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Obstetrics and Fertility Prognosis of Patients With Ovarian Granulosa Cell Tumors: A Retrospective Study in Northwest Iran

Vahideh Rahmani[1], Elham Shahhosseini[1*], Manizheh Sayyah-Melli[1], Hosein Azizi[1], Maryam Vaezi[1], Mehri Jafari[1], Parvin Mostafa-Gharabaghi[1]

Abstract

Objectives: Ovarian granulosa cell tumors (GCT) are rare tumors with a late recurrence and a good prognosis. The current study investigated the fertility and obstetrics situation, survival, and the factors influencing the mortality of patients with these uncommon ovarian neoplasms.

Materials and Methods: This is a retrospective study on ovarian GCT patients admitted to the Al-Zahra hospital oncology department, the tertiary referral hospital in Tabriz, between 2009 and 2022. Data were collected from medical records. Chi-square/Fisher exact tests and t tests were used to compare categorical and quantitative variables between the alive and dead patients, respectively. The Kaplan-Meier curve was used to present patients' survival.

Results: The study involved 65 patients with ovarian GCT. The presence of ovarian cysts statistically increased the survival of GCT patients ($P=0.028$). The advanced tumor stage ($P=0.023$), fast tumor growth ($P=0.001$), and tumor relapse ($P=0.001$) are significantly correlated with mortality in the affected patients. However, age and adjuvant chemotherapy were not associated with survival.

Conclusions: There was no evidence of increased survival with the use of adjuvant chemotherapy. Tumor staging is an important prognostic factor. Advanced stages were associated with inferior survival, and only prospective studies can ascertain their definite role.

Keywords: Ovarian granulosa cell tumors, Prognosis, Survival

Introduction

The granulosa cell tumor (GCT) is one of the most common subgroups of ovarian sex cord-stromal tumors, accounting for about 5% of all ovarian cancers (1). The incidence of GCT is reported to be between 0.47 and 1.6 in 100 000 (2). Histologically, about 95% of GCTs belong to adult granulosa cell tumors (AGCTs), and the rest (5%) are attributed to juvenile granulosa cell tumors (JGCTs) (3). The distinction between GCT subgroups is not based on the age of the patient but on the appearance of tumor tissue (4). AGCTs occur in older women, while JGCT occurs only in people younger than 30 years of age with clinical characteristics, hypoestrogenism symptoms, and abnormal abdominal mass (5). Clinically, JGCTs appear mainly with premature puberty due to abnormal secretion of high estrogen (6). Unlike ovarian epithelial cancers, GCT often does not cause papillary protrusions and is limited to the ovaries, so in this type of patient, the formation of ascites is rare (7). These tumors actually have specific clinical, histological, and evolutionary characteristics and may recur up to 40 years after re-diagnosis (6). The main risk factors for GCT include obesity, oral contraceptives, and family cancer history (2). Many factors are important to the prognosis, including the stage of referral, the age of diagnosis, the size of the tumor, and some histological parameters (8). Although there is no standard treatment for this condition, surgical intervention, especially in the early stages, has been reported to be the mainstay of treatment (9). Chemotherapy has been reported to be recommended in patients with relapses or metastases (9). Although several studies have reported clinical manifestations, prognostic examinations, and factors affecting the mortality of patients with ovarian GCT, no studies have yet examined the prognostication and factors affecting the mortality of patients in Tabriz. So, in this study, we decided to thoroughly explore the prognosis and potential factors affecting the mortality of infected patients from 2009 to 2022 in Tabriz.

Materials and Methods

Study Design and Setting

In this retrospective study, information on pathological clinical findings with ovarian GCT diagnosis was obtained from 65 patients (the study population) who were treated from 2009 to 2022 in the oncology department of Al-Zahra hospital, northwest Iran. We included all 65 patients with confirmed pathological findings for GCTs in the study. All patients had full medical records in the

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[1]Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
***Corresponding Author:** Elham Shahhosseini, Telefax: +984135541221, Email: elhamshahhosseini1981@gmail.com

oncology department of Al-Zahra hospital.

