

¹⁸F-FDG PET/CT in therapy response and in predicting responders or non-responders in malignant pleural mesothelioma patients, by using semi-quantitative mRECIST and EORTC criteria

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Abstract

Objective: To evaluate the role of fluorine-18-fluorodeoxyglucose positron emission tomography/ computed tomography (¹⁸F-FDG PET/CT) in therapy response assessment according modified response evaluating criteria of solid tumors (mRECIST) and the predictive role of volume-based semi-quantitative parameters in patients with malignant pleural mesothelioma (MPM). Furthermore modified RECIST criteria for MPM mRECIST and the European Organization for Research and Treatment of Cancer (EORTC) criteria were compared and the predictive role of ¹⁸F-FDG PET/CT in the post-therapy outcome. **Subjects and Methods:** Thirty five selected patients with MPM underwent ¹⁸F-FDG PET/CT scan at baseline (1) and after therapy (2). Semi-quantitative ¹⁸F-FDG PET/CT parameters were collected for each scan and also differences (Δ) Δ SUVmax, Δ SUVav, Δ MTV, Δ TLG, response index (RI)max% and RIav% were evaluated. Radiologic response to therapy was assessed by using the mRECIST and EORTC. **Results:** The correlation between response to therapy assessed by EORTC and mRECIST criteria was moderate ($K=0.418$; 95%CI:0.099-0.736). According to mRECIST, statistical differences between responders and non-responders were significant in the analysis of semi-quantitative parameters. According mRECIST criteria, all parameters defined a good area under the curve (AUC) but the better AUC resulted for Δ MTV (cut-off ≤ 11.3 , sensitivity=91.3%, specificity=91.7%) and Δ TLG (cut-off ≤ 59.1 , sensitivity=82.6%, specificity=100%). Kaplan-Meier curves between responders and non-responders did not show statistically significant differences. **Conclusion:** The semi-quantitative analysis of ¹⁸F-FDG PET/CT has an important role in MPM therapy response assessment and has a predictive role in distinguishing responders and non-responders.

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Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive tumor with high mortality, strictly connected to asbestos exposure with a 20-30 years time lag in the onset. Mesothelioma incidence varies markedly from one country to another; the highest annual crude incidence rates (about 30 cases per million) are observed in Australia, Belgium, and Great Britain. Due to the large use of asbestos in the 1970s-1980s, recently MPM incidence has grown and further increase is expected [1-3]. Chemotherapy with Cisplatin and Pemetrex represents the first line care in patients with MPM, whereas extra-pleural pneumonectomy and radiotherapy are useful in specific clinical conditions [4-6].

Currently, contrast enhancement computed tomography (CECT) is the gold standard imaging technique in MPM assessment. However, since the pleural surface is not a solid organ and the pleural lining has a complex shape, CT imaging may have some difficulties in depicting real tumor extension, because of adjacent pleural effusion or atelectasis and thus in determining the T stage of MPM. In addition, true tumor volume in MPM is a critical factor in determining patients' prognosis and response after therapy [7-9]. The response evaluation criteria in solid tumor (RECIST) used until few years ago are considered only morphologic criteria and the circumferential growth pattern of MPM [10-12]. An alternative measurement protocol specified as "modified RECIST" for MPM (mRECIST) has been proposed and has become the standard protocol in MPM [13-15], although its use did not completely overcome the difficulties in response interpretation [16, 17].

Fluorine-18-labelled fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) plays a critical role in MPM staging, therapeutic strategy decision and prediction of prognosis [18-21]. Recently, ¹⁸F-FDG PET/CT achieved an impor-

tant role also in therapy response assessment, thanks to some semi-quantitative parameters. Volume based parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), allow to better fit to MPM the therapy response assessment, showing the real tumor burden [22].

The purpose of our study was to evaluate the role of ^{18}F -FDG PET/CT in therapy response assessment according the mRECIST criteria and the European Organization for Research and Treatment of Cancer (EORTC) criteria compared. Furthermore, we studied the predictive role of ^{18}F -FDG PET/CT in the post-therapy outcome of patients with MPM. This is the first similar study in which both semi-quantitative criteria of mRECIST and EORTC were evaluated in cancer patients.

