Ann Med Res 2021;28(11):1961-6

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.11.1150

Original Article

The value of posttreatment CA125 and PET/CT in predicting prognosis of epithelial ovarian cancer

Adnan Budak[1], Emine Budak[2], Abdurrahman Hamdi Inan[1], Ahkam Goksel Kanmaz[1], Gokhan Tosun[1], Emrah Beyan[3], Onur Suleyman Aldemir[4], Alper Ileri[5], Mehmet Ozeren[1]

[1]Department of Obstetrics and Gynecology, Tepecik Training and Research Hospital, Izmir, Turkey
[2]Department of Nuclear Medicine, Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, Izmir, Turkey
[3]Clinic of Obstetrics and Gynecology, Private Water Hospital, Izmir, Turkey
[4]Clinic of Obstetrics and Gynecology, Private Cinarli Hospital, Izmir, Turkey
[5]Department of Obstetrics and Gynecology, Buca Seyfi Demirsoy Training and Research Hospital, Izmir, Turkey

Abstract

Aim: To investigate the association between post treatment F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and post treatment cancer antigen 125 (CA125) results and overall survival (OS) of patients with epithelial ovarian cancer (EOC).

Material and Methods: Survival was analyzed with Kaplan-Meier, Log-Rank and Cox proportional-hazards regression analyses. All cases and PET+ cases were evaluated separately. In addition, PET and CA125 results were evaluated together in the overall case group, and a survival analysis was made for the four defined groups.

Results: The mean age of the 112 EOC-diagnosed patients was 54.9±0.9 years. Based on the PET/CT results, 48 patients were PET- and 64 patients were PET+; and 59 patients were CA125- and 53 patients were CA125+. In the overall case group, OS was found to be significantly shorter in advanced stage patients when compared to the early stage patients, in the CA125+ patients when compared to the CA125- patients, and in the PET+ patients when compared to the PET- patients. A univariate analysis revealed a significant association between stage, CA125 and PET results, and OS. In a multivariate analysis, the association between stage and CA125 with OS was maintained, although the PET results were not significant. When the PET and CA125 results were evaluated together, the OS was significantly shorter in the CA125+/PET+ group than in the CA125-/PET-and CA125-/PET+ groups. In the PET+ group, CA125 and the time from diagnosis to positive PET result were identified as independent prognostic factors.

Conclusion: Although OS had a tendency to be poorer in PET+ cases than negative cases, the PET results were not established as an independent prognostic factor for survival. Our findings suggest that the post treatment CA125 value is more beneficial than PET results for the estimation of prognosis in EOC.

Keywords: CA125; epithelial ovarian cancer; FDG PET/CT; prognosis; survival

INTRODUCTION

Ovarian cancer (OC) is the gynecological malignancy with the highest death-to-incidence rate (1). Epithelial OC (EOC) is the most common histologic type (90–95%) (2). For the most patients with a pre-diagnosis of OC, the main therapy is surgical cytoreduction and chemotherapy (3). Despite the high rate of response to optimum treatment strategies, in 50–75% of patients recurrence occurs (4), which makes close follow-up important in OC, including clinical assessment, biochemical tests and various imaging methods. Cancer antigen 125(CA125) is the most extensively used marker in EOC (5). A rising CA125 level has high accuracy in the detecting of the disease (6), yet normal values cannot completely rule out disease presence (7). Furthermore elevated values may be observed in other malignancies and in benign and physiological processes such as pregnancy, endometriosis and menstruation (8). Therefore, CA125 is typically evaluated alongside imaging methods. F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is widely used in oncological practice and is reported to be useful for OC diagnosis, treatment response assessment and residual disease detection (9). PET/CT may overcome morphological imaging limitations by detecting overlooked metastatic lymph nodes smaller than 1 cm or by separating tumoral tissue from fibrosis (10) and reveal the areas of disease that are not noticed in CT (11). There are few studies investigating the relation between PET / CT results and prognosis in OC. In the present study, we

Received: 27.11.2020 **Accepted:** 25.03.2021 **Available online:** 22.11.2021
Corresponding Author: Adnan Budak, Department of Obstetrics and Gynecology, Tepecik Training and Research Hospital, Izmir, Turkey **E-mail:** drabudak@gmail.com

evaluate the association between post treatment PET/CT results and CA125 measurements, and overall survival (OS) in patients treated with primary cytoreductive surgery and at least one chemotherapy cycle due to EOC.

