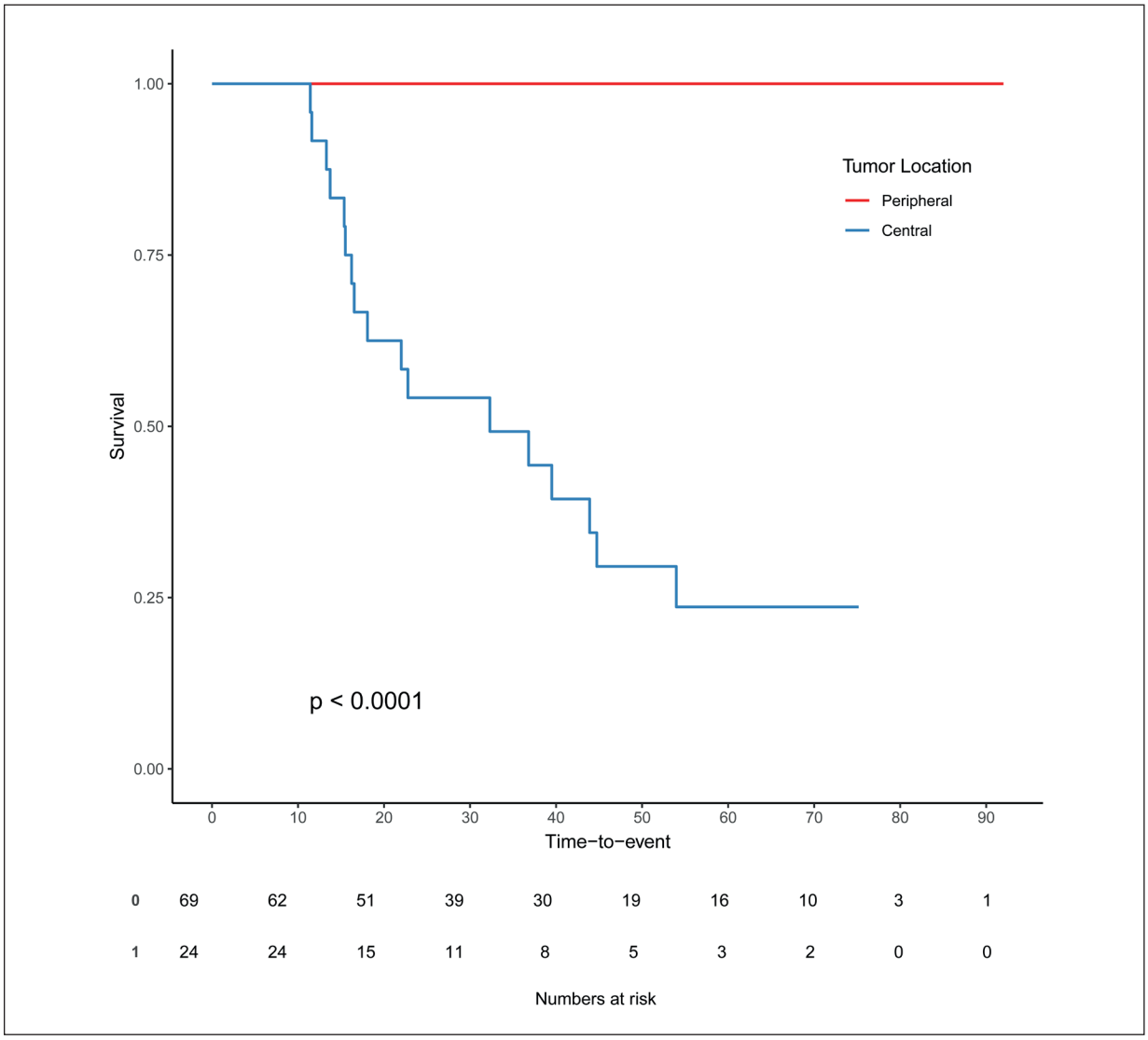

Figure 1. Kaplan-Meier survival curve showing distribution of survival in patients with central and peripheral tumors.

FDG uptake was correlated with increased survival compared to the baseline examination[14]. In our study, gross tumor volume and SUV values were found to be lower in surviving patients. However, GTV and Pretreatment SUVmean appeared as significant predictors of mortality in patients with early stage NSCLC.

