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Malignant Peritoneal Mesothelioma Features Shown by FDG-PET/CT

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Abstract. *Background/Aim: Malignant peritoneal mesothelioma (MPeM) has no specific imaging findings that can distinguish it from other peritoneal tumors and the accuracy of peritoneal cytology is low, therefore definitive diagnosis is usually performed by histology. This study investigated whether ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography representing glucose metabolism is a useful modality for identifying biopsy sites using the tumor viability of MPeM. Patients and Methods: Sixty MPeM patients underwent pre-biopsy FDG-PET/CT examination. The findings were retrospectively evaluated, and histopathological subtype differences were investigated. Results: The diffuse MPeM type was found in 45 (75.0%) and the localized type in 15 (25.0%) cases. The most frequent site of occurrence was the peritoneum (91.7%), followed by the omentum (51.7%). FDG-avid results were noted in 55 patients (91.7%), while 5 (8.3%) showed no FDG uptake with a variety of maximum standardize uptake value (SUV_{max}) values (range=0-16.77, mean=7.32±4.05). In the 53 epithelial cases, mean SUV_{max} (7.09±4.07, range=0-16.77) was slightly lower compared to the 4 biphasic (8.30±4.70, range=2.35-13.36) and 3 sarcomatoid (10.08±2.64, range=8.21-13.10) cases, without any significant difference (p=0.12). Diffuse and focal disease patterns showed similar percentages in the three types. Six cases (10.0%) had nodal metastases and 6 (10.0%) extra-abdominal metastases. Compared to the biphasic and sarcomatoid groups, nodal metastases were more common in the epithelial group, while extra-abdominal metastases were more often seen in the biphasic and sarcomatoid groups. Ascites was seen in 53 (83.3%), pleural effusion in 43 (71.7%), and pleural plaque in 31 (51.7%) cases. Conclusion: Through reviewing and elucidation of the FDG-PET/CT features of MPeM, it was shown that FDG-PET/CT is an extremely useful modality for identifying biopsy sites of MPeM.*

Malignant peritoneal mesothelioma (MPeM) is a rare but aggressive type of cancer of mesothelial cells in the peritoneum that represents 7-30% of all mesothelioma cases diagnosed and commonly caused by exposure to asbestos (1, 2). MPeM is typically presented as a rapid, diffuse, and extensive spread throughout the abdomen, with most patients dying from the disease within a year. Related signs and symptoms are non-specific and include abdominal pain, abdominal distension, and weight loss. However, diagnosis is often delayed because of rarity and non-specific presentation. A median period of 4-6 months between initial presentation and diagnosis has been reported (3). Confirmation of diagnosis is challenging, with performance of a biopsy and histological and immunohistochemical findings required for definitive determination.

Computed tomography (CT) is the first-line imaging modality used as part of a diagnostic workup of suspected MPeM and typical findings include ascites, peritoneal thickening, omental disease, small bowel involvement with solid and cystic masses, and pleural plaque (4-7). However, CT findings are nonspecific and similar to metastatic peritoneal carcinomatosis, primary peritoneal serous carcinoma, malignant lymphoma, peritoneal lymphomatosis, pseudomyxoma peritonei, cystic lymphangioma, tuberculous peritonitis, and nontuberculous peritonitis, are thus considered inadequate for a

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Table I. *Patient characteristics*.

	Total patients (n=60)	%
Age	62.5±14.8 (range=23-83)	
Sex (Male/Female)	40/20	66.7%/33.3%
Present exposure to asbestos	42	70.0%
Symptom		
Abdominal distension	31	57.7%
Abdominal pain	9	15.0%
Epigastralgia and anorexia	5	8.3%
Ascites	4	6.7%
Accidental discovery during the surgery of other disease	3	5.0%
Abdominal discomfort	2	3.3%
Follow-up FDG-PET/CT of other malignancy	2	3.3%
Others	4	6.7%
Histological subtypes		
Epithelial/Biphasic/Sarcomatoid	53/4/3	88.3%/6.7%/5.0%
Diagnostic tool		
Laparoscopic peritoneal biopsy	55	91.7%
Biopsy during the surgery of other disease	3	5.0%
Utrasound-guided core-needle biopsy	2	3.3%

FDG-PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography.

specific diagnosis of MPeM. On the other hand, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has recently been reported as effective, as shown in a few studies of diagnosis of a single case (8-11) or small groups of patients (12), though its clinical utility remains to be established. The present study was performed to identify the characteristic features of pretreatment FDG-PET/CT in MPeM cases aiming to establish imaging diagnostic factors.

