Value of ^{18}F -FDG PET/CT in the Detection of Ovarian Malignancy

Taegyu Park · Sinae Lee · Soyeon Park ·
Eunsub Lee · Kisoo Pahk · Seunghong Rhee · Jaehyuk Cho ·
Chulhan Kim · Jae Seon Eo · Jae Gol Choe · Sungeun Kim

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Abstract

Purpose Ovarian cancer is a leading cause of gynecologic malignancy. As symptoms of ovarian cancer are nonspecific, only 20 % of ovarian cancers are diagnosed while they are still limited to the ovaries. Thus, early and accurate detection of disease is important for an improved prognosis. For the accurate and effective diagnosis of ovarian malignancy on ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT), we analyzed several parameters, including visual assessment.

Method A total of 51 peritoneal lesions in 19 patients who showed ovarian masses with diffuse peritoneal infiltration were enrolled. Twelve patients were confirmed to have ovarian malignancy and seven patients with benign disease by pathologic examination. All patients were examined by ^{18}F -FDG PET/CT, and an additional 2-h delayed ^{18}F -FDG PET/CT was also performed for 15 patients with 42 peritoneal lesions. We measured semiquantitative parameters including maximum and mean standardized uptake values (SUVmax, SUVmean), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) on a 1-h initial ^{18}F -FDG PET/CT image (Parameter₁) and on a 2-h delayed image (Parameter₂). Additionally, retention indices of each parameter were calculated, and each parameter among the malignant and benign lesions was compared by Mann-Whitney *U* test. We also assessed the

visual characteristics of each peritoneal lesion, including metabolic extent, intensity, shape, heterogeneity, and total visual score. Associations between visual grades and malignancy were analyzed using linear by linear association methods. Moreover, a receiver operating characteristic (ROC) curve was analyzed to compare the effectiveness of significant parameters.

Result In a comparison between the malignant and benign groups in the analysis of 51 total peritoneal lesions, SUVmax₁, SUVmean₁, and TLG₁ showed significant differences. Also, in the analysis of 42 peritoneal lesions that underwent an additional 2-h ^{18}F -FDG PET/CT examination, SUVmax_{1,2}, SUVmean_{1,2}, TLG₂, and the RI of TLG showed significant differences between the malignant and benign groups. MTV did not show significant differences in either the analysis of 51 peritoneal lesions or of 42 lesions. Regarding visual assessments, metabolic intensity, shape, heterogeneity, and total visual score showed an association with malignancy. In the ROC analysis, the AUC of the visual score was larger than the AUC of other parameters in both the analyses of 51 peritoneal lesions and of 42 lesions.

Conclusion Although further study with a larger patient population is needed, the visual assessment of ^{18}F -FDG PET/CT imaging has a primary role in the detection of malignancy in ovarian cancer patients with assistance from other semiquantitative parameters.

T. Park · S. Lee · S. Park · E. Lee · J. S. Eo
Department of Nuclear Medicine, Korea University Guro Hospital,
Seoul, South Korea

K. Pahk · S. Rhee · J. Cho · J. G. Choe · S. Kim (✉)
Department of Nuclear Medicine, Korea University Anam Hospital,
#73, Incheon-ro, Seoungbuk-gu, Seoul 136-705, South Korea
e-mail: seiong@korea.ac.kr

C. Kim
Department of Nuclear Medicine, Korea University Ansan Hospital,
Ansan, South Korea

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Introduction

Ovarian cancer is the second most common gynecological cancer in Western women, and also in Korea, next to uterine

cervical cancer [1, 2]. As the symptoms are nonspecific, only 20 % of ovarian cancers are diagnosed while they are still limited to the ovaries [3]. This is why ovarian cancer is the leading cause of death among gynecological cancers. Therefore, early detection and characterization are important and continuing challenges. Imaging modalities including computed tomography (CT) and magnetic resonance imaging (MRI) have been proposed as adjunct methods to conventional transvaginal ultrasonography. However, despite having higher sensitivity and specificity than ultrasonography, a preoperative diagnosis using CT or MRI is often indeterminate [4, 5]. Recently, ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/CT has gained widespread acceptance in diagnosing and staging various cancers. Nevertheless, most studies using ^{18}F -FDG PET/CT in ovarian cancer patients have been limited to detecting recurrence or distant metastasis, and relatively few studies have demonstrated the effectiveness of ^{18}F -FDG PET/CT in detecting primary ovarian cancer [6, 7]. Moreover, although these studies suggest the high diagnostic value of ^{18}F -FDG PET/CT in detecting primary ovarian cancer, some pitfalls also exist. False-positive results, including those resulting from pelvic inflammatory disease, an ovarian cyst, and endometriosis, and false-negative results including those from borderline malignancies have been reported [6, 8, 9].

