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Positron Emission Tomography/Computed Tomography in Platinum-sensitive Recurrent Ovarian Cancer: A Single-center Italian Study

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Abstract. *Aim: To assess the correlation between contrast-enhanced computed tomography (CE-CT) and positron-emission tomography (PET)/CT results and surgical and pathological findings in patients with recurrent platinum-sensitive ovarian cancer who underwent secondary cytoreduction. Patients and Methods: ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT with/without CE-CT were performed before 56 cytoreductive surgeries in 49 patients with suspicious recurrent ovarian cancer. Results: ^{18}F-FDG PET/CT showed higher sensitivity and diagnostic accuracy compared with CE-CT for both the whole series (100% versus 90.6%, respectively, and 97.8% versus 85.3%), and the 24 cases in which both examinations were performed (100% versus 87.0% and, respectively, 95.8% versus 83.3%). The addition of CE-CT to ^{18}F-FDG PET/CT did not improve its diagnostic reliability. Conclusion: ^{18}F-FDG PET/CT appears to be the more reliable imaging technique for the evaluation of patients with suspicious recurrent ovarian cancer, and for the selection of those more suitable for secondary cytoreductive surgery.*

GLOBOCAN estimates of incidence and mortality worldwide for 36 cancer types in 185 countries showed 295,414 new cases of ovarian cancer and 184,799 deaths due to this malignancy in 2018 (1). This tumor accounts for 2.5% of all malignancies among females, but for 5% of all cancer deaths due to relatively high fatality rate, since approximately 80% of patients are diagnosed in advanced stage (2, 3). The standard treatment of ovarian cancer apparently confined to the gonad(s) consists of surgery with comprehensive staging followed by adjuvant platinum-based chemotherapy in high–risk cases (4, 5). However, up 30% of the cases recur after a median time ranging from 11 to 29 months (6). Primary debulking surgery followed by paclitaxel/platinum-based chemotherapy is the gold standard treatment for advanced ovarian cancer, if resection of all macroscopic disease can be obtained with an acceptable operative morbidity (5). Two randomized trials detected similar progression-free survival (PFS) and overall survival (OS) for patients with stage IIIC-IV ovarian cancer treated with neoadjuvant chemotherapy followed by interval debulking surgery and for those treated with primary debulking surgery followed by chemotherapy (7, 8). However, both trials have several bias, represented especially by the low rates of complete cytoreduction. The Trial on Radical Upfront Surgical Therapy (TRUST), including only centers with high certified surgical skill, is currently ongoing to compare these two treatment strategies (5). Most patients with advanced ovarian cancer achieve a complete response after first-line chemotherapy but almost 75% of clinically complete responders will experience recurrence after a median of 18-24 months (6, 9). There is no agreement in the literature about the type and timing of examinations to perform for the follow-up of these patients (6, 10). A minimalist surveillance protocol consists of periodical history, physical examinations and serum CA125 assay, while an intensive approach also includes planned diagnostic imaging procedures in asymptomatic patients.

Secondary cytoreductive surgery, with the aim to remove all macroscopic recurrent tumor, can be taken into consideration before second-line chemotherapy in highly selected patients with platinum-sensitive recurrent ovarian cancer, although the benefit of this strategy in terms of OS is still debated (5, 11-14). The probability of achieving a macroscopically complete secondary cytoreduction is dependent on good performance

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status, absence of gross residual disease after-first surgery, lack of ascites at the time of relapse, and the sites and extension of recurrent disease. Theoretically, earlier detection of relapse should enhance the chance of finding disease of limited extent fit for a secondary surgery (11, 15). Contrast material–enhanced (CE) computed tomography (CT) has a sensitivity ranging from 40 to 93% for detecting recurrent ovarian cancer (6, 15-22). In this clinical setting, the sensitivity of [^{18}F]-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET/CT), which provides combined metabolic and anatomic information, is above 90% in most series (6, 15-21, 23-25). In most studies directly comparing these two imaging techniques, the sensitivity for recurrent ovarian cancer was higher for ^{18}F-FDG PET/CT (ranging from 74% to 100%) than for CE-CT (ranging from 53% to 76%) (18, 26-29.) ^{18}F-FDG PET/CT can be especially useful for the selection of patients suitable for secondary cytoreduction (15, 19, 22, 30-33).

