Prognostic Factors in Advanced Ovarian Cancer – A Clinical Trial

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Rezumat

Factori de prognostic în cancerul de ovar avansat – un trial clinic

Introducere: Cancerul ovarian reprezintă cea mai letală afecțiune onco-ginecologică. Marea majoritate a pacientelor se diagnostichează în stadii avansate de boală, în care rata recidivelor este crescută, iar șansa de supraviețuire la 5 ani este sub 45%.

Scopul: evaluarea unor corelații ale supraviețuirii globale cu caracteristici clinico paraclinice, tumorale sau de tratament pentru identificarea factorilor de prognostic, la pacientele cu cancer ovarian avansat – stadiile III și IV FIGO.

Material și Metodă: Am efectuat o analiză retrospectivă la 65 paciente cu cancer ovarian avansat – stadiile III și IV FIGO operate în perioada 2010-2018, cu o perioadă de urmărire de cel puțin un an. S-au efectuat corelații cu caracteristici clinico-paraclinice, tumorale sau de tratament cu supraviețuirea globală.

Rezultate: În analiza statistică univariată de supraviețuire se obține o asociere semnificativă statistică cu prezența durerilor pelvine la internare ($p_value=0.033744$), în cadrul substadiului III ($p_value = 0.007595$, respectiv $p_value=0.022090$), cu tipul de citoreducție ($p_value = 0.035554$), cu complicațiile postoperatorii ($p_value = 0.000685$) în cadrul subtipurilor histopatologice ($p_value = 0.046266$), cu tratamentul adjuvant ($p_value = 0.000083$). Analiza de regresie multivariată Cox a arătat că chimioterapia adjuvantă ($HR=0.046$, $95\%CI = (0.008, 0.261)$, ($p_value = 0.000492$), citoreducția sub-optimală ($HR= 0.346$, $95\%CI = (0.140, 0.853)$, ($p_value = 0.021219$) și

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complicațiile postoperatorii (HR=53.751, 95%CI=(4.672, 618.365), (p_value = 0.001389) sunt factori de prognostic independenți.

Concluzii: Lipsa durerilor pelvine la momentul diagnosticului, stadiul FIGO IIIC, citoreducția sub-optimală, prezența complicațiilor postoperatorii, lipsa tratamentului adjuvant și tipul histopatologic de cancer cu celule clare s-au dovedit factori de prognostic pentru supraviețuirea globală. La paciențele cu cancer ovarian avansat, tipul de citoreducție optimală și efectuarea tratamentului adjuvant sunt factori de protecție independenți pentru supraviețuirea globală, iar prezența complicațiilor postoperatorii s-a dovedit factor de risc independent.

Cuvinte cheie: cancer ovarian, factori de pronostic, citoreducție chirurgicală

Abstract

Introduction: Ovarian cancer is one of most fatal gynecological condition. The number of patients diagnosed in advanced stages is very high, hence the recurrence rate is high, and the chance of survival at 5 years is less than 45%.

Purpose: To evaluate correspondance between overall survival with clinical, paraclinical, tumor or treatment characteristics and to identify prognostic factors in patients with advanced ovarian cancer - stage III and IV FIGO.

Material and Method: We performed a retrospective study in 65 patients with advanced ovarian cancer - stages III and IV FIGO operated during 2010-2018, with a follow-up period of at least one year. There were correlations with clinical and paraclinical characteristics, tumor or treatment characteristics and with overall survival.

Results: In the univariate statistical analysis of survival, a significant statistical association is obtained by the presence of pelvic pain at presentation (p_value = 0.033744), with the stage III (p_value = 0.007595, respectively p_value = 0.022090), with the type of citoreduction (p_value = 0.035), with postoperative complications (p_value = 0.000685) within the pathological subtypes (p_value = 0.046266), with adjuvant treatment (p_value = 0.000083). Cox multivariate regression analysis showed that adjuvant chemotherapy (HR = 0.046, 95% CI = (0.008, 0.261), (p_value = 0.000492), suboptimal cytoreduction (HR = 0.346, 95% CI = (0.140, 0.853), (p_value) = 0.021219) and postoperative complications (HR = 53,751, 95% CI = (4,672, 618,365), (p_value = 0.001389) are independent prognostic factors.

