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***Original Article** / Özgün Makale*

The prognostic value of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography parameters in patients with malignant pleural mesothelioma

Malign plevral mezotelyomalı hastalarda ^{18}F-florodeoksiglukoz pozitron emisyon tomografi/bilgisayarlı tomografi parametrelerinin prognostik değeri

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ABSTRACT

Background: In this study, we aimed to investigate the prognostic value of metabolic ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography parameters in malignant pleural mesothelioma patients.

Methods: A total of 65 patients with malignant pleural mesothelioma (34 males, 31 females; median age: 60 years; range, 39 to 84 years) who underwent whole-body ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography for staging before treatment between March 2008 and January 2018 were included. Relationships between clinicopathological factors and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography parameters and overall survival were evaluated using a log-rank test and Cox regression analysis.

Results: The median follow-up was 13 (range, 4 to 55) months. The Kaplan-Meier analysis revealed a mean survival time of 17±2.6 months. The cumulative two- and five-year survival rates were 34.8% and 7.8%, respectively. Univariate analysis showed that ≥60 age, left hemithorax involvement, a maximum standardized uptake value of ≥9.8, c-T4 status, c-M1 status, and non-surgery were negatively associated with overall survival ($p<0.05$). Multivariate analysis showed that ≥60 age, left hemithorax involvement, a maximum standardized uptake value of ≥9.8, c-M1 status, and a total lesion glycolysis of ≥180.2 g were negatively associated with overall survival ($p<0.05$).

Conclusion: Metabolic parameters of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography have the potential to provide prognostic information for malignant pleural mesothelioma patients who are receiving surgery and/or chemotherapy.

Keywords: Computed tomography, malign mesothelioma, positron emission tomography, prognostic factor, thoracic surgery.

ÖZ

Amaç: Bu çalışmada malign plevral mezotelyomalı hastalarda ^{18}F-florodeoksiglukoz pozitron emisyon tomografi/bilgisayarlı tomografi parametrelerinin prognostik değeri araştırıldı.

Çalışma planı: Mart 2008 - Ocak 2018 tarihleri arasında tedavi öncesi evreleme için tüm vücut ^{18}F-florodeoksiglukoz pozitron emisyon tomografi/bilgisayarlı tomografisi çekilen malign plevral mezotelyomalı 65 hasta (34 erkek, 31 kadın; medyan yaş: 60 yıl; dağılım, 39-84 yıl) çalışmaya dahil edildi. Log-rank testi ve Cox regresyon analizi ile klinikopatolojik faktörler ve ^{18}F-florodeoksiglukoz pozitron emisyon tomografi/bilgisayarlı tomografi parametreleri ve genel sağkalım arasındaki ilişkiler değerlendirildi.

Bulgular: Ortalama takip süresi 13 (dağılım, 4-55) ay idi. Kaplan-Meier analizi, ortalama sağkalım süresinin 17±2.6 ay olduğu hesaplandı. Kümülatif iki ve beş yıllık sağkalım oranları sırasıyla %34.8 ve %7.8 idi. Tek değişkenli analizde ≥60 yaş, sol hemitoraks tutulumu, ≥9.8 maksimum standardize tutulum değeri, c-T4 durumu, c-M1 durumu ve cerrahi uygulanmamasının genel sağkalım ile olumsuz ilişkili olduğu izlendi ($p<0.05$). Çok değişkenli analizde ≥60 yaş, sol hemitoraks tutulumu, ≥9.8 maksimum standardize tutulum değeri, c-M1 durumu ve ≥180.2 g total lezyon glikolizinin genel sağkalım ile negatif ilişkili olduğu izlendi ($p<0.05$).

Sonuç: ^{18}F-florodeoksiglukoz pozitron emisyon tomografi/bilgisayarlı tomografinin metabolik parametreleri, cerrahi yapılan veya kemoterapi gören malign plevral mezotelyomalı hastalarda prognostik bilgi sağlama potansiyeline sahiptir.

Anahtar sözcükler: Bilgisayarlı tomografi, malign mezotelyoma, pozitron emisyon tomografi, prognostik faktör, göğüs cerrahisi.