In the present retrospective investigation, we assessed the correlation between ^{18}F-FDG PET/CT and CE-CT results and surgical and pathological findings in patients with recurrent platinum-sensitive ovarian cancer who underwent secondary cytoreduction.

Patients and Methods

This retrospective investigation assessed 49 consecutive patients who underwent secondary cytoreductive surgery for platinum-sensitive recurrent ovarian cancer at our Hospital between January 2009 and December 2019. Patients submitted to secondary palliative surgery for bowel occlusion were excluded from this study.

At presentation, the choice for primary debulking surgery followed by chemotherapy *versus* neoadjuvant chemotherapy followed by interval debulking surgery and additional chemotherapy was individually established on the basis of an accurate evaluation of both the spread of disease at clinical, imaging, and, sometimes laparoscopic examinations, and the patient general conditions, after an exhaustive discussion with the patient herself by a multidisciplinary team (9).

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 International Federation of Gynecology and Obstetrics (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 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 CA125 assay, chest x-ray, abdominal-pelvic ultrasound and CE-CT scan. Additional investigations, such as magnetic resonance imaging (MRI), ^{18}F-FDG PET/CT or colonoscopy, 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 in

Table I. *Patients characteristics (n=49).*

Variable	Subgroup	N (%)
At presentation		
Age, years	Median (range)	58 (35-76)
PS		
	0-1	44 (89.8)
	>1	5 (10.2)
FIGO stage, n (%	I	11 (22.5)
	II	1 (2)
	III	35 (71.4)
	IV	2 (4.1)
Histological type, n (%)	Serous	36 (73.5)
	Endometrioid	5 (10.3)
	Clear-cell	3 (6.1)
	Mucinous	2 (4)
	Mixed	2 (4)
	Undifferentiated	1 (2.1)
Tumor grade, n (%)	1-2	8 (16.3)
	3	41 (83.7)
Ascites, n (%)	No	29 (51.2)
	Yes	20 (48.8)
First treatment, n (%)	PDS + chemotherapy	45 (91.8)
	NACT + IDS	4 (8.2)
RD after surgery, n (%)	0	34 (69.4)
	0-10 mm	3 (6.1)
	>10 mm	7 (14.3)
	Unknown	5 (10.2)
First-line chemotherapy, n (%)	Paclitaxel/platinum-based	37 (75.5)
	Paclitaxel/platinum/bevacizumab	9 (18.4)
	Platinum-based	2 (4.1)
	Other	1 (2)
At recurrence		
Age, years	Median (range)	62 (37-79)
Symptoms, n (%)	No	53 (94.6)
	Yes	3 (5.4)
CA125 before SCS, n (%)	<35 UI/ml	28 (50)
	≥35 UI/ml	18 (32.1)
	Unknown	10 (17.9)
Number of recurrence sites, n (%)	1	29 (51.8)
	>1	25 (44.6)
	0	2 (3.6)
Site of recurrence, n (%)	Pelvis	28 (20.1)
	Abdominal peritoneum	78 (56.1)
	Retroperitoneal nodes	23 (16.5)
Extra-abdominal	Groin	3 (2.2)
	Lateral-cervical nodes	1 (0.7)
	Axillary nodes	1 (0.7)
	Lung	4 (3)
	Pleura	1 (0.7)
Imaging techniques before SCS, n (%)	CE-CT + ^{18}F-FDG PET/CT	24 (42.9)
	Only CE-CT	10 (17.9)
	Only ^{18}F-FDG PET/CT	22 (39.3)

PS: Performance status; FIGO: International Federation of Gynecology and Obstetrics; PDS: primary debulking surgery; NACT: neo-adjuvant chemotherapy; IDS: interval debulking surgery; RD: residual disease; CA125: cancer antigen 125; SCS: secondary cytoreductive surgery; CE-CT: contrast enhanced computed tomography; ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography.

