CA-125 Correlates with Metastatic Status at [18F]FDG PET/CT in Patients with Relapsed Ovarian Cancer

Francesco Dondi[1,*], Pietro Bellini[1], Domenico Albano[2] and Francesco Bertagna[2]

[1]Nuclear Medicine, ASST Spedali Civili di Brescia, Brescia, Italy and [2]Nuclear Medicine, Università degli Studi di Brescia and ASST Spedali Civili di Brescia, Brescia, Italy

Abstract: ***Background:*** ovarian cancer (OC) relapse can be diagnosed with the evaluation of tumor markers and 18F-fluorodoxyglucose positron emission tomography/computed tomography ([18F]FDG PET/CT) findings. The aim of our study was to assess the correlation between CA-125 and [18F]FDG PET/CT findings in terms of metastatic disease in patients with OC relapse. ***Material and Methods:*** 68 PET/CT scans positive for OC relapse were analyzed qualitatively and semiquantitatively by measuring the maximum and mean standardized uptake value body weight max (SUVmax, SUVmean), SUV lean body mass (SUVlbm), SUV body surface area (SUVbsa), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of hypermetabolic lesions. These parameters and CA-125 were correlated with the metastatic status of patients. ***Results:*** correlation of presence of distant metastases with MTV (p value <0.001), TLG (p value <0.001) and CA-125 (p value 0.010) were reported; no correlation with SUVmax, SUVmean, SUVlbm and SUVbsa were underlined. Moreover, correlation between the type of distant metastases (nodal or extranodal) with MTV (p value 0.021), TLG (p value 0.044) and CA-125 (p value 0.037) were underlined; no correlation with SUVmax, SUVmean, SUVlbm and SUVbsa were reported. Receiving operating characteristic (ROC) curve analysis revealed acceptable performances in both cases. ***Conclusions:*** Correlation between volumetric [18F]FDG PET/CT parameters and CA-125 with the metastatic status was reported.

Keywords: PET, Positron Emission Tomography, Ovarian Cancer, CA-125.

INTRODUCTION

Ovarian cancer (OC) is characterized by high mortality and is on of the leading cause of death among all gynecological cancers. Typically symptomatic only in advanced stages, most of the patients are diagnosed when the disease has become metastatic [1-2]. The staging of this neoplasm is usually performed by multiple conventional imaging (CI) modalities such as ultrasonography (US), particularly useful for the assessment of ovarian masses, computed tomography (CT) and magnetic resonance (MR). 18F-fluodeoxyglucose positron emission tomography/computed tomography ([18F]FDG PET/CT) is an imaging modality that has proven its usefulness in many different gynecological malignancies [3]. In this setting, it is not usually performed for staging purposes in OC, but its role for the assessment of retroperitoneal lymph nodes has been proved [4].

Cancer antigen 125 (CA-125) is a high-molecular-weight glycoprotein expressed on the surface of the epithelial cells and has a particular role as a tumor marker in staging and restaging of different malignancies included OC [1,5]. Standard treatment of the disease includes aggressive cytoreductive surgery followed by chemotherapy [6]. In this setting, prognosis of the patients is strictly related to recurrence that, in the case of OC, is extremely frequent: 75-80% of all patients and 90-95% of subjects with advanced disease (FIGO stage III/IV) will relapse within 2 years after primary treatment [7]. As a consequence and according to these evidences, early identification of tumor recurrence is crucial to defining subsequent therapeutic approach.

CA-125 is a particularly sensitive to investigate the possible presence of relapse or persistence of OC: accuracy of 79-95% has been reported in literature [8–9]. Its low and progressive increase is strongly predictive of disease relapse among patients who are in apparent complete clinical remission [10]. Moreover, also CI has a pivotal role for the evaluation of recurrence or persistence of disease, with high variability in terms of sensitivity and specificity reported in literature [1]. [18F]FDG PET/CT is frequently performed in the work-up of possible recurrence, given its ability to identify relapse of OC in both asymptomatic and symptomatic patients [11].

The purpose of our study was to assess the correlation between CA-125 and [18F]FDG PET/CT findings in terms of metastatic disease in patients with OC relapse.

