Original Article

자궁의 악성 혼합성 뮬러리안 종양 환자에서의 FDG PET의 역할

원자력의학원 핵의학과[1], 산부인과[2], 해부병리과[3], 하산 사디킨병원 핵의학과[4]
바수키[1,4] · 천기정[1] · 채민정 · 김문홍[2] · 김민석[3] · 최창운[1] · 임상무[1]

The Role of F-18 Fluorodeoxyglucose Positron Emission Tomography in Patients with Malignant Mixed Mullerian Tumors of the Uterus

Basuki Hidayat, M.D.[1,4], Gi Jeong Cheon, M.D.[1*], Min Jeong Chae, M.D.[1], Moon Hong Kim, M.D.[2], Min Suk Kim M.D.[3], Chang Woon Choi, M.D.[1], and Sang Moo Lim, M.D.[1]

[1]Department of Nuclear Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Korea; [2]Departement of Obstetric & Gynecology, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Korea; [3]Departement of Pathology, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Korea; and [4]Department of Nuclear Medicine, School of Medicine Padjadjaran University/Hasan Sadikin Hospital, Bandung, Indonesia

Purpose: Malignant Mixed Mullerian Tumor (MMMT) of the uterine corpus is one of the very uncommon and the most lethal tumors in the uterus. The aim of this study was to evaluate the role of FDG PET in detecting distant metastasis and residual and/or recurrent disease. **Methods:** Ten patients who underwent FDG PET for detecting distant metastasis and recurrence were included. Focal FDG accumulation was regarded as abnormal. We also reviewed serum CA 125 levels, anatomical images, and histopathological examination. **Results:** Three patients of 10 FDG PET showed abnormal FDG uptake. One had high serum CA 125 levels and high fractions of carcinomatous element on histopathologic examination. FDG PET showed metastatic lesions in unexpected locations, which could not be detected by anatomical images. Another had normal serum CA 125 levels with high sarcomatous element and CT could only detect a few lesions. The other had high serum CA 125 levels and also had high carcinomatous element. Seven patients who had no abnormal uptake on FDG PET had no clinical evidence of recurrence during the follow up period (51.7±12.2 months). The mean disease free intervals of these 7 patients were 36.4±6.0 months. Two patients with abnormal findings had never become disease-free condition during the follow up period (6.0±4.2 months. **Conclusion:** FDG PET could be a useful modality for unexpected distant metastasis and follow up tool in patients with MMMT. (Nucl Med Mol Imaging 2006;40(1):16-22)

Key Words: FDG-PET, malignant mixed Mullerian tumors

Introduction

Malignant Mixed Mullerian Tumor (MMMT) of the uterine corpus are uncommon tumors representing less than 5% of all malignant uterine tumors and these tumors are the one of the most lethal neoplasm in the uterus.[1-3] MMMT contains both carcinomatous and sarcomatous elements. The carcinomatous element is usually glandular, whereas the sarcomatous element may resemble the normal endometrial stroma (homologous) or it may be composed of foreign tissue for the uterus, such as cartilage or bone (heterologous).[1,2,4] The carcinomatous element of MMMT frequently expressed tumor-associated antigen, such as carcinoembryonic antigen 125 (CA 125).[5] The most frequent spreading sites of MMMT are the pelvic lymph nodes, peritoneal cavity, lung and liver.[4] The extent of tumor is the most important single factor of prognosis. This disease has already extended outside the uterus in 40-60% at the time of diagnosis.[1,4] The main strategy of management for MMMT is surgery, followed by external

