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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Management of Granulosa Cell Ovarian Tumors: 10-Year Experience in a Tertiary Center

Granüloza Hücreli Over Tümörlerinin Yönetimi: Tersiyer Bir Merkeze Ait 10 Yıllık Deneyim

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Abstract

Objective: Granulosa cell tumors (GCT) arise from the mesenchymal cells and sex cords of the ovaries and can be observed in women of all age groups. This study presented our 10 year-long gynecology oncology experience on the clinical course and outcome of GCT cases.

Methods: Thirty-one patients who were operated due to suspicious adnexal masses in our hospital between January 2011 and January 2018 and whose final pathology report confirmed the diagnosis of GCT was included in the study. The data of the patients were evaluated. Preoperative ultrasound findings and serum tumor marker results are noted.

Results: Twenty-nine (94%) patients were diagnosed with AGCS and only two (6%) patients were diagnosed with JGCS. The mean age of the study population was 47.74 14.47 years and the mean body mass index was 32.51 7.1. Most patients presented with heavy menstrual bleeding (29%). 48.4% of the patients underwent hysterectomy with bilateral salpingo-oophorectomy, and complete lymph-node dissection, whereas 22.6% of them had hysterectomy with bilateral salpingo-oophorectomy, and 29% of them had oophorectomy only. Three patients (9.3%) had a disease recurrence. The overall survival was 54.4 29.3 months and disease free survival was 49.6 24.2 months.

Conclusion: The most important predictor of survival among patients with GCT is a disease stage at the time of initial diagnosis. Long-term surveillance, including routine clinical follow-up and evaluation of tumor markers is mandatory.

Keywords: Granulosa cell tumor, prognosis, surgery, tumor markers

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Öz

Amaç: Granüloza hücreli tümörler (GCT) yumurtalıkların mezenkimal hücrelerinden ve cinsiyet kordonlarından ortaya çıkar ve her yaş grubundaki kadınlarda görülebilir. Bu çalışma, GCT olgularının klinik seyri ve sonuçları hakkında 10 yıllık jinekoloji onkoloji deneyimimizi sunmayı amaçladı.

Yöntem: Ocak 2011-Ocak 2018 tarihleri arasında hastanemizde şüpheli adneksiyal kitle nedeniyle ameliyat edilen ve son patoloji raporu GHT tanısı ile doğrulanan 31 hasta çalışmaya dahil edildi. Hastaların verileri değerlendirildi. Preoperatif ultrason bulguları ve serum tümör belirteç sonuçları not edildi.

Bulgular: Yirmi dokuz (%94) hastaya AGCS tanısı kondu ve sadece iki (%6) hastaya JGCS tanısı kondu. Çalışma popülasyonunun ortalama yaşı 47,74 14,47 yıl ve ortalama vücut kitle indeksi: 32,51 7,1 idi. Hastaların çoğu ağır adet kanaması (%29) ile başvurdu. Hastaların %48,4'üne bilateral salpingo-ooferektomi ve tam lenf nodu diseksiyonu ile histerektomi, %22,6'sına bilateral salpingo-ooferektomi ile histerektomi, %29'una sadece ooferektomi yapıldı. Üç hastada (%9,3) hastalık nüksü vardı. Genel sağkalım 54,4 29,3 aydı ve hastalıksız sağkalım 49,6 24,2 aydı.

Sonuç: GCT'li hastalar arasında sağkalımın en önemli prediktörü, ilk tanı anındaki hastalık evresidir. Tümör belirteçlerinin rutin klinik takibi ve değerlendirmesini içeren uzun vadeli sürveyans zorunludur.

Anahtar Kelimeler: Granüloza hücreli tümör, prognoz, cerrahi, tümör belirteçleri

Introduction

Granulosa cell tumors (GCT) arise from the mesenchymal cells and sex cords of the ovaries. It represents about 70% of sex cord-stromal tumors and accounts around 5-8% of all ovarian malignancies[1]. There are two different types of GCT, namely, adult-type GCTs (AGCTs) and juvenile type GCTs (JGCTs). 5% of GCT could occur in pre-pubertal girls who are named the juvenile type of GCT. The different classification of the tumor is based on histological appearance rather than patient age[2,3].