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Malignant pleural mesothelioma (MPM) is rare and aggressive malignancy arising from mesothelial cells. It is usually located in the thorax, but it rarely originates from the peritoneum, pericardium, and the tunica vaginalis of the testicles.[1-4] Malignant pleural mesothelioma is often resistant to chemotherapy and radiotherapy with a median survival of less than one year.[5] After 1990s, multimodal treatments including surgery, chemotherapy, and radiotherapy have improved survival in selected patients.[6] Several prognostic factors such as sarcomatous histological type, sex, and performance status have been described in MPM patients.[7,8] From the aspect of the imaging tool, there is only a limited number of data on prognostic factors.[9-11]

The ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) has been utilized to staging of many types of solid tumors.[12-14] Behind standardized uptake value (SUV), prognostic importance of metabolic volumetric parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been described for different tumors.[14-16] In this study, we aimed to evaluate the prognostic value of metabolic ^{18}F-FDG PET/CT parameters in MPM patients.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ankara University Faculty of Medicine between March 2008 and January 2018. A total of 232 consecutive patients with MPM were screened and 65 of them (34 males, 31 females; median age: 60 years; range, 39 to 84 years) who underwent whole-body ^{18}F-FDG PET/CT for initial staging before treatment were included. All patients also underwent routine diagnostic chest and abdominal CT. In all patients, the diagnosis was made based on CT scan-guided Abrams' needle pleural biopsy or by video-assisted thoracoscopic surgery. Pathological diagnosis was based on standard histological, histochemical, and/or immunohistochemical criteria in all patients. Histopathological definitions and assessments were based on the 2004 World Health Organization lung and pleural tumor classification.[7] Routine blood examinations and functional evaluation of the respiratory system, with or without diffusing capacity of the lung for carbon monoxide, and ventilation/perfusion scan and cranial magnetic resonance imaging (MRI)/CT scan were also performed to patients who underwent surgery. A written informed consent was obtained from each patient. The study protocol was approved by the Ankara University School of Medicine Ethics Committee (Approval Date: November 27, 2020, No: İ10-616-20). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The operability was evaluated either clinically or videothoracoscopically based on performance status, pulmonary function, and staging. Echocardiography or cardiac MRI were performed, when necessary. The patients diagnosed as having MPM throughout the study period were followed until death, loss to follow-up, or January 2020. Follow-up was performed based on medical records or consulting the treating physician and occasionally the patients' self-reports.

Radical surgery, including extra-pleural pneumonectomy (EPP) and pleurectomy/decortication (P/D), was performed in patients with resectable Stage I-III MPM who could tolerate aggressive surgery. In the patients who were not candidates for surgical resection, chemotherapy was typically administered with pemetrexed and cisplatin. Palliative radiotherapy was administered, when indicated. Tumor staging was done according to the eighth edition of Tumor, Node, Metastasis (TNM) system of the International Mesothelioma Interest Group.[17]

^{18}F-FDG PET/CT

The ^{18}F-FDG PET/CT images were acquired with a GE Discovery PET/CT 710 series scanner (General Electric, Milwaukee, WI, USA). The patient fasted at least 6 h before imaging and blood glucose levels were checked. Those with a blood glucose above 150 mg/dL did not undergo scanning. Oral contrast was given to all patients. Images from the vertex to the proximal femur obtained, while the patient was in the supine position. The whole-body ^{18}F-FDG PET/CT imaging was performed approximately 1 h after an intravenous injection of 296 to 370 MBq ^{18}F-FDG. During the waiting period, the patient rested in a quiet room without taking muscle relaxants. The PET images were acquired for two min per bed position. The emission PET images were reconstructed with non-contrast-enhanced CT images. The CT images were also obtained from the patient's integrated ^{18}F-FDG PET/CT with the use of a standardized protocol of 120 kV, 70 mA, tube rotation time of 0.5 sec per rotation, a pitch of 1.375, and a slice thickness of 3.3 mm. The patient was allowed to breathe normally during the procedure. Attenuation-corrected PET/CT fusion images were reviewed in three planes (transaxial, coronal

and sagittal) on Advanced Workstation Volume Share 5 (GE Medical Systems Waukesha, WI, USA). The ^{18}F-FDG PET/CT images were evaluated and confirmed visually and semi-quantitatively with SUV by consensus of two experienced nuclear medicine specialists. The MTV (cm^3) was measured using an automatic isocontour threshold method, which is based on a value greater than 40% of SUV_{max} of the primary tumor. The TLG (g) was calculated by multiplying the SUV_{mean} by MTV.