Subjects and Methods

Study population

We selected retrospectively 35 patients with histological proven MPM. All patients had initial diagnosis of epithelioid MPM and underwent conventional diagnostic procedures (e.g. thoracic RX, blood biomarker, CT).

The selected patients underwent baseline total body CECT and ^{18}F -FDG PET/CT at the moment of the diagnosis and also post-therapy, at least 6 weeks after the end of treatment (chemotherapy and/or radiotherapy). The interval between the two methods was approximately 3.1 days (range 1-7 days) both in the baseline and post-therapy study.

The following exclusion criteria were applied: patients who received talc pleurodesis within 1 month from PET/CT in order to exclude the acute phase of inflammation; age younger than 18 years old; history of further malignancy. Written informed consent was obtained from all patients. Characteristics of the 35 selected patients are reported in Table 1.

Table 1. Clinical characteristics of patients' cohort

Characteristics	Value
Total, n	35
Sex, n	
Male/Female	25/10
Age (years)	
Mean \pm SD	68.29 \pm 8.05
Range	52-83
Stage, n	
I	15
II	20
Therapy	
Chemotherapy (2 lines)	28
Chemotherapy + Radiotherapy Both	7

Imaging techniques

CECT imaging

Contrast enhancement computed tomography examinations were performed with a 16-slice CTMD equipment (TSX-101 $^{\circ}$, Aquilion 16, Toshiba Medical Systems, Tokyo, Japan) using the following acquisition parameters: slice thickness 1mm, pitch 1.75, increment 0.6mm, rotation time 0.5s, kV/mAs 120/250. All examinations included intravenous (i.v.) contrast enhancer administration.

^{18}F -FDG PET/CT

Images were acquired with a combined modality PET/CT Discovery LSA (GE Healthcare, Waukesha, Wisconsin, USA) that integrates a PET (advance nxl) with 16-slice CT scanner (light speed plus). Prior to administration of ^{18}F -FDG, all patients fasted for at least 8h and had a capillary blood glucose of <160mg/mL. The image acquisition was obtained 50min after the i.v. injection of 4.0MBq/kg of ^{18}F -FDG. Patients were hydrated by drinking 500mL of water. The CT acquisition parameters were: 340mA (auto), 120kV, slice thickness 3.75mm, tube rotation time 0.8ms and collimation field of view (FOV) 50cm. The CT images were reconstructed with a filtered back-projection. The CT data were used for attenuation correction of PET scanning, which was performed immediately after the acquisition of CT images. The PET acquisition was obtained in caudal-cranial direction, carried out from the external acoustic meatus to the root of the thigh; PET was reconstructed with a matrix of 128x128, ordered subset expectation maximum iterative reconstruction algorithm (two iterations, 28 subsets), 8mm Gaussian filter, and 50cm field of view.

Rigorous quality controls were performed to ensure correct and stable semi-quantitative parameters properly comparable.

Imaging interpretation

CECT image analysis

Contrast enhancement computed tomography baseline and post-therapy images were analyzed by two radiologists with 8 years of experience each. Therapy response assessment was performed according to mRECIST and to EORTC criteria.

Patients were classified as: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Complete response was defined as disappearance of all target lesions with no evidence of tumor elsewhere. Stable disease was defined as neither meeting the criteria of PR nor PD [11, 14-16]. Partial response was defined as a reduction of at least 30% in the total tumor measurement. Progressive disease was defined as an increase of at least 20% in total tumor measured size over the nadir, or as the appearance of one or more new lesions.

^{18}F -FDG PET/CT image analysis

Fluorine-18-FDG PET/CT images were analyzed qualitatively and semi-quantitatively by using "MultiVol PET/CT" program of AdvantageTM Workstation (GE Healthcare, Waukesha, Wisconsin, USA). Two nuclear physicians with 8 years

of experience blindly analyzed both baseline and post-therapy ^{18}F -FDG PET/CT images.

