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Original Article

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Prognostic factors of adult granulosa cell tumors of the ovary: a Turkish retrospective multicenter study

Okan Oktar,[1] **Vakkas Korkmaz**,[1] **Alp Tokalıoğlu**,[2] **Çağatayhan Öztürk**,[3] **Özgür Erdoğan**,[4] **Yeşim Uçar**,[2] **Hande Esra Koca Yıldırım**,[1] **Candost Hanedan**,[1] **Fatih Kılıç**,[2] **Burak Ersak**,[2] **Necim Yalçın**,[5] **Fatma Özmen**,[6] **Alper Kahraman**,[5] **Selin Aktürk Esen**,[7] **Sevda Baş**,[6] **Emel Doğan Özdaş**,[4] **İlker Selçuk**,[2] **Gökhan Uçar**,[7] **Özgür Koçak**,[8] **Caner Çakır**,[1] **Sevgi Koç**,[9] **Çiğdem Kılıç**,[8] **Günsu Kimyon Cömert**,[2] **Işın Üreyen**,[5] **Tayfun Toptaş**,[5] **Mehmet Ali Narin**,[6] **Tolga Taşçı**,[10] **Salih Taşkın**,[3] **Nurettin Boran**,[9] **Muzaffer Sancı**,[4] **Fahriye Tuğba Köş**,[7] **Özlem Moraloğlu Tekin**,[2] **Yaprak Engin Üstün**,[9] **Fırat Ortaç**,[3] **Taner Turan**[2]

[1]Department of Gynecologic Oncology, Ankara Etlik City Hospital, Faculty of Medicine, University of Health Sciences, Ankara, Turkey
[2]Department of Gynecologic Oncology, Ankara Bilkent City Hospital, Faculty of Medicine, University of Health Sciences, Ankara, Turkey
[3]Ankara University, Faculty of Medicine, Ankara, Turkey
[4]Department of Gynecologic Oncology, Tepecik Training and Research Hospital, Faculty of Medicine, University of Health Sciences, Izmir, Turkey
[5]Department of Gynecologic Oncology, Antalya Training and Research Hospital, Faculty of Medicine, University of Health Sciences, Antalya, Turkey
[6]Department of Gynecologic Oncology, Adana City Hospital, Faculty of Medicine, University of Health Sciences, Adana, Turkey
[7]Department of Medical Oncology, Ankara Bilkent City Hospital, Faculty of Medicine, University of Health Sciences, Ankara, Turkey
[8]Department of Gynecologic Oncology, Hitit University, Corum, Turkey
[9]Department of Gynecologic Oncology, Etlik Zubeyde Hanim Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences, Ankara, Turkey
[10]Department of Gynecologic Oncology, Bahcesehir University, Istanbul, Turkey

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Correspondence to
Caner Çakır
Department of Gynecologic Oncology, Ankara Etlik City Hospital, Faculty of Medicine, University of Health Sciences, Varlık, Halil Sezai Erkut Street, Yenimahalle, Ankara 06170, Turkey.
Email: caner4084@gmail.com

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ORCID iDs
Okan Oktar
https://orcid.org/0000-0002-9696-7886
Vakkas Korkmaz
https://orcid.org/0000-0001-8895-6864
Alp Tokalıoğlu
https://orcid.org/0000-0002-1776-2744
Çağatayhan Öztürk
https://orcid.org/0000-0003-2190-9718
Özgür Erdoğan
https://orcid.org/0000-0002-0319-3560
Yeşim Uçar
https://orcid.org/0000-0002-6629-0149
Hande Esra Koca Yıldırım
https://orcid.org/0000-0002-3715-9424

ABSTRACT

Objective: To define the clinical, histopathological features and the prognostic factors affecting survival in patients with adult granulosa cell tumors of the ovary (AGCT).
Methods: A 322 patients whose final pathologic outcome was AGCT treated at nine tertiary oncology centers between 1988 and 2021 participated in the study.
Results: The mean age of the patients was 51.3±11.8 years and ranged from 21 to 82 years. According to the International Federation of Gynecology and Obstetrics 2014, 250 (77.6%) patients were stage I, 24 (7.5%) patients were stage II, 20 (6.2%) patients were stage III, and 3 (7.8%) were stage IV. Lymphadenectomy was added to the surgical procedure in 210 (65.2%) patients. Lymph node involvement was noted in seven (3.3%) patients. Peritoneal cytology was positive in 19 (5.9%) patients, and 13 (4%) had metastases in the omentum. Of 285 patients who underwent hysterectomy, 19 (6.7%) had complex hyperplasia with atypia/endometrial intraepithelial neoplasia, and 8 (2.8%) had grade 1 endometrioid endometrial carcinoma. It was found that 93 (28.9%) patients in the study group received adjuvant treatment. Bleomycin, etoposide, cisplatin was the most commonly used chemotherapy protocol. The median follow-up time of the study group was 41 months (range, 1–276 months). It was noted that 34 (10.6%) patients relapsed during this period, and 9 (2.8%)