Patients and Methods

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of the Hyogo Medical College of Medicine (Date 2021/3/26/No 1894). Written informed consent was obtained from all participants included in the study.

Patients. The records of 69 consecutive patients treated at our Institution between January 2007 and March 2021 with histopathologically proven MPeM were reviewed, and those without pre-biopsy FDG-PET/CT examination results were excluded. As a result, the study cohort included 60 patients (40 males, 20 females; mean age 62.5 years; range=23-83 years) who underwent pretreatment FDG-PET/CT examination before the biopsy. MPeM was histopathologically diagnosed by biopsy, based on FDG-PET/CT examination results. Histopathologic subtypes in the present 60 cases included epithelial mesothelioma (n=53), biphasic mesothelioma (n=4), and sarcomatoid mesothelioma (n=3). Characteristics of patients are shown in Table I. A history of asbestos exposure was noted in 42 (70.0%) cases.

FDG-PET/CT. One of four different PET/CT scanners: Gemini GXL16, Gemini TF64, or Ingenuity TF (Philips Medical Systems, Eindhoven, The Netherlands) and Discovery IQ (GE Healthcare, Waukesha, WI, USA) were used to perform the FDG-PET/CT examinations. Patients fasted for five hours prior to the scan appointment, then blood glucose was measured immediately prior to injection of FDG at 4.0 MBq/kg body weight for the GXL16, 3.0 MBq/kg body weight for the TF64, or 3.7 MBq/kg body weight for the Ingenuity TF and Discovery IQ. Blood glucose levels in each of the patients was less than 160 mg/dl. Approximately 60 minutes after the injection, static emission images were obtained. Helical CT scan imaging from the top of the head to the mid-thigh for attenuation correction and anatomic localization was performed using the following parameters: tube voltage 120 kV (all scanners), effective tube current auto-mA up to 120 mA (GXL16), 100 mA (TF64), 155 mA (Ingenuity TF), or 15-190 mA (smart mA/noise index: 25) (Discovery IQ), gantry rotation speed 0.5 seconds (all), detector configuration of 16×1.5 mm (GXL16), 64×0.625 mm (TF64 and Ingenuity TF), or 16×1.25 mm (Discovery IQ), slice thickness 2 mm (all), and transverse field of view 600 mm (GXL16, TF64, Ingenuity TF) or 700 mm (Discovery IQ). Upon completion of CT scanning, PET imaging was immediately performed in a 3-dimensional mode from the head to mid-thigh for 90 (GXL16, TF64, Ingenuity TF) or 180 (Discovery IQ) seconds per bed position. Normal breathing was allowed during PET scanning. A line-of-response row-action maximum likelihood algorithm for the GXL16, an ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm (33 subsets, 3 iterations) for the TF64 and Ingenuity, and Q.Clear (block sequential regularized expectation maximization (BSREM) (β=400) for the Discovery IQ were used for reconstruction of attenuation-corrected PET images.

Imaging analysis. A single board-certified nuclear medicine expert with 12 years of experience with oncological FDG-PET/CT

retrospectively reviewed all FDG-PET/CT images, without knowledge regarding patient clinical or histopathological data. The reader recorded the sites and FDG uptake of each lesion noted and classified them as diffuse or localized type (13). For semi-quantitative analysis, maximum standardized uptake value (SUV_{max}), defined as the maximum concentration in the lesion (injected dose/body weight), was performed using the commercially available GI-PET software package (AZE Co., Ltd., Tokyo, Japan), which features the ability to harmonize SUVs obtained with different PET/CT systems using phantom data (14). In cases with multiple lesions with FDG uptake, maximum SUV_{max} was defined based on the SUV_{max} of each patient.

Statistical analysis. The Cochran's Q test was used to analyze SUV_{max} differences among the three histological subtypes (epithelial, sarcomatoid, biphasic), after which differences between any two protocols were tested using McNemar's test with Bonferroni adjustment. SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA), was utilized to perform statistical analyses, with $p<0.05$ considered to indicate significance.