Recently, it is thought that the simultaneous application of low-dose fractionated radiotherapy and induction chemotherapy in patients with locally advanced NSCLC positively affects the prognosis. In a study by Mattoli et al[15], the response to treatment of 44 patients who received simultaneous low-dose fractionated radiotherapy and induction chemotherapy was evaluated using PERCIST criterias[15]. Mortality rates were found to be high in patients with primary tumor volume and high SUV values in metastatic lymph nodes[15]. In our study, minimum dose, maximum dose, mean dose and number of fractions were found to be lower in surviving patients. However, the only significant difference observed was minimum radiotherapy dose; 5158.0 ± 1048.4 cGy in surviving patients and 5647.7 ± 708.1 cGy in deceased patients.

Numerous studies have shown excellent outcomes achieved by SABR for treating early-stage NSCLC, with the majority of treatment regimens using dose-fractionation schedules with a BED of over 110 Gy, and many up to 150 Gy[16-19]. Nevertheless, the optimal fractionation schedule in this setting has not been established and remains

Table V. Univariate and Multivariate Cox regression models for determination of independent predictors of mortality.

	Univariate Cox Regression Model		Multiple Cox Regression Model	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age	0.95 [0.88-1.02]	0.161	0.94 [0.84-1.06]	0.315
GTV	1.03 [1.01-1.06]	**< 0.001**	1.04 [1.02-1.07]	**< 0.001**
SUV_{mean} (Pretreatment)	1.04 [1.01-1.07]	**0.003**	1.07 [1.03-1.10]	**< 0.001**
SUVmax	1.05 [0.96-1.14]	0.291	1.03 [0.94-1.12]	0.556
$Dose_{mean}$	1.00 [1.00-1.00]	0.051	1.00 [1.00-1.00]	0.173

Localization was not included because there were no patients who died in the peripheral location group. GTV: Gross tumor volume, HR: Hazard Ratio, CI: Confidence Interval.

a controversial topic[20]. Some investigators have tried to better define the optimal BED for the treatment of early-stage NSCLC, but results have been mixed. In a meta-analysis of 34 studies, Zhang et al[20] found that OS was best when using a BED in the range of 83-146 Gy. BEDs over 146 Gy resulted in lower OS likely due to increased toxicity. A multi-institutional study by Onishi et al[21] showed significantly superior outcomes using a BED of 100 Gy or more compared to a BED below 100 Gy. Many fractionation schemes were employed in that study ranging from 1 to 22 fractions. An analysis of patients in the National Cancer Database found that the median BED used was 150 Gy and that for patients with T2 tumors OS was improved with higher-dose SABR (BED >150 Gy)[22]. This same study found no difference in OS for patients with T1 tumors when treated with lower-dose (BED<150 Gy) versus higher-dose SABR. Zhu et al[23] show that treating early-stage NSCLC with SABR fractionation schedules with a BED10 of 100–105.6 Gy yielded excellent local and local-regional control rates[23]. In our study, we stratified patients into groups based on BED10 values as below and over 100 Gy and below and over 150 Gy. There were 24 patients whose BED10 was below 100 Gy, whereas 70 patients had BED10 values over 100 Gy. The patient numbers did not change when we grouped patients with a BED10 cutoff of 150 Gy. Significantly more patients died in patients who had BED values below 100 Gy compared to patients who had BED values over 100 Gy. This mortality difference disappeared when patients were stratified as BED10 values below and over 150 Gy. Moreover, Minimum, maximum and median radiotherapy doses were significantly lower in patients who had BED_{10} value over 150 Gy. However, the mean biologically effective dose (BED10) was significantly lower in deceased patients compared with surviving patients. BED_{10} values showed a significant and strong positive correlation with total radiation dose, whereas it showed a significant strong negative correlation with number of fractions.

Conclusions

Whether FDG-PET is a new marker to determine the prognosis of NSCLC is an important issue. We obtained strong evidence that tumor metabolic parameters (Pretreatment SUVmean, GTV, and BED_{10}) can be used in the evaluation of biological aggressiveness and prognosis. However, it was concluded that GTV and Pretreatment SUVmean values may be important predictors of survival in patients with early stage NSCLC. If studies with a high number of cases support these data, metabolic tumor parameters will contribute to predicting prognosis and survival in cases with NSCLC.

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Ethics Approval and Consent to Participate

The study was approved by the local ethics committee of Celal Bayar University Medical Hospital (Approval No. 20478486-050.04.04).

Consent for Publication

None of the authors have any relevant conflicts of interest to disclose. We confirm that we have read the journal's position on issues involved in ethical publication and we affirm that this report is consistent with those guidelines.

Conflict of Interests

The authors report no declarations of interest.

Authors' Contributions

Concept – F.A, A.O.; Design – F.A, A.O.; Supervision – F.A, A.O.; Data Collection and/or Processing – F.A, A.O.

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