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• Address for reprints: Gi Jeong Cheon, MD, PhD, Department of Nuclear Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, #215-4, Gongneung-dong, Nowon-gu, Seoul 139-706, Korea
Tel: 82-2-970-1341, Fax: 82-2-970-1341
E-mail: larry@kcch.re.kr

irradiation and/or chemotherapy. Unfortunately, both local and distant relapsing rate after surgery are high.[4,6] The most common sites of recurrence are peritoneum, pelvic cavity, and lung. For patients who had recurrence after treatment, the 5-year survival rate was only 4%, with a median survival was 6 months.[6] Therefore, early detection for disease in patients with MMMT is important to make decision of treatment at the time of diagnosis and during the follow up period after treatment. Metabolic imaging such as FDG PET can be used for detecting distant metastasis and recurrence or residue after treatment. The advantage of FDG PET is easily to perform whole body imaging and could detect the unexpected distant metastasis. Also FDG PET could not depend on on the size of lesions and anatomical change after surgery. We reviewed FDG PET images of ten patients with MMMT. Serum CA 125 levels, anatomical images and histopathological results were also reviewed. The aim of this study was to evaluate the role of FDG PET, comparing with anatomical images, and serum CA 125 levels in detecting for distant metastasis and residual or recurrence of disease.

Materials and methods

Patients

The medical record of eleven patients diagnosed with MMMT of the uterus, who underwent whole body FDG PET between 1997 and 2004 were reviewed, retrospectively. We reviewed 11 patients totally. 1 of 11 patients had been excluded from this study; because of this patient had two kind of malignancy; MMMT and colon cancer. Among 10 patients included (mean age; 59±11 years, range; 45-78 years), 1 patient underwent FDG PET 4 months before surgery and 9 patients after surgery for work up (8 in 9) of recurrence or residual tumor (1 in 9). Treatment strategy for MMMT of the uterus consisted of surgery, followed by external irradiation and/or chemotherapy. Serum CA 125 levels, anatomical images, and FDG PET were used to determine distant metastasis and residual or recurrence of the disease. The cause of death was determined by review of medical and correspondence records.

FDG PET

FDG PET was obtained using a dedicated PET scanner (ECAT HR plus; Siemens/CTI, Knoxville, TN). After the patients fasted for 6 hours, 370 MBq (10 mCi) FDG was administrated intravenously. Serum glucose levels were obtained immediately before the FDG injection. The image acquisition started at 50 min after FDG injection. Images were acquired in 2-dimensional over 5-6 bed from orbitomeatal line to the midfemoral line. Emission data were acquired for 8 min per bed and transmission data for 3 to 5 min. To reduce urinary tract artificial activity, a foley catheter was placed before injection of FDG. All patients received intravenous hydration and diuretics (intravenous furosemide, 20 mg) immediately before FDG PET image acquisition. Two nuclear medicine physicians interpreted FDG PET. Focal accumulation of FDG, which could be distinguished from physiologic accumulation, was regarded as abnormal or pathologic. The maximal standardized uptake values (SUV) were used for quantitative analysis. The SUV were obtained by placed region of interest (ROI) around the lesion that had been suspected metastasis or recurred sites on visual analysis. The SUV was calculated as follows: SUV = (decay correction activity [kBq] per milliliter of tissue volume)/(injected FDG activity [kBq] / body mass [g]).

Histopathological Evaluation

In review of histopathological surgical specimen, we evaluate the fractions about the two elements. The percentage of fraction of carcinomatous and sarcomatous elements was determined by microscopic re-examination of entire glass slides from tumor specimen at the first time of diagnosis.

Results

One patient underwent FDG PET 4 months before surgery and 9 patients within 1 to 26 months after surgery. Clinical stage at the time of operation were stage I in 5 patients, stage III in 4 patients and stage IV in 1 patient. 5 of 10 patients had high fractions of sarcomatous elements and the other 5 patients had high fractions of carcinomatous element based on histophatologic re-examination.