MATERIALS and METHODS

Study participants

The study was approved by Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital at the 8th TUEK meeting dated 15.05.2020 with the 5th decision number. The study included 112 patients who were diagnosed histopathologically with EOC between January 2010 and May 2018.

All patients included in the study met the conditions:

- histopathologically diagnosed with EOC

-surgically staged according to the classification by the International Federation of Gynecology and Obstetrics (FIGO)

-received primary cytoreductive surgery and at least one cycle of chemotherapy

-had post treatment initial F-18 FDG PET/CT with an indication for treatment response assessment, recurrence assessment or re-staging during follow-up

-had a CA125 measurement that was made within one month of the PET/CT

The study excluded patients, who were diagnosed with borderline or non-epithelial OC, and those not subjected to a PET/CT assessment at the first suspicion of relapse.

Patients were invited to a follow-up visit once every 3 months for the first postoperative 2 years, during which the medical history was taken, a physical examination was made and CA125 levels were measured. In the event of a treatment response assessment, re-staging or relapse suspicion, CT and PET/CT were performed. Post treatment PET / CT and CA125 assessment dates of the patients included in the study varied between 6 and 55 months after diagnosis.

PET/CT

PET/CT scans were made using a "PHILIPS GEMINI TF 16 Slice PET/CT" scanner. An intravenous injection of 7–10 mCi FDG was administered to the patients with a blood glucose level of <200 mg/dl following a minimum 6-hour of fasting. Approximately 60 minutes after the injection, the vertex-to-femur region of the patients were scanned. The initial CT scan (140 kV, 100mAs, 5-mm slice) was followed by a PET emission (1.5 minutes/bedside) scan.

The PET/CT examination results were considered negative PET (PET-) when there was no FDG uptake, aside from in the physiological areas. The PET/CT result was interpreted as positive PET (PET+) when FDG uptakes higher than background activity corresponding to a CT finding were observed, aside from physiological uptakes. According to the localization of FDG uptake in PET+ cases, the findings were evaluated as intrapelvic disease, lymph node metastasis, extrapelvic peritoneal disease or distant metastasis. Furthermore, a classification of intrapelvic disease:1, lymph node metastasis:2, extrapelvic peritoneal disease:3 and distant metastasis:4 was made to indicate disease severity in PET+ cases, and PET disease scoring was made on the assumption of an increase in disease severity from 1 to 4. The maximum standardized uptake value of the lesion with the highest FDG affinity (SUVmax-M) was measured.

Serum Ca-125

CA125 levels were measured within 1 month of the PET/CT. In a study that evaluated serum CA125 value; while CA125 was found to be less than 35 U/ml in 99% of healthy individuals, it was found to be higher than 35 U/ml in 82% of patients with EOC surgically demonstrated (12). Therefore, in the present study, 35 U/ml value was accepted as cut-off for CA125, and the result was considered positive if> 35 U/ml, and negative if ≤35 U/ml.

Statistical Analysis

For survival knowledge, patients' latest situations were controlled from the "National Mortality Database" (MERNIS). OS was interpreted as the time from diagnosis to death or, for survivors, from the time of diagnosis to the patient's last visit to the hospital.

Survival was assessed with Kaplan-Meier, Log-Rank and Cox proportional-hazards regression analyses. All cases and PET+ cases were evaluated separately. Furthermore, the PET and CA125 results were evaluated together in the overall case group, and survival of the four groups was compared using a Log-Rank test.

The OS curves of the patients were drawn using a Kaplan-Meier analysis. A Log-Rank test was used to compare OS in the PET-/+, CA125-/+ and initial FIGO stage (1-2/3-4) groups for all cases, and in the CA125-/+, initial FIGO stage (1-2/3-4), intrapelvic disease -/+, lymph node metastasis -/+, extrapelvic peritoneal disease -/+ and distant metastasis -/+ groups for PET+ cases.

The associations of OS with the PET results, the CA125 results, the initial FIGO stage (1-2/3-4) and age for all cases were evaluated with a univariate Cox proportional-hazards regression analysis. Variables that were significant in univariate analysis (stage, PET, CA125) were included in multivariate analysis.