Some parameters are used as diagnostic criteria for ^{18}F -FDG PET/CT to increase the accuracy of detecting malignancy. The most typical diagnostic criterion parameter is the maximum standardized uptake value (SUVmax). However, SUVmax has limitations, because it is also increased in benign conditions related to physiologic variations, degeneration, and infection or inflammation, as well as in malignant lesions [10]. One of the methods to overcome this problem is to use dual-time point PET imaging in the identification of malignant lesions. Various studies have reported the effectiveness of dual-time point PET imaging in different malignancies [11–14]. They suggested the retention index (RI), the percentage change between the 1-h SUVmax and the 2-h SUVmax, as a diagnostic criterion. However, there are few studies on patients with ovarian cancers. Furthermore, from the view of cost-effectiveness, there is some inefficiency, as delayed 2-h ^{18}F -FDG-PET/CT requires additional costs and radiation exposure.

Recently, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have become remarkable parameters as prognostic factors for various cancers [15–18]. However, there are only a few studies using MTV or TLG in ovarian cancer patients; most of these studies used MTV and TLG as prognostic factors of recurrence rather than as diagnostic factors [19, 20].

In practice, visual analysis is the most important factor when interpreting ^{18}F -FDG-PET/CT imaging. Miller et al. [21] suggested the visual scoring of ^{18}F -FDG PET as a

prognostic factor in cervical cancer patients. They analyzed characteristics of the primary tumor by size, shape, and heterogeneity of ^{18}F -FDG uptake. However, to our knowledge, there are no reports regarding the visual assessment of ^{18}F -FDG-PET/CT imaging for ovarian cancer diagnosis.

The aim of our study was to find the optimal parameters for ^{18}F -FDG-PET/CT imaging to improve the diagnostic accuracy of ovarian cancers.

Methods

Patients

We retrospectively reviewed patients who underwent ^{18}F -FDG PET/CT for staging work up of ovarian masses with peritoneal infiltration that were identified on abdomen–pelvis CT or pelvic MRI from March 2009 to February 2011 at our hospital. All patients were examined by physical examination, pelvic ultrasonography, abdomen–pelvis CT, or pelvic MRI. Patients who had a history of other types of cancers or a previous treatment history of ovarian cancer were excluded. All patients underwent a gynecologic operation and the intra-peritoneal lesions were pathologically confirmed. Total of 19 patients were selected for this study evaluation.

^{18}F -FDG PET/CT Image Acquisition

^{18}F -FDG PET/CT images were obtained on a PET/CT scanner (Gemini TF; Philips Medical Systems, Cleveland, OH). All patients fasted for at least 6 h and had serum glucose levels less than 140 mg/dL before scanning. Dual-time point PET/CT images were obtained at 60 and 120 min. One hour and 2 h after an intravenous injection of 370–555 MBq ^{18}F -FDG according to the body weight, CT scans were obtained followed by PET scans for 1 min per bed. The PET unit has an axial field-of-view of 18 cm and a spatial resolution of 4.4 mm. A low-dose CT scan was obtained for attenuation correction and localization on a 16-slice multidetector helical CT unit using the following parameters: 120 kVp; 50 mA; 0.75-s rotation time; 0.75-mm slice collimation; 4-mm scan reconstruction, with a reconstruction index of 4 mm; 50-cm field of view, and 512×512 matrices. PET data were reconstructed iteratively using a three-dimensional row action maximum likelihood algorithm (RAMLA) with low-dose CT datasets used for attenuation correction. Maximum intensity projection (MIP), cross-sectional views, and fusion images were reviewed.

