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Have Volume-based Parameters of Positron Emission Tomography/Computed Tomography Prognostic Relevance for Patients With Potentially Platinum-responsive Recurrent Ovarian Cancer? A Single Center Italian Study

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Abstract. *Background/Aim: To assess the prognostic relevance of volume-based parameters [whole body (wb)-metabolic tumor volume (MTV) and wb-total lesion glycolysis (TLG)] of pretreatment PET/CT in patients with potentially platinum-responsive recurrent ovarian cancer. Patients and Methods: This retrospective investigation analyzed 67 patients at first relapse. Results: At univariate analysis, post-relapse survival and overall survival correlated with residual disease after primary surgery (RD) (p=0.015 and 0.049, respectively), time to recurrence (p=0.005 and p=0.0003), number of recurrence sites (p=0.001 and p=0.0005), treatment at recurrence (p=0.044 and 0.043) and wb-MTV (p=0.023 and 0.021) but not with wb-TLG. RD, time to recurrence and number of recurrence sites, but not wb-MTV, were independent prognostic variables for post-relapse survival, and time to recurrence and number of recurrence sites, but not wb-MTV, were independent prognostic factors for overall survival. Conclusion: Volume-based parameters of PET/CT are not independent predictors of clinical outcome in potentially platinum-responsive recurrent ovarian cancer.*

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Epithelial ovarian cancer is the gynecological malignancy with the worst prognosis because of the frequent advanced stage at presentation and the elevated biological aggressiveness. Approximately 70-80% of the patients will develop recurrent disease despite improvement in the primary treatment of the tumor (1, 2). Chemotherapy is the standard of care of these patients, whereas secondary cytoreductive surgery should be reserved for accurately selected cases (2-8). Although platinum-free interval (PFI) continues to be an important parameter for the choice of salvage chemotherapy, other factors, (*i.e.* BRCA status, residual toxicity, eligibility to platinum re-treatment, and patient preference) should be taken into consideration, and on the other hand, the classical categories, platinum-refractory/resistant (PFI <6 months), partial-platinum sensitive (PFI=6-12 months), and platinum-sensitive disease (PFI >12 months) have been resized by the Tokyo consensus conference (8, 9). The time elapsed since last platinum chemotherapy reflects a continuum of probability of response to further chemotherapy, and moreover the time to recurrence is influenced by type and timing of surveillance procedures. The term platinum-sensitive should be changed into potentially-platinum responsive, corresponding to a patient who responded to prior platinum without early symptomatic relapse. This patient should receive a platinum-based doublet, eventually combined with bevacizumab or followed by PARP inhibitors as maintenance.

2-deoxy-2-[^{18}F]-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) is very useful for detecting recurrent ovarian cancer and for identifying the patients who are more likely to benefit from secondary cytoreductive surgery (10-21).

The maximum standardized uptake value (SUVmax) obtained for a 1-pixel region of interest (ROI) does not necessarily reflect the activity of the whole tumor mass (22). Whole body (wb)-metabolic tumor volume (MTV) and wb-total lesion glycolysis (TLG) are volume-based parameters developed to measure the metabolic activity in the entire tumor (23, 24). Wb-MTV is a volumetric measurement of tumor cells with high glycolytic activity, while wb-TLG is defined as the product of the SUV and the lesion volume.

A systematic review and meta-analysis of literature data have shown that pretreatment volume-based metabolic parameters of ^{18}F-FDG-PET can be correlated with the clinical outcome of patients with different malignancies including ovarian cancer (25-32).

In the present retrospective investigation, we assessed the prognostic relevance of SUVmax, wb-MTV and wb-TLG in ^{18}F-FDG-PET/CT performed in patients with potentially platinum-responsive recurrent ovarian cancer.

Patients and Methods

This retrospective investigation assessed 67 patients with potentially platinum-responsive recurrent ovarian cancer who underwent ^{18}F-FDG- PET/CT at the time of first relapse at our Hospital between January 2009 and December 2019. The hospital records, including surgical notes, pathological reports, chemotherapy and follow-up data, were collected using a common form with standardized items.