MATERIAL AND METHODS

This study was carried out including a subgroup of patients that were part of the cohort of a previously published work [12]. A total of 68 [18F]FDG PET/CT scans were retrospectively included. Such scans were performed in our center in patients with a previous diagnosis of OC from July 2007 to October 2019. Patients with a history of multiple tumors expressing CA-125 (i.e. breast) were excluded from the study. All PET/CT were performed at least 1 month after the end of chemotherapy and 3 months after surgery or the end of radiotherapy.

A dose of 3–3.5 MBq/kg of [18F]FDG was intravenously injected to the patient 60 minutes before image acquisition. Patients were instructed to void before acquisition; written consent was also obtained before studies. PET/CT scans were performed from the skull base to the midthigh on a Discovery ST or Discovery 690 PET/CT tomograph (General Electric Company, GE, Milwaukee, Wisconsin) with standard parameters (CT: 80 mA, 120 kV; PET: 2.5–4 min per bed position, PET step of 15 cm). Reconstruction of images was performed in a 256×256 matrix and 60 cm field of view. All PET/CT scans were visually and

*Address corresponding to this author at the Nuclear Medicine, ASST Spedali Civili di Brescia, P.le Spedali Civili, 1, 25123, Brescia, Italy; Tel: +39-030-3995461; Fax: +39-030-3995420; Email: f.dondi@outlook.com

semiquantitatively analyzed by two experienced nuclear medicine physicians by consensus. For semiquantitative analysis the measure of the maximum and mean standardized uptake value body weight max (SUVbw max, SUVbw mean), SUV lean body mass (SUVlbm), SUV body surface area (SUVbsa), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of hypermetabolic lesions were performed. In this setting, MTV was extracted from [18F]FDG PET images corrected for attenuation, with an SUV-based automated contouring program (Advantage Workstation 4.6, GE HealthCare). This operation was performed with an isocontour threshold method based on 41% of the SUVmax, as previously recommended by the European Association of Nuclear Medicine (EANM), because of its high interobserver reproducibility [13]. Furthermore, TLG was calculated by summing the product of MTV of each lesion with its SUVmean.

Cancer antigen 125 (CA-125) values were collected in a range of times within 2 months from the PET/CT scan.

Statistical analyses were performed using MedCalc Software version 17.1 for Windows (Ostend, Belgium). Categorical variable were presented with the calculation of simple and relative frequencies while the numeric variables were described with mean, standard deviation, minimum and maximum values. To assess the possible correlation between PET/CT results in terms of presence or absence of nodal metastases with CA-125 values and PET semiquantitative parameters, T-test was used. The same test was also applied when searching for correlation between the presence of distant metastases at PET/CT scan with CA-125 values and the aforementioned semiquantitative parameters. Moreover, the same analyses were also performed in order to assess a possible relationship between PET/CT semiquantitative parameters and CA-125 with the status of distant metastases (nodal or extranodal). P-value was considered statistically significant if < 0.05.

In order to identify the best CA-125 value able to discriminate between the aforementioned classification of PET/CT scans, receiver operating characteristic (ROC) curve analysis was performed. Area Under Curve (AUC), sensitivity and specificity were then obtained from this analysis.

RESULTS

Mean age of patients was 65 (range 45–85) years. FIGO stage I disease was present in 1 patients, stage II in of 4 subjects, stage III in 47 patients while 16 subjects had a stage IV disease. All PET/CT were performed after surgical removal of the primary tumor and subsequent adjuvant therapy. In particular 66 were performed after the completion of chemotherapy while 2 after radiotherapy. Speaking about histology, 59 hybrid imaging scans were performed in patients affected by serous carcinoma, endometrioid carcinoma was present in 5 patients, carcinosarcoma in 2, 1 patient had clear cell carcinoma and 1 subject had undifferentiated carcinoma (Table **1**).

All the PET/CT scans included in the study were positive for relapse of OC. In particular 11 scans had nodal localization of disease, 6 had both nodal and distant metastases, 5 had the presence of local relapse of disease and distant metastases, 9 had the presence of local relapse and both nodal and distant metastases, 4 scans demonstrated both local relapse and nodal metastases while 33 had only the presence of local relapse.

