



^{18}F -FDG PET/CT can predict chemosensitivity and proliferation of epithelial ovarian cancer via SUVmax value

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Abstract

Purpose This study aimed to explore the clinical and prognostic significance of ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) in epithelial ovarian cancer (EOC).

Methods We retrospectively investigated 48 EOC patients who underwent preoperative ^{18}F -FDG PET/CT and primary cytoreductive surgery at our hospital between January 2010 and June 2015. None of these patients received neoadjuvant chemotherapy. PET/CT parameters including the maximum and average standardized uptake value (SUVmax, SUVavg), the metabolic tumor volume (MTV) were measured. Tumor proliferation marker Ki67 was evaluated using immunohistochemistry. The relationships between the PET/CT parameters and chemosensitivity, tumor proliferation, and overall survival (OS) were analyzed, respectively.

Results The median (range) SUVmax, SUVavg, and MTV values were 11.42 (3.14–20.20), 4.8 (2.55–9.47), and 150.11 (0.19–792.46), respectively. Overall, 93.8% (45/48) of patients had high-grade serous ovarian cancer. The SUVmax value had a positive correlation with the Ki67 index ($P=0.030$, $r=0.314$), and a higher SUVmax level was associated with chemosensitivity ($P=0.026$). However, neither SUVavg nor MTV had associations with the patients' clinicopathological parameters. None of these three PET/CT parameters were found to be potential predictors of OS.

Conclusions Preoperative ^{18}F -FDG PET/CT had a predictive value on chemosensitivity and proliferation after primary debulking surgery in EOC patients noninvasively.

Keywords ^{18}F -FDG PET/CT · Epithelial ovarian cancer · Proliferation · Chemosensitivity · Maximum standardized uptake value

Introduction

Ovarian cancer is one of the most commonly diagnosed and lethal gynecological malignancies among females worldwide [1]. About half of the patients will relapse within 16 months after primary debulking surgery and platinum-based

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adjuvant chemotherapy [2]. Thus, effective indicators are urgently required to earlier estimate the biological behavior and treatment efficacy of tumor cells to guide individual treatments.

^{18}F -FDG PET/CT is an important molecular imaging modality for preoperative and therapeutic effect assessment in ovarian cancer. Previous studies have shown that semi-quantitative parameters of PET/CT, such as SUVmax, SUVavg, and MTV, are associated with patients' clinical characteristics and prognoses in ovarian cancer [3–9]. Several investigators have found that higher PET/CT parameters are associated with an advanced FIGO stage and a higher tumor burden and could indicate a poorer prognosis [7–11]. However, other studies have failed to draw similar conclusions [12, 13].

Moreover, tumor cell proliferation and chemosensitivity are also two vital factors of malignant tumors. Nevertheless, research on the relationship between PET/CT parameters and ovarian cancer's proliferative activity and chemosensitivity is limited. Thus, our study aimed to explore both clinical and prognostic significance of ^{18}F -FDG PET/CT in epithelial ovarian cancer.

Materials and methods

Clinicopathological data

We retrospectively investigated 48 epithelial ovarian cancer patients who had preoperative ^{18}F -FDG PET/CT scan and subsequent primary debulking surgery between January 2010 and June 2015 in our hospital. All patients had PET/CT scan within 2 weeks before primary surgery. Patients were excluded if they received neoadjuvant chemotherapy, or were treated for recurrent disease. The study protocol was approved by the institution's review board.

All pathological slides were independently reviewed by two experienced gynecologic pathologists according to the WHO criteria. Immunohistochemical staining was performed for Ki67 (Roche 30-9) using a Ventana Benchmark XT autostainer (Ventana Medical Systems Inc., Tucson, AZ, USA).

The clinical data were collected from medical records, cancer registries, and pathology reports. Surgical outcome has been classified as R0, R1 and R2, according to residual disease (RD). R0 indicated no macroscopic residual disease, while R1 and R2 were defined as the maximum RD diameter of < 1 cm or ≥ 1 cm, respectively. The optimal surgery comprised R0 and R1. Chemosensitivity was defined as that we previously reported, a time interval of 6 months or longer between the completion of platinum-based chemotherapy and recurrence. Otherwise, the patient was chemoresistant [14, 15]. All of the patients were followed up until December

31, 2016. Overall survival (OS) was defined as the time interval from the date of operation to the date of death or the last follow-up.

