

Aim of the study: Fallopian tube cancer is very rare in the literature and so there are not enough data about the therapeutic approaches. The approaches are generally determined in accordance with the data obtained from ovarian cancer. Many prognostic factors have been investigated in an effort to better estimate patient outcome. Stage, age, and residual tumor after surgery are consistently important prognostic factors. In this study, we aimed to evaluate the prognostic factors and survival rates of primary fallopian tube cancer (PFTC), which is rare among gynecological cancers.

Material and methods: Thirty-eight patients with a diagnosis of PFTC were identified through the gynecologic oncology service database of our Research and Training Hospital in the period 1995–2013. Clinicopathological and surgical data were collected. All patients were evaluated for survival and disease-free survival between the dates specified.

Results: A significant relationship and correlation was found between optimal surgery and life expectancy. Better results were obtained in patients treated with optimal surgery. The survival probability was found to be higher in patients with lower CA-125 levels and serous histologic type adenocarcinoma.

Conclusions: Stage is one of the factors affecting the survival probability. We determined that the pathological type of tumor, the diameter of residual tumor remaining after surgery, tumor grade, preoperative CA-125 levels and presence of ascites affect the survival probability.

Key words: primary fallopian tube cancer, prognostic factor, management and treatment.

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Prognostic factors of primary fallopian tube carcinoma

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Introduction

Primary fallopian tube carcinoma (PFTC) is a rare neoplasm, accounting for 0.3–1.6% of all gynecological malignancies [1, 2]. Because of the fallopian tube neighborhood, secondary fallopian tumors are more commonly seen. Due to its clinical and histologic similarity to ovarian cancers, PFTC is treated as ovarian cancer. Primary fallopian tube carcinoma can show sequential growth or it may be associated with other cancers. It has been reported that 25% of the cases have another cancer before PFTC and 22% of the cases have another gynecological cancer simultaneously [3].

Primary fallopian tube carcinoma was described for the first time in 1847 by Rokitsansky and in 1861 by Renaud. It usually occurs between 50 and 60 years of age. The youngest patient reported in the literature is 19 years old, the oldest 87 years old. The mean age is between 52.7 and 57. Approximately 90% of PFTCs are adenocarcinomas and most of them are serous and endometrioid types [1, 2].

The spread pattern is similar to ovarian cancer. Primary fallopian tube carcinoma spreads very quickly, so the number of patients diagnosed early is very small. Generally, the diagnosis is made during operations performed for other reasons. It is most commonly spread by intraperitoneal and lymphoid routes. However, unlike ovarian cancer, PFTC has higher rates of retroperitoneal and distant metastases [4]. It has no obvious symptoms and 20% of patients are asymptomatic. The most common symptom is vaginal bleeding. Fifty percent of patients have vaginal bleeding. Discharge or bleeding is accompanied by pain in 26–50% of patients and a palpable mass may be present in the pelvic area. The International Federation of Gynecology and Obstetrics (FIGO) also adapted the staging of ovarian cancer to PFTC and suggested that it is surgically staged like ovarian cancer.

Primary fallopian tube carcinomas are rare, so there are insufficient data on treatment approaches in the literature. The approaches are generally determined in accordance with the data obtained from ovarian cancer. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and infracolic omentectomy, appendectomy, peritoneal washing, and peritoneal biopsy constitute the primary treatment of choice for PFTC; inclusion of pelvic and para-aortic lymphadenectomy has been controversial [5].

The overall 5-year survival for patients with PFTC is 22–57% [6]. Many prognostic factors have been investigated in an effort to better estimate patient outcome. Stage, patient age, and residual tumor after initial surgery are consistently important prognostic factors. In addition, according to some reports, a closed fimbriated end of the fallopian tube, positive peritoneal cytology, lesion site within the tube (fimbrial vs. non-fimbrial), human epidermal growth factor receptor 2/nu-positive expression, p53 alteration, elevated pretreatment cancer antigen 125 (CA-125), and lymphovascular space involvement are also important prognostic factors [6, 7].