When evaluating the correlation between the presence of nodal metastasis at [18F]FDG PET/CT with CA-125 values and PET semiquantitative parameters, we did not reported any significant results. When the same analysis was performed in order to assess a correlation with the presence of distant metastases, statistical significant correlation with MTV (p value <0.001), TLG (p value <0.001) and CA-125 (p value 0.010) values were reported; the others PET/CT semiquantitative parameters did not reveal any significant difference. Moreover, when analyzing these relationship in the group of patients with distant metastases in order to discriminate between the presence of nodal or extranodal localization of disease, the correlations between MTV (p value 0.021), TLG (p value 0.044) and CA-125 (p value 0.037) were confirmed, while other semiquantitative parameters confirmed the absence of correlation (Table **2**) (Figure **1**).

ROC analyses were performed to find the best CA-125 value able to discriminate between the presence or the absence of distant metastases and between the presence or the absence of nodal and extranodal localization of disease. In the first case a value of 315 UI/mL for CA-125 had the best discriminating accuracy (AUC 0.669, sensitivity 43%, specificity 95% and p value 0.011) while in the second analysis a value of 596 UI/mL revealed the best performances (AUC 0.729, sensitivity 54%, specificity 89% and p value 0.017) (Figure **2**).

Figure 1: Maximum intensity projection (MIP) of a [18F]FDG PET/CT scan, performed in a patient with relapse of OC, demonstrating multiple localization of disease on cervical, mediastinal and abdominal nodes (arrows). MTV, TLG and CA-125 values were 34.7, 368.1 and 948 UI/mL respectively.

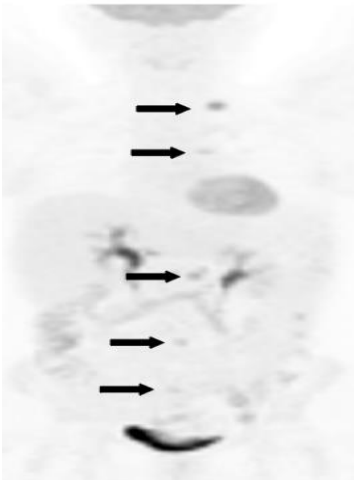

Figure 2: ROC curve analyses for CA-125 values when classifying between PET/CT scans with or without the presence of distant metastases (A) and between the presence of nodal or extranodal distant localization of disease (B).