Conclusions: Absence of pelvic pain at diagnosis, FIGO IIIC stage, suboptimal cytoreduction, presence of postoperative complications, inadequate adjuvant treatment and pathological type of clear cell cancer have been shown to be prognostic factors for overall survival. In patients with advanced ovarian cancer, the type of optimal citoreduction and adjuvant treatment are independent protective factors for overall survival, and the presence of postoperative complications has been shown to be an independent risk factor.

Key words: ovarian cancer, prognostic factors, surgical cytoreduction

Introduction

Ovarian cancer is one the most fatal gynecological disease. Surgical treatment is one of the most important step in the management of

disease, either as a primary treatment or following neoadjuvant chemotherapy. The great majority of patients are diagnosed with progressive of disease, in which the recurrence rate is upraised, and the chance of

survival at 5 years is below 45% and for stages III and IV the disease is 25%. (1)

For high-grade serous epithelial ovarian cancer type, median survival period less than 5 years, but for about 15% of patients it can reach over 7-10 years. Studying the survival analysis, it was observed that in these patients the subsequent prognostic factors were identified: young age, early stage of disease, low-grade or non-serous histopathological type, absence of ascites and optimal surgical cytoreduction (2).

The main objective of prevention, screening protocols and early stage diagnosis of ovarian tumors are to improve survival and disease-free interval (3).

Observations of the last 30 years, showed that the incidence of the disease has collapsed mainly because increased utilisation of combined oral contraceptive pills and the decreased administration of postmenopausal HRT (4).

In the USA, the incidence of the disease dropped by 1.9% annually between 2004-2013 while the mortality decreased by 2.2% annually in the same period (5). In France, the prevalence of the disease dropped in the period between 1980-2012 with about 0.6% per year while mortality decreased by 1.2% per year (6).

Also, it seems that the mortality in ovarian cancer has declined but it could not be demonstrated that the real cause of this dropping is not in fact the direct correlation with the decrease of the incidence of the disease. Some studies have concluded that because patients with complete cytoreduction have survived longer than those with optimal intervention, this fact demonstrates that the absence of the macroscopic tumor residue is the most important prognostic factor for long-term survival (7). Another important study showed that patients with stage III/IV ovarian cancer who had complete cytoreduction had a 5.5% increase in the median survival rate, which we can translate by an increase of 2-3 months, compared to the patients who have undergone optimal surgery (8).

Some authors states that, balancing the

two main protocols for ovarian tumors treatment, particularly: neoadjuvant chemotherapy followed by cytoreductive surgery versus the other way around, using the treatment protocol that primary recommends debulking would improve survival by about 5.2 months (9).

Other authors dispute that neoadjuvant chemotherapy increases the chances of optimal cytoreduction, but in terms of long term survival, no statistically significant distinction could be proven between the two distinctive protocols (10).

Regarding the comparison of the use of intraoperative or intraperitoneal postoperative chemotherapy in patients with optimal cytoreduction versus standard chemotherapy as a single treatment in ovarian neoplasm, there was an increase in the survival of 3 years in favor of patients with optimocytoreduction followed by chemotherapy (11).

On one study from 2018 comparing the long-term survival of ovarian cancer patients with other comorbidities: cardiovascular disease, including HTN, showed that patients over 60 years of age with beta-blockers over 1 year had a longer distance survival than those without this cardiac treatment (12).

From a pathological point of view, invasive serous tumors into pelvis are associated with a mortality rate of 34%, while mucinous tumors with up to 50% (13).

Some authors had analyzed the presence of BRCA 1 and 2 genes on long-term survival and disease-free interval, deducing that patients expressing these genes had better survival compared to rest of the patients (14).

Anyhow in patients with ovarian tumors the 5-year survival rate is boosting due to, most likely, the development and optimization of treatment (15).

Material and Method

The study comprise patients treated for with stage III and IV ovarian cancer between 01.01.2010 - 01.11.2018 in the General and Esophageal Surgery department at Sfanta Maria Clinical Hospital, Bucharest.