^{18}F -FDG PET/CT protocol

^{18}F -FDG was produced automatically by cyclotron (Siemens CTI RDS Eclipse ST, Knoxville, TN, USA) using the Explora FDG4 module in our center. Radiochemical purity was over 95%. All patients were asked to fast at least 6 h before the ^{18}F -FDG PET/CT procedure. The patient's blood glucose level was below 10 mmol/L at the time of radio-tracer injection. The standard dosage of intravenous ^{18}F -FDG administration was 7.4 MBq/kg. Before and after injection, patients were kept lying comfortably in a quiet, dimly lit room. Examination was performed 60 min after ^{18}F -FDG injection. A Siemens Biograph 16HR PET/CT scanner (Knoxville, TN, USA) with 4 mm transaxial intrinsic spatial resolution (full width at half maximum) and 16.2 cm axial field width was used for image scanning. Whole-body PET/CT data acquisition began with low-dose CT from the inguinal region to the head, with 120 kV, a 80–250 mA automatic adjustment, a pitch of 3.6, and a 0.5 s rotation time, followed by PET emission scan in a 3-dimensional mode, with 2–3 min per bed position. The PET data were reconstructed using the ordered-subset expectation maximization technique selecting eight subsets and four iterations, a 168×168 matrix. The CT data were used for attenuation correction of the PET images, and coregistered images were displayed on a workstation. The reconstructed images were then converted to a semiquantitative image corrected by the injection dose and the subject's body weight (SUV).

Imaging interpretation

All PET/CT images were independently evaluated by two experienced nuclear medicine physicians. Consensus was reached in case of discrepancy. Analysis of the ^{18}F -FDG PET/CT images was performed using a multimodality computer platform (Syngo, Siemens, Knoxville, TN, USA). SUVmax for each patient was calculated by placing a spheroid-shaped volume of interest (VOI) within the primary ovarian lesion. The SUV was calculated as [decay-corrected activity (kBq) per milliliter of tissue volume]/[injected ^{18}F -FDG activity (kBq) per gram of body mass]. MTV and SUVavg were measured by drawing a contour of the ovarian lesion large enough to encase the primary tumor in the axial, coronal, and sagittal PET images. We used a threshold of SUV of 2.5 [16–18], which is usually used in clinical settings, to define the margins around the target. The boundaries of voxels, the SUV of which exceeded a threshold of 2.5 SUV, were automatically produced. The voxels

presenting an SUV intensity of greater than 2.5 within the contouring margin were incorporated to define the MTV, and the mean voxels within this contouring were measured as SUVavg. The kidneys, ureters, and the urinary bladder were manually subtracted to ensure the correct voxel.

Statistical analysis

SPSS statistical software (version 21.0, SPSS, IBM Inc., Armonk, NY, USA) was used for statistical analyses. For demographic data, a descriptive statistical analysis method was used for analysis, and the results were summarized as means with standard deviations (SD), medians with ranges, or frequencies with percentages. The categorical data were compared using Chi-square or Fisher's exact tests. Correlations between SUVmax, SUVavg, MTV, and Ki67 were tested using Pearson's correlation analysis. OS was analyzed using the Kaplan–Meier method, and log-rank tests were used in the univariate analyses. $P < 0.05$ was considered statistically significant, and all P values reported were 2-sided.

Results

Patients' characteristics

Patients' characteristics are described in Table 1. Among the 48 patients, the median (range) age of the patients was 52 (27–76) years, and 43 (89.6%) had advanced FIGO (stage III–IV). The majority of the patients (93.8%) had high-grade serous ovarian cancer. The median (range) Ki67 index was 70% (15–95%).

Optimal surgery was achieved for 42 patients (87.5%), including 17 debulked to R0 and 25 to R1. All patients received platinum-based adjuvant chemotherapy after surgery. Among these, 6 patients had disease progression during chemotherapy, and 32 (66.7%) were sensitive to platinum-based chemotherapy. The median (range) follow-up time was 27 (8–61) months. Nineteen patients (39.6%) relapsed during the follow-up period. At the end of the follow-up, 30 patients were still alive, seven were dead, and the other 11 were censored.