Table 1. Patients Characteristics and the Results of Images, Pathology, and Tumor Marker

No	Age (yrs)	Stage	CE : SE (%)	CA 125 (U/ml)	FDG PET (SUV)	Anatomical image
1	78	IIIa	60 : 40	474.73	Rt. supraclavicular node (2.1) LLL (2.8 and 6.2)GB fossa (5.4) Flexure hepatica (4.6) flexure lienalis (4.3) omentum (4.6)	Omental mass, peritoneal seeding
2	56	IV	30 : 70	7.67	Retroperitoneum (11.1) both paraaortic nodes (7.0 and 5.6) both iliac nodes (6.8 and 8.9)	Lt. paraaortic node 1.8 cm Lt aortocaval node < 1 cm
3	57	IIIa	5 : 95	13.66	-	-
4	46	IIIc	10 : 90	13.25	-	-
5	63	Ic	50 : 50	12.58	-	-
6	69	Ic	20 : 80	16.34	-	-
7	72	Ib	90 :10	9.55	-	-
8	50	Ib	80 : 20	9.09	-	-
9	56	Ic	60 : 40	-	-	-
10	45	IIIa	70 : 30	49.31	Posterior area of bladder (8.9) pelvic mass (14.8)RLQ mass(6.8)	Endometrial mass, Rt. Ovary, posterolateral mass of cervix, RLQ mass

CE:SE= carcinomatous element:sarcomatous element fraction from histopatologic specimen, Rt=right, LLL=left lower lobe of the lung, GB =gall bladder, Lt=left, RLQ=right lower quadrant of abdomen

Table 2. Duration of Follow-up Period and Disease-free Interval in Subjects with and without Abnormal FDG Uptake on FDG PET

No	Age (years)	FDG PET	Interval from surgery to FDGPET (mo)	Disease free-interval (mo)	Duration of follow up (mo)
1	78	+	1	-	3
2	56	+	5	-	9
3	57	-	7	34	41
4	46	-	16	27	43
5	63	-	13	34	47
6	69	-	26	44	70
7	72	-	25	43	68
8	50	-	9	34	43
9	56	-	11	39	50

mo = months

Treatment strategy using combination surgery and/or external radiotherapy and chemotherapy underwent in 9 of 10 patients. One patient only underwent surgery. FDG PET after surgery detected residual disease in 2 patients, while 7 patients had not showed any abnormality of FDG PET. Table 1 represents the profile of the patents. One patient who performed FDG PET before surgery, patient had high levels of CA 125 and high fractions (70%) of carcinomatous element. FDG PET of this patient showed pathologic mass with central metabolic defect in posterior and the upper areas of bladder (uterus and ovary) and pathologic lesion in right lower quadrant of abdomen. MRI and CT showed same results for pathologic lesions located in the uterus, right ovary, posterolateral aspect of cervix and right lower quadrant of abdomen. Nine patients who performed FDG PET during follow up period. Two of 9 patients (patient No. 1, No. 2) had clinically recurred. One of 2 patients had high sarcomatous element, while the other one had high carcinomatous element. Serum CA 125 levels elevated only in the last patient, while FDG PET images of all 2 patients showed pathologic lesions (Table 3). In patient No. 1, the location of abnormal uptake FDG PET performed at 5 months after surgery, were in left lung, abdomen (omentum, flexure hepatic and flexure lienalis), right supraclavicular lymph node and area of gall bladder fosse (Fig. 1). This findings were concordance with high serum CA 125 levels (473.73 U/ml) and abdominopelvic CT findings. Chest x-ray at the time of

Table 3. Diagnostic Performance of Serum CA 125 Level and FDG PET Scan in Detecting Recurrence of MMMT After Treatment

		Clinically Recurrence	
		+	-
Serum CA 125 Levels	+	1	0
	-	1	7
FDG PET	+	2	0
	-	0	7

diagnosis did not showed any metastatic lesions in both lungs. Histopathologic re-examination of this patient showed high fraction of carcinoma element. This patient died because of recurred disease at 4 months after FDG PET. In patient No. 2, FDG PET performed 1 month after surgery, showed pathologic FDG uptake in retroperitoneal, both paraaortic, and iliac lymph nodes chains. This patient had 7.62 U/ml in serum CA 125 levels (within normal limit: 0-<35 U/ml) and 70% sarcomatous element based on histopathologic re-examination. CT finding was concordance with FDG PET for lymph nodes in both paraaortic area, but CT could not show iliac lymph node enlargement and detect mass in retroperitoneal area (Fig. 2). This