Data Collection

A checklist was used to collect the data. Demographics, clinical, and pathological characteristics included diagnostic age, marital status, occupation, citizenship, rural or urban, educational status, weight, menstrual and menopausal status, childbirth, pathological symptoms, tumor stage, and initial treatment, according to the International Federation of Gynecology and Obstetrics (FIGO). Information on patient follow-up included medical records, dates and characteristics of relapse, tumor relapse time, overall survival (OS), and chemotherapy. In the current study, OS was calculated from the date of initial treatment to the date of death or last follow-up. Phone calls and patient re-visits were used to keep track of patients' conditions.

All patients were staged for ovarian cancer based on the new classification of FIGO (2014). The study's exit criteria included individuals diagnosed with a malignancy other than adult GCT or endometrial carcinoma. Additionally, six cases were excluded due to pregnancy. Prior to conducting our scoping study, informed written consent was obtained from each patient.

Statistical Analysis

The statistical analyses were done using SPSS software v.21.0. The normality of the data was assessed using the Kolmogorov-Smirnov test. Patients were categorized into two groups: alive and dead. Based on the results of normality, the independent *t* test and Mann-Whitney U test were used for quantitative values with parametric and non-parametric distributions. The Kaplan-Meier survival curve was used to plot survival probabilities, and the log-rank test was used to test for significance. A *P* value < 0.05 was taken as statistically significant.

Results

Demographic Profile

A total of 65 confirmed patients with GCT participated in the study. The mortality proportion was 11 (17%). In this study, 47 cases in the age range of less than 60 years were alive, and 8 cases died, while in the age range above 60 years, about 7 cases were alive, and three people died. Among the 65 patients included in the study, the largest group consisted of homemakers, totaling 61 individuals. Out of these homemakers, 50 were still alive, while 11 had passed away. Out of the total of 65 patients who were included in the study, the majority (n = 61) were homemakers, 50 of them were alive, and 11 of them had died. The rest of the people (4) were working and alive. Out of 50 residents of the city, 43 were alive, and seven had died. Out of the 15 people in the village, 11 were alive, and 4 of them died. Regarding literacy level, 20 of 27 people who were illiterate or had primary education were alive; 23 of 27 individuals with high school education were alive; and all 11 individuals with an academic education were alive. Our results showed no statistically significant difference in terms of age at diagnosis, marital status, occupation, place of residence, and educational status in living and dead patients (all $P < 0.05$) (Table 1).

Clinical Laboratory Findings and the Mortality of Patients With Ovarian Granulosa Cell Tumor

In this study, a statistically significant difference was observed between the presence of ovarian cysts and the survival of patients ($P = 0.028$). Out of the 54 individuals, a total of four incidences of amenorrhea were reported, whereas the remaining individuals did not exhibit this condition. Parity has been reported to be about 3.11 in living people and about 3.7 in deceased patients. Bleeding after menopause was observed in nine cases; seven of them were alive, and the rest died, and 56 cases did not show bleeding after menopause, of which about 47 cases were alive, and the rest died. The history of tumors in the family was observed in 7 living people, while there was no report of tumor history in 47 cases. Ovarian neoplasm was reported in 3 cases, while it was not reported in 51 cases. Tumor markers before surgery were not observed in 13 cases out of a total of 54 people who were alive. In

Table 1. The Association Between Demographic Characteristics and Mortality in Patients With Ovarian Granulosa Cell Tumor

Variable		Alive (n= 54, 83%)	Dead (n= 11, 17%)	*P* Value	Statistical Test
Age (at diagnosis)	Average	46/7	49/45	0.495	T-test
	<60 years	47	8	0.231	χ^2
	>60 years old	7	3		
Marital status	Married	50	9	0.260	χ^2
	Single	4	2		
Job	Housewife	50	11	0.355	Fisher exact
	Employee	4	0		
Residency	City	43	7	0.251	χ^2
	Village	11	4		
Education	Illiterate or elementary	20	7	0.062	χ^2
	Middle school or high school	23	4		
	Academic	11	0		

comparison, tumor markers were found to be elevated in 21 cases and normal in 20 cases before surgery. However, there is no statistically significant difference between live and dead patients in terms of weight, fertility, amenorrhea, postmenopausal bleeding, myoma, abnormal uterine bleeding, or tumor history in the family ($P < 0.05$; Table 2).

