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Feasibility and performance of an adaptive contrast-oriented 18F-FDG PET/CT quantification technique for global disease assessment of malignant pleural mesothelioma and a brief review of the literature

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Abstract

Objective: Treatment of malignant pleural mesothelioma (MPM) remains very challenging. Assessment of response to treatment is necessary for modifying treatment and using new drugs. Global disease assessment (GDA) by implementing image processing methods to extract more information out of positron emission tomography (PET) images may provide reliable information. In this study we have shown the feasibility of this method of quantification in patients with MPM, and compared it with the conventional techniques. We also presented a review of the literature about this topic. **Methods**: Nineteen subjects with histologically proven MPM who had undergone fluoride-18-fluorodeoxyglucose PET/computed tomography (18F-FDG PET/CT) before and after treatment were included in this study. An adaptive contrast-oriented thresholding algorithm was used for the image analysis and quantification. Metabolic tumor volume (MTV), maximum and mean standardized uptake volume (SUVmax, SUVmean) and total lesion glycolysis (TLG) were calculated for each region of interest. The global tumor glycolysis (GTG) was obtained by summing up all TLG. Treatment response was assessed by the European Organisation for Research and Treatment of Cancer (EORTC) criteria and the changes of GTG. Agreement between global disease assessment and conventional method was also determined. **Results**: In patients with progressive disease based on EORTC criteria, GTG showed an increase of 150.7 but in patients with stable or partial response, GTG showed a decrease of 433.1. The SUVmax of patients before treatment was 5.95 (SD:2.93) and after the treatment it increased to 6.38 (SD:3.19). Overall concordance of conventional method with GDA method was 57%. Concordance of progression of disease based on conventional method was 44%, stable disease was 85% and partial response was 33%. Discordance was 55%, 14% and 66%. **Conclusions**: Adaptive contrast-oriented thresholding algorithm is a promising method to quantify TLG in patients with MPM. We were able to assess MTV, TLG, SUVmax, tumor SUVmean and GTG for this particular tumor. Also we were able to demonstrate the potential use of this technique in the monitoring of treatment response. More studies comparing this technique with conventional and other global disease assessment methods are needed in order to clarify its role in the assessment of treatment response and prognosis of these patients.

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor of serosal surfaces, such as the peritoneum and the pleura, almost uniformly fatal within a year of diagnosis [1, 2]. Imaging in MPM plays a critical role in diagnosis, prediction or monitoring of response to therapy, prognostication and monitoring of disease recurrence after aggressive treatment [3] but the particular morphology and asymmetric growth create difficulties and challenges in the assessment of this disease.

Currently, contrast-enhanced computed tomography (cCT) is the primary modality for the staging and assessment of treatment response and although it is fairly accurate at differentiating normal tissue from disease, it may underestimate regional and distant metastasis and the degree of local invasion. Also, a measurable response is not usually detectable by CT until after multiple cycles of chemotherapy and the standard for MPM tumor response assessment (manual acquisition of linear tumor thickness across a series of CT examinations) has a high inter-observer variability rate and does not take into account the viability of tumor tissue. Because of that, standard Response Evaluation Criteria In Solid Tumors (RECIST) criteria have been felt to be an inadequate method to yield reliable imaging biomarkers. Byrne et al (2004) [4] have proposed a modified RECIST, based on two CT-measurements of tumor thickness perpendicular to the chest wall at three different levels. This seems to represent an improvement in the accuracy of response as-

Original Article

sessment but it still falls short in depicting the total tumor burden and subtle growth extension in non-axial planes such as along the pleural fissures and it is still based on structure and takes no account of the viability of tumor masses [1].

In recent years, fluorine-18-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) scans are gaining popularity in the management of mesothelioma. In different studies various quantitative and qualitative parameters including standardized uptake value (SUV), total lesion glycolysis (TLG), and metabolic tumor volume (MTV) have been suggested as reliable biomarkers in survival models and response to treatment assessment [1, 3, 5].

The concept of global disease assessment (GDA) was first introduced by Alavi et al (1993) [6] in assessment of the brain in patients with Alzheimer's disease and then was investigated in a variety of disorders for the past two decades [5, 7-13]. Francis et al (2007) [5], for the first time used volume-based parameters such as MTV and TLG, and reported that these parameters predicted overall survival better than SUVmax and also objective response on cross-sectional imaging.