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Candost Hanedan
https://orcid.org/0000-0003-3435-8943
Fatih Kılıç
https://orcid.org/0000-0002-7333-4883
Burak Ersak
https://orcid.org/0000-0003-3301-062X
Necim Yalçın
https://orcid.org/0000-0001-5980-3244
Fatma Özmen
https://orcid.org/0000-0002-8837-4554
Alper Kahraman
https://orcid.org/0000-0002-1689-2782
Selin Aktürk Esen
https://orcid.org/0000-0002-3426-9505
Sevda Baş
https://orcid.org/0000-0002-6454-6470
Emel Doğan Özdaş
https://orcid.org/0000-0003-3112-0091
İlker Selçuk
https://orcid.org/0000-0003-0499-5722
Gökhan Uçar
https://orcid.org/0000-0002-7649-1075
Özgür Koçak
https://orcid.org/0000-0002-3906-9422
Caner Çakır
https://orcid.org/0000-0003-2559-9104
Sevgi Koç
https://orcid.org/0000-0002-1703-0690
Çiğdem Kılıç
https://orcid.org/0000-0002-4433-8068
Günsu Kimyon Cömert
https://orcid.org/0000-0003-0178-4196
Işın Üreyen
https://orcid.org/0000-0002-3491-4682
Tayfun Toptaş
https://orcid.org/0000-0002-6706-6915
Mehmet Ali Narin
https://orcid.org/0000-0002-8145-9053
Tolga Taşçı
https://orcid.org/0000-0001-8645-4385
Salih Taşkın
https://orcid.org/0000-0002-9651-2224
Nurettin Boran
https://orcid.org/0000-0002-0367-5551
Muzaffer Sancı
https://orcid.org/0000-0002-8494-4302
Fahriye Tuğba Köş
https://orcid.org/0000-0002-6980-4942
Özlem Moraloğlu Tekin
https://orcid.org/0000-0001-8167-3837
Yaprak Engin Üstün
https://orcid.org/0000-0002-1011-3848
Fırat Ortaç
https://orcid.org/0000-0001-6735-5760
Taner Turan
https://orcid.org/0000-0001-8120-1143

patients died because of the disease. The entire cohort had a 5-year disease-free survival (DFS) of 86% and a 5-year disease-specific survival of 98%. Recurrences were observed only in the pelvis in 13 patients and the extra-abdominal region in 7 patients. The recurrence rate increased 6.168-fold in patients with positive peritoneal cytology (95% confidence interval [CI]=1.914–19.878; p=0.002), 3.755-fold in stage II–IV (95% CI=1.275–11.063; p=0.016), and 2.517-fold in postmenopausal women (95% CI=1.017–6.233; p=0.046) increased.
Conclusion: In this study, lymph node involvement was detected in 3.3% of patients with AGCT. Therefore, it was concluded that lymphadenectomy can be avoided in primary surgical treatment. Positive peritoneal cytology, stage, and menopausal status were independent prognostic predictors of DFS.

Keywords: Granulosa Cell; Disease-Free Survival; Prognostic Factors; Ovarian Carcinoma

Synopsis
Lymph node involvement is rare in patients with adult granulosa cell tumors of the ovary, so lymphadenectomy can be avoided in primary surgical management. Positivity of peritoneal cytology, stage, and menopausal status are found to be independent prognostic predictor of disease-free survival.

INTRODUCTION

Adult granulosa cell tumors of the ovary (AGCT) are rare and account for approximately 2%–5% of all ovarian malignancies [1,2]. AGCT is the most common type among malignant ovarian sex cord tumors, accounting for 90% of cases [3]. Although they can occur throughout life, they are usually diagnosed in perimenopausal and postmenopausal women between 50 and 55 [2,4].

AGCTs are ovarian tumors that can secrete hormones, especially estrogen. The hyperestrogenism observed in these cases results from the tumor's production of estrogens, anti-Mullerian hormone, and inhibin B [5]. Due to the hormonal effects, endometrial pathologies such as endometrial hyperplasia and endometrial cancer may occur. These pathologies lead to abnormal uterine bleeding, the most important clinical finding. In addition, abdominal pain and distension are other critical clinical findings in these patients [6,7]. The most sensitive and specific serum tumor marker for diagnosing granulosa cell tumors is inhibin, produced in the ovaries in response to follicle-stimulating hormone and luteinizing hormone [8].

Surgical excision is the basis of histologic diagnosis and initial treatment aimed at appropriate staging [9,10]. The surgical approach to AGCT includes the same principles traditionally recommended for epithelial ovarian tumors [10]. Complete surgical excision of the uterus, ovaries, and fallopian tubes, along with staging procedures (peritoneal cytology, biopsies, and infracolic omentectomy), is the gold standard [11]. Since only 2% of AGCTs are bilateral, the preferred surgical approach in women of reproductive age is unilateral salpingo-oophorectomy and staging [12,13]. The incidence of nodal involvement in AGCT is very low. For this reason, the need for lymph node dissection is still debated [14,15].

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
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Most granulosa cell tumors have a slow growth pattern and are diagnosed at stage I. Also, they have quite a good prognosis. For these reasons, they are considered low-grade malignancies [16,17]. The early stage's 5-, 10-, and 20-year survival rates were reported as 94, 82, and 62 percent, respectively [18]. However, they have metastatic potential and tend to relapse late. The median duration of recurrence is five years after surgical treatment of the primary tumor. Recurrences can occur even in early-stage disease that has been followed for decades. Moreover, many relapses have been reported 20–40 years after initial diagnosis [19-22]. Therefore, long-term follow-up is necessary [2,6,7,9]. The stage at diagnosis, the status of postoperative residual disease, and tumor size have been reported as significant prognostic factors [7,23,24].

