High Metabolic Tumor Volume and Total Lesion Glycolysis Derived from Baseline ^{18}F-FDG PET/CT may Predict the Metabolic Abnormalities in Newly Diagnosed Cancer Patients

Aysun CETIN[1], Ummuhan ABDULREZZAK[2], Semih YILMAZ[1,7], Gokmen ZARARSIZ[3], Soner AKKURT[4], Mahmut UCAR[5], Leylagül KAYNAR[5], Esra YILDIZHAN[5], Esra E. TURAK[5], Ersin OZASLAN[5], Kursat GUNDOGAN[6], Mevlude INANC[5], Mustafa KULA[2], Mustafa CETIN[5]

[1] Erciyes University, Faculty of Medicine, Department of Medical Biochemistry
[2] Erciyes University, Faculty of Medicine, Department of Nuclear Medicine
[3] Erciyes University, Faculty of Medicine, Department of Biostatistics
[4] Erciyes University, Faculty of Medicine, Department of Sports Medicine
[5] Erciyes University, Faculty of Medicine, Department of Haematology and Oncology
[6] Erciyes University, Faculty of Medicine, Department of Internal Medicine
[7] Erciyes University, Faculty of Agriculture, Department of Enzyme and Microbial Biotechnology, Kayseri, TURKEY

ABSTRACT

The present study was conducted to investigate the role of total body Metabolic Tumor Volume (MTV, mm^3) and Total Lesion Glycolysis (TLG) values obtained by PET/CT imaging for predicting metabolic abnormalities in newly diagnosed cancer patients. Patients having solid tumors with initial PET/CT staging were evaluated in a prospective cohort study. MTV and TLG values of all patients were measured besides SUV values as PET/CT parameters. Initial metabolic status of patients was evaluated based on basal metabolic rates, serum vitamin, mineral, and biochemical metabolite levels and antioxidant enzyme capacities. The MTV and TLG levels revealed significant relationships with cancer-induced metabolic abnormalities as high BMR and LDH, and low albumin levels as well as advanced stage and presence of metastasis ($p< 0.05$). Cut-off values along with sensitivity and specificity rates in terms of high BMR (>20 Kcal/kg) were obtained to be > 52400 mm3 for MTV (0.84 and 0.63) and >274208 for TLG (0.84 and 0.63). The same values for high LDH were ≥ 219520 mm^3 (0.52 and 0.88) for MTV and ≥ 411792 (0.78 and 0.58) for TLG, respectively. The values for low albumin levels were ≥89520 mm^3 (0.63 and 0.10) for MTV, and ≥ 887840 (0.75 and 1.00) for TLG, respectively. In conclusion, MTV and TLG cut-off values determined by ROC analysis can predict metabolic abnormalities in initial BMR, LDH and albumin levels with high specificity and sensitivity. It is recommended to test MTV and TLG levels to determine initial metabolic status of diverse patient groups with various types of cancer.

Keywords: MTV, TLG, BMR, lung cancer, breast cancer

ÖZET

Başlangıç 18F-FDG PET/CT Temelli Yüksek Metabolik Tümör Volümü (MTV) ve Toplam Lezyon Glikoliz Değerleri Yeni Tanı Konulmuş Kanser Hastalarında Metabolik Bozuklukları Gösterebilir

Bu çalışma PET/CT'den elde edilen tüm vücut Metabolik Tümör Volümü (MTV, mm^3) ve Toplam Lezyon Glikoliz (TLG) değerlerinin kanser hastalarında metabolik bozuklukları tahmin etmedeki rolünü araştırmak için yapıldı. Prospektif kohort çalışmada başlangıç PET/CT evrelemesi yapılan yeni tanı konmuş solid tümör hastaları değerlendirildi. Tüm hastalarda PET/CT parametresi olarak SUV değerlerinin yanında MTV ve TLG değerleri de ölçüldü. Hastaların başlangıç metabolik durumu bazal metabolizma hızları, serum vitamin, mineral ve biyokimyasal metabolit düzeyleri ve antioksidan enzim kapasiteleri ile değerlendirildi. MTV ve TLG değerleri ileri evre hastalık ve metastaz varlığının yanı sıra artmış BMR, yüksek LDH ve düşük albümin değerleri gibi kanserin yol açtığı metabolik bozukluklar ile anlamlı ilişki gösterdi ($p< 0.05$).