PET/CT parameters and their associations with clinicopathological characteristics and prognosis

As for preoperative PET/CT scan parameters, the median (range) SUVmax, SUVavg, and MTV values were 11.42 (3.14–20.2), 4.8 (2.55–9.47), and 150.11 (0.19–792.46), respectively. We analyzed the relationships between the clinical features and the PET/CT parameters. SUVmax, SUVavg, and MTV had no association with age, FIGO stage,

Table 1 Patients' characteristics

Patients' characteristics ($n=48$)		
Age, median (range)	52 (27–76)	
FIGO stage		
I	1	2.1%
II	4	8.3%
III	37	77.1%
IV	6	12.5%
CA125, IU/ml, median (range)	1222.5 (28.72–11420.80)	
HE4, IU/ml, median (range)	580.21 (57.77–1500)	
Ascites (ml)		
No	4	8.3%
< 500	14	29.2%
≥ 500	30	62.5%
Residual disease		
R0	17	35.4%
R1	25	52.1%
R2	6	12.5%
Recurrence		
Progression	6	12.5%
Yes	19	39.6%
No	21	43.8%
NA	2	4.2%
Chemosensitivity		
Yes	32	66.7%
No	13	27.1%
NA	3	6.3%
Histology		
HGSC	45	93.8%
Mixed	2	4.2%
Undifferentiated	1	2.1%
Ki67, %, median (range)	70 (15–95)	
SUVmax, median (range)	11.42 (3.14–20.20)	
SUVavg, median (range)	4.80 (2.55–9.47)	
MTV, median (range)	150.11 (0.19–792.46)	
Follow-up time, months, median (range)	27 (8–61)	
Status		
Died	7	14.6%
Censored	11	22.9%
Alive	30	62.5%

HGSC high-grade serous cancer, NA not available, SUVmax maximum standardized uptake value, SUVavg average standardized uptake value, MTV the metabolic tumor volume

CA125 level, HE4 level, ascites and postoperative residual disease.

Overall, 83.3% of our patients had a high Ki67 index (> 50%), and the remaining seven patients had a moderate Ki67 index (5–50%). There was a significant positive correlation between the SUVmax value and the Ki67 index ($P=0.030$, $r=0.314$). Nevertheless, neither SUVavg nor

MTV values were associated with Ki67 index ($P=0.051$ and $r=0.283$ and $P=0.586$ and $r=-0.081$, respectively) (Fig. 1). Furthermore, chemosensitive patients had higher SUVmax values than those who were chemoresistant. However, there were no differences in SUVavg and MTV values between these two groups (Table 2).

