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The importance of CA-125 and clinical markers in ovarian cancer

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ABSTRACT

Aims: In this study, considering all the known facts about ovarian cancer; The aim of this study is to retrospectively examine the factors related to the etiopathogenesis, diagnosis and prognosis of ovarian cancer, to determine the population at risk, and to try to catch cancer before it progresses or at an early stage by controlling it more frequently and early.

Methods: A total of 99 patients who were operated for adnexal mass in Dicle University Faculty of Medicine, Department of Obstetrics and Gynecology between 1 January 2011 and 31 December 2020 and whose final pathology resulted as malignant were included in our study. Patients with borderline results were not included in our study. Of these 99 patients age, gravity-parity, menopausal status, presence of additional disease, symptoms, CA-125 level, tumor burden, tumor diameter and structure, presence of ascites, presence of implant, lymph node involvement, frozen pathology result, tumor type, stage, complications were investigated.

Results: In this study, the mean age at diagnosis was 51.04 years. It was observed that 55.6% of the patients were postmenopausal. The most common tumor type was identified as epithelial tumors. It has been determined that the patients are mostly in the advanced stage. When the relationship between the stage and the presence of lymph node and ascites fluid was examined, it was observed that lymph node involvement and presence of ascitic fluid increased in advanced stages. It has been observed that the universe progresses as the CA-125 level rises. It has been demonstrated that CA-125 is higher in patients with residual tumors. In addition, CA-125 levels were higher in patients with lymph node involvement than in those without involvement, in patients with bilateral tumours than in those with unilateral tumours, in patients with ascites than in those without ascites, and in epithelial type tumours than in other tumour types.

Conclusion: Although scientific research has been carried out on many markers for ovarian cancer, especially Ca-125, it is difficult to detect it at an early stage since routine ovarian cancer screening is not possible under today's conditions. Even though it is not specific, if some symptoms such as abdominal pain are present in older women, considering ovarian cancer among the preliminary diagnoses may help detect more patients at an early stage.

Keywords: Ca-125, ovarian cancer, postmenopausal, lymph node, acid fluid

INTRODUCTION

Ovarian cancer is the third most common gynecologic cancer in women in addition, less common in breast cancer, but three times more lethal.[1] The lifetime risk of developing ovarian cancer in a woman in the general population is approximately 1.3%. The overall incidence of ovarian cancer in the US was 11.5 per 100,000 women between 2010 and 2014. Population differences in ovarian cancer risk have been attributed mainly to ethnicity and partly to the prevalence of risk factors. The five-year survival rate is approximately 40%.[2,3] Ovarian cancers are usually asymptomatic in early stages. Therefore, when they are diagnosed, they are usually at an advanced stage. Some important risk factors of ovarian cancer are early menarche, late menopause, nulliparity and infertility. Apart from abdominal pain, some nonspecific

symptoms such as bloating, fast eating or difficulty in satiety, and changes in urinary frequency may also be seen in ovarian cancers. In the presence of a palpable mass on palpation of the pelvis, pathologies of the ovaries, uterus, tubae, intestines and urinary system should come to mind. Therefore, systemic examination is important. The incidence of ovarian cancer is parallel to age. Early diagnosis of patients with adnexal masses is very important to reduce mortality, improve the patient's quality of life and reduce treatment costs. 90% of ovarian cancers originate from epithelial tissues. The epithelium covering the ovarian surface originates embryologically from the cholomic epithelium. Other ovarian tumors include germ cell tumors, sex cord stromal tumors and metastatic ovarian tumors.[1]

Some tumor markers such as cancer antigen 125 (CA125), alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-HCG), carcinoembryonic antigen (CEA) are tumor markers used in ovarian tumors.[4] Another method that will help in the diagnosis is imaging. Ultrasonography (USG) can reveal the localization, size, solid or cystic structure, border irregularity and relationship with other pelvic organs of an adnexal mass.[5]

The stage of the disease at the time of diagnosis and the size of residual tumor tissue are the most important prognostic factors in ovarian cancer. The primary treatment modality for ovarian cancer is surgery. Primary staging surgery is performed in early stage ovarian cancers and cytoreductive (debulking) surgery is performed in advanced ovarian cancers.[6]

In this study, we retrospectively examined the factors related to the etiopathogenesis, diagnosis and prognosis of ovarian cancer; We aimed to retrospectively examine the factors related to the etiopathogenesis, diagnosis and prognosis of ovarian cancer and to determine the population at risk and to try to catch it before it progresses to cancer or at an early stage so that it can be controlled more frequently and early.