Image Interpretation and Quantitation

All images were interpreted and analyzed by two experienced nuclear medicine physicians on a dedicated workstation (Extended Brilliance Workspace 4.0 with a PET/CT viewer for

automated image registration; Philips, Amsterdam, Netherlands). We used all available clinical information, including radiological examinations such as CT and MRI.

We defined each intraperitoneal lesion that showed relatively increased metabolism compared with the metabolisms of adjacent normal tissues. CT and MRI findings were also considered to select lesions. And the characteristics of each lesion, including ovarian lesions, were evaluated independently, as lesion-by-lesion analysis.

For the visual assessment, we evaluated each intraperitoneal lesion by using several parameters, including metabolic extent, shape, intensity, and heterogeneity (Table 1). Metabolic extent was measured on background CT and was scored as 0 for less than 4 cm, 1 for 4–10 cm, and 2 for more than 10 cm. Shape was scored as 0 for spherical, 1 for mixed, and 2 for non-spherical. Metabolic intensity of each intraperitoneal lesion was scored based on a comparison with liver activity, as 0 for hypometabolism or isometabolism, 1 for mild hypermetabolism, 2 for moderate hypermetabolism, and 3 for intense hypermetabolism. Heterogeneity was scored as 0 for homogeneous, 1 for moderate, and 2 for marked, where moderate heterogeneity was approximately a 10–30 % count variation across the tumor and marked was a variation of more than 30 % [21]. Then, the scores of each parameter were summed for a “visual score.” Thus, the visual score could range from a minimum of 0 to a maximum of 9. Discordant results were fully discussed and interpreted by consensus of the two physicians.

For a semi-quantitative analysis, we measured the standardized uptake values (SUVs) of intraperitoneal lesions by drawing a region of interest (ROI).

$$\text{SUV} = \text{tissue concentration} \times \text{injected dose}^{-1} \\ \times \text{body weight}^{-1}$$

Table 1 Scoring method for visual assessment

Parameters	Score	Scoring criteria
Metabolic extent	0	<4 cm
	1	4–10 cm
	2	>10 cm
Metabolic intensity	0	Hypo/Isometabolism
	1	Mild hypermetabolism
	2	Moderate hypermetabolism
	3	Intense hypermetabolism
Metabolic shape	0	Spherical
	1	Mixed
	2	Non-spherical
Metabolic heterogeneity	0	Homogeneous
	1	Moderate heterogeneous (10–30 %)
	2	Marked heterogeneous (>30 %)

All parameters were measured on 1-h ^{18}F -FDG PET/CT image

An ROI was placed over the area of maximum activity within the intraperitoneal lesions, and the SUVmax was obtained as the highest SUV of the pixels within the ROI.

Furthermore, we measured the MTV of each ROI. We delineated a volume of interest (VOI) over the intraperitoneal lesions and the SUV-based automated contouring software calculated the MTV. Fifty percent of the local maximum intensity was used as the threshold intensity value, and this was deemed reasonable from phantom studies [17, 22]. The program also analyzed the mean of the SUV (SUVmean) as well as the TLG of each VOI, which was calculated by multiplying MTV by SUVmean. All semi-quantitative parameters were measured on 1-h and 2-h ^{18}F -FDG PET-CT imaging by using the same VOIs. Additionally, the RI of each parameter was calculated by subtracting the parameter from the 1-h image (Parameter₁) from the parameter from the 2-h image (Parameter₂) and dividing by Parameter₁.

$$\text{RI} = (\text{Parameter}_2 - \text{Parameter}_1) \times 100 \times \text{Parameter}_1^{-1}$$

Statistical Analysis

Statistical calculations were performed using SPSS version 18.0 (SPSS, Chicago, IL). Semi-quantitative parameters including SUVmax, SUVmean, MTV, and TLG on both the 1-h and 2-h images and the RI of each parameter were compared between the malignant and benign groups by using a Mann–Whitney *U* test.

Visual parameters including metabolic extent, shape, intensity, heterogeneity, and total visual score were compared between the two groups using a linear by linear association for trend test. A value of $P < 0.05$ was considered statistically significant.

