

## PROGNOSTIC FACTORS IN EPITHELIAL OVARIAN CARCINOMA: A REFERENCE INSTITUTION EXPERIENCE

Tufan ÖGE, S. Sinan ÖZALP, Ömer T. YALÇIN

Department of Obstetrics and Gynecology, Osmangazi University School of Medicine, Eskisehir, Turkey

### SUMMARY

**Aim:** To evaluate epidemiologic and prognostic factors of the patients with epithelial ovarian cancer retrospectively and to investigate the factors that effect overall survival.

**Material and methods:** Between January 1990 and December 2004, 149 patients with malign epithelial ovarian tumor were included to this study. Age, parity, primary complaint and postoperative histopathology, surgical stage and maximal diameter of residual tumor of the patients were obtained and factors that effect overall survival were evaluated.

**Results:** Mean age of the patients was  $52.8 \pm 13$  years. Most of the patients were multipar (85.9%) and most frequent (n: 88) (59.1%) complaint was abdominal swelling. Postoperative surgical stages were stage I in 24 (16.1%), stage II in 11 (7.4%), stage III in 87 (58.4%) and stage IV in 27 (18.1%) patients. Maximal diameter of residual tumor was  $<1$  cm in 68 patients (45.6%),  $\geq 1$  cm in 57 patients (38.3%) while there was no residual tumor in 24 patients (16.1%). Histopathologic cell types distributed as: serous (53.6%), endometrioid (16.7%), mucinous (10.7%), clear cell (10.7%), others (7.8%). The patients  $<65$  years old had similar overall survival compared to those who were  $\geq 65$  years old ( $p > 0.05$ ). The mean overall survival of the patients with maximal residual tumor size  $\leq 1$  cm,  $> 1$  cm and no residual tumor were obtained to be 54.8 months, 22.7 months and 43.5 months respectively ( $p < 0.001$ ). According to the surgical stages I, II, III and IV mean survival was 78.5 months, 60.1 months, 33.9 months and 16.1 months respectively and significantly different ( $p < 0.001$ ).

**Conclusion:** The data of the study revealed that surgical stage and postoperative maximum residual tumor diameter had significantly effect on overall survival where it was not effected by the age of the patients in epithelial ovarian cancers. So, early diagnosis and optimal cytoreduction should be attempted to improve the prognosis of the patients.

**Key words:** epidemiologic factors, epithelial ovarian cancer, prognosis

*Journal of Turkish Society of Obstetrics and Gynecology, (J Turk Soc Obstet Gynecol), 2011; Vol: 8 Issue: 1 Pages: 51-6*

### ÖZET

#### EPİTELİYAL OVER KANSERLERİNDE PROGNOZİK FAKTÖRLER: BİR REFERANS MERKEZİNİN DENEYİMİ

**Amaç:** Over kanserli vakaları retrospektif olarak inceleyerek, epidemiyolojik ve prognostik faktörleri araştırmak ve sağkalıma etki eden parametreleri incelemek.

**Gereç ve yöntemler:** Ocak 1990 - Aralık 2004 tarihleri arasında kliniğimizde takibi yapılan 149 malign epitelyal over tümörlü vaka incelendi. Hastaların yaşı, paritesi, primer şikayetleri, postoperatif tümör histopatolojileri, cerrahi evreleri ve maksimum rezidü tümör çapları kayıt edilerek bu parametlerin sağkalımlarına etkisi değerlendirilmiştir.

**Bulgular:** Hastaların ortalama tanı yaşı  $52.8 \pm 13$  yıl olarak saptanmıştır. Olguların büyük çoğunluğu (%85.9) multipar olup, en sık şikayet (n: 88 %59.1) karın şişliği olarak tespit edilmiştir. Cerrahi sonrası hastaların 24'ü

**Address for Correspondence:** Dr. Tufan Öge, Esmangazi Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum ABD, 26480 Eskişehir, Turkey  
Phone.: +90 (222) 229 20 02  
e-mail: tufanoge@yahoo.com

Received: 20 January 2010, revised: 11 October 2010, accepted: 12 November 2010, online yayın tarihi: 15 December 2010

