JBUON 2017; 22(4): 966-972
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Evaluation of clinical characteristics linked with the survival of patients with advanced-stage ovarian malignancies

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Summary

Purpose: *To evaluate the potential influence of clinical characteristics on survival of patients with advanced-stage of ovarian malignancies.*

Methods: *The study included 163 women with FIGO stages 3 and 4 ovarian malignancies. Detailed history (family history of malignancies, age, menopausal status, body mass index (BMI), parity, comorbidities, symptoms/signs) was taken from all patients including tumor histopathological findings. Patients were postoperatively followed up to 5 years and adverse events were recorded. Univariate and multivariate survival analyses were applied.*

Results: *Patient median survival was 22.77 months (range 1-91). Almost 74% of women survived in the first postoperative year, but only 12.9% had 5-year survival. In the postoperative period, each additional 6 months presented significant risk for unfavorable outcome. Women who were menopausal (p=0.033) and especially if older than 65 years (p=0.016) had worse prognosis. Patients with BMI ≤25 kg/m^2 had significantly longer postoperative survival (p=0.005; obesity hazard ratio/HR=1.525). Women with other gynecological or chronic illnesses had a significantly shorter postoperative survival (p=0.038; hazard ratio/HR=1.450). There were no significant differences in postoperative survival regarding patients' parity, presence of symptoms or positive family history. Two significant models adjusted for FIGO stage (p=0.046) and histological tumor type (p=0.003) encompassing all assessed patient characteristics that could influence survival were obtained.*

Conclusions: *The most important clinical characteristics that can be predictors of survival of patients with advanced ovarian malignancies are comorbidities and being overweight.*

Key words: *advanced stage ovarian carcinoma, age, BMI, comorbidities, history, survival*

Introduction

Epithelial ovarian cancer is the leading cause of death among women diagnosed with gynecologic cancers. Early-stage ovarian carcinoma has unspecific clinical presentation causing frequent misinterpretation of symptomathology [1,2]. As a result, 60-70% of ovarian carcinomas are diagnosed in advanced stages, which could be one of the explanations for the short survival after diagnosis, even with applications of all current treatment methods [3,4]. According to literature data 5-year overall survival of patients with ovarian carcinoma is still <50% after diagnosis [5].

The etiology of ovarian carcinoma is multifactorial. Numerous risk factors for ovarian carcinoma development have been identified such as genetic predisposition, positive family history, previously having carcinoma of the breast or endometrium, lower parity or infertility, late menopause, older age, obesity and smoking [6-9]. On the other hand, there has been little research done

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Received: 07/02/2017; Accepted: 27/02/2017

so far to investigate patient characteristics which may contribute to survival outcomes [10]. Studies have confirmed that predictors of adverse prognosis and shorter survival are older age at the time of diagnosis and obesity [11,12]. Moreover, comorbidities can significantly reduce patient survival time [5,13]. Establishing all potential risk factors form a pool of clinical, personal and family history, socio-demographic or lifestyle parameters that could be important for developing a plan of treatment and postoperative care. Therefore, the purpose of this study was to evaluate the potential influence of clinical characteristics on the survival of patients with advanced-stage ovarian carcinoma.

Methods

This study included all women operated for advanced-stage (FIGO 3 and 4) ovarian carcinoma in the Clinic of Obstetrics and Gynecology, University Clinical Centre of the Republic of Srpska. The study started on January 1st, 2009. and lasted until December 31st, 2015. In the preoperative evaluation detailed history was taken from all patients (age, menopausal status based on the last menstrual period, BMI calculated from patient height and weight using standard formula, parity, presence of other benign gynecological and/or chronic illnesses, malignancies and gynecological diseases/disorders in the family, presence of ovarian tumor symptoms/signs such as pain, abdominal bloating, bleeding, etc.). Patient age and menopausal status were recorded and 3 age groups were formed (premenopausal <45 years; peri and post menopausal 45-65 years and women >65 years). BMI was divided into standard categories. Postoperatively, histopathological findings and tumor FIGO stage were defined and registered. According to the current literature data, these two parameters (tumor histopathology and FIGO stage) are well known predictors of patient survival and as such were considered to be potential cofactors in this study. All the obtained data were tested according to their categories.

Patients were postoperatively followed up to 5 years. Data on patient health status or death were obtained through telephone interviews with the patient/family or from the Death Registry. All patients signed informed consent for all diagnostic and therapeutic procedures as well as the participation in the study and the study was approved by the Institutional Ethics Board.