Results

Patients' Characteristics

A total of 19 patients were enrolled and reviewed. The mean age of the patients with malignancy was 59.6 ± 10.0 years and that of patients with benign lesions was 42.7 ± 11.9 years. All 19 patients showed diffuse peritoneal infiltration on preoperative CT or MRI. The preoperative CT or MRI findings of all patients suggested malignancy as the first differential diagnosis, but other conditions could not be excluded. Twelve patients were pathologically diagnosed with primary ovarian cancers: eight serous adenocarcinomas, three mucinous adenocarcinomas, and one endometrioid carcinoma. We considered all intraperitoneal lesions in patients with malignancy as

malignant lesions, while only some were pathologically confirmed. The remaining seven patients had benign lesions: two due to tuberculosis, one due to pelvic inflammatory disease (PID), and four due to endometriosis. In the same way, we regarded all intraperitoneal lesions from patients with benign lesions as non-cancerous.

A total of 51 intraperitoneal lesions from 19 patients were detected. Thirty-two lesions were identified in patients with malignancy and 19 lesions in non-cancerous patients. The mean numbers of identified intraperitoneal lesions from patients with malignancy was $2.7 (\pm 1.2)$ and from patients with benign lesions was $2.7 (\pm 1.6)$. They were not significantly different ($P=0.761$). The characteristics of the enrolled patients and intraperitoneal lesions are summarized in Table 2.

¹⁸F-FDG PET/CT Findings and Statistical Results

Because four patients did not undergo an additional delayed ¹⁸F-FDG PET/CT examination, we analyzed the delayed parameters and RI of each parameter for only 15 patients with 42 intraperitoneal lesions. On the other hand, the parameters of 1-h imaging including SUVmax₁, SUVmean₁, MTV₁, TLG₁, and all visual parameters were analyzed in a total of 51 intraperitoneal lesions. All nine intraperitoneal lesions from the four patients who were not examined by delayed ¹⁸F-FDG PET/CT were malignant.

Analysis of Quantitative and Visual Parameters on 1-h ¹⁸F-FDG PET/CT

The mean SUVmax₁ of 32 malignant lesions was 7.559 (95 % confidence interval [CI], 6.633–8.486), whereas that of the 19 benign lesions was 4.179 (95 % CI, 3.259–5.099). Because of the limitation of the nonparametric distribution of the patients, direct comparisons of the mean value of SUVmax₁ between the two groups would be meaningless. However, we could identify a significant difference between the two groups by a

Mann–Whitney *U* test, and malignant lesions had higher SUVmax₁ values than benign lesions ($P<0.001$). Moreover, the SUVmean₁ of malignant lesions was 4.5 (95 % CI, 3.961–5.039), while it was 2.579 (95 % CI, 1.915–3.243) in benign lesions; the values were significantly different ($P<0.001$). The mean TLG₁ value of malignant lesions was 302.196 (95 % CI, 75.669–528.723), while that of benign lesions was 130.458 (95 % CI, 8.508–252.408). They also showed a significant difference ($P=0.035$). However, the mean MTV₁ value of malignant lesions was 61.015 (95 % CI, 15.331–106.698), while that of non-cancerous lesions was 113.825 (95 % CI, –24.025 to 251.674), and they were not significantly different ($P=0.173$).

In the visual assessment, we analyzed whether higher scores had a tendency to predict malignancy by using a trend test. In the visual assessment of metabolic extent, extended hypermetabolism of intraperitoneal lesions had no statistically significant tendency to predict malignancy ($P=0.372$). However, non-spherical hypermetabolic lesions tended to be more malignant than spherical types ($P<0.001$). Moreover, intense hypermetabolic lesions ($P<0.001$) and heterogeneous hypermetabolic lesions ($P=0.004$) had tendencies to predict malignancy. Regarding total visual scoring, a high visual score had a statistically significant tendency to predict malignancy ($P<0.001$). The mean score of malignant lesions was 5.63 (95 % CI, 4.94–6.31), while that of benign lesions was 2.26 (95 % CI, 1.50–3.03). ¹⁸F-FDG PET/CT images of some patients are shown in Fig. 1 and these results are summarized in Table 3.