Table II. *Correlation between imaging findings and secondary cytoreductive surgery findings: Patient-based analysis.*

Variable	Finding	Histological findings		Sensitivity (95% CI)	PPV (95% CI)	Accuracy (95% CI)
		Positive	Negative			
CE-CT (n=34)	Positive	29	2	90.6% (80.5-100%)	93.5% (85-100%)	85.3% (73.4-97.2%)
	Negative	3	0			
^{18}F-FDG PET/CT (n=46)	Positive	45	1	100	97.8% (93.6-100%)	97.8% (93.6-100%)
	Negative	0	0			
CE-CT with ^{18}F-FDG PET/CT (n=24)						
CE-CT	Positive	20	1	87.0% (73.2-100%)	95.2% (86.1-100%)	83.3% (68.4-98.2%)
	Negative	3	0			
^{18}F-FDG PET/CT	Positive	23	1	100	95.8% (87.8-100%)	95.8% (87.8-100%)
	Negative	0	0			
^{18}F-FDG PET/CT+ CE-CT	Positive	23	1	100	95.8% (87.8-100%)	95.8% (87.8-100%)
	Negative	0	0			

CE-CT: Contrast-enhanced computed tomography; ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography; PPV: positive predictive value; CI: confidence interval.

clinical, serological and imaging examinations, and were then followed-up at regular scheduled intervals with the modalities reported in a previous article (10).

All 49 patients developed clinically or radiologically detectable recurrent disease with absence of ascites, diffuse bulky peritoneal nodules, peritoneal nodules confluent in plaques and mesenteric retraction, and with a platinum free-interval longer than 6 months. CE-CT with/without ^{18}F-FDG PET/CT were performed before secondary cytoreduction and imaging results were compared with surgical and pathological findings, in order to evaluate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of the two imaging techniques.

Image acquisitions. CE-CT studies were performed with various scanners (GE Healthcare Technologies, Milwaukee, WI, USA) and protocols were tailored to each scanner. However, standard collimation was 1.25 mm. A dynamic power injection of 150 ml of nonionic intravenous contrast material was given at 3 ml/s (or slower when mandated by suboptimal venous access). Images from all CE-CT examinations were sent to the picture archiving and communication system of our hospital for interpretation. Axial plane images were used for image interpretation on picture archiving and communication system workstations.

^{18}F-FDG PET/CT studies were performed using two dedicated scanners (Discovery ST CT/PET and Discovery 710 CT/PET; GE Medical Systems, Milwaukee, WI, USA). Both systems combined a high-resolution PET scanner and a helical multisection CT scanner. All patients fasted for at least 6 hours and had blood glucose levels <180 mg/dl before radiotracer administration. ^{18}F-FDG PET/CT scans were acquired after intravenous injection of 3.7 MBq/kg ^{18}F-FDG and an average uptake period of 60 minutes. Images were reconstructed with an iterative algorithm, 256×256 matrix, and segmented attenuation correction. Oral contrast medium or intravenous contrast medium were not used.

Analysis criteria. ^{18}F-FDG PET/CT images were retrospectively and independently analyzed by three readers (D.V., G.M. and F.G.) on a Xeleris 3.0 GE Medical Systems workstation. The readers were aware that the patients had been treated for ovarian cancer and were suspected to have a recurrence. However, all three readers were blinded to the patients' prospective PET/CT and/or CE-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 by the three readers when maximum standardized uptake value (SUVmax) within the suspected lesion was greater than liver SUVmax. Uncertain findings were considered as negative. A positive or negative finding resulted from the concordance between two out of the three reviewers.