Patient data were collected from clinical notes, operating notes, pathological and cytological reports and oncology letters prior to admission. The study included a total of 65 patients. As possible factors with prognostic role in patients with ovarian cancer we analyzed: comorbidities, gynecological surgical background, high blood pressure, diabetes, obesity, clinical factors like age, nulliparous / multiparous status, reproductive status, presence of pelvic pain, metrorrhagia, abdominal distension, paraclinical factors - CA 125 marker level at admission, imaging aspects of abdominal-pelvic USS / tomography, radiological aspects of abdominal voids, colonoscopies, tumor characteristics - pathological / cytological examination, histopathological type of postoperative specimens, tumor grading, FIGO stage, presence of tumor recurrence and therapeutic factors.

Preoperative pathological diagnosis was based on ascites fluid cytology obtained by paracentesis or biopsy of abdominal/pelvic tumors by exploratory laparotomy / laparoscopy according to the classic histo-pathological standards for establishing malignancy. The histo-pathological types were divided into 6 classes according to the AJCC (American Joint Commission of Cancer) criteria. The clinical stages of the disease were divided into 4 stages according to FIGO criteria.

Among the therapeutic factors we analyzed the neoadjuvant treatment, type of resection: optimal/suboptimal, type of resection complex /non-complex, postoperative complications and postoperative chemotherapy treatment.

The pre-operative neoadjuvant treatment performed in patients in which the primary surgical treatment was not appropriate consisted of 5-6 cycles of chemotherapy performed 1 month apart, and the most common chemotherapeutic agents used were based on Taxols and Platinum Salts. The surgical treatment aimed for maximum cytoreduction, according to the latest ESMO recommendations. Data from the literature recommend standardization of surgical treatment in ovarian cancer, thus, ovarian cancer surgery

can be evaluated as optimal or suboptimal cytoreduction depending on the presence and size of the postoperative tumor residue. To achieve this goal, the surgical treatment may include resection of the tumor invaded organs within the complex resections for ovarian cancer. Surgery was considered optimal if the residual tumor diameter was less than 1 cm and suboptimal if it was greater than 1cm. Adjuvant chemotherapy treatment was given according to oncological standards for ovarian neoplasm. The follow-up of the patients was carried out by periodic clinical and paraclinical checks every 6 months in order to diagnose the tumor recurrence at an earlier stage.

Study Design

The patients included in the study were those with advanced stages of the disease (stages III and IV FIGO). Their clinical, pathological, radiological and therapeutic characteristics (age, antecedents and comorbidities, symptomatology at diagnosis, CA-125 value at diagnosis, imaging aspect, FIGO stage, neoadjuvant chemotherapy, histological type, tumor grading, recurrence, and degree of complexity surgery) were evaluated in the survival analysis.

Statistical Analysis

In the analysis of survival, time was defined from the time of diagnosis to the date of death by disease or the date of completion of the study (1.11.2019).

Survival curves were plotted using the Kaplan-Meier method, and statistical significance analysis was performed with Log Rank (Mantel-Cox) tests and Cox multivariate regression analysis to evaluate independent prognostic factors. Survival and median survival were calculated and survival was estimated at 6, 12, 24, 48, 60 months. Statistical assessment was carry out by utilisation of SPSS software (version 23.0), and $p < 0.05$ was considered statistically significant.

Results

At the end of the study period, 36 patients (55.38%) were deceased. Median survival time was approximately 58.7 months and survival rate was 46.15% at 5 years. The average age was 62.47, with limits between 40 and 85 years. There was no statistically significant difference for survival in terms of involving the age of patients in the overall survival. Neither was for the other epidemiological factors analyzed like parity status ($p_{\text{value}} = 0.247$, Log Rank (Mantel-Cox)), reproductive status ($p_{\text{value}} = 0.450$, Log Rank (Mantel-Cox)), gynecological surgical history ($p_{\text{value}} = 0.083$, Log Rank (Mantel-Cox)), or comorbidities HTN ($p_{\text{value}} = 0.937$, Log Rank (Mantel-Cox)), DM ($p_{\text{value}} = 0.290$, Log Rank (Mantel-Cox)), obesity ($p_{\text{value}} = 0.959$, Log Rank (Mantel-Cox)) were not proven factors associated with global survival (Table 1).