In this study, we aimed to evaluate the prognostic factors and survival rates of PFTC, which is rare among gynecological cancers.

Material and methods

Thirty-eight patients with a diagnosis of PFTC were identified through the gynecologic oncology service database of our Research and Training Hospital in the period 1995–2013. Clinicopathological and surgical data were collected. All patients were evaluated for survival and disease-free survival (DFS) between the dates specified. Cases were identified according to the PFTC diagnostic criteria established by Hu *et al.* [8] and modified by Sedlis [9]. The following clinical data were collected from patient medical, surgical, pathological, and chemotherapy reports: demographic characteristics, presenting symptoms, serum CA-125 level, date and type of surgical procedure, presence or absence of residual tumor after surgery, number of excised and positive lymph nodes, presence or absence of ascites, tumor pathological characteristics (grade and size), type of first-line chemotherapy, date of recurrence, treatment after recurrence, date of last medical examination, and date of death. Federation of Gynecology and Obstetrics (FIGO) staging according to the 2009 revised classification system was used. Patients were classified as not having been staged if only a unilateral salpingo-oophorectomy, total hysterectomy with unilateral or bilateral salpingo-oophorectomy with or without omentectomy was performed. Partial staging was defined as pelvic washing, peritoneal biopsy, omentectomy, bilateral pelvic lymph node dissection with a unilateral salpingo-oophorectomy, or total hysterectomy with unilateral or bilateral salpingo-oophorectomy. Complete staging was defined as pelvic washing, peritoneal biopsy, omentectomy, bilateral pelvic and para-aortic lymph node dissection with a unilateral salpingo-oophorectomy, or total abdominal hysterectomy with unilateral or bilateral salpingo-oophorectomy. Optimal debulking was defined as a procedure that left a maximum residual tumor < 1 cm in diameter. Patients returned for a follow-up evaluation every three months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually. The survival analysis was based on the Kaplan-Meier method, and the results were compared using the log-rank test. Progression-free survival (PFS) was defined as the time from the date of primary surgery to detection of recurrence or the latest observation. Overall survival (OS) was defined as the time from the date of primary surgery to death or the latest observation. The χ^2 test and Student's *t* test for unpaired data were used for the statistical analysis. Cox regression analysis was used to determine factors affecting survival, and results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS ver. 11.5). A *p*-value of < 0.05 was considered significant.

Results

The average patient age was 55 years and ages ranged from 30 to 72. Vaginal bleeding was observed as the most common complaint. It was observed that most of the patients were menopausal during diagnosis. 42.1% of cases were considered adnexal masses and 57.9% of them were considered ovarian cancer in the preoperative period. The distribution of CA-125 values was 5–802 U/ml preoperatively and the distribution of tumor size was 2–14 cm. Ascites was present in 21.8% of patients. After different surgical procedures, residual tumor was determined as 1 cm or less in 65.8% and more than 1 cm in 34.2% of patients. Sixteen patients (42.1%) had FIGO stage I disease, 5 (13.2%) had stage II, and 17 (44.7%) had stage III disease. A detailed description of the operative procedures performed is shown in Table 1. Optimal surgery with residual tumor < 1 cm was achieved in 65.8% of cases. When the postoperative grade was examined, 78.9% of the cases were grade 3. When postoperative pathologies were examined, 63.2% of the cases were found to be serous adenocarcinoma type and 89.5% of the patients had received adjuvant chemotherapy. Demographic and morphological characteristics of the patients are summarized in Table 1.

At patient follow-up, a significant relationship between survival probability and stage at the time of diagnosis was found (Fig. 1).

A significant relationship and correlation was found between optimal surgery and life expectancy. Better results were obtained in patients treated with optimal surgery (Fig. 2).