(%16.1) evre I, 11'i (%7.4) evre II, 87'si (%58.4) evre III ve 27'si (%18.1) evre IV ve rezidü tümör çapları, maksimum 1 cm olan 68 (%45.6), 1 cm ve üzerine olan 57 hasta (%38.3) saptanmış, 24 hastada ise (%16.1) rezidü tümör kalmadığı saptanmıştır. Histopatolojik olarak: seröz (%53.6), endometrioid (%16.7), müsinöz (%10.7), berrak hücreli (%10.7), diğer (% 7.8) tespit edilmiştir. Yaşı < 65 olan hastaların sağkalımlarının yaşı ≥65 olanlarla benzer olduğu belirlenmiştir (p>0.05). Postoperatif rezidü tümörü kalmayan grupta ortalama yaşam süresi 43.5 ay bulunurken, 1 cm'nin altı ve 1 cm'nin üstünde tümör kalan gruplarda ise ortalama yaşam süresi sırasıyla 54.8 ve 22.7 ay olarak bulunmuştur. (p<0.001). Hastaların evrelerine göre ortalama yaşam süreleri evre I, evre II, evre III ve evre IV'de sırasıyla 78.5 , 60.1 , 33.9 ve 16.1 ay olarak tespit edilmiştir (p<0.001).

**Sonuç:** Araştırmamızda yaşın prognoz üzerine önemi saptanmazken, evre ve postoperatif rezidü tümör çapı sağkalıma etki eden faktörler olarak saptanmıştır. Hastaların daha iyi prognozu için over kanserini erken evrede yakalamak ve opere edilen olgularda rezidü tümör çapını maksimum derecede küçültmek hedeflenmelidir.

**Anahtar kelimeler:** epidemiyolojik faktörler, epitelial over kanseri, prognoz

**Türk Jinekoloji ve Obstetrik Derneği Dergisi, (J Turk Soc Obstet Gynecol), 2011; Cilt: 8 Sayı: 1 Sayfa: 51- 6**

## INTRODUCTION

In women, ovarian cancer is the fifth most common cancer, it is the second most common one among the gynecologic cancers, and the most common cause of gynecologic cancer deaths<sup>(1,2)</sup>. The incidence of ovarian cancer increases with age, and the average age at diagnosis is 63. The highest incidence is in the age group of 75-79<sup>(2)</sup>. ovarian cancer symptoms might not be seen for a long time in the vast majority of women. Most of the time developing symptoms are not specific. For this reason, they are often at an advanced stage when they are diagnosed<sup>(3)</sup>. surgical staging is being performed in ovarian cancer, and since the stage has a great effect on the prognosis staging laparotomy is of great importance<sup>(4)</sup>. Treatment depends on the stage of the patient following primary surgery. The main purpose is surgically removing the maximum amount of tumor and leaving no tumor behind, because there is a significant relationship between the residual tumor volume and survival<sup>(5)</sup>.

The purpose of this study is to review the cases of epithelial ovarian cancer retrospectively and to investigate the epidemiological and prognostic factors, to examine the parameters influencing the survival.

## MATERIALS AND METHODS

In this research 149 cases among the 289 cases of malignant ovarian tumor with a planned treatment, that were diagnosed in Eskisehir Osmangazi University School of Medicine, Department of Obstetrics and

Gynecology, Gynecologic Oncology Unit during the period of January 1990 and December 2004, whose file and prognostic information were approachable were included and permission was provided from University Research Ethics Board with a date of 28/09/2006 and sequence number of 07. After the information of the patients were provided from the patient files and operation book they were evaluated retrospectively. During these evaluation age of the patient, parity and complaints were recorded. Staging laparotomy was performed after the preoperative evaluation. With a preferred vertical midline incision during the first attempt acid fluid was taken. When there was no acid fluid sample for cytologic examination was obtained by washing. All the intra-abdominal organs such as the lower side of diaphragm, liver surface, small intestine and colon was palpated and biopsies were taken from suspected areas. Both ovaries, tubes, uterus and omentum were removed along with the tumor tissue that could be removed. Retroperitoneal pelvic and para-aortic lymph nodes were dissected until the level of the IMA and lymph node sampling was performed. In cases with an extensive tumor as much tumor tissue as possible was excised in order to reduce the volume of residual tumor. Pathology reports were evaluated according to FIGO staging. The postoperative pathologic diagnosis of primary ovarian cancer cases were included in the study. From the file records stage and survival of the patient were evaluated by the maximum diameter of tumor remaining after the surgery. Statistical Package for the Social Sciences (SPSS) for Windows 13.0 was used for statistical calculations and comparisons. While Kaplan-Meier

test was used for the analysis of survival, log rank test was used for the comparison of these curves. Data were given as arithmetic mean  $\pm$  standard deviation and p values of  $<0.05$  was considered as statistically significant.