To compare the usefulness of each parameter that showed a statistically significant diagnostic value for malignancy, we evaluated a receiver operating characteristic (ROC) curve (Fig. 2). The area under the curve (AUC) of SUVmax₁ was 0.898 ($P<0.001$); that of SUVmean₁ was 0.856 ($P<0.001$); that of TLG₁ was 0.678 ($P=0.035$); and that of visual score was 0.905 ($P<0.001$). From these results, visual score had the highest value in diagnosing malignancy, and the estimated optimal cut-off value was 4.5 (Table 4).

Table 2 Characteristics of patients

Characteristics	Ovarian cancer patients	Non-cancerous patients
Number of patients	12	7
Median age at diagnosis (years)	59.6±10.0	42.7±11.9
Histopathology	8 serous adenocarcinomas 3 mucinous adenocarcinomas 1 endometrioid carcinoma	1 PID 2 tuberculosis 4 endometriosis
Total numbers of pelvic lesions	32	19
Mean numbers of pelvic lesions per patient	2.7±1.2	2.7±1.6

Data are presented as mean±SD

PID pelvic inflammatory disease

Fig. 1 ^{18}F -FDG PET/CT images of intraperitoneal lesions. **a** Patient with endometrioid carcinoma shows intense, marked heterogeneous and non-spherical hypermetabolic lesion. Visual score of the lesion was 9. **b** Patient with tuberculosis shows intense, homogeneous and spherical hypermetabolic lesion. Visual score of the lesion was 4. **c** Patient with endometriosis shows mild, moderate heterogeneous and mixed-spherical hypermetabolic lesion. Visual score of the lesion was 4

Analysis of Semi-quantitative Parameters on Dual-Time ^{18}F -FDG PET/CT

The 42 intraperitoneal lesions consisted of 23 malignant lesions and 19 benign lesions, and were analyzed to identify the usefulness of various parameters measured on delayed 2-h ^{18}F -FDG PET/CT. The parameters were SUVmax₁, SUVmax₂, RI (SUVmax), SUVmean₁, SUVmean₂, RI (SUVmean), MTV₁, MTV₂, RI (MTV), TLG₁, TLG₂, and RI (TLG). Additionally, visual parameters were analyzed. Because the 19 benign lesions were the same as those

previously analyzed, the statistical results of the 1-h quantitative parameters were also the same.

The mean values of the various parameters are shown in Table 3. By the Mann–Whitney *U* test, there were statistically significant differences between the malignant and benign groups in SUVmax₁, SUVmax₂, SUVmean₁, SUVmean₂, TLG₂, and the RI of TLG. MTV₁, MTV₂, TLG₁, and the RI of other parameters did not show significant differences.

By visual assessment, there was a significant association between malignancy and high metabolic shape scores ($P < 0.001$), intensity ($P < 0.001$), and heterogeneity

Table 3 Analysis of quantitative and visual parameters on 1-h ^{18}F -FDG PET/CT

	Malignant lesions		Benign lesions		Pvalue
Quantitative parameters	Mean	95 % CI	Mean	95 % CI	
SUVmax ₁ ^a	7.559	6.633–8.486	4.179	3.259–5.099	0.000
SUVmean ₁ ^a	4.5	3.961–5.039	2.579	1.915–3.243	0.000
MTV ₁ ^a (mL)	61.0145	15.331–106.698	113.825	–24.025 to 251.674	0.173
TLG ₁ ^a	302.1958	75.669–528.723	130.458	8.508–252.408	0.035
Visual parameters					
Metabolic extent					0.372
Metabolic intensity					0.000
Metabolic shape					0.000
Metabolic heterogeneity					0.004
Total visual score					0.000

Quantitative Parameters were analyzed by a Mann–Whitney *U* test, and visual parameters were analyzed using a linear by linear association for trend test
SUV standardized uptake value, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis, *CI* confidence interval

^a Parameters measured on 1-h ^{18}F -FDG PET/CT

Fig. 2 ROC curve of significant parameters measured on 1-h ^{18}F -FDG PET/CT

($P=0.005$). The total visual score was also significantly associated with malignancy ($P<0.001$). The mean score of malignant lesions was 5.70 (95 % CI, 4.86–6.53), and that of benign lesions was 2.26 (95 % CI, 1.50–3.03). These results are shown in Table 5.

