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Prognostic factors and oncological outcomes of ovarian yolk sac tumors: a retrospective multicentric analysis of 99 cases

Gokhan Boyraz[1] · Yasin Durmus[1] · Irfan Cicin[2] · Oguzhan Kuru[3] · Esra Bostanci[4] · Gunsu Kimyon Comert[1] · Hanifi Sahin[5] · Hulya Ayik[6] · Isin Ureyen[7] · Alper Karalok[1] · Mehmet Mutlu Meydanli[5] · Mehmet Coskun Salman[3] · Nejat Ozgul[3] · Anil Onan[4] · Tayup Simsek[6] · Kunter Yuce[3] · Taner Turan[1]

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Abstract

Purpose To investigate the clinico-pathological prognostic factors and treatment outcomes in patients with ovarian yolk sac tumors (YST).

Methods A multicenter, retrospective department database review was performed to identify patients with ovarian YST who underwent surgery between 2000 and 2017 at seven Gynecologic Oncology Centers in Turkey.

Results The study group consisted of 99 consecutive patients with a mean age of 23.9 years. While 52 patients had early stage (stage I–II) disease, the remaining 47 patients had advanced stage (stage III–IV) disease. The uterus was preserved in 74 (74.8%) of the cases. The absence of gross residual disease following surgery was achieved in 76.8% of the cases. Of the 54 patients with lymph node dissection (LND), lymph node metastasis was detected in 10 (18.5%) patients. Of the 99 patients, only 3 patients did not receive adjuvant therapy, and most of the patients (91.9%) received BEP (bleomycin, etoposide, cisplatin) chemotherapy. Disease recurred in 21 (21.2%) patients. The 5-year disease-free survival (DFS) and overall survival (OS) in the entire cohort were 79.2% and 81.3%, respectively. In multivariate analysis, only residual disease following initial surgery was found to be significantly associated with DFS and OS in patients with ovarian YST ($p=0.026$ and $p=0.001$, respectively).

Conclusions Our results demonstrate the significance of achieving no visible residual disease in patients with ovarian YST. Fertility-sparing approach for patients with no visible residual disease affected neither DFS nor OS. Although high lymphatic involvement rate was detected, the benefit of LND could not be demonstrated.

Keywords Ovarian cancer · Yolk sac tumors · Germ cell tumors · Endodermal sinus tumors · Residual disease

Introduction

Malignant ovarian germ cell tumors (MOGCTs) comprise a fairly small proportion (approximately %5) of all ovarian malignant neoplasm and occur primarily in young women [1, 2]. Yolk sac tumors (also known as endodermal sinus tumors) are the second most frequent form of malignant germ cell tumors following ovarian dysgerminoma, accounting for 14–20% of all MOGCTs [3, 4]. From histopathological point of view, yolk sac tumors originate from germ cells that differentiate toward extraembriyonic yolk sac [5]. Alpha-fetoprotein (AFP) is originated from two main sources including the fetal liver and the yolk sac. Therefore, this differentiation may explain the elevated serum AFP levels, and serum AFP levels are used not only for diagnostic process but also for follow-up after treatment in patients with ovarian yolk sac tumors [6].

Surgery is required for diagnosis, staging, and also treatment in patients with yolk sac tumors. Total hysterectomy with bilateral salpingo-oophorectomy, pelvic and paraaortic lymph node dissection, and omentectomy is the standard staging procedure for ovarian cancer. However, ovarian yolk sac tumors generally affect adolescents or young women. Therefore, fertility-sparing surgery is performed when possible, and for these patients, the uterus and the contralateral ovary could be preserved if these organs appear normal [7, 8]. Platinum-based adjuvant chemotherapy regimens have been used after surgery for ovarian yolk sac tumor similar to

✉ Gokhan Boyraz
gokhan.boyraz@gmail.com

Extended author information available on the last page of the article

other MOGCTs [9]. As a matter of fact, most of the recommendations related with ovarian yolk sac tumor are based on data from the other MOGCTs like dysgerminomas due to the rarity of these tumors. Consequently, the majority of the data related with ovarian yolk sac tumors are limited to small retrospective case series, and because there are no large series on prognostic factors and oncological outcomes in patients with ovarian yolk sac tumor, limited data are available. Therefore, we designed this multicenter retrospective study to investigate the clinico-pathological prognostic factors and treatment outcomes in patients with ovarian yolk sac tumors.