Of the 58 patients with pelvic pain at present complaint included in the study group 30 died, and for 28 (48.3%) the death was not registered until 01.11.2019, and of the 7 patients who did not complain of pain 6 died and one survived until the end of the study. Comparing the survival on the 2 lots, the statistically significant difference is obtained ($p_{\text{value}} = 0.033744$, Log Rank (Mantel-Cox)).

The 5-year survival of patients with pelvic pain at admission is 36% while for patients without pelvic pain 5-year survival is 0% (Fig. 1, Table 1).

The other symptoms presented by the patients in the group at the time of diagnosis – metrorrhagia ($p_{\text{value}} = 0.714$, Log Rank (Mantel-Cox)), abdominal distension ($p_{\text{value}} = 0.398$, Log Rank (Mantel-Cox)) did not cause statistically significant differences between survival curves (Table 1).

For the values of CA125 we considered for the statistical correlation: 0 = CA125 indeterminate; 1 = CA125 <100; 2 = CA125 between 100-1000 and 3 = CA125 > 1000. Comparing the survival of the 4 groups, no statistically significant difference is obtained ($p_{\text{value}} = 0.679$, Log Rank (Mantel-Cox)) (Table 1).

Figure 1. Kaplan Meier survival curves for pelvic pain

The imaging aspects analyzed USS/pelvis CT scan showing carcinomatosis, pelvic tumor or both ($p_{\text{value}} = 0.250$, Log Rank (Mantel-Cox)), normal or pathological aspect of chest xray ($p_{\text{value}} = 0.804$, Log Rank (Mantel-Cox)), of plain abdominal xray ($p_{\text{value}} = 0.782$, Log Rank (Mantel-Cox)) or of the colonoscopy ($p_{\text{value}} = 0.223$, Log Rank (Mantel-Cox)) did not prove factors associated with overall survival (Table 1).

Of the 39 patients in stage IIIA included in study group 19 died, and for 20 (51.3%) death was recorded until 01.11.2019, and of the 4 patients in stage IIIB included in study group 3 died, and for one the death was not recorded, for the 5 patients in stage IIIC included in the study group 3 died, and for two the death was not recorded. Of the 17 stage IV patients included in the study group 11 died and 6 (35.3%) death was not registered. Comparing the survival of the 4 groups, we obtain a statistically significant difference ($p_{\text{value}} = 0.026791$, Breslow (Generalized Wilcoxon)). We encountered significant differences between stages IIIA and IIIB ($p_{\text{value}} = 0.007595$), and between stages IIIB and IIIC ($p_{\text{value}} = 0.022090$).

The 5-year survival of patients with stage FIGO IIIA is 41.4%, for patients with stage FIGO IIIB is 0%, for patients with stage FIGO IIIC is 0%, and for patients with stage FIGO

Table 1. Survival analysis of prognostic factors

Prognostic factor	Deceased (n)	Mean – Estimate	Median – Estimate	Five-year survival rate (%)	Univariate	Multivariate	
				p_value	HR (95% CI)	p_value	
Age	36/65				0.801		
Parity							
Nulipara	23/31	97.625	-	62.5%	0.247		
Multiparity	3/8	29.743	15.000	19.7%			
Menopause							
Yes	34/59	57.762	27.000	32.1%	0.450		
No	2/6	33.000	36.000	Max 42			
Surgical h/x							
Yes	3/11	56.455	-	72.7%	0.083		
No	32/53	48.963	27.000	25.1%			
HTN							
Yes	19/34	40.527	30.000	34.4%	0.937		
No	17/31	60.095	27.000	30.2%			
DM							
Yes	4/6	19.333	12.000	Max 40	0.290		
No	32/59	60.565	36.000	33.4%			
Obesity							
Yes	2/4	24.250	30.000	-	0.959		
No	34/60	57.782	27.000	31.8%			
Pelvic pain							
Yes	30/58	63.475	44.000	36.0%	0.033744	-	-
No=Ref	6/7	17.571	12.000	-			
Methrorragy							
Yes	3/7	26.643	-	Max 41	0.714		
No	33/58	57.849	30.000	31.6%			
Abd distension							
yes	6/9	23.000	18.000	Max 45	0.398		
No	30/56	61.112	36.000	34.0%			
CA125							
0	26/47	54.292	27.000	34.6%	0.679		
1	3/5	34.000	48.000	0.0%			
2	4/8	48.250	54.000	46.9%			
3	2/3	20.333	15.000	Max 36			
Aspects Carcinomatosis							
Ref	8/13	28.031	15.000	24.6%		-	-
T pelvina	12/2	68.343	48.000	41.6%	0.250		
T pelvina, carcinomat	2/2	16.000	10.000	-			
Pulm mets							
Yes	2/3	29.333	10.000	33.3%	0.804		
No	34/62	56.941	30.000	30.8%			
Abd Xray							
Da	2/3	53.667	5.000	33.3%	0.782		
Nu	1/2	8.500	3.000	-			
Colonoscopy							
Yes	2/6	19.143	12.000	Max 41	0.223		
No	5/7	33.125	-	Max 45			
FIGO							
IIIA	19/39	68.804	44.000	41.45%		-	-
IIIB	3/4	6.750	6.000	-			
IIIC	3/5	37.750	27.000	0.0%	0.026791		
IV	11/17	32.235	12.000	33.6%			
Pathol preop exam							
Cytologic	7/12	24.250	14.000	Max 46	0.271		
Tum biopsy	7/9	14.259	5.000	Max 36			
Neoadjuvant treatment							
Yes	11/19	68.598	22.000	40.2%	0.625		
No	24/45	41.345	44.000	33.0%			

