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18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography as a Valuable Diagnostic Tool in Patients with Ovarian Cancer and Its Correlation with Tumor Marker Cancer Antigen-125

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Ovarian carcinoma (OC), ranking among the top ten diseases in women globally, with a prevalence of 6.6% per 100,000 women in 2020, necessitates early and accurate diagnosis due to its asymptomatic early stages and frequent advanced presentation with metastasis.[1-3]

Non-invasive approaches, such as 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) with computed tomography (CT) and the utilization of serum biomarkers [e.g. cancer antigen-125 (CA-125); human epididymis protein 4; Risk of Ovarian Malignancy Algorithm Index], notably CA-125, are gaining prominence for staging, assessing therapy response, and early recurrence detection.[4,5]

PET/CT excels in comprehensive whole-body imaging, proving particularly valuable for detecting peritoneal involvement in pelvic and abdominal regions, as well as identifying metastatic lymph nodes and hematogenous metastatic sites in patients with ovarian cancer.[6,7] However, CA-125 evaluation has been employed to assist in the diagnosis and monitoring of OC.[8] Researchers are actively exploring synergies between these diagnostic techniques to improve the reliability of OC detection and management.

In this prospective study, we explored the correlation between 18F-FDG PET/CT findings and CA-125 blood levels in patients with OC. We aimed to assess the potential synergy of these techniques in enhancing OC detection. In addition, we investigated their correlation with malignant involvement patterns, ovarian cancer histological types, and disease activity/remission.

The study was approved by the Medical University Pleven's Ethics Committee (approval number: 721, date: 20.03.2023) and adhered to the ethical standards outlined in the Helsinki Declaration. Before enrollment, each patient willingly signed an informed consent form, and strict confidentiality measures were implemented to safeguard patient identity.

Our prospective study was conducted in a Nuclear Medicine Laboratory in Pleven, Bulgaria from January 2023 to September 2023 and included 42 patients with a mean age of 56.9 ± 13.4 years. The inclusion criteria comprised a suspected ovarian mass, recent OC diagnosis, assessment of therapeutic response, restaging, and suspected recurrence.

For each eligible patient, blood sampling and CA-125 measurements were conducted on the day of the PET/CT study. To determine the concentration of CA-125 in the serum, an automatic immunoanalyzer (TOSOH AIA 360) was used. As per the manufacturer's specifications, CA-125 values higher than 35 U/ml were considered abnormally elevated and suggested active disease (positive), whereas values below 35 U/ml were considered normal and registered as remission (negative).

The PET/CT examination adhered to European standards[9], employing a Biograph™ mCT 64 device (Siemens Healthineers, Germany) for whole-body imaging. Flow-motion 3D PET registration was obtained from the proximal thighs to the skull base at a speed of 0.7 mm/s, with an acquisition time of approximately 12 minutes. The data obtained were subsequently reconstructed using OSEM. The four-ring CT system provided low-dose 3D imaging for attenuation correction and anatomical localization of 18F-FDG distribution. Images were analyzed by the principal investigator (a nuclear medicine physician). Each imaging finding was evaluated based on both size and

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metabolic activity (using the maximum standardized uptake value, SUV_{max}). Based on a recent meta-analysis[10] an SUV_{max} cut-off of 3.97 was employed to differentiate findings. SUV_{max} values below 3.97 were considered indicative of no pathological uptake (registered as negative PET/CT), while higher SUV_{max} values were considered indicative of active malignancy (positive PET/CT).

Similar to the research model of Kosinska et al.[11], the selected patients in our study underwent serological follow-up (measurement of CA-125), along with imaging modalities (i.e., CT, magnetic resonance, PET/CT), or histological assessments (biopsy or surgery) for a period of 3 to 6 months after the study. This follow-up aimed to determine whether the disease was active (positives, *P*) or in remission (negatives, *N*). Based on these outcomes, the performance of CA-125 blood levels, SUV_{max} values, and their combination as predictors of patient outcome was evaluated. For each method, the number of accurately predicted patients with active disease (true positive), accurately predicted patients in remission (true negative), falsely predicted patients with active disease (false positive), and falsely predicted patients in remission (false negative) were tabulated and utilized to calculate standard performance metrics (Table 1). All results are summarized in Table 1.