The aim of this study was to evaluate a quantitative global disease assessment method using on an adaptive contrast-oriented thresholding algorithm in patients with MPM and to compare that with the conventional methods.

Subjects and methods

Nineteen subjects (7 women and 12 men; median age: 65 years, range 39-83 years) with histologically proven MPM who had undergone ^{18}F-FDG PET/CT before and after treatment were included in this study. We excluded patients who had undergone pleurodesis or prior chemotherapy or surgery. Two consecutive PET scans in each patient were studied and analyzed. The mean time between the two scans was 150±102 days. This retrospective study was performed at the Hospital of the University of Pennsylvania following Institutional Review Board approval and Health insurance portability and accountability act (HIPAA) waiver.

PET/CT image acquisition
All PET/CT scans were acquired using a 16-detector row LYSO whole-body PET/CT scanner with time-of-flight capabilities (Gemini TF, Philips Healthcare, Bothell, WA). 3D PET data were acquired from the skull base to mid thighs ~60 minutes after intravenous (IV) administration of 444-555MBq of ^{18}F-FDG for 3minutes per bed position. All subjects fasted for at least 6 hours before ^{18}F-FDG injection, and serum glucose levels were verified to be <200mg/dL prior to IV administration of ^{18}F-FDG. The system model included time-of-flight as well as normalization, attenuation, random, and scatter corrections. Rescaled low-dose CT images were utilized for attenuation correction of PET images. Images of PET and CT were reconstructed at 4mm nominal slice thickness.

Imaging and quantitative data analysis
To measure tumor metabolic response, we measured MTV, SUVmax, SUVmean and TLG of ^{18}F-FDG avid thoracic lesions on both before and after treatment PET/CT scans. To accomplish this, we employed an adaptive contrast-oriented thresholding algorithm [14-18], which permits delineation of the boundaries of lesions based on PET images alone. This modified adaptive thresholding delineation technique automatically combines determined background correction and local adaptive thresholding in an iterative algorithm model [14-17] (ROVER software, ABX, Radeberg, Germany). The performance of this methodology has previously been investigated in various settings [7, 14, 17, 19-22]. This approach improves the ability of calculating the disease burden by combining both volumetric and metabolic characteristics of the disease rather than factoring these parameters independently. In addition to semi-automatic measurements, we also utilized standard approaches of measurement of SUVmean and SUVmax of the mesothelioma tumor by means of image visualization and analysis software (Extended Brilliance Workstation, Philips Healthcare, Bothell, WA). The global tumor glycolysis (GTG) was obtained by summing up TLG of each region of interest (ROI).

To classify patients based on the conventional method, an expert nuclear medicine physician compared SUVmax of the pre and post treatment images according to recommendations of the European Organisation for Research and Treatment of Cancer (EORTC) PET study group [23]. A complete metabolic response was defined as resolution of ^{18}F-FDG uptake within the tumor volume so that it was indistinguishable from surrounding normal tissue. A partial metabolic response was defined as a 25% or more reduction in tumor ^{18}F-FDG uptake. Progressive metabolic disease was defined as an increase in tumor SUVmax 25% or more within the ROI defined on the baseline scan, or the appearance of new ^{18}F-FDG uptake in another region. Patients with an increase in tumor SUVmax of less than 25% or a decrease of less than 25% were classified as stable metabolic disease. To classify patients based on GTG, we used a method, which was suggested by Veit-Haibach et al (2010) [24].

Statistical analysis
To summarize the variables of this study, standard descriptive statistics were calculated (mean, standard deviation, 95% confidence interval). To compare the values of before and after treatment, paired t-test or Wilcoxon signed-rank test were used. Analysis was performed using Stata 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

Results

We noticed a decrease in GTG after treatment, from 979.7 (SD±510.5) before treatment to 823.32 (SD± 325) after treatment. In patients with progressive disease based on EORTC criteria (n=9), GTG showed an increase of 150.7 but in patients with stable (n=7) or partial response (n=3) based on EORTC criteria, GTG showed a decrease of 433.1. The SUVmax of patients before treatment was 5.95 (SD±2.93) and after the treatment it increased to 6.38 (SD±3.19). The MTV increased (37.5cc) in patients with progressive disease based on EORTC criteria and decreased (19.3cc) in patients with stable or par-

Original Article

tial response disease. However, these changes were not statistically significant.