Survival probability was found to be higher in patients with lower CA-125 levels and serous histologic type adenocarcinoma (Figs. 3 and 4).

Survival probability was found to be higher in patients without ascites (Fig. 5).

Patients with higher grade tumors were found to have lower survival probability during follow-up (Fig. 6).

Results of univariate and multivariate analyses carried out to determine the effect of demographic characteristics and clinical features on median survival are provided in Table 2.

Discussion

Primary fallopian tube carcinoma (PFTC) is a rare neoplasm, accounting for 0.3–1.6% of all gynecological malignancies [1, 2]. The incidence of PFTC is 0.41 per 100,000 women in the United States. The incidence of PFTC varies depending on age. It is 0.02 per 100,000 young women, but the rate rises to 1.63 per 100,000 after age 70. Unlike PFTC, a downward trend has been observed in the incidence of ovarian cancer in the US over the years [10]. There are also opinions that the real incidence may be higher due to the difficulties in diagnosis [11, 12].

In the literature, the mean age of patients with PFTC is 55 years [6]. The mean age and menopausal status of the patients in our study were in accordance with the literature. The average age of the patients in our study was 55, while 47.4% of the patients were younger than 60 years and 52.6% were older than 60 years. Age was not found

to be statistically significant for DFS or OS time in univariate and multivariate analyses. 73.7% of the patients were menopausal during diagnosis. Schneider *et al.* [13] reported that PFTC is diagnosed at an earlier stage than ovarian cancer, possibly as a result of abdominal pain resulting from tubal distention and intermittent serosanguineous discharge. During the diagnosis 73.7% of patients were in menopause. The symptoms of the patients in our study were consistent with the literature. Abnormal vaginal bleeding was detected in 21.1% of patients and 13.2% of patients complained of pain and swelling. Because PFTC usually spreads very quickly, early diagnosis of PFTC is extremely difficult. Primary fallopian tube carcinoma is usually diagnosed by operations performed for another reason. The preoperative diagnosis rate is 0.3–15% [14, 15]. Preoperative diagnosis is usually ovarian tumor or pelvic abscess in many patients and diagnosis is difficult before the laparotomy. The study involving 26 patients by Yu-Jin Koo *et al.* showed that 65.4% of cases were diagnosed as adnexal masses, and 23.1% of them were diagnosed as hydrosalpinx preoperatively [16]. In our study, preoperatively 57.9% of the patients were diagnosed with ovarian cancer and 42.1% of them were diagnosed with adnexal masses.

There is no specific tumor marker for PFTC. However, CA-125 is often used as a tumor marker for fallopian tube carcinomas like ovarian malignancy [17]. CA-125 levels are lower in the early stages but higher at advanced stages [3]. Pre-treatment CA-125 levels are an independent prognostic factor for disease-free survival and overall survival. The median time between the increase in CA-125 levels during the follow-up and the appearance of clinical and radiological recurrences is 3 months (0.5–7 months) [15]. In our study, preoperative CA-125 levels were between and 802 U/ml and the average level of CA-125 was 41.5 U/ml. In our study, there was statistically significant relationship between the CA-125 levels and the survival probability. The survival rate of the patients who had low CA-125 levels were higher at the time of diagnosis (HR: 3.7; 95% CI: 1.6–8.4; $p = 0.003$). In this study CA-125 was found to be statistically significant for DFS and OS time in univariate analyses but not in multivariate analyses.

Tumor grade of the patients included in our study was consistent with the literature [1, 4]. 5.3% of patients had grade 1, 15.8% had grade 2, and 78.9% had grade 3. An inverse association was found between tumor grade and survival probability (HR: 1.3; 95% CI: 0.6–2.7; $p = 0.42$).