The tumor stage and histological diagnosis of each case were determined according to the FIGO criteria and the histological typing system of the World Health Organization [WHO], respectively. Tumors were graded as well [G1], moderately [G2], or poorly [G3] differentiated. The baseline characteristics [age, FIGO stage, histological type, tumor grade, presence or absence of ascites, residual disease (RD) after primary debulking or interval debulking surgery, type of first-line chemotherapy] were reported for each case. The total number of first-line chemotherapy cycles ranged from six to eight. The evaluation of the course of disease was based on clinical examination, serum Ca 125 assay, chest x-ray, abdominal-pelvic ultrasound and CT scan. Additional investigations were performed when appropriate.

At the end of primary treatment all the patients were in complete clinical response, defined as the lack of evidence of disease at clinical, serological and imaging examinations, and were then followed-up at regular scheduled intervals with the modalities reported in a previous article (33).

All the patients developed a clinically and/or radiologically detectable first recurrence with a PFI longer than 6 months. A secondary cytoreductive surgery was taken into consideration in patients in good general conditions and performance status < or = 1 and without ascites, diffuse bulky peritoneal nodules or peritoneal nodules confluent in plaques, mesenteric retraction, and extra-abdominal disease (except groin metastases) (3, 9, 34). Each case had been debated within a multidisciplinary team meeting and discussed with the patient herself. All the patients performed ^{18}F-FDG-PET/CT before any treatment of recurrence.

Image acquisitions. The [^{18}F]FDG PET/CT scans were performed in two different Nuclear Medicine Centers: the Regional Center of Nuclear Medicine at the University Hospital of Pisa and the Nuclear Medicine Unit at the National Council of Research (CNR) of Pisa. A Discovery 710 scanner (GE Healthcare, Milwaukee, WI, USA) a Discovery VCT scanner (GE Healthcare, Waukesha, WI, USA) with a 3D acquisition modality were used for all the PET/CT studies. All scans were performed with a PET/CT about 60 minutes after the injection of [^{18}F]FDG (3.7 MBq/Kg). Low-dose helical CT scan (automatic exposure control with 100 mA max, 120KVp) was obtained for attenuation correction with a 3.75-mm slice thickness and 3.27-mm reconstruction interval. During both PET and CT scan patients could breathe freely. Acquisition included the cranial vertex to half thigh, requiring 7 to 9 bed positions. Patients fasted for at least 4 hours and finger stick blood glucose levels were <200 mg/dl prior to injection. Images were reconstructed with an iterative algorithm, 256×256 matrix, and segmented attenuation correction. Oral contrast medium or intravenous contrast medium have not been used.

Analysis criteria. Two readers were aware that patients had been treated for ovarian cancer and had suspected of having a recurrence. However, they were blinded to the patients' prospective PET/CT results. On ^{18}F-FDG-PET/CT images for each patient, in each location, readers recorded the presence/absence of recurrent lesions. Findings were considered positive when SUVmax within the suspected lesion was greater than the liver SUVmax.

Freeware LIFEx software was used to enable calculation of several metabolic indices from the PET images imported in DICOM format on a dedicated personal computer (35). A 40% threshold of SUVmax was used to segment the volume of each recurrent lesion of ovarian cancer disclosed on the PET/CT images. If physiologic areas of hyperactivity were within the ROI, manual adjustments were performed in order to exclude them from the analysis.

SUVmax, SUVmean, MTV, and TLG, were calculated within the selected ROI. All these parameters were calculated for each site of recurrence, subdivided as follows: pelvis, abdominal peritoneum, retroperitoneal nodes, abdominal parenchymal relapses, extra-abdominal relapses. Then, in each patient the global tumor burden was considered for the analysis calculating the wb-MTV and the wb-TLG parameters, that represent the overall volume (ml) and total lesion glycolysis (SUVmean*ml) of the recurrent disease.