Importance of Chemotherapy, Tumor Recurrence, and Disease Stage in Mortality of Patients With Ovarian GCT

Tumor recurrence was statistically significant in both living and deceased patients ($P < 0.001$). Also, there was a significant difference in OS between patients with the local stage and those with the advanced tumor stage ($P = 0.023$). In addition, ovarian GCT with slow growth (n=52) showed a statistically significant difference with the survival status of patients ($P = 0.001$). However, no statistically significant difference was observed between adjuvant treatment and chemotherapy with living and deceased patients ($P > 0.05$) (Table 3).

Fertility Status in Patients With Ovarian Granulosa Cell Tumor

In the present study, we examined the fertility status of patients with GCT of the ovary. Reproductive desire was reported in 16 cases of living people, while it was not reported in 38 cases. Pregnancy after treatment was not

Table 2. The Association Between Clinical Laboratory Findings With the Mortality of Patients With Ovarian Granulosa Cell Tumor

Variable		Alive (n= 54, 83%)	Dead (n= 11, 17%)	*P* Value	Statistical Test
Gravity	Average	3.57	4.55	0.375	Mann–Whitney
Parity	Average	3.11	3.7	0.360	Mann–Whitney
Amenorrhea	Yes	4	0	0.351	Fisher exact
	No	50	11		
Ovarian cysts	Yes	24	1	0.028	χ^2
	No	30	10		
Post-menopausal bleeding	Yes	7	2	0.658	χ^2
	No	47	9		
Myoma	Yes	3	1	0.657	χ^2
	No	51	10		
Abnormal uterine bleeding	Yes	12	2	0.766	χ^2
	No	42	9		
History of tumor in the family	Yes	7	2	0.658	χ^2
	No	47	9		
Ovarian neoplasm	Yes	3	0	0.285	Fisher exact
	No	51	11		
Tumor marker before surgery	No	13	2	0.851	χ^2
	Increase	21	4		
	Normal	20	5		

Table 3. The Relationship of Treatment, Tumor Recurrence, and Disease Stage in the Mortality of Patients With Ovarian Granulosa Cell Tumor

Variable		Alive (n= 54, 83%)	Dead (n= 11, 17%)	*P* Value[a]
Recurrence	Yes	7	7	0.001
	No	47	4	
Adjuvant treatment	No	50	9	0.260
	Yes	4	3	
Tumor stage	IA	47	7	0.023
	IC	1	2	
	III	3	0	
	IB	1	1	
	IIIC	0	1	
	IC2	1	0	
Tumor growth	Slow	52	4	0.001
	Fast	2	7	
Chemotherapy	Yes	3	2	0.155
	No	51	9	

[a] χ^2 test.

reported in 46 cases, while it was observed in 8 cases. However, there was no statistically significant difference between pregnancy after treatment and living and deceased patients ($P = 0.173$). Furthermore, in the current study, no statistically significant difference was observed between the desire for fertility, use of assisted reproductive technology, delivery after treatment, and live birth after treatment with living and deceased patients ($P < 0.05$) (Table 4).

Prognosis of Patients With Ovarian Granulosa Cell Tumor

It has been found that the diagnosis time until the recurrence of ovarian GCT and the survival of patients in living people is significantly longer than in dead people, which had a statistically significant difference ($P = 0.001$ and $P = 0.041$, respectively) (Table 5). Figure 1 demonstrates the Kaplan-Meier curve for the OS of included patients with ovarian GCT.