As shown in Fig. 3, visual score had the highest AUC at 0.911 ($P<0.001$) in the ROC curve analysis of significant

parameters. The AUC of SUVmax₁ was 0.900 ($P<0.001$); that of SUVmax₂ was 0.896 ($P<0.001$); that of SUV mean₁ was 0.852 ($P<0.001$); that of SUVmean₂ was 0.862 ($P<0.001$); that of TLG₂ was 0.698 ($P=0.029$); and that of the RI of TLG was 0.700 ($P=0.027$). The estimated optimal cut-off value for visual score was 4.50, and the same as in the previous analysis. These results are shown in Table 6.

Table 4 Analysis of significant parameters on 1-h ^{18}F -FDG PET/CT by ROC curve

Parameters	AUC	SE ^b	Asymptotic Significance ^c	Asymptotic 95 % CI	
				Lower bound	Upper bound
Visual Score	0.905	0.043	0.000	0.821	0.988
SUVmax ₁ ^a	0.898	0.053	0.000	0.790	1.000
SUVmean ₁ ^a	0.856	0.062	0.000	0.734	0.978
TLG ₁ ^a	0.678	0.087	0.035	0.506	0.849

SUV standardized uptake value, TLG total lesion glycolysis, AUC area under curve, SE standard error, CI confidence interval

^a Parameters measured on 1-h ^{18}F -FDG PET/CT

^b Under a nonparametric assumption

^c Null hypothesis: true area =0.5

Table 5 Analysis of quantitative and visual parameters on dual-time ^{18}F -FDG PET/CT

	Malignant lesions		Benign lesions		<i>P</i> value
	Mean	95 % CI	Mean	95 % CI	
Quantitative parameters					
SUVmax ₁ ^a	7.804	6.579–9.029	4.179	3.259–5.099	0.000
SUVmax ₂ ^b	10.817	7.762–13.873	5.058	4.130–5.985	0.000
RI (SUVmax)	32.8678	18.927–46.809	23.5644	12.869–34.26	0.324
SUVmean ₁ ^a	4.6348	3.941–5.329	2.579	1.915–3.243	0.000
SUVmean ₂ ^b	5.6826	4.826–6.540	3.8095	2.419–3.760	0.000
RI (SUVmean)	23.9813	14.417–33.546	21.1811	14.259–28.104	0.889
MTV ₁ ^a (mL)	53.6216	3.485–103.758	113.825	–24.025 to 251.674	0.318
MTV ₂ ^b (mL)	62.9454	1.846–124.045	103.6025	–24.533 to 231.739	0.098
RI (MTV)	20.9251	–0.293 to 42.143	–5.0718	–23.285 to 13.141	0.075
TLG ₁ ^a	304.9973	15.187–594.808	130.458	8.508–252.408	0.079
TLG ₂ ^b	447.1736	6.263–888.084	134.0635	7.985–260.142	0.029
RI (TLG)	48.3698	20.730–76.009	14.4603	–7.933 to 36.854	0.027
Visual parameters ^a					
Metabolic extent					0.474
Metabolic intensity					0.000
Metabolic shape					0.000
Metabolic heterogeneity					0.005
Total visual score					0.000

Quantitative Parameters were analyzed by a Mann–Whitney *U* test and visual parameters were analyzed using a linear by linear association for trend test
SUV standardized uptake value, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis, *RI* retention index, *CI* confidence interval

^a Parameters measured on 1-h ^{18}F -FDG PET/CT

^b Parameters measured on 2-h ^{18}F -FDG PET/CT

Discussion

Compared with other gynecologic malignancies, ovarian cancer is often a fatal disease resulting from late diagnosis. Actually, in our studies, all of the ovarian malignancy patients had advanced disease with peritoneal carcinomatosis. It is hard to detect ovarian malignancy earlier, because its symptoms are not specific. Therefore, it is important to distinguish malignancy from benign disease during the initial work-up process instead of during early patient visits.