Statistics

For statistical analysis methods of descriptive (numbers and percents, minimum-maximum, mean and standard deviation/SD) and analytical statistics (x^2 test) were used to describe the investigated patient characteristics and their differences in the study sample. The impact of potential clinical prognostic factors on survival was examined by univariate and multivariate analyses. All survival analyses (Kaplan-Meier analysis with log-rank test, life table analysis and Cox proportional regression model in Enter mode with hazard ratio - HR determination) were applied to evaluate the postoperative survival time of the whole study population and to investigate the influence of the investigated parameters on patient survival.

Results

The study included 163 patients with advanced-stage ovarian carcinoma. During the first three postoperative years 39 women were lost to follow-up, while an additional 50 were lost in remaining two years of the study. The majority of women were menopausal, with mean age 59.03±11.81 years (median=59.00; range 29-83). The average BMI of the investigated patients was within limits (mean±SD=26.40±2.89; median=26.40; range 19.10-35.40). The pregnancies of the patients ranged from 0-14, but in the majority of the cases (46.6%) the patients were secundiparous (mean±SD=3.17±2.25; median=2). Most women did not have any chronic (hypertension, diabetes, endocrinological and other) or gynecological illness and their family history was also negative for any hereditary disease (Table 1).

All patients were operated and most of them had FIGO stage 3 and 4. Histopathological findings revealed 7 tumor types, out of which serous adenocarcinoma was the most frequent (Table 1).

Figure 1 shows the Kaplan-Meier survival for the whole cohort. The mean postoperative survival time was 29 months with a median of 22.77 months. At the end of the first postoperative year the majority of women (n=128) were alive. On the other hand, not many patients survived 5 years after operative treatment (n=21). According to the life table analysis, each additional 6 months in the postoperative period presented a significant risk for unfavorable outcome (Table 2). Kaplan-Meier survival analysis of 5-year overall survival in relation to the investigated parameters is displayed in Table 3.

While the expected survival time of patients in stage 3a reached almost 4 years (mean=47.45), the mean survival time in stage 4 was shorter than one year (4a=11.15; 4b=9.20 months). As expected, our results confirmed significantly shorter survival time of patients with more advanced FIGO stage ovarian malignancies (log-rank, x^2=77.003; p=0.001) (Table 3).

Patients had the best survival if histopathological analysis revealed mucinous or serous adenocarcinoma, then borderline tumors, while survival from Krukenberg tumors did not last more than one year. Still, there were no significant differences in survival between women with different histopathological diagnoses (log-rank, x^2=11.037;

p=0.201). This can be explained by the fact that a couple of tumor types had similar maximal survival time around 50 months.

Significant differences in survival were obtained regarding patient age (log-rank, x^2=8.221; p=0.016). Women older than 65 years had worse prognosis from the very start. Conversely, during the first postoperative year, survival seemed to be similar between women younger than 45 years and those aged from 45 to 65 years. On the other hand, in the later months of follow-up, women younger than 45 years had better prognosis. Moreover, the menopausal status of the patients had significant influence on postoperative survival time (log-rank, x^2=4.571; p=0.033) (Table 3).

BMI also had significant influence on postoperative survival (log-rank, x^2=10.732; p=0.005). There were no significant differences between obese and women with normal weight but patients with BMI ≤25 had significantly longer postoperative survival (Table 3).

Women with other benign gynecological or chronic illnesses had a significantly shorter postoperative survival (log-rank, x^2=4.314; p=0.038).

Table 1. Patient clinical characteristics

Characteristics		*n*	*%*	x^2	*p value*
Family history of malignancy	Negative	149	91.4	111.810	0.001
	Positive	14	8.6		
Illnesses/Comorbidities	No	83	50.9	0.516	0.473
	Yes	74	45.4		
Menopausal status	Pre	33	20.2	57.724	0.001
	Post	130	79.8		
Age groups, years	<45	12	7.4	71.571	0.001
	45-65	100	61.3		
	>65	51	31.3		
BMI, kg/m^2 categories	≤25	49	30.1	62.663	0.001
	25-30	98	60.1		
	≥30	16	9.8		
Symptoms	No	28	17.2	70.239	0.001
	Yes	135	82.8		
Parity	0	16	9.8	106.080	0.001
	1	20	12.3		
	2	30	18.4		
	≥3	97	59.5		
Alive after 1 year follow-up (n=163)	No	41	25.2	40.252	0.001
	Yes	122	74.8		
Alive after 3 years follow-up (n=124)	No	74	45.4	4.645	0.031
	Yes	50	30.7		
Alive after 5 years follow-up (n=74)	No	53	32.5	13.838	0.001
	Yes	21	12.9		