Discussion

Ovarian GCT is a rare malignancy that accounts for less than 5% of ovarian cancers (10). The present study examined the importance of various factors of demographic findings in patients with GCTs. The results indicated that there was no statistical difference between living and dead patients in terms of age of diagnosis, marital status, occupation, place of residence, and educational status. The peak incidence of GCT is reported in the postmenopausal period, with an average diagnosis age of 50-55 years (11). The average age in our study was 46 ± 7 in living people and 49 ± 45 in deceased people, which was different from other studies and can be attributed to poor prognosis and follow-up for treatment in our society. The study by Ayhan et al showed that patients aged 60 or younger had a high survival rate compared to older people (12). A study by Mangili et al on 97 patients with ovarian GCT found that age over 50 could be a significant risk factor for survival in patients with GCTs (13). Zhao et al demonstrated that the age of over 50 had a significant difference in the death of affected patients after a recurrence of the GCT tumor (14). The study of Wang et al was not consistent with the above studies and reported that the age of diagnosis has no prognostic value for patients with GCTs (15). The current study showed no statistically significant correlation between demographic findings, especially age of diagnosis.

The second part of the present study showed that clinical laboratory findings, such as the presence of ovarian cysts, have a statistically significant difference in patient survival. In contrast, parity, postmenopausal bleeding, abnormal uterine bleeding, and the history of tumors in the family do not show a statistically significant correlation with patient survival. Le et al reported that menopause status was significantly associated with the survival of patients with ovarian GCT (16). The most common manifestations in the pre-menopausal and menopausal age groups of this condition are abnormal uterine bleeding, which may appear as postmenopausal bleeding, severe or irregular menstruation, or amenorrhea (17). Other major risk factors for GCT include a history of family cancer, which did not show a significant correlation

Table 4. Fertility Status in Patients With Ovarian Granulosa Cell Tumor

Variable		Alive (n= 54, 83%)	Dead (n= 11, 17%)	*P* Value	Statistical Test
Fertility desire	Yes	16	3	0.875	χ^2
	No	38	8		
Pregnancy after treatment	Yes	8	0	0.173	Fisher exact
	No	46	11		
Assisted reproductive technology utilization	Yes	5	0	0.164	Fisher exact
	No	49	11		
Gravid after treatment	0	45	11	0.164	Fisher exact
	1	7	0		
	2	2	0		
Live birth after treatment	0	45	11	0.345	Fisher exact
	1	8	0		
	2	1	0		

Table 5. The Survival, Follow-Up Period, and Time of Tumor Recurrence in Patients With Ovarian Granulosa Cell Tumor

Variable		Alive (n= 54, 83%)	Dead (n= 11, 17%)	*P* Value[a]
Diagnosis until recurrence (months)	Median	48	18	0.001
	Average	67	29.9	
Survival	Median	72	60	0.041
	Average	73.65	50.09	

[a] Mann–Whitney test.

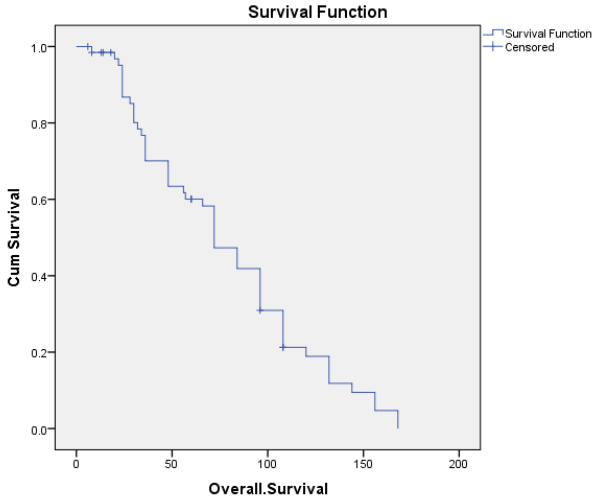

Figure 1. The Overall Survival of Included Patients With Ovarian Granulosa Cell Tumor.

with patient survival in this study.