However, despite all treatment options, these tumors still have recurrences. Because of these recurrences, AGCTs remain a significant cause of mortality and morbidity in women's lives. Given all this information, the clinicopathologic characteristics of patients with AGCT, the prognostic factors for surgical management, adjuvant treatment, and recurrence of AGCT still need to be fully elucidated. So, we aimed to define the clinical and histopathological features of AGCT and the prognostic factors affecting survival in the Turkish population with the results of a total of 34 years of experience from 9 tertiary oncology centers.

MATERIALS AND METHODS

1. Study design

The study enrolled 322 patients whose final pathologic outcome was AGCT at nine tertiary oncology centers between 1988 and 2021. Approval was obtained from the local ethics committee for the study. Patients not followed up after surgery, had concurrent non-gynecologic malignancies, had received prior radiotherapy or chemotherapy, and had ovarian tumors other than AGCT were excluded from the study.

Clinical, demographic, and histopathologic information on included patients was obtained from patient registries, pathology reports, and electronic databases. Treatments for those who underwent surgery at a center other than gynecologic oncology and were referred because they were AGCT were evaluated and regulated by the gynecologic oncology council of the respective hospital.

2. Definitions

The surgical procedure in which no hysterectomy is performed, and at least part of one ovary is left in place was defined as “conservative surgery”, and the surgical procedure in which at least hysterectomy and bilateral salpingo-oophorectomy is performed was defined as “definitive surgery”. The senior surgeon decided whether to include omentectomy and lymphadenectomy in the surgical procedure and whether to perform lymphadenectomy thoroughly or sampling.

In all clinics, surgical specimens are evaluated by experienced gynecopathologists. The International Federation of Gynecology and Obstetrics (FIGO) 2014 system was used for staging [25]. Those operated on before 2014 were restaged according to the pathology report using the 2014 FIGO criteria.

Depending on the final pathology result, the decision on adjuvant treatment is made by the Gynecologic Oncology Council. After surgery and adjuvant treatment, patients were enrolled in the routine surveillance program. They were examined every three months for the first two years, then every six months until the 5th year, and then once a year, with pelvic examination, abdominal ultrasonography, complete blood count, and biochemical blood tests. If clinically suspected, a chest radiograph was performed. Thoracic or abdominal computed tomography was performed if needed. Postoperative patients were not routinely followed up with computed tomography. However, computed tomography was performed when recurrence was suspected; symptoms were present, a suspicious lesion was detected on control ultrasound, or abnormal tumor marker results were present. Recurrence below the linea terminalis was defined as pelvic recurrence, recurrence between the linea terminalis and diaphragm as upper abdominal recurrence, and recurrence outside of it as extra-abdominal recurrence. Recurrences in the liver parenchyma, and bone were considered extra abdominal recurrences, cytologically defined ascites, and upper abdominal recurrences to peritonitis carcinomatosis.

Time from first surgical intervention to recurrence of disease or to last contact was defined as disease-free survival (DFS), and time to death from disease or to last contact was defined as disease-specific survival (DSS).

3. Statistical analysis

Statistical analysis was performed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). The distribution of the data was determined by Kolmogorov-Smirnov test. The continuous data's mean, standard deviation, median, minimum, and maximum values were calculated using the descriptive statistical test. The numbers and percentages of the categorical variables were calculated using the chi-square test. DFS and DSS were determined using the Kaplan-Meier method. The log-rank test was used to compare survival curves. Multivariate analysis was performed with a Cox proportional hazards model, and a multivariate analysis model was constructed with variables that were statistically significant in the univariate analysis. Odds ratios with 95% confidence intervals (CIs) were calculated. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of the 322 patients included in the study was 51.3±11.8 years, ranging from 21 to 82 years. One hundred and sixty-three (50.6%) of the patients were postmenopausal. According to FIGO 2014, 250 (77.6%) patients were stage I, 24 (7.5%) patients were stage II, 20 (6.2%) patients were stage III, and 3 (7.8%) were stage IV. It was found that 220 (68.3%) patients had their first surgery in gynecologic oncology clinics, the cyst was not ruptured in 255 (79.2%) patients at the first surgery, and conservative surgery was performed in 35 (10.9%) patients. Lymphadenectomy was added to the surgical procedure in 210 (65.2%) patients, and in 197 of them, lymphadenectomy was performed as pelvic+paraaortic lymphadenectomy. In patients with lymphadenectomy, a median of 38 lymph nodes were removed (range, 2–129). Lymph node involvement was noted in seven (3.3%) patients. Omentectomy was performed in 238 (73.9%) patients, and 13 (4%) had metastases in the omentum. Ascites were present in 55 (17.1%) patients, and the median ascites volume was 100 mL (range, 20–10,000 mL). Peritoneal cytology was positive in 19 (5.9%) patients. The demographic, surgical, and pathologic characteristics of the entire study group are shown in **Table 1**.

