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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Correspondence to: Angiolo Gadducci, MD, Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy; +39 50992609, e-mail: a.gadducci@med.unipi.it

Key Words: Epithelial ovarian cancer, potentially platinum-sensitive recurrence, positron emission tomography/computed tomography, prognosis.

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

ANGIOLO GADDUCCI1, ENRICO SIMONETTI1, FEDERICA GUIDOCCIO2, GIANPIERO MANCA2, ASSUERO GIORGETTI3, TOMMASO DEPALO2, STEFANIA COSIO1, MARIO MICCOLI1 and DUCCIO VOLTERRANI2

1Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy;
2Regional Center of Nuclear Medicine, Department of Translational Research, University of Pisa, Pisa, Italy;
3Fondazione CNR/Regione Toscana "Gabriele Monasterio", Pisa, Italy
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 18F-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 18F-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 18F-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). Each case had been debated within a multidisciplinary team meeting and discussed with the patient herself. All the patients performed 18F-FDG-PET/CT before any treatment of recurrence.

**Image acquisitions.** The [18F]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 [18F]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, 256x256 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 18F-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. 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 18F-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                | 61 (37-81)   |
| 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

| Variable                  | n (%)          |
|---------------------------|----------------|
| Age, years                | 61 (37-81)     |
| Time to recurrence        | 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

18F-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, 35-42). 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. (35) retrospectively assessed 55 patients who underwent 18F-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 18F-FDG-PET/CT performed prior to cytoreductive surgery independently.
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 \((p<0.05)\) \((37)\). 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 \((36)\). 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 \((41)\). 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 \((42)\). Only three studies have assessed the prognostic relevance of volume-based parameters of \(^{18}\)F-FDG-PET/CT.

### 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  | 1.021  | 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  | 0.497-1.000 | 0.0003  | 0.937  | 0.497-1.000 | 0.0003  |
| 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  | 0.497-1.000 | 0.043   | 0.918  | 0.382-2.203 | 0.848   |
| SUVmax                             | 1.014  | 0.991-1.038 | 0.230   | 0.999  | 0.981-1.018 | 0.932   |
| Wb-MTV                             | 1.018  | 1.003-1.033 | 0.221   |        |            |         |
| 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.

### 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  | 0.497-1.000 | 0.0003  | 0.937  | 0.497-1.000 | 0.0003  |
| 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  | 0.497-1.000 | 0.043   | 0.918  | 0.382-2.203 | 0.848   |
| SUVmax                             | 1.014  | 0.991-1.038 | 0.230   | 0.999  | 0.981-1.018 | 0.932   |
| Wb-MTV                             | 1.018  | 1.003-1.033 | 0.221   |        |            |         |
| 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.
PET/CT in patients with recurrent ovarian cancer (38-40). 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) (38). Mayoral et al. (40) 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 18F-FDG-PET/CT before secondary cytoreductive surgery (39). 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 18F-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 (39). 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 18F-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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