The tumor is almost always unilateral, and bilateral involvement has only been observed in 2% of the cases. GCTs usually present with excess secretion of estrogen and can be observed in women of all age groups. Patients AGCTs usually present with estrogen-related abnormalities such as menstrual irregularities and endometrial hyperplasia[4]. On the other hand, JGCTs mostly present with precocious puberty in about 75% of the cases[5].

Indeed, the clinical presentation and manifestation of GCT are non-specific and a detailed medical history and a great suspicion is entirely required. The definitive diagnosis of GCTs is mainly possible with histopathological analysis of the tissue obtained by adnexal surgery[3].

The treatment of GCT is similar to all epithelial ovarian tumors and a staging-surgery is recommended. However, due to the lack of information regarding fertility preservation, the role of adjuvant treatment, and the accurate extensity of index surgery, more data are still needed to clarify the descent management of GCTs[3].

In this study, we presented our 10 year-long gynecology oncology experience on the clinical course and outcome of GCT cases.

Materials and Methods

Thirty-one patients who were operated due to suspicious adnexal masses in a tertiary referral hospital between January 2010 and January 2020 and whose final pathology report was confirmed the diagnosis of GCT was included in the study. The data of the patients were evaluated after obtaining ethical approval from the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Education and Research Hospital (approval number: 2020/501, date: 2020). The inclusion criterion was the patients histopathologically confirmed granulosa tumors of the ovary. The exclusion criteria were as follows: patients with any other ovarian malignancies instead of GCT and patients with missing medical records. The basic data of patients such as age, gravida, parity, body mass index (BMI), and complaints on admission, were recorded. Preoperative ultrasound findings and serum tumor marker results are noted. The types of surgeries and the final pathology reports were also evaluated. The diagnosis of GCT was based on the morphological features of the excised ovarian tissue; however in suspicion, inhibin staining was also performed to confirm the diagnosis. To determine the type of surgery the decision making was based on the patients' fertility desire in patients with reproductive age. On the other hand, additional lymphadenectomy was performed in patients with palpable or bulky pelvic lymph nodes, otherwise hysterectomy and bilateral oophorectomy were performed as the standard approach.

Postoperative follow-up duration, survival rate and time to recurrence were also analyzed.

Statistical Analysis

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences version 22.0 software (IBM

Corp., Armonk, NY, USA). Descriptive data were expressed as mean and standard deviation, median (minimum-maximum) values, number (n), and frequencies (%). Kaplan-Meier survival analysis was performed to define overall survival and disease-free survival.

Results

Twenty-nine (94%) patients were diagnosed with AGCS and only two (6%) patients were diagnosed with JGCS. The mean age of the study population was 47.74±14.47 years and the mean BMI was 32.51±7.1 kg/m^2. The distribution of premenopausal and postmenopausal patients had almost the same rates (51.6% and 48.4%, respectively). Most patients presented with heavy menstrual bleeding (29%). 48.4% of the patients underwent hysterectomy with bilateral salpingo-oophorectomy, and complete lymph-node dissection, whereas 22.6% of them had hysterectomy with bilateral salpingo-oophorectomy, and 19.4% of them had oophorectomy only. Nine (29%) patients required a fertility preserving approach. The mean serum levels of CA125 and CA19-9 were 93.7±250.73 U/mL and 44.1±161.56 U/mL, respectively. Eight (26%) patients had a CA125 level above 35 U/mL. Twenty-eight (90.3%) patients had unilateral involvement whereas only 3 (9.7%) patients had bilateral tumor attachment. 70.9% of the patients had with stage 1 disease and 19.4% of them were with stage 3 disease. Adjuvant chemotherapy was started for 16 (52%) patients. Fourteen (45%) patients had Carboplatin+paclitaxel (carbotaxol) protocol, whereas 2 of them received bleomisin+etoposid+cisplatin (BEP) protocol. 90.3% patients had inhibin stain positivity in the immunohistochemistry investigation. Three patients (9.3%) had a disease recurrence. The overall survival was 54.4±29.3 months and disease free survival was 49.6±24.2 months (Figures 1, 2). Only two patients died during the follow-up due to accompanying metabolic disorders (Tables 1, 2).