Materials and methods

This retrospective multicenter study included 7 participating gynecologic oncology centers from Turkey: Etlik Zubeyde Hanim Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences (Ankara), Zekai Tahir Burak Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences (Ankara), Trakya University Faculty of Medicine (Edirne), Hacettepe University Faculty of Medicine (Ankara), Akdeniz University Faculty of Medicine (Antalya), Antalya Education and Research Hospital Faculty of Medicine, University of Health Sciences (Antalya) and, Gazi University Faculty of Medicine (Ankara). From January 2000 and December 2017, patients who had been diagnosed with ovarian yolk sac tumor in the gynecology oncology division of each hospital were recruited. Research protocol was approved by the institutional ethics committee (Zekai Tahir Burak Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences, 28.09.2018/1) and all patients signed an informed consent that allows the participating institution to use their clinical data.

Original pathology reports of 99 patients who underwent surgical treatment for ovarian yolk sac tumor were analyzed. The clinical and pathological characteristics of the patients were evaluated, including patient's age, histologic subtype (mixed or pure type), preoperative serum AFP level, surgical procedure, stage, residual disease, lymph node metastasis, adjuvant therapy, recurrence, and survival. Ovarian yolk sac tumor was classified as pure (consisting of only yolk sac component) and mixed (including additional germ cell element, such as dysgerminoma) type histology. All operations were performed by gynecologic oncologists. The surgical procedures consisted of unilateral salpingo-oophorectomy or total hysterectomy with bilateral salpingo-oophorectomy, and staging procedures with lymph node dissection (LND), omentectomy, and cytology. All patients were staged according to the 1988 International Federation of Gynecology and Obstetrics (FIGO) staging system. If the patients did not have complete staging surgery including lymph node dissection, clinical staging was performed based on thoracoabdominal computed tomography. Adjuvant treatment decisions for all patients were made by gynecologic oncology tumor board in each center, and consisted of platinum-based chemotherapy. Patients entered a routine surveillance program, and visits were scheduled for every 3 months for the first 2 years, every 6 months until 5 years, and annually thereafter. The survival status of patients was determined as dead or alive at the time of last follow-up.

Statistical analyses were performed using SPSS software version 17.0 statistical package. Overall survival (OS) was calculated from time of diagnosis until death or time of last follow-up. Disease-free survival (DFS) was calculated from time of diagnosis until the diagnosis of disease recurrence. The Kaplan–Meier method was used to estimate OS and DFS, and survival differences were analyzed by log-rank test. Cox regression analysis was performed to account for the potential influence of confounding factors. Differences were considered statistically significant at $p < 0.05$.

Results

A total of 99 consecutive patients with a mean age of 23.9 years (range 10–68 years) were analyzed including 33 (33.3%) adolescent (≤ 18 years), 63 (63.6%) reproductive age (19–49 years) and 3 (3%) postmenopausal (> 50 years) patients. Of the 99 patients, 73 (73.7%) had pure ovarian yolk sac tumor, and the remaining 26 (26.3%) had mixed type histology. While 52 (52.5%) patients had early stage (stage I–II) disease, the remaining 47 (47.5%) patients had advanced stage (stage III–IV) disease. Only three (3%) patients had bilateral involvement of the ovaries. Although hysterectomy was performed in 25 (25.2%) patients, the uterus was preserved and fertility-sparing surgery was performed in the remaining 74 (74.8%) of the cases. The absence of gross residual disease following surgery was achieved in 76.8% of cases. While pelvic and paraaortic lymphadenectomy was performed in 54 (54.5%) patients, the remaining 45 (45.5%) patients did not have lymphadenectomy. Median number of removed lymph nodes was 22 (interquartile [IQ] range 15). Of the 54 patients with lymph node dissection, lymph node metastasis was detected in 10 (18.5%) patients. Among the 10 patients, 4 had isolated pelvic lymph node metastasis, 4 had both pelvic and paraaortic metastases, and 2 had isolated paraaortic metastasis. Of the 99 patients, only 3 (3%) patients did not receive adjuvant therapy, and 91 (91.9%) patients received BEP (bleomycin, etoposide, cisplatin) chemotherapy. The remaining 4 (4%) patients had VBP (vinblastine, bleomycin, and cisplatin) and 1 (1%) had EP (etoposide and cisplatin). The clinical and