Statistical analysis. The time from initial diagnosis to death from any cause or last observation was defined as overall survival. The time from detection of the first recurrence to death from any cause or last observation was defined as post-relapse survival. The analyzed prognostic variables included FIGO stage, histological type, tumor grade, RD after initial surgery, interval time between the last cycle of first-line chemotherapy and first recurrence [time to recurrence], patterns of recurrence treatment at recurrence, SUVmax, wb-MTV and wb-TLG in ^{18}F-FDG- PET/CT performed at the time of first recurrence.

Survival analysis were performed according to the Kaplan–Meier product-limit method. Patients were dichotomized based on median cutoff values of age at diagnosis of primary tumor, age at diagnosis of recurrence, time to recurrence, SUVmax, wb-MTV and wb-TLG to determine the association with overall survival and post-relapse survival. A multiple regression analysis based on the Cox proportional hazard model was used to jointly test the relative importance of variables as predictors of survival times. Cox univariable regressions were performed in order to select the factors for the multivariate model. Significance level was set to 5%, and the statistical software R 4.0.3 was used to carried out the analysis.

Table I. *Patient characteristics (n=67).*

Variable	n (%)
At presentation	
Age, years	
Median (range)	59 (36-77)
FIGO stage	
I	4 (6)
II	2 (3)
III	60 (89.6)
IV	1 (1.4)
Histological type	
Serous	58 (86.6)
Endometrioid	3 (4.5)
Clear Cell	3 (4.5)
Mucinous	1 (1.4)
Mixed	2 (3)
Tumor grade	
G1-G2	8 (11.9)
G3	59 (88.1)
BRCA 1-2 status	
Wild type	32 (47.8)
Unknown	22 (32.8)
Mutated	13 (19.4)
First treatment	
PDS + Chemotherapy	60 (89.6)
NACT + IDS	7 (10.4)
RD after surgery	
0	46 (68.7)
0-10 mm	13 (19.4)
>10 mm	8 (11.9)
First-line chemotherapy	
PTX/Platinum-based	38 (56.7)
PTX/Platinum/Bev	24 (35.8)
Platinum-based	5 (7.5)
At recurrence	
Age, years	
Median (range)	61 (37-81)
Time to recurrence	
Median (range)	22 (6-117)
Number of recurrence sites	
1	48 (71.6)
2	14 (20.9)
≥3	5 (7.5)
Site of recurrence (n=94)	
Pelvis	15 (16)
Abdominal peritoneum	37 (39.4)
Retroperitoneal nodes	21 (22.3)
Abdominal parenchymal relapses	5 (5.3)
Extra-abdominal relapses	16 (17)
Treatment	
Chemotherapy	41 (61.2)
SCS + Chemotherapy	26 (38.8)
PET/CT parameters (median)	
SUVmax	11.150
Wb-MTV	7.150
Wb-TLG	45.920

PDS: Primary debulking surgery; NACT: neo-adjuvant chemotherapy; IDS: interval debulking surgery; RD: residual disease; PTX: paclitaxel; Bev: bevacizumab; SCS: secondary cytoreductive surgery; PET/CT: positron emission tomography/computed tomography; SUVmax: maximum standardized uptake value; wb-MTV: whole body-metabolic tumor volume; wb-TLG: whole body-total lesion glycolysis.

Results

Patient characteristics at presentation and at the time of recurrence are shown in Table I. Median age of patients at diagnosis was 59 years (Table I). Most of the patients had stage III disease (89.6%), had high grade serous histology (86.6%), had G3 tumor grade (88.1%), underwent primary debulking surgery (89.6%), and received platinum/paclitaxel-based chemotherapy with or without bevacizumab (92.5%). Of the 45 patients tested for germline or somatic *BRCA* mutations, 13 (28.9%) had a pathogenic mutation. Median time to first recurrence was 22 months and abdominal peritoneum was the most common site of relapse (39.4%), followed by retroperitoneal nodes (22.3%) and pelvis (16.0%). Treatment at recurrence consisted of chemotherapy alone in 61.2% and secondary cytoreductive surgery plus chemotherapy in 38.8%.