Semi-quantitative parameters were collected both on ^{18}F -FDG PET/CT scan baseline and after therapy.

Volumes of interest (VOI) were semi-automatically drawn on each pleural area with elevated ^{18}F -FDG uptake. Volumes of interest were drawn to include all pleural areas with ^{18}F -FDG uptake without overlap of MPM tumor boundaries; so the number of VOI depended on the extension of MPM.

Standardized uptake value maximum and average (SUVmax and SUVav) were collected from the VOI with the highest value.

In order to assess response to treatment, SUV at the baseline (SUV1) and the post-therapy (SUV2) scans were employed to calculate the difference ΔSUV ($\text{SUV1}-\text{SUV2}$) and the response index ($\text{RI}=[(\text{SUV1}-\text{SUV2})/\text{SUV1}]\times 100$); ΔSUV were calculated both for SUVmax and SUVav (ΔSUVmax and ΔSUVav) as well as the RI (RI_{max} and RI_{av}).

Metabolic tumor volume was calculated automatically for each VOI by using a threshold of 40% of SUVmax, as reported in the literature [23, 24]. Metabolic tumor volume value both baseline (MTV1) and post-therapy (MTV2) was obtained by adding MTV values of all VOI drawn for each scan.

Total lesion glycolysis at baseline (TLG1) and post-therapy (TLG2) scans were calculated as: $\text{SUVav}\times\text{MTV}$.

Response assessment

Evaluation of response to therapy was performed according to mRECIST criteria. Patients were classified into 2 groups, the "mRECIST responders" including CR and PR patients and "mRECIST non-responders" including SD and PD patients.

Response to therapy was also evaluated according to the EORTC criteria and patients were classified into the groups of "PET/CT responders" if $\text{RI}_{\text{max}} \geq 25\%$ and "PET/CT non-responders" if $\text{RI}_{\text{max}} < 25\%$ [25].

Representative images of a responder and a non-responder patient, according both to mRECIST and EORTC criteria, are shown in Figures 1 and 2, respectively.

Statistical analysis

Each ^{18}F -FDG PET/CT semi-quantitative parameter (at baseline and post-therapy and the differences between two scans) were compared between "mRECIST responders" and "mRECIST non-responders" using Student's t test for independent samples; P value < 0.05 was considered indicative of a significant difference.

Receiver operating characteristic (ROC) analysis was performed to evaluate the semi-quantitative ^{18}F -FDG PET/CT parameters in predicting therapy response.

The correlation between response to therapy assessed by mRECIST criteria and by EORTC criteria was calculated by Cohen's K coefficient.

Survival curves were estimated using the Kaplan–Meier method.

All statistical analysis was carried out using IBM SPSS Statistics for Mac OS, version 20.0, 2012.