Statistical analysis

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The relationship between sex, age, white blood cell (WBC) count, platelet count, histopathological subtype of tumor, localization of the tumor (right hemithorax involvement/left hemithorax involvement), clinical TNM status, type of treatment, SUV_{max} of pleural surface, MTV, TLG, and overall survival (OS) was analyzed. During statistical analysis, the patients were divided into subgroups according to below and above of the median values for age, WBC count, platelet count, SUV_{max}, MTV, and TLG (Table 1). The median survival was calculated using the Kaplan-Meier method and the results were compared using the log-rank test. To identify the independent risk factors affecting the OS, we used multivariate Cox regression analysis following univariate analysis. A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

The median follow-up was 13 (range, 4 to 55) months. Of a total of 65 patients, 34 (52%) in the epithelial, three (7%) in the sarcomatoid, and nine (13.8%) in the biphasic subtypes were included in the analysis. Nineteen patients (29.2%) had no subtype of MPM. Almost all patients had a history of asbestos exposure. Fifteen patients (23.1%) underwent radical surgery (EPP n=1, P/D n=14). In the radical surgery group, four patients received neoadjuvant chemotherapy, while 11 patients received adjuvant chemotherapy and/or chemoradiotherapy (CRT). Of 50 patients in the non-surgery group, 36 received definitive chemotherapy and 10 received definitive CRT, while four patients did not receive any treatment. No mortality was observed in the early postoperative period. The morbidity rate was 13%.

The primary lesion was located in the right and left hemithorax in 40 (61.5%) and 25 patients (38.5%), respectively. Descriptive data and ^{18}F-FDG PET/CT findings are summarized in Table 2.

A total of 55 patients (85%) died from MPM. The Kaplan-Meier analysis revealed an mean survival time of 17±2.624 (range, 2 to 64) months. The cumulative two- and five-year survival rates were 34.8% and 7.8%, respectively. The overall five-year survival rate and median survival time are shown in Figure 1 and Table 3. There were no statistically significant differences in the OS between the other groups (Table 4).

Univariate analysis identified that ≥60 age (hazard ratio [HR] 2.5, 95% CI: 1.4-4.4), left hemithorax involvement (HR 1.7, 95% CI: 1.1-3.1), SUV_{max} ≥9.8 (HR 2.2, 95% CI: 0.9-6.2), c-T4 status (HR 3.5, 95% CI: 1.3-9.3), c-M1status (HR 6.03, 95% CI: 1.7-20.9), and non-surgery group (HR 0.4, 95% CI: 0.2-0.9) were negatively associated with OS.

Multivariate analysis identified that ≥60 age (HR 2.4, 95% CI: 1.4-4.5), left hemithorax involvement (HR 2.4, 95% CI: 1.3-4.4), SUV_{max} ≥9.8 (HR 1.8, 95% CI: 1.04-3.2), M1 status (HR 6.3, 95% CI: 1.6-24.07), and TLG ≥180.2 g (HR 1.9, 95% CI: 1.09-3.5) were negatively associated with OS (Table 5).

Table 1. Cut-off values for continuous variables

Variables	Min and max range	Group 1	Group 2
Age (year)	39-84	<60	≥60
White blood cell count ($\times10^9$/L)	5-17	<8.75	≥8.75
Platelet count ($\times10^9$/L)	165-699	<346	≥346
Maximum standardized uptake value	3-29.6	<9.8	≥9.8
Metabolic tumor volume (cm^3)	0.6-801	<35.2	≥35.2
Total lesion glycolysis (g)	12.7-8051	<180.2	≥180.2

Table 2. Demographic and clinical characteristics of patients with MPM

Patient characteristics	n	%	Median	Range
Age (year)			60	39-84
<60	31	47.7		
≥60	34	52.3		
Sex				
Male	34	52.3		
Female	31	47.7		
White blood cell count ($\times 10^9$/L)				
<8.75	30	46.2		
≥8.75	35	53.8		
Platelet count ($\times 10^9$/L)				
<346	32	49.2		
≥346	33	50.8		
Maximum standardized uptake value				
<9.8	31	47.7		
≥9.8	34	52.3		
Metabolic tumor volume (cm^3)				
<35.2	32	49.2		
≥35.2	33	50.8		
Total lesion glycolysis (g)				
<180.2	32	49.2		
≥180.2	33	50.8		
Histological subtypes				
Epithelioid	34	52.3		
Non-epithelioid	31	47.7		
Sarcomatoid	3	4		
Biphasic	9	13.8		
Malignant pleural mesothelioma	19	29.2		
Localization of the tumor				
Right hemithorax involvement	40	61.5		
Left hemithorax involvement	25	38.5		
T status				
cT1	40	61.5		
cT2	4	6.2		
cT3	16	24.6		
cT4	5	7.7		
N status				
cN0	34	52.3		
cN1	27	41.5		
cN2	4	6.2		
M status				
cM0	62	95.4		
cM1	3	4.6		
Type of treatment				
Non surgery group				
Chemotherapy	36	55.5		
Chemoradiotherapy	10	15.6		
No additional treatment	4	6.1		
Radical surgery group				
EPP + CRT	1	1.5		
P/D + CRT	9	13.8		
P/D + RT	1	1.5		
Neoadjuvant chemotherapy + P/D + adjuvant CRT	1	1.5		
Neoadjuvant chemotherapy + P/D + adjuvant CT	2	3		
Neoadjuvant chemotherapy + P/D	1	1.5		

