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Monitoring of Chemotherapy Response in Malignant Pleural Mesothelioma

Tatsuo Kimura, Shinzoh Kudoh and Kazuto Hirata
Department of Respiratory Medicine, Graduate School of Medicine
Osaka City University
Japan

1. Introduction

Malignant pleural mesothelioma (MPM), typically associated with asbestos exposure, is an insidious neoplasm with findings of malignant unilateral pleural effusion or increase in pleural thickness (Jaurand and Fleury-Feith, 2005; Sterman and Albelda, 2005). Currently, imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are widely used to evaluate the effects of chemotherapy on thoracic tumors. However, evaluation of the clinical response of MPM is difficult because it exhibits a non-spherical growth pattern and irregular edges.

MPM shows some technical problems to measure sizes of tumors in determining the response to chemotherapy. Cross-sectional CT or MRI appears inadequate for measuring the size of non-spherical tumors such as MPM. Response evaluation criteria in solid tumor (RECIST) criteria determine the method for measuring the longest diameter of the tumor (Therasse et al., 2000), but the appropriateness of these methods to MPM has not been determined. Recently, modified RECIST criteria were reported (Byrne and Nowak, 2004). Modified RECIST criteria determine the method of measuring tumor thickness perpendicularly to the chest wall or mediastinum in nonspherical tumors.

In positron emission tomography (PET), altered glucose metabolism is visualized using the radiolabeled glucose analogue ^{18}F-fluoro-2-deoxy-D-glucose (FDG). Evaluation of glucose metabolism using FDG-PET plays a critical role in early tumor diagnosis, staging, therapeutic strategy, and prognosis prediction (Kalff et al., 2001; Pieterman et al., 2000; Swisher et al., 2004; Vansteenkiste et al., 1998). FDG-PET imaging to evaluate responses to chemotherapy or irradiation is useful for patients with a variety of carcinomas (Kostakoglu and Goldsmith, 2003; Mac Manus et al., 2003). However, few studies involving MPM patients have been performed to assess the usefulness of FDG-PET for monitoring treatment responses (Ceresoli et al., 2006; Francis et al., 2007; Steinert et al., 2005; Veit-Haibach et al., 2010). Here, we present a case involving the use of FDG-PET for monitoring responses to chemotherapy in a patient with MPM. FDG-PET and CT were performed before chemotherapy and after the first and second courses of chemotherapy. The tumor lesion exhibited shrinkage according to CT and a decrease in the SUVmax after the first course of chemotherapy, but exhibited size enlargement with an increase in SUVmax after the second

course of chemotherapy. These findings suggest that quantification of metabolic responses using FDG-PET may be related to the objective response as determined by modified RECIST in patients with MPM. We also discuss current data regarding FDG-PET in the clinical management of MPM.

2. Case

A 56-year-old non-smoking man was referred to our medical center for further examination of massive pleural effusion in the right lobe according to chest radiography. He had a 6-month history of dyspnea and had been diagnosed with tuberculous pleuritis. He was treated with tuberculous drugs without improvement. His height was 162 cm, and his body weight was 63.5 kg, with no body weight loss in the preceding 6 months. He worked as a bus driver for 30 years without known asbestos exposure. Results of physical examination were nearly normal, and he exhibited no weakness of breath sounds in the right lung. Results of full hematological and biochemistry testing were all within normal limits, except for γGTP of 67 IU/L due to fatty liver. CRP was not elevated, and tumor markers CEA, NSE, and pro-GRP were all within normal ranges; CYFRA 21-1 was elevated to 6.7 ng/mL. A chest wall biopsy specimen obtained upon admission revealed biphasic-type MPM. Thoracic drainage of pleural effusion and OK-432 was performed. Pleural thickening was noted in the upper right hemithorax on chest computed tomography (Fig. 1a). FDG-PET scanning was performed as a part of a study of the usefulness of functional imaging of MPM at the Osaka City University Hospital (Osaka, Japan) (Kimura et al., 2008). FDG-PET imaging and CT scanning were performed before chemotherapy, as well as after the first and second courses of chemotherapy, with written informed consent.