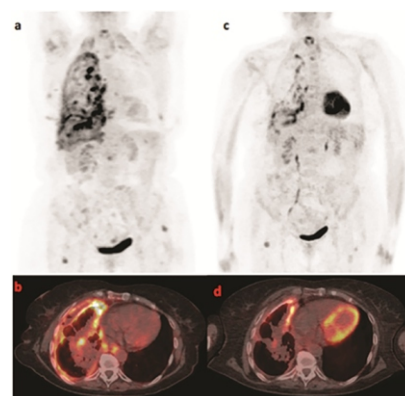


Figure 1. A female, age 77 patient with relapsed MPM evaluated as "mRECIST and EORTC responders". Images of ^{18}F -FDG PET/CT maximal intensity projection (MIP) a and axial b images showed intense ^{18}F -FDG uptake in the right pleural profile and in the thoracic nodes. Semi-quantitative parameters were: $\text{SUV}_{\text{max1}}=15.6$, $\text{SUV}_{\text{av1}}=8.3$, $\text{MTV1}=257.11$, $\text{TLG1}=2134.01$. Fluorine-18-FDG PET/CT MIP c and axial d: ^{18}F -FDG uptake reduction in right pleural profile; semi-quantitative parameters: $\text{SUV}_{\text{max2}}=8.3$, $\text{SUV}_{\text{av2}}=4.4$, $\text{MTV2}=58.24$, $\text{TLG2}=256.256$. Analysis of the difference between the two scans showed: $\Delta\text{SUV}_{\text{max}}=7.3$, $\Delta\text{SUV}_{\text{av}}=3.9$, $\text{RI}_{\text{max}}=46\%$, $\text{RI}_{\text{av}}=46\%$, $\Delta\text{MTV}=198.87$ and $\Delta\text{TLG}=1877.757$.

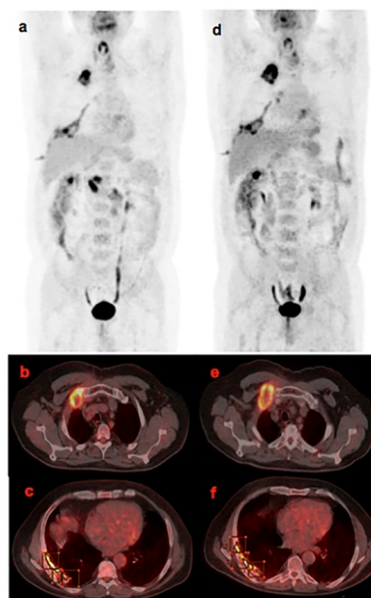


Figure 2. A non-responder patient, male, aged 72 with relapsed MPM by "mRECIST and by EORTC criteria". Fluorine-18-FDG PET/CT MIP and axial baseline a, b, c and post therapy d, e, f images show intense ^{18}F -FDG uptake in right pleural profile. Semi-quantitative parameters: $\text{SUV}_{\text{max1}}=13.5$, $\text{SUV}_{\text{av1}}=7.7$, $\text{MTV1}=34.04$, $\text{TLG1}=262.108$, $\text{SUV}_{\text{max2}}=18.5$, $\text{SUV}_{\text{av2}}=9.9$, $\text{MTV2}=90.29$ and $\text{TLG2}=893.871$. Analysis of the difference between the two scans showed $\Delta\text{SUV}_{\text{max}}=-5.0$, $\Delta\text{SUV}_{\text{av}}=-2.2$, $\text{RI}_{\text{max}}=-37\%$, $\text{RI}_{\text{av}}=-28\%$, $\Delta\text{MTV}=-56.25$ and $\Delta\text{TLG}=-631.763$.

Results

Response to therapy according to mRECIST criteria

Patients "mRECIST responders" were 12/35 while "mRECIST non-responders" were 23/35.

Among "mRECIST responders" 8/12 were PR, 4/12 CR; among

"mRECIST non-responders": 13/23 were SD, 10/23 PD.

Semi-quantitative ^{18}F -FDG PET/CT parameters

The average values for all ^{18}F -FDG PET/CT parameters are shown in Table 2.

Table 2. ^{18}F -FDG PET/CT analyses in the population studied.

^{18}F -FDG PET/CT	Parameter	Mean \pm SD (Range)
Baseline	SUVmax1	9.7 \pm 4.11 (2.8-18.5)
	SUVav1	5.56 \pm 2.39 (1.6-10.2)
	MTV1 (cm ³)	130.09 \pm 135.75 (8.5-413.3)
	TLG1	665.50 \pm 687.69 (18.7-2219.1)
Post-therapy	SUVmax2	12.05 \pm 6.4 (1.9-31.1)
	SUVav2	7.2 \pm 4.04 (1.1-19.5)
	MTV2 (cm ³)	91.87 \pm 64.67 (3.1-215.39)
	TLG2	807.27 \pm 950.01 (3.41-3036.99)
Difference between the two scan	ΔSUVmax	-2.38 \pm 7.03 (-21.8-9.1)
	ΔSUVav	-1.6 \pm 4.29 (-13.7-6.1)
	RImax%	-38.35 \pm 77.71 (-234-88.34)
	RIav%	-49.09 \pm 99.09 (-236-73)
	ΔMTV	-22.13 \pm 47.54 (-160.05-62.37)
	ΔTLG	443.18 \pm 926.96 (-3612.66-2172.4)

Comparison of ^{18}F -FDG PET/CT semi-quantitative parameters showed statistically significant differences between "mRECIST responders" and "mRECIST non-responders" for all parameters except for SUVmax1 ($P=0.90$) and SUVav1 ($P=0.94$), as reported in Table 3.