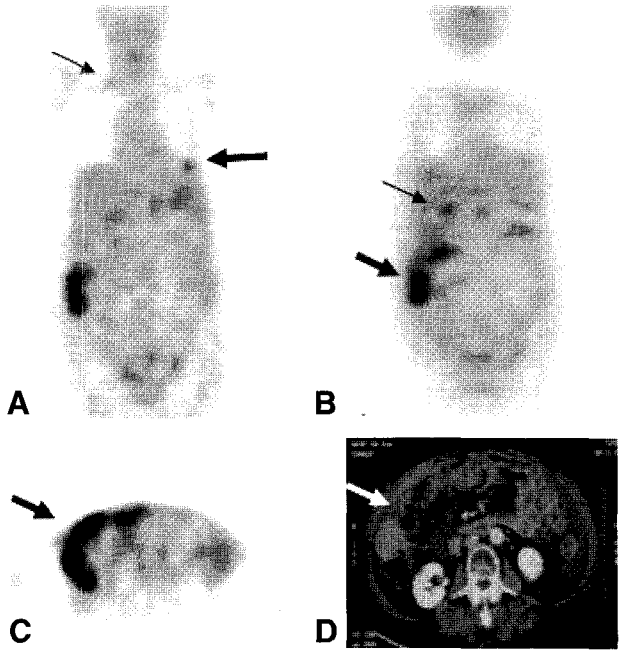

Fig 1. FDG PET and CT of patient No. 1 who had high level of serum CA 125. FDG PET shows pathologic lesions in supraclavicular lymph nodes (A; thin black arrow), left lower lobe of lung (A; thick black arrow), gall bladder fosse area (B; black arrow) and omentum (B and C; thick black arrow). CT image shows an omental mass only (D; arrow). The other lesions cannot show by CT.