BMI : body mass index, n: number

Table 2. Life table analysis of overall survival of patients with ovarian cancer

Interval Start time (months)	*Number of patients entering interval*	*Number of diseased patients during interval*	*Hazard rate*
0	163	16	0.02
6	147	19	0.02
12	128	29	0.04
18	99	22	0.04
24	77	16	0.04
30	61	11	0.03
36	50	8	0.03
42	42	10	0.05
48	32	5	0.03
54	27	5	0.03

Hazard rate: the rate of adverse event occurring during time period

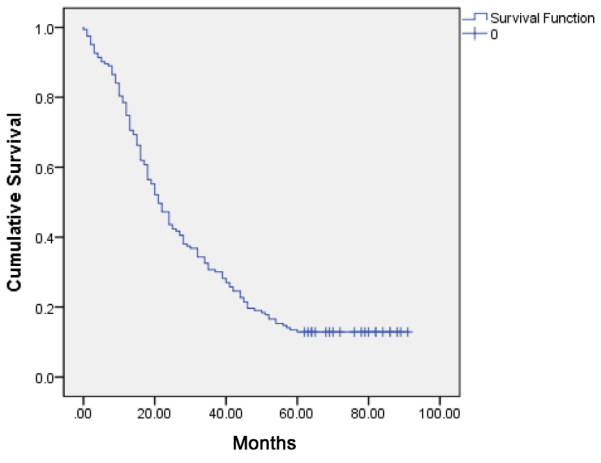

Figure 1. Kaplan-Meier overall survival of the investigated women with advanced-stage ovarian malignancies (all malignant histologies included).

Table 3. Kaplan-Meier analysis of 5-year overall survival in relation to the investigated parameters

Characteristics	*Median estimated survival (months)*	*95% confidence interval*		*Log-rank; p*
		Lower	*Upper*	
FIGO stage 3a	42.00	34.90	47.09	0.003
FIGO stage 3b	15.00	2.60	21.39	
FIGO stage 3c	20.70	16.17	23.82	
FIGO stage 4a	11.14	5.61	14.38	
FIGO stage 4b	9.00	0.01	18.73	
Serous adenoCa	23.52	18.60	25.39	0.201
Mucinous adenoCa	24.00	0.01	38.46	
Endometrioid Ca	24.00	0.01	26.62	
Clear cell carcinoma	45.00	0.01	48.01	
Granulosa/theca cell tumor	24.00	9.99	34.00	
Krukenberg tumor	13.50	5.19	20.80	
Mixed Mullerian tumor	42.00	22.00	22.00	
Other tumor types	54.00	0.01	37.47	
Borderline tumors	15.00	15.00	15.00	
<45 years of age	39.00	3.85	74.14	0.016
From 45 to 65 years	25.63	18.72	29.27	
>65 years of age	17.18	13.18	20.81	
Pre-menopause	35.83	24.80	49.19	0.033
Post-menopause	20.83	17.06	22.93	
BMI ≤25 kg/m²	31.50	21.26	46.73	0.005
BMI from 25 to 30 kg/m²	20.40	16.01	21.98	
BMI ≥30 kg/m²	22.50	14.12	25.88	
Pregnancies 0	40.00	3.64	66.36	0.236
Pregnancies 1	23.33	18.82	23.18	
Pregnancies 2	25.00	16.48	31.51	
Pregnancies ≥3	20.62	16.29	23.70	
Family history neg	22.36	17.67	24.32	0.551
Family history pos	20.00	3.33	32.66	
Illnesses no	25.50	18.05	31.94	0.038
Illnesses yes	19.54	13.73	24.26	
Symptoms no	35.00	12.14	45.85	0.164
Symptoms yes	21.40	16.81	23.18	