METHODS

The study was carried out with the permission of the Dicle University Faculty of Medicine Ethics Committee (Date: 21.01.2022, Decision No: 37). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A total of 99 patients with adnexal masses and have complaints such as abdominal pain, bloating who were operated in Dicle University Faculty of Medicine, Department of Obstetrics and Gynecology between 1 January 2011 and 31 December 2020 and whose final pathology was malignant were included in our study. Patients with Borderline pathology results were not included in the study. In addition, patients with hypertension, diabetes, drug and alcohol abuse and smoking were excluded from the study. Patient data were obtained by retrospectively scanning hospital digital records and archive files.

The age, gravida-parity, menopausal status, presence of comorbidities, symptoms, and CA-125 levels of the operated patients were obtained from archival files and hospital digital record system. Tumor burden was calculated from the surgery notes based on the intraoperative tumor size >1cm. USG imaging was performed abdominally and transvaginal. According to this imaging, tumor diameter and structure, presence of ascites were recorded. The presence or absence of implants during the operation was obtained from the surgery notes. Lymph node involvement, frozen pathology result and tumor type were obtained from the final pathology reports. Stages of the patients were calculated and recorded according to the 2013 FIGO (International federation of gynecology and obstetrics) criteria. Finally, the presence or absence of intraoperative complications was obtained from the surgery notes and files of the patients.

Statistical Analysis

The data obtained from the study were analyzed using the SPSS package program (Statistical Package for Social Sciences; IBM SPSS Statistics for Macintosh, Armonk, NY) version 25. Descriptive analyses were expressed as number (n) and percentage (%) for categorical data and mean±standard deviation (mean±standard deviation) for continuous data. The compatibility of continuous variables with normal distribution was evaluated by Kolmogorov-Smirnov test. Pearson chi-square test was used to compare categorical variables between groups. Mann-whitney U-test was used to compare variables that did not conform to normal distribution in two groups and Kruskal-Wallis test was used to compare variables in more than two groups. Statistical significance level was accepted as $p<0.05$ in the analyzes.

RESULTS

A total of 99 female patients, the youngest of whom was 17 and the oldest of whom was 81 years old, were included in this study and their mean age was 51.04±14.89 years. The mean gravida was 5.55±4.37 and the mean parity was 5.07±3.86. It was observed that 21.2% of our patients were nulliparous.

Patients were divided into two age groups as under 45 years and 45 years or older. While 66.7% (n:66) of the patients were 45 years and older, 33.3% (n: 33) were younger than 45 years. When the menopausal status of the patients was analyzed, 55.6% (n:55) were postmenopausal.

When the symptoms of the patients admitted with adnexal mass and included in the study were examined, it was found that the most common symptom was abdominal pain (n:67), which was observed in 67.7% of the patients, followed by menstrual irregularity (n:15) and bloating.[13]

CA-125 levels of the patients included in the study were examined as a tumor marker. The patients were divided into three groups on the basis of 35 units, which is accepted as a positive value for CA-125 in our laboratory, and 300 units, which has been shown to be significant in studies: 21 patients (21.20%) had CA-125 values <35,51 patients had CA-125 values between 35-300 and 27 patients had CA-125 values >300 (Table 1). Regarding the nature of the mass, the most common type (59.6%) was solid-cystic tumor, followed by cystic tumor in 21.2% and solid tumor in 18.2%. Lymph nodes were positive in 20.2% of patients. In addition, ascites was detected in 45.5% of all patients included in the study. Details are shown in Table 1.

Frozen pathology was requested in 80 of the patients during the operation. Accordingly, 88.7% (n:71) of the frozen pathology results were reported as malignant. In 7 patients (8.7%), the frozen result was borderline, while 2(2.5%) patients were reported as benign. In 19 patients, frozen pathology was not requested.

Table 1. Evaluation of patients according to CA-125 values, mass structure, lymph node positivity, presence of ascitic fluid, presence of implant

		Count (n)	Percent (%)
CA-125 Groupings	Below 35 units	21	21.20%
	Between 35-300 units	51	51.50%
	Above 300 units	27	27.30%
	Total	99	100.00%
Mass structure	Solid	18	18.20%
	Cystic	21	21.20%
	Solid + cystic	59	59.60%
	No lesion	1	1.00%
	Total	99	100.00%
Lymph node involvement	Positive	20	20.20%
	Negative	79	79.80%
	Total	99	100.00%
Presence of acidic fluid	Present	45	45.50%
	Absent	54	54.50%
	Total	99	100.00%

The results of pathologic evaluation of all postoperative material were also analyzed. Accordingly, the most common tumor type in patients with adnexal masses was epithelial tumors with 74.75% (n:74). Sex cord stromal tumors were found in 12.1% (n:12) and germ cell tumor types in 13.15% (n:13) of the patients. While 54.5% (n:54) of the tumors were unilateral, 45.5% (n:45) were bilateral.