EPP: Extra-pleural pneumonectomy; CRT: Chemoradiotherapy; P/D: Pleurectomy/decortication; RT: Radiotherapy; CT: Computed tomography.

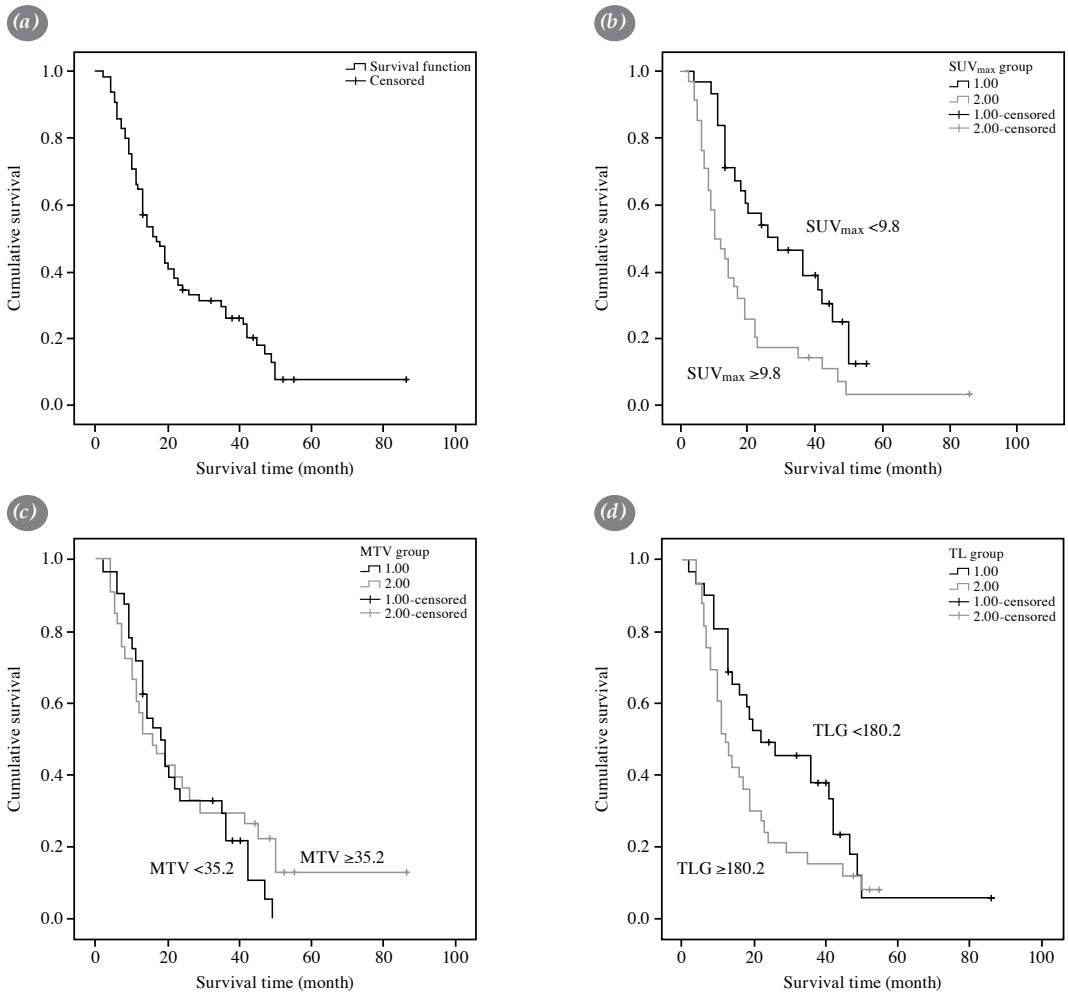

Figure 1. Kaplan-Meier overall survival curves for patients with MPM according to **(a)** all patients, **(b)** SUV_{max} (p=0.002), **(c)** MTV (p=0.483), **(d)** TLG (p=0.085).