Boyce et al reported no statistically significant differences between GCT and a family history of ovarian cancer (18), which was consistent with the results of our research. Since granulosa tumors have little ability to become malignant, it has been reported that about 90% of these tumors are in Stage IA. A study found that 87.1% of patients were in the early stages of the disease when they came to check for GCT (19).

In the present study, patients with early-stage (stage I) GCT had higher survival than those with advanced-stage (stage IC—IC2) GCT, so the detection of patients with GCT in the early stages was much higher than in the advanced stages.

Jung and colleagues have shown that patients with advanced stages of GCTs, i.e., stages II and III, have worse survival than patients with stage I tumors (20). Also, a study has shown that patients with stages III and IV have a weaker prognosis compared to patients with stages I and II (18).

The strong prognostic prognosis for the diagnosis of GCT in stage IA can be attributed to hormonal secretion, especially estrogen, from tumors, as well as to clinical manifestations such as abnormal bleeding, which causes early detection of this condition (21).

In this study, advanced stages, tumor growth, and recurrence showed a significant association with patient survival. In contrast, no significant relationship was observed between adjuvant treatment and chemotherapy and patient survival. Since the treatment of this condition depends on the age of the patient and the progression of the disease, in most patients, complete removal of the tumor can be considered the primary treatment for GCTs (22). The choice of chemotherapy for the optimal treatment of GCT patients is still disputed (23). Van Meurs et al have shown that chemotherapy is not worth a significant prognosis in patients with GCTs (24). Mangili et al have reported that adjuvant chemotherapy does not improve the prognosis for patients with GTCs in the IC phase (25). The results of the present study were consistent with the studies mentioned above and did not show a significant difference between adjuvant treatment and chemotherapy in terms of patient survival.

Strengths and Limitations

The study has several strengths. First, the present study has thoroughly examined the prognostic factors affecting the mortality of patients with ovarian GCT. Second, this study is the first to investigate ovarian GCT in the northwestern region of Iran. However, the study suffers from potential limitations, the most notable being the retrospective nature of the study, the long period of study, and the small sample size. Probably, many women did not undergo surgical procedures or receive chemotherapy from the gynecologist. The next limitation was the incompleteness of some medical records. To solve this issue, we obtained the information through phone calls.

Conclusions

Patients with ovarian GCT have a favorable prognosis in the early stages, while the advanced stage of GCT is associated with a poor prognosis. The present study did not report evidence of the role of adjuvant chemotherapy in survival and preventing relapse.

Authors' Contribution

Conceptualization: Parvin Mostafa-Gharabaghi, Vahideh Rahmani, Hosein Azizi, and Elham Shahhosseini.
Data curation: Parvin Mostafa-Gharabaghi, Maryam Vaezi, Manizheh Sayyah-Melli, Vahideh Rahmani, Elham Shahhosseini.
Formal analysis: Hosein Azizi.
Funding acquisition: Vahideh Rahmani and Parvin Mostafa-Gharabaghi.
Investigation: Elham Shahhosseini, Vahideh Rahmani, and Hosein Azizi.
Methodology: Hosein Azizi.
Software: Hosein Azizi.
Supervision: Vahideh Rahmani, Parvin Mostafa-Gharabaghi.
Validation: Vahideh Rahmani and Parvin Mostafa-Gharabaghi.
Writing–original draft: Elham Shahhosseini and Hosein Azizi.
Writing–review & editing: All authors.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study received approval from the Ethics Committee of Tabriz University of Medical Sciences (Approval No. IR.TBZMED.REC.1402.656). Informed consent was obtained from participants at the Al-Zahra Oncology Unit prior to the commencement of the study.

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This study was approved by Tabriz University of Medical Sciences under approval number 72339.

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