pathological characteristics of the cases are summarized in Table 1.

Disease recurred in 21 (21.2%) patients. Characteristics of patients with recurrent disease are summarized in Table 2. After a median follow-up of 42 months (range 10–203 months), 14 (14.1%) patients died. The 5-year DFS and OS in the entire cohort were 79.2% and 81.3%, respectively. Of the factors analyzed for correlation with DFS in patients with ovarian yolk sac tumor, the presence of residual disease (62.4% vs 84.3%) and FIGO stage (86% vs 71.1%) was significantly correlated with DFS in the Kaplan–Meier analysis ($p=0.008$, and $p=0.014$, respectively) (Table 3). The possible risk factors for DFS were added into the multivariate analysis and only residual disease following initial surgery ($p=0.026$; hazard ratio (HR), 2.76; 95% confidence interval (CI), 1.12–6.79) was found to be significantly associated with the DFS in patients with ovarian yolk sac tumor. Similarly, potential risk factors associated with OS are shown in Table 3 and residual disease (49.7% vs 90.3%) and FIGO stage (93.5% vs 63.4%) were significantly associated with OS ($p<0.001$, and $p=0.003$, respectively). In addition, according to multivariate analysis, only residual disease following initial surgery (HR 5.69; 95% CI 2.02–9.01; $p=0.001$) was identified as an independent risk factor for OS. The effect of residual disease on DFS and OS is shown in Figs. 1 and 2, respectively. On the other hand, there were no statistically significant differences in OS and DFS when evaluated by age (≤ 18 vs > 18 years), histology (pure vs mixed), hysterectomy, lymph node dissection, omentectomy, or preoperative serum AFP levels (Table 3).

Discussion

Since small case series are usually significant in rare malignancies, such as ovarian yolk sac tumors, we presented the results of 99 patients in this retrospective multicentric cohort study. Our data suggest that residual disease after primary surgery is the only independent predictor of OS and DFS in patients with ovarian yolk sac tumor.

In the literature, there is limited information about the role of residual disease in patients with ovarian yolk sac tumor. Nawa et al. [10] found residual disease < 2 cm in diameter showed a significantly better prognosis than larger residual tumors. Similarly, Kawai et al. [11] reported better 5-year survival rates in patients with residual disease smaller than 2 cm (82% vs 36%). In the study by Cicin et al. [12], the overall survival rate was found to be lower among the patients who had residual disease after initial surgery (30%) when compared to the patients who had no residual disease (72%) and the difference was statistically significant. Conversely, Nasioudis et al. [13] reported that the presence of gross residual disease was not

Table 1 Demographic and surgicopathological characteristics of 99 patients with ovarian yolk sac tumor

Characteristics	All population $n=99$
Age (years)[a]	23.9 ± 10.3
Age(distribution)[b]	
Adolescent (≤ 18 years)	33 (33.3)
Reproductive age (19–49 years)	63(63.6)
Postmenopausal (> 50 years)	3 (3)
Histology[b]	
Pure yolk sac	73 (73.7)
Mixed	26 (26.3)
Dysgerminoma	14
Immature teratoma + dysgerminoma	1
Choriocarcinoma + dysgerminoma	1
Immature teratoma	8
Embryonal carcinoma	2
FIGO Stage[b]	
Stage I	45 (45.5)
IA	29
IB	1
IC	15
Stage II	7 (7)
IIA	2
IIB	4
IIC	1
Stage III	42(42.5)
IIIA	10
IIIB	4
IIIC	28
Stage IV	5 (5)
AFP level	
≤ 1000 ng/ml	35 (35.4)
> 1000 ng/ml	32 (32.3)
Unknown	32 (32.3)
Laterality[b]	
Unilateral	96 (97)
Bilateral	3 (3)
Type of surgery[b]	
USO	32 (32.3)
Hysterectomy + BSO	9 (9.1)
USO + LND + omentectomy	42 (42.4)
Hysterectomy + BSO + LND + omentectomy	16 (16.2)
Lymphadenectomy procedure[b]	
Yes	54 (54.5)
No	45 (45.5)
Hysterectomy procedure[b]	
Yes	25 (25.2)
No	74 (74.8)
Ascites[b]	
Yes	35 (35.4)
No	64 (64.6)