The associations of OS with the CA125 results, initial FIGO stage (1-2/3-4), age, time from diagnosis until positive PET results, PET score, positive PET results (intrapelvic disease, lymph node metastasis, extrapelvic peritoneal disease, distant metastasis) and SUVmax-M for PET+ cases were evaluated with univariate Cox proportional-hazards regression analyses. Variables that were significant in univariate analysis (stage, CA125, time from diagnosis to PET, lymph node metastasis, extrapelvic peritoneal disease) were included in multivariate analysis.

A p value of <0.05 was considered significant in the statistical analyses.

RESULTS

The mean age of the 112 EOC-diagnosed patients included in the study was 54.9±0.9 (29–77) years. The most common histopathological EOC type was serous adenocarcinoma (n:88), while the others were clear cell (n:10), endometrioid (n:6), mucinous (n:2), Brenner (n:2) and mixed type (n:4). At the time of diagnosis, 13 patients were FIGO stage 1, 20 were stage 2, 74 were stage 3 and 5 were stage 4. The patient characteristics are presented in Table 1.

Table 1. Characteristics of Patients

Characteristics	Number	Percent (%)
FIGO stage at diagnosis		
1	13	11.6
2	20	17.8
3	74	66
4	5	4.4
Histology		
Serous	88	78.5
Clear Cell	10	8.9
Endometrioid	6	5.3
Mucinous	2	1.7
Brenner	2	1.7
Mixed Type	4	3.5

Based on the post treatment initial PET/CT results, 48 patients were PET- and 64 patients were PET+. Furthermore, 59 patients were CA125- and 53 patients were CA125+. An evaluation of the PET and CA125 results together revealed 38 patients to be CA125-/PET-, 43 patients to be CA125+/PET+, 21 patients to be CA125-/PET+ and 10 patients to be CA125+/PET- (Table 2).

Table 2. Patient numbers and percentages based on PET / CT and CA125 findings

	CA125 -	CA125 +	Total
PET-	38 (33.9%)	10(8.9%)	48(42.8%)
PET+	21(18.7%)	43(38.3%)	64(57.1%)
Total	59 (52.6%)	53(47.3%)	112

Among PET+ cases, there were 49 intrapelvic disease +, 37 lymph node metastasis +, 34 extrapelvic peritoneal disease + and 17 distant metastasis + patients. When classified by disease severity, 12 patients were scored as 1, 12 patients as 2, 23 patients as 3 and 17 patients as 4.

The mean duration of follow-up of the patients was 51.2±2.6 (5–130) months; 52 patients died during follow-up; and the 60 surviving patients were censored in the survival analysis. For all patients, the median OS was 70±8.2 months.

The Log-Rank analysis revealed that OS was significantly shorter in advanced stage patients than in early stage patients; in patients with CA125+ than in patients with CA125-; and in patients with PET+ than in patients with PET- (Table 3) (Figure 1). The univariate analysis showed that OS was significantly associated with initial stage, and CA125 and PET results. In the multivariate analysis, the association of stage (hazard ratio:2.311, p:0.024) and CA125 (hazard ratio:2.961, p:0.001) with OS was maintained, but the PET results were not significant. Age was not found to be predictive of patient survival. The findings are presented in Table 4.

Table 3. Survival comparison of patient groups by Log Rank test

	Overall Survival (mean±SE, months)	P
All patients		
Serous ovarian carcinoma	75.8±5.6	0.884
Non-serous ovarian carcinoma	73.8±9.8	
Stage 1-2	100±8.3	0.007*
Stage 3-4	64.3±5.2	
CA125-	96.1±6.6	<0.001*
CA125+	53.4±6	
PET-	83.1±6.3	0.004*
PET+	65.7±6.3	
PET+ patients		
Serous ovarian carcinoma	68.4±6.9	0.398
Non-serous ovarian carcinoma	52.2±13.1	
Stage 1-2	90.9±12.4	0.036*
Stage 3-4	55±6.3	
CA125-	100.5±9.9	0.001*
CA125+	49.4±6.1	
Intrapelvic disease -	84.8±13.5	0.154
Intrapelvic disease +	58.9±6.5	
Lymph node metastasis -	81.1±9.8	0.018*
Lymph node metastasis +	47.5±5.5	
Extrapelvic peritoneal disease -	81.4±9.2	0.030*
Extrapelvic peritoneal disease +	48.2±5.9	
Distant metastasis -	65.8±7	0.596
Distant metastasis +	61.9±11.6	