Results

FDG-PET/CT findings of MPeM cases. Of the 60 enrolled MPeM cases, 45 (75.0%) were of diffuse type and 15 (25.0%) of the localized type. Intra-abdominal lesions in the peritoneum were noted in 55 (91.7%), abdominal lesions in the omentum in 31 (51.7%), abdominal lesions in the mesentery in 9 (15.0%), abdominal lesions in the diaphragm in 4 (6.7%), abdominal lesions in the digestive wall in 2 (3.3%), and abdominal lesions in the umbilical part in 2 (3.3%) cases (Table II). Furthermore, ascites was found in 50 (83.3%). In 55 cases (91.7%), FDG-avid results were noted, while no FDG uptake was shown in FDG-PET/CT images in 5 (8.3%), while there was a wide variety of SUV_{max} values (range=0-16.77, mean 7.32±4.05). Nodal metastasis was noted in 6 (10.0%) and extra-abdominal metastases in 6 (pleural cavity in 4, subcutaneous and bony metastases in 1, muscular and bony metastasis in 1) cases. As for the lung field, pleural effusion was seen in 43 (71.7%) cases and 31 (51.7%) had pleural plaque. Two representative cases are shown in Figure 1 and Figure 2.

Table II. *Localization and extent of disease by fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) findings.*

	Number	%
Present ascites	50	83.3%
Present pleural effusion	43	71.7%
Present pleural plaque	31	51.7%
Peritoneal disease form		
Diffuse	45	75.0%
Localized	15	25.0%
Intra abdominal location		
Peritoneum	19	31.7%
Peritoneum, omentum	21	35.0%
Peritoneum, omentum, mesentry	6	10.0%
Peritoneum, mesentry	3	5.0%
Peritoneum, diaphragm	2	3.3%
Peritoneum, omentum, diaphragm	1	1.7%
Peritoneum, digestive wall	1	1.7%
Peritoneum, omentum, digestive wall	1	1.7%
Peritoneum, umbilical part	1	1.7%
Omentum	1	1.7%
Diaphragm	1	1.7%
Omentum, umbilical part	1	1.7%
Paragastric space	1	1.7%
Right middle abdomen	1	1.7%
Present nodal metastasis	6	10.0%
Present extra-abdominal metastases	6	10.0%

FDG-PET/CT findings according to histopathological type. FDG-avid results were shown in FDG-PET/CT images in 48 of 53 (90.6%) epithelial cases, whereas the biphasic (n=4) and sarcomatoid (n=3) types showed FDG-avid results (100% sensitivity) (Table III). The mean SUV_{max} value for the 53 epithelial cases (7.09±4.07, range=0-16.77) was slightly lower than that for the 4 biphasic (8.30±4.70, range=2.35-13.36) and 3 sarcomatoid (10.08±2.64, range=8.21-13.10) cases, with the difference not being significant ($p=0.12$). The three types showed similar percentages of diffuse and focal disease patterns (75.5% and 24.5% in epithelial cases, 75.0% and 25.0% in biphasic case, and 66.7% and 33.3% in sarcomatoid cases). Compared to the biphasic and sarcomatoid groups, nodal metastasis was more common in the epithelial group, while extra-abdominal metastasis findings were more often noted in the biphasic and sarcomatoid groups compared to the epithelial group.

Discussion

To the best of our knowledge, the data presented herein represent the largest number of MPeM patients who underwent pretreatment FDG-PET/CT examinations reported. Diffuse type was found in 45 (75.0%) and localized type in 15 (25.0%) cases. Although previous reports each reported positive FDG-PET scans (8-12), 55 patients (91.7%) in our series showed FDG-avid results, while 5 (8.3%) showed no FDG uptake, with a variety of SUV_{max} values noted (mean=7.32±4.05, range=0-16.77). The mean SUV_{max} of the 53 epithelial cases (mean=7.09±4.07, range=0-16.77) tended to be slightly lower than that of the 4 biphasic (mean=8.30±4.70, range=2.35-13.36) and 3 sarcomatoid (mean=10.08±2.64, range=8.21-13.10) cases, though they were not significantly different. Among the three, similar percentages of diffuse and focal disease patterns were noted. Nodal metastasis was more common in the epithelial group, while the biphasic and sarcomatoid groups more often