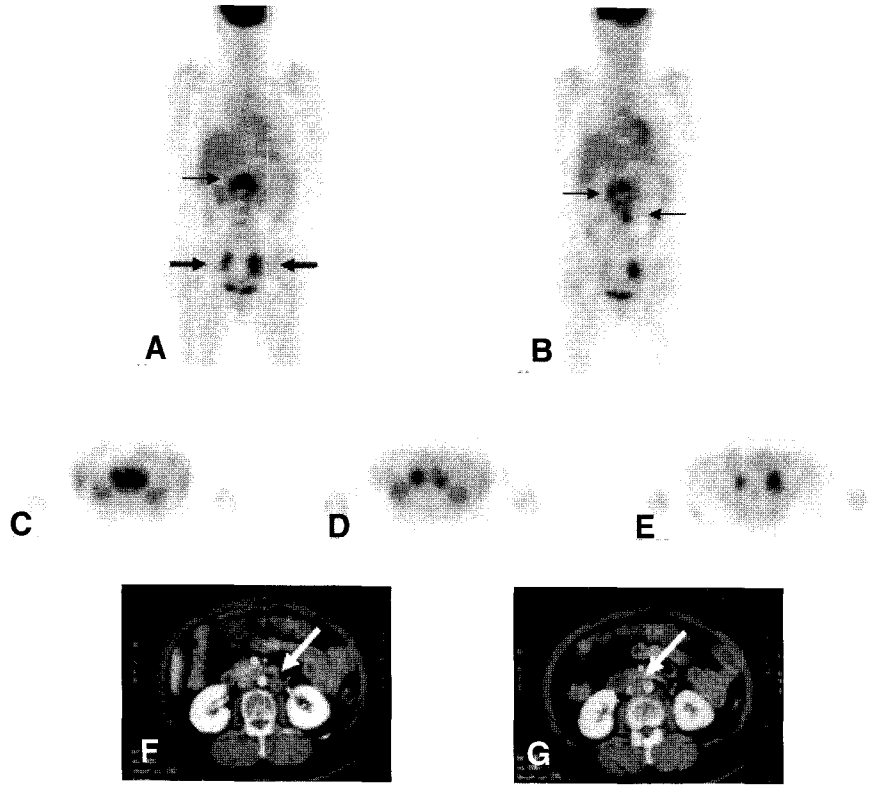

Fig. 2. FDG PET and CT of patient No. 2 who had normal level of serum CA 125 level and high fraction of sarcomatous element. FDG PET image show pathologic lesions in retroperitoneal lymph nodes (A; thin black arrow and C), paraaortic lymph node chains (B; thin black arrow and D) and iliac lymph node chains (A; black thick arrow and E). CT also show paraaortic lymph nodes enlargement (F and G).

Table 4. Mean Follow-up Period and Disease-free Interval Difference Between Subjects with and without Abnormality in FDG PET after Treatment

FDG PET (n)	Mean follow up period (mo)	Mean disease free Interval (mo)
- (n=7)	51.7±12.2	36.4±6.0
+ (n=2)	6.0±4.2	-

mo = months

patient hospitalized because recurred diseases at 2 days after FDG PET study (1 month after surgery). Seven of 9 patients performed FDG PET during follow up period; FDG PET did not showed any suspected pathologic lesions. Anatomical images were concordance with FDG PET. Also those findings were concordance with serum tumor marker levels. The range of serum CA 125 levels in these 6 patients was within normal limit (9.09 - 16.34 U/ml). In 1 patient, squamous cell carcinoma antigen (SCC) had been used by tumor marker and the SCC level in serum was normal ($\leq$ 2 ng/ml). No one of 7 patients had high level of tumor marker and pathologic lesions on anatomical imaging during follow up time. 3 of 7 patients had high fractions of sarcomatous element, 3 of 7 patients had high fractions of carcinomatous elements and 1 patient had even fraction of both elements. The mean disease free-intervals for these 7 patients were 36.4±6.0 months, while those of 2 patients who had abnormality on FDG PET were 0.0 month. The mean follow up period of those 7 patients (51.7±12.2 months) was longer comparing to 2 patients who had pathologic lesions on FDG PET (6.0±4.2 months) (Table 4).

Discussion

MMMT are containing both carcinomatous and sarcomatous elements. The carcinomatous element is usually glandular, whereas the sarcomatous element may resemble the normal endometrial stroma (homologous) or it may be composed of foreign tissue for uterus, such as cartilage or bone (heterologous). [1,2,4] Elevated levels of tumor-associated antigen such as CA 125 have been reported in some patients with MMMT. The carcinomatous element frequently expressed that antigen. Histological work for 35 MMMT tissue samples revealed positive staining for CA 125 showed in 46% of the tumors.[5] Ginath et al have assessed the correlation between the presence of CA 125 in endometrial cancer tissue and elevated CA 125 serum levels. They reported that positive staining for CA 125 represented 72.7% of MMMT tissue, but only 54.4% of MMMT patients were having elevated serum CA 125 levels.[7] In the endometrial carcinoma, serial CA 125 assay is a good indicator of disease activity and a useful biochemical tool for post-treatment surveillance.[8] Cherchi et al reported that high CA 125 level (>35 U/ml) were detected in 50% of relapsed cases during follow up and only in 5.1% of disease-free cases.[9] In the study of Takami et al, patients with endometrial cancer showed decreased serum CA 125 levels after surgery and then became the same as for those of the normal postmenopausal women.[10] In this study, 3 patients had abnormal finding on FDG PET. 1 patient (patient No. 10) underwent FDG PET before surgery and this patient had high serum CA 125 level and high fraction (70%) of carcinomatous element. 2 patients performed FDG PET during follow up period. 1 of 2 patients (patient No. 1) had high serum CA 125 level and high fraction of carcinomatous element. The other one subject (patient No. 2) had serum CA 125 level <35 U/ml and high fraction of sarcomatous element. According to the discrepancy between FDG PET and serum CA 125 level, it could be occurred because of the expression of CA 125 antigen related to the carcinomatous element. Other possible explanation might be mechanism preventing the access of CA 125 into the circulation.[7,8] Among 7 patients did not show any pathologic lesions on FDG PET during follow up period. These patients had normal serum CA 125 levels and anatomical imaging also did not show any abnormal finding. Three of 7 patients had high fractions of sarcoma elements, and another 3 patients had high fractions of carcinoma elements and 1 patient had even fraction of both elements. In consistence of serum CA 125 levels as we mentioned before, diagnostic performance of serum CA 125 for detecting recurrence of MMMT after treatment could be affected. In this study, serum CA 125 levels only could detect recurrence in patients who had