Post-relapse survival and overall survival by prognostic variables are shown in Table II.

At univariate analysis post-relapse survival significantly correlated with RD after primary debulking surgery or interval debulking surgery (HR=1.748, p=0.015), time to recurrence (HR=0.955, p=0.005), number of recurrence sites (HR=2.260, p=0.001), treatment at recurrence (HR=0.434, p=0.044) and MTV (HR=1.017, p=0.023), but not with SUVmax and wb-TLG (Table III). RD (HR=1.764, p=0.031), time to recurrence (HR=0.961, p=0.037), and number of recurrence sites (HR=1.964, p=0.025), but not wb-MTV, were independent prognostic variables for survival after recurrence.

At univariate analysis, overall survival significantly correlated with RD after primary debulking surgery or interval debulking surgery (HR=1.596, p=0.049), time to recurrence (HR=0.939, p=0.0003), number of recurrence sites (HR=2.474, p=0.0005), treatment at recurrence (HR=0.431, p=0.043) and wb-MTV (HR=1.018, p=0.021), but not with SUVmax and wb-TLG (Table IV). Time to recurrence (HR=0.937, p=0.001), and number of recurrence sites (HR=1.920, p=0.034), but not wb-MTV, were independent prognostic variables for overall survival.

Discussion

^{18}F-FDG-PET/CT has become a standard imaging method for the staging, monitoring of treatment response, and follow-up of patients with different tumors including ovarian cancer (23).

A meta-analysis of eight studies showed that MTV and TLG were independent prognostic variables for both progression-free survival (HR=2.50, 95%CI=1.79-3.48 and HR=2.42, 95%CI=1.61-3.65, respectively) and overall survival (HR=8.06, 95%CI=4.32-15.05, and HR=7.23, 95%CI=3.38-15.50, respectively) of patients with ovarian cancer (29, 36-43). However, the analyzed studies included patients in different

Table II. *Post-relapse survival and overall survival by Kaplan-Meier analysis.*

Variables		Post-relapse survival		Overall survival	
	Pts	2-years (%)	5-years (%)	2-years (%)	5-years (%)
Age at diagnosis of primary tumor (years)					
>59	31	74.8	44.5	100	61.3
≤59	36	85.8	55.4	100	74.3
FIGO stage					
III-IV	61	79.3	47.5	100	67.5
I-II	6	100	80	100	80
Histological type					
Serous	58	81.6	46.8	100	68.9
Other	9	77.8	66.7	100	66.7
Tumor grade					
G3	59	79.9	50.2	100	65.6
G1-G2	8	87.5	52.5	100	87.5
BRCA 1-2 status					
Wild type	32	86.4	53.8	100	73.3
Unknown	22	76.1	38.7	100	62.4
Mutated	13	83.9	58.7	100	66.7
Residual disease (mm)					
>10	8	42.9	21.4	100	46.9
0-10	13	66.6	28.6	100	59.8
0	46	91	59.9	100	74.8
Age at diagnosis of recurrence (years)					
>61	31	78.2	48.3	100	64.7
≤61	36	82.9	52.4	100	71.5
Time to recurrence (months)					
≤22	35	66.9	33.6	100	37.9
>22	32	96.8	69.3	100	100
Recurrence site					
Pelvis and/or abdominal peritoneum and/or retroperitoneal nodes	48	80.1	58.7	100	76.1
Abdominal parenchymal relapses and/or extra-abdominal relapses	19	83	28	100	49.9
Number of recurrence sites					
≥3	5	75	0	100	25
2	14	57.1	10.7	100	42.9
1	48	88.9	66.3	100	80.3
Treatment of recurrence					
Chemotherapy	41	77.1	41.3	100	59.1
SCS + Chemotherapy	26	87.8	64	100	83.8
SUVmax					
>11.150	33	72.5	49	100	59.8
≤11.150	34	90	50.8	100	78
Wb-MTV					
>7.150	33	81	40.9	100	61.9
≤7.150	34	80.9	60.8	100	75.1
Wb-TLG					
>45.920	33	71.8	31.8	100	56
≤45.920	34	90.5	73.0	100	81.1