In a study by E. Kalampokas and colleagues 15% of the patients had acid [6]. Our study was compatible with the literature and 21.8% of our patients had preoperative acid. When the survival rate was compared according to the presence of preoperative acid, the survival rate was higher in non-acidic patients. (HR: 3.4; 95% CI: 1.4–8.0; $p = 0.01$). Presence of preoperative acid was found to be statistically significant for DFS and OS time in univariate and multivariate analyses.

During the diagnosis, the disease is a prognostic factor for the disease, and those with localized disease live longer than those with advanced disease [1]. In the studies of Rosen *et al.*, the 5-year survival rate for stage I and stage II cases was 59% and for stage III and IV cases was 19% [18].

Table 1. Demographic and morphological features

Parameter	No.	%
Age (years)		
≤ 60	18	47.4
> 60	20	52.6
Median range	55 (30–72)	
Menopause	28	73.7
Parity, median range	2.5 (0–5)	
Symptom		
Vaginal bleeding/discharge	8	21.1
Abdominal pain	5	13.2
Others	22	57.9
None	3	7.9
Presence of ascites	21.8	
Preoperative diagnosis		
Adnexal mass	16	42.1
Ovarian malignancy	22	57.9
CA-125 (U/ml), median (range)	41.5 (5.0–802.0)	
FIGO Stage		
I	16	52.1
II	5	13.2
III	17	44.7
IV	–	–
Grade		
I	2	5.3
II	6	15.8
III	30	78.9
No. of removed lymph nodes, median (range)		
Pelvic	13.5 (6–24)	
Para-aortic	10 (3–23)	
Recurrence	14	36.8
Duration of follow-up	34.5 (14–78)	
Disease-free survival	25.5 (11–76)	
Overall survival	34.5 (14–78)	
Surgical procedures		
USO	1	2.6
TAH + BSO	2	5.3
TAH + BSO + washing cytology + PLD + omentectomy	15	39.5
TAH + BSO + washing cytology + PPLD + omentectomy	20	52.6
Residual tumor at initial surgery (cm)		
≤ 1	25	65.8
> 1	13	34.2
Chemotherapy		
Yes	25	89.5
No	4	10.5
Radiotherapy		
Yes	38	89.5
No	100	10.5
Histological type		
Serous	24	63.2
Non-serous	14	36.8

USO – unilateral salpingo-oophorectomy; TAH – total abdominal hysterectomy; BSO – bilateral salpingo-oophorectomy; PLD – pelvic lymphadenectomy; PPLD – pelvic and para-aortic lymphadenectomy

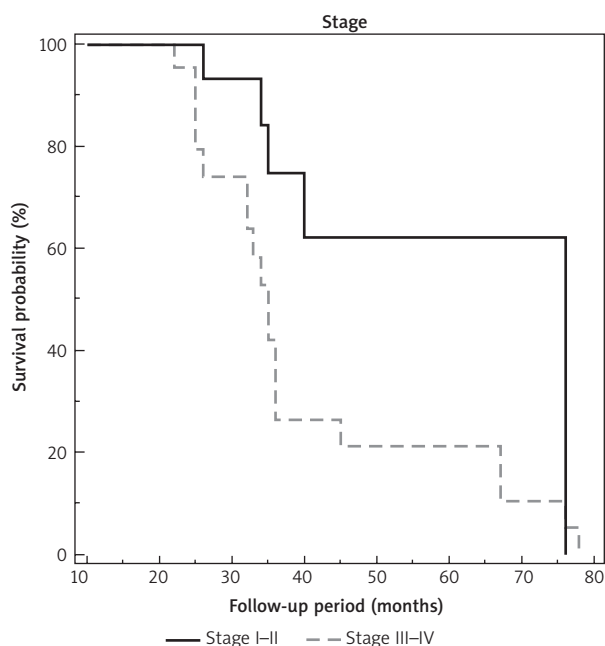


Fig. 1. Effect of stage of disease and survival probability (HR: 2.6; 95% CI: 1.1–5.9; $p = 0.02$)