Yüksek BMR için MTV ve TLG eşik değerleri ve duyarlılık ve seçicilik oranları sırası ile MTV için ≥ 52400 mm3 (0.84 ve 0.63) ve TLG için ≥ 274208 (0.84 ve 0.63) olarak bulundu. Aynı değerler yüksek LDH bakımından MTV ve TLG için sırasıyla ≥ 219520 mm^3 (0.52 ve 0.88) ve ≥ 411792 (0.78 ve 0.58) olarak bulundu. Bu değerler düşük albümin yönünden sırasıyla MTV için ≥ 89520 mm^3 (0.63 ve 1.00), TLG için ≥ 887840 (0.75 ve 1.00) olarak belirlendi. Sonuç olarak, ROC analizi ile saptanan MTV ve TLG eşik değerleri başlangıç BMR, LDH ve albümin düzeylerindeki metabolik bozuklukları yüksek seçicilik ve duyarlılık ile tahmin edebilmektedir. Kanser hastalarının başlangıç metabolik durumlarını saptamada MTV ve TLG düzeylerinin klinik önemi farklı kanser tiplerinde geniş bir hasta grubuyla test edilmesi önerilmektedir.

Anahtar Kelimeler: MTV, TLG, BMR, akciğer kanseri, meme kanseri

INTRODUCTION

The basic feature of cancer cell metabolism is the ability to obtain the required nutrients from a low-nutrient environment for maintaining viability and using them to build a tumoral biomass.[1,2] Cancer cells, unlike healthy cells, indicate sustained proliferation and due to their expansion capabilities in local and remote areas, they meet their energy requirements and metabolic needs indifferently from macro and micro nutrients providing homeostasis in the body they invade. Cancer rapidly leads to reduction in essential vitamins such as C, E, B, and D, and trace cofactors such as Zn, Mn, Cu, and Se.[3,4] In many studies, it was proved that the local antioxidant adaptation mechanisms developed by the tumor, protects itself by destroying antioxidant enzyme systems of the healthy cells of the occupied body through secreting free oxygen radicals from transformed tissues.[5,6]

The energy required for tumoral biosynthetic reactions has been met preferentially via glucose and glycolysis systems known as "The Warburg Effect" all along.[7] Increased and preferential glucose uptake ability of tumors provide important information about placement and distribution of tumors through positron emission tomography (PET) imaging, developed by using F-18-labeled glucose analogue 2-deoxy-D-glucose (FDG). For clarifying the prognostic value of metabolic activity of patients, FDG PET/CT scans have been utilized in a number of studies. However, in most of them used only the SUVmax (maximum standardized uptake value) was used for estimating the metabolic activity of tumor with somewhat inconsistent reported values. Currently, it was shown that MTV (metabolic tumor volume) and TLG (total lesion glycolysis) values, measurable by FDG PET/CT, could be better than SUVmax alone for assessing and predicting entire tumor burden, overall metabolic activity and prognosis of several malignancies.[8-10]

Recently, the correction of metabolic disorders and external replacement of decreased essential vitamins and minerals in patients before receiving chemotherapy and radiotherapy is considered as an adjunct to cancer treatment and thus, therapeutic response can be improved, the adverse effects of chemotherapy and radiotherapy can be better tolerated, and as a result patient's quality-of-life be improved.[3,4,11,12] However, measurement and evaluation of most of the specific vitamins and minerals are non-cost-effective and cause intensive labor and time loss. Thus, the ability to predict metabolic disturbances through routine screening and imaging will not only increase the success of cancer treatment, but also will be a time and cost effective approach. In present study, we investigated whether MTV and TLG values, calculated by FDG PET/CT imaging routinely performed in cancer patients, could predict abnormalities in patient's metabolic parameters or not.

PATIENTS AND METHODS

Patients

The current prospective study was performed in 75 cancer patients, including 35 men and 40 women, age range of 21-68 years (mean age: 52.89) and ECOG performance status of ≤ 1. Exclusion criteria were previous cancer diagnosis, brain metastasis, hyperthyroidism and/or diabetes, active infection findings, major surgery history within the past 4 weeks, heart failure, unstable angina pectoris, cardiac arrhythmia, psychosis or uncontrolled diseases that may influence the study. Whole body FDG PET/CT scans were obtained on patients dur-