## RESULTS

The age of the patients at diagnosis were between 19-80, and the average age was found as  $52.8 \pm 13$ . The most common application was in the age group of 51-60 with 52 patients (34.9%), and this was followed by 38 (25.5%) and 26 (17.4%) patients in the age groups of 61-70 and 41-50, respectively (Table I). When the distribution of parity was examined the vast majority of patients (85.9%) were multiparous, in 68 patients (45.6%) the parity was 4 or above, and in 60 of them (40.3%) had a parity between 1-3. The number of nulliparous patients were found 21 (14.4%). When the patients were evaluated according to complaints at the first application abdominal swelling was found in 88 cases (59.1%), abdominal pain in 31 patients (20.8%), vaginal bleeding in 14 cases (9.4%), pelvic pain in 13 patients (8.7%) and 3 cases were asymptomatic, but during the routine gynecological examination adnexial mass was found. Following the surgery 24 patients (16.1%) were found stage I, 11 (7.4%) of them stage II, 87 (58.4) in stage III and 27 (18.1%) were stage IV. In addition, small bowel resection was performed in nine patients and splenectomy was performed in three patients. Tumor implants were detected in spleen in three of the patients and in liver in seventeen of the patients, and four patients had pleural effusion. Pelvic and paraaortic lymph node metastases in stage I, II, III and IV were found as 8.3%, 27.2%, 55.1%, 66.6%, respectively. After the operation, no residual tumor was detected in 24 patients (16.1%), while in 68 patients the maximum diameter of remaining residual tumor was 1 cm (45.6%), and in 57 patients it was found 1 cm and over (%38.3).

Histopathological evaluation of these cases revealed the cell types as following: serous in 80 patients (53.6%), endometrioid in 25 patients (16.7%), mucinous in 16 cases (10.7%), clear cell in 16 cases (10.7%), and others in 12 patients (7.8%).

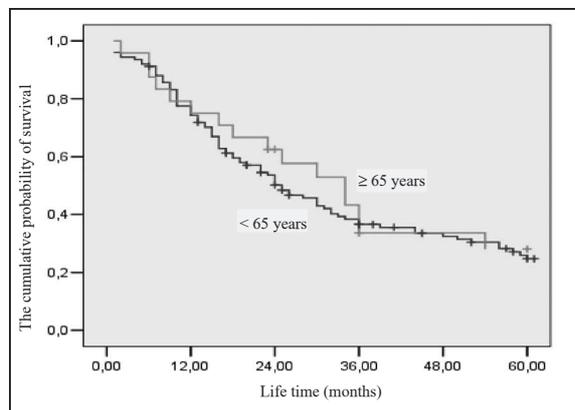
**Table I:** Patient and clinicopathological features (n=149).

	Patient number (n)	Value percent (%)
Age		
<30	11	7.3
31-40	14	9.4
41-50	26	17.4
51-60	52	34.9
61-70	38	25.5
71-80	8	5.4
Parity		
0	21	14.1
1-3	60	40.3
$\geq 4$	68	45.6
Complaint		
Abdominal distension	88	59.1
Abdominal pain	31	20.8
Vaginal bleeding	14	9.4
Groin pain	13	8.7
Detected in control	3	2.0
Histopathology		
Serous	80	53.6
Endometrioid	25	16.7
Mucinous	16	10.7
Clear cell	16	10.7
Other	12	1.2
Stage		
I	24	16.1
II	11	7.4
III	87	58.4
IV	27	18.1
Maximum residual tumor (cm)		
0	24	16.1
<1	68	45.6
$\geq 1$	57	38.3