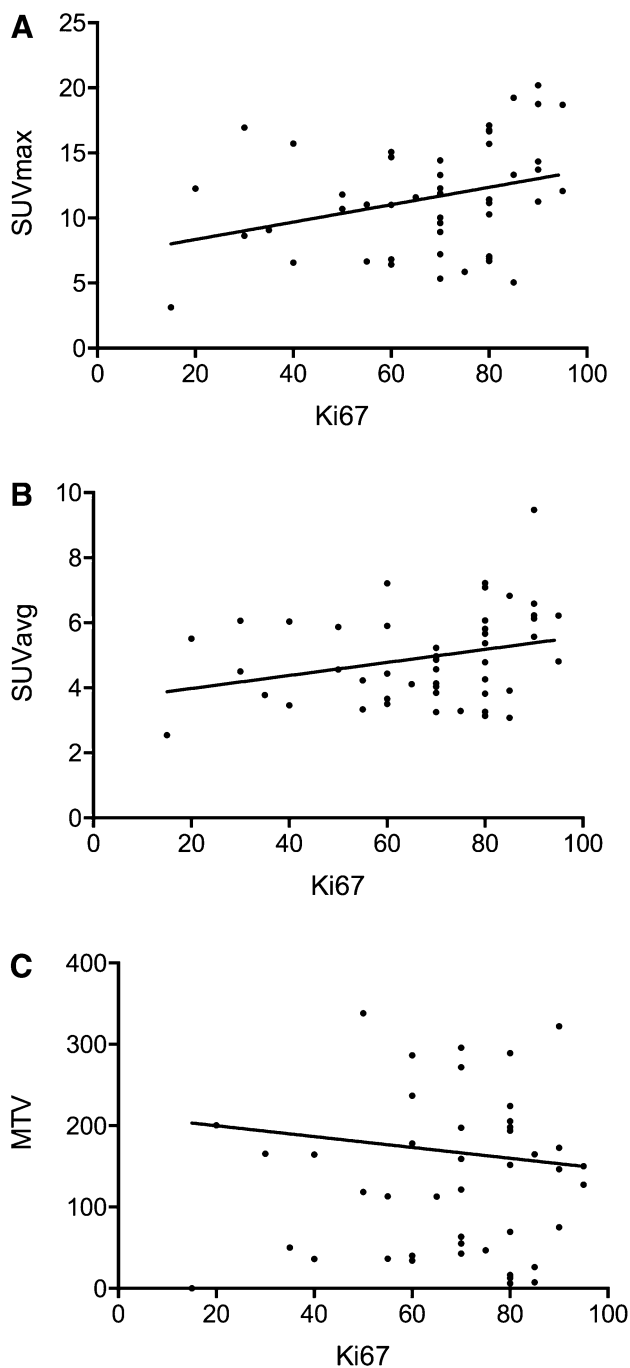


Fig. 1 a–c Correlation between cell proliferation and SUVmax, SUVavg, and MTV. The SUVmax value had a positive correlation with the Ki67 index (a)

Table 2 PET/CT parameters and chemosensitivity

Chemosensitivity	PET parameters (mean \pm SD)		
	SUVmax	SUVavg	MTV
Yes	12.36 \pm 4.26	5.14 \pm 1.48	176.23 \pm 162.10
No	9.39 \pm 2.79	4.47 \pm 1.13	149.35 \pm 178.70
<i>P</i> value	0.026	0.150	0.627

SUVmax maximum standardized uptake value, SUVavg average standardized uptake value, MTV the metabolic tumor volume

In addition, patients were dichotomized by the median of each PET/CT parameter into high and low level groups for prognostic analyses, respectively. There were no differences in OS between the high and low SUVmax, SUVavg, or MTV groups, respectively (Fig. 2).

Discussion

Our study demonstrated that the SUVmax value is associated with Ki67 index and chemosensitivity. However, neither SUVavg nor MTV had associations with patients' clinicopathological parameters, and none of these three PET/CT parameters were found to be potential predictors of OS.

Compared to conventional imaging technologies such as CT, MR, and ultrasound, ^{18}F -FDG PET/CT could not only assess anatomical or morphological features of malignant tumors, but also provide their functional or metabolic characteristics [19, 20]. PET/CT scan is used increasingly during ovarian cancer treatment for its noninvasive and multifunctional advantages [5, 10, 12, 21] (Figs. 3, 4).

The Ki67 index is a vital predictive and prognostic marker for malignant tumors [22]. It is routinely used to estimate tumor proliferative activity in daily clinical practice. Several studies have shown that PET/CT parameters are correlated with the Ki67 index and thus could indicate tumor proliferation in several types of cancer [22–26]. Data for ovarian cancer proliferation are limited. Our study found that SUVmax had a positive correlation with the Ki67 value, while SUVavg or MTV did not. This may be because higher proliferative tumor cells have increasing glucose transporter proteins and hexokinase and glucose-6-phosphatase activities [27]. This will lead to higher ^{18}F -FDG uptake accumulation, which could be directly reflected by SUVmax. However, SUVavg and MTV are also affected by many other factors such as viable tumor cell numbers and intra-tumor heterogeneity [28]. Thus, our research provides a noninvasive method using PET/CT scan to examine tumor cell proliferation.

Chemosensitivity is a vital prognostic factor for ovarian cancer. Previous studies have attempted to earlier estimate chemosensitivity during ovarian cancer neoadjuvant