Table 1. Clinical characteristics of patients according to cancer types

Clinical Characteristics and Variables	Lung cancer (n= 33)	Breast cancer (n= 32)	Other cancers (n= 10)	All patients (n= 75)	p
Gender (Female/male)	5 (15)/28 (85)a	32 (100)/0 (0)b	3 (30)/7(70)a	40 (53)/35 (47)	< 0.001
Age (years)	57.6±8.9a	50.06±10.47b	46.4±15.9b	52.9±11.4	0.003
BMI	24.9±4.7a	32.03±3.99b	31.8±7.7b	28.9±5.9	< 0.001
BMR (Kcal/kg)	22.9±2.4a	18.80±1.23b	21.6±2.7a	20.9±2.8	< 0.001
TNM					
Stage II	3 (9.1)a	11 (34.4)b	2 (20.0)ab	16 (21.3)	0.013
Stage III	10 (30.3)	14 (43.8)	2 (20.0)	26 (34.7)	
Stage IV	20 (60.6)	7 (21.9)	6 (60.0)	33 (44.0)	
Metastasis/Non-Metastasis	31 (94)/2(6)	28 (88)/4(13)	8 (80)/2 (20)	67 (89)/8 (11)	0.414
LDH (U/L)	227 (193-354)	215 (176-251)	244 (177-449)	219 (177-303)	0.203
Albumin (g/dL)	4.04 (3.9-4)a	4.6 (4.4-4.9)b	4.27 (3.8-4.5)a	4.3 (3.9-4.6)	< 0.001

Values are expressed as n(%), mean±standard deviation or median (1st-3rd quartiles). Different superscripts in the same row indicates a significant difference between groups.

ing November 2015-November 2017. Study protocol was approved by the Clinical Research Ethics Committee of Erciyes University Hospital, Turkey (Decision no: 2015/469). An informed consent was obtained from all patients included in the study. A total of 75 newly diagnosed patients consisted of lung cancer (n= 33), breast cancer (n= 32), and other cancers types (n= 10) (Table 1).

FDG PET/CT Imaging and Analysis

All patients fasted for at least 6 h. Blood glucose concentrations were checked before the PET studies (<120 mg/dL for non-diabetic patients and <200 mg/dL for diabetic patients). Patients were prohibited to take caffeine, alcohol, and nicotine 24 h before imaging and, after 6h of fasting blood sugar glucose were measured using a glucometer. The patients in resting state were intravenously injected with FDG (555-740 MBq (15-20 mCi; 0.22 mCi/kg). PET/CT views were obtained using GEMINI PET/CT scanner (Philips Medical Systems, Cleveland OH, USA). PET and CT scans' axes aligned via software help. CT scans were performed from the skull base to the mid-thigh (without intravenous contrast) for attenuation correction and anatomic localization using a standardized protocol of 120 kV, 50 mA, tube-rotation time of 0.75 s per rotation, pitch of 1.5, and section thickness of 5 mm. PET images were obtained after the CT, via a conventional three-dimensional protocol.[13]

All images were reviewed and evaluated at Nuclear Medicine Center at Erciyes University. Volumetric regions of interest were placed over areas of the malignant lesion. The standardized uptake value (SUV) was defined as the concentration of FDG divided by the injected dose and normalized to the body weight of the patient. SUVmax of the primary tumor (primary tumor SUVmax) and the highest SUVmax on the torso images (torso SUVmax) were obtained.[14] The metabolic tumor volume (MTV, mm^3) was measured from attenuation-corrected torso FDG PET/CT images by an SUV-based automated contouring program. Initially, the voxels on a threshold of 40% of the SUVmax in the volume of interest within the contouring margin were incorporated to define the tumor margin accurately. If the tumor margin was not correctly defined, the SUVmax threshold was adjusted. Whole MTV was calculated by adding up the MTVs of all malignant lesions in each patient. The total lesion glycolysis (TLG) was calculated by multiplying the MTV of each lesion by the corresponding average SUV determined in a selected contouring volume of interest. Whole TLG was calculated by adding up the TLGs of all malignant lesions in each patient.[15]

Basal Metabolism Rate

Measurements were carried out at laboratories of Sports Medicine, Erciyes University. Basal metabolism rate was measured by bioimpedance method. Patients were not allowed to have exercise and drink coffee for at least 24 hours before the test. They were stood with their soles in contact with the foot electrodes and also grasped the hand electrodes for accurate measurement. Tests were performed at 21-22^{0}C in the morning after at least 12 hours of resting following an overnight fasting (Tanita BC 418 MA, Tokyo, Japan).[16] Because the BMR values can vary according to body weight, the values were calculated as BMR/kg.