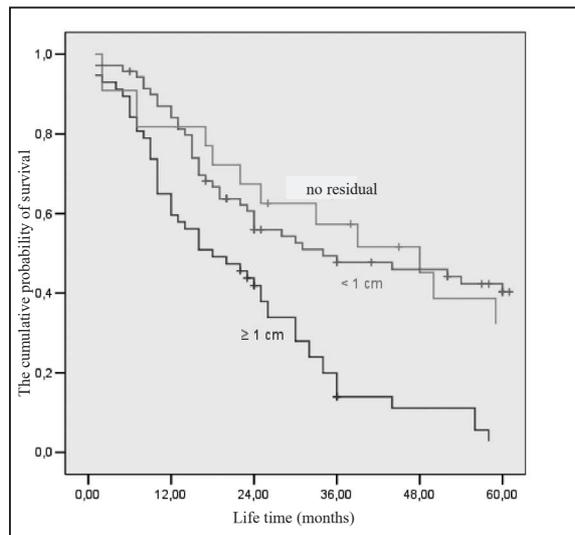
When the patients were classified as older or younger than 65 years-old and the effect of age on survival was investigated there was no significant difference between the two groups ( $p > 0.05$ ) (Table II, Figure 1). According to maximum diameter of tumor left behind after the operation the median survival time in the group with no residual tumor was found 43.5 months, while in the groups with a residual tumor below 1 cm or over 1 cm the average survival time was found as 54.8 and 22.7 months, respectively, and the decreased survival time in the group with a residual tumor over 1 cm was statistically significant ( $p < 0.001$ ) (Figure 2). When the average survival time of patients according to the stage was evaluated the mean survival time in stage I, stage II, stage III and stage IV were 78.5 months and 60.1 months, 33.9 months and 16.1 months, respectively, and a statistically significant difference was found between the groups ( $p < 0.001$ ) (Figure 3).

**Table II:** Prognostic factors affecting the average survival time.

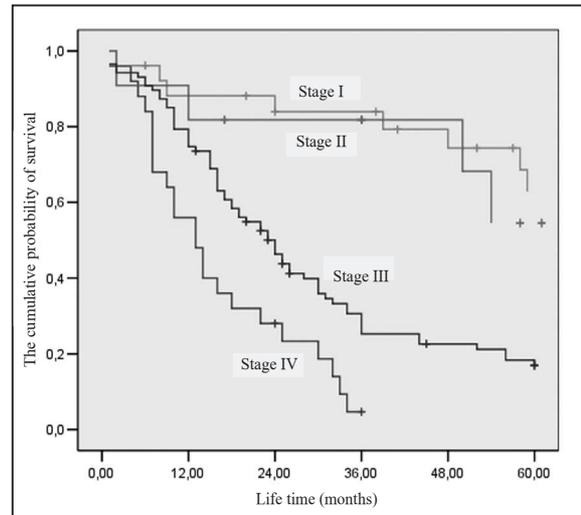
	Average survival time (month)	Standard error	p
Age			
<65	41.2	4.2	
≥65	48.0	10.7	>0.05
Stage			
I	78.5	10.8	
II	60.1	8.9	
III	33.9	4.2	
IV	16.1	2.1	<0.001
Maximum residual tumor (cm)			
0	43.5	6.4	
<1	54.8	6.5	
≥1	22.7	2.3	<0.001



**Figure 1:** Survival by age groups.



**Figure 2:** The maximum diameter of residual tumor according to the times.



**Figure 3:** According to the stages of life times.

## DISCUSSION

Epithelial ovarian cancer is commonly seen in perimenopausal and postmenopausal women, while the incidence of peak period is emphasized as the 60 years of age<sup>(6)</sup>. The mean age in our patients was  $52 \pm 13$  years and in the vast majority of cases the ages were between 51-70 with a rate of 60.4%. Scholz et al<sup>(7)</sup> retrospectively evaluated Stage IV ovarian cancer cases and found the average age as 59.9 (37-76)<sup>(7)</sup>. In another study, it was emphasized that approximately 85% of patients with ovarian cancer are over 50 years-old<sup>(8)</sup>. Ovarian cancer appears to be particularly a disease of an advanced age, and it is almost hiding behind the curtain of a fog because of other diseases accompanying at this age and complaints depend on them. In our study abdominal distension was seen in 59.1% of patients and was the most common complaint which was followed by abdominal pain with a rate of 20.8%. vaginal bleeding was found in 8.7%, and pelvic pain was found in 8.7%. In accordance with our study Olson SH et al.<sup>(9)</sup> also reported abdominal fullness, swelling and pressure sensation as the most common complaint (71%), and the second most frequent complaint was reported as abdominal pain (52%). These non-specific symptoms cause delays in diagnosis, thus patients are often diagnosed at an advanced stage. 16.1% of our cases were at stage I, and 7.4%, 58.4% and 18.4% of the patient were at stage II, stage III and stage IV, respectively. Also in the literature the rate of stage I, II, III and IV patients were as 17-21%, 7-10%, 49-52% and 20-24%, respectively<sup>(10,11)</sup>. When