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Table 1. Clinical, surgical and pathological features of entire cohort

Characteristics	Values
Age at initial diagnosis (yr)	
Mean±SD	51.3±11.8
Median (range)	51 (21–82)
Tumor size (mm)	
Mean±SD	111.6±90.1
Median (range)	85 (7–900)
Preoperative CA 125 (IU/mL)	
Mean±SD	73.6±148.8
Median (range)	25 (1–995)
Total removed lymph node count	
Mean±SD	40.5±24.5
Median (range)	38 (2–129)
Ascites (mL)	
Mean±SD	721±1,738
Median (range)	100 (20–10,000)
FIGO stage	
I	250 (77.6)
II	24 (7.5)
III	20 (6.2)
IV	3 (0.9)
Unidentified	25 (7.8)
Menopausal status	
Premenopause	157 (48.8)
Postmenopause	163 (50.6)
Not reported	2 (0.6)
First operation clinic	
Gynecologic oncology	220 (68.3)
Other	96 (29.8)
Not reported	6 (1.9)
Rupture of cyst	
Unruptured	255 (79.2)
Iatrogenic rupture	31 (9.6)
Presurgical rupture	13 (4.0)
Not reported	23 (7.1)
Hysterectomy	
Performed	285 (88.5)
Not performed*	35 (10.9)
Hysterectomy performed before disease	2 (0.6)
Ovarian tumor site	
Left	150 (46.6)
Right	128 (39.8)
Bilateral	27 (8.4)
Not reported	17 (5.3)
Lymphadenectomy	
Performed	210 (65.2)
Not performed	111 (34.5)
Not reported	1 (0.3)
Type of lymphadenectomy†	
Only pelvic	10 (4.8)
Only paraaortic	3 (1.4)
Pelvic and paraaortic	197 (93.8)
Lymph node metastasis†	
Negative	203 (96.7)
Positive	7 (3.3)
Omentectomy	
Performed	238 (73.9)
Not performed	83 (25.8)
Not reported	1 (0.3)
Omental metastasis‡	
Negative	225 (94.5)
Positive	13 (4.0)
Ascites	
Absent	219 (68)
Present	55 (17.1)
Not reported	48 (14.9)
Peritoneal cytology	
Negative	235 (73.0)
Positive	19 (5.9)
Not reported	68 (21.1)

Values are presented as number (%) not otherwise specified.
FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation.
*Conservative surgery; †210 patients; ‡238 patients.

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While only 30 (9.3%) patients were asymptomatic at admission, abnormal uterine bleeding (postmenopausal bleeding and menstrual irregularity) was the most common finding. It was found that 139 (43.1%) patients had symptoms of abnormal uterine bleeding (**Table 2**).

Four of the seven patients who underwent lymph node dissection were premenopausal, and three were postmenopausal. Definitive surgery was performed on all patients. Peritoneal cytology was negative in six patients, and no peritoneal cytology information was provided for one patient. According to the FIGO 2014 staging system, four patients were stage IIIC, one was stage IVB, and two provided no stage information. Only one patient had positive omental metastasis. While only one patient received external beam radiotherapy (EBRT), the other six underwent bleomycin, etoposide, cisplatin (BEP) chemotherapy. While no recurrence was detected in four patients after primary surgery and adjuvant treatment, recurrence was detected in three during follow-up. The recurrences were located in the lung in one patient, the pelvis in one patient, and the rectus sheath in one patient. During follow-up, one of the patients died from the disease. The median duration of DFS was 37.2 months and ranged from 1 to 108 months. The median overall survival was 52.5 months, ranging from 1 to 108 months (**Table 3**).

Of 285 patients who underwent hysterectomy, 19 (6.7%) had complex hyperplasia with atypia/endometrial intraepithelial neoplasia, and 8 (2.8%) had grade 1 endometrioid endometrial carcinoma (**Table 2**). While one of eight patients defined as having endometrioid carcinoma had no myometrial invasion, six had myometrial invasion depth <1/2, and one had myometrial invasion depth ≥1/2. It was noted that 13 of 35 patients who underwent conservative surgery had endometrial sampling. Endometrial sampling results in these

Table 2. Symptoms and endometrial pathology

Features	Values
Main symptom	
No symptom	30 (9.3)
Postmenopausal bleeding	79 (24.5)
Abdominal distention	69 (21.4)
Abdominal or suprapubic pain	63 (19.6)
Menstrual irregularity	60 (18.6)
Not reported	21 (6.5)
Endometrial pathology on hysterectomy specimen*	
Atrophic endometrium	24 (8.4)
Endometritis	6 (2.1)
Endometrial polyp	10 (3.5)
Proliferative endometrium	108 (37.9)
Secretuary endometrium	20 (7.0)
Simple hyperplasia without atypia	48 (16.8)
Complex hyperplasia without atypia	9 (3.2)
Complex hyperplasia with atypia/EIN	19 (6.7)
Endometrioid cancer grade 1	8 (2.8)
Not reported	33 (11.6)
Endometrial pathology on endometrial sampling†	
Atrophic endometrium	2 (5.7)
Endometritis	7 (20.0)
Endometrial polyp	1 (2.9)
Proliferative endometrium	1 (2.9)
Simple hyperplasia without atypia	2 (5.7)
Not performed	22 (62.9)

Values are presented as number (%).
*n=285; The patients underwent hysterectomy because of adult granulosa cell tumor (definitive surgery); †n=35; The result of endometrial sampling in patients didn't underwent hysterectomy (conservative surgery).