Determination of Metabolic Parameters

The levels of Zn, Se, P, K, Mg, Ca, Fe, and Cu in serum samples were measured using the ICP-MS Agilent 7500a (Infinity LC Agilent Technologies, Germany) instrument at Technology Research and Application Center (TAUM), Erciyes University. Preparation of multi element standard solution for calibration curve was prepared using single-element standard solutions. Samples were solubilized using hydrochloric acid and nitric acid. Blood samples after coagulation were centrifuged at 3000 rpm for 20 minutes and supernatant was used as serum sample. 1 ml of concentrated HNO_3 was added to the serum samples and incubated at 110^{0}C for 5 hours. Subsequently, the samples were solubilized together with internal standard elements in 5 ml of 0.1M HNO_3 and analyzed using ICP-MS.[17]

Blood samples were centrifuged at 5000 rpm for 5 minutes for the analysis of antioxidants in serum samples. Levels of SOD with superoxide dismutase assay kit (Cayman, 706002), GSH-Px with Glutathione assay kit (Cayman, 703102), TBARS with malondialdehyde activity kit (Cayman, 10009055), and T-AOC with total antioxidant capacity assay kit (Cayman, 709001) were determined using ELISA reader (Biotek synergy HT 47002, Biotek Technologies Vermont, USA) according to the manufacturers protocol.

Serum albumin (g/dL), creatinine (mg/dL), and alkaline phosphatase (ALP, U/L) levels were measured spectrophotometrically, and alanin aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L), gamma-glutamyl transferase (GGT, U/L), glucose (mg/dL), lactate dehydrogenase (LDH, U/L), and blood urea nitrogen (BUN, mg/dL) levels were measured using spectrophometric, enzymatic and kinetic UV methods in Biochemistry Laboratories of Erciyes University.

Statistical Analysis

Histogram and q-q plots were examined. Shapiro-Wilk's test was used to assess the data normality. Levene test was applied to assess the variance homogeneity. Mann-Whitney U, one-way analysis of variance (ANOVA), Kruskal-Wallis test and Pearson χ^2 analyses were used for group comparisons. Tukey, Tamhane's T2 and Bonferroni corrected Dunn's test was applied as post-hoc analysis. Spearman and point biserial correlation coefficients were calculated to assess the relationship between PET/CT markers and other parameters. Moreover, receiver operating characteristic (ROC) curve analysis was performed to identify the predictive performance of PET/CT markers on metabolic abnormalities. Areas under the ROC curves were calculated with 95% confidence intervals. Youden index was used to obtain cut-off values for each PET/CT marker and sensitivity, specificity, positive and negative predictive values were calculated with 95% confidence intervals. Analyses were conducted using R 3.4.3. (www.r-project.org), MVN18 and easyROC19 softwares. A p value less than 5% was considered as statistically significant.

RESULTS

Patient Characteristics

The clinical characteristics of the patients are summarized in Table 1. Lung cancer, breast cancer and other cancers groups differed from each other depending on patient gender, BMI, BMR, disease stage, albumin and vitamin A levels ($p< 0.05$). Notably, in breast cancer the BMR values were low, and the stage as well as albumin levels were high. Another noteworthy point is that average age was higher in lung cancer cases compared to others ($p< 0.05$). Also, vitamin A levels were lower and nega-

Table 2. FDG PET/CT variables of patients in different cancer groups

FDG PET/CT variables	Lung cancer (n= 33)	Breast cancer (n= 32)	Other cancers (n= 10)	All Patients (n= 75)	p
SUVmean					
Median	5.60[a]	3.85[b]	4.40[ab]	4.80	0.017
1st-3rd quartiles	4.35-7.45	2.08-6.00	2.90-6.85	3.10-6.70	
SUVmax					
Median	13.30	10.30	11.05	12.30	0.249
1st-3rd quartiles	9.90-17.45	7.28-17.28	6.43-20.15	8.40-17.60	
Max. activity concentration (Bq/ml)					
Median	24850	18027	20749	21035	0.138
1st-3rd quartiles	18065-34275	9509-28117	10384-33334	14782-28843	
Mean activity concentration (Bq/ml)					
Median	9383[a]	6564[b]	5027[ab]	8766	0.019
1st-3rd quartiles	7585-13609	4215-11501	8623-11090	5440-12515	
MTV (mm^3)					
Median	97760[a]	42160[b]	242440[a]	80480	0.003
1st-3rdquartiles	62560-313040	12680-105960	47900-650332	34400-242720	
TLG					
Median	697000[a]	171248[b]	1045160[a]	456504	0.002
1st-3rd quartiles	384356-1486392	48792-707574	272681-2800178	151960-1229312	

Different superscripts in the same row indicate a statistically significant difference among groups

tively correlated with MTV and TLG in other cancers group. The other variables didn't indicate any significance in examined cancer groups (p> 0.05).

