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The role of ^{18}F-FDG PET/CT-based quantitative metabolic parameters in patients with ovarian clear cell carcinoma

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Abstract.
BACKGROUND: Ovarian clear cell carcinoma (CCC) is enriched in genes associated with glucose metabolism.
OBJECTIVE: To evaluate the ^{18}F-FDG PET/CT-based metabolic variables and the correlations with clinicopathologic features in OCCC patients.
METHODS: We measured quantitative parameters including maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG).
RESULTS: A total of 22 patients were included. PET/CT-based metabolic parameters were calculated for 20 patients because two had low glucose-uptake tumor. The median SUVmax was 7.25 (range 2.50–14.80). Spearman's correlation test revealed that the level of pre-operative serum cancer antigen 125 (CA 125) correlated significantly with MTV ($P = 0.020$) and TLG ($P = 0.023$). Interestingly, platinum-sensitive patients tended to have higher MTV/TLG though significance not achieved. On univariate analysis, the following four variables (stage, residual disease, platinum sensitivity and MTV50) were significant for both progression-free survival and overall survival. Besides, four metabolic parameters (MTV40, TLG40, TLG50 and TLG60) were significantly associated with patients' overall survival. Out of expectation, ovarian CCC patients with higher level of MTV/TLG tended to have better survival.
CONCLUSIONS: ^{18}F-FDG PET/CT-based metabolic volumetric parameters might be predicators for survival in ovarian CCC patients. Cautions should be taken when interpreting the results due to the small sample size.

Keywords: Ovarian clear cell carcinoma, ^{18}F-FDG PET/CT, metabolic tumor volume, total lesion glycolysis, prognosis

List of abbreviations

CCC:	clear cell carcinoma
^{18}F-FDG	^{18}F-fluorodeoxyglucose positron
PET/CT:	emission tomography/computed tomography
SUVmax:	maximum standardized uptake value
MTV:	metabolic tumor volume
TLG:	Total lesion glycolysis
FIGO:	The International Federation of Gynecology and Obstetrics
CRS:	Cytoreductive surgery
PFS:	Progression-free survival
OS:	Overall survival
CA125:	Cancer antigen 125

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1. Background

Ovarian clear cell carcinoma (CCC), as a subtype of epithelial ovarian cancer, has distinct morphologic and biologic features [1,2]. Ovarian CCC patients tend to have worse survival when compared to the more common serous counterpart [1,3]. Resistance to platinum-based chemotherapy might partly be responsible for the grave survival outcome [3,4]. Researchers have been focused on the study of genomic landscape of ovarian CCC [5–8], hoping to shed light on the underlying mechanism and possible treatment target. Colleagues from Japan identified a gene expression profile characteristic of ovarian CCC, which is enriched in genes associated with stress response and glucose metabolism [5]. According to a review article with profound influence, reprogramming energy metabolism especially glucose metabolism is considered as an emerging hallmark of cancer [9].

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is a molecular imaging technique, which can be used to evaluate tumor distribution and glucose metabolism in different kinds of cancers including gynecologic malignancy [10]. A few publications have explored the role of ^{18}F-FDG PET/CT quantitative parameters in epithelial ovarian cancer, usually lumping all histologic subtypes together [11–20]. PET/CT-based metabolic variables include maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG). MTV refers to the estimated volume of tumor with increased tracer uptake while TLG is an estimation of summed metabolic activity inside MTV [21].

In the current study, we specifically evaluated the role of PET/CT-based variables in patients with ovarian CCC. The associations between metabolic parameters and clinicopathologic features including survival outcome were further investigated.

2. Methods

2.1. Patients

The study was approved by the institutional review board and the requirement for the written informed consent was waived due to its retrospective design. We included all the patients with ovarian CCC who received ^{18}F-FDG PET/CT scan before surgery in our department between May 2010 and September 2017.