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Table 3. Patients with lymph node involvement (n=7)

Characteristics	1. Patient	2. Patient	3. Patient*	4. Patient	5. Patient	6. Patient	7. Patient
Age (yr)	42	46	28	70	48	48	39
Menopausal status	Premenopausal	Premenopausal	Premenopausal	Postmenopausal	Postmenopausal	Postmenopausal	Premenopausal
Surgery type	Definitive	Definitive	Definitive	Definitive	Definitive	Definitive	Definitive
Tumor size (mm)	200	NR	120	75	60	55	100
Number of removed lymph node	35	63	37	41	33	39	24
Peritoneal cytology	Negative	Negative	Negative	Negative	NR	Negative	Negative
FIGO stage	IIIC	IIIC	IVB	NR	IIIC	IIIC	NR
Omental metastasis	Negative	Negative	Positive	Negative	Negative	Negative	Negative
Adjuvant therapy	BEP	BEP	BEP	BEP	EBRT	BEP	BEP
Recurrence	Negative	Negative	Negative	Positive	Positive	Positive	Negative
First recurrence site	-	-	-	Pulmoner	Pelvic	Rectus sheath	-
DFS (mo)	35	35	1*	10	36	36	108
Exitus because of disease	Negative	Negative	Negative	Positive	Negative	Negative	Negative
OS (mo)	35	35	1	21	96	72	108

BEP, bleomycin, etoposide, cisplatin; DFS, disease-free survival; EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; NR, not reported; OS, overall survival.
*Unfollowed patient.

13 patients were reported as atrophic endometrium, endometrial polyp, endometritis, proliferative endometrium, and simple hyperplasia without atypia (**Table 2**).

1. Adjuvant treatment

It was found that 93 (28.9%) patients in the study group received adjuvant treatment. Adjuvant treatment was chemotherapy only in 85 of them, radiotherapy only in 3, and chemotherapy and radiotherapy in 2. In addition, detailed records of adjuvant treatment could not be obtained for three patients. The most commonly used chemotherapy protocol was BEP (**Table 4**). Radiotherapy was delivered as EBRT in 5 patients.

Table 4. Features of the adjuvant treatment

Features	Values
Adjuvant treatment	
Not received	229 (71.1)
Received	93 (28.9)
Type of adjuvant treatment*	
Only CT	85 (91.4)
Only RT‡	3 (3.2)
CT plus RT‡	2 (2.2)
Unidentified	3 (3.2)
Chemotherapy protocol†	
BEP	33 (37.9)
CFP	17 (19.5)
CP	11 (12.6)
VAC	8 (9.2)
EP	2 (2.3)
CE	1 (1.2)
CAP	2 (2.3)
Paclitaxel plus CbP	8 (9.2)
Paclitaxel plus Cis	3 (3.5)
Not reported	2 (2.3)

Values are presented as number (%) not otherwise specified.
BEP, bleomycin, etoposide, cisplatin; CAP, cyclophosphamide, adriamycin, cisplatin; CbP, carboplatin; CE, cyclophosphamide, etoposide; CFP, cyclophosphamide, farmarubicin, prednisone; Cis, cisplatin; CP, cyclophosphamide, cisplatin; CT, chemotherapy; EP, etoposide, cisplatin; RT, radiotherapy; VAC, vincristine, adriamycin, cyclophosphamide.
*93 patients; †87 patients (85 patients received only chemotherapy and 2 patients received chemotherapy plus radiotherapy); ‡External beam radiotherapy.

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The mean age of patients who received adjuvant chemotherapy was 50.4±10.95 years and ranged from 24 to 82 years. The mean age of patients who received adjuvant radiotherapy was 50.3±12.42 years and ranged from 36 to 58 years. The mean age of patients who received adjuvant chemotherapy + radiotherapy was 53.5±23.33 years and ranged from 37 to 70 years.

According to FIGO 2014, 39 (45.9%) patients who received adjuvant therapy were stage I, 13 (15.3%) patients were stage II, 18 (21.2%) patients were stage III, and 3 (3.5%) patients were stage IV. In addition, detailed records of the stage who received adjuvant therapy could not be obtained for 12 (14.1%) patients.

Hysterectomy was performed in 78 (91.8%) patients who received adjuvant chemotherapy. In addition, hysterectomy was not performed in 6 (7.1%) patients, and hysterectomy was performed in 1 (1.2%) patient before AGCT was diagnosed (**Table S1**).

All eight patients with concurrent endometrial cancer were grade 1. Seven are stage IA, and one of them is stage IB. Two of these patients received adjuvant therapy. One of the patients with stage IA endometrial cancer received chemotherapy for AGCT, and the patient with stage IB received radiotherapy for endometrial cancer and chemotherapy for AGCT.

2. Recurrence and survival

The median follow-up time of the study group was 41 months (range, 1–276 months). It was noted that 34 (10.6%) patients relapsed during this period, and 9 (2.8%) patients died because of the disease.

The symptoms of the 34 patients who experienced recurrence were as follows: The most common symptom was abdominal/pelvic pain at 55.8% (n=19), followed by asymptomatic patients at 29.4% (n=10). The remaining patients (14.7%, n=5) had abdominal distension.