Sensitivity, specificity, PPV, NPV and diagnostic accuracy were determined on patient and region level. Anatomical locations were grouped into six general regions for the purposes of analysis: diaphragm, liver–pancreas–spleen, peritoneal deposits, pelvic lesions, abdominal and pelvic lymph nodes, extra-abdominal metastases.

Results

Patient characteristics at presentation and at the time of recurrence are shown in the Table I. The large majority of the patients underwent primary debulking surgery (91.8%), and received paclitaxel/platinum-based chemotherapy with or without bevacizumab (93.9%) (Table I). Macroscopic residual disease after first surgery was absent in 69.4% and less than 10 mm in 6.1%. All 49 patients underwent secondary cytoreductive surgery for platinum-sensitive recurrent ovarian cancer, six underwent tertiary cytoreduction for platinum-sensitive recurrent disease, and one patient underwent quaternary cytoreduction for platinum-sensitive recurrent disease. Therefore, 56 surgical cytoreductions were performed in these patients.

Abdominal peritoneum was the most common site of recurrence (56.1%), followed by the pelvis (20.1%) and retroperitoneal lymph nodes (16.5%) (Table I). In most cases, peritoneal lesions were <5 mm. ^{18}F-FDG PET/CT and

Table III. *Correlation between imaging findings and secondary cytoreductive surgery findings: Lesion-based analysis (n=91).*

Variable	Histological findings		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
	Positive	Negative					
CE-CT							
Positive	25	4	59.5% (44.7-74.4%)	91.8% (84.2-99.5%)	86.2% (73.7-98.8%)	72.6% (61.4-83.8%)	76.9% (68.3-85.6%)
Negative	17	45					
^{18}F-FDG PET/CT							
Positive	29	6	69.01 (55.1-83%)	87.8% (78.6-96.9%)	82.9% (70.4-95.3%)	76.8% (65.7-87.8%)	79.1% (70.8-87.5%)
Negative	13	43					
^{18}F-FDG PET/CT+CE-CT							
Positive	32	7	76.2% (63.3-89.1%)	85.7% (75.9-95.5%)	82.1% (70-94.1%)	80.8% (70.1-91.5%)	81.3% (76.5-85.4%)
Negative	10	42					

CE-CT: Contrast-enhanced computed tomography; ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

CE-CT were performed before surgery in 46 (82.1%) and 34 (60.7%) cases, respectively. Both examinations were carried out in 24 (42.9%) cases.

Histologically proven recurrent ovarian cancer was detected in 54 (96.4%) out of the 56 surgeries. Of the two patients without recurrent disease, one had suspicious nodules in her upper abdomen at CE-CT and the other had suspicious left external iliac lymph nodes at both ^{18}F-FDG PET/CT and CE-CT. These suspicious lesions were surgically removed and the pathological examination did not reveal the presence of tumor.

In the whole population patient-based analysis, ^{18}F-FDG PET/CT showed higher sensitivity (100% *versus* 90.6%), higher PPV (97.8% *versus* 93.5%) and higher diagnostic accuracy (97.8% *versus* 85.3%) compared with CE-CT (Table II). In the 24 cases in which both imaging techniques were performed, ^{18}F-FDG PET/CT had better sensitivity (100% *versus* 87.0%), better diagnostic accuracy (95.8% *versus* 83.3%) and similar PPV (95.8% *versus* 95.2%) compared with CE-CT (Table II). The addition of CE-CT to ^{18}F-FDG PET/CT did not improve its diagnostic reliability.

A lesion-based analysis was considered in the 24 cases in which both ^{18}F-FDG PET/CT and CE-CT scans were performed (Table III). Of the 91 lesions removed, 42 (46.2%) were found to be histologically proven recurrent ovarian cancer, and of these 29 were detected by ^{18}F-FDG PET/CT and 25 by CE-CT, with a sensitivity of 69.0% and 59.5%, a PPV of 82.9% and 86.2%, and a diagnostic accuracy of 79,1% and 76.9%, respectively.