According to tumor staging, it was determined that patients were most frequently diagnosed in Stage 3C (34.3%), and the second most frequently in Stage 1A (29.3%). The results of the evaluation of the patients according to their stages are shown in Figure 1.

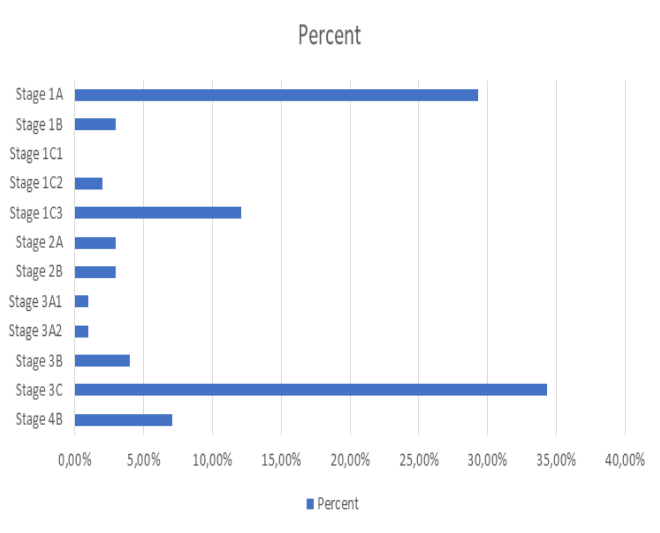

Figure 1. Evaluation of patients with adnexal masses according to their stages

The relationship between tumor stage and CA-125 levels in patients with adnexal masses was also examined. Accordingly, when the patients who were divided into 3 groups according to CA-125 levels were evaluated according to their stages, it was determined that the stage progressed as the CA-125 level

Table 2. Association between grouped CA-125 level and tumor stage

	CA-125 < 35		CA-125 between 35-300		CA-125 > 300		Total	
Stage	Count (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)
Stage 1A	17	58.60%	9	31.00%	3	10.30%	29	100.00%
Stage 1B	0	0.00%	3	100.00%	0	0.00%	3	100.00%
Stage 1C2	2	100.00%	0	0.00%	0	0.00%	2	100.00%
Stage 1C3	2	16.70%	9	75.00%	1	8.30%	12	100.00%
Stage 2A	0	0.00%	3	100.00%	0	0.00%	3	100.00%
Stage 2B	0	0.00%	3	100.00%	0	0.00%	3	100.00%
Stage 3A1	0	0.00%	1	100.00%	0	0.00%	1	100.00%
Stage 3A2	0	0.00%	0	0.00%	1	100.00%	1	100.00%
Stage 3B	0	0.00%	4	100.00%	0	0.00%	4	100.00%
Stage 3C	0	0.00%	18	52.90%	16	47.10%	34	100.00%
Stage 4B	0	0.00%	1	14.30%	6	85.70%	7	100.00%
Total	21	21.20%	51	51.50%	27	27.30%	99	100.00%

The presence of lymph nodes and ascites were also evaluated according to the stages. Accordingly, patients with lymph node positivity were found to be at significantly more advanced stages. Similarly, patients with ascites were at more advanced stages, while patients without ascites were at earlier stages. The findings are shown in Table 3. The mean CA-125 levels in patients with residual tumors were also evaluated. Accordingly, the mean CA-125 value of patients with residual tumor after surgery (1079.1±1484.5) was significantly higher than that of patients without residual tumor (314.5±877.4) (p:0.001). In addition, the mean CA-125 value was higher in patients with bilateral tumors (p: 0.001).CA-125 values were also evaluated according to the presence of lymph nodes and ascites. The mean CA-125 values were significantly higher in patients with positive lymph nodes and ascites compared to patients with negative lymph nodes and ascites (p values:p: 0.001 and p:0.001, respectively) (Table 4).