After the introduction of combined ^{18}F -FDG PET/CT in 2000 [23], ^{18}F -FDG PET/CT has been widely used as an imaging modality, and especially in cancer diagnosis, staging, and post-therapeutic response monitoring [24]. However, despite the previously reported high sensitivity of ^{18}F -FDG PET/CT, false-positive findings mimicking malignancies also exist. They include not only physiologic activity, muscle activity, and urine activity, but infection and inflammation as well [10]. Especially in the pelvic cavity, the physiologic ovarian and endometrial activities resulting from the menstrual cycle can mimic malignancy. Lerman et al. [25] reported physiologic ovarian FDG uptakes in 21 premenopausal women out of 112

with an SUVmean of 5.7 ± 1.5 . Therefore, several parameters have been previously introduced to increase the specificity of ^{18}F -FDG PET/CT.

In our study of 51 peritoneal lesions, there were significant differences in SUVmax₁, SUVmean₁, and TLG₁ between malignant and benign lesions. SUVmax is the most commonly used parameter in practice. Generally, malignant lesions are known to have a much higher SUVmax than benign lesions. Our results also showed that higher median SUVmax values were observed in malignant lesions than in benign lesions. However, the SUVmax of two tuberculous lesions were 10.3 and 7.7. Therefore, there is an obvious limitation in predicting malignancy with SUVmax alone. Despite SUVmean values of malignant lesions that were not high enough, there were significant differences between the malignant and benign groups. In general, SUVmean is known to have some limitations as a diagnostic parameter. Firstly, it is difficult to set the cut-off value, and secondly, there is variability between observers when drawing the ROI [26]. However, in our study, we used a VOI automatically drawn by a computer program so that interobserver variation would be minimal. Interestingly, TLG₁ showed a significant difference between the two

Fig. 3 Curve of significant parameters measured on dual-time ^{18}F -FDG PET/CT

groups, although MTV_1 did not. This can be explained by a limitation of MTV, especially in the case of a huge cystic mass. Although the SUVmax and SUVmean values of the mass were low enough to regard it as a benign lesion, the MTV of the mass was too large, and could not represent the

exact characteristics of the lesion. When considering this limitation, TLG can be used as a complementary parameter. TLG is a volume-based parameter that represents metabolic tumor burden. Many previous studies reported the effectiveness of MTV and/or TLG as a prognostic factor in various

Table 6 Analysis of significant parameters on dual-time ^{18}F -FDG PET/CT by ROC curve

Parameters	AUC	SE^c	Asymptotic significance ^d	Asymptotic 95 % CI	
				Lower bound	Upper bound
Visual score ^a	0.911	0.044	0.000	0.825	0.996
SUVmax_1 ^a	0.900	0.052	0.000	0.795	1.000
SUVmax_2 ^b	0.896	0.049	0.000	0.800	0.992
SUVmean_1 ^a	0.898	0.053	0.000	0.790	1.000
SUVmean_2 ^b	0.856	0.062	0.000	0.734	0.978
TLG_2 ^b	0.698	0.089	0.029	0.524	0.872
RI (TLG)	0.700	0.088	0.027	0.529	0.872

SUV Standardized uptake value, TLG total lesion glycolysis, RI retention index, AUC area under curve

^a Parameters measured on 1 h ^{18}F -FDG PET/CT

^b Parameters measured on 2 h ^{18}F -FDG PET/CT

^c Under the nonparametric assumption

^d Null hypothesis: true area = 0.5

cancers [15, 17, 27–29]. In ovarian cancer, Chung et al. [25] reported that MTV and TLG had a significant association with recurrence [16]. As in our study, TLG showed a significant difference between the two groups, and we consider that TLG has potential as a diagnostic parameter.