Receiver operating characteristic analysis of post-treatment ^{18}F -FDG PET/CT semi-quantitative parameters showed good diagnostic capability for all of them (Figure 3a); ROC analysis of Δ values showed good diagnostic capability for all parameters, but better performance was detected for ΔMTV (cut-off \leq 11.3, sensitivity 91.3%, specificity 91.7%) and ΔTLG (cut-off \leq 59.1, sensitivity 82.6%, specificity 100%) (Figure 3b).

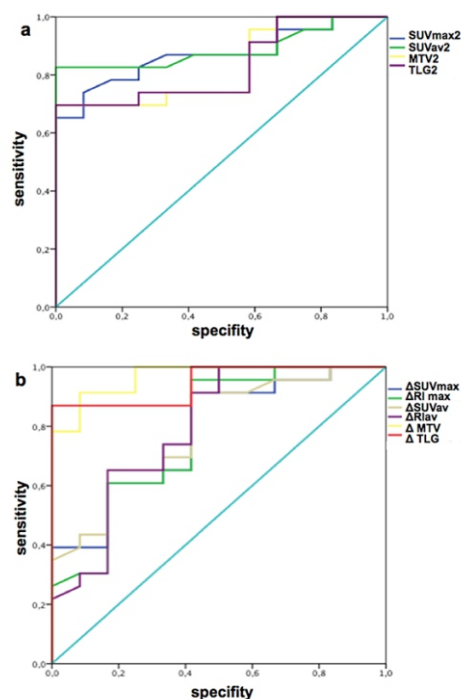


Figure 3. **a.** The ROC curves of semi-quantitative parameters of the post-treatment ^{18}F -FDG PET/CT showed good diagnostic capability for all parameters. **b.** The ROC curves of Δ values of the semi-quantitative parameters showed good diagnostic capability for all parameters, better for ΔMTV and ΔTLG .

Response to therapy according to EORTC criteria

According to EORTC criteria, "PET/CT responders" patients were 13/35 while "PET/CT non-responders" were 22/35.

The concordance between response to therapy assessed by ^{18}F -FDG PET/CT between EORTC and mRECIST criteria was moderate ($K=0.418$; 95% CI: 0.099-0.736).

Survival results

Survival was calculated from the date of the end of the last treatment to the date of the last follow-up or till death.

Patients were followed-up for an average period of 25.8 months (range 3 to 60 months). At the end of the follow-up period 16/35 patients were still alive, while 19/35 patients were dead. Among "mRECIST responders" 9/12 patients were alive while 3/12 patients were dead. Among "mRECIST non-responders", 10/23 patients were alive while 13/23 patients were dead. Median survival in "mRECIST responders" was 27 months (95%CI: 20.7 to 33.2), while in "mRECIST non-responders" was 24 months (95%CI: 11.4 to 36.5).

Among "PET/CT responders" 7/13 patients were alive while 6/13 patients were dead. Among "PET/CT non-responders" 10/22 patients were alive while 12/22 patients were dead.

Table 3. ^{18}F -FDG PET/CT parameters in patients "responders" and "non-responders" according to mRECIST.