Table 1 (continued)

Characteristics	All population $n=99$
Residual disease[b]	
No	76 (76.8)
Yes	23 (23.2)
Adjuvant chemotherapy[b]	
Yes	96 (97)
No	3 (3)
Recurrences[b]	
Yes	21 (21.2)
No	78 (78.8)

USO unilateral salpingo-oophorectomy, *BSO* bilateral salpingo-oophorectomy, *LND* lymph node dissection

[a]Numerical variables are expressed as mean ± standard deviation (SD)

[b]Categorical variables are expressed as number (%)

Table 2 Demographic and surgicopathological characteristics of patients stratified by recurrent disease

Variables	Recurrent disease Yes $n=21$
Age (years)[a]	
≤ 18	6 (28.6)
> 18	15 (71.4)
FIGO stage[a]	
Stage I–II	7 (33.3)
Stage III–IV	14 (66.7)
Histology[a]	
Pure yolk sac	18 (85.7)
Mixed	3 (14.3)
AFP levels[a]	
≤ 1000 ng/ml	4 (19)
> 1000 ng/ml	3 (14.3)
Unknown	14 (66.7)
Hysterectomy[a]	
Yes	7 (33.3)
No	14 (66.7)
Lymph node dissection[a]	
Yes	9 (42.9)
No	12 (57.1)
Residual disease[a]	
Yes	17 (80.9)
No	4 (19.1)
Ascites[a]	
Yes	11 (52.4)
No	10 (47.6)
Adjuvant treatment[a]	
No	1 (4.8)
Yes	20 (95.2)

AFP alpha-fetoprotein

[a] Categorical variables are expressed as number (%)

Table 3 Five-year overall survival (OS) and disease-free survival (DFS) rates by prognostic factors

Variables	5-year DFS		5-year OS	
	%	*p*	%	*p*
Age (years)				
≤ 18	77.1%	0.74	83.9%	0.59
> 18	79.8%		78%	
FIGO stage				
Stage I–II	86%	**0.014***	93.5%	**0.003***
Stage III–IV	71.1%		63.4%	
Residual disease				
Yes	62.2%	**0.008***	49%	**< 0.001***
No	84.3%		90.3%	
Histology				
Pure	76.1%	0.19	78%	0.57
Mixed	87.1%		84.7%	
Hysterectomy				
Yes	74.5%	0.36	69.5%	0.16
No	80.5%		83.7%	
Lymph node dissection				
Yes	84.6%	0.12	87.6%	0.05
No	72.2%		69.6%	
Omentectomy				
Yes	80.7%	0.65	81.2%	0.48
No	76.2%		77.5%	
Preoperative AFP levels				
≤ 1000 ng/ml	81.6%	0.62	83.2%	0.55
> 1000 ng/ml	79.2%		77.6%	