FDG PET/CT Variables

FDG PET/CT variables of patients regarding cancer types were given in Table 2. Of the PET/CT variables, SUVmean and activity concentrations were considerably higher in lung cancer compared with those of breast cancer group (p< 0.05). Conversely, other important parameters MTV and TLG values were lower in breast cancer group compared to lung cancer and other cancers group (p< 0.05). No significant difference was observed with other PET/CT parameters examined in cancer groups (p> 0.05).

Correlation Analysis

In lung cancer, the stage, BUN, Cu and K levels were found to be positively correlated with both MTV (rho= 0.416, p< 0.05; rho= 0.671, p< 0.05; rho= 0.375, p< 0.05; rho= 0.391, p< 0.05, respectively) and TLG levels (rho= 0.347, p< 0.05; rho= 0.642, p< 0.05; rho= 0.378, p< 0.05, rho= 0.441, p< 0.05, respectively) (Table 2). In the same patient group, GSH-Px was negatively correlated only with TLG (rho= -0.377, p< 0.05). In addition, the stage, presence of metastasis, LDH, and Cu levels in breast cancer were found to be positively correlated with both MTV (rho= 0.816, p< 0.05; rpb= 0.512, p< 0.05; rho= 0.429, p< 0.05; rho= 0.436, p< 0.05, respectively) and TLG (rho= 0.738, p< 0.05; rpb= 0.481, p< 0.05; rho= 0.378, p< 0.05, rho= 0.443, p< 0.05, respectively). ALP was positively correlated only with TLG (rho= 0.482, p< 0.05). In other cancers group, Cu levels were found to be positively correlated with both MTV (rho= 0.700, p< 0.05) and TLG (rho= 0.683, p< 0.05). LDH and K were positively correlated only with MTV (rho= 0.663, p<0.05; rho= 0.683, p< 0.05, respectively). Ca was positively correlated with TLG (rho= 0.883, p< 0.05). The common point in all the cancers examined was that the level of albumin was found to be negatively correlated with MTV and TLG (for lung cancer: MTV rho=-0.740, TLG rho= -0.774, p< 0.05; for breast cancer: MTV rho= -0.410, TLG rho= -0.394, p< 0.05; for other