All the patients were staged by The International Federation of Gynecology and Obstetrics (FIGO) staging system [22]. Patients with early stage disease (FIGO I+II) underwent complete staging surgery, while those with late stage tumor (FIGO III+IV) received debulking surgery. Optimal cytoreductive surgery (CRS) was defined as residual disease less than (or including) 1 cm after primary debulking. Platinum-based chemotherapy was routinely administered after primary surgery. Patients were considered to have platinum-sensitive disease if the interval time was $>$ 6 months from the completion of the last platinum based chemotherapy to disease recurrence. Progression-free survival (PFS) was defined as the time interval from the date of primary surgery to the date of disease progression or recurrence. Overall survival (OS) was defined as the time interval from the date of the primary surgery to the date of death or last contact.

2.2. ^{18}F-FDG PET/CT protocol and image analysis

The ^{18}F-FDG PET/CT protocol was introduced specifically in our previous publication [19]. The images were retrospectively interpreted by a gynecologic oncology dedicated nuclear medicine physician (Dr. Shuai Liu) who was blind to the clinicopathologic information. Standardized uptake value (SUV) is defined as [decay corrected activity (kBq) per milliliter of tissue volume]/[injected 18 F-FDG activity (kBq) per gram of body mass]. In line with our previous publication, SUVmax was calculated by placing a spheroid-shaped volume of interest within the primary ovarian tumor. MTV and SUVaverage were evaluated by drawing a contour of the ovarian tumor large enough to encase the tumor in the axial, coronal and sagittal section. In the current work, two methods were used for defining threshold SUV to delineate MTV: 1) a threshold of SUV of 2.5 (designated as MTV); 2) a fixed ratio including 40% (MTV40), 50% (MTV50) and 60% (MTV 60) of SUVmax. The boundaries of voxels exceeding the defined threshold were automatically produced and those presenting an SUV greater than the threshold were incorporated to MTV measurement. TLG was calculated as MTV $\times$ SUVaverage.

2.3. Statistic analysis

Statistical Package for Social Science (SPSS) (Version 20.0, SPSS, Inc., Chicago, IL, USA) and GraphPad Prism (Version 6.0, GraphPad Software, Inc., La Jolla, CA, USA) were used for the analyses. Paramet-

ric Student's t-tests were used in evaluating continuous variables, while chi-square tests for the categorical ones. Spearman correlation was applied in comparison between serum cancer antigen 125 (CA125) level and PET/CT-based parameters. Kaplan-Meier model and log-rank test were employed for univariate analysis of survival outcome. Multivariate analysis was not conducted due to the small sample size. All P values reported were two tailed, and $P < 0.05$ was considered statistically significant.

3. Result

3.1. Patient characteristics

A total of 22 ovarian CCC patients were included into the study. Table 1 presents the clinicopathologic characteristics of the patients. Nine patients (40.9%) had early-stage disease (FIGO I + II). The median level of pre-operative serum CA 125 was 162.1 U/mL (range, 15.0–5000). Optimal cytoreduction was achieved in about 80% of the patients. After a mean follow-up time of 20 months (range, 1–73), 8 patients (36.4%) experienced disease recurrence. At last follow-up, six patients were dead from disease, while two patients were still alive with disease.

3.2. Quantitative metabolic parameters

Among 22 patients, two presented with low glucose-uptake tumor. Therefore, PET/CT-based metabolic parameters were calculated for a total of 20 patients, which is demonstrated in Table 1. The mean SUVmax was 7.25 (range 2.50–14.80).

3.3. Associations between clinicopathologic variables and metabolic parameters

We further evaluated the relationship between clinicopathologic variables and metabolic parameters. The level of pre-operative serum CA 125 correlated significantly with MTV ($P = 0.020$) and TLG ($P = 0.023$) on Spearman's correlation test. Clearly seen from Supplementary Table S1, patients with advanced tumor tended to have higher SUVmax, MTV and TLG. However, no statistic significance was achieved. Interestingly, patients who were sensitive to platinum-based chemotherapy had relatively higher level of all metabolic parameters excluding SUVmax, though significance was not achieved.