SUV_{max}: Maximum standardized uptake value; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis.

Table 3. Kaplan-Meier survival analysis (statistically significant results are shown in the table)

Variables	5 years OS (%)	Median survival (month)	95% CI	*p*
Age <60 years	17.1	24	3.9-44.09	0.001
Age ≥60 years	0	13	10.1-15.8	
Radical surgery	24.9	24	6.1-41.8	0.034
Non-surgery	3	13	9.1-16.8	
Right hemithorax involvement	13.2	22	6.4-37.5	0.041
Left hemithorax involvement	0	14	9.1-18.8	
SUV_{max} <9.8	12.7	29	13.3-44.6	0.002
SUV_{max} ≥9.8	3.7	10	5.4-14.5	
M0	8	18	12.6-23.3	0.001
M1	0	7	2.1-11.8	
T1 vs. T4	8	22	11.2-32.7	0.021
	0	9	2.5-15.4	
T2 vs. T4	25	20	0-42.54	
	0	9	2.5-15.4	

OS: Overall survival; CI: Confidence interval; SUV_{max}: Maximum standardized uptake value.

Table 4. Kaplan Meier survival analysis with log-rank test

	p
Sex	0.339
Histological subtypes of MPM	0.194
c-N status	0.677
WBC count	0.156
Platelet count	0.343
MTV	0.483
TLG	0.085

MPM: Malignant pleural mesothelioma; WBC: White blood cell; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis.

DISCUSSION

The management of patients with MPM is extremely challenging and overall reported survival is less than one year.[5] In our study, the Kaplan-Meier analysis revealed a mean survival time of 17±2.6 months. The cumulative two- and five-year survival rates were 34.8% and 7.8%, respectively.

The mean age of patients with MPM is approximately 60 years; however, it may vary depending on genetic factors and environmental/industrial asbestos exposure. The male-to-female ratio is 4:1 with a predominance of right side over the left (60:40).[18,19] The best-known clinical prognostic scoring systems for MPM was developed by the European Organisation for Research and Treatment of Cancer (EORTC) and the Cancer and Leukemia Group B, and the use a combination of biological and clinical factors. Poor performance status, non-epithelioid histology, male sex, low hemoglobin, high platelet count, high WBC count, and high lactate dehydrogenase were found to be poor prognostic indicators in MPM, and subsequently validated.[20,21] In our study, we found the five-year OS rate to be 17.1% and 0% with a median OS time of 24 months and 13 months in <60 age and ≥60 age, respectively (p=0.001). The five-year OS was 13.2% and 0% with a median OS time of 22 months and 14 months in right hemithorax involvement and left hemithorax involvement group, respectively (p=0.041). Univariate and multivariate analysis identified that ≥60 age and left hemithorax involvement were negatively associated with OS.

Table 5. Univariate and multivariate Cox regression models

	Univariate		Multivariate	
Variables	*p*	Hazard ratio	*p*	Hazard ratio
Sex	0.351	1.2 (0.7-2.2)	0.802	1.08 (0.5-2.09)
Age	0.002	2.5 (1.4-4.4)	0.004	2.4 (1.4-4.5)
White blood cell count	0.961	0.6 (0.4-2.1)	0.637	0.8 (0.4-1.7)
Platelet count	0.296	0.7 (0.4-1.3)	0.071	0.5 (0.3-10.48)
Localization of the tumor	0.048	1.7(1.1-3.1)	0.005	2.4 (1.3-4.4)
SUV_{max}	0.003	2.2 (0.9-6.2)	0.035	1.8 (1.04-3.2)
Metabolic tumor volume	0.492	0.8 (0.4-1.4)	0.934	1.03(0.4-2.2)
Total lesion glycolysis	0.095	1.5 (0.9-2.6)	0.024	1.9 (1.09-3.5)
Histological subtypes of MPM	0.206	1.4 (0.8-2.3)	0.889	1.06 (0.4-2.3)
c-T status	0.035		0.419	
c-T2	0.907	0.9 (0.2-3.07)	0.195	2.6 (0.6-11.6)
c-T3	0.051	1.8 (0.9-3.4)	0.313	1.5(0.6-3.8)
c-T4	0.012	3.5 (1.3-9.3)	0.519	0.6 (0.1-2.7)
c-N status	0.690		0.416	
c-N1	0.466	1.2 (0.7-2.1)	0.193	0.4 (0.1-1.4)
c-N2	0.537	1.3 (0.4-3.9)	0.575	0.6 (0.1-2.9)
c-M status	0.005	6.03 (1.7-20.9)	0.007	6.3 (1.6-24.07)
Type of treatment	0.042	0.4 (0.2-0.9)	0.152	0.5 (0.1-1.2)

SUV_{max}: Maximum standardized uptake value; MPM: Malignant pleural mesothelioma.