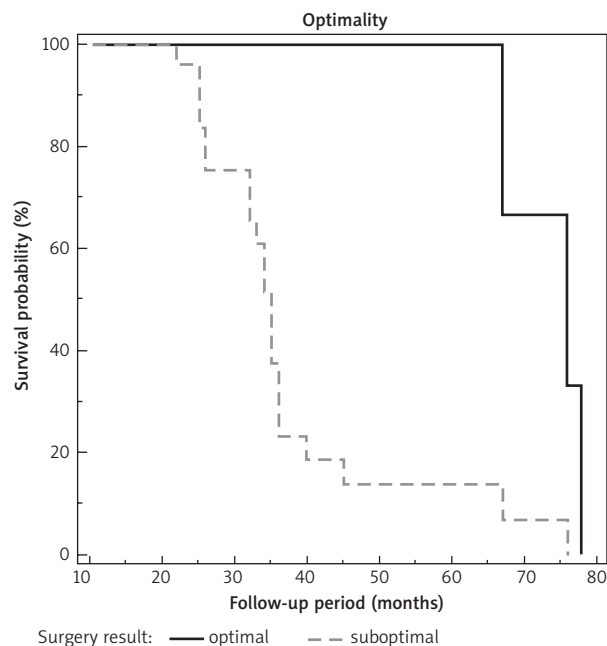


Fig. 2. Effect of optimality and survival probability (HR: 5.8; 95% CI: 2.6–13.0; $p = 0.0003$)

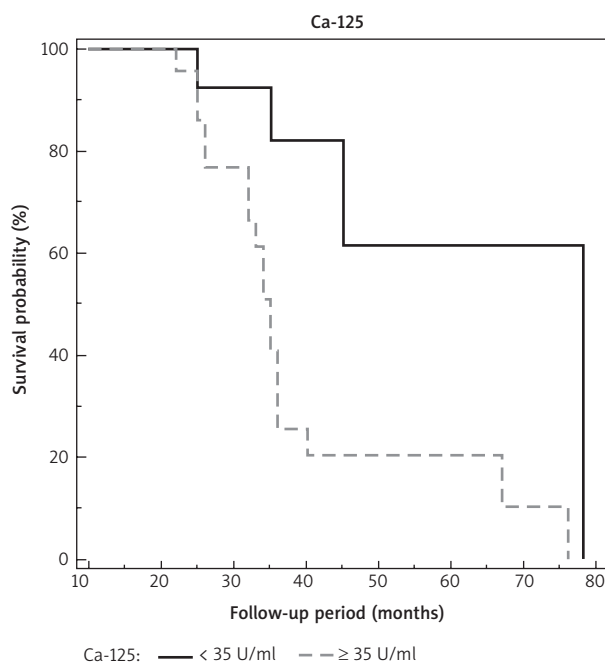


Fig. 3. Ca-125 and survival probability (HR: 3.7; 95% CI: 1.6–8.4; $p = 0.003$)

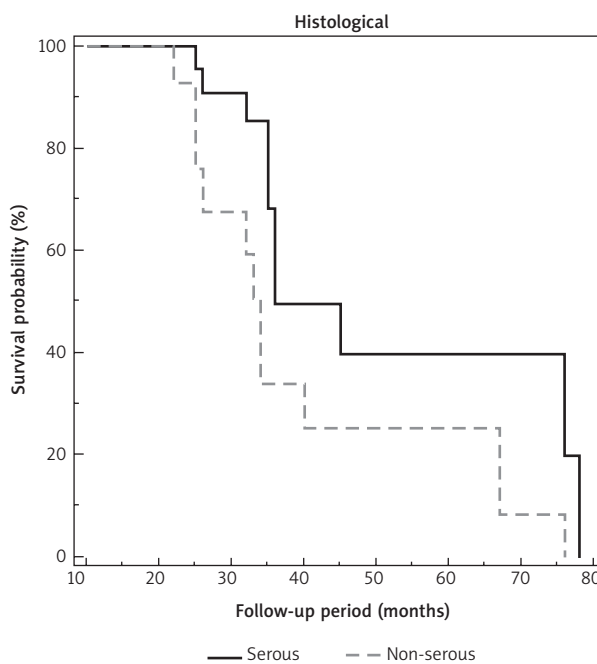


Fig. 4. Histological type and survival probability (HR: 2.1; 95% CI: 0.9–5.2; $p = 0.03$)