3.4. Prediction of survival outcome

Lastly, we investigated the possible predictors for patients' survival and the results were shown in Table 2. The following variables including stage, residual disease, platinum sensitivity and MTV50 were significant for both PFS and OS on univariate analysis. In addition, four metabolic parameters (MTV40, TLG40, TLG50 and TLG60) were significantly associated with patients' overall survival. Surprisingly, ovarian CCC patients with higher level of volumetric parameters (MTV/TLG) tended to have better survival. Multivariate analysis was not conducted due to the small sample size.

Table 1
Patient characteristics ($n = 22$)

Variables	
Age (years), median (range)	52 (28–83)
FIGO stage (%)	
Early (I+II)	9 (40.9%)
Advanced (III+IV)	13 (59.1%)
Serum CA 125 (U/mL), median (range)	162.1 (15.0–5000)
Residual disease (%)	
$\leqslant$ 1 cm (optimal)	18 (81.8%)
$>$ 1 cm (suboptimal)	4 (18.2%)
Follow up time (months), mean (range)	20 (1–73)
Disease recurrence (%)	
Without recurrence	14 (63.6%)
With recurrence	8 (36.4%)
Platinum response (%)*	
Sensitive	14 (66.7%)
Resistant	7 (33.3%)
Disease status at last follow up	
Dead	6 (27.3%)
Alive with disease	2 (9.1%)
Alive without disease	14 (63.6%)
Metabolic parameters#	
SUVmax (g/mL), median (range)	7.25 (2.50–14.80)
MTV (mL), median (range)	53.28 (0.09–668.77)
TLG (g), median (range)	197.85 (0.23–3156.59)
MTV40 (mL), median (range)	54.11 (4.16–168.06)
TLG40 (g), median (range)	215.07 (16.27–1027.57)
MTV50 (mL), median (range)	31.01 (2.81–85.54)
TLG50 (g), median (range)	144.76 (12.17–480.73)
MTV60 (mL), median (range)	14.60 (1.08–43.34)
TLG60 (g), median (range)	85.70 (4.22–271.74)

*One patient received last cycle of platinum-based chemotherapy four months ago. #A total of 20 patients had calculated metabolic parameters. Abbreviations: FIGO = The International Federation of Gynecology and Obstetrics; Cancer Antigen 125 = Cancer Antigen; SUVmax = Maximum Standardized Uptake Value; MTV = Metabolic Tumor Volume; TLG = Total Lesion Glycolysis.

4. Discussion

In our previous study, we assessed the prognostic roles of PET/CT-based metabolic parameters in patients with recurrent ovarian CCC [23]. The present work might be the first study, to the best of our knowledge, on the clinical utility of quantitative metabolic

Table 2
Univariate analysis for survival outcome ($n = 20$)

Variables	Category	P value	
		Progression-free survival	Overall survival
Stage	Early vs. Late	**0.010**	**0.038**
CA-125	$\leqslant$ 162.05 U/mL vs. $>$ 162.05 U/mL	0.060	**0.037**
Residual disease	$\leqslant$ 1 cm vs. $>$ 1 cm	$<$ **0.001**	**0.045**
Platinum sensitivity	Resistant vs. Sensitive	$<$ **0.001**	**0.001**
SUVmax	$\leqslant$ 7.25 g/mL vs. $>$ 7.25 g/mL	0.408	0.751
MTV	$\leqslant$ 53.28 mL vs. $>$ 53.28 mL	0.369	0.856
TLG	$\leqslant$ 197.85 g vs. $>$ 197.85 g	0.408	0.751
MTV40	$\leqslant$ 54.11 mL vs. $>$ 54.11 mL	0.057	**0.035**
TLG40	$\leqslant$ 215.07 g vs. $>$ 215.07 g	0.274	**0.024**
MTV50	$\leqslant$ 31.01 mL vs. $>$ 31.01 mL	**0.042**	**0.034**
TLG50	$\leqslant$ 144.76 g vs. $>$144.76g	0.274	**0.024**
MTV60	$\leqslant$ 14.6 mL vs. $>$ 14.6 mL	0.274	0.221
TLG60	$\leqslant$ 85.7 g vs. $>$ 85.7 g	0.274	**0.024**