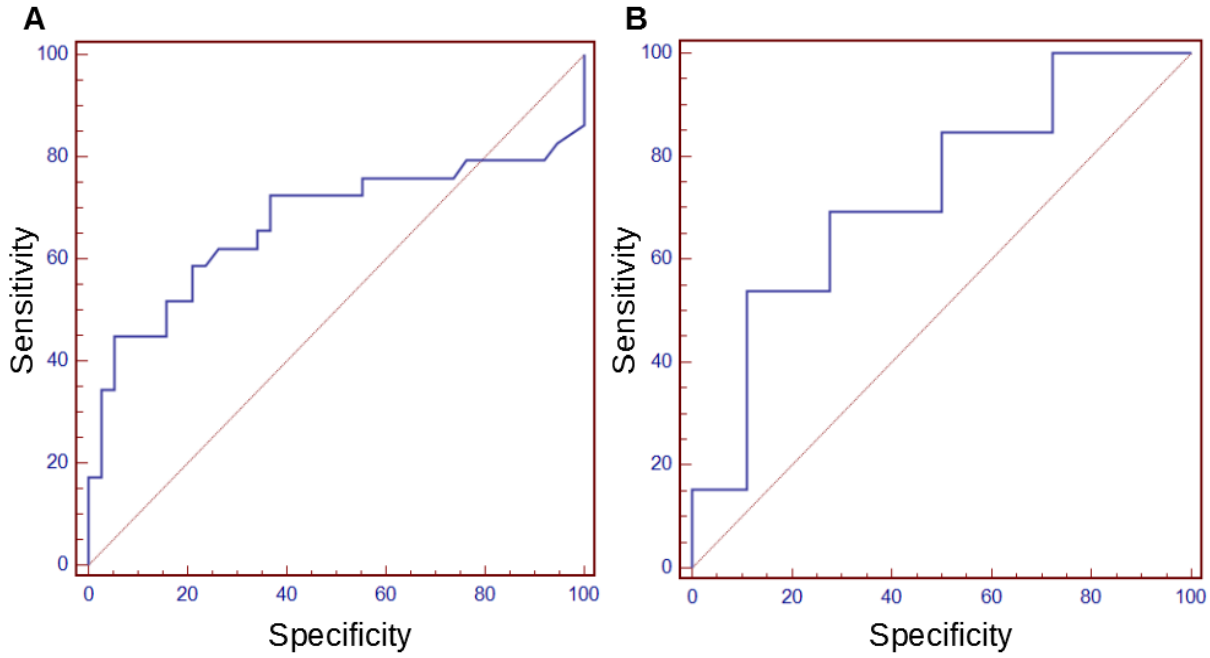

Table 1: The main features of our cohort.

	n (%)
Age, years (mean, range)	65 (45-85)
FIGO stage	
I	1 (1%)
II	4 (6%)
III	47 (69%)
IV	16 (24%)
Therapy	
Surgery + chemotherapy	66 (97%)
Surgery + radiotherapy	2 (3%)
Histology	
Carcinosarcoma	2 (3%)
Clear cell	1 (1%)
Endometrioid	5 (7%)
Serous	59 (87%)
Undifferentiated	1 (1%)
PET/CT results	
T+N-M-	33 (49%)
T+N+M-	4 (6%)
T+N+M+	9 (13%)
T-N+M+	6 (9%)
T-N+M-	11 (16%)
T+N-M	5 (7%)

T+/-: positive or negative T status; N+/-: positive or negative N status; M+/-: positive or negative M status.

Table 2: Correlation between metastatic status with PET/CT parameters and CA-125 values.

	SUVmax	P value	SUVmean	P value	SUVlbm	P value	SUVbsa	P value	MTV	P value	TLG	P value	CA-125	P value
N status		0.68		0.70		0.59		0.67		0.05		0.13		0.8
Positive	9,9		4,93		6,93		2,61		29,74		243,02		458,68	
Negative	9,2		5,23		6,46		2,39		15,4		135,86		530,86	
M status		0.46		0.23		0.35		0.31		<0.01		<0.01		0.01
Positive	10,21		5,62		7,25		2,73		36,67		327,56		944,83	
Negative	8,97		4,68		6,21		2,3		10,3		71,94		145,16	
M status		0.33		0.89		0.22		0.20		0.02		0.04		0.03
Nodal	11,01		5,57		8		3,03		51,83		455,97		1578,85	
Extranodal	9,6		5,66		6,67		2,5		25,08		229,36		460	

DISCUSSION

Relapse of OC is extremely frequent and presents in approximately 75-80% of all patients, with 90-95% of patients with advanced disease (FIGO stage III/IV) experiencing relapse within 2 years after primary treatment [7]. Furthermore, the role of [18F]FDG PET/CT for the evaluation of relapse or persistence of this disease and in the follow-up of patients has been underlined in the past with great results [11]. In this setting it has been proposed that this imaging modality may be the most accurate to diagnose suspected recurrence of OC and to assess the disease extension, with high sensitivity and specificity [14]. In fact, the greatest values of [18F]FDG PET/CT in OC is its high accuracy in detecting residual disease after primary treatment and its capability to identifiy recurrent disease in both symptomatic and asymptomatic patients [11]. Moreover, PET/CT has also demonstrated a role in guiding the therapy of patients, since it has the ability to optimize the management plan in subjects with recurrence of disease [15-16].

Speaking about serum tumor markers, CA-125 has proven to be a sensitive and reliable marker when investigating the possible relapse of OC, with a reported accuracy of 79-95%. Furthermore, its values increase 3-6 months before the clinical presentation of recurrence, making it a pivotal tool to determine the presence of relapse of disease and for the follow-up of these patients [8–9].