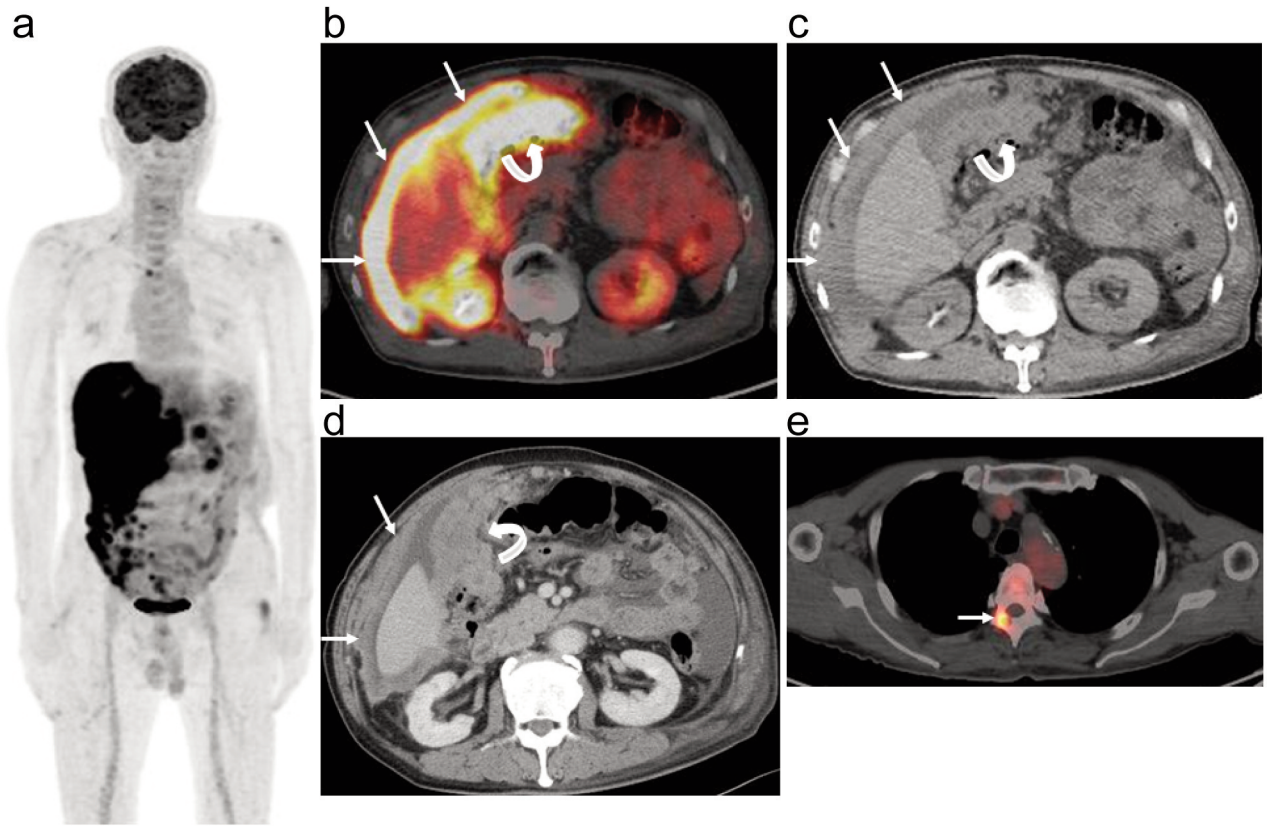

Figure 1. *A 70-year-old male with sarcomatoid malignant pleural mesothelioma (diffuse type). (a) Maximum intensity projection (MIP) of fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) shows a diffuse strong FDG uptake in the abdomen and pelvis, and tiny uptake in thoracic spine. (b) Axial fused FDG-PET/CT and (c) CT of PET/CT show diffuse and strong FDG uptakes [maximum standardized uptake value (SUV_{max}), 8.21] in the peritoneum (arrows) and the omentum (curved arrow). (d) Contrast enhanced CT shows peritoneal thickening (arrows) and omental caking (curved arrow) with contrast enhancement. (e) Axial fused FDG-PET/CT shows focal FDG uptake (SUV_{max}, 3.01) of the osteolytic change in the Th4 vertebral arch (arrow), reflecting bone metastasis.*

showed extra-abdominal metastasis. Many of the present patients had findings indicating diffuse type, ascites, pleural effusion, and pleural plaque.