Upon completion of each scan, the patient was injected with intravenous FDG 185-370 MBq. The degree of FDG accumulation was evaluated using scanned images acquired 40 to 55 minutes after injection. FDG was produced using an NKK-Oxford superconducting cyclotron and an NKK synthesis system (AMFG01, NKK, Muroran, Japan). PET images were obtained using a PET scanner (HEADTOME IV; Shimadzu, Kyoto, Japan) with 4 detector rings providing 7 contiguous slices at 13-mm intervals and an intrinsic resolution of 4.5-mm full width at half maximum (FWHM). Attenuation correction of reconstructed images was accomplished through a patient-specific transmission study using a 68 Ge ring source. FDG-PET images were compared with the corresponding CT images, allowing accurate identification of tumors by using anatomical landmarks. For quantitative evaluation, a region of interest (ROI) (circle 6 mm in diameter) was placed on the area of maximum FDG uptake within the lesion. A background ROI was then placed on a non-tumorous region of the lung. The standardized uptake value (SUV), a quantitative measure of activity in the region of interest (ROI), was determined using the following formula:

$$SUV = \frac{\text{Radioactivity Concentration in ROI (Bq / mL)}}{\text{Injected dose (Bq) / body weight (g)}}$$

He received chemotherapy with cisplatin and irinotecan. Severe diarrhea due to irinotecan, a different chemotherapy regimen, including cisplatin and docetaxel, was administered as a second course. The tumor lesion exhibited shrinkage according to CT images (Fig. 1), and SUVmax (Table 1) decreased after the first course of chemotherapy; however, size

enlargement and an increase in SUVmax after the second course of chemotherapy occurred. Progression-free survival and overall survival were 90 days and 320 days, respectively.
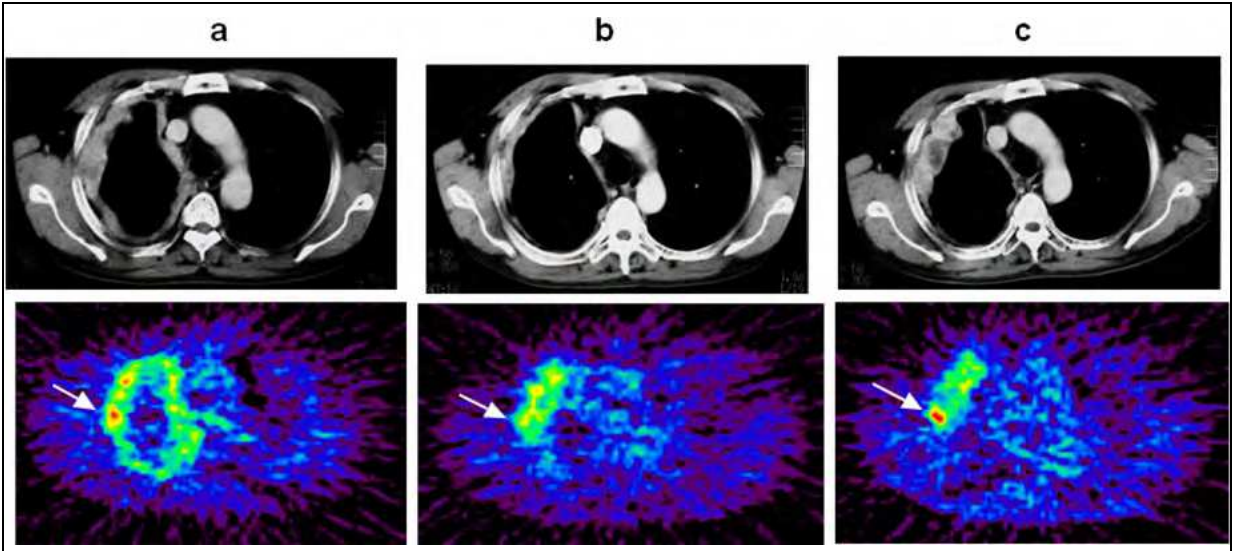

Fig. 1. Monitoring chemotherapy response of malignant pleural mesothelioma using CT-based modified RECIST criteria and FDG-PET-based SUVmax. CT and PET monitoring before chemotherapy (a), after the first course of chemotherapy (b), and after the second course of chemotherapy (c). Arrows show the target lesions.

	a	b	c
SUVmax	3.78	2.47	3.67
Modified RECIST	10.38	6.45	10.08

Table 1. Comparison of SUVmax and Modified RECIST in Fig 1.

3. Brief reviews

3.1 Differentiating malignant from benign disease

Pleural disease has 3 fundamental pathologic features: effusion, thickening, and calcification of pleural surfaces, with overlapping radiological findings. Differentiation of malignant from benign lesions on the basis of clinical findings alone is often difficult. Furthermore, the results of thoracentesis, percutaneous biopsy, and even thoracotomy may be ambiguous, and nonfatal complications can occur in up to 10% of patients undergoing such procedures. FDG-PET imaging is highly accurate and reliable in differentiating malignant from benign pleural effusion and/or involvement (Gupta et al., 2002; Mavi et al., 2009). When an SUV cut-off of 2.0 was used to differentiate malignant from benign disease, a sensitivity of 91% and specificity of 100% were achieved, although the activity in some epithelial mesotheliomas was close to the threshold value (Benard et al., 1998). Another study found that PET scanning sensitivity was 96.8% and specificity was 88.5% in distinguishing benign from malignant pleural disease (Duysinx et al., 2004). Additionally, another study showed that a cut-off value of 2.2 for SUV provided the best accuracy, with 94.1% and 100% for sensitivity and specificity (Yildirim et al., 2009). Furthermore, the usefulness of dual time