AFP alpha-fetoprotein

* Values in bold represent statistically significant results

associated with unfavorable oncological outcomes and this result was attributed to the efficacy of the current adjuvant chemotherapy regimens. On the other hand, in our study, the recurrent disease was detected among 17 (73.9%) of 23 patients with residual disease compared with only 4 (5.3%) of 76 patients without residual disease. In other words, despite receiving platinum-based adjuvant chemotherapy, of the 21 patients with recurrent disease 17 (81%) had gross residual disease following initial surgery. Additionally, 5-year OS was 90.3% in patients who had no macroscopic residual disease, while it was 49.0% in patients with residual disease and residual disease after primary surgery was found as an independent prognostic factor in the present study. Since ovarian yolk sac tumors generally affect adolescents or young women, this finding is particularly important for patients who desire future fertility. Because, if the uterus and contralateral ovary are grossly involved by tumor, fertility-sparing surgery should be reconsidered for oncological safety and our study strongly supports the most important surgical oncology principle, which is to

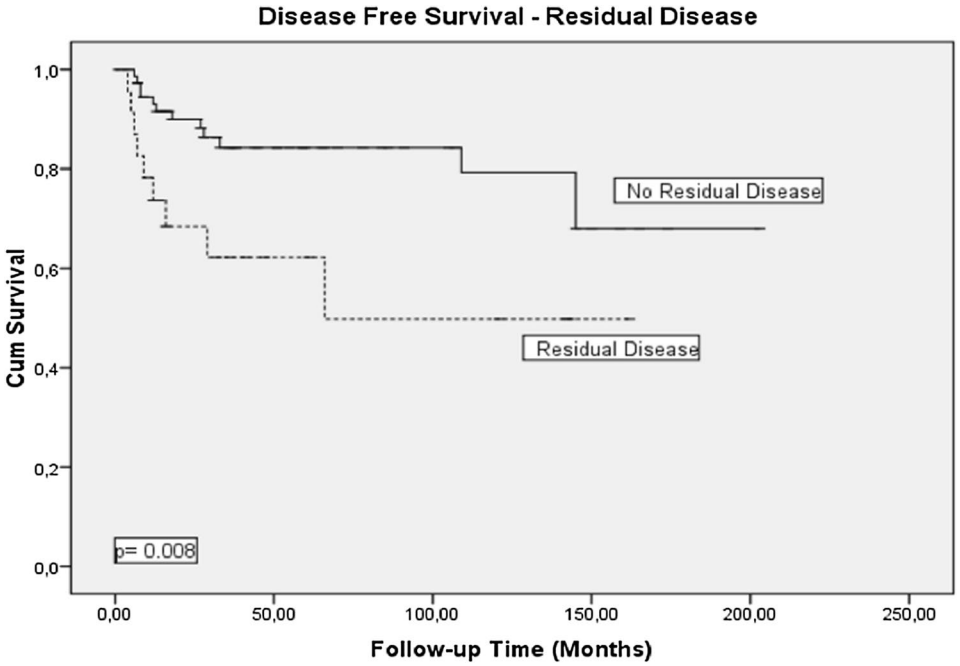

Fig. 1 The effect of residual disease on DFS

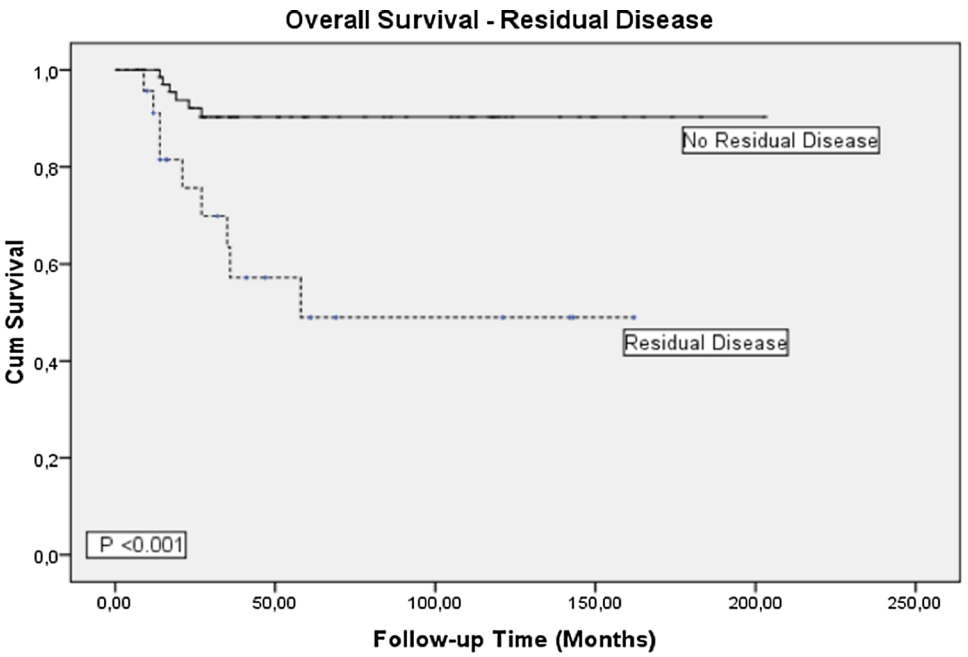

Fig. 2 The effect of residual disease on OS

achieve no visible residual disease even in patients with ovarian yolk sac tumor.

Another important finding of the present study was the oncological safety of preservation of a normal appearing uterus and contralateral ovary, allowing for future fertility options. Similarly, previous studies have shown that fertility-sparing surgery appears to be safe with excellent oncological outcomes almost equivalent to patients undergoing hysterectomy with bilateral salpingo-oophorectomy [10, 12, 14, 15]. Although bilaterality rate was 3% in the present study, it has been reported up to 8.5% in the literature [5, 16]. Therefore, uterus and contralateral ovary should be carefully examined to make sure that there is no gross tumoral involvement. Fertility-sparing approach may cause adverse oncological outcomes if the uterus and contralateral ovary are involved and should be reconsidered if the surgery does not result in any visible disease. In contrast, Nasioudis et al. [13] have recommended fertility-sparing approach even in patients with disseminated disease.