In a study by Domènech-Vilardell *et al*. (12), who evaluated pretreatment FDG-PET/CT examination results of 11 patients with MPeM, the entire cohort showed abnormal FDG uptake (100% sensitivity), while images of five cases (45.5%) showed a diffuse distribution pattern, another five (45.5%) a focal distribution pattern, and one (9.1%) a mixed distribution pattern. In addition, five (45.5%) of their patients demonstrated lymph node disease in scan images, while none showed direct invasion of organs or metastatic disease. Moreover, that study clarified FDG-PET findings indicating MPeM histopathologic subtype, including epithelial type in a total of 65 scans and biphasic type in 14 scans in pretreatment, during treatment, and in posttreatment imaging examinations. Based on visual interpretation results, there were similar percentages regarding diffuse and focal disease patterns in the epithelial and biphasic groups. On the other hand, metastasis or remote nodal disease was more common in the biphasic group (43% *vs*. 26% in epithelial group), while pleural disease was more often seen in epithelial MPeM cases (25% *vs*. 7% in biphasic group). The authors also noted that the mean SUV_{max} for epithelial mesothelioma (6.5±3.9, range=1.2-19.0) had a tendency to be slightly higher compared to that for biphasic mesothelioma (5.2±2.3, range=1.2-10.5), without a significant difference (p=0.13). Claimon *et al*. (8) reported two MPeM cases, one localized and one epithelial case, in the right suprarenal region with extremely high FDG uptake (SUV_{max}: 15.6), with nodal, bone, and lung metastases, as well as another diffuse type case with moderate FDG uptake (SUV_{max}: 5.5). The report of Kodama *et al*. (9) noted two MPeM cases, one localized in the hepatoduodenal ligament with extremely high FDG uptake (SUV_{max}: 16.8), and another localized and desmoplastic (specific subtype of sarcomatoid) in the small