Significant p values (p<0.05) are indicated by *

Table 4. Overall survival analysis of all patients

	Univariate analysis		Multivariate analysis	
	p	HR	p	HR
Age	0.065	1.027	-	-
Stage (1-2/3-4)	0.010*	2.579	0.024*	2.311
CA125-/+	<0.001*	3.569	0.001*	2.961
PET-/+	0.005*	2.397	0.400	1.352

Significant p values (p<0.05) are indicated by *

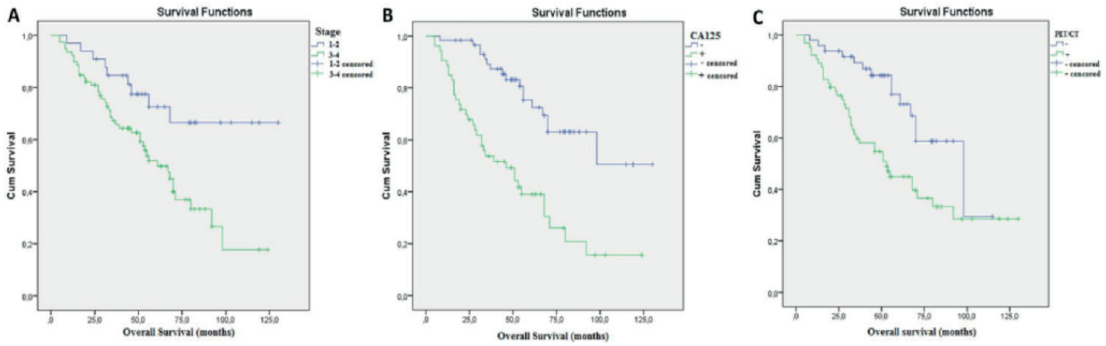

Figure 1. Kaplan Meier survival curves of patients grouped by stage, CA125 and PET results

Patients were divided into 4 groups by evaluating the PET and CA125 results together. Table 5 shows the mean OS time of the groups, from which it can be seen that the OS was significantly shorter in the group with both CA125 and PET positivity than in the group with negativity in both (p<0.001) and the group with CA125-/PET+ (p:0.001). The survival curve indicated a poorer OS in CA125 and PET positive patients (Figure 2). There was no significant difference established in the other between-group comparisons.

Table 5. Overall survival times of the groups formed by evaluating the CA125 and PET findings together

	Overall Survival (mean±SE, months)
CA125-PET-	85.2±6.5
CA125-PET+	100.5±9.9
CA125+PET-	60.8±8.7
CA125+PET+	49.4±6.1

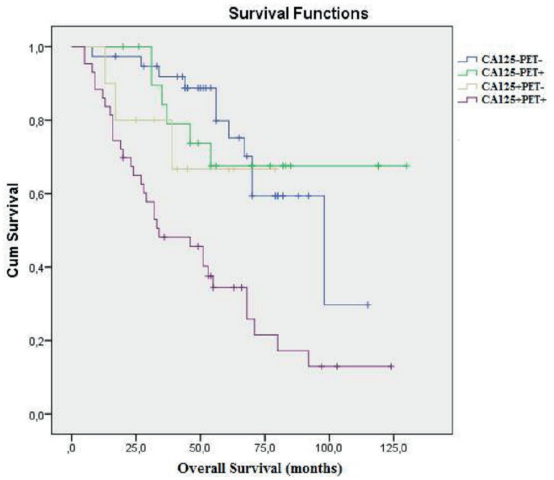

Figure 2. Kaplan Meier survival curves of patients who were divided into groups by evaluating CA125 and PET findings together

Table 6. Overall survival analysis of PET+ patients

	Univariate analysis		Multivariate analysis	
	p	HR	p	HR
Age	0.058	1.038	-	-
Stage (1-2/3-4)	0.044*	2.475	0.134	1.986
CA125-/+	0.002*	3.917	0.012*	3.422
Time from diagnosis to PET	0.037*	0.967	0.046*	0.964
SUVmax-M	0.730	0.988	-	-
Intrapelvic disease -/+	0.163	1.860	-	-
Lymph node metastasis -/+	0.021*	2.250	0.766	1.124
Extrapelvic peritoneal disease-/+	0.035*	2.041	0.699	1.147
Distant metastasis -/+	0.599	1.208	-	-
PET score	0.107	1.277	-	-

SUVmax-M: maximum standardized uptake value of the lesion with the highest FDG affinity. Significant p values (p<0.05) are indicated by *