Pts: Patients; SCS: secondary cytoreductive surgery; SUVmax: maximum standardized uptake value; wb-MTV: whole body-metabolic tumor volume; wb-TLG: whole body-total lesion glycolysis.

phases of disease, *i.e.* before primary surgery, after primary surgery, after neo-adjuvant chemotherapy and at the time of recurrence. Chung *et al.* (36) retrospectively assessed 55 patients who underwent ^{18}F-FDG-PET/CT before initial surgery. High MTV and high TLG values were independent prognostic factors for shorter progression-free survival (HR=5.571, 95%CI=1.279-24.272, and HR=2.967, 95%CI=1.065-8.265, respectively). In a retrospective investigation of 175 patients, TLG of ^{18}F-FDG-PET/CT performed prior to cytoreductive surgery independently

Table III. *Post-relapse survival by Cox proportional-hazard model.*

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age at diagnosis of primary tumor	1.028	0.990-1.068	0.149			
FIGO stage	3.723	0.506-27.380	0.197			
Histological type	1.310	0.455-3.770	0.616			
Tumor grade	1.490	0.451-4.924	0.513			
BRCA 1-2 status*	1.103	0.378-3.216	0.858			
Residual disease	1.748	1.113-2.745	0.015	1.764	1.055-2.951	0.031
Age at diagnosis of recurrence	1.019	0.981-1.058	0.334			
Time to recurrence	0.955	0-0.986	0.005	0.961	0-0.998	0.037
Recurrence site	2.039	0.949-4.383	0.068			
Number of recurrence sites	2.260	1.404-3.639	0.001	1.964	1.090-3.536	0.025
Treatment of recurrence	0.434	0-0.978	0.044	0.972	0.398-2.374	0.950
SUVmax	1.011	0.988-1.034	0.368			
Wb-MTV	1.017	1.002-1.033	0.023	0.997	0.978-1.016	0.727
Wb-TLG	1.001	0.999-1.003	0.267			

HR: Hazard ratio; CI: confidence interval; FIGO: Federation Internationale de Gynecologie et d'Obstetrique; SUVmax: maximum standardized uptake value; wb-MTV, whole body-metabolic tumor volume; wb-TLG: whole body-total lesion glycolysis. *Wild type *versus* mutated.

Table IV. *Overall survival by Cox proportional-hazard model.*

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age at diagnosis of primary tumor	1.021	0.984-1.059	0.266			
FIGO stage	3.568	0.484-26.280	0.212			
Histological type	1.271	0.442-3.653	0.657			
Tumor grade	1.534	0.464-5.067	0.483			
BRCA 1-2 status*	0.985	0.341-2.845	0.978			
Residual disease	1.596	1.001-2.545	0.049	1.657	0.977-2.811	0.061
Age at diagnosis of recurrence	1.009	0.973-1.046	0.631			
Time to recurrence	0.939	0-0.971	0.0003	0.937	0-0.975	0.001
Recurrence site	1.819	0.858-3.855	0.119			
Number of recurrence sites	2.474	1.491-4.105	0.0005	1.920	1.052-3.503	0.034
Treatment of recurrence	0.431	0-0.974	0.043	0.918	0.382-2.203	0.848
SUVmax	1.014	0.991-1.038	0.230			
Wb-MTV	1.018	1.003-1.033	0.021	0.999	0.981-1.018	0.932
Wb-TLG	1.001	0.999-1.003	0.179			