the cases were evaluated according to the maximum diameter of residual tumor after the operation performed in our clinic, 16.1% of cases did not have remaining tumor left, 45.6% of the cases had residual tumor below 1 cm, and 38.3% of the cases had residual tumor over 1 cm. While the importance of the diameter of residual tumor was emphasized in the literature, when the operations were evaluated cases with a tumor diameter below 1 cm ranges from 33% to 67%<sup>(12,13)</sup>. The cases of our clinic are consistent with the literature. In addition the need for experienced surgeons in this subject for optimal cytoreduction is emphasized and in the literature the differences in the distribution of patients were explained in this way<sup>(14)</sup>.

In our study, there was no significant effect of age on survival. Similarly, studies in the literature investigating the prognostic significance of age studied the survival time of patients as well, and emphasized that young age is an independent prognostic factor<sup>(15,16)</sup>. Another study in which only the reproductive period was evaluated revealed that age does not have a prognostic effect on survival<sup>(17)</sup>. However, the duration of survival in the geriatric group was significantly less than the group of non-elderly, and there are studies showing that even if adjusting for stage and residual disease is performed older groups have lower survival rate<sup>(18,19)</sup>. The majority of studies show that there is a larger tumor left post-operatively in older patients and that the patients have a shorter survival time. In these studies, it has been emphasized that aggressive surgery cannot be performed in the geriatric group, that is why the residual tumor diameter might be larger in size<sup>(18-21)</sup>. In our study, while we had 125 cases under 65 years-old, we had 24 cases over 65 years-old and due to this small number of geriatric patients a meaningful conclusion could not be reached.

The studies emphasized that maximum diameter of residual tumor remaining after the operation has a prognostic value<sup>(22,23)</sup>. In our patients the mean survival time of patients with no residual tumor or residual tumor <1 cm were similar, while the decrease in mean survival time of patients with residual tumor 1 cm or more was statistically significant (Figure 4.3). In the literature the definition of optimal surgery according to remaining residual tumor diameter has changed in the recent years. In 1970s  $\leq 2$  cm was sufficient for optimal surgery<sup>(24,25)</sup>. Afterwards, in the early 1980s optimal surgery was defined as  $\leq 3$  cm, and in the late

1980s it has been revised as  $\leq 1$  cm<sup>(26,27)</sup>. In accordance with our study, publications in the literature also indicate the maximum residual tumor diameter as a prognostic factor and observed that survival increases as the residual tumor size decreases<sup>(12,13,22,23)</sup>. In our study, although the survival time in the group with a residual tumor diameter <1 cm was not statistically different, the fact that it is 11.3 months better than the group with no residual tumor could be explained by the small number of cases or with the discussion that cases with a residual tumor <1 cm could be considered as optimal as well.

When the survival of the patients were evaluated according to the stage the average survival time in Stage I, II, III, and IV were 78 months, 60 months, 33 months and 16 months, respectively. Another study, in accordance with our study, stated survival diminishes as the stage advances by showing that 5-year survival rates were 72% in patients at early stage (stage I-II), and 27% in patients with advanced stages of disease<sup>(28)</sup>. In another 5-year survival rates of stage I, II, III and IV were reported as 72% and 42%, 21% and 6%, respectively, and stage was emphasized as the prognostic factor concerning the survival<sup>(10)</sup>. In the literature, even though there is a consensus on decreased survival by the advanced stage, the survival times vary. In a study remarking on this variety, the mean time in the advanced cases were emphasized as 12-21 months and it was stated that ovarian cancer surgery should be performed by the gynecologic oncologists<sup>(29)</sup>.

In conclusion, stage and residual tumor size after surgery was found as the prognostic factors that influence the survival. For a better prognosis of patients, early diagnosis of ovarian cancer and in the cases operated maximum reduction in the residual tumor size should be targeted.

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