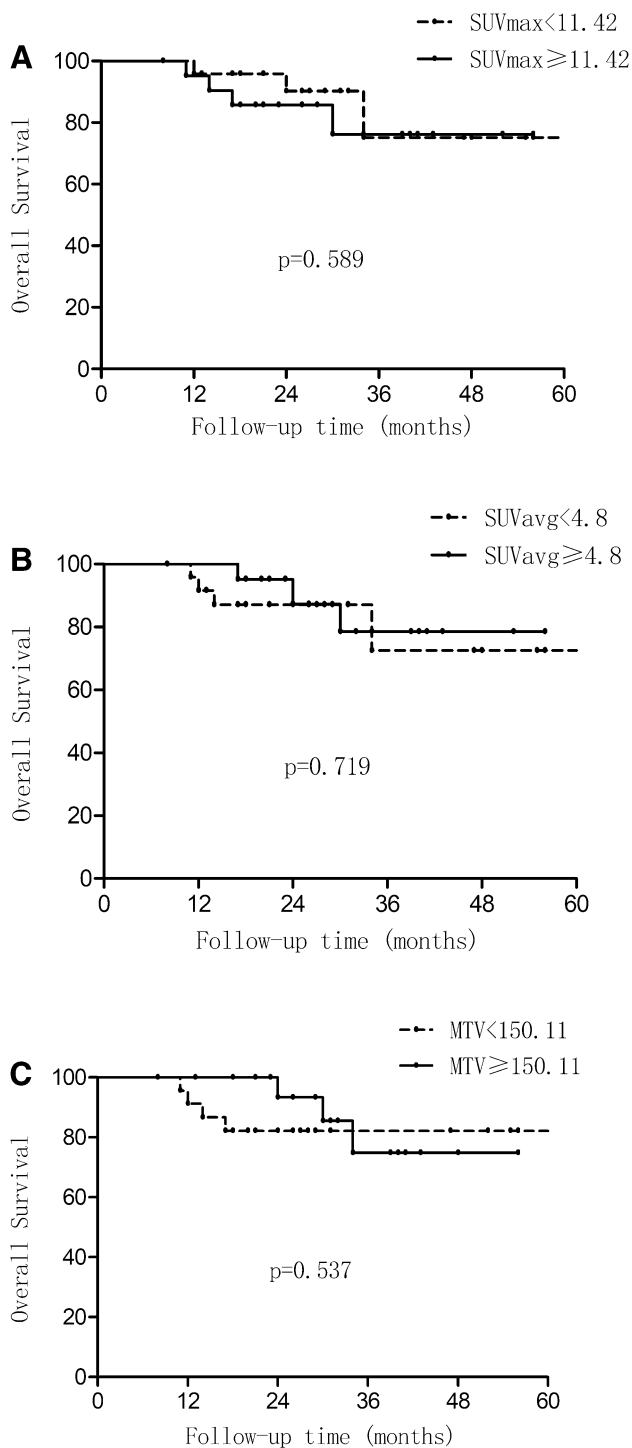


Fig. 2 a–c Kaplan–Meier curves of OS. None of these three PET/CT parameters were found to be potential predictors of OS

chemotherapy (NACT). Tuulia et al. [29] found that over 57% of SUV_{max} reduction after four cycles NACT was associated with a better histopathological response. Avril et al. [30] further indicated that PET/CT after the first cycle of NACT could earlier predict chemotherapy response instead of PET/CT after three cycles. Compared to those above, our study showed that we can predict treatment sensitivity before chemotherapy for the first time. According to the SUV_{max} value, we might select the proper patients for NACT or another individual treatment in a future clinical study.

Previous studies have also shown the promising prognostic significance of PET-derived parameters for ovarian cancer [6, 7, 12, 30]. Yamamoto et al. [12] demonstrated that MTV could, but SUV_{max} could not, serve as a prognostic factor for PFS in primary ovarian cancer patients. Konishi et al. [6] showed that SUV_{max} represented a prognostic factor in clear cell adenocarcinoma. Our study failed to find the prognostic value of SUV and MTV. This may be due to the limited number of patients and short follow-up time.

The limitation of our study was that it was a retrospective study with potential recall bias. More patient enrollment and further follow-up are needed in the future to strengthen our findings.

Notwithstanding its limitation, our study involved a homologous group of patients with high-grade serous ovarian cancer, up to 93.8%. Moreover, we focused on ovarian cancer proliferation and chemosensitivity prediction using PET/CT, which is vital but was always neglected by previous studies.

Conclusions

In conclusion, our study suggests that preoperative SUV_{max} of ¹⁸F-FDG PET/CT has a predictive value on proliferation and chemosensitivity after debulking surgery in epithelial ovarian cancer patients noninvasively. Future prospective cooperative multicenter studies are needed to further identify the predictive significance of PET/CT in ovarian cancer.