Abbreivations: SUVmax = Maximum Standardized Uptake Value; MTV = Metabolic Tumor Volume; TLG = Total Lesion Glycolysis.

parameters measured on PET/CT in patients with primary ovarian CCC. However, the most significant limitation is the small sample size of the patients. Firstly, disease rarity might be partly the reason. According to a previous publication from our institution, a total of 122 ovarian CCC patients underwent primary surgery between 1999 and 2014 [24]. Secondly, a significant proportion (57–81%) of the patients have early-stage disease and present with a large pelvic mass [1]. In this circumstance, ^{18}F-FDG PET/CT is not routinely administered due to the economic reason (not covered by insurance in China). Thirdly, PET/CT has only been incorporated to preoperative assessment in patients highly suspicious for ovarian cancer and widespread tumor dissemination since the year 2010. In a summary, cautions should be taken when interpreting the final results of the study due to the relatively small sample size.

Publications assessing the clinical utility of ^{18}F-FDG PET/CT particularly in ovarian CCC patients are limited. Ovarian CCC tumor was usually assumed to be low FDG uptake. In a Japanese study with small cases, positive FDG accumulation was shown in 54.5% (6/11) patients and the median SUVmax was 3.52 [25]. In contrast, about 90% of the patients (20/22) presented with high-FDG tumors and the median SUVmax was 7.25 (range 2.50–14.80) in our study. In addition to SUVmax, we also included volume-based parameters (MTV/TLG), which might better reflect the metabolic burden of active tumor [11]. Another Japanese study, consisting of 27 cases of ovarian CCC, only evaluated the role of SUVmax in survival [13]. We and other colleagues believe that volumetric metabolic variables (MTV/TLG) might be more sensitive than the single-pixel SUV [11]. We reported that high TLG60, together with platinum-resistant recurrence and peritoneal carcinomatosis, was negative predicator of OS in recurrent ovarian CCC patients [23]. For defining the threshold SUV to delineate metabolic tumors, different methods have been used in published literature, mainly divided in to three criteria: the absolute (SUV 2.5), relative (a fixed ratio such as 40% of SUVmax) and background-related relative thresholds (mediastinal background SUV plus two standard deviations) [12,26]. As an exploratory study, we used two methods including absolute and relative thresholds, with the hope of finding a more appropriate threshold method in ovarian CCC patients.

In the present study we found that pre-operative serum CA 125 level correlated significantly with MTV and TLG. Volume-based metabolic parameters were significant for overall survival (MTV40, TLG40, MTV50, TLG50 and TLG60) and progression-free survival MTV50) on univariate analysis. However, ovarian CCC patients with higher level of volumetric parameters (MTV/TLG) tended to have better survival, which was inconsistent from some of the previous publications [11,14,17,23]. It is noteworthy that in our study, patients who were platinum-sensitive had relatively higher level of volumetric metabolic parameters, though not statistically significant. It still needs to be investigated whether or not it is related to the survival analysis. Table 3 presents a very brief summary of the relevant literatures, which include all histologic subtypes. Gallicchio et al evaluated 31 ovarian cancer patients who underwent PET/CT after surgery [18]. They found that patients with higher MTV (42% threshold) had a significantly higher OS [18]. Our previous study,

Table 3
A review of the studies focusing on the predictive value of PET/CT-based volumetric parameters in ovarian cancer