Our study was consistent with the literature and the relationship between stage and survival probability was found to be significant, and the survival probability of early stage patients was found to be higher (Fig. 1). Stage was found to be statistically significant for DFS and OS time in univariate and multivariate analyses.

The primary surgical principles in tubal carcinoma are as in ovarian cancer and include total abdominal hysterecto-

my, bilateral salpingo-oophorectomy, infracolic omentectomy and pelvic para-aortic lymphadenectomy. Peritoneal washing fluid should be taken at the beginning of laparotomy. Different surgical procedures were performed on patients in our study. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed in 5.3% of patients, unilateral salpingo-oophorectomy was performed in 2.6% of patients, total abdominal hysterecto-

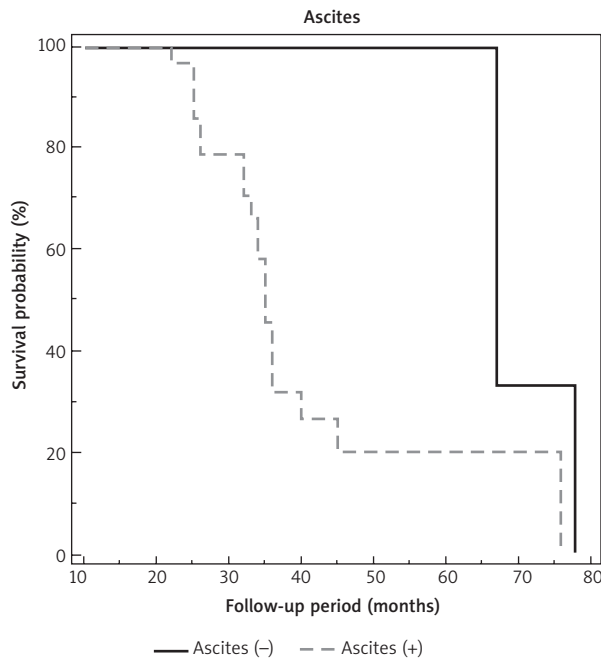


Fig. 5. Ascites and survival probability (HR: 3.4; 95% CI: 1.4–8.0; $p = 0.01$)

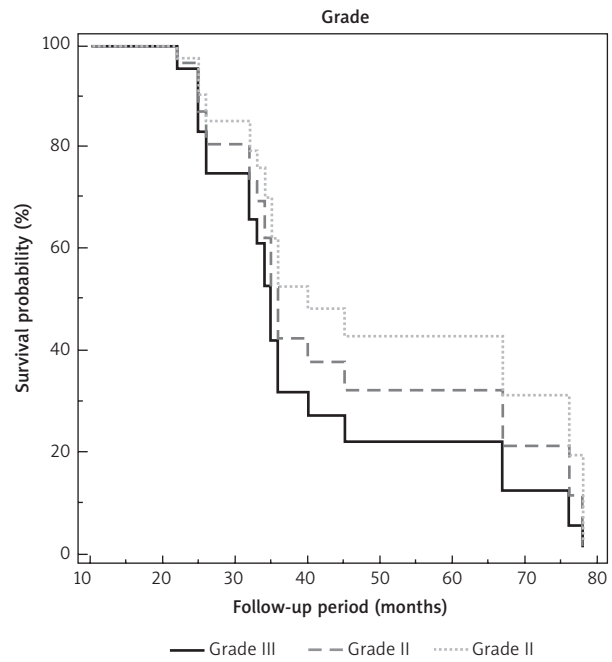


Fig. 6. Grade and survival probability (HR: 1.3; 95% CI: 0.6–2.7; $p = 0.42$)