The entire cohort had a 5-year DFS of 86% and a 5-year DSS of 98%. Recurrences were observed only in the pelvis in 13 patients and the extra-abdominal region in 7 patients. The recurrence pattern is shown in **Table S2**.

Age, peritoneal cytology, menopausal status, stage, and cyst rupture (iatrogenic or preoperative) were significant for DFS in univariate analysis. In contrast, the original surgical center, tumor size, presence of ascites, conservative surgery, lymphadenectomy, and omentectomy as part of the surgical procedure, and adjuvant treatment were not associated with DFS (**Table 5**). Because age and menopausal status were highly correlated among factors found to be significant in univariate analysis, excluding age at diagnosis, a model was created for multivariate analysis that accounted for peritoneal cytology (negative vs. positive), stage (I vs. II–IV), menopausal status (premenopausal vs. postmenopausal), and cyst rupture (unruptured vs. ruptured) (**Fig. 1**). The recurrence rate increased 6.168-fold in patients with positive peritoneal cytology (95% CI=1.914–19.878; p=0.002), 3.755-fold in stage II–IV (95% CI=1.275–11.063; p=0.016), and 2.517-fold in postmenopausal women (95% CI=1.017–6.233; p=0.046) increased. Statistical analysis could not be performed for DSS due to insufficient numbers of disease-related deaths.

It was found that two of eight patients whose endometrial pathology was defined as grade 1 endometrioid carcinoma received adjuvant treatment. The adjuvant treatment was chemotherapy in one of them and chemotherapy plus EBRT in the other. The depth of myometrial invasion was ≥1/2 in the patient who underwent radiotherapy, and of these eight

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Table 5. Factors related with DFS

Parameter	Univariate analysis		Multivariate analysis	
	5-yr DFS		Recurrence	
	%	p-value	OR (95% CI)	p-value
Age at initial diagnosis*		0.043		
≤51 yr	88			
>51 yr	84			
Peritoneal cytology		0.002		0.002
Negative	89		1 (Reference)	
Positive	73		6.168 (1.914–19.878)	
Stage		<0.001		0.016
I	92		1 (Reference)	
II–IV	65		3.755 (1.275–11.063)	
Menopausal status		0.002		0.046
Premenopause	91		1 (Reference)	
Postmenopause	81		2.517 (1.017–6.233)	
Rupture of cyst		0.007		0.199
Unruptured	89		1 (Reference)	
Ruptured†	76		2.198 (0.661–7.301)	
First operation clinic		0.390		
Gynecologic oncology	89			
Other	82			
Ovarian tumor size*		0.610		
≤85 mm	81			
>85 mm	91			
Ascites		0.978		
Absent	89			
Present	88			
Surgery type		0.128		
Definitive surgery‡	85			
Conservative surgery	100			
Lymphadenectomy		0.992		
Performed	87			
Not performed	84			
Omentectomy		0.944		
Performed	87			
Not performed	86			
Adjuvant treatment		0.273		
Not received	90			
Received	79			

CI, confidence interval; DFS, disease-free survival; OR, odds ratio.
*Median value; †Iatrogenic or presurgical rupture; ‡287 patients (285 patients performed because of adult granulosa cell tumor and 2 patients had underwent hysterectomy before adult granulosa cell tumor).

patients, recurrence occurred only in the patient who received adjuvant radiotherapy, ten months after treatment in the lung. Despite salvage treatment, this patient died at month 21 because of disease progression.

DISCUSSION

AGCTs have a low malignant potential. Therefore, their prognosis is much better than epithelial ovarian carcinomas. However, despite all treatment options, these tumors still have recurrences. Because of these recurrences, AGCTs remain a significant cause of mortality and morbidity in women's lives. Therefore, there is a need to clarify the clinicopathologic characteristics of patients with AGCT and the prognostic factors that may be associated with recurrence. In light of this information, 322 AGCT patients were studied in detail in this large multicenter retrospective study.