Based on changes in GTG (Table 1), 5 patients had progressive disease, 8 patients had stable disease and 6 cases were classified as partial response. An example of a patient with partia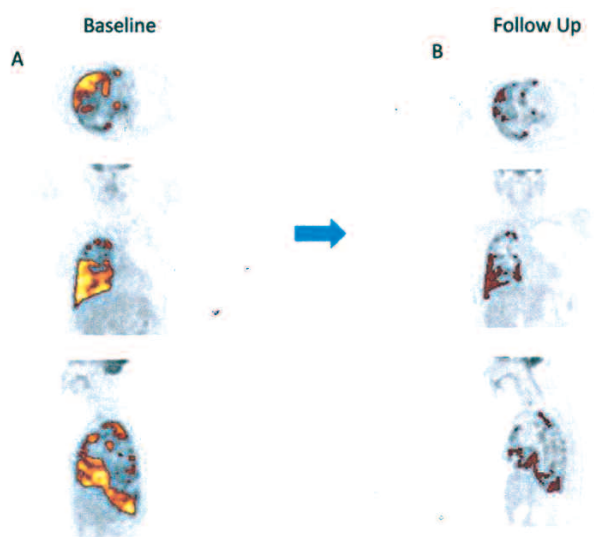l response can be seen in Figure 1. Overall concordance of conventional method with GDA method was 57% (11/19). Concordance of progression of disease based on conventional method was 4/9, stable disease was 6/7 and partial response disease was 1/3. Likewise, discordance was 5/9, 1/7 and 2/3 in the same order.

Figure 1. The images demonstrate the ability of a semi-automatic adaptive thresholding method to segment active disease in the pleura. In this patient (No. 10) with extensive right pleural mesothelioma, ^{18}F-FDG PET images were performed at baseline (A), and two months follow-up (B) of the patient in transaxial, coronal, and sagittal planes. As seen above, there is partial response of disease activity from the baseline to the follow-up study.

Discussion

Fluorine-18-FDG PET/CT has been used for the investigation of MPM in several aspects. It shows an optimal disease characterization, high negative predictive value for the diagnosis, superior disease staging, optimal monitoring of treatment response (Table 2), and accurate assessment of target volume for radiotherapy planning. Ceresoli et al (2006) [25] reported one of the earliest studies investigating the role of ^{18}F-FDG PET in treatment response evaluation in patients with MPM. They used ^{18}F-FDG PET in 20 patients to assess treatment response (palliative chemotherapy with a pemetrexed-based regimen) and patient outcome in the early course of treatment. They compared the variation of SUVmax with modified-RECIST criteria and found that early metabolic response, after 2 cycles of chemotherapy, was significantly correlated to median time-to-tumor progression (TTP) for metabolic responders of 14 months versus 7 months for non-responders, but no correlation was found between TTP and anatomic response assessed by CT.

Although, SUV as an observer-independent measure is commonly used for semi-quantitative analysis of PET images [37], it has some limitations and it cannot necessarily describe

Table 1. *Response to treatment*

No.	Sex	Age	Conventional method %SUVmax variation	GDA	1rst PET/CT GTG	2nd PET/CT GTG	% GTG variation
Patients with progressive disease based on EORTC criteria						
1	M	71	50.00	Stable	469	417	-11.09
2	F	68	62.79	Stable	316	383	21.20
3	M	53	30.30	Progression	100.1	134.3	34.17
4	»	73	36.5	Progression	222.3	346	55.65
5	F	69	45.1	Progression	95.6	346.5	262.45
6	»	78	63.89	Partial response	605.8	266.9	-55.94
7	M	72	38.81	Progression	601.1	2437.6	305.52
8	»	83	27.03	Partial response	611	352	-42.39
9	»	69	40.00	Partial response	464.5	158.4	-65.90
Patients with stable disease based on EORTC criteria						
10	F	72	-14.5	Partial response	9910.1	6174.9	-37.69
11	M	44	5.17	Stable	304.5	331.7	8.93
12	F	69	-3.57	Stable	118.5	145.8	23.04
13	M	65	11.76	Stable	208.3	194.3	-6.72
14	»	58	17.68	Stable	171	159.8	-6.55
15	F	39	-15.38	Stable	293.9	312.1	6.19
16	»	45	-16	Stable	257.8	269.3	4.46
Patients with partial response based on EORTC criteria						
17	M	83	-43.55	Partial response	2406.1	792.6	-67.06
18	»	57	-55.32	Progression	352	891	153.13
19	»	66	-5.4	Progression	1107.7	1528	37.94