Authors	Metabolic parameters	MTV threshold	Sample size	Main findings
Chung et al. 2012	SUVmax, SUVavg, MTV, TLG	40% SUVmax	$N = 56$ (clear cell = 1)	MTV and TLG were significant for PFS
Liao et al. 2013*	SUVmax, MTV, TLG	SUV = 2.5 background method	$N = 47$ (clear cell = 5)	TLG obtained from background method was significant for OS
Konishi et al. 2014	SUVmax	Not applicable	$N = 80$ (clear cell = 27)	SUVmax was significant for 5-year survival
Lee et al. 2014	SUVmax, MTV, TLG	40% SUVmax	$N = 166$ (clear cell = 20)	TLG was significant for PFS
Lee et al. 2015	SUVmax, SUVavg, MTV, TLG, IFH	40% SUVmax	$N = 61$ (clear cell = 3)	Preoperative IFH was significantly associated with recurrence
Yamamoto et al. 2016	SUVmax, MTV, TLG	40% SUVmax	$N = 37$(clear cell $\leqslant$ 18)	MTV correlated with CA125; TLG correlated with SUVmax and CA125; TLG was significant for PFS
Gallicchio et al. 2017*	SUVmax, MTV, TLG	42% SUVmax	$N = 31$(clear cell = 0)	MTV was significant for OS (positive predictor)
Liu et al. 2018	SUVmax, SUVavg, MTV	SUV = 2.5	$N = 48$ (clear cell $\leqslant$ 3)	A higher SUVmax level was associated with chemosensitivity
Ye et al. 2019	SUVmax, MTV, TLG	SUV = 2.5 40%/50%/60% SUVmax	$N = 35$ (clear cell = 35)	TLG60 was negative predicators of OS

Abbreviations: SUVmax = Maximum Standardized Uptake Value; SUVavg = Average Standardized Uptake Value; MTV = Metabolic Tumor Volume; TLG = Total Lesion Glycolysis; IFH = Intratumoral FDG uptake Heterogeneity; HI = Intratumoral Heterogeneity Index; PFS = Progression Free Survival; OS = Overall Survival. * PET/CT was conducted after surgery.

including 56 cases of high-grade serous carcinoma, also presented that higher FDG uptake was associated with better survival [19]. Several possible reasons might be suggested for the inconsistent conclusions: 1) Different patient population. As clearly seen from Table 3, most published works included various kinds of histology, whereas only ovarian CCC was involved in our study; 2) Different thresholds for MTV delineations. No consensus has ever been achieved when it comes to the selection of volume of interest in delineating tumor MTV.

As aforementioned, a more accurate and sufficient conclusion awaits future studies. First and foremost, given the disease rarity, a multicenter study should be designed to ensure a relatively large sample size. PET/CT images could be collected and sent to an experienced nuclear medicine physician to minimize inter-observer bias. Besides, both primary and recurrent cases should be included given the inconsistent findings of our study. If possible, the metabolic parameters in primary disease presentation and tumor recurrence pertaining to the same patient might be evaluated to investigate the possible changes in tumor progression.

5. Conclusions

PET/CT-based metabolic volumetric parameters might be predicators for survival in ovarian CCC patients. More patients should be included in further study.

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Conflict of interest

The authors declare that they have no conflict of interest.

Supplementary data

The supplementary files are available to download from http://dx.doi.org/10.3233/CBM-190904.

References

[1] M.S. Anglesio, M.S. Carey, M. Kobel, H. Mackay and D.G.

Huntsman, Clear cell carcinoma of the ovary: A report from the first Ovarian Clear Cell Symposium, June 24th, 2010, *Gynecologic Oncology* **121** (2011), 407–15.

[2] M.G. del Carmen, M. Birrer and J.O. Schorge, Clear cell carcinoma of the ovary: A review of the literature, *Gynecologic Oncology* **126** (2012), 481–90.