Prognostic factor	Deceased (n)	Mean – Estimate	Median – Estimate	Five-year survival rate (%)	Univariate	Multivariate	
					p_value	HR (95% CI)	p_value
Cytoreduction							
Optimal	7/21	81.528	72.000	68.9%	0.035554	0.346 (0.140, 0.853)	0.021219
Subop=Ref	29/44	32.742	18.000	21.7%			
Complex Op					0.772		
Yes	10/17	34.545	36.000	21.2%			
No	26/48	61.474	27.000	36.3%			
Morbidity					0.000685	53.751 (4.672, 618.365)	0.001389
Yes	1/1	2.000	2.000	0.0%			
No	35/64	59.584	30.000	32.8%			
Pathologic type					0.014835		
Clear cells=Ref	1/1			0.0%			
Endometrioid	1/1			0.0%			
Granulosa	0/1			-			
Mucinous	0/5			Max 45			
Undifferentiate	5/9			Max 43			
Serous	24/41			26.4%			
Grading					0.963		
1	3/6	46.333	12.000	50.0%			
2	5/6	32.167	16.000	16.7%			
3	21/37	35.217	30.000	24.2%			
PO Treatment					0.000083	0.046 (0.008, 0.261)	0.000492
Yes	32/59	59.962	36.000	32.8%			
No=Ref	2/2	2.500	2.000	0.0%			
Recurrence					0.945		
Yes	29/53	37.483	27.000	28.9%			
No	7/12	67.917	30.000	38.1%			

IV is 33.6% (Fig. 2, Table 1).

Comparing the survival on the 2 groups of patients those with preoperative diagnosis of ovarian cancer established by cytological analysis of ascites fluid obtained by paracen-

tesis and those with preoperative diagnosis of ovarian cancer obtained by histopathological examination of the peritoneal or omental biopsy during the exploratory laparotomy no statistically significant difference is noted ($p_value = 0.271$, Log Rank (Mantel-Cox) (Table 1).

Of the 19 patients with neoadjuvant chemotherapy treatment included in the study group 11 died and 8 (42.1%) survived until 01.11.2019. For the 45 patients with initial surgical resection in group 24 died and for 21 (46.7%) death was not recorded until the end of the study. Comparing the survival on the 2 groups, no statistically significant difference is obtained ($p_value = 0.625$, Log Rank (Mantel-Cox) (Table 1).

Of the 21 patients with optimal resections included in the study group 7 died, and for 14 (66.7%) survived until 01.11.2019, and of the 44 patients with suboptimal resections in the group 29 of them died, and for 15 (34.1%) patients death was recorded until the end of the study. Comparing the survival on the 2

Figure 2. Survival curves Kaplan Meier test according to FIGO stage

lots, statistically significant difference is observed ($p_{\text{value}} = 0.035554$, Log Rank (Mantel-Cox)).