Table 1. The basic characteristic of the study population, laboratory and surgical results

Age (years)		47.74±14.47
Gravidity		2.2±1.9
Parity		2.1±1.5
BMI (kg/m^2)		32.51±7.1
Postoperative follow-up (years)		4.4±2.6
Menopausal status	**Premenopausal**	16 (51.6%)
	Postmenopausal	15 (48.4%)
Presenting symptoms	**None**	3 (9.7%)
	HMB	9 (29%)
	Postmenopausal bleeding	3 (9.7%)
	Pelvic mass	3 (9.7%)
	Pelvic pain	12 (38.7%)
	Amenorrhea	1 (3.2%)
Tumor diameter (cm)		11.4±7.7
Ca 125 (U/mL)		93.7±250.73
Ca 15-3 (U/mL)		14.8±6.2
Ca 19-9 (U/mL)		44.1±161.56
CEA (U/mL)		1.3±1.3
Inhibin (U/mL)		37.7±91.5
Surgery	**Hyst+BSO**	7 (22.6%)
	Hyst+BSO+ complete lymph-node dissection	15 (48.4%)
	Oophorectomy	9 (29%)
Fertility preserving	**Yes**	9 (29%)
	No	22 (71%)

BMI: Body mass index

Discussion

In our study, the prevalence of the GCT subtypes was at the same line with the literature as 94% patients were with AGCT diagnosis and only 6% of them had with JGCT[6,7].

Regarding the patients' characteristics in the literature, the reported age at the time of diagnosis could vary between 46 and 50 years, and most of them are in the postmenopausal period[6-8]. However, those patients diagnosed with JGCT are reported to be younger and 45.5% of them being premenarchal period[6]. Our study group also had the same age group at around 48 years. However, the patients with JGCT diagnosis were in 20 and 30 years in our study group.

According to a recent study including 104 patients with the diagnosis GCT, the median BMI was 29 (range, 12-57) kg/m^2. The authors also reported an equal distribution of GCT among the normal-weight and obese patients[8]. However, our study group showed an average BMI of 32.5 kg/m^2 which could be accepted as an obese population. These results could be associated with ethnicity and different dietary habits.

Although the definitive diagnosis of GCT is possible with surgery, the most GCT patients present with the following symptoms, such as vaginal bleeding (16.7-46%), palpable abdominal mass (28.4%), pelvic pain (17.6-44.3%), and amenorrhea (3.9-10%)[6,9]. Moreover, about 18.6-21% of

Table 2. Postoperative findings of the study population		
Number of pelvic lymph nodes	8.6±11.3	
Number of paraaortic lymph nodes	5.7±7.2	
Overall survival	54.4±29.3	
Disease free survival	49.6±24.2	
Mean follow-up (months)	50.6±37.2	
Exitus	**Alive**	29 (93.5%)
	Exitus	2 (6.5%)
Recurrence	**Yes**	3 (9.7%)
	No	28 (90.3%)
Stage	**I**	22 (70.9%)
	II	3 (9.7%)
	III	6 (19.4%)
	IV	0 (0)
Recurrence treatment	**Surgery**	1 (3.2%)
	Surgery+CT	1 (3.2%)
	CT	1 (3.2%)
Adjuvan chemoteraphy	**Yes**	16 (51.6%)
	No	15 (48.4%)
LVSI	**Yes**	2 (6.5%)
	No	29 (93.5%)
Laterality	**Unilateral**	28 (90.3%)
	Bilateral	3 (9.7%)
Ascites	**Yes**	4 (12.9%)
	No	27 (87.1%)
Fertility preserving	**Yes**	9 (29%)
	No	22 (71%)
Inhibin staining	**Negative**	3 (9.7%)
	Positive	28 (90.3%)

patients with advanced disease may present with ascites. Only about 20% patients are asymptomatic and are diagnosed incidentally[6]. In our study, the common symptoms were pelvic pain and abnormal vaginal bleeding. The pain could be related to compression of the pelvic structures and innervation of pelvic sensory nerves due to the presence of a pelvic mass. Abnormal uterine bleeding could be related to increased estrogen levels that result from distorted endometrial proliferation.