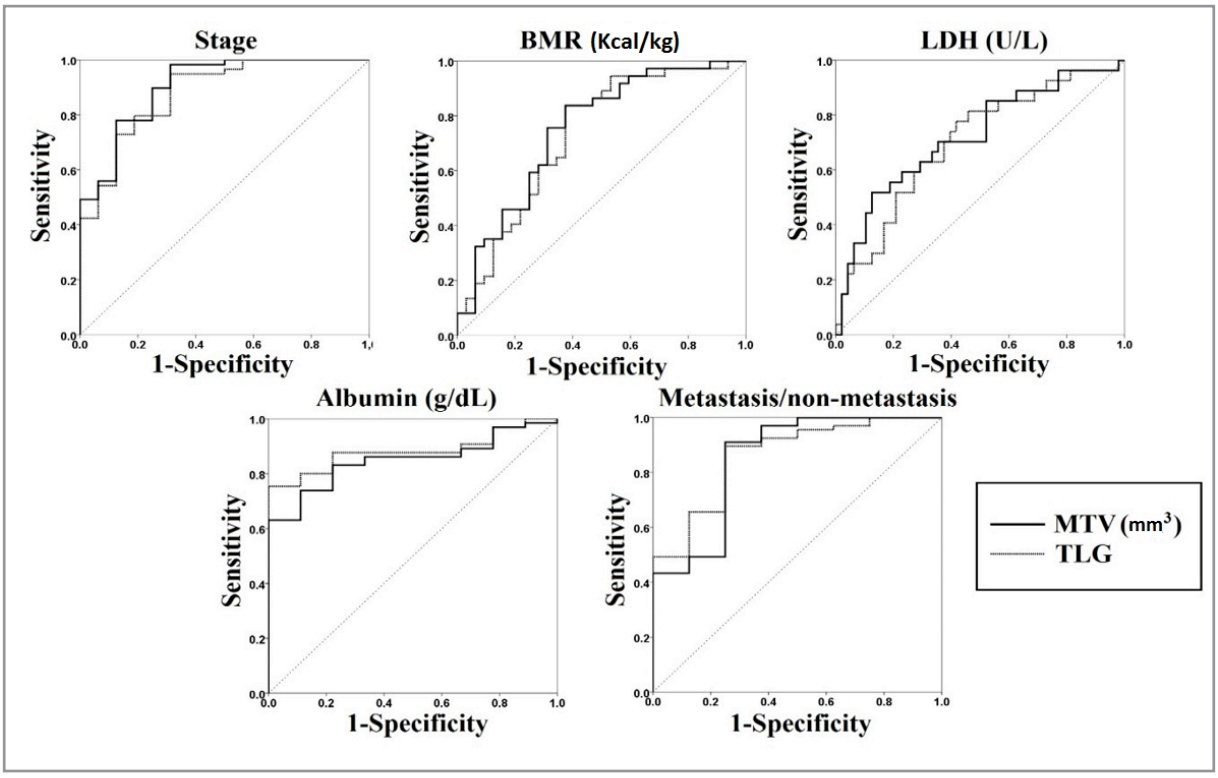


Figure 1. Comparison of ROC curves of MTV and TLG for predicting the decreased levels of albumin, and advanced stage, presence of metastasis, high metabolic rate, and high LDH in newly diagnosed cancer patients

cancers group: MTV rho= -0.709 and TLG rho= -0.770, p< 0.05).

It was suggested from ROC curve analysis that MTV and TLG levels could efficiently be used to predict the decreased albumin levels, advanced stages of cancer, presence of metastasis, high metabolic rate, and high LDH in newly diagnosed cancer patients (Figure 1). In predicting the stage (>2), area under the ROC curves was 0.90 for MTV and 0.88 for TLG; in predicting BMR (>20 Kcal/kg), area under the ROC curves was 0.75 for MTV and 0.73 for TLG; in predicting LDH (>250 U/L), the values were measured as 0.72 for MTV and 0.70 for TLG; in predicting albumin (>3.5 g/dL), the values were 0.85 for MTV and 0.88 for TLG; in predicting the presence of metastasis, the values were 0.85 and 0.86 for MTV and TLG, respectively.

Cut-off values were identified for MTV and TLG markers based on predictive performances in terms of stage, BMR, LDH, albumin and presence of metastasis as follows; In predicting the disease stage (>2), sensitivity and specificity values were obtained as 0.98 and 0.69 for MTV (>23680 mm^3), as 0.95 and 0.69 for TLG (>111616). In predicting BMR (>20 Kcal/kg), sensitivity and specificity values were obtained as 0.84 and 0.63 for both MTV (>52400 mm^3) and TLG (>274208). In predicting LDH (>250 U/L), the values were identified as 0.88 and 0.70 for MTV (>219520 mm^3), as 0.78 and 0.58 for TLG (>411792). In predicting albumin levels (>3.5 g/dL), the values were determined as 0.63 and 1.00 for MTV (<89520 mm^3), as 0.75 and 1.00 for TLG (<887840). In predicting the presence of metastasis, sensitivity and specificity values were obtained as 0.91 and 0.75 for MTV (>23680 mm^3), as 0.90 and 0.76 for TLG (>95744) (Table 3). It was clear that the stage of disease (≤2, >2), BMR (≤20, >20 Kcal/kg), LDH (≤250, >250 U/L), albumin (≤3.5, >3.5 g/dL) and presence of metastasis (metastasis/non-metastasis) were significant as compared to MTV and TLG (p< 0.05). While serum Vit A, B_1, B_6, B_{12}, E, folic acid, Zn, Mg, and P levels had negative correlations with MTV and TLG, K and Cu had positive correlations

Table 3. ROC analysis results and statistical diagnostic measures for MTV (mm^3) and TLG in predicting the metabolic abnormalities in newly diagnosed cancer patients