^{18}F -FDG PET/CT	Parameter	mRECIST Non Responders Mean \pm SD (Range)	mRECIST Responders Mean \pm SD (Range)	Student's t test	P
Baseline	SUVmax1	9.66 \pm 4.1 (2.8-18.5)	9.84 \pm 4.19 (4.3-15.6)	-0.116	0.90
	SUVav1	5.54 \pm 2.43 (1.6-10.2)	5.6 \pm 2.44 (2.0-8.5)	-0.065	0.948
	MTV1 (cm ³)	69.75 \pm 55.92 (8.5-187.03)	245.74 \pm 158.72 (15.81-413.3)	-3.73	0.03
	TLG1	383.39 \pm 347.32 (18.7-1375.586)	1206.22 \pm 857.40 (131.223-2219.1)	-3.259	0.006
Post-therapy	SUVmax2	12.05 \pm 6.4 (3.7-31.1)	6.03 \pm 2.4 (1.9-8.9)	3.994	0
	SUVav2	7.2 \pm 4.04 (2.0-19.5)	3.3 \pm 1.2 (1.1-4.9)	4.21	0
	MTV2(cm ³)	91.87 \pm 64.67 (18.78-215.39)	28.74 \pm 23.40 (3.1-58.24)	4.186	0
	TLG2	807.27 \pm 950.01 (36.55-3036.99)	114.28 \pm 98.35 (3.41-256.256)	3.463	0.002
Difference between the two scans	Δ SUVmax	-2,38 \pm 7,03 (-21.8-8.7)	3.8 \pm 4.03 (-2.6-9.1)	-2.835	0.008
	Δ SUVav	-1.6 \pm 4.29 (-13.7-4.1)	2.25 \pm 2.56 (-1.9-6.1)	-2.906	0.006
	RI _{max} %	-38.35 \pm 77.71 (-234-47)	25.83 \pm 49.05 (3.3-88.34)	-2.594	0.014
	RI _{av} %	-49,09 \pm 99.09 (-236-41)	24.5 \pm 53.74 (-69-73)	-2.385	0.023
	Δ MTV	-22.13 \pm 47.54 (-160.05-62.37)	217.00 \pm 160.27 (-66.45-47.55)	-5.132	0
	Δ TLG	-443.18 \pm 926,96 (-3612.66-435.43)	1091.93 \pm 847.81 (123.22-2172.4)	-4.783	0

ders" 13/22 patients were alive while 9/22 patients were dead. Median survival in "PET/CT responders" was 26.4 months (95%CI: 20.3 to 34.4), while in "PET/CT non-responders" was 23 months (95%CI: 11.1 to 33.2).

Kaplan Meier curves of "mRECIST responders" compared to "mRECIST non-responders" did not show statistically significant differences, as well as "PET/CT responders" compared to "PET/CT non-responders".

Discussion

Given the particular growth pattern of MPM, characterized by 'rind' around the hemithorax and along interlobar fissures [2], standard RECIST criteria resulted to be not appropriate

in the therapy response evaluation. Currently "mRECIST criteria" represent the mesothelioma guidelines of reference but even they don't fit adequately to the complete evaluation of MPM [11, 14-16].

The SUVmax is already known as a significant prognostic factor and a guide of treatment response evaluation in many malignant tumors and is the most validated semi-quantitative ^{18}F -FDG PET/CT parameter [25, 26]. Despite this, SUVmax role is still debated. In a study of 57 patients, Niccoli et al. (2013) concluded that ^{18}F -FDG PET/CT through SUVmax is a useful tool to evaluate the metabolic response to chemo-radiotherapy and to monitor the follow-up in MPM [27]. The measurement of SUVmax represents a simple method not strictly dependent on the size of the VOI drawn, however, it expresses only pixels with the highest ^{18}F -FDG concentration in the VOI, and does not reflect the heterogeneous nature and the irregular shape of the tumor.

Our results showed a difference statistically significant in Δ SUVmax and Δ SUVav. between the mRECIST responders and non-responders groups, confirming that the SUV values are reliable parameters for treatment response evaluation of MPM patients.

On the other hand, there is an increasing interest in the use of semi-quantitative ^{18}F -FDG PET/CT parameters, like MTV and TLG, able to measure the metabolic activity in the entire tumor volume and potentially being more sensitive than SUVmax [21, 23, 26].