The 5-year survival of patients with optimal cytoreduction is 68.9%, and for patients with suboptimal cytoreduction it is 21.7% (Fig. 3, Table 1).

Comparing the survival of the 2 groups of patients with complex resections and those without complex resections, no statistically significant difference is obtained ($p_{\text{value}} = 0.772$, Log Rank (Mantel-Cox) (Table 1).

Of the 64 patients without post-operative complications included in the study group, 35 died, and for 29 (45.3%) death was not recorded until 01.11.2019. Comparing the survival on the 2 lots, statistically significant difference is obtained ($p_{\text{value}} = 0.000685$, Log Rank (Mantel-Cox)).

The 5-year survival rate of patients without postoperative complications is 32.8%, and for patients with postoperative complications it is 0% (Fig. 4, Table 1).

One patient with clear cell carcinoma included in the study group died, as did the patient with endometrioid carcinoma, for the patient with granulous and for the 5 patients with mucinous carcinomas the death was not registered until 01.11.2019. For the 9 patients with undifferentiated carcinomas from group 5 died, and for the 41 patients with serous carcinomas 17 of them were still surviving at the end of the study. Comparing the survival on the 5 lots, we obtain a statistically significant difference ($p_{\text{value}} = 0.014835$, Log Rank (Mantel-Cox)). We found significant differences on survival between patients with clear cell carcinomas and those with mucinous tumor type ($p_{\text{value}} = 0.025347$), between patients with clear cell carcinomas and those with serous carcinomas ($p_{\text{value}} = 0.003063$), between endometrioid and mucinous type ($p_{\text{value}} = 0.025347$) and between mucinous and serous types ($p_{\text{value}} = 0.046266$).

Survival analysis shows different survival curves and that the mucinous type carcinoma has led to the best survival rate: 100% at 36 months with a maximum of 45% at 5 years, while clear cell and endometrioid carcinoma

Figure 3. Kaplan Meier survival curves based on the type of cytoreduction

recorded the lowest survival rate of 0% at 5 years. Intermediate curves were observed for undifferentiated tumors with a 5-year survival rate of maximum 43%, and for the case of serous tumors of 26.4% (Fig. 5, Table 1).

Comparing the survival on the 3 groups of patients with well differentiated tumors G1, medium differentiated G2 and poorly differentiated G3, no statistically significant difference is obtained ($p_{\text{value}} = 0.963$, Log Rank (Mantel-Cox) (Table 1).

Of the 59 patients with adjuvant chemo-

Figure 4. Kaplan Meier survival curves for presence of post-operative complications

Figure 5. Kaplan Meier survival curves according to histopathological type

Figure 6. Kaplan Meier survival curves according to the postoperative chemotherapy treatment

therapy for ovarian cancer included in the study group 32 died and for 27 (45.8%) death was not registered until 01.11.2019. For the 2 patients without adjuvant chemotherapy in the group, both died until the end of the study. Comparing the survival on the 2 lots, the statistically significant difference is obtained ($p_value = 0.000083$, Log Rank (Mantel-Cox)).

The 5-year survival of patients with adjuvant chemotherapy is 32.8%, and for patients without adjuvant chemotherapy it is 0% (Fig. 6, Table 1).

Comparing the survival on the 2 groups of patients those who had tumor recurrence and those without recurrence during the follow-up period, no statistically significant difference is obtained ($p_value = 0.945$, Log Rank (Mantel-Cox)) (Table 1).

Comparing survival in patients without postoperative complications with those who had postoperative complications, the chances/risk of death for cases with postoperative complications were calculated - $HR = 53,751$, 95% $CI = (4,672, 618,365)$ ($p_value = 0.001389$) (Table 1) - the presence of postoperative complications is an independent risk factor.

Comparing survival in patients with suboptimal cytoreduction with those with optimal cytoreduction, the odds/risk of death were calculated - $HR = 0.346$, 95% $CI = (0.140,$

$0.853)$, ($p_value = 0.021219$) (Table 1) Optimal cytoreduction is an independent protective factor

Comparing survival in patients with adjuvant chemotherapy with those without postoperative treatment, the odds/risk of death for patients with adjuvant treatment were calculated - $HR = 0.046$, 95% $CI = (0.008, 0.261)$, ($p_value = 0.000492$) (Table 1) Postoperative chemotherapy treatment is an independent protective factor.