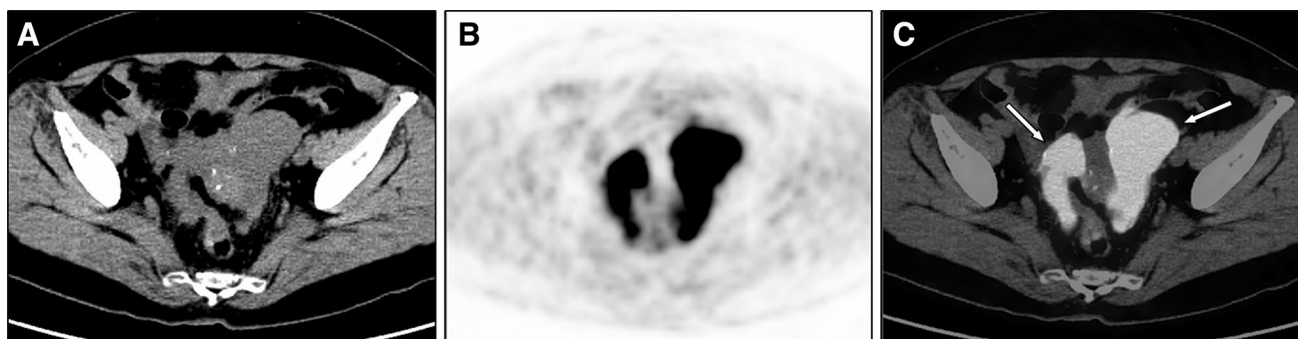


Fig. 3 a–c Representative transaxial CT (a), PET (b) and PET/CT fused (c) ovarian tumor (white arrow showed) images of a 68-year-old chemosensitive patient with a FIGO stage IIIC. Postoperative pathology was HGSC with a 85% Ki67 value. The patient under-

went six cycles' chemotherapy after debulking surgery, and had no recurrence and metastasis until the last follow-up date. The SUVmax, SUVavg and MTV of ovarian tumor were 19.2, 6.8 and 164.96, respectively

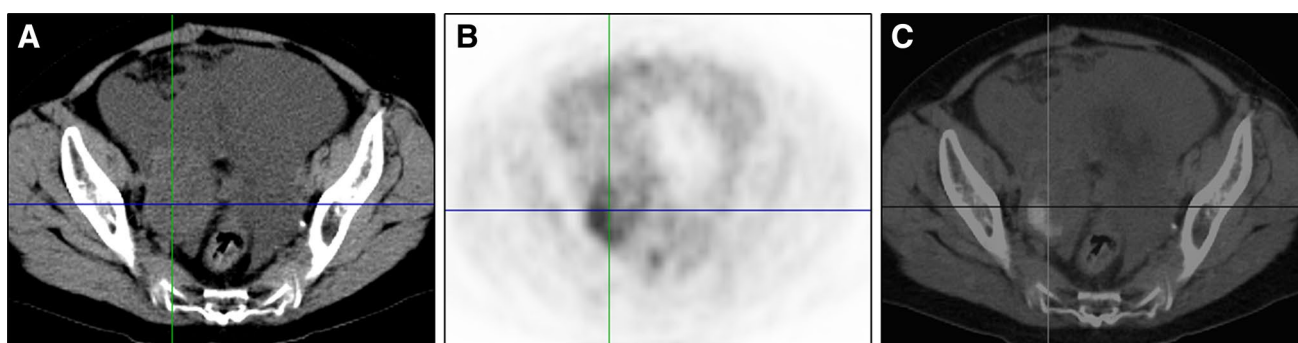


Fig. 4 a–c Representative transaxial CT (a), PET (b) and PET/CT fused (c) images of ovarian tumor (cross showed) in a 60-year-old chemoresistant patient staged IIIC. Postoperative pathology was HGSC with a 55% Ki67 value. The patient underwent eight cycles'

chemotherapy and recurred 12 months after cytoreductive surgery. The SUVmax, SUVavg and MTV were 6.4, 3.5 and 40.31, respectively

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Compliance with ethical standards

The ethics committee of our institution does not require patient consent for retrospective review of imaging studies.

Conflict of interest The authors declare that they have no conflict of interest.