In the evaluation of PET + cases; 38 patients died during the follow-up; the mean OS was 65.7±6.3 months; the mean time from diagnosis to positive PET findings was 15.2±1.5 (1–55) months; and the mean SUVmax-M was 10.6±0.6 (2.6–25.2). The Log-Rank analysis revealed OS to be significantly shorter in advanced stage patients than in early stage patients; in patients with CA125+ than in patients with CA125-; in patients with lymph node metastasis than in patients without lymph node metastasis; and in patients with extrapelvic peritoneal disease than in patients without extrapelvic peritoneal disease (Table 3). A univariate analysis indicated a significant association of OS with stage, CA125, time from diagnosis to positive PET results, lymph node metastasis and extrapelvic peritoneal disease. The multivariate analysis showed that CA125 (hazard ratio:3.422, p:0.012) and time from diagnosis to positive PET results (hazard ratio:0.964, p:0.046) were predictive of OS, while there was no association of OS with other parameters. Age, SUVmax-M, intrapelvic disease, distant metastasis and PET scores were not predictive of OS. The analysis results are summarized in Table 6.

DISCUSSION

OC is the fifth most common cause of cancer-related death among women in Europe (13). Most ovarian tumors develop from the surface epithelium (14). Cytoreductive surgery is proposed as the first line therapy for ≥Stage 2 patients, and postoperative systematic chemotherapy is administered to many patients (3). The absence of postsurgical residual tumors is reported to be one of the most important factors prolonging survival (15). In the present study we investigated the prognostic significance of initial PET/CT in EOC-diagnosed patients who underwent primary cytoreductive surgery and at least one cycle of chemotherapy.

Literature contains a limited number of studies in this regard. The study by Evangelista et al. (7) found that older age, high CA125 levels, positive PET results and PET-detected peritoneal recurrence were associated with poor prognosis in a univariate analysis, however, in a multivariate analysis, only age and PET-detected peritoneal recurrence were independent variables. Kurosaki et al. (16) found no significant difference in 2-year survival of OC patients with a positive or negative initial PET/CT. The authors reported CA125 levels to be more beneficial than PET/CT results for the assessment of patient prognosis. Another study (17) reported that the addition of PET/CT results to post treatment CA125 was more predictive of the prognosis. A study involving 168 OC-diagnosed patients (18) found a significantly shorter 4-year progression-free survival (PFS) and OS in patients with a positive PET/CT result than those with a negative result. However, no significant association was established between semi-quantitative PET parameters and survival. In a study involving recurrent OC, the number, size, and SUVmax of distant lymph node metastasis (M1) or peritoneal involvement were reported as prognostic factors (19). Another study found a significant association between increased whole-body total lesion glycolysis (WBTLG) and reduced survival (20). In a study involving 30 recurrent OC, OS was found to be significantly longer in patients with a longer time to recurrence than those with a shorter time to recurrence (21). The present study found poorer OS in PET positive cases than in negative cases, although PET results were not identified as an independent prognostic factor for survival. A multivariate analysis revealed a significant association between CA125 and OS both in the overall patient group and in the PET+ group. Our findings suggest that CA125 is more valuable than PET results in prognostic terms.

There is no consensus on the prognostic value of PET results in the literature. Heterogeneous patient groups may be one of the reasons. Survival outcomes may have been affected especially by postoperative residual tumor tissue and different the treatment protocols administered to patients. Due to the retrospective design of our study, we were unable to access information about postoperative residual tumor tissue. Furthermore, we only examined the prognostic value of SUVmax-M in the present study, and did not investigate volumetric parameters such as metabolic tumor volume (MTV) and TLG, due to the difficulty and the lack of standardization in obtaining. However, volume-based whole body PET parameters, which are believed to represent tumoral load better, are more likely to be associated with survival, rather than the activity of a single pixel with the highest SUV value.

The retrospective design, heterogeneous patient population, lack of information on postoperative residual tumor, and the wide range of time between diagnosis and PET / CT date are among the limitations of our study. However, this study included only EOCs, had a relatively high number of patients, and many parameters that could affect prognosis were subjected to multivariate analysis.

CONCLUSION

Our findings indicate that CA125 is more beneficial than PET results in estimating prognosis in cases with post treatment EOC. Therefore, in patients with CA125 +, even if PET is negative, the possibility of progression should be considered in disease management.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: The study was approved by Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital at the 8th TUEK meeting dated 15.05.2020 with the 5th decision number.

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