[3] S. Ye, J. Yang, Y. You, D. Cao, H. Huang, M. Wu, J. Chen, J. Lang and K. Shen, Comparison of clinical characteristic and prognosis between ovarian clear cell carcinoma and serous carcinoma: A 10-year cohort study of chinese patients, *PloS One* **10** (2015), e0133498.

[4] H. Itamochi, J. Kigawa and N. Terakawa, Mechanisms of chemoresistance and poor prognosis in ovarian clear cell carcinoma, *Cancer Science* **99** (2008), 653–8.

[5] K. Yamaguchi, M. Mandai, T. Oura, N. Matsumura, J. Hamanishi, T. Baba, S. Matsui, S.K. Murphy and I. Konishi, Identification of an ovarian clear cell carcinoma gene signature that reflects inherent disease biology and the carcinogenic processes, *Oncogene* **29** (2010), 1741–52.

[6] T. Okamoto, M. Mandai, N. Matsumura, K. Yamaguchi, H. Kondoh, Y. Amano, T. Baba, J. Hamanishi, K. Abiko, K. Kosaka, S.K. Murphy, S. Mori and I. Konishi, Hepatocyte nuclear factor-1beta (HNF-1beta) promotes glucose uptake and glycolytic activity in ovarian clear cell carcinoma, *Molecular Carcinogenesis* **54** (2015), 35–49.

[7] S.I. Kim, J.W. Lee, M. Lee, H.S. Kim, H.H. Chung, J.W. Kim, N.H. Park, Y.S. Song and J.S. Seo, Genomic landscape of ovarian clear cell carcinoma via whole exome sequencing, *Gynecologic Oncology* (2017).

[8] R. Murakami, N. Matsumura, J.B. Brown, K. Higasa, T. Tsutsumi, M. Kamada, H. Abou-Taleb, Y. Hosoe, S. Kitamura, K. Yamaguchi, K. Abiko, J. Hamanishi, T. Baba, M. Koshiyama, Y. Okuno, R. Yamada, F. Matsuda, I. Konishi and M. Mandai, Exome sequencing landscape analysis in ovarian clear cell carcinoma shed light on key chromosomal regions and mutation gene networks, *The American Journal of Pathology* **187** (2017), 2246–58.

[9] D. Hanahan and R.A. Weinberg, Hallmarks of cancer: the next generation, *Cell* **144** (2011), 646–74.

[10] A. Amit, J. Schink, A. Reiss and L. Lowenstein, PET/CT in gynecologic cancer: present applications and future prospects – a clinician's perspective, *Obstetrics and Gynecology Clinics of North America* **38** (2011), 1–21, vii.

[11] H.H. Chung, H.W. Kwon, K.W. Kang, N.H. Park, Y.S. Song, J.K. Chung, S.B. Kang and J.W. Kim, Prognostic value of preoperative metabolic tumor volume and total lesion glycolysis in patients with epithelial ovarian cancer, *Annals of Surgical Oncology* **19** (2012), 1966–72.

[12] S. Liao, X. Lan, G. Cao, H. Yuan and Y. Zhang, Prognostic predictive value of total lesion glycolysis from 18F-FDG PET/CT in post-surgical patients with epithelial ovarian cancer, *Clinical Nuclear Medicine* **38** (2013), 715–20.

[13] H. Konishi, K. Takehara, A. Kojima, S. Okame, Y. Yamamoto, Y. Shiroyama, T. Yokoyama, T. Nogawa and Y. Sugawara, Maximum standardized uptake value of fluorodeoxyglucose positron emission tomography/computed tomography is a prognostic factor in ovarian clear cell adenocarcinoma, *International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society* **24** (2014), 1190–4.

[14] J.W. Lee, A. Cho, J.H. Lee, M. Yun, J.D. Lee, Y.T. Kim and W.J. Kang, The role of metabolic tumor volume and total lesion glycolysis on (1)(8)F-FDG PET/CT in the prognosis of epithelial ovarian cancer, *European Journal of Nuclear Medicine and Molecular Imaging* **41** (2014), 1898–906.