point FDG-PET imaging in distinguishing malignant from benign localizing pleural disease has been reported (Mavi et al., 2009). The SUVmax and its change over time in MPM patients were significantly higher than those in the benign pleural disease group (*P* < 0.0001). Yamamoto also described the usefulness of dual time point FDG-PET (Yamamoto et al., 2009). Sensitivity, specificity, and accuracy in detecting MPM by using both early and delayed PET were 88%. Mean values of SUVearly and SUVdelayed in MPM were significantly higher than the corresponding values in benign pleural disease (*P* < 0.01, respectively).

We also treated a 66-year-old man with the benign pleural thickness with no tumor involvement. Pleural thickness was found during an annual check-up. He was an office worker and had smoked 20 cigarettes per day for 40 years; he had not been exposed to asbestos and did not complain of symptoms. However, his father had been exposed to asbestos for a long period of time. CT-guided needle biopsy of left side pleura revealed an increase in the collagen structure and infiltration of lymphocytes with no tumor involvement. CT, PET, and PET-CT images are shown in Fig. 2. Bilateral pleural thickness was shown in CT image(Fig 2a,c). Almost normal FDG uptake in the bilateral pleural thickness was shown in PET images (Fig 2b,d). A Biograph 16 (Siemens Medical, Germany), which has 39 detector ring providing 81 contiguous slices at 2-mm intervals, was employed for PET-CT examination.

Thus, a combination of metabolic and anatomical information is useful for differentiating malignant from benign tissue. CT scans are most commonly used, although the use of PET scans has increased. Although multi procedures are valuable, false negative findings occur with both. These methods can be used in combination for a more accurate diagnosis.