Marker	ROC Statistics		Statistical diagnostic measures			
	AUC	p	SEN	SPE	PPV	NPV
Stage (>2)						
MTV (>23680)	0.90 (0.8-1.0)	< 0.001	0.98 (0.9-1.0)	0.69 (0.4-0.9)	0.92 (0.8-1.0)	0.92 (0.7-1.0)
TLG (>111616)	0.88 (0.8-1.0)	< 0.001	0.95 (0.9-1.0)	0.69 (0.4-0.9)	0.92 (0.8-1.0)	0.79 (0.5-0.9)
BMR (>20 Kcal/kg)						
MTV (>52400)	0.75 (0.6-0.9)	0.002	0.84 (0.7-0.9)	0.63 (0.4-0.8)	0.72 (0.6-0.9)	0.77 (0.6-0.9)
TLG (>274208)	0.73 (0.6-0.9)	0.005	0.84 (0.7-0.9)	0.63 (0.4-0.8)	0.72 (0.6-0.9)	0.77 (0.6-0.9)
LDH (>250 U/L)						
MTV (>219520)	0.72 (0.6-0.9)	< 0.001	0.52 (0.3-0.7)	0.88 (0.8-1.0)	0.70 (0.5-0.8)	0.76 (0.6-0.9)
TLG (>411792)	0.70 (0.6-0.8)	0.002	0.78 (0.6-0.9)	0.58 (0.4-0.7)	0.51 (0.4-0.8)	0.82 (0.7-0.9)
Albumin (>3.5 g/dL)						
MTV (<89520)	0.85 (0.7-1.0)	< 0.001	0.63 (0.5-0.8)	1.00 (0.7-1.0)	1.00 (0.9-1.0)	0.27 (0.2-0.4)
TLG (<887840)	0.88 (0.7-1.0)	< 0.001	0.75 (0.6-0.9)	1.00 (0.7-1.0)	1.00 (0.9-1.0)	0.36 (0.2-0.5)
Metastasis/Non-Metastasis						
MTV (>23680)	0.85 (0.7-1.0)	< 0.001	0.91 (0.8-1.0)	0.75 (0.4-1.0)	0.97 (0.9-1.0)	0.50 (0.3-0.9)
TLG (>95744)	0.86 (0.7-1.0)	< 0.001	0.90 (0.8-1.0)	0.76 (0.4-1.0)	0.97 (0.8-1.0)	0.46 (0.3-0.9)

ROC: Receiver operating characteristics, AUC: Area under the curve, SEN: Sensitivity, SPE: Specificity, PPV: Positive predictive value, NPV: Negative predictive value

with the same parameters. Similarly, serum SOD, GSH-Px, and T-AOC levels had negative correlations with MTV and TLG. However, only the correlations between TLG and GSH-Px levels were found to be significant in lung cancer.

DISCUSSION

Currently, MTV and TLG measurements based on FDG PET/CT have been routinely used for detecting cancer stage as well as prognosis in clinical practices.[15,20] Contrary to other PET/CT-based conventional modalities, these two markers (MTV and TLG) provide valuable information about the whole tumor body metabolic activity volume, and thus the total volume of metastatic lesions.[21] In present study, ROC curve analysis of MTV and TLG levels revealed quite high sensitivity and specificity values not only for predicting the clinically advanced stage and presence of metastasis, but also metabolic abnormalities in BMR, LDH, and albumin levels of newly diagnosed cancer patients. In present study, highly sensitive and specific cut-off values were detected for MTV and TLG levels in predicting abnormal changes in these metabolic parameters.

Energy metabolism represents the consumption of nutrients needed to provide energy for metabolic processes involved in maintaining the function and integrity of cells and body organs. In the last few decades, researchers studied the energy expenditure in cancer patients, and found that cancer patients had elevated resting energy expenditure, which significantly contributed to the development of malnutrition.[3,4,22,23] In present study, energy expenditure in cancer patients was estimated by taking the basal metabolic rate into consideration. One of the remarkable points in present study was that BMR levels were found to be positively correlated with both MTV (rho= 0.395, p< 0.05)

and TLG (rho= 0.368, p< 0.05) levels in all cancer types. The cut-off values for predicting high BMR level for MTV was higher than 52400 mm^3 and for TLG higher than 274208, and also their respective sensitivity and specificity rates were estimated to be 0.84 and 0.63.

Lactate dehydrogenase (LDH) is a metabolic enzyme widely expressed in different tissues and is detectable in serum, which catalyzes the interconversion of pyruvate and lactate during glycolysis and gluconeogenesis.[24] It has long been known that many human cancers have higher LDH levels compared with normal tissues. In a study carried out on 311 cancer patients, serum LDH levels of higher than 1000 IU/L (four times upper limit of the normal) was used for predicting the terminal stage in metastasis.[25] High serum LDH level was associated with a poor survival in solid tumors and could be used as a useful and inexpensive prognostic biomarker in metastatic carcinomas.[26] Agrawal et al. evaluated the LDH levels in newly diagnosed 83 patients with breast cancer and indicated that increased serum levels of LDH were associated with poor prognosis, surgical outcome or metastatic disease. Persistent high levels of serum LDH or its sudden increase in the preceding six months or more after the surgery may indicate poor outcome or increased risk of metastasis. Thus, high levels of serum LDH in such kind of patients may be considered as an early warning sign of recurrence or metastasis.[27] In present study, both MTV and TLG levels were found to be positively correlated with serum LDH in all cancer types (for MTV: rho= 00.417, p< 0.05; for TLG: rho= 0.365, p< 0.05). Highly sensitive and specific cut-off values were also detected in predicting high LDH for MTV (>219520 mm^3) as 0.88 and 0.70, for TLG as 0.58 and 0.51 (>411792), respectively.