GDA: Global disease assessment; GTG: Global tumor glycolysis; SUVmax: standardized uptake volume

Original Article

Table 2. *Studies used ^{18}F-FDG PET for treatment response assessment and prognostication in patients with MPM*

Study (first authors, year)	Clinical setting	No	Evaluated parameters	Findings and conclusions
Bernard F, 1999 [26]	Prognostic value of ^{18}F-FDG PET	22	SUVmax	SUV were highly correlated survival after the PET study (r=0.87, P<0.05). Survival distribution of the high SUV group showed shorter survivals compared with the low SUV group (P<0.01). Patients with high active mesotheliomas in ^{18}F-FDG PET imaging have a poor prognosis.
Flores RM, 2005 [27]	Staging and prognosis	63	SUVmax	High SUV tumors were associated with a 3.3 times greater risk of death than low SUV tumors (P=0.03). SUV>4 and mixed histology are poor risk factors. ^{18}F-FDG PET can be used to stratify patients for treatment and clinical trials.
Flores RM, 2006 [28]	SUV value and prediction of survival	137	SUVmax> 10: high uptake SUVmax, 10: low uptake	Median survivals were 9 and 21 months for the high and low SUV groups, respectively (P=0.02). In a high SUV value tumors were associated with a 1.9 times greater risk of death than low SUV tumors (P=0.01) SUV>10 is a poor risk factor.
Ceresoli GL, 2006 [25]	Prediction of response and patient outcome early in the course of treatment	20	SUVmax variation EORTC criteria CT	Early Metabolic Response was correlated to median time-to-tumor progression (TTP) for metabolic responders of 14 months versus 7 months for non responders (P=0.02). No correlation was found between TTP and radiologic response evaluated by CT. Patients with a metabolic response had longer overall survival.
Francis RJ, 2007 [5]	Assessment of response to chemotherapy in patients with mesothelioma. Early prediction after 1 cycle	23	TGV SUVmax Modified RECIST	TGV is feasible and may predict response to chemotherapy and patient survival after 1 cycle of treatment. Fall in TGV and improved patient survival was correlated (P=0.015). Neither a reduction in the SUVmax (P=0.09) nor CT (P=0.1) demonstrated a significant association with patient survival.
Lee ST, 2009 [29]	Prognostic value Correlate histopathological subtype with SUVmax	46	SUVmax	Patients without metastases had better survival (P=0.05). Mean SUVmax of primary pleural lesions on patients with metastatic disease was significantly higher than in patients without metastatc disease (P=0.05). Patients with extrathoracic metastasis had a significantly higher SUVmax in the primary pleural.
Yan TD, 2009 [30]	Evaluate prognostic features of long-term survivors	42	None	Preoperative PET scan was strongly associated with 18 months survivors (P=0.012).
Nowak AK, 2010 [31]	Quantitative ^{18}F-FDG PET has prognostic information and contributes to construct a new nomogram	89	CT SUVmax (EORTC good and bad prognosis) TGV	Significant prognostic factors: TGV on ^{18}F-FDG PET (P=0.003), EORTC "good" prognostic score (P=0.05). TGV was more predictive than CT stage in both