The lesion site-based analysis showed a good sensitivity of ^{18}F-FDG PET/CT for upper abdominal parenchymal metastases (100%), pelvic lesions (83.3%), retroperitoneal nodes (81.8%) and extra-abdominal metastases (100%), but not for peritoneal deposits (46.7%) (Table IV).

Discussion

The whole population patient-based analysis of the present series showed that ^{18}F-FDG PET/CT had sensitivity, PPV and diagnostic accuracy of 100%, 97.8%, and 97.8% respectively, in detecting recurrent ovarian cancer, and that these values compared favorably with those reported in the literature (15, 17, 22, 24, 25, 34, 35). Bristow *et al.* performed ^{18}F-FDG PET/CT before secondary cytoreductive surgery in 22 patients with ovarian cancer with increasing serum CA125 and negative or equivocal CT findings after 6 or more months after primary therapy. Eighteen patients were found to have residual disease ≥1 cm. The overall patient-based sensitivity, PPV and diagnostic accuracy of ^{18}F-FDG PET/CT in detecting residual tumor ≥1 cm were 83.3%, 93.8% and 81.8% respectively (15). Similarly, a Taiwanese investigation reported that PET/CT had sensitivity of 100%, PPV of 92%, and diagnostic accuracy of 94% for identification of recurrent ovarian cancer in patients with histologically proven relapse of any size (24). Sironi *et al.* performed ^{18}F-FDG PET/CT before second-look surgery in 31 patients with ovarian cancer, of whom 17 (55%) had persistent tumor at pathological examination (34). The overall lesion-based sensitivity, PPV and diagnostic accuracy of this examination were 78%, 89% and 77% respectively. In a recent investigation, Lee *et al.* reviewed 134 patients with ovarian cancer who underwent secondary cytoreduction after either ^{18}F-FDG PET/CT or CE-CT. One hundred and twenty-four (92.5%) patients were found to have recurrent tumor. Among the 73 patients who underwent PET/CT, 65 (89.0%) were confirmed to have a relapse, and this imaging technique had a sensitivity of 98.5%, a PPV of 88.9%, and a diagnostic accuracy of 87.7%. Of the 169 lesions removed from patients examined with ^{18}F-FDG PET/CT, 135 (79.9%) were confirmed to be positive for malignancy and 124 of these were

Table IV. *Analysis based on lesions stratified by disease site.*

Variable	TP, n	FP, n	TN, n	FN, n	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
CE-CT & ^{18}F-FDG PET/CT (n=91)									
CE-CT									
Diaphragm	1	0	11	1	50.0% (0-100%)	100	100	91.7% (76-100%)	92.3% (77.8-100%)
Liver – pancreas – spleen	2	0	0	2	50.0% (1-99%)		100		50% (1-99%)
Peritoneal deposits	5	0	23	10	33.3% (9.5-57.2%)	100	100	69.7% (54-85.4%)	73.7% (59.7-87.7%)
Pelvic lesions	4	0	0	2	66.7% (28.9-100%)		100		66.7% (28.9-100%)
Abdominal and pelvic lymph nodes	10	4	11	1	90.9% (73.9-100%)	73.3% (51-95.7%)	71.4% (47.8-95.1%)	91.7% (76-100%)	80.8% (65.6-95.9%)
Extra-abdominal metastases	3	0	0	1	75.0% (47.7-100%)		100		75% (47.7-100%)
^{18}F-FDG PET/CT									
Diaphragm	0	0	11	2		100		84.6% (65-100%)	84.6% (65-100%)
Liver – pancreas – spleen	4	0	0	0	100		100		100
Peritoneal deposits	7	0	23	8	46.7% (21.4-71.9%)	100	100	71.9% (56.3-87.5%)	78.9% (66-91.9%)
Pelvic lesions	5	0	0	1	83.3% (53.5-100%)		100		83.3% (53.5-100%)
Abdominal and pelvic lymph nodes	9	6	9	2	81.8% (59-100%)	60.0% (35.2-84.8%)	60.0% (35.2-84.8%)	81.8% (59-100%)	69.2% (51.6-86.8%)
Extra-abdominal metastases	4	0	0	0	100		100		100
CE-CT + ^{18}F-FDG PET/CT									
Diaphragm	1	0	11	1	50.0% (0-100%)	100	100	91.7% (76-100%)	92.3% (77.8-100%)
Liver – pancreas – spleen	4	0	0	0	100		100		100
Peritoneal deposits	8	0	23	7	53.4% (28.1-78.6%)	100	100	76.7% (61.5-91.8%)	81.6% (69.3-93.9%)
Pelvic lesions	5	0	0	1	83.3% (53.5-100%)		100		83.3% (53.5-100%)
Abdominal and pelvic lymph nodes	10	7	8	1	90.9% (73.9-100%)	53.3% (28.1-78.6%)	58.8% (35.4-82.2%)	88.9% (68.4-100%)	69.2% (51.5-86.9%)
Extra-abdominal metastases	4	0	0	0	100		100		100