3.2 International TNM staging system for MPM

For the past 30 years, several staging systems have been used for MPM. The TNM system is used to evaluate tumor size, lymph nodes, and distant metastasis. The clear need for an internationally accepted staging system prompted a group of International Mesothelioma Interest Group (IMIG) members to hold a consensus meeting in June 1994, and the new International TNM Staging System for MPM was developed as a result of this meeting. These guidelines reconcile the multiple previous staging systems, provide a staging system similar to those used for other solid tumors, and take into consideration recent data regarding the influence of T and N status on overall survival in MPM (Rusch, 1995). The TNM system of MPM consists of 4 stages. In Stage I, the MPM is in the membrane lining the chest (right or left pleura), and the MPM has not spread to the lymph nodes. In Stage II, the MPM involves the right or left pleura lining the chest. The MPM has also spread from the lining of the chest into the outer lining of the lung, into the diaphragm, or into the lung. In addition to involvement of the chest pleura, Stage III MPM has spread into the first layer of the chest wall, part of the mediastinum (the chest cavity behind the breastbone that lies between the lungs), or a single location in the chest wall. It may have also spread to the outer covering layer of the heart or to the lymph nodes on one side of the chest. In Stage IV MPM, the disease has advanced to other organs in the body such as the liver, brain, or bone or to lymph nodes on both sides of the chest. Tables 2 and 3 show TNM staging definitions and descriptions.
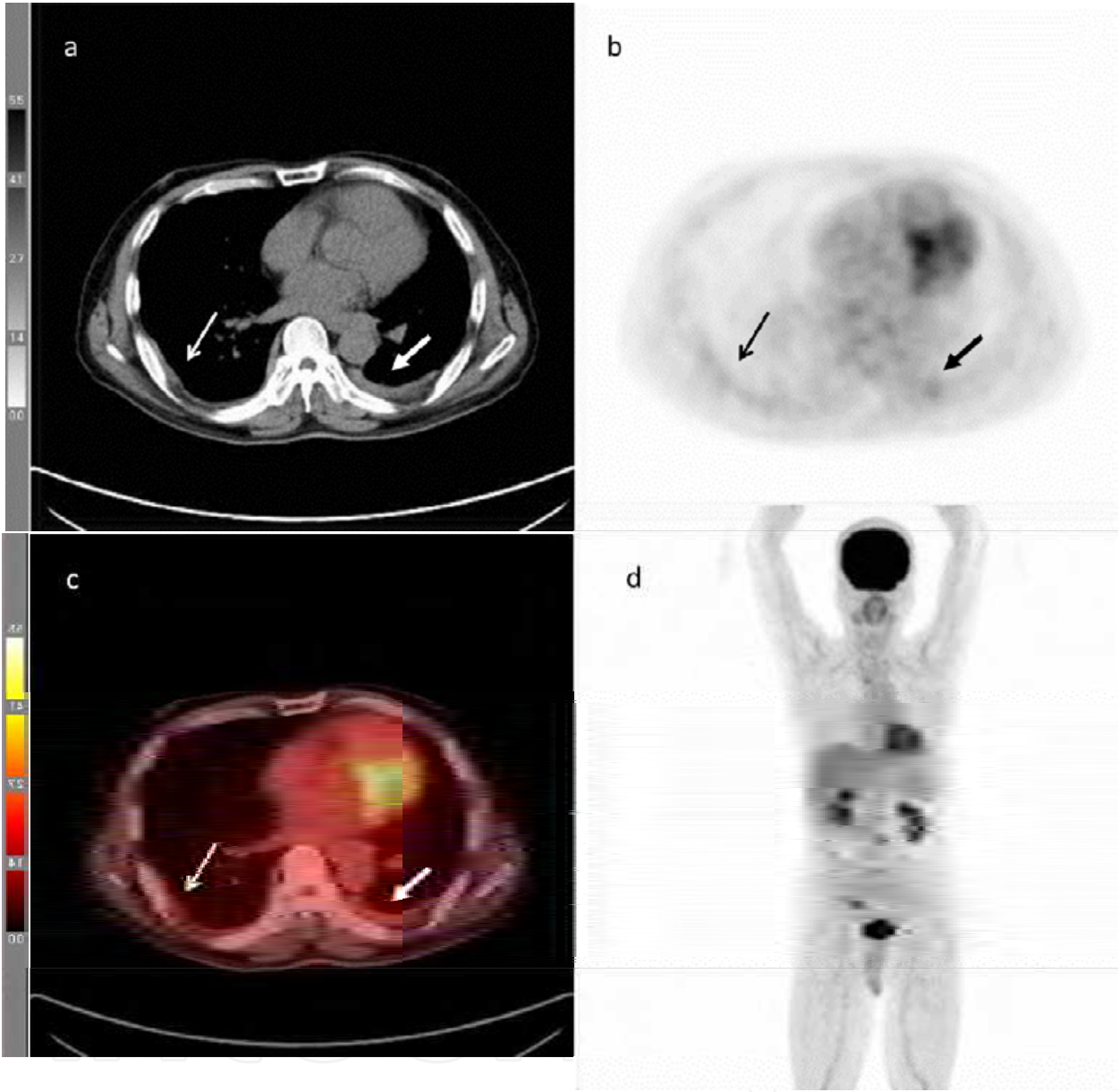
Fig. 2. Benign pleural thickness with no tumor involvement. PET-CT images of bilateral pleural thickness (narrow and large arrows). The trans-axial views of CT image (a), PET image (b) and PET-CT image (c), and coronal view of whole-body PET image (d). The SUVmax of the left side pleura (large arrow) and the right side pleura (narrow arrow) were 2.019 and 1.452, respectively.

T	
T1a	Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura No involvement of the visceral pleura
T1b	Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura Scattered foci of tumor also involving the visceral pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: involvement of diaphragmatic muscle confluent visceral pleural tumor (including fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Describes locally advanced but potentially resectable tumor Tumor involving all ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: involvement of the endothoracic fascia extension into the mediastinal fat solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall nontransmural involvement of the pericardium
T4	Describes locally advanced technically unresectable tumor Tumor involving all ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features: diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction direct extension of tumor to the contralateral pleura direct extension of tumor to one or more mediastinal organs direct extension of tumor into the spine tumor extending through to the internal surface of the pericardium with or without a pericardialeffusion; or tumor involving the myocardium
N	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph nodes
M	
MX	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Table 2. New International Staging System for diffuse MPM

Stage	T	N	M
I	T1	N0	M0
Ia	T1a	N0	M0
Ib	T1b	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T1,T2	N2	M0
	T3	N0,N1,N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	AnyN	M1

Table 3. Stage by tumor (T), lymph node (N), metastasis (M), and Description of International TNM staging system for diffuse MPM

3.3 PET for staging and preoperative evaluation for MPM

The combination of metabolic and anatomical information provided by PET is useful in determining the stage and conducting a preoperative evaluation of MPM. Recent studies indicate the potential in the use of PET in diagnosing MPM and determining MPM staging or the extent to which tumors have spread. In a comparative study by Plathow et al., the diagnostic values of CT, PET, PET/CT, and MRI for staging were evaluated in 54 patients with limited MPM (Plathow et al., 2008). The accuracies of CT, PET, MRI, and PET/CT were 0.77, 0.86, 0.8, and 1.0, respectively, for limited MPM patients, and 0.75, 0.83, 0.9, and 1.0, respectively, for patients in Stages II and III. FDG-PET/CT is significantly more accurate in Stages II and III compared with all other techniques.