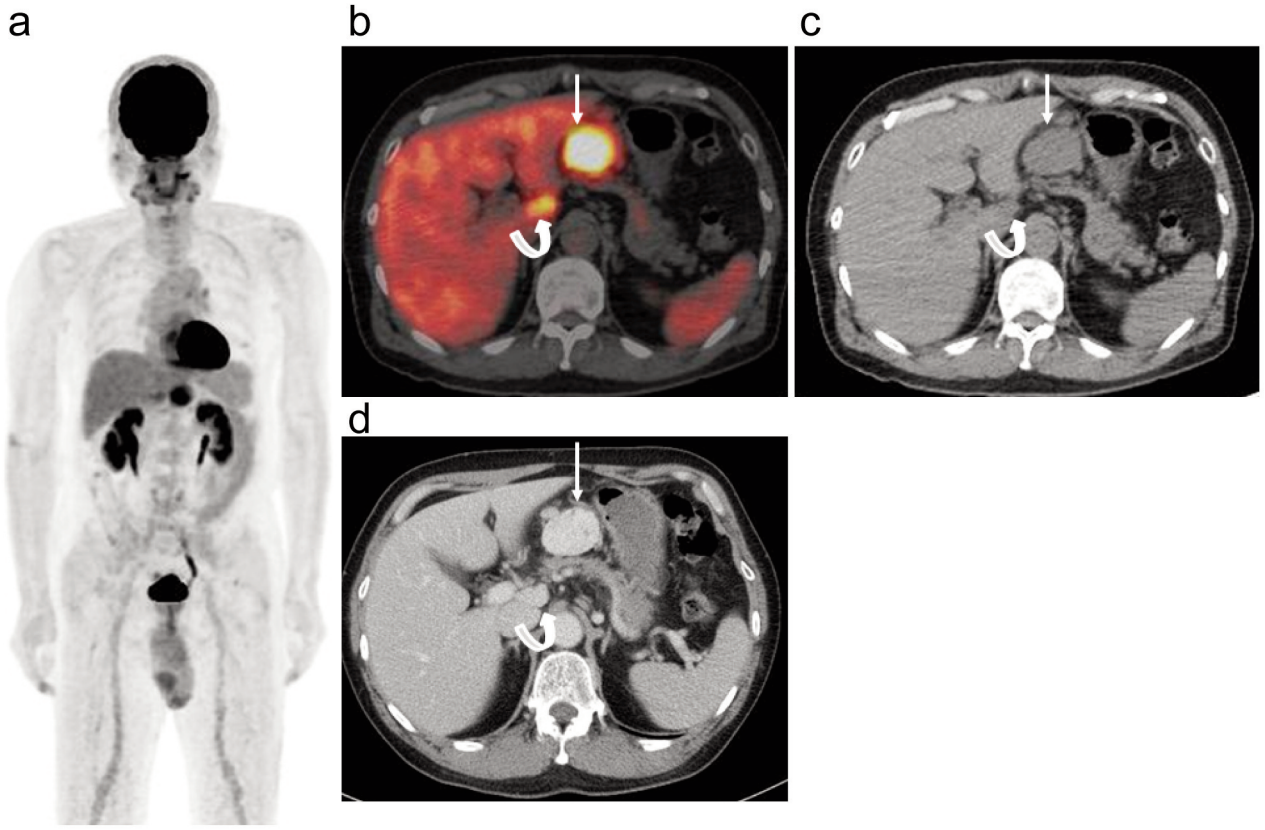

Figure 2. *A 64-year-old male with epithelial malignant pleural mesothelioma (localized type). (a) Maximum intensity projection (MIP) of fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) shows two FDG uptakes in the upper abdomen. (b) Axial fused FDG-PET/CT and (c) CT of PET/CT show medium FDG uptake [maximum standardized uptake value (SUV_{max}), 5.71] in the mass located in the hepatogastric ligament (arrow) and mild FDG uptake (SUV_{max}, 3.2) in the hilum lymph node (curved arrow), suggesting hilum lymph node metastasis. (d) Contrast enhanced CT shows a well-defined enhanced, 43 mm in size, mass in the hepatogastric ligament (arrow) and a small hilum lymph node (curved arrow).*

bowel mesentery with mild FDG uptake (SUV_{max}: 4.0). The latter sarcomatoid case did not show a strong FDG uptake because of rich fibrosis, thus they concluded that FDG uptake varies and is independent of histopathological subtype. Also, Kobayashi Shimizu *et al*. (10) reported findings of one localized and epithelial MPeM case in the right lower abdomen with extremely high FDG uptake (SUV_{max}: 32.7) and Xu *et al*. (11) reported one localized MPeM case under the left diagraph with moderate FDG uptake (SUV_{max}: 8.0).

A definitive diagnosis of MPeM must be based on pathological results, because of the nonspecific nature of symptoms, imaging findings, and serum markers. Many affected patients are presented with ascites and a cytological examination of abdominal paracentesis fluid can occasionally yield a diagnosis. However, there is a low number of malignant cells in ascites and significant cytological diversity in tumor cells, thus cytological analysis of sample ascitic fluid is often inconclusive, with a low diagnostic yield (15). Using immunohistochemistry, fine-needle aspiration of a tumor implant can yield useful findings, though due to the variability of tumor marker expression, diagnostic accuracy increases with solid tumor samples, which can be obtained using direct sampling during a diagnostic laparoscopy or with an ultrasound-guided core-needle biopsy procedure. An advantage of diagnostic laparoscopy is direct visualization of the peritoneal cavity, which can assist with diagnosis and planning future therapy. Additionally, in cases with pleural effusion, thoracentesis, or video-assisted thoracic surgery (VATS) is indicated for thoracic spread evaluation (1). Diagnosis of MPeM based solely on histological patterns can be difficult, thus immunohistochemical markers are important.

MPeM is classified histologically into three subtypes; epithelial, sarcomatoid, and biphasic (mixed). The epithelioid subtype is the most common, noted in approximately 75% of MPeM patients, and also has the best prognosis. Approximately 25% of MPeM patients are biphasic, while the

Table III. *Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) findings according to histopathological type.*

	Epithelial (n=53)	Biphasic (n=4)	Sarcomatoid (n=3)
Positive scan	48 (90.6%)	4 (100%)	3 (100%)
Peritoneal disease form			
Diffuse	40 (75.5%)	3 (75.0%)	2 (66.7%)
Localized	13 (24.5%)	1 (25.0%)	1 (33.3%)
SUV_{max}	7.09±4.07 (range=0-16.77)	8.30±4.70 (range=2.35-13.36)	10.08±2.64 (range=8.21-13.10)
Ascites	43 (81.1%)	4 (100%)	3 (100%)
Nodal metastasis	6 (11.3%)	0 (0%)	0 (0%)
Extra-abdominal metastases	4 (7.5%)	1 (25.0%)	1 (33.3%)
Pleural effusion	37 (69.8%)	4 (100%)	2 (66.7%)
Pleural plaque	25 (47.2%)	4 (100%)	2 (66.7%)