TP: True positive; FP: false positive; TN: true negative; FN: false negative; CE-CT: contrast-enhanced computer tomography; ^{18}FDG-PET/CT: ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

detected by ^{18}F-FDG PET/CT, with a sensitivity of 91.9%, a PPV of 85.5% and a diagnostic accuracy of 81.1% accuracy. Foreign body granuloma was detected in seven (33.3%) of 21 lesions with false-positive ^{18}F-FDG PET/CT findings (22).

Tawakol *et al*. performed ^{18}F-FDG PET/CT followed immediately by CE-CT in 111 prospectively recruited patients with clinical suspicion of ovarian cancer recurrence, and found that ^{18}F-FDG PET/CT was significantly more sensitive (96% *versus* 84%, p=0.002), more specific (92% *versus* 59%, p=0.001) and more accurate (95% *versus* 76%, p<0.0001) compared with CT (25).

A systematic review and meta-analysis of 34 studies assessing the ability of different examinations in detecting recurrent ovarian cancer found that ^{18}F-FDG PET/CT had the highest pooled sensitivity (91%), followed by PET alone (88%), CE-CT (79%), MRI (75%), and CA125 (69%) (35).

In the present study, the analysis of the 24 cases in which both ^{18}F-FDG PET/CT and CE-CT were performed before secondary cytoreductive surgery confirmed that ^{18}F-FDG PET/CT had better sensitivity and diagnostic accuracy than CE-CT (25, 34) and showed that the addition of CE-CT to ^{18}F-FDG PET/CT did not improve its diagnostic reliability.

In a retrospective study of the Memorial Sloan-Kettering Cancer Center, three independent readers reviewed ^{18}F-FDG PET/CT and CE-CT performed within 8 weeks of surgery in 35 women with histologically proven recurrent ovarian cancer (17). Since there were no false-positive or true-negative results, only sensitivity was calculated, which ranged from

91% to 94% for both ^{18}F-FDG PET/CT and CE-CT. At pathological examination, 93 sites of recurrence were found. Both imaging techniques were accurate in the detection of peritoneal and pelvic node lesions, whereas the ability in the detection of pelvic recurrences, supra-renal node metastases, and liver and splenic metastases was rather limited. ^{18}F-FDG PET/CT performed better than did CE-CT in the detection of para-aortic node involvement. Conversely in our experience, the lesion site-based analysis revealed that ^{18}F-FDG PET/CT was more sensitive for upper abdominal parenchymal metastases and pelvic recurrences compared with abdominal peritoneal lesions. The low sensitivity for these latter lesions might be due to their small size, <5 mm in most cases. In fact, patients with ascites, diffuse bulky peritoneal nodules, peritoneal nodules confluent in plaques and mesenteric retraction were excluded from surgical reassessment.

In conclusion, ^{18}F-FDG PET/CT appears to be the more reliable imaging technique for the evaluation of patients with suspicious recurrent ovarian cancer, and for the selection of those more suitable for secondary cytoreductive surgery.

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

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