It has been reported that [18F]FDG PET/CT could be useful for current surveillance of OC patients, in particular for those with increasing CA-125 levels and negative CT or MR imaging. In fact, evaluation of neoplasm status in patients radically treated for OC with rising CA-125 levels but without evidence of disease at CI is the most frequent indication to perform a PET/CT scan; sensitivity of 97% has been reported when using PET/CT in asymptomatic patients with high serum CA-125 levels and non-conclusive results at CT [5,17–19]. In this setting, the correlation between PET/CT and CA-125 is very useful since it can provide metabolic information allowing for differentiation between tumor recurrence and post-therapy scarring/fibrosis [1].

The correlation between CA-125 and [18F]FDGPET/CT results has been reported in the past by demonstrating that serum marker levels were higher in patients whit positive PET/CT compared with patients with negative one. Moreover, the degree of tracer uptake has been reported as significantly correlated with the serum marker levels [1,12,18]. As previously underlined, the prognostic impact of recurrence of OC is evident and therefore these information are particularly important in the management of these patients. It has been reported that overall survival is significantly higher in patients with negative CA-125 values at the time of PET/CT, with negative PET/CT scan, and with no evidence of peritoneum recurrence and distant metastases [20]. In this setting, we reported a significant difference in terms of CA-125 values between patients with and without the presence of distant metastases. Furthermore, such insights were also confirmed when analyzing MTV and TLG, a finding that confirms the reflection of these parameters of the metabolic extension of the disease. ROC analysis revealed a value of 315 UI/mL of CA-125 as the one with the best discriminating accuracy. Similar results were also confirmed when discriminating between distant nodal and distant extranodal metastases, since both of them define a positive M stage in the tumor nodes metastasis (TNM) system. The correlation for PET/CT results with MTV and TLG were confirmed also in this case and the same append when considering CA-125, with a value of 596 UI/mL that revealed the best performances (AUC 0.729, sensitivity 54%, specificity 89% and p value 0.017). Lastly, no correlation between the presence of nodal metastases and [18F]FDG PET/CT parameters or CA-125 have been reported. These findings were not previously underlined in literature.

Our work is not without limitations. First of all, its retrospective nature with heterogeneous clinical features of the population. Moreover the fact that the aforementioned analyses were in some case performed in limited cohorts of patients is another important issue of our study.

CONCLUSION

In conclusion, we reported a significant correlation between volumetric [18F]FDG PET/CT parameters and CA-125 with the M status in patients with relapsed OC. Furthermore, the same insight were also confirmed when considering the different localization of such metastases (nodal or extranodal).

Compliance with Ethical Standards

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

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Given the retrospective nature of the study, no specific ethical approval was required.

Informed consent: Informed consent was obtained from all individual participants included in the study.

References

[1] Marzola MC, Chondrogiannis S, Rubello D. Fludeoxyglucose F 18 PET/CT Assessment of Ovarian Cancer. PET Clin. 2018; 13(2): 179–202. https://doi.org/10.1016/j.cpet.2017.11.005

[2] Colombo N, Sessa C, Bois Adu, et al. ESMO–ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Int J Gynecol Cancer. 2019 [Epub ahead of print]. https://doi.org/10.1136/ijgc-2019-000308

[3] Bellini, P., Albano, D., Dondi, F. et al. Clinical Meaning of 18F-FDG PET/CT Incidental Gynecological Uptake: An 8-Year Retrospective Analysis. Indian J Gynecol Oncolog 19, 99 (2021). https://doi.org/10.1007/s40944-021-00596-8

[4] Signorelli M, Guerra L, Pirovano C, et al. Detection of nodal metastases by 18F-FDG PET/CT in apparent early stage ovarian cancer: a prospective study. Gynecol Oncol. 2013; 131(2): 395–399. https://doi.org/10.1016/j.ygyno.2013.08.022

[5] Gu P, Pan LL, Wu SQ, et al. CA 125, PET alone, PET-CT, CT and MRI in diagnosing recurrent ovarian carcinoma: a systematic review and meta-analysis. Eur J Radiol. 2009; 71(1): 164–174'. https://doi.org/10.1016/j.ejrad.2008.02.019