There is no large series related with the prognostic significance of LND in patients with ovarian yolk sac tumor in the literature. In the study by Nasioudis et al. [13], lymph node metastasis was detected in 14.2% of the patients who had lymph node dissection. However, they have found that LND was not related with better oncological outcomes even for patients with apparent early stage disease. Similarly, several studies have failed to demonstrate a survival benefit for patients with ovarian yolk sac tumor who had LND [10, 17–19]. Another study published by Ayhan et al. [16] evaluated 29 patients with ovarian yolk sac tumor. In this study, LND was performed in 14 patients; none of them had metastatic involvement. In the present study, 18.5% of patients with ovarian yolk sac tumor undergoing lymphadenectomy had lymph node metastases. Although there is a trend of having a better OS rate (87.6% vs 69.6%) in patients with lymph node dissection, this difference did not reach statistical significance. Therefore, larger studies are required to confirm this tendency and lymph node dissection may be considered in the surgical management of patients with ovarian yolk sac tumor based on current guidelines [20].

There are different results in the literature related with the stage and prognosis in patients with ovarian yolk sac tumor. Several studies have suggested that the tumor stage was an important prognostic factor [7, 10, 13, 21, 22], while others did not find independent role of tumor stage at diagnosis in multivariate analysis [12]. In our study, while 52.5% of patients had early stage disease, the remaining 47.5% had advanced stage disease. The 5-year OS rate was found to be less among the patients diagnosed at advanced stages (63.4%) when compared to the patients who had early stage disease (93.5%). However, the tumor stage was not an independent prognostic factor in multivariate analysis. In other words, optimal outcomes are achieved in patients who had no visible residual disease after primary surgery and received platinum-based adjuvant chemotherapy even in patients with advanced stage disease. In addition, most of the patients had received platinum-based adjuvant chemotherapy based on European Society of Medical Oncology guidelines [23] and only three patients did not receive adjuvant therapy in the present study. This small sample size of patients who did not receive adjuvant treatment makes it difficult to arrive at any meaningful conclusion regarding the role of adjuvant treatment. Moreover, consistent with the previous studies, age, serum AFP levels, histology (pure vs mixed) and omentectomy were not found as prognostic factors in this study [4, 10, 12, 24].