Original Article

Author, Year	Aim	N	Parameters	Results
				pleurodesed (TGV, P=0.01; CT, P=0.04) and then SUVmax (P=0.055). A nomogram was presented: TGV contributed and CT-assessed tumor-node-metastasis stage did not contributed.
Lee HY, 2010 [32]	Assessing volume-based parameters of ^{18}F-FDG PET/CT for prediction or response and patient outcome	13	SUVmax, SUVmean, TLG MTV	Between subgroups with and without progression, differences were noted in MTV (P=0.045).The difference between the 2 subgroups in terms of SUVmax and SUVmean was not significant. MTV and TLG showed good predictive performance for tumor progression. MTV (HR 1.003, P=0.025) and TLG (HR 1.001, P=0.031) were independent factors associated with tumor progression. Time to tumor progression was shorter in patients with a high volume-based parameter of PET than in those with a low value.
Veit-Haibach P, 2010 [24]	Therapy response evaluation concerning prediction of survival after 3 cycles of therapy	41	Modified RECIST, EORTC criteria TLG Tumor volume (PETvol)	None of the baseline CT-initial PET-parameters were predictive for survival. CT-response was related to OS (P=0.001). SUVmax-response (P=0.61) and SUVmean-response (P=0.68) were not related to survival. A decrease of TLG and PETvol was predictive (TLG: P=0.01; PETvol: P=0.002). Modified RECIST by CT as and response evaluation by TLG and PETvol in ^{18}F-FDG PET, but not SUVmax-measurements are predictive for survival.
Genestreti G, 2012 [33]	Treatment response evaluation in patients with pleurodesis and chemotherapy	8	Modified RECIST-SUVmax: EORTC criteria Tumor SU-Vmean (volume)	There was a concordance between the radiologic and metabolic SUVmean and SUVmax responses in 6 (75%) and 3 (37.5%) patients, respectively. Response measured by SUVmean seems to be in better agreement with the radiologic response compared to the SUVmax.
Schaefer NG, 2012 [34]	Continued pemetrexed and platin-based chemotherapy treatment response/ overall survival [5]	41	Modified RECIST, SUVmax (EORTC criteria), TLG ^{18}F-FDG volume (PETvol)	SUVmax: high variance change in SUVmax did not predict OS. Mod RECIST had higher correlation with OD than TLG/PET volume. TLG/PETvol, compared to the pre-therapeutic scan, is predicting a continuous response and a longer overall survival.
Terada T, 2012 [35]	Clinical utility of PET in diagnosis and survival	47	SUVmax (cut level: 3.5)	The difference in overall survival between the groups with SUVmax levels lower and higher than 3.5 was significant (P=0.02).
Tsutani Y, 2012 [36]	Usefulness of PET/CT after neoadjuvant chemotherapy to predict prognosis with respectable malignant mesothelioma	50	SUVmax (EORTC criteria)	No correlation was observed between overall survival [5] and radiologic response. Metabolic responders correlated to OS. SUVmax decrease (HR 0.80; 95% CI, 0.67-0.95; P=0.01) was independent prognostic factor for OS.

TLG: Total lesion glycolysis; PETvol: PET volume; TGV: Total glycolytic volume; MTV: Metabolic tumor volume. Different studies used different terms for equivalent concepts. The terms "TGV" and "MTV", "TLG" and GTG" are interchangeable.

Original Article

the total tumor activity, for tumors with irregular and diffuse distribution [38, 39]. Because of that, some parameters including SUVpeak, SUVmean, MTV and GTG have been suggested as alternative measures. Alavi et al (1993) [6] introduced the concept of GDA in 1993. This concept has been used in several studies in various types of cancers with promising results. These studies have shown that the volume-based PET parameters are useful indices of tumor burden and they are potentially useful parameters for the prognostication and evaluation of treatment response in cancer patients [9, 12, 13, 19, 37, 40]. Fonti et al (2012) showed that the measurement of tumor burden using the MTV in patients with multiple myeloma is a useful prognostic tool to predict progression free and overall survival [8]. Lim et al (2012) found that volume-based parameters of ^{18}F-FDG PET (MTV and TLG were important prognostic factors in patients with oropharyngeal squamous cell carcinoma [9].

In this study we showed the feasibility of a new method of global disease assessment based on an adaptive thresholding algorithm, for image segmentation that permits delineation of tumor lesions based on PET images to provide MTV, TLG, SUVmean, and SUVmax. Mean GTG of all patients decreased from the pretreatment ^{18}F-FDG PET to the post treatment PET scan; however, it increased in patients with progressive disease and decreased in patients with partial response or stable disease, based on the EORTC criteria.

The growth pattern of mesothelioma provides a challenge in the measurement of response to chemotherapy and prognosis by morphological RECIST, modified-RECIST, and conventional metabolic techniques (EORTC criteria), which all show discordant results in different studies (Table 2). Based on that, we believe that GDA could be used for assessing patients with mesothelioma quantifying the global tumor activity and not only the most active tumor location which could be variable in the same patient and not always show the real general tumor growth. Our preliminary data show feasibility of this method for assessing disease activity in this particular malignancy.