Table 2. Univariate and multivariate analysis of prognostic factors

Parameter	Median survival (months)					
	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p -value	Hazard ratio	95% CI	p -value
Age (< 60 years vs. > 60 years)	1.8	6.2–8.1	0.97			
Comorbidity (presence vs. absence)	4.2	4.8–10.1	0.77			
Tumor stage (I/II vs. III/IV)	2.6	1.1–5.9	0.02	3.6	1.6–8.7	0.01
Tumor grade (I vs. II vs. III)	1.3	0.6–2.7	0.42			
Ascites (presence vs. absence)	3.4	1.4–8.0	0.01	2.1	1.3–5.8	0.03
Preoperative CA-125 value (< 35 U/ml vs. 35 U/ml)	3.7	1.6–8.4	0.003	1.3	0.4–3.8	0.61
Residual tumor size (< 1 cm vs. > 1 cm)	5.8	2.6–13.0	0.003	3.2	1.2–5.9	0.001
Histology (serous vs. non-serous)	2.1	0.9–5.2	0.003			

CI – confidence interval; CA-125 – cancer antigen 125; HR – hazard ratio

my and bilateral salpingo-oophorectomy with only pelvic lymph node dissection was performed in 39.5% of patients, total abdominal hysterectomy, and bilateral salpingo-oophorectomy with pelvic-para-aortic lymph node dissection was performed in 52.6% of patients. Residual tumor is an important prognostic factor after surgery. Survival of patients with remaining residue less than 1 cm is better so optimal cytoreduction should be performed [16]. In a study conducted in stage III–IV patients, the survival rate at 5 years was 55% for patients with a 1 cm or smaller residual tumor diameter and 21% for those with a larger residual diameter [4]. The median survival was 35 months in patients with residual tumor mass < 2 cm but > 11 months in patients with > 2 cm residual tumor, and this difference was statistically significant [18]. 65.8% of patients had < 1 cm

residual tumor but 34.2% of patients had > 1 cm residual tumor in our study. The survival probability of patients undergoing an optimal surgical procedure was found to be higher in this study (HR: 5.8; 95% CI: 2.6–13.0; $p = 0.0003$)

When the postoperative histopathologic findings of the patients were evaluated in our study, serous adenocarcinoma of 63.2% and nonserous adenocarcinoma of 36.8% were detected. In a literature review, Wethington *et al.* reported that 48% of patients had serous adenocarcinoma and 52% had nonserous adenocarcinoma [19]. Gadducci *et al.* reported that 59.1% of patients had serous adenocarcinoma and 40.9% of patients had nonserous adenocarcinoma [4]. In our study, the survival probability of patients with serous adenocarcinoma histopathology was found to be higher than the patients with non-serous adenocarcinoma his-

topathology according to the literature when the survival probabilities of the patients were compared with the survival histopathology (HR: 2.1; 95% CI: 0.9–5.2; $p = 0.03$).

In conclusion, stage is one of the factors affecting the survival probability. The pathological type of the tumor, the diameter of the residual tumor after surgery, the tumor grade, preoperative CA-125 levels and the presence of ascites were found to be factors influencing the survival probability. Among the independent factors determining the prognosis of the disease, it was found that the residual tumor amount was a factor that could change the effect. Although preoperative diagnosis of tubal carcinomas is impossible in the literature, it is observed that in the literature and in our series, a significant proportion of these patients (57.9%) were operated on with the pre-diagnosis of ovarian carcinoma. Therefore undergoing an operation by gynecological oncologists will affect the prognosis of patients. Complete staging and the amount of residual tumor less than 1 cm should be surgical purposes.

The authors declare no conflict of interest.

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