References

- Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
- Berek JS, Crum C, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet*. 2015;131(Suppl 2):S111–22.
- Risum S, Loft A, Hogdall C, Berthelsen AK, Hogdall E, Lundvall L, et al. Standardized FDG uptake as a prognostic variable and as a predictor of incomplete cytoreduction in primary advanced ovarian cancer. *Acta Oncol* (Stockholm, Sweden). 2011;50(3):415–9.
- Nakamura K, Hongo A, Kodama J, Hiramatsu Y. The pretreatment of maximum standardized uptake values (SUVmax) of the primary tumor is predictor for poor prognosis for patients with epithelial ovarian cancer. *Acta Med Okayama*. 2012;66(1):53–60.
- Tanizaki Y, Kobayashi A, Shiro M, Ota N, Takano R, Mabuchi Y, et al. Diagnostic value of preoperative SUVmax on FDG-PET/CT for the detection of ovarian cancer. *Int J Gynecol Cancer*. 2014;24(3):454–60.
- Konishi H, Takehara K, Kojima A, Okame S, Yamamoto Y, Shroyama Y, et al. Maximum standardized uptake value of fluorodeoxyglucose positron emission tomography/computed tomography is a prognostic factor in ovarian clear cell adenocarcinoma. *Int J Gynecol Cancer*. 2014;24(7):1190–4.
- Lee JW, Cho A, Lee JH, Yun M, Lee JD, Kim YT, et al. The role of metabolic tumor volume and total lesion glycolysis on ¹⁸F-FDG PET/CT in the prognosis of epithelial ovarian cancer. *Eur J Nucl Med Mol Imaging*. 2014;41(10):1898–906.
- Chung HH, Kwon HW, Kang KW, Park NH, Song YS, Chung JK, et al. Prognostic value of preoperative metabolic tumor volume and total lesion glycolysis in patients with epithelial ovarian cancer. *Ann Surg Oncol*. 2012;19(6):1966–72.
- Fanfani F, Monterossi G, Fagotti A, Gallotta V, Costantini B, Vizzielli G, et al. Positron emission tomography–laparoscopy based method in the prediction of complete cytoreduction in