A few other methods have been suggested to calculate ^{18}F-FDG PET global disease burden parameters. In one of the earliest reports, Francis et al (2007) [5] studied 23 patients to assess the early treatment response after 1 cycle of chemotherapy using modified-RECIST on CT, the SUVmax and the volume-based parameter total glycolytic volume (TGV) from ^{18}F-FDG PET. They showed that TGV is a useful measure in mesothelioma. They used a semiautomated 3D volume-based region-growing algorithm to calculate the volume-based parameters. They found a statistically significant relationship between a fall in TGV and improved patient survival. The reduction of SUVmax and CT did not show association with survival. Following that Nowak et al (2010) used the same method to quantify the volume-based parameters in ^{18}F-FDG PET [31]. They studied 89 patients with MPM who had undergone CT and ^{18}F-FDG PET treated and followed for survival and proposed a new prognostic model for MPM. They found that TGV on ^{18}F-FDG PET, sarcomatoid subtype, weight loss of more than 10kg, and EORTC "good" prognostic score were significant prognostic factors. Furthermore, TGV contributed to the presented predictive model in patients with nonsarcomatoid histology

but CT-assessed tumor-node-metastasis stage did not.

Following this first approach, some other groups have used the concept of the GDA in order to assess the treatment response or the prognosis in patients with MPM. Schaefer et al (2012) [34] studied 41 patients after continued pemetrexed and platinum-based chemotherapy treatment and compared modified-RECIST, SUV variation (EORTC criteria), SUVmean, TLG and tumor volume (PETvol). They showed that SUVmax had a high variance over time for individual patients and variation in SUVmax did not predict overall survival. Morphological response in CT using modified-RECIST had highest correlation with overall survival and predicted survival up to the 15th cycle of continued pemetrexed and platin-based treatment. Total Lesion Glycolysis and PETvol, compared to the pre-therapeutic scan, predicted a continuous response and a significant longer overall survival but these parameters only predicted overall survival up to the 6th cycle. Veit-Haibach et al (2010) [24], studied 41 patients comparing modified RECIST, SUVmax variation, SUVmean, TLG and PETvol assessing the therapy response and prediction of survival after three cycles of chemotherapy. They found that overall survival was related to CT response but not to SUVmax variation or to SUVmean response. However a decrease of TGV and PETvol was predictive. They also proposed new thresholds (< -25%, -25% until -75% and > -75% reduction) for TLG and PETvol, showing predictive value too. In these two later studies, similar methods were used to quantify the volume-based parameters. They used a commercially available workstation (General Electrics Advanced Workstation, USA) to draw a rectangular volume of interest (VOI) over the corresponding hemithorax. The VOI margins covered the whole area in all three planes. They separated the kidneys and the myocardium from hemithorax VOI with a second VOI positioned over them and subtracted the values of these VOI from the first VOI. The minimal SUV within the hemithorax VOI was set to a level of 2.5.

Lee HY et al (2010) [32] studied 13 patients who were scheduled to undergo curative extrapleural pneumonectomy or palliative chemotherapy based in SUV max, SUVmean, TLG and MTV. They used volume viewer software on a commercial workstation (GE Advantage Workstation 4.4 USA). This software provided an automatic method to delineate the VOI, using an isocontour threshold method based on SUV. They calculated MTV, SUVmax, and SUVmean of the primary tumor. The total tumor volume segmented via threshold SUV of liver mean SUV plus 2 standard deviations was defined as MTV. They found that between subgroups with and without progression, significant differences were noted in MTV. In contrast, the difference between the 2 subgroups in terms of SUVmax and SUVmean was not significant. Metabolic tumor volume and TLG showed good predictive performance for tumor progression and were independent factors associated with it.

Our study had some limitations. First, because of the retrospective nature of this study we could not control the parameters of how and when the patients received their scans and treatment. In addition, we did not include data about clinical outcome of patients in this study. Future prospective studies with larger number of subjects as well as prognostic and survival information are needed to assess the real role

Original Article

of global disease assessment parameters and to determine which of these methods is better to quantify the global burden of MPM using ^{18}F-FDG PET/CT.

In conclusion, this study showed that adaptive contrast-oriented thresholding approach is a promising method to quantify TLG in patients with mesothelioma. With this method we are able to assess the MTV, TLG, SUVmax, tumor SUVmean and the GTG for this particular tumor. Furthermore, we are able to find differences of these parameters between pre-treatment and post-treatment images demonstrating their potential use in the monitoring of treatment response. More studies comparing this technique with conventional and other global disease assessment methods are needed in order to appreciate its role in the treatment response and prognosis of these patients.

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Domenico Ghirlandaio (1449-1494): Senile man with rhinophyma with his grandson (1488). An imaginary landscape is seen through the window. Tempera in wood, Louvre Museum, Paris.