Table 3. Evaluation of lymph node positivity and presence of ascites according to stages

	Lymph Node Positive		Lymph Node Negative		Total		
Stage	Count (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)	P value
Stage 1A	0	0.00%	29	100.00%	29	100.00%	
Stage 1B	0	0.00%	3	100.00%	3	100.00%	
Stage 1C2	0	0.00%	2	100.00%	2	100.00%	
Stage 1C3	0	0.00%	12	100.00%	12	100.00%	
Stage 2A	0	0.00%	3	100.00%	3	100.00%	
Stage 2B	0	0.00%	3	100.00%	3	100.00%	0.001***
Stage 3A1	0	0.00%	1	100.00%	1	100.00%	
Stage 3A2	0	0.00%	1	100.00%	1	100.00%	
Stage 3B	2	50.00%	2	50.00%	4	100.00%	
Stage 3C	11	32.40%	23	67.60%	34	100.00%	
Stage 4B	7	100.00%	0	0.00%	7	100.00%	
Total	20	20.20%	79	79.80%	99	100.00%	
	Acidic fluid present		**Acidic fluid absent**		**Total**		
Stage	Count (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)	P Value
Stage 1A	8	27.60%	21	72.40%	29	100.00%	
Stage 1B	1	33.30%	2	66.70%	3	100.00%	
Stage 1C2	1	50.00%	1	50.00%	2	100.00%	
Stage 1C3	3	25.00%	9	75.00%	12	100.00%	
Stage 2A	0	0.00%	3	100.00%	3	100.00%	
Stage 2B	0	0.00%	3	100.00%	3	100.00%	0.001***
Stage 3A1	1	100.00%	0	0.00%	1	100.00%	
Stage 3A2	1	100.00%	0	0.00%	1	100.00%	
Stage 3B	3	75.00%	1	25.00%	4	100.00%	
Stage 3C	22	64.70%	12	35.30%	34	100.00%	
Stage 4B	5	71.40%	2	28.60%	7	100.00%	
Total	45	45.50%	54	54.50%	99	100.00%	

***Pearson chi-square test was used and a significant difference was found

increased (p: 0.001). Stage evaluation according to grouped CA-125 level is shown in Table 2.

Table 4. CA-125 Evaluation according to lymph node involvement and presence of ascites in the patient

	CA-125		
	Mean	Standard deviation	p value
Lymph node positive	810.35	861.17	
Lymph node negative	469.67	1,192.20	0.001**
Total (lymph node)	538.49	1,137.52	
Acidic fluid present	947.42	1,421.14	
Acidic fluid absent	197.72	675.01	0.001**
Total (Acidic fluid)	538.49	1,137.52	

** Mann-Whitney U test was used and a significant difference was found.

DISCUSSION

Our study revealed that ovarian cancer is mostly detected in older, postmenopausal women and frequently in advanced stages. CA-125, the most commonly used tumor marker, was found to be associated with stage, residual tumor, lymph node involvement, presence of ascites, bilaterality of the tumor and tumor type. In addition, lymph node involvement and asciticemia, which may be related to stages, were also examined and it was found that lymph node involvement and asciticemia were parallel with the increase in stage.

It has been observed that the frequency of ovarian cancer, which is also detected at an early age, increases with advancing age,[7] in addition, in some studies, when patients were divided into two groups: under 45 years of age and 45 years and over, it was observed that 58.8-83% of the patients were over 45 years of age and when menopause was accepted as the cut-off point, the rate of postmenopausal women with ovarian cancer was reported to be 45-71% in the literature.[8,9] In our study, 55.6% of the patients were in the postmenopausal period and 66.7% of the patients were 45 years of age or older, 33.3% were younger than 45 years of age. In addition, the mean age at the time of diagnosis of ovarian cancer was found to be compatible with the data in the literature.

The most common symptoms reported in patients with ovarian cancer are pelvic pain/ abdominal pain; symptoms such as bloating, urinary incontinence, and weight loss may also be observed.[10] Vine et al.[11] showed abdominal pain (64%), bloating or feeling of fullness (62%) and abdominal distension or hardness (59%) as the most common symptoms. In this study, abdominal pain was the most common symptom in 67.7% of the patients.

Regarding the histological type of ovarian tumors, Reid et al.[12] showed that the rate of epithelial ovarian tumors was 90%, sex-cord stromal tumors 5%- 6% and germ cell tumors 2%-3%. In another study, these rates were 77.4%, 11.3% and

7.5%, respectively.[8] In this study, the most common tumor type was epithelial tumors with 74.75%. Sex cord stromal tumors were found in 12.1% of the patients and germ cell tumor type in 13.15%.