In addition, FDG-PET is particularly useful for identifying occult distant metastases. Twenty-eight consecutive patients referred for the evaluation of suspected MPM underwent FDG-PET imaging at the University of Pennsylvania Medical Center (Benard et al., 1998). PET imaging was compared with thoracoscopy and surgical biopsies and was found to successfully indicate the presence of disease in 24 patients and of benign conditions in the remaining 4 patients. FDG uptake was significantly higher in diseased cells, and PET analysis showed tumors in the lymph nodes of 9 patients. Lymph nodes appeared normal based on CT scans. Another study at Brigham and Women's Hospital and Harvard Medical School in Boston evaluated 15 patients, 11 of whom had MPM and 4 who were disease–free (Gerbaudo et al., 2002). PET results were compared with laboratory analysis of biopsied fluids and tissues. PET was used to detect all 11 primary tumors and confirm the absence of disease in the other 4 patients. For biopsied lesions, overall sensitivity, specificity, and accuracies for FDG-PET were 97%, 80%, and 94%, respectively, compared with 83%, 80%, and 82%, respectively, for CT. FDG-PET was used to identify extrathoracic metastases in 5 patients, excluding these patients from surgical therapy. Sorensen et al. compared the accuracy of preoperative staging with different imaging modalities and found that non-curative surgery could be avoided in 29% of 42 MPM patients using preoperative PET/CT and in another 14% by employing mediastinoscopy (Sorensen et al., 2008). Wilcox et al. reported the utility of PET/CT in the initial staging and assessed 35 patients with MPM

included in the Mayo clinic database. PET/CT excluded 14 of 35 patients from surgical intervention (Wilcox et al., 2009). Upstaging from PET/CT was noted in 70% of patients when surgical pathology was available.

These studies indicate that although CT scans are a standard test for evaluating MPM patients, PET can also be used for MPM diagnosis. PET/CT increases staging accuracy in patients with MPM and improves patient selection for curative surgical procedures. Distant metastases have historically been considered to be an uncommon late manifestation of MPM (Truong et al., 2006). But, accurate determination of the presence or absence of distant metastases is crucial for potentially curative surgical resection of MPM.

3.4 PET for restaging and survival

Accurate restaging of disease after treatment has also implications for survival. Two retrospective studies have concluded that FDG-PET/CT is useful for detecting metastases. The first was reported by Tan et al. and involved the evaluation of 44 patients using PET/CT after multimodality therapy for MPM (Tan, 2010). The other study was reported by Lee and was a retrospective study involving 46 patients who were evaluated using PET/CT for staging or re-staging after therapy for MPM (Lee et al., 2009). Both studies concluded that detecting extrathoracic metastases using FDG-PET/CT indicates poor prognosis in patients with MPM.

A correlation between PET parameters and prognosis has been shown in some reports. Nowak et al. reported that 93 patients underwent PET/CT assessments at baseline; these patients were then treated clinically and survival was followed (Nowak et al., 2010). In univariate analysis, significant prognostic factors included total glycolytic volume (TGV), sarcomatous history, weight loss, CT stage, and European Organization for Research and Treatment of Cancer (EORTC) good prognosis category. In multivariate analysis, TGV and weight loss remained as significant prognostic factors in patients with non-sarcomatoid histology and no pleurodesis. Gerbaudo et al. reported 50 patients subjected to PET/CT assessments after therapy, and survival after relapse was independently predicted based on the pattern of FDG uptake and PET nodal status; overall survival was predicted based on the maximum standard uptake value (Gerbaudo et al., 2011).

3.5 PET for response assessment

3.5.1 Modified RECIST criteria

Modified RECIST criteria have been published with particular reference to MPM (Byrne and Nowak, 2004). Response to treatment is evaluated by measuring uni-dimensional tumor thickness perpendicular to the chest wall in 2 positions at 3 different levels on CT. The sum of these 6 measurements is defined as the pleural uni-dimensional measure. Transverse cuts at least 1 cm apart and related to anatomical landmarks in the thorax were chosen to allow reproducible assessment at later time points. If a measurable tumor was present, transverse cuts in the upper thorax, above the level of the main bronchi division were preferred. At reassessment, pleural thickness was measured at the same position and at the same level by the same observer. This measurement did not necessarily represent the greatest tumor thickness at the level. Nodal, subcutaneous, and other bi-dimensionally measurable lesions

were measured uni-dimensionally based on the RECIST criteria. Uni-dimensional measurements were included to obtain the total tumor measurement. The RECIST definition is listed in Table 4. A confirmed response required repeat observation on 2 occasions 4 weeks apart.