Rusch et al.[22] reported that T stage, N stage, and M stage significantly affected survival, with the exception of T1 and T2 and N1 and N2 in an international database analysis.[22] In our study, significant differences were found between c-T1 vs. T4, c-T2 vs. T4 and c-M0 vs. M1 in terms of five-year survivals. Univariate analysis identified that c-T4 status and c-M1 status were negatively associated with OS. Multivariate analysis revealed that M1 status was negatively associated with OS.

Multimodal treatment of MPM with surgery, radiotherapy, and neoadjuvant or adjuvant chemotherapy is the sole path to extended survival for selected patients with favorable prognostic factors. If MPM is in a resectable stage (Stage I-III), macroscopic complete resection via EPP or P/D is the basic concept for surgical approach.[17] The preoperative cardiorespiratory evaluation is necessary for the selection of EPP or P/D cases using the following measurements: pulmonary function test, diffusion capacity, pulmonary scan, complete cardiological study with a stress test for inducible myocardial ischemia, echocardiogram with Doppler, and pulmonary artery measurement.[22] In our study, we found the five-year OS to be 24.9% and 3% with a median OS time of 24 and 13 months in radical surgery group and non-surgery group, respectively (p=0.034). Univariate analysis revealed that non-surgery group was negatively associated with OS.

The ^{18}F-FDG PET/CT is a non-invasive imaging modality which has the ability to visualize and quantify the glucose metabolism of malignancies including MPM. It can be utilized to distinguish malignant from benign pleural effusion and it has better diagnostic consistency than contrast-enhanced CT.[23] The reported SUV_{max} for malignant effusions in the literature ranges between 1.2 and 27.2.[9,24] These wide variations may be due to pleural thickness differences and histopathological subtypes evaluated. Despite its limitations, ^{18}F-FDG PET/CT seems to be superior to other imaging methods in the diagnosis of MPM. Flores et al.[25] incorporated SUV_{max} into a prognostic model with stage and histology, suggesting that a SUV_{max} of >10 was associated with poor prognosis. Similarly, the SUV_{max} was an independent predictor of survival in two other patient series, with cut-off values of 10.7 and 5, respectively.[26,27] In contrast, Nowak et al.[28] reported that FDG-PET volumetric parameters significantly predicted survival, whereas the SUV_{max} did not. In our study, all patients with MPM showed detectable FDG uptake (median SUV_{max} =9.8). In particular, baseline total glycolytic volume was included in a nomogram of pre-treatment prognostic factors for MPM. Recently, Klabatsa et al.[29] confirmed TLG and histology as independent prognostic factors, whereas Hooper et al.[30] found baseline total glycolytic volume to be an independent predictor of worse OS in this disease.[31] Moreover, Kadota et al.[32] reported that the baseline level of SUV_{max} could also identify the subgroup having a worse prognosis among patients with epithelial histologyy.

Hooper et al.[30] evaluated metabolic PET parameters in 21 MPM patients who received platinum/pemetrexed chemotherapy. They accepted metabolic response as 25% drop in the SUV_{max}, SUV_{mean}, and TLG and reported no prognostic effect of metabolic response after chemotherapy. However, the authors reported that baseline SUV_{max} and SUV_{mean} were found to predict for OS. Finally, they concluded that baseline SUV_{max} >15 and SUV_{mean} >5 were indicators of poor prognosis. Similarly, Lee et al.[33] evaluated pre-treatment PET parameters in 13 MPM patients. They found a significant difference in MTV between subgroups with and without tumor progression. In their multivariate analysis adjusted for treatment modality showed that MTV and TLG were independent factors associated with tumor progression. In the current study, we additionally attempted to describe pre-treatment prognostic factors in our specific epidemic MPM patient group. In the same geographic region, Ozmen et al.[9] reported the results of 51 patients. The authors did not mention the epidemic nature of their sample, but found pleural thickening greater than 13 mm, SUV_{max} higher than 8.6, and MTV greater than 112 cm^3 were associated with poor survival. In our study, we found the five-year OS to be 12.7% and 3.7% with a median OS time of 29 months and 10 months in the patient groups with a SUV_{max} of <9.8 cm^3 and SUV_{max} of ≥9.8 cm^3, respectively (p=0.002). On univariate and multivariate analyses revealed that a SUV_{max} of ≥9.8 and a SUV_{max} of ≥9.8 and TLG ≥180.2 g to be negatively associated with OS, respectively.