Discussions

In this study, we analyzed the clinicopathological characteristics and survival outcomes of ovarian cancer patients treated at Sf.Maria Hospital between 2010-2018. We found that the epidemiological factors: nulliparous status, reproductive status, gynecological surgical history, history of high blood pressure, diabetes, obesity; clinico-paraclinic factors: metrorrhagia, abdominal distension, level of CA125 marker at admission, chest Xray or abdominal Xray; the colonoscopic aspect; the therapeutic factors: neoadjuvant chemotherapy were not risk factors for the overall survival. While the clinical-paraclinical factors like pelvic pain, FIGO stage and therapeutic ones like type of optimal/sub-

optimal resection, postoperative complications, adjuvant chemotherapy, pathological type has been proved to be prognostic factors for long-term survival.

Ovarian tumors is the leading cause of death from malignancy disease for women and is the 4th on mortality among women. Databases and reports from 2019 show that the estimated number of new cases is 22 240, and the number of deaths around 14 170 cases (16). In Romania, the incidence of ovarian cancer has been stable in recent years, according to Globocan (6, 3/100 000 in 2008 and 6.1/100,000 in 2012) (17,18), and mortality was among the five main causes of cancer deaths (19). The highest incidence of ovarian tumors in the batch analysed was in the age interval of 60 and 69, which keeps in line with data from the literature (20). In our study, the age of the patients included in the lot was not demonstrated to have significant statistical power for survival rate, unlike other studies, which verified that the age is an independent prognostic variable in patients with advanced ovarian cancer (21-23).

The majority of females in our study were multiparous, and the 5-year survival rate was 19.7%. Although the nulliparous patients had a much better 5-year survival (62.5%), the difference was not statistically significant, unlike other studies in the literature, which obtained for the nulliparous patients a survival at 5 years similar (61.1%) but demonstrated statistical significance compared to the multiparous patients (24).

Obesity and lack of physical activity are associated with increased mortality from ovarian cancer (25). Excessive weight and increased fat deposits, that comes with weight gain, have been shown to promote tumor progression by producing growth factor I - insulin like and hyperinsulinemia (26) and by promoting chronic inflammation by increasing CRP level and tumor necrosis factor alpha. (27) Obese women with ovarian cancer receive less aggressive treatment to avoid adverse reactions. (28) Obesity has not been shown in our group. risk to global survival. And other studies emphasize that

the combination between high BMI and survival of patients with ovarian tumors remains unambiguous and that the body mass index at the time of diagnosis cannot be a prognostic factor for these patients (29).

In our study, FIGO stage proved it's relevance in prognosis, but not an independent factor, as other authors have demonstrated (8,30). More than half of the patients were diagnosed in stage IIIA FIGO, where the five-year survival was only 41.4%, this stage causing a statistically significant difference from the stage IIIB. The small number of patients in stage IIIC is a possible explanation for the lower survival of these patients (0%) compared to those in stage IV (33.6%).

Some recent studies dispute that there is still not enough evidence that neoadjuvant chemotherapy followed by cytoreduction is superior to the primary surgical approach. They recommended that clinical background, tumor type, and the response to chemotherapy should be considered for individualization of treatment: nonserous tumors (type 1) with a favorable prognosis are in fact less chemosensitive, and the omission of neoadjuvant treatment with primary cytoreduction would have better results, and for patients with high stage serous ovarian tumors (type 2) with severe illnesses or poor performance, the authors recommend neoadjuvant treatment first followed by interval cytoreduction. (31). For the patients included in the study, these recommendations were not applied, surgical treatment was the first line, and when it was not possible patient followed neoadjuvant chemotherapy and then interval surgery. From the statistical analysis, administration of neoadjuvant therapy has not been demonstrated to be a prognostic factor for long-term survival.

The most common histopathological type found in the study group was serous cancer (71%), with five year survival of 26.4%, turning out to be statistically significant in terms of survival compared to the type of clear cell carcinoma or serous tumors. For the patients with mucinous type tumors, we found the best survival rate of 100% at 36 months

with a maximum survival at 5 years of 45%. Other authors report a mortality rate of about 50% for mucinous tumors and 34% for clear cell tumors (13). Other studies reported that the pathological type influences statistically significant the survival, highlighting that endometrioid and serous tumors have a better prognosis than clear cell carcinoma and mucinous types (21).