high fractions of carcinomatous elements. But CA 125 levels could not detect recurrence in patient who had high fractions of sarcomatous elements. Serum CA 125 levels had lower sensitivity than FDG PET (50% vs. 100%). However, both modalities had equal specificities (Table 3). MMMT have been traditionally regarded as subtype of sarcoma.[2,11] However, initially the behavior of uterine MMMT is dictated by carcinomatous element.[2,11-13] Nevertheles, tumor phenotype often alters during time. The metastasis mechanism of sarcoma is known to through hematogenous spread and that of carcinoma is lymphatic spread.[2,13-15] Because of that, the most frequently spreading areas of MMMT are not only in pelvis, abdomen and retroperitoneal lymph nodes (lymphatic spread), but also in lung and liver (hematogenous spread).[4,14,16] In our study, 1 patient (patient No. 2) who had high fraction of sarcomatous element base on histopathologic re-examination, had abnormal findings in retroperitoneal, paraaortic and iliac lymphatic chains on FDG PET. The other patient (patient No. 1) was in opposite condition, she had high fraction of carcinomatous element and FDG PET showed pathologic FDG uptake in right supraclavicular lymph node, flexura hepatica, flexure lienalis, omentum, left lung and gall bladder fosse area. These findings implied that two routes of metastasis are interlinked and inseparable.[15] In the patient No. 2, CT only could show enlargement of l paraaortic lymph nodes. FDG PET, as already well recognized, has been widely used for detection of early recurrence that cannot be diagnosed with conventional radiology imaging studies. Also FDG PET is known to be more accurate than CT or MRI in detecting distant metastasis or recurrent lymph nodes in several human cancers.[17] Saga et al. had reported that detecting ability for recurrence of endometrial carcinoma, FDG PET had 93.3% accuracy, 100% sensitivity and 88.2% specificity. These value are better than CT and/or MRI which had 85.0% accuracy, 84.6% sensitivity and 85.7% specificity.[18] The higher capability of FDG PET over CT and/or MRI could be caused by the reason that FDG PET did not depend on size of lesion and could differentiate between malignant from benign beyond size. Malignant lesions even less than 1 cm in diameter that manifest high FDG uptake, can be differentiated from benign by using FDG PET.[19,20] The other advantage of FDG PET is that it can show whole body image at once and detect unexpected distant metastasis or recurrence especially in the unusual location. In Saga et al. study, FDG PET can detect peritoneal dissemination, bone, lung and lymph nodes metastasis that cannot detect by CT or MRI.[18] In our study, FDG PET showed abnormal uptake in supraclavicular lymph nodes, lung and gall bladder fosse area (patients No. 1). To evaluate prognostic factors or survival rates was not the purpose of our study. Because of that, we did not want to find out both of the survival rate and the median disease-free interval. But, based on medical record reviewed, we obtained 7 patients who did not showed any abnormal findings on FDG PET and anatomical imaging during follow up period. The mean disease free-interval for these 7 patients was 36.4±6.0 months and mean follow up period was 51.7±12.2 months. While in 2 patients who had pathologic lesions on FDG PET, mean follow up period were 6.0±4.2 months and never became disease-free condition (Table 4). One of 2 patients underwent FDG PET at 5 months after surgery. This patient died at 4 months after FDG PET. In the other 1 patient, FDG PET was performed at 1 month after surgery and she hospitalized at the same time. Based on this finding, we thought the extent of disease on FDG PET could be one of the prognostic factor for MMMT patients. This study had limitation in sample size, spectrum of disease and histopathologic examination as gold standards in follow up study. However, we found that FDG PET had higher capability than serum CA 125 levels or anatomical imaging for detecting recurrence of MMMT during follow up period. In conclusion, we would like to suggest that FDG PET could be useful modality for detecting distant metastasis of the diagnosis stage and recurrence during follow up MMMT patients after treatment. FDG PET could be one of the significant modality for distant metastasis and follow up, especially in the case, which had high fractions of sarcomatous elements, because in those cases, serum CA 125 levels were not reliable and some lesions could be missing in anatomical images.