The initial experience for recently developed integrated PET/MRI systems for MPM was reported from Germany.[10] The evaluation of SUV_{mean} on ^{18}F-FDG PET/CT and apparent diffusion coefficient (ADC) on PET/MRI showed that there was an inverse correlation between the SUV_{mean} and ADC_{min}. As a novel diagnostic tool, future perspectives of PET/MRI in MPM patients should be well-defined, as well as other tumors.

The limitation of present study; this study was retrospectively performed with patients enrolled from a single center. Therefore, further studies with

multi-center and long-term follow-up are necessary to validate the results of the study.

In conclusion, our study results show that the maximum standardized uptake value, a metabolic positron emission tomography-derived parameter, has a significant prognostic value in patients with malignant pleural mesothelioma. Total lesion glycolysis also appears to be an independent prognostic indicator. Metabolic parameters of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography have the potential to provide prognostic information for malignant pleural mesothelioma patients who are receiving surgery and/or chemotherapy. Despite the limited number of studies and sample sizes, metabolic positron emission tomography parameters seem to have a prognostic value in malignant pleural mesothelioma. Further large-scale, prospective studies are needed to confirm these findings.

Declaration of conflicting interests

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REFERENCES

1. Robinson BW, Lake RA. Advances in malignant mesothelioma. N Engl J Med 2005;353:1591-603.
2. Baris YI, Saracci R, Simonato L, Skidmore JW, Artvinli M. Malignant mesothelioma and radiological chest abnormalities in two villages in Central Turkey. An epidemiological and environmental investigation. Lancet 1981;1:984-7.
3. Baris I, Simonato L, Artvinli M, Pooley F, Saracci R, Skidmore J, et al. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: a four-year study in the Cappadocian region of Turkey. Int J Cancer 1987;39:10-7.
4. Metintas M, Hillerdal G, Metintas S, Dumortier P. Endemic malignant mesothelioma: exposure to erionite is more important than genetic factors. Arch Environ Occup Health 2010;65:86-93.
5. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-44.
6. Sugarbaker DJ, Heher EC, Lee TH, Couper G, Mentzer S, Corson JM, et al. Extrapleural pneumonectomy, chemotherapy, and radiotherapy in the treatment of diffuse malignant pleural mesothelioma. J Thorac Cardiovasc Surg 1991;102:10-4.
7. Pass HI, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, et al. Supplementary prognostic variables for pleural mesothelioma: a report from the IASLC staging committee. J Thorac Oncol 2014;9:856-64.
8. Tsim S, Kelly C, Alexander L, McCormick C, Thomson F, Woodward R, et al. Diagnostic and Prognostic Biomarkers in the Rational Assessment of Mesothelioma (DIAPHRAGM) study: protocol of a prospective, multicentre, observational study. BMJ Open 2016;6:e013324.
9. Ozmen O, Koyuncu A, Koksal D, Tatci E, Alagoz E, Demirag F, et al. The potential value of volume-based quantitative PET parameters and increased bone marrow uptake for the prediction of survival in patients with malignant pleural mesothelioma. Nucl Med Commun 2016;37:43-9.
10. Schaarschmidt BM, Sawicki LM, Gomez B, Grueneisen J, Hoiczyk M, Heusch P, et al. Malignant pleural mesothelioma: initial experience in integrated (18)F-FDG PET/MR imaging. Clin Imaging 2016;40:956-60.
11. Rusch VW, Gill R, Mitchell A, Naidich D, Rice DC, Pass HI, et al. A multicenter study of volumetric computed tomography for staging malignant pleural mesothelioma. Ann Thorac Surg 2016;102:1059-66.
12. Gallamini A, Zwarthoed C, Borra A. Positron emission tomography (PET) in oncology. Cancers (Basel) 2014;6:1821-89.
13. Rockall AG, Cross S, Flanagan S, Moore E, Avril N. The role of FDG-PET/CT in gynaecological cancers. Cancer Imaging 2012;12:49-65.
14. Zhu A, Lee D, Shim H. Metabolic positron emission tomography imaging in cancer detection and therapy response. Semin Oncol 2011;38:55-69.
15. Yamamoto M, Tsujikawa T, Fujita Y, Chino Y, Kurokawa T, Kiyono Y, et al. Metabolic tumor burden predicts prognosis of ovarian cancer patients who receive platinum-based adjuvant chemotherapy. Cancer Sci 2016;107:478-85.
16. Obara P, Pu Y. Prognostic value of metabolic tumor burden in lung cancer. Chin J Cancer Res 2013;25:615-22.
17. Berzenji L, Van Schil PE, Carp L. The eighth TNM classification for malignant pleural mesothelioma. Transl Lung Cancer Res 2018;7:543-9.
18. Weder W, Opitz I. Multimodality therapy for malignant pleural mesothelioma. Ann Cardiothorac Surg 2012;1:502-7.
19. Connelly RR, Spirtas R, Myers MH, Percy CL, Fraumeni JF Jr. Demographic patterns for mesothelioma in the United States. J Natl Cancer Inst 1987;78:1053-60.
20. Fennell DA, Parmar A, Shamash J, Evans MT, Sheaff MT, Sylvester R, et al. Statistical validation of the EORTC prognostic model for malignant pleural mesothelioma based on three consecutive phase II trials. J Clin Oncol 2005;23:184-9.
21. Edwards JG, Abrams KR, Leverment JN, Spyt TJ, Waller DA, O'Byrne KJ. Prognostic factors for malignant mesothelioma in 142 patients: validation of CALGB and EORTC prognostic scoring systems. Thorax 2000;55:731-5.
22. Rusch VW, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, et al. Initial analysis of the international association for the study of lung cancer mesothelioma database. J Thorac Oncol 2012;7:1631-9.
23. Sugarbaker DJ, Wolf AS. Surgery for malignant pleural mesothelioma. Expert Rev Respir Med 2010;4:363-72.
24. Sun Y, Yu H, Ma J, Lu P. The Role of 18F-FDG PET/CT integrated imaging in distinguishing malignant from benign pleural effusion. PLoS One 2016;11:e0161764.