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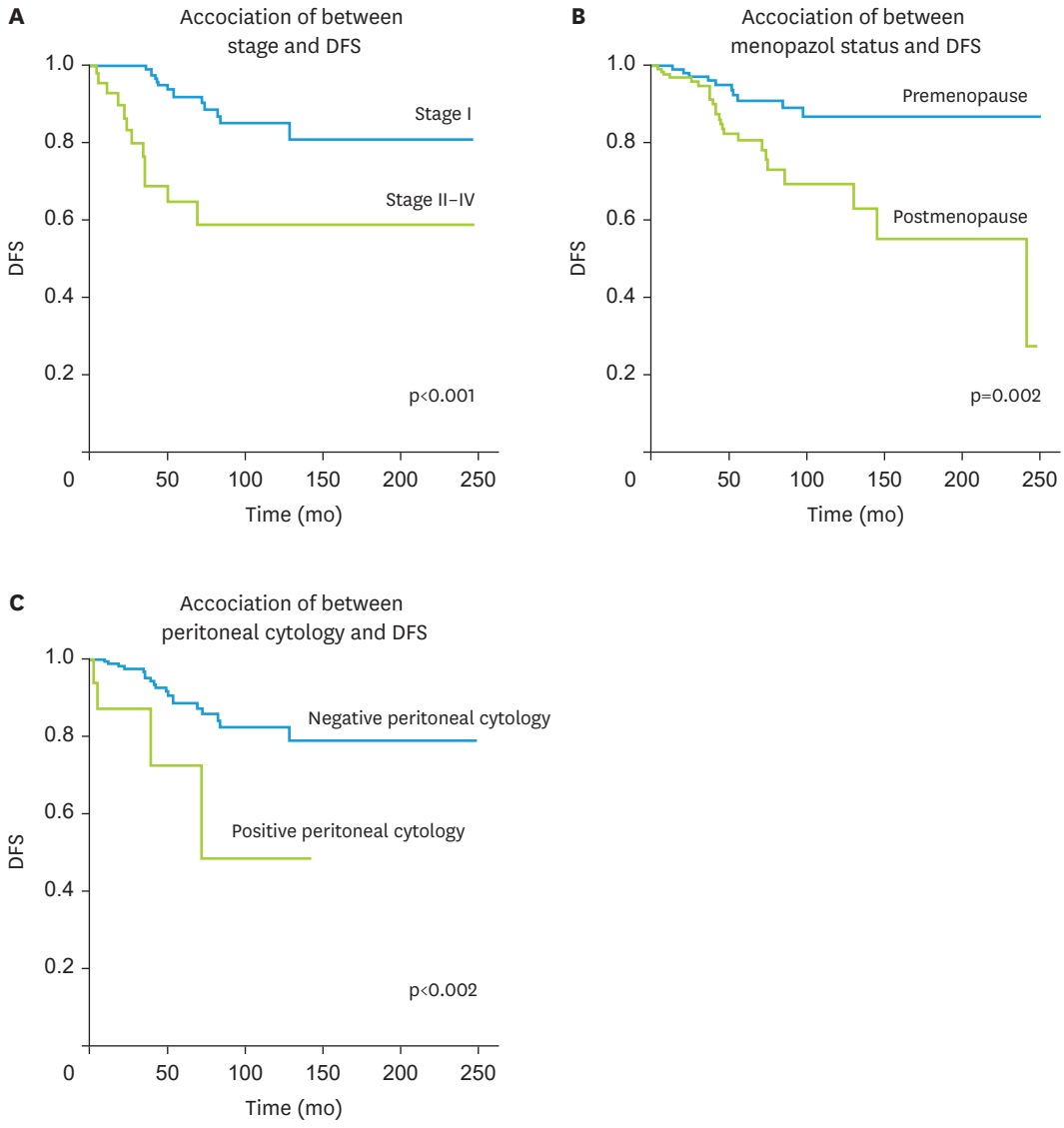


Fig. 1. Association of between stage, menopazol status, peritoneal cytology and DFS.
DFS, disease-free survival.

One of the essential features of AGCT tumors is the endometrial pathologies that occur due to the estrogen they secrete. A study examining 150 patients with primary adult AGCT found that 29.2% had hyperplasia and 7.5% had endometrial carcinoma. The same study highlighted that almost all patients with endometrial hyperplasia and endometrial cancer were over 40. For this reason, it was indicated that endometrial sampling should be performed in AGCT patients over 40 years of age [26]. In another study evaluating 1,031 cases with AGCT, it was found that 58 patients (5.9%) had concurrent endometrial carcinoma, 251 patients (25.5%) had endometrial hyperplasia, 89 patients (9.1%) had complex hyperplasia, and 162 patients (16.5%) had simple hyperplasia. In this study, almost all (96.6%) patients diagnosed with endometrial cancer were older than 45. Also, they found that most of the diagnosed endometrial cancers were low-grade, endometrioid type, and early-stage [27]. In another study presented by Lee et al., [28] examining 68 patients with AGCT, 26.4% of the included patients had endometrial pathology. Among the endometrial pathologies detected, 14% were simple hyperplasia without atypia, 1.4% were simple hyperplasia with atypia, 2.9% were

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complex hyperplasia without atypia, 4.4% were complex hyperplasia with atypia, and 2.9% were endometrial cancer [28]. Pathologic examination of the hysterectomy material in our study revealed simple hyperplasia without atypia in 48 (16.8%) patients, complex hyperplasia without atypia in 9 (3.2%) patients, complex hyperplasia with atypia/ EIN in 19 (6.7%) patients, and grade 1 endometrial cancer in 8 (2.8%) patients. These findings are consistent with the results of studies published in the literature and demonstrate the importance of endometrial examination in patients scheduled for fertility-preserving surgery due to AGCT.

Whether lymph node dissection should be added to the standard surgical treatment of AGCTs remains controversial. Kuru et al., [29] examining 151 patients with AGCT, found that pelvic and para-aortic lymph node dissection was performed in 134 patients. Only 6 (4.5%) patients had lymph node metastases [29]. Another study by Ayhan et al. [30] found that only 1 of 18 patients who underwent lymphadenectomy had lymph node metastases. In another study by Erkılınç et al., [31] lymph node dissection was performed in 53 of 98 patients, and lymph node metastasis was found to be 3.1%. The same study highlighted that lymph node dissection did not affect survival [31]. In our study, lymph node metastases were found in 7 (3.3%) patients, similar to the literature. Studies have shown that lymph node metastases occur, especially in recurrent disease [32]. Abu-Rustum et al. [14] found that lymph node metastasis was 15% in patients with AGCT who had the first recurrence. Brown et al. [15] reported that 6 of 117 (5%) patients with recurrent ovarian tumors had lymph node metastasis. These results suggest that the status of retroperitoneal lymph nodes should be investigated in patients with recurrent AGCT and that lymphadenectomy should be performed in patients with only bulky lymph nodes.