Complete response (CR)	Disappearance of all target lesions with no evidence of tumors elsewhere
Partial response (PR)	At least a 30% reduction in the total tumor measurement
Progressive disease (PD)	Increase of at least 20% in the total tumor measurement over the nadir measurement or the appearance of one or more new lesions
Stable disease (SD)	Those who fulfilled the criteria for neither PR and PD

Table 4. Response criteria of Modified RECIST

3.5.2 PET in RECIST version 1.1

Currently, most clinical trials evaluating cancer treatments for objective responses in solid tumors are using RECIST. The RECIST Working Group, consisting of clinicians with expertise in early drug development from academic research organizations, government, and industry, together with imaging specialists and statisticians, has met regularly to set an agenda to update RECIST, determine the evidence needed to justify various changes made, and to review emerging evidence (Eisenhauer et al., 2009). RECIST 1.1, published in January 2009, is an update to the original criteria. A critical aspect of the revision process was to create a database of prospectively documented solid tumor measurement data obtained from industry and academic group trials. However, the Working Group and particularly those involved in imaging research, did not believe that there was sufficient standardization and widespread availability to recommend adoption of either volumetric anatomical assessment or to functional assessment (e.g. dynamic contrast enhanced MRI, CT, or FDG-PET techniques assessing tumor metabolism). The only exception to this is the use of FDG-PET imaging as an adjunct to determine progression. The RECIST Working Group looks forward to such data emerging in the next few years to allow appropriate changes to be made to the next iteration of the RECIST criteria.

3.5.3 PERCIST— Positron Emission tomography Response Criteria In Solid Tumors

Therapy monitoring with FDG-PET is generally based on consensus criteria from the European Organization for Research and Treatment of Cancer (EORTC) (Young et al., 1999). Based on the extensive literature now supporting the use of 18F-FDG PET as well as the known limitations of anatomic imaging to assess early treatment response, updated draft PET criteria have been proposed that may be useful for consideration in clinical trials and potentially in clinical practice. We refer to these draft criteria as "PERCIST"—Positron Emission tomography Response Criteria In Solid Tumors (Wahl et al., 2009). The premise of the PERCIST 1.0 criteria is that cancer response as assessed by PET is a continuous and time-dependent variable. A tumor may be evaluated at a number of times during treatment and

glucose use may rise or fall from baseline values. SUV will likely vary for the same tumor and the same treatment at different times. For example, tracer uptake by a tumor is expected to decline over time with effective treatment. Thus, capturing and reporting the fractional change in SUV from the starting value and when the scan was obtained are important.

Complete metabolic response (CMR)	Complete resolution of ^{18}F-FDG uptake within a measurable target lesion such that it is less than the mean liver activity and indistinguishable from surrounding background blood-pool levels. Disappearance of all other lesions to background blood-pool levels.
Partial metabolic response (PMR)	Reduction by a minimum of 30% in target measurable tumor ^{18}F-FDG SUL peak. Absolute drop in SUL must be at least 0.8 SUL units as well. Measurement is commonly in same lesion as baseline but can be another lesion if that lesion was previously present and is the most active lesion after treatment. Reduction in the extent of tumor 18F-FDG uptake is not a requirement for PMR.
Progressive metabolic disease (PMD)	>30% increase in ^{18}F-FDG SUL peak, with >0.8 SUL unit increase in tumor SUV peak from baseline scan in pattern typical of a tumor and not of infection/treatment effect OR: visible increase in extent of ^{18}F-FDG tumor uptake (75% in TLG volume with no decline in SUL OR: new ^{18}F-FDG–avid lesions.
Stable metabolic disease (SMD)	Not CMR, PMR, or PMD.