Our results came to the conclusion that poorly differentiated (G3) tumors were most frequently identified (75.5%), with a 5-year survival of 24.2% comparable to that obtained in other studies (23.5%) (24). Univariate analysis showed that grading was not statistically relevant, compared to data from other studies who identified poorly differentiated tumors as a prognostic factor (24,32).

Since 1968, some authors have observed that in patients with ovarian cancer the prognosis was most severe if the residual disease was > 1.5 cm (33). In 1975, other authors found that in patients with residual disease ≤ 1.5 cm, survival improved as the size of the tumor decreased. Survival time was 39, 29, 18 and 11 months for patients with residual disease from 0 cm to < 0.5 cm, 0.6-1 cm, 1.1-1.5 cm, respectively > 1.5 cm (8). These aspects were supported by the results of subsequent studies that found that a "definitive cytoreduction" before chemotherapy resulted in improved survival compared to "partial removal" or "biopsy only" (34).

Another study that included patients with advanced stages of the disease, (35) and two other studies (37, 38) showed that suboptimal cytoreduction resulted in survival as low as for exploratory laparotomy. More and more authors agree that cytoreduction is very important and influences the outcome of surgery. According to the GOG guidelines of 2001/2002, the main target of all surgical procedures is to completely resect the tumour (total cytoreduction) or resection with residual mass of less than 1cm (optimal cytoreduction). In our study, approximately one third of patients underwent optimal cytoreduction with a 5-year survival of 68.9%, which was

validated as an valid prognostic factor in univariate analysis ($p < 0.05$), while the multivariate analysis validated suboptimal cytoreduction as an independent factor. Such data have also been reported by other studies of patients with advanced ovarian cancer (23). A 2002 meta-analysis of 6885 patients with stage III and IV ovarian cancer compared multiple determinants for survival, concluding that total cytoreduction influences the median survival curve (39). Some reports state that the target of surgery for cytoreduction for ovarian tumors should aim for a complete resection (7,40,41). For our patients with optimal cytoreduction, the estimated median survival time was 72 months. Other studies report median survival of 99 months (42) and 106 months (41), which is achievable for those patients that underwent complete resection. Other published endorsements show a survival of only 23.8% reported after surgery that failed to achieve optimal cytoreduction (23), close to the 21.7% survival obtained in our group in patients with suboptimal cytoreduction.

In our study, 97% of patients received chemotherapy after recover from surgery, with paclitaxel/carboplatin as first-line chemotherapy with a 5-year survival of 32.8%. The univariate analysis showed that survival was statistically significantly better in patients who received postoperative polychromy than those who did not receive chemotherapy, proving to be an independent prognostic factor in multivariate analysis, as opposed to another study that reported a survival at 5 years of 46% in patients who received chemotherapy schemes similar to those in our study, this did not prove statistically different from that of patients who did not undergo postoperative chemotherapy (27). Research identified that multiple lines of chemotherapy proved to be statistically valid only in conjunction with optimal resection. According to data from a study, the best survival rate was achieved in patients that followed chemotherapy after being treated by surgery with complete resection (40).

Conclusions

1. Epidemiological factors: parity status, reproductive status, gynecological surgical history, history of HTN, DM, obesity; clinical and paraclinical factors: metrorrhagia or abdominal distension at the time of diagnosis, high level of tumor marker CA125; aspect of chest xray or abdominal xray, colonoscopy findings and therapeutic factors: neoadjuvant chemotherapy, were not prognostic factors for overall survival.
2. The following clinical and paraclinical factors: absence of pelvic pain at the time of diagnosis, stage FIGO IIIC; treatment type: suboptimal cytoreduction, postoperative morbidity, absence of adjuvant treatment and histopathological type of clear cell cancer have been shown to be prognostic factors global survival.
3. For patients with ovarian cancer, optimal cytoreduction and administration of adjuvant chemotherapy are independent protective factors for long-term survival, and the presence of post-operative complications has been shown to be an independent risk factor.

Conflict of Interest

The authors declare no conflicts of interests.

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