SUV_{max} values were significantly different between patients with active disease (13.89 ± 8.12) and those in remission (3.21 ± 0.66) within 3 to 6 months ($p < 0.0001$), demonstrating reliable predictive capabilities. Similarly, CA-125 values were also significantly correlated with patient outcomes; however, the predictive power was comparatively lower ($p < 0.05$). Our results are consistent with the recent findings reported by Antunovic et al.[12]

Combining CA-125 with PET/CT outcome predictions achieved the highest accuracy and sensitivity compared to using either SUV_{max} or CA-125 alone, which is in agreement with the study conducted by Evangelista et al.[13] The correlation between SUV_{max} and CA-125 values was relatively low with a Pearson's r value of 0.217.

Histology exerted a substantial impact on predictive performance, with SUV_{max} demonstrating superior performance over CA-125 values for both serous carcinoma and endometrioid carcinoma (Table 1). Combining SUV_{max} and CA-125 values reduced misdiagnosis in serous OC but not in endometrioid cancer. These data align with the findings of Colombo et al.[2] and Dondi et al.[14], indicating that CA-125 is not a reliable tumor marker in non-serous OC.

SUV_{max} values were also superior in predicting outcomes for patients with positive PET/CT findings, while tumor marker values

TABLE 1. Patient Outcome Predictions are Categorized by SUV_{max} values, CA-125 blood levels, or a combination of both. The predictions are summarized and grouped according to tumor histology and the localization of findings.

		SUV_{max} values				CA-125 levels				SUV_{max} values and CA-125 levels			
		TP	TN	FP	FN	TP	TN	FP	FN	TP	TN	FP	FN
	All cases	14	23	3	2	9	26	0	7	15	23	3	1
Histology of ovarian cancer	Serous carcinoma	10	13	2	2	7	15	0	5	11	13	2	1
	Endometrioid carcinoma	3	5	1	0	1	6	0	2	3	5	1	0
	Granulosa-cell tumor	0	4	0	0	0	4	0	0	0	4	0	0
	Brenner's tumor	1	1	0	0	1	1	0	0	1	1	0	0
PET/CT findings' localization	Local recurrence	2	0	0	0	2	0	0	0	2	0	0	0
	Peritoneal dissemination	7	2	0	1	5	2	0	3	8	2	0	0
	Lymph nodes (regional and distant)	6	0	0	0	4	0	0	2	6	0	0	0
	Distant metastases (parenchymal organs, pleura)	3	0	0	0	1	0	0	2	3	0	0	0
	Calcifications	1	1	0	0	1	1	0	0	1	1	0	0
	Ascites	1	0	0	0	1	0	0	0	1	0	0	0
	No findings associated with ovarian cancer	0	21	3	1	0	24	0	1	0	21	3	1
Variables	Accuracy	0.881				0.833				0.905			
	F-score	0.848				0.720				0.882			
	Sensitivity	0.875				0.562				0.938			
	Specificity	0.885				1.000				0.885			
	Positive predictive value	0.824				1.000				0.833			
	Negative predictive value	0.920				0.788				0.958			

Predictions were classified as TP, TN, FP, and FN, where the positive class corresponds to patients with active disease and the negative class to patients in remission. SUV_{max} values ≥ 3.97 and CA-125 levels ≥ 35 U/ml were interpreted as indicative of potential active disease. CA-125, cancer antigen-125; TP, true positive; TN, true negative; FP, false positive; FN, false negative.

demonstrated better performance in predicting outcomes for patients without PET/CT findings. Incorporating both SUV_{max} and CA-125 values accurately predicted disease outcomes in the entire cohort of patients with these findings.

No significant correlation was found between lesion localization, CA-125 levels, SUV_{max} values, and histological type. This finding is consistent with the current literature and mirrors the results reported by Marzola et al.[3] and García-Talavera et al.[15]

In summary, integrating PET/CT and CA-125 in routine practice can enhance the accuracy and sensitivity of OC detection, surpassing individual methods. Despite limitations, including a modest patient cohort, a concise nine-month assessment period, and insufficient follow-up time, our prospective study is one of the first in Bulgaria and contributes valuable insights. This data and research model should be applied to larger cohorts and further explored in future studies within the field.

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