Serum albumin level is one of the most commonly used markers for assessing patients' nutritional status. It is produced in liver as the major protein in blood serving as nutrient transporter, key antioxidant, and detoxifier. In advanced stage patients, biosynthesis of serum albumin is suppressed and indicate a sharp decline due to malnutrition and systematic inflammatory response to tumors.[28] Numerous studies have evaluated the association between albumin and patient survival, and indicated low serum albumin levels as independent indicators for worse survival rates of various cancers. In a large sample size of non-metastatic patients with breast cancer, pretreatment levels of albumin, LDH and bilirubin were evaluated and concluded that they were all prognostic factors for overall survival in non-metastatic breast cancer.[29] In present study, it was clear that albumin levels negatively correlated with both MTV and TLG levels in all cancer types (rho= -0.681, p< 0.05; rho = -0.712, p<0.05, respectively). Highly sensitive and specific cut-off levels were detected in predicting low albumin levels for MTV as 0.63 and 1.00 (<89520 mm^3), and for TLG as 0.75 and 1.00 (<887840), respectively.

Indeed, it was indicated that vitamins C, D, E and some vitamin B types were found to be reduced in cancer patients when compared to healthy populations in such a way that the vitamin C levels decreased enough to cause scurvy-like symptoms in some cancer cases.[3] It has also been reported that reduction of vitamin A and vitamin E was responsible for the increased oxidative stress in cancer patients. Likewise, in present study, the levels of vitamin A, B_1, B_6, B_{12}, E and folic acid were found to be low and such low levels indicated negative correlation with MTV and TLG levels; however, the correlations were not found to be significant. It is known that trace elements play a role as cofactor in many metabolic reactions of the body and especially Fe, Cu, Se, Zn, Ca, Mg, and Cl elements have crucial role and their deficiency/redundancy may cause serious problems in various metabolic activities even in healthy populations.[4] Many essential minerals in cancer patients are markedly reduced, and those having mineral deficiencies can better cope with chemotherapy and radiotherapy after replacement therapy, and hence their performance status and quality of life are improved.[30,31] In present study, MTV and TLG levels were found to be negatively correlated with Zn, Mg, and P deficiencies but not significantly different. On the other hand, several intracellular elements can possibly pass to blood stream as acute phase reactants and sometimes as a consequence of tumoral lysis syndrome. Positively correlated high serum levels of K and Cu with MTV and TLG in the present study can be explained with such a process.

The oxidative pattern monitored in cancer patients is not only related to increased reactive oxygen species (ROS) but also to brazenly consumed antioxidants of healthy tissues and to decreasing amounts of minerals with a role in antioxidant reactions.[32,33] Badjatia et al. reported that serum vitamin C, vitamin E, SOD and GSH-Px levels and antioxidant activity were significantly low ($p< 0.001$); however, TBARS level was significantly high ($p< 0.001$) as compared to control groups.[34] In present study, as indicated in most other cancer studies, declines in serum SOD, GSH-Px, and T-AOC levels were found to be negatively correlated with the indicators of tumoral burden (MTV and TLG). However, only the TLG and GSH-Px levels in lung cancer were found to be significant.

Based on present findings, PET/CT based MTV and TLG values indicating the stage, tumor burden and prognosis of cancer could also be used for reliable and strong prediction of the metabolic abnormalities monitored in cancer patients. Considering the cut-off values for MTV and TLG levels detected in prediction and resultant metabolic abnormalities in newly diagnosed cancer patients, it was concluded that it could be possible to improve the performance status and quality of life of patients as well as providing better tolerance to chemotherapy and radiotherapy. Despite all these reliable and accurate findings, further research is recommended to be carried out with diverse patient groups with specific cancer types to prove the reliability of PET/CT based estimation of metabolic abnormalities in cancer patients.

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Correspondence:
Dr. Aysun ÇETİN
Erciyes Üniversitesi Tıp Fakültesi
Biyokimya Anabilim Dalı
Talas, KAYSERİ / TURKEY

Tel: (+90-352) 207 66 66 – 23288
e-mail: aysuncetin@yahoo.com