- platinum-sensitive recurrent ovarian cancer. *Ann Surg Oncol*. 2015;22(2):649–54.
10. Vargas HA, Burger IA, Goldman DA, Micco M, Sosa RE, Weber W, et al. Volume-based quantitative FDG PET/CT metrics and their association with optimal debulking and progression-free survival in patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery. *Eur Radiol*. 2015;25(11):3348–53.
 11. Kitajima K, Suenaga Y, Ueno Y, Maeda T, Ebina Y, Yamada H, et al. Preoperative risk stratification using metabolic parameters of ¹⁸F-FDG PET/CT in patients with endometrial cancer. *Eur J Nucl Med Mol Imaging*. 2015;42(8):1268–75.
 12. Yamamoto M, Tsujikawa T, Fujita Y, Chino Y, Kurokawa T, Kiyono Y, et al. Metabolic tumor burden predicts prognosis of ovarian cancer patients who receive platinum-based adjuvant chemotherapy. *Cancer Sci*. 2016;107(4):478–85.
 13. Kim CY, Jeong SY, Chong GO, Son SH, Jung JH, Kim DH, et al. Quantitative metabolic parameters measured on F-18 FDG PET/CT predict survival after relapse in patients with relapsed epithelial ovarian cancer. *Gynecol Oncol*. 2015;136(3):498–504.
 14. Feng Z, Wen H, Bi R, Duan Y, Yang W, Wu X. Thrombocytosis and hyperfibrinogenemia are predictive factors of clinical outcomes in high-grade serous ovarian cancer patients. *BMC Cancer*. 2016;16:43.
 15. Feng Z, Wen H, Ju X, Bi R, Chen X, Yang W, et al. Expression of hypothalamic-pituitary-gonadal axis-related hormone receptors in low-grade serous ovarian cancer (LGSC). *J Ovarian Res*. 2017;10(1):7.
 16. Yang Z, Shi Q, Zhang Y, Pan H, Yao Z, Hu S, et al. Pretreatment ¹⁸F-FDG uptake heterogeneity can predict survival in patients with locally advanced nasopharyngeal carcinoma—a retrospective study. *Radiat Oncol (London, England)*. 2015;10:4.
 17. Kurtipek E, Cayci M, Duzgun N, Esme H, Terzi Y, Bakdik S, et al. ¹⁸F-FDG PET/CT mean SUV and metabolic tumor volume for mean survival time in non-small cell lung cancer. *Clin Nucl Med*. 2015;40(6):459–63.
 18. Lee HJ, Lee JJ, Park JY, Kim JH, Kim YM, Kim YT, et al. Prognostic value of metabolic parameters determined by preoperative ¹⁸F-FDG PET/CT in patients with uterine carcinosarcoma. *J Gynecol Oncol*. 2017;28(4):e43.
 19. Czernin J, Weber WA, Herschman HR. Molecular imaging in the development of cancer therapeutics. *Annu Rev Med*. 2006;57:99–118.
 20. Jager PL, de Korte MA, Lub-de Hooge MN, van Waarde A, Koopmans KP, Perik PJ, et al. Molecular imaging: what can be used today. *Cancer Imaging*. 2005;5 Spec No A:S27–32.
 21. Bono Y, Mizumoto Y, Nakamura M, Iwadare J, Obata T, Fujiwara H. FDG-PET-positive ovarian thecoma with GLUT5 expression: five cases. *J Obstet Gynaecol Res*. 2017;43(3):599–603.
 22. Del Gobbo A, Pellegrinelli A, Gaudioso G, Castellani M, Zito Marino F, Franco R, et al. Analysis of NSCLC tumour heterogeneity, proliferative and 18F-FDG PET indices reveals Ki67 prognostic role in adenocarcinomas. *Histopathology*. 2016;68(5):746–51.
 23. Hu SL, Yang ZY, Zhou ZR, Yu XJ, Ping B, Zhang YJ. Role of SUV(max) obtained by ¹⁸F-FDG PET/CT in patients with a solitary pancreatic lesion: predicting malignant potential and proliferation. *Nucl Med Commun*. 2013;34(6):533–9.
 24. Abgral R, Leboulleux S, Deandreis D, Auperin A, Lumbroso J, Dromain C, et al. Performance of ¹⁸fluorodeoxyglucose-positron emission tomography and somatostatin receptor scintigraphy for high Ki67 ($\geq 10\%$) well-differentiated endocrine carcinoma staging. *J Clin Endocrinol Metab*. 2011;96(3):665–71.
 25. Ueda S, Tsuda H, Saeki T, Omata J, Osaki A, Shigekawa T, et al. Early metabolic response to neoadjuvant letrozole, measured by FDG PET/CT, is correlated with a decrease in the Ki67 labeling index in patients with hormone receptor-positive primary breast cancer: a pilot study. *Breast Cancer (Tokyo, Japan)*. 2011;18(4):299–308.
 26. Onishi R, Noguchi M, Kaida H, Moriya F, Chikui K, Kurata S, et al. Assessment of cell proliferation in renal cell carcinoma using dual-phase 18F-fluorodeoxyglucose PET/CT. *Oncol Lett*. 2015;10(2):822–8.
 27. Aloj L, Caraco C, Jagoda E, Eckelman WC, Neumann RD. Glut-1 and hexokinase expression: relationship with 2-fluoro-2-deoxy-D-glucose uptake in A431 and T47D cells in culture. *Cancer Res*. 1999;59(18):4709–14.
 28. Tanimoto K, Yoshikawa K, Obata T, Ikehira H, Shiraishi T, Watanabe K, et al. Role of glucose metabolism and cellularity for tumor malignancy evaluation using FDG-PET/CT and MRI. *Nucl Med Commun*. 2010;31(6):604–9.
 29. Vallius T, Peter A, Auranen A, Carpen O, Kempainen J, Matomaki J, et al. 18F-FDG-PET/CT can identify histopathological non-responders to platinum-based neoadjuvant chemotherapy in advanced epithelial ovarian cancer. *Gynecol Oncol*. 2016;140(1):29–35.
 30. Avril N, Sassen S, Schmalfeldt B, Naehrig J, Rutke S, Weber WA, et al. Prediction of response to neoadjuvant chemotherapy by sequential F-18-fluorodeoxyglucose positron emission tomography in patients with advanced-stage ovarian cancer. *J Clin Oncol*. 2005;23(30):7445–53.