SUV_{max}: Maximum standardized uptake value.

sarcomatoid subtype is exceedingly rare, and both of these subtypes have a significantly worse prognosis, similar to corresponding pleural mesothelioma variants (1). Solid organs are not typically invaded by epithelial mesothelioma, while omentum infiltration is found in most cases (16). Generally, the disease remains confined to the abdomen, with multiple sites reported throughout the peritoneum. The sarcomatoid type tends to be more infiltrative and grows more rapidly, while the biphasic type has radiological and gross pathological features of both the epithelial and sarcomatoid types. In advanced stage cases, pleural cavity involvement and distant metastatic disease may be encountered.

Cases of MPeM show two basic forms, diffuse and localized type, in which the first is composed of diffuse nodules and plaques that tend to envelope the bowel viscera, while the other is manifested by a large tumor mass, usually in the upper abdomen, and discrete nodules scattered throughout the peritoneum (13). Another study noted that the diffuse type accounts for approximately 82.1% of all cases (17). Contrast-enhanced CT is universally accepted as the best imaging modality for management of MPeM, with advantages that include exquisite spatial anatomical details, examination speed, and wide availability. Common CT findings indicating MPeM are ascites, peritoneal thickening, caking, thickening or masses in the omentum, mesenteric nodules, small bowel involvement with solid and cystic masses, scalloping of intraabdominal organs, and pleural plaque (1, 4-7). Cases with local–regional invasion are commonly encountered. On the other hand, lymph node involvement (5-10%) and extra-abdominal metastasis (3-5%) are relatively rare complications and considered to be associated with advanced late-stage disease (18, 19).

Cisplatin and pemetrexed-based systemic chemotherapy are used to treat MPeM, though poor tumor response rates and negligible improvement in overall survival have been reported, in contrast with use of those for pleural mesothelioma (20). Research is presently underway for new drugs, such as antiangiogenic medications, immunotherapy, and growth factor agents (17). Because of its locoregional nature, contemporary treatment options for MPeM have been evolving towards aggressive surgical approaches in combination with intraperitoneal chemotherapy in the form of hyperthermic intraperitoneal chemoperfusion (19).

Our study has several limitations. First, it was conducted as a retrospective review and included a small number of patients treated at a single Center, with the numbers of biphasic and sarcomatoid type cases being especially small. As a result, generalization of the findings is limited, and statistical errors are possible. Nevertheless, the findings presented are considered a first step towards a future prospective study with a greater number of patients. Additionally, because four different types of PET/CT scanners were used, PET quantitative values were harmonized by use of a software program developed to harmonize SUVs obtained with different PET/CT systems using phantom data (14).

On the other hand, despite its limitations, considering the rarity of the disease, the new findings of this study from the relatively high volume of patients for a single institution, show that FDG-PET/CT is an extremely useful modality for identifying the biopsy site of MPeM.

In addition, as CRS/HIPEC for MPeM patients with good performance status (PS) remains the gold standard of treatment, it is highly important to detect patients with MPeM who often present only with vague, nonspecific symptoms including abdominal distention, pain, nausea, and weight loss using FDG-PET/CT (21).

In conclusion, FDG-PET/CT findings showed a variety of FDG uptake (SUV_{max}) values, which were nonspecific and inadequate to pinpoint specific diagnosis. FDG-PET/CT representing glucose metabolism is a useful modality to evaluate tumor viability of MPeM as guidance for biopsy. When a diagnosis of MPeM is suggested from FDG-PET/CT imaging, examinations to determine history of exposure to asbestos as well as presence of ascites, pleural effusion, and

pleural plaque are important, because histological and immunohistochemical results are needed for diagnostic accuracy. FDG-PET/CT can help in decision-making for the therapeutic management of MPeM.

Conflicts of Interest

The Authors have no relevant financial or non-financial interests to disclose.

Authors' Contributions

Kozo Kuribayashi: Conceptualization/writing – original draft and supervision; Kazuhiro Kitajima: methodology and project administration; Toshiyuki Minami: formal analysis and visualization; Masataka Ikeda: data curation; Koichiro Yamakado: investigation; Takashi Kijima: funding acquisition, validation, writing/reviewing and editing. All Authors have read and approved the final article.

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