The reported mean tumor size among GCT patients varies between 9.2-10.4 cm in the literature. Besides, the most cases tend to be unilateral[6,7]. In our study, almost the same rates were observed. 90.3% patients had unilateral involvement whereas only 3 (9.7%) patients had bilateral tumor attachment. The mean tumor size was around 11 cm.

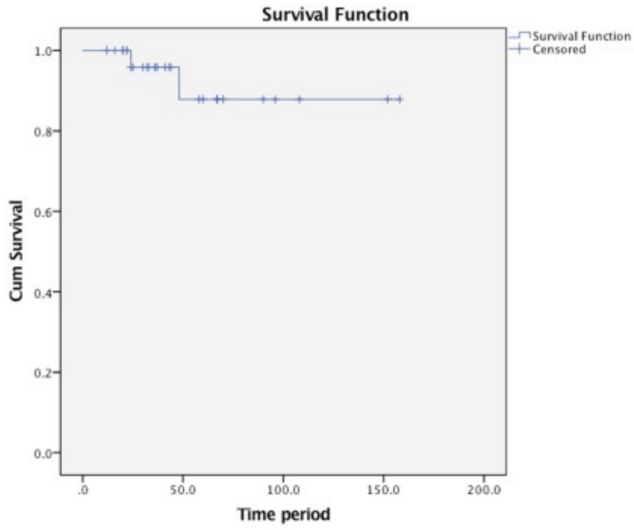

Figure 1. Kaplan-Meier overall survival plots of the study population

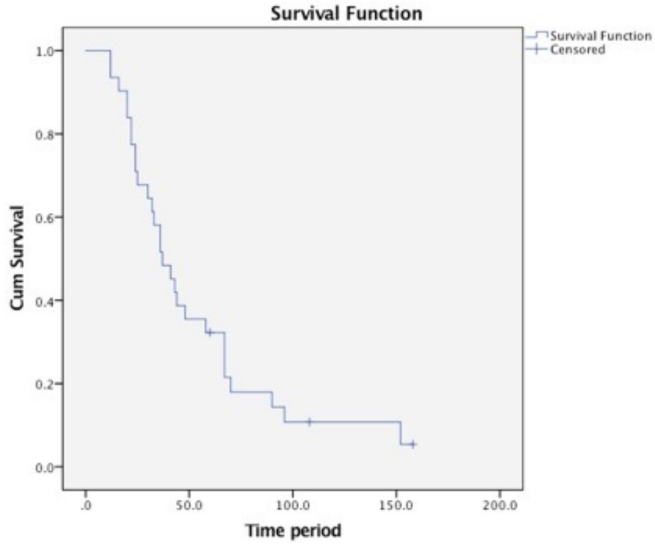

Figure 2. Kaplan-Meier disease-free survival plots of the study population

The efforts have been put for the preoperative diagnosis of GCT on various serum markers so far. In a longitudinal, partially prospective study including 123 patients[10], serum anti-mullerian hormone (AMH) and inhibin B levels were investigated. The authors have reported that AMH could be a useful serum marker for the diagnosis of primary and recurrent GCT cases with high sensitivity (92%) and specificity (81%) rates. Besides, the authors concluded that AMH could be correlated with tumor size[10].

CA 125 that is the most commonly analyzed tumor marker in epithelial over tumors, also studied in GCTs. Lee et al.[6] reported the results of a study covering 76 patients with the diagnosis of GCT. They concluded that only 13.1% of the patients had an elevated CA125 level (>35 IU/mL). In another study by Yesilyurt et al.[7], the mean CA 125 level was 64.5±130.3.

IU/mL in GCT patients. In our study, 8 (26%) patients had a CA125 level above 35 IU. Although there is still a lack of proven preoperative diagnostic tool yet, serum CA125, AMH, and inhibin B could be promising serum markers.

Regarding the prognostic factor of GCT, the stage of the disease is the most reliable factor[3]. Fortunately, most of the cases are diagnosed in the early stage of the disease because of its symptomatic nature. The reported incidence of stage 1 disease varies between 74% and 95%, and it is 5.1-11% for stage 2, 0.8-10% for stage 3, and 0.5-8.6% for stage 4 disease[3]. In our study, 70.9% of the patients were diagnosed in the stage 1 and the second most observed disease stage was stage 3 with a rate of 19.4%. The two deaths in our study were with a history of recurrence and stage 4 disease with accompanying metabolic disorders.