25. Flores RM, Akhurst T, Gonen M, Zakowski M, Dycoco J, Larson SM, et al. Positron emission tomography predicts survival in malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2006;132:763-8.
26. Gerbaudo VH, Mamede M, Trotman-Dickenson B, Hatabu H, Sugarbaker DJ. FDG PET/CT patterns of treatment failure of malignant pleural mesothelioma: relationship to histologic type, treatment algorithm, and survival. Eur J Nucl Med Mol Imaging 2011;38:810-21.
27. Abakay A, Komek H, Abakay O, Palanci Y, Ekici F, Tekbas G, et al. Relationship between 18 FDG PET-CT findings and the survival of 177 patients with malignant pleural mesothelioma. Eur Rev Med Pharmacol Sci 2013;17:1233-41.
28. Nowak AK, Francis RJ, Phillips MJ, Millward MJ, van der Schaaf AA, Boucek J, et al. A novel prognostic model for malignant mesothelioma incorporating quantitative FDG-PET imaging with clinical parameters. Clin Cancer Res 2010;16:2409-17.
29. Klabatsa A, Chicklore S, Barrington SF, Goh V, Lang-Lazdunski L, Cook GJ. The association of 18F-FDG PET/CT parameters with survival in malignant pleural mesothelioma. Eur J Nucl Med Mol Imaging 2014;41:276-82.
30. Hooper CE, Lyburn ID, Searle J, Darby M, Hall T, Hall D, et al. The South West Area Mesothelioma and Pemetrexed trial: a multicentre prospective observational study evaluating novel markers of chemotherapy response and prognostication. Br J Cancer 2015;112:1175-82.
31. Zucali PA, Lopci E, Ceresoli GL, Giordano L, Perrino M, Ciocia G, et al. Prognostic and predictive role of [18 F]fluorodeoxyglucose positron emission tomography (FDG-PET) in patients with unresectable malignant pleural mesothelioma (MPM) treated with up-front pemetrexed-based chemotherapy. Cancer Med 2017;6:2287-96.
32. Kadota K, Kachala SS, Nitadori J, Suzuki K, Dunphy MP, Sima CS, et al. High SUVmax on FDG-PET indicates pleomorphic subtype in epithelioid malignant pleural mesothelioma: supportive evidence to reclassify pleomorphic as nonepithelioid histology. J Thorac Oncol 2012;7:1192-7.
33. Lee HY, Hyun SH, Lee KS, Kim BT, Kim J, Shim YM, et al. Volume-based parameter of 18)F-FDG PET/CT in malignant pleural mesothelioma: prediction of therapeutic response and prognostic implications. Ann Surg Oncol 2010;17:2787-94.