Dual-time point ^{18}F -FDG PET was suggested to distinguish malignancy from benign lesions in 1999 [30]. Zhuang et al. [13] reported that the average SUV of malignant lesions increased on delayed PET imaging, while the average SUV of benign lesions decreased or remained stable, and several studies have reported the usefulness of dual-time point ^{18}F -FDG PET or PET/CT as diagnostic modalities. Also in our previous report, we evaluated the effectiveness of dual-phase ^{18}F -FDG PET/CT for differentiating benign ovarian lesions from malignant lesions [31]. However, a recent report by Cheng et al. [32] suggested that it is difficult to distinguish active inflammation and infection from malignancy. They reviewed multiple studies and indicated that active inflammatory and infectious lesions may have higher FDG activity on delayed PET imaging, especially in tuberculosis-endemic regions. Concordant with these study results, in our analysis of 42 peritoneal lesions, there were no significant differences in the RI values of SUVmax, SUVmean, or MTV between the malignant and benign groups, although SUVmax₁, SUVmax₂ and SUVmean₁, SUVmean₂ showed a significant difference. Only the RI of TLG showed a significant difference between the two groups. However, TLG₁ showed no significant difference between the two groups, and this was not in agreement with the previous results of TLG₁ analyzed in a total of 51 lesions. When considering these coincident results, the reliability of RI of TLG seems to be low, and further studies are needed. These results that delayed parameters did not show significant differences between the two groups are discordant with our previous study [31] and it might be due to the lesion based analysis in this study. Two peritoneal tuberculosis patients showed eight intraperitoneal lesions among the 19 benign lesions and their FDG activities were markedly high, compared with the other benign lesions. As a result, mean values of several delayed parameters of benign group could be higher than mean value assessed by patient based method. Tuberculosis is typical case of active inflammatory condition as above mentioned.

We performed a visual assessment for 51 total peritoneal lesions and also in 42 lesions for which 2-h delayed ^{18}F -FDG PET/CT imaging had been acquired. We used a linear-by-linear association for trend test to find associations between each visual parameter and malignancy. In the analysis of both 51 peritoneal lesions and 42 lesions, visual parameters including metabolic intensity, shape, and heterogeneity showed significant associations with malignancy. However, metabolic

extent did not show a significant association with malignancy. It might have resulted from the size criteria we used. Because there is no previous study about metabolic size of ovarian malignancy or benign pelvic disease, we scored metabolic extent in the same way as a previous study that evaluated metabolic extent of cervical cancer [19]. A follow-up study on the metabolic size of intraperitoneal lesions will be needed to identify the optimal criteria.

Nevertheless, the total visual score did show a significant association. Furthermore, in the ROC curve analysis, visual score was the most effective parameter to diagnose malignancy compared with other significant diagnostic parameters. Therefore, we considered that visual assessment is a reliable parameter.

Our study has some inherent limitations. First of all, we analyzed each peritoneal lesion independently. However, lesion by lesion analysis could lead to correlation bias among the intraperitoneal lesions from same patient. And also, our data showed nonparametric distribution due to the small number of patients included in this study. These limitations could decrease statistical reliability. So, further study of a larger patient population will be needed. Secondly, because it was a retrospective study, selection bias was introduced. Because all of patients were taken ^{18}F -FDG PET/CT as a part of stage workup process for ovarian cancer, benign group of this study could not reflect general characteristics of benign pelvic diseases. Thirdly, we could not confirm all intraperitoneal lesions pathologically. We considered all intraperitoneal lesions in patients with malignancy as malignant lesions, in patient with benign disease as benign lesions. However, we retrospectively reviewed the status of malignant patients after chemotherapy, and we identified most of intraperitoneal lesions in malignant patients that showed a to the chemotherapy on follow-up abdomen-pelvis CT, pelvic MRI or ^{18}F -FDG PET/CT. So, it is quite reasonable that intraperitoneal lesions from malignant patients were considered as malignant lesions.

Conclusion

In conclusion, we found that visual assessment was the most significant parameter in differentiating malignancy from benign lesions in ovarian cancer patients, although other semi-quantitative parameters including SUVmax₁, SUVmax₂, SUVmean₁, SUVmean₂, TLG, and RI of TLG were also identified as showing significant diagnostic value. In practice, visual assessment is the simplest and most common method to interpret ^{18}F -FDG PET/CT imaging and requires no additional time or cost to measure volume-based parameters, and no additional delayed images to measure delayed parameters. Thus, visual assessment has a primary role in detecting

malignancy in ovarian cancer patients with assistance from other semi-quantitative parameters.

Conflict of Interest Taegyu Park, Sinae Lee, Soyeon Park, Eunsub Lee, Kisoo Pakh, Seunghong Rhee, Jaehyuk Cho, Chulhan Kim, Jae Seon Eo, Jae Gol Choe and Sungeun Kim declare that they have no conflict of interest.

Ethical Statement The institutional review board approval number of this study is KUGH14038. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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