Ca : carcinoma, BMI : body mass index, neg : negative, pos : positive

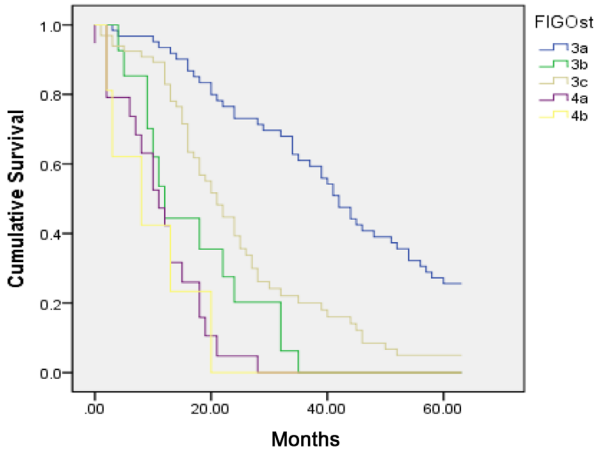

Figure 2. Cox overall survival of all investigated patient characteristics adjusted for FIGO stage of ovarian malignancies (all histologies included)(x^2=77.003, p=0.001).

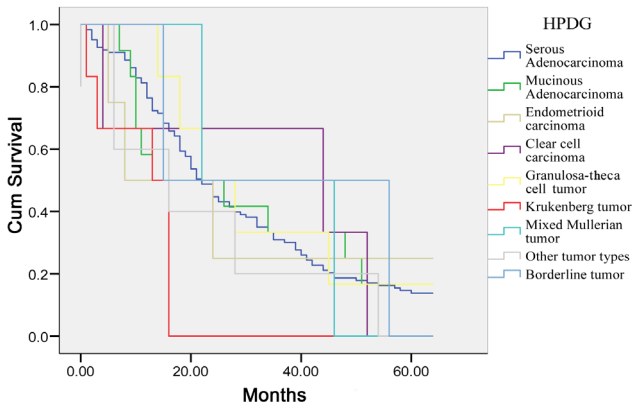

Figure 3. Cox overall survival analysis of all investigated patient characteristics in relation to histopathological diagnosis (x^2=11.037; p=0.201).

Conversely, positive family history of gynecologic and other illnesses did not influence considerably the postoperative survival (log-rank, x^2=0.357; p=0.551). Moreover, there were no significant differences in the postoperative survival time regarding patients' parity (Mantel-Cox x^2=4.252; p=0.236) or presence of symptoms (log-rank, x^2=1.938; p=0.164) (Table 3).

Finally, applying Cox regression analysis, two significant models of patient characteristics that could influence patient survival were formed. In the first we adjusted data for FIGO stage (x^2=14.319; p=0.046) and in the second for histopathological analysis (x^2=21.820; p=0.003) as possible confounding factors (Figures 2 and 3). In the first model the most important predictor of shorter postoperative survival was having other gynecological and chronic illnesses (p=0.027; HR=1.490). In the second model the risk factors for shorter postoperative survival were having comorbidities (p=0.024; HR=1.450) and being obese (p=0.022; HR=1.525).

Discussion

Literature data show that survival rates of serous ovarian carcinoma gradually drop to 50% after 5-year follow-up and to less than 40% after 10-year follow-up [14]. Some authors found that the relative survival rates at 2 and 5 years after epithelial ovarian carcinoma diagnosis were 75.8% and 63.1% respectively [1,14]. The fact that the survival of ovarian carcinoma patients in some studies significantly decreases two years after diagnosis, might imply the higher risk of recurrence and disease progression [11]. Multivariate analyses performed in some studies confirmed that age, histological subtype and FIGO stage can affect the survival of patients with invasive epithelial ovarian carcinoma [14-16]. Moreover, variables such as disease stage, age at diagnosis and BMI as continuous variables were proven to be associated with progression-free survival [10]. Current smoking, having comorbidities and BMI ≥35kg/m^2 significantly correlate with a greater likelihood of dying [10]. This is the first study to investigate survival of advanced ovarian carcinoma patients and the influence of clinical and history parameters on patients survival in Bosnia and Herzegovina.

As expected, the FIGO stage is one of the most important independent prognostic factors for invasive epithelial ovarian carcinoma outcomes. The 5-year relative survival rate is much worse for advanced stages (FIGO 3 and 4) compared with early disease. This emphasizes the essence of early diagnosis [14,16-18].