[15] C.Y. Kim, S.Y. Jeong, G.O. Chong, S.H. Son, J.H. Jung, D.H. Kim, S.W. Lee, B.C. Ahn and J. Lee, Quantitative metabolic parameters measured on F-18 FDG PET/CT predict survival after relapse in patients with relapsed epithelial ovarian cancer, *Gynecologic Oncology* **136** (2015), 498–504.

[16] H.A. Vargas, I.A. Burger, D.A. Goldman, M. Micco, R.E. Sosa, W. Weber, D.S. Chi, H. Hricak and E. Sala, 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, *European Radiology* **25** (2015), 3348–53.

[17] M. Yamamoto, T. Tsujikawa, Y. Fujita, Y. Chino, T. Kurokawa, Y. Kiyono, H. Okazawa and Y. Yoshida, Metabolic tumor burden predicts prognosis of ovarian cancer patients who receive platinum-based adjuvant chemotherapy, *Cancer Science* **107** (2016), 478–85.

[18] R. Gallicchio, A. Nardelli, A. Venetucci, D. Capacchione, A. Pelagalli, C. Sirignano, P. Mainenti, P. Pedicini, G. Guglielmi and G. Storto, F-18 FDG PET/CT metabolic tumor volume predicts overall survival in patients with disseminated epithelial ovarian cancer, *European Journal of Radiology* **93** (2017), 107–13.

[19] S. Liu, Z. Feng, Z. Jiang, H. Wen, J. Xu, H. Pan, Y. Deng, L. Zhang, X. Ju, X. Chen and X. Wu, Prognostic predictive value of preoperative intratumoral 2-deoxy-2-(18F)fluoro-D-glucose uptake heterogeneity in patients with high-grade serous ovarian cancer, *Nuclear Medicine Communications* (2018).

[20] S. Liu, Z. Feng, H. Wen, Z. Jiang, H. Pan, Y. Deng, L. Zhang, X. Ju, X. Chen and X. Wu, (18)F-FDG PET/CT can predict chemosensitivity and proliferation of epithelial ovarian cancer via SUVmax value, *Japanese Journal of Radiology* (2018).

[21] F.Y. Liu, A. Chao, C.H. Lai, H.H. Chou and T.C. Yen, Metabolic tumor volume by 18F-FDG PET/CT is prognostic for stage IVB endometrial carcinoma, *Gynecologic Oncology* **125** (2012), 566–71.

[22] FIGO staging for carcinoma of the vulva, cervix, and corpus uteri, *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics* **125** (2014), 97–8.

[23] S. Ye, S. Liu, L. Xiang, X. Wu and H. Yang, (18)F-FDG PET/CT-based metabolic metrics in recurrent tumors of ovarian clear cell carcinoma and their prognostic implications, *BMC Cancer* **19** (2019), 226.

[24] J. Zhu, H. Wen, R. Bi, Y. Wu and X. Wu, Prognostic value of programmed death-ligand 1 (PD-L1) expression in ovarian clear cell carcinoma, *Journal of Gynecologic Oncology* **28** (2017), e77.

[25] Y. Tanizaki, A. Kobayashi, M. Shiro, N. Ota, R. Takano, Y. Mabuchi, S. Yagi, S. Minami, M. Terada and K. Ino, Diagnostic value of preoperative SUVmax on FDG-PET/CT for the detection of ovarian cancer, *International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society* **24** (2014), 454–60.

[26] W. Yu, X.L. Fu, Y.J. Zhang, J.Q. Xiang, L. Shen, G.L. Jiang and J.Y. Chang, GTV spatial conformity between different delineation methods by 18FDG PET/CT and pathology in esophageal cancer, *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology* **93** (2009), 441–6.