HR: Hazard ratio; CI: confidence interval; FIGO, Federation Internationale de Gynecologie et d'Obstetrique; SUVmax: maximum standardized uptake value; wb-MTV: whole body-metabolic tumor volume; wb-TLG: whole body-total lesion glycolysis. *Wild type *versus* mutated.

correlated with progression-free survival (p=0.008), whereas SUVmax and MTV were associated with progression-free survival at univariate but not at multivariate analysis (p<0.05) (38). TLG was an independent predictor of overall survival (HR=1.043, 95%CI=1.01-1.078) in series of 47 patients who underwent ^{18}F-FDG-PET/CT after surgery (37). SUVmax was not related to overall survival in a series of 31 patients who underwent ^{18}F-FDG-PET/CT for an early restaging after cytoreductive surgery (42). There was a significant longer overall survival in patients with high MTV than those with lower MTV (p=0.01), whereas TLG had no significant prognostic relevance. MTV reduction after neoadjuvant chemotherapy independently correlated with progression-free survival in a series of 29 patients with advanced disease (43).

Only three studies have assessed the prognostic relevance of volume-based parameters of ^{18}F-FDG-

PET/CT in patients with recurrent ovarian cancer (39-41). MTV and TLG independently correlated with post-relapse survival (HR=1.36, 95%CI=1.2-1.6 and HR=2.24, 95%CI=1.4-3.5, respectively) in a series of 56 patients at first recurrence with a median PFI of 10 months (range=0-106 months) (39). Mayoral *et al*. (41) reported that MTV and TLG, but not SUVmax, were significant predictors of progression-free survival at univariate analysis in a study including 26 patients with a median PFI of 19.5 months (range=2-144 months). MTV and TLG, but not SUVmax, were associated with debulking status in 55 patients who underwent ^{18}F-FDG-PET/CT before secondary cytoreductive surgery (40). Patients with high MTV and/or high TLG had significantly shorter progression-free survival at univariate analysis.

In the present investigation, that included 67 patients with potentially platinum-responsive recurrent ovarian cancer, RD after initial surgery, time to recurrence and number of recurrence sites were independent prognostic variables for post-relapse survival and time to recurrence and number of recurrence sites were independent prognostic factors for overall survival. Wb-MTV, but not SUVmax and wb-TLG, of the ^{18}F-FDG-PET/CT performed before any treatment of recurrence (chemotherapy or secondary cytoreductive surgery) correlated with both post-relapse survival (HR=1.017, 95%CI=1.002-1.033, p=0.023) and overall survival (HR=1.018, 95%CI=1.003-1.033, p=0.021) at univariate analysis, but failed to retain statistical significance at multivariate analysis. The lack of any prognostic relevance of SUV can be at least partially explained by the fact that it is a single-voxel measurement that does not consider the number of voxels included in the tumor volume (40). Therefore, it may be easily affected by statistical noise and not reflect the metabolism of the whole tumor burden. The reason why only the wb-MTV has presented a statistical significance could be explained by the fact that, while the MTV essentially represents the disease burden expressed in ml, the TLG is partly affected by the heterogeneity of the SUV values of the different lesions disclosed in each patient. Thus, what seems to be more relevant from a prognostic point of view is the overall amount of the recurrent disease rather than the total metabolic activity of the disease itself.

In conclusion, in our experience a volume-based parameter of ^{18}F-FDG-PET/CT such as the wb-MTV of recurrent disease may have a better prognostic significance than SUVmax, however, it seems to be not an independent predictor of clinical outcome in patients with potentially platinum-responsive recurrent ovarian cancer.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Study concepts: A.G; D.V.; Study design: A.G., E.S., S.C., D.V. Recruitment and quality control of data: A.G., E.S., G.M, F.G., A. G., T. D., S.C. Data analysis and interpretation: A.G., E.S., G.M, F.G, D.V. Statistical analysis: M.M. Article preparation: A.G.; Article editing: All Authors; Article review: All Authors.

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