Our study has a number of limitations. Firstly, a central pathological slide review could not be performed. Because of the retrospective nature of the study, the presence of other possible confounding variables such as selection bias that might have affected our results could not be ruled out. Another limitation of the present study is that data were collected from seven different institutions with potential differences in surgical and clinical management. Despite these limitations, our study contributes to the limited body of knowledge on this topic because of the large number of patients with ovarian yolk sac tumor. In addition, most of the patients received platinum-based BEP adjuvant chemotherapy regimen in our study group and the relative homogeneity of the delivered adjuvant treatments may be underlined as an advantage of this study.

In conclusion, only residual disease after initial surgery was an independent risk factor for both OS and DFS, and our results demonstrate the significance of achieving no visible residual disease in patients with ovarian yolk sac tumor. In other words, maximal cytoreductive surgery to achieve no visible residual tumor would improve the oncological outcomes. In addition, fertility-sparing approach for patients with no visible residual disease after surgery affected neither DFS nor OS in our study group. Although high lymphatic involvement rate was detected, the benefit of LND could not be demonstrated and further studies are needed with larger sample size to clarify the effect of LND on oncological outcomes for patients with ovarian yolk sac tumor.

Author contributions GB: project development, data collection, manuscript writing. YD: project development, data management, manuscript writing. IC: manuscript writing, manuscript editing. OK: data collection, manuscript writing. EB: data collection. GKC: manuscript writing, manuscript editing. HS: data collection. HA: data collection. IU: manuscript writing, data management. AK: manuscript writing, data management. MMM: manuscript writing, data management. MCS: project development, data management, manuscript writing. NO: project development, data management, manuscript writing. AO: project development, data management, manuscript writing. TS: manuscript writing, manuscript editing. KY: manuscript writing, manuscript editing. TT: project development, data collection, manuscript writing, manuscript editing.

Compliance with ethical standards

Conflict of interest There are no potential conflicts of interest to declare and no relevant sources of funding for this study.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Affiliations

Gokhan Boyraz[1] · Yasin Durmus[1] · Irfan Cicin[2] · Oguzhan Kuru[3] · Esra Bostanci[4] · Gunsu Kimyon Comert[1] · Hanifi Sahin[5] · Hulya Ayik[6] · Isin Ureyen[7] · Alper Karalok[1] · Mehmet Mutlu Meydanli[5] · Mehmet Coskun Salman[3] · Nejat Ozgul[3] · Anil Onan[4] · Tayup Simsek[6] · Kunter Yuce[3] · Taner Turan[1]

Yasin Durmus
dr_yasindurmus@hotmail.com

Irfan Cicin
irfancicin@hotmail.com

Oguzhan Kuru
droguzhankuru@yahoo.com

Esra Bostanci
dresrai@yahoo.com.tr

Gunsu Kimyon Comert
gunsukimyon@gmail.com

Hanifi Sahin
hanifi.81_@hotmail.com

Hulya Ayik
hulya_ayik@hotmail.com

Isin Ureyen
isin.ureyen@gmail.com

Alper Karalok
alperkaralok@yahoo.com

Mehmet Mutlu Meydanli
mmmeydanli@gmail.com

Mehmet Coskun Salman
csalman@hacettepe.edu.tr

Nejat Ozgul
nozgul@gmail.com

Anil Onan
aonan68@yahoo.com

Tayup Simsek
tsimsek@akdeniz.edu.tr

Kunter Yuce
kyuce@hacettepe.edu.tr

Taner Turan
turantaner@yahoo.com

[1] Division of Gynecologic Oncology, Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital, Etlik, 06010 Ankara, Turkey

[2] Department of Medical Oncology, Trakya University Hospital, 22030 Edirne, Turkey

[3] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[4] Department of Gynecologic Oncology, Faculty of Medicine, Gazi University, Ankara, Turkey

[5] Department of Gynecologic Oncology, Zekai Tahir Burak Women's Health, Education and Research Hospital, Ankara, Turkey

[6] Department of Gynecologic Oncology, Faculty of Medicine, Akdeniz University, Antalya, Turkey

[7] Antalya Education and Research Hospital Faculty of Medicine, University of Health Sciences (Antalya), Antalya, Turkey