Table 5. Response criteria of PERCIST

Patients should fast for at least 4 to 6 h before undergoing scanning, and the measured serum glucose level (no correction) must be less than 200 mg/dL. Patients may be on an oral hypoglycaemic but not on insulin. A baseline PET scan should be obtained 50 to 70 min after tracer injection. A follow-up scan should be obtained within 15 min (but always 50 min or later) of the baseline scan. All scans should be performed using the same PET scanner with the same injected dose ±20% of radioactivity. Appropriate attenuation correction along with evaluation for proper PET and CT registration of the quantitated areas should be performed. Lean body mass (SUL) is determined for up to 5 tumors (up to 2 per organ) with the most intense ^{18}F-FDG uptake. These will typically be lesions identified using RECIST 1.1. The SUV peak (this is a sphere with a diameter of approximately 1.2 cm to produce a 1-cm^3-volume spherical ROI) centered near the hottest point in the tumor foci should be determined and the image planes and coordinates should be noted (SUL peak). This SUL peak ROI will typically include the maximal SUL pixel (which should also be recorded) but is not necessarily centered on the maximal SUL pixel. Tumor sizes should be noted and should be 2 cm or larger in diameter for accurate measurement, although smaller lesions of sufficient ^{18}F-FDG uptake, including those not well observed anatomically, can be assessed. Each baseline (pretreatment) tumor SUL peak must be 1.5 × mean liver SUL + 2 SDs of mean SUL. If the liver is diseased, 2.0 × blood-pool ^{18}F-FDG activity + 2 SDs in the mediastinum is suggested as the minimal metabolically measurable tumor activity. In PERCIST, the response to therapy is assessed as a continuous variable and expressed as the percentage change in SUL peak (or sum of lesion SULs) between pre- and post-treatment scans. After

chemotherapy, waiting a minimum of 10 d before performing FDG-PET is advised. This time permits bypassing of the chemotherapeutic effect and of transient fluctuations in ^{18}F-FDG uptake that may occur early after treatment, including stunning or flaring of tumor uptake. The response criteria are listed in Table 5.

3.6 PET for therapeutic response assessment in MPM

PET and CT examinations can play important roles in the management of patients with MPM. Particularly, an emerging role for FDG-PET/CT is that of therapeutic response assessment. Steinert et al. performed assessments on 17 patients after 3 cycles of chemotherapy and reported that total lesion glycolysis (TLG), defined as (SUVmax) × (Vol), more accurately identifies patients responding to chemotherapy (Steinert et al., 2005). Ceresoli et al. measured CT and PET responses in 22 patients after 2 cycles of chemotherapy and found that an early metabolic response as a 25% decrease in SUVmax was significantly correlated to median time-to-tumor progression and was tended to be associated with longer overall survival (Ceresoli et al., 2006). Francic et al. reported a prospective study, including patients who had undergone both FDG-PET and conventional radiological response assessment before and after 1 cycle of chemotherapy (Francis et al., 2007). Twenty-three patients were evaluated and a statistically significant relationship between a fall in TGV and improved patient survival was shown. Veit-Haibach et al. reported a study involving 41 patients evaluated by FDG-PET/CT at baseline and after 3 cycles of pemetrexed plus platinum-based chemotherapy (Veit-Haibach et al., 2010). Neither SUVmax-response nor SUVmean-response was related to survival; however, a decrease in TLG and PETvol was found to be significantly predictive of survival. Flores et al. reported a statistically significant association between a decrease in SUV after chemotherapy and overall survival in 24 MPM patients treated with cisplatin-based induction chemotherapy and surgery (Flores et al., 2005).

Our group conducted a small study involving 11 patients with MPM (Kimura et al., 2005). FDG-PET scanning was performed at the Osaka City University Hospital (Osaka, Japan) as part of a prospective study to examine the usefulness of functional imaging of MPM. This study was conducted between March 1999 and December 2004 and all patients had a proven histological diagnosis of MPM treated using chemotherapy. Each patient underwent both FDG-PET imaging and CT scanning before treatment and after the first courses of chemotherapy. Written informed consent was obtained from all patients. A total of 33 lesions in 11 patients with MPM were studied. The Spearman rank correlation test was used to compare ratios of pre-therapy to post-therapy SUVs. In an examination of CT evaluation, the mean SUV of the 8 lesions exhibiting a clinical response after the first course of the chemotherapy significantly decreased from 4.03 + 1.28 SD to 2.83 + 0.69 SD (P = 0.050) (Fig. 3a). The mean SUV of the 5 lesions exhibiting clinical progression after the first course of chemotherapy tended to increase from 2.42 + 0.90 SD to 2.74 + 0.88 SD (P = 0.072) (Fig. 3b). The mean SUV of the 20 lesions exhibiting no clinical change after the first course of chemotherapy significantly decreased from 3.71 + 1.85 SD to 3.03 + 1.63 SD (P = 0.0002) (Fig. 3c).