Forty-five patients were analyzed in a study describing surgical and clinical outcomes and spread pathways in the primary and recurrent setting of the disease. Significantly different tumor spread patterns were noted between primary and recurrent patients, with the latter having a significantly higher rate of diffuse peritoneal involvement and extraovarian tumor involvement of the mid-and upper abdomen [33]. A retrospective review of patients with ovarian granulosa cell tumors revealed that 34 patients with recurrent granulosa cell tumors were treated during the study; 31 (91%) had AGCT, and 3 had juvenile histology. The location of the first recurrence included pelvis (70%), pelvis and abdomen (9%), retroperitoneum only (6%), pelvis and retroperitoneum (6%), pelvis/abdomen/retroperitoneum (3%), abdomen only (3%), and bone (3%) [14]. In another study to determine prognostic predictors and patterns of spread in AGCT, the rates of definitive retroperitoneal lymph node metastases at baseline and recurrence were found to be 5.1% (3/58) and 21.4% (3/14), respectively. In the same study, the disease was found to recur in 18 (16.6%) patients, and 8 (7.4%) patients died from the disease. The first sites of recurrence were the pelvic peritoneum in 10 patients, the liver/liver capsule in 5 patients, the rectosigmoid colon in 4 patients, the retroperitoneal lymph nodes in 3 patients, the omentum in 3 patients, the small bowel mesentery in 2 patients, and the vaginal cuff region in 2 patients. Multisite recurrence was observed in 9 (50%) patients. The 5- and 10-year survival rates were 93.3% and 90.9%, respectively. Both stage and residual tumor status were significantly associated with recurrence in univariate and multivariate analyses [34]. According to Mangili et al., [35] 97 AGCTs were evaluated in a study, and 33 patients were found to have recurrence with a median follow-up of 88 months. It was found that 47% of these recurrences occurred five years after the initial diagnosis. The same study highlighted that although the 5-year survival rate was 97%, the 20-year survival rate decreased to 66.8%. In multivariate regression analysis, age and stage were found to be independent poor prognostic factors for survival [35]. Karalok et al. [36] found that menopausal status, advanced age, cyst rupture,

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poorly differentiated tumor, and advanced stage were associated with recurrence in patients with AGCT. The stage was the only independent prognostic factor for the development of recurrence [36]. In another study by Sun et al., [37] the prognosis was found to be related to the initial stage, the presence of residual tumor after initial surgery, and tumor size (>13.5 cm). In our study, 13 (4%) patients had omental metastases, and 19 (5.9%) patients had positive peritoneal cytology. During the follow-up period, recurrence was observed in 34 patients. Recurrences occurred in the pelvis in 13 (38.2%) patients, in the extra-abdominal region only in 4 (11.8%) patients, and in the upper abdomen only in 4 (11.8%) patients. The positivity of peritoneal cytology, stage, and menopausal status were independent predictive parameters in univariate and multivariate regression analysis.

The efficacy of adjuvant treatment for women with advanced and recurrent AGCT remains poorly established. The National Cancer Database analysis of 2,680 women with AGCT revealed no evidence of prolonged survival with adjuvant chemotherapy. Early and complete surgical resection remains the best-evidenced treatment for AGCT [38]. However, Park et al. [5] concluded that optimal debulking followed by six cycles of BEP chemotherapy is recommended for advanced-stage GCT. There are insufficient data on the efficacy of radiotherapy in adjuvant therapy. In a previous study, a total of 103 patients with histologically confirmed AGCT were studied; Hauspy et al. [39] showed that the median DFS was 251 months in patients who underwent adjuvant radiotherapy compared with 112 months in patients who did not receive adjuvant radiotherapy. On multivariate analysis, adjuvant radiotherapy remained a significant prognostic factor for DFS [39]. In our study, 28.9% of the included patients received adjuvant treatment. Of the patients who received adjuvant therapy, 91% received chemotherapy only, 3.2% received radiotherapy only, and 2.2% received chemotherapy plus radiotherapy. The most commonly used chemotherapy regimen in adjuvant therapy was the BEP protocol. The most recent ESMO, ESGO, and SIOPE guidelines also continue to recommend the most commonly used BEP regimen [40].

The main limitation of our study is the retrospective study design. Another significant limitation is the lack of a central pathologic examination. However, the large number of participants and the presentation of long-term follow-up results of the included patients are important strengths of our study. Therefore, our study provides additional information on the state of knowledge on this topic.

In conclusion, patients with AGCT should be carefully evaluated for endometrial cancer because of increased estrogen activity. In these cases, lymph node metastasis was found in 3.3%, so that systematic lymph node dissection can be avoided in the primary treatment of patients with AGCT. In our cohort, recurrences also occurred most frequently in the pelvis. Positivity of peritoneal cytology, stage, and menopausal status were found to be independent prognostic predictors of DFS.

SUPPLEMENTARY MATERIALS

Table S1

Adjuvant therapy (n=90)

Table S2

Recurrence pattern, patients (n=34)

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