Ovarian cancer represents a heterogeneous group of tumors (low grade type 1 and high grade type 2 and 3) with different pathogenesis, clinical course and prognosis, histology and molecular characteristics [12]. In numerous studies the histological type of ovarian carcinoma is proven as a prognostic factor for patient survival [11,19]. Literature data showed that women with type 1 tumors, such as mucinous and endometrioid carcinoma, have better outcomes and prognosis than patients with type 2 serous carcinoma. On the other hand, histologicaly undifferentiated carcinomas or carcinosarcomas have shorter survival than serous carcinoma [11,14]. Nevertheless, compared with other histological subtypes, advanced stages of serous cystadenocarcinoma generally have a relatively good prognosis [19]. Conversely, some authors showed that histological subtype was not a significant prognostic factor in advanced epithelial ovarian cancer [16,20]. Our results correspond with these findings as we did not obtain significant link between histopathological findings and patient survival. Based on all literature data, which are quite inconsistent, it was recently concluded that the impact of histological subtype on survival of advanced ovarian cancer is not always consistent [16].

Large population-based studies found that the age at the time of diagnosis is a prognostic factor for survival of women with epithelial ovarian carcinomas [11,16]. Recent investigations found that the risk for death (HR) ranges from 1.85 for women younger than 40 years to 7.50 for women older than 70 years [11]. Numerous data confirm that women younger than 50 years have significantly longer survival than those aged 50-69 years, which in turn show significantly better prognosis than the age group of ≥70 years [14]. This might be due to better performance status, earlier stage and lower grade at presentation, improved response and more tolerance to chemotherapy of younger women [9]. Moreover, elderly ovarian cancer patients are also less likely to receive standard treatments and are more often treated conservatively than younger patients [14,16]. Still, in some studies association of age and survival was confirmed only for serous carcinomas, while the correlation was not significant for non-serous ovarian malignancies [17]. We proved that older age could shorten postoperative survival of patients with advanced-stage ovarian cancers.

Population-based studies indicate that the average age of women at the time of cancer diagnosis is 63 years and comorbidities are therefore frequent [5,13]. Symptoms/signs of other illnesses can even more mislead the diagnostic process and cause delay in treatment. Presence of chronic ill-

nesses may increase the risk of complications resulting in lowering the patient functional status. Therefore, these patients may tolerate anticancer treatment less well and may therefore receive treatment in a reduced/compromised form. Consequently, some studies found that after stratifying on comorbidity level, both 1-year and 5-year survival was the lowest for women with high comorbidity scores [5,13]. In our sample, although the majority of women were postmenopause, comorbidities were not frequent. Nevertheless, having comorbidities was found to have significant influence on survival from advanced-stage of ovarian cancer.

The link between BMI and survival of patients with ovarian cancer is still uncertain [15]. Some studies [21,22] found that obesity does not negatively impact surgical outcomes, prognosis or survival when controlling for adequate cytoreduction and whether the patient received optimal adjuvant therapy. Conversely, results from other studies suggest that obesity was independently associated with both shorter time to recurrence and overall survival [12,23]. BMI prior to and after diagnosis, as well as weight gain during adulthood, has also been associated with an increase in ovarian cancer mortality. The role of obesity, which is a modifiable risk factor, may be multifactorial. Obese women usually have higher insulin resistance, bioavailability of sex hormones and chronic inflammation that may promote tumor metastases [12,23]. Furthermore, some findings imply that ovarian tumors from type 1 group are more influenced by the obese environment [12,23]. This is in accordance with the findings of our study. We showed that obesity was a risk factor for shorter postoperative survival after adjusting for histological type of tumor.

Limited data is available regarding the potential influence of parity on the prognosis of ovarian carcinoma. According to available data in univariate analysis both gravidity and parity were found to be significant predictors of patient survival. Still, this association was not confirmed in multivariate analysis [20]. We also did not find significant relationship of parity and postoperative survival time. Nevertheless, further studies on this matter are needed

Conclusions

This study included 163 patients whose median survival time was 22.77 months. Almost 74% of women had 1-year survival, but only 12.9% survived for 5 years. In the postoperative period, each additional 6 months presented a significant risk for unfavorable outcome. Postmenopausal women, especially if older than 65 years, with other gynecological or chronic illnesses had a significantly shorter postoperative survival time. On the contrary, patients with BMI ≤25kg/m^2 had significantly longer postoperative survival. Patient parity, presence of symptoms or positive family history did not significantly impact postoperative survival. Based on two significant models adjusted for FIGO stage and histological tumor type that were obtained, the most important predictors of advanced ovarian carcinoma patient survival from a pool of history and clinical patient characteristics were having comorbidities and being overweight.

Conflict of interests

The authors declare no confict of interests.

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