Metabolic tumor volume and TLG are three-dimensional (3D) measurements, which incorporate the total tumor volume and its metabolic activity. The role of volume-based ^{18}F -FDG PET/CT parameters were already studied for several tumors such as lung cancer, colorectal cancer, and glioma [23, 28-36]. Currently there is not a consensus about the method of measurement of these parameters, especially for MPM [37].

It has been reported that MTV was calculated using commercially available workstation, through a single rectangular VOI on the entire corresponding hemithorax, excluding possible interferences from kidneys and myocardium by subtracting a second VOI positioned over them [38]. Lee et al. (2010) calculated MTV through an automatic VOI, using an isocontour threshold based on liver SUVmean, but the most published methods used a fixed threshold too [39, 40]. The method of the single VOI is poorly suited to MPM patients because of the characteristic plaque-like tumor mass and also the problems associated with differentiating tumor from adjacent tissues and organs, such as chest wall, mediastinum, heart and liver.

The evaluation of semi-quantitative parameters requires a very rigorous and precise method that has to be replicable, reliable and not operator-dependent. In our study we chose a fixed threshold and calculated MTV by adding MTV of every VOI drawn in order to cover the whole extent of the tumor and to eliminate possible interferences by other organs. This small time-consuming method, yields a more precise calculation of MTV, and consequently also of TLG, revealing the real metabolic status of the entire neoplastic process.

In a study of 131 MPM patients, some authors demonstrated that Δ SUVmax and Δ TLG are useful in predicting therapy response according to mRECIST criteria, in particular they considered an interim ^{18}F -FDG PET/CT study [41]. In our study, even if on a smaller number of patients, all parameters analyzed were predictive of the treatment response, confirming the significant correlation of the metabolic changes on ^{18}F -FDG PET/CT with treatment efficacy. In particular, Δ MTV and Δ TLG were the best predictors, because they reflected the burden of the entire tumor. This result also suggests the necessity to perform both baseline and post-treatment ^{18}F -FDG PET/CT scans with the same rigorous and precise method.

We found a statistically significant difference between "mRECIST responders" and "mRECIST non-responders" for all parameters except for SUVmax1 and SUVav1. Furthermore, we evidenced that MTV1 and TLG1 were statistically different between the responders and non-responders mRECIST groups, because they also reflected the metabolic differences in the whole tumor mass such as necrosis areas

that could invalidate treatment efficacy.

European Organization for Research and Treatment of Cancer criteria for distinguishing treatment responders from non-responders in MPM are also based on ^{18}F -FDG PET/CT imaging considering the SUVmax as the reference parameter and are easier to applying respect to mRECIST criteria [15, 25]. Despite this and their moderate concordance with mRECIST criteria, the EORCT criteria cannot be applied routinely for MPM because they have not yet been validated by a large MPM population study.

The survival in MPM patients is extremely different depending on the treatments applied and can be longer than 30 months in case of multimodality treatments [42].

A study by Ceresoli et al. (2006), showed a longer overall survival in patients who were ^{18}F -FDG PET/CT metabolic responders [43]. In another study, Francis et al. (2007), concluded that Δ TLG was significantly related to survival [22]. Schaefer et al. (2012), in a study of 41 patients, showed that mRECIST had higher correlation with the overall survival than ^{18}F -FDG PET/CT [44, 45].

In our study the survival was in accord with other papers in medical literature and we didn't find any difference statistically significant between responders and non-responders, neither for mRECIST criteria, nor for EORCT criteria. This could be explained by the small number of our patients studied that is anyway appropriate considering the rarity of the MPM and the selective inclusion criteria.

In conclusion, our study suggested the important role of ^{18}F -FDG PET/CT in therapy response assessment of MPM. The semi-quantitative analysis of ^{18}F -FDG PET/CT using the mRECIST and less the EORCT criteria has a predictive role in distinguishing responders and non-responders to treatment MPM patients.

The authors declare that they have no conflicts of interest

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