Thus, some PET parameters used to evaluate metabolic response may be associated with overall survival as well as predict anatomical response. The differences between these studies are the timing of assessments for early evaluation of metabolic response. The best

timing and best parameters in patients with MPM remain to be clearly determined. Further clinical studies are necessary to determine the usefulness of FDG-PET as a monitoring method for response to chemotherapy.
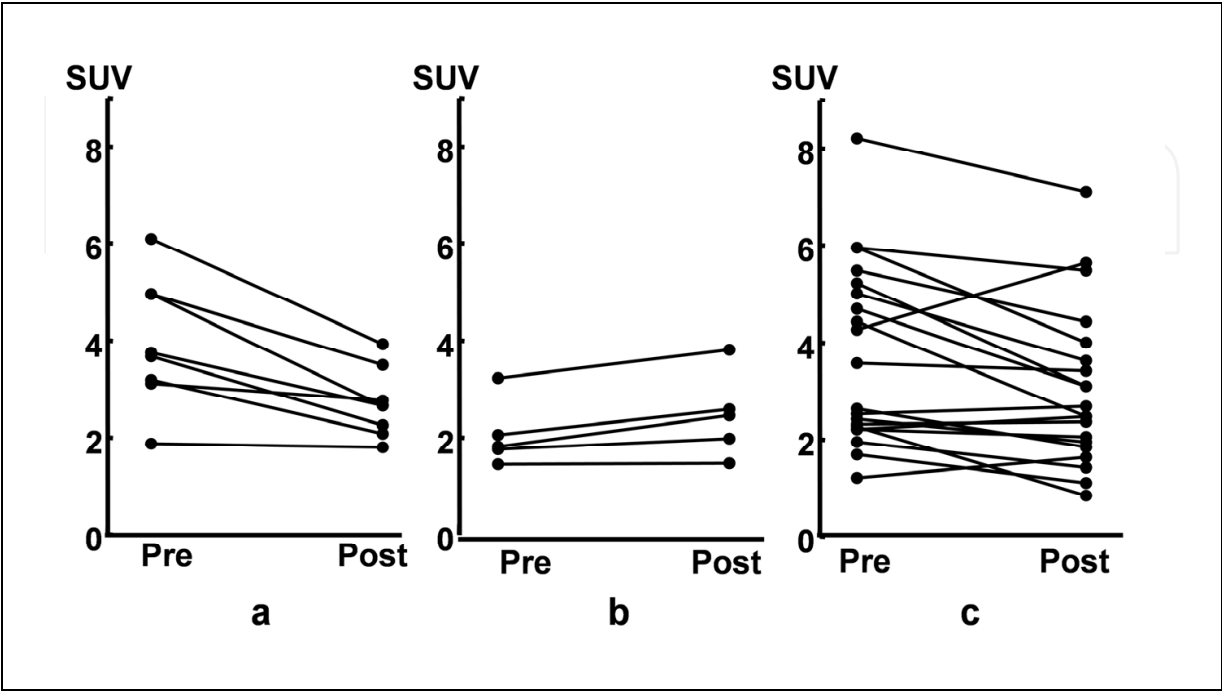

Fig. 3. FDG uptake (SUV) changes assorted to CT responses. Lesions exhibiting clinical response (a), clinical progression (b), and without change (c) before and after the first course of chemotherapy.

4. Limitations and pitfalls

FDG-PET has been reported to yield false-negative results for lesions smaller than 1 cm and false-positive results for lesions with inflammatory change (Kostakoglu and Goldsmith, 2003). In the current state of technology, it is impossible to detect small clusters of tumor cells that will cause a clinically detectable recurrence of disease in the future (Hueltenschmidt et al., 2001). Tumors exhibit heterogeneous biological activity in single tumors; however, it is difficult to obtain cytological and histological materials from patients with MPM from multiple lesions at multiple time points and histological confirmation of metabolic response. Unfortunately, in this chapter, it has been impossible to cite all references referring to the use of FDG-PET in MPM.

5. Conclusion

The present case suggests that the results of quantification of metabolic response by FDG-PET may be related to objective response as determined by modified RECIST in patients with MPM. It also is important to acknowledge that SUVs are not strictly quantitative, and repeated biopsies are sometimes required. Information derived from FDG-PET during treatment may require assessment based on standard follow-up procedures. Final interpretations of images reported are based on total analysis and not SUV alone.

6. Acknowledgment

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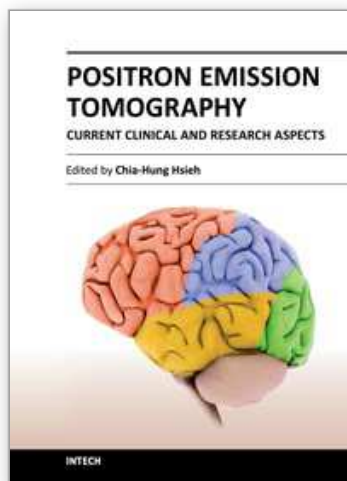
Positron Emission Tomography - Current Clinical and Research Aspects

Edited by Dr. Chia-Hung Hsieh

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