요 약

목적 : 악성 혼합 뮬러리안 종양(malignant mixed Mullerian

tumor, MMMT)은 매우 드문 자궁의 악성질환으로 매우 치명적인 임상경과를 보인다. 현재까지의 적절한 치료법은 수술적으로 완전제거를 하는 것이다. 이 연구에서는 MMMT 환자에서 진단시 병기결정과 추적관찰에 재발 및 잔류암을 진단하는데 FDG PET의 역할을 알아보고자 하였다. **대상 및 방법**: MMMT로 진단 후 수술적 치료전 병기결정을 위해 검사한 환자가 1명, 수술 및 치료후 재발 및 잔류암을 검사하기 위해 9명의 환자가 FDG PET을 시행하였다. PET의 판독은 국소 대사항진 병소를 주로 육안적으로 판정하였다. 추적관찰 기간 동안의 종양표지자 CA 125 값과 영상검사, 병리조직 소견을 비교 평가하였다. **결과**: 10명의 환자 중 3명에서 PET에서 이상 섭취소견이 있었다. FDG 양성인 환자의 한 예에서는 CA 125가 증가하였으며 이 경우 병리학적 소견에서 선암분획(carcinomatous element)이 높은 양상이었다. 이 경우 해부학적 영상법으로 찾을 수 없는 병소를 PET 영상에서만 찾을 수 있었다. 이에 반하여 다른 한 예에서는 CA 125가 추적관찰기간 동안 정상이었는데 PET 영상에서 재발 병소를 찾을 수 있었으며 해부학적 영상법보다 더 많은 병소를 찾을 수 있었다. 이 경우는 병리학적인 소견이 주로 육종분획(sarcomatous element)이 높은 양상이었다. 다른 한 예에서도 추적 기간 동안의 CA 125 상승이 관찰되었고 이 경우 선암분획이 역시 높게 관찰되었다. PET 검사에서 이상 소견이 없는 7 예에서는 추적관찰 기간(51.7±12.2 개월) 동안 종양표지자의 상승이나 재발의 소견은 없었으며 평균 재발없는 생존기간이 36.4±6.0 개월이었다. 추적기간 중 PET상 이상 소견이 있었던 2명의 예에서는 추적관찰 기간(6.0±4.2 개월) 내에 모두 재발이 확인되었다. **결론**: FDG PET은 MMMT 환자의 진단 당시 예상치 못했던 원위부의 전이나 치료 후 추적관찰 기간 동안 재발이나 잔류암의 진단에 유용한 검사법으로 이용할 수 있겠다.

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