[6] Kim TH, Kim J, Kang YK, et al. Identification of Metabolic Biomarkers Using Serial F-FDG PET/CT for Prediction of Recurrence in Advanced Epithelial Ovarian Cancer. Transl Oncol. 2017; 10(3): 297–303. https://doi.org/10.1016/j.tranon.2017.02.001

[7] Antunovic L, Cimitan M, Borsatti E, et al. Revisiting the clinical value of 18F-FDG PET/CT in detection of recurrent epithelial ovarian carcinomas: correlation with histology, serum CA-125 assay, and conventional radiological modalities. Clin Nucl Med. 2012; 37(8): e184–e188. https://doi.org/10.1097/rlu.0b013e31825b2583

[8] Goonewardene TI, Hall MR, Rustin GJS. Management of asymptomatic patients on follow-up for ovarian cancer with rising CA-125 concentrations. Lancet Oncol. 2007; 8(9): 813–821. https://doi.org/10.1016/s1470-2045(07)70273-5

[9] Rustin GJ, Nelstrop AE, McClean P, et al. Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. J Clin Oncol. 1996; 14(5): 1545–1551. https://doi.org/10.1200/jco.1996.14.5.1545

[10] Santillan A, Garg R, Zahurak ML, et al. Risk of epithelial ovarian cancer recurrence in patients with rising serum CA-125 levels within the normal range. J Clin Oncol. 2005; 23(36): 9338–9343. https://doi.org/10.1200/jco.2005.02.2582

[11] Ghosh J, Thulkar S, Kumar R, et al. Role of FDG PET-CT in asymptomatic epithelial ovarian cancer with rising serum CA-125: a pilot study. Natl Med J India. 2013; 26(6): 327–331.

[12] Dondi F, Albano D, Bertagna F, Giubbini R. [18F]FDG PET/CT and CA-125 in the evaluation of ovarian cancer relapse or persistence: is there any correlation? Nucl Med Rev Cent East Eur. 2022;25(2):78-84. https://doi.org/10.5603/nmr.a2022.0018

[13] Boellaard R, Delgado-Bolton R, Oyen WJG, et al. European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015; 42(2): 328–354.

[14] Limei Z, Yong C, Yan Xu, et al. Accuracy of positron emission tomography/ computed tomography in the diagnosis and restaging for recurrent ovarian cancer: a meta-analysis. Int J Gynecol Cancer. 2013; 23(4): 598–607. https://doi.org/10.1097/igc.0b013e31828a183c

[15] Ebina Y, Watari H, Kaneuchi M, et al. Impact of FDG PET in optimizing patient selection for cytoreductive surgery in recurrent ovarian cancer. Eur J Nucl Med Mol Imaging. 2014; 41(3): 446–451.

[16] Soussan M, Wartski M, Cherel P, et al. Impact of FDG PET-CT imaging on the decision making in the biologic suspicion of ovarian carcinoma recurrence. Gynecol Oncol. 2008; 108(1): 160–165. https://doi.org/10.1016/j.ygyno.2007.07.082

[17] Palomar A, Nanni C, Castellucci P, et al. Value of FDG PET/CT in patients with treated ovarian cancer and raised CA125 serum levels. Mol Imaging Biol. 2012; 14(1): 123–129. https://doi.org/10.1007/s11307-010-0468-9

[18] Menzel C, Döbert N, Hamscho N, et al. The influence of CA 125 and CEA levels on the results of (18)F-deoxyglucose positron emission tomography in suspected recurrence of epithelial ovarian cancer. Strahlenther Onkol. 2004; 180(8): 497–501. https://doi.org/10.1007/s00066-004-1208-3

[19] Thrall MM, DeLoia JA, Gallion H, et al. Clinical use of combined positron emission tomography and computed tomography (FDG-PET/CT) in recurrent ovarian cancer. Gynecol Oncol. 2007; 105(1): 17–22. https://doi.org/10.1016/j.ygyno.2006.10.060

[20] Evangelista L, Palma MD, Gregianin M, et al. Diagnostic and prognostic evaluation of fluorodeoxyglucose positron emission tomography/computed tomography and its correlation with serum cancer antigen-125 (CA125) in a large cohort of ovarian cancer. https://doi.org/10.5152/jtgga.2015.15251