The recommended treatment of GCT is a complete surgery[3]. The suggested surgical procedure involves hysterectomy and bilateral salpingo-oophorectomy, and endometrial biopsy. Evidence regarding lymph node dissection is scarce, particularly in early-stage cases and is still not recommended in routine management. However, a complete cytoreductive surgery is recommended for the patients with advanced disease (stages 2-4)[3].

Another issue to consider is fertility preservation since the patients with reproductive age could be observed. The recommended surgical approach is ipsilateral salpingo-oophorectomy and staging procedure for the patients in early-stage and with fertility desire. In a study by Lee et al.[6], including 36 patients with fertility-sparing surgery due to GCT, 22% of them had one pregnancy and 16% they delivered successfully. In our study, most patients underwent hysterectomy and bilateral salpingo-oophorectomy including complete lymph node dissection. Only 9 (29%) patients underwent oophorectomy due fertility desire. In the same line as in the literature, hysterectomy and bilateral salpingo-oophorectomy were preferred only for those patients with early stage of the disease.

Although the role of adjuvant chemotherapy has not been completely proven yet, it is commonly used for patients with advanced, recurrent, or metastatic disease[11]. The most preferred adjuvant chemotherapy protocols are BEP (77%)[6], cyclophosphamide, adriamycin, and cisplatin and vincristine, bleomycin, and cisplatin protocols[6]. The use of adjuvant chemotherapy for the patients in early stage disease remains controversial, but the decision should be made on an individualized basis[12]. In our study 52% of the patients received an adjuvant chemotherapy protocol after careful discussion with the patients on the costs and benefits of the treatment.

The reported rate of recurrence in GCT is varied between 10 and 64% and the mean surgery to recurrence period is 48-57 months[6,9,13]. The recurrence could be diagnosed with histological evaluation, imaging, or less likely increased tumor marker levels[13]. The recurrence is directly correlated with disease stage and a 40% recurrence rate was reported in stage 3 patients[6,9,13,14]. Besides, the tumor size and higher BMI are also considered independent risk factors for the recurrence[14]. The histological features predicting recurrence are mitotic rate above 4/10 HPF[14], nuclear pleomorphism[15], CD56, inhibin, HER2, and SMAD3 expression[15]. In our study, 90.3% patients had inhibin stain positivity in the immunohistochemistry investigation.

The reported overall 5-year and 10-year survivals of GCT were 92.6-97% and 91-95%, respectively. Additionally, the 5-year and 10-year disease free survival rates were reported as 91.8% and 71.6%, respectively[9,13]. In our study, the overall survival was 54.4±29.3 months and disease free survival was 49.6±24.2 months.

Study Limitations

The retrospective characteristic of the study and small number of the patients could be mentioned as study limitations.

Fertility-preserving surgery can be performed safely among women of childbearing age with early-stage disease, -however, definitive surgery is recommended following completion of family planning[3,13]. The role of adjuvant chemotherapy treatment is debatable as it has not shown to improve survival rates, and is currently recommended only in those with advanced, recurrent, or metastatic disease. Long-term surveillance, including routine clinical follow-up and evaluation of tumor markers is mandatory[3,12,13].

Conclusion

In our study, most patients were diagnosed with AGCT and they mostly presented with heavy menstrual bleeding. Besides, about half of the study population underwent hysterectomy with bilateral salpingo-oophorectomy, and complete lymph-node dissection, whereas about 1/4 of them had only hysterectomy with bilateral salpingo-oophorectomy.

Ethics

Ethics Committee Approval: This study was a retrospective study and was approved by the Local Ethics Committee of the University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Education and Research Hospital (approval number: 2020/501, date: 2020).

Informed Consent: Informed consent was obtained from the parents of all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K., A.B.Ö., G.D., C.C., A.Ö., S.A., Concept: S.K., A.B.Ö., G.D., S.S.Ç., B.A., Design: S.K., A.B.Ö., G.D., Data Collection, or Processing: G.D., C.C., Analysis, or Interpretation: S.K., A.B.Ö., G.D., S.S.Ç., B.A., Literature Search: G.D., C.C., Writing: S.K., A.B.Ö., G.D.

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