In 2020, in a review of 871 cases, the concordance rate between frozen section and final diagnoses was 93.8%.[13] In a study for frozen section, diagnostic accuracy, sensitivity and specificity were 95.8%, 98.7% and 94.7% for benign ovarian tumors, 91.1%, 82.0% and 93.0% for borderline ovarian tumors, and 93.1%, 88.2% and 99.7% for malignant ovarian tumors, respectively. According to tumor types, the positive predictive value of frozen section analysis was highest in germ cell tumors (99.3%). This was followed by sex cord stromal tumors (96.7%). The most discordant group was found to be epithelial ovarian tumors.[14] In another meta-analysis, 40% of patients with at least borderline diagnosis on frozen section had invasive carcinoma on paraffin section.[15] In this study, 88.7% of the patients were reported as malignant on frozen section. In 7 patients (8.7%), the frozen result was borderline and in 2 patients the material was reported as benign. Frozen pathology was not performed in 19 patients.

CA-125 is a marker that is examined in ovarian tumors in many aspects such as tumor type, stage, presence of ascites mai, presence of residual tumor after surgery. When the literature is reviewed in terms of the relationship between tumor stage and CA-125 levels, there are studies suggesting that there is a relationship between CA-125 and stage, but there are also studies reporting that there is no relationship.[16,17] In this study, when the patients who were divided into 3 groups according to CA-125 levels were evaluated according to their stages, it was observed that the stage progressed as the CA-125 level increased and there was a relationship between stage and CA-125.

There are also studies showing that CA-125 level is associated with suboptimal resection and is higher in patients with suboptimal resection.[17,18] Modarres-Gilani et al.[19] showed that when the cut-off value for CA-125 was taken as 450 U/ml, optimal resection was performed in 86% of patients below this value and in 52% of patients above this value. In this study, residual tumor and CA-125 levels were evaluated. Accordingly, the mean CA-125 value of the patients who had residual tumor at the time of surgery was significantly higher than the patients who did not have residual tumor. In addition, postoperative residual tumor volume has been emphasized in many studies and it has been argued that residual tumor volume is prognostic and affects survival.[20,6] In some studies, the rate of cases with a residual tumor size of less than 1 cm has been observed between 33% and 87%.[19,21-22] In this study, the rate of patients with residual tumor diameter <1 cm was 70.7%.There are many studies examining the relationship between tumor stage and lymph node metastases and it has been reported that lymph node metastases is more common in advanced stages and lymph node metastases in early stage ovarian cancers is between 6 - 30%.[23-25] In this study, lymph node positivity was evaluated according to the stages and although patients with positive lymph nodes were found to be at significantly more advanced stages, the fact that no positive lymph node was observed in any of the patients with early stage ovarian cancer suggests that studies involving a larger patient group are needed. The majority of women with ovarian cancer present to hospital at an advanced stage (stage III or stage IV), which may include ascites.[26] Fewer studies have compared LGSOC (low grade serous ovarian cancer) and HGSOC (high grade serous ovarian cancer) and found a higher prevalence of ascites in HGSOC. And the presence of ascites showed a significant difference between these two groups. The presence of ascites is also highly correlated with the extent of the disease. The presence of ascites was observed in >90% of women with stage III and IV ovarian cancer. It was also found that patients with high levels of ascites (>1000 ml) had higher CA-125 levels than those with low levels of ascites (<200 ml), which was associated with better surgical outcomes and late recurrence.[27] Although the amount of ascites was not evaluated in this study, when we evaluated CA-125 values according to the presence of ascites, the mean CA-125 values were found to be significantly higher in patients with ascites compared to those without ascites as in the study by Ivanov et al.[18] Again, when we evaluated the presence of ascites detected in 45.5% patients in this study according to the stages; it was observed that patients with ascites were in more advanced stages while patients without ascites were in earlier stages. The rate of ascites in patients in advanced stages was 68%, which supports the literature. In addition, when we evaluated CA-125 values according to lymph node positivity in this study, the mean CA-125 values were significantly higher in patients with positive lymph nodes compared to those with negative lymph nodes. The reason for this positivity may be that CA-125 values is higher in advanced stages and both lymph node positivity and ascites are more common in advanced stage tumors.

Limitations

The limitations of our study were the small number of patients and the inability to perform frozen sections in some patients.

CONCLUSION

Since routine ovarian cancer screening is not possible in today's conditions, the increasing frequency of ovarian cancer with age and its rates in the postmenopausal period are important in terms of early diagnosis and better understanding of age-related risk factors, identification of common symptoms, patient information, and may contribute to the development of strategies for symptom management in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Dicle University Faculty of Medicine, Ethics Committee (Date: 21.01.2022, Decision No: 37).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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