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## **PROGNOSTIC FACTORS AND TREATMENT MODALITIES OF GRANULOSA CELL TUMOR IN SOUTH OF IRAN**

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### **ABSTRACT**

Granulosa Cell Tumors (GCTs) are uncommon ovarian tumors which are divided into adult and juvenile types. These tumors appear with different symptoms such as Abnormal Uterine Bleeding (AUB), abdominal pain, and distension. Moreover, these tumors have the potential of low grade malignancy and may relapse several years after treatment. Numerous prognostic factors are important in survival of the patients such as tumor stage, rupture, size, number of mitoses, patient's age, etc. The aim of this study was to investigate prognostic factors in GCT patients who were followed in clinics and hospitals affiliated to Shiraz University of Medical Sciences. In a retrospective study, all patients with Granulosa Cell Tumor who referred to Shahid Motahari Tumor Clinic affiliated to Shiraz University of Medical Sciences were selected as subjects. Medical records of 32 patients were investigated for 2 and 5 years' of survival of the patients based on the patients' age, parity, periodic condition, clinical symptoms, and tumor information (rupture, relapse, size, location, type, distinction, differentiation grade, and stage). In addition, information on treatment and disease relapse was collected. Total 32 patients aged between 15-80 were investigated (the average age=43±15). Among them, 30 patients had adult type and 2 had juvenile type of this disease. The patients were followed from 6 to 120 months and 3 relapses were reported among them. Comparison of the 2 types of the disease in patients revealed that only AUB had a statistically significant relationship with the tumor type (Chi-square Test,  $p<0.05$ ), so that 70% of the adult patients had AUB. 5 years and 10 years of disease-free survival were observed in 93.5% and 90.6% of subjects, respectively. Studying the effect of different factors on the disease-free survival indicated that other factors such as the stage, size, and location of tumor, patients' parity, number of mitoses, adjuvant therapy, and age had no statistically significant impact on the tumor relapse. Only tumor rupture had a significant relationship with the disease-free survival. Survival rate in patients with tumor rupture and without tumor rupture was 50±1 months and 114±5, respectively, which shows a statistically significant difference (Log Rank Test,  $p<0.05$ ). These ruptures occurred before the surgery. According to the present study, among different effective factors, only tumor rupture has a statistically significant impact on GCT relapse. However, further research with larger sample size and longer follow-up time is required for better evaluation.

**Keywords:** *Granulosa Cell Tumors, Survival, Relapse, Follow-Up*

### **INTRODUCTION**

Granulosa cells are the somatic cells of the ovarian sex cord which play a crucial role in the maturation of the egg. The most important role of these cells is production of sex steroids and peptides which are used in development of follicles and ovulation (Kottarathil *et al.*, 2013). Granulosa Cell Tumors (GCTs) are uncommon ovarian tumors which are derived from the stromal cells of the ovarian sex cord. These tumors have a low malignant potential and account for 2-5% of total ovarian tumors. GCTs are divided into adult and juvenile groups depending on tissue characteristics and clinical symptoms, while 95% of them are adult (Pectasides *et al.*, 2008. and Geetha and Nair, 2010).

Most of these tumors appear with unspecific symptoms such as abdominal pain and distention. The symptoms of increased estrogen are also seen in all ages which cause breast enlargement and pain. About 25-50% of these tumors appear with endometrial hyperplasia. Sometimes they may also have some parts of sertoli leydig cells which cause androgen secretion and symptoms of virilisation and hirsutism

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(Kottarathil *et al.*, 2013 and Ranganath *et al.*, 2008 and Lee *et al.*, 2011). In women, changes in menstrual pattern such as menorrhagia, hypermenorrhea or amenorrhea at the fertility ages can be seen. Bleeding is the most common symptom of these tumors among postmenopausal women as well. In the elderly women, GCT symptoms may be similar to the ovarian epithelial tumors. About two-thirds of these patients have the symptoms of the tumor which is due to tumor hormone secretion. According to these secretions, GCTs can appear with hyperplasia and endometrial adenocarcinoma (Ranganath *et al.*, and Segal *et al.*, 2008).

Several prognostic factors are reported on GCTs which have a crucial effect on the disease relapse and patient's survival.

Weak prognostic factors which are reported for the disease relapse and low survival rate of the patients are tumor's high grade, high number of mitoses, bilaterality, sizes more than 5 cm, ruptures including surgical rupture, lymphatic damage, atypia, etc. Extensive molecular markers (Ki-67 and p53) are related to high disease relapse and low survival rate of the patients (Ayhan *et al.*, 2009).

Because the tumor is very rare and there is no study about this tumor in the south of Iran, we evaluated the prognostic factors in this population in a long term.

## **MATERIALS AND METHODS**

### **Methods**

This research was a retrospective cross-sectional study conducted on patients with GCT. The patients were treated at hospitals affiliated to Shiraz University of Medical Sciences and followed in Shahid Motahari Clinic of Shiraz, Iran.

At First, 42 patients were investigated and among them, 8 patients because of not having pathology report and 2 of them because of non-referral to the clinic were excluded from the study. Finally, 32 patients with GCT were selected as subjects.

The data of the patients including their age, gravidity and parity, menstrual condition, chief complaint, tumor size, primary location of the tumor, rupture, and grade were collected based on FIGO, surgical and treatment modalities and adjuvant treatment modalities, relapse and death, and survival rate of the patients. Again, the slides were reviewed by two pathologists and after confirming the diagnosis, histopathological findings such as atypia, mitoses, tumor's pattern (micro- or macro-follicular, insular, etc.) and differentiation grade were investigated and recorded.

After investigating the clinical records, pathological reports and treatment information of the patients were analysed using SPSS-17 Software. For determining the survival rate of the patients, Kaplan-Meier Test was applied and the results were compared by Log Rank Test. For analysis of different proportions, Fisher Exact and Pearson's Chi-square tests were used.

## **RESULTS AND DISCUSSION**

### **Results**

The files of 32 patients aged 15-80 with a mean age of 43 were investigated. As to parity condition, 62.5% of them (20 patients) were multiparous, 21.9% (7 patients) were uniparous, and 15.6% (5 patients) were nulliparous. Among them, 56.3% (18 patients) were menopause and 48.8% of them (14 patients) were pre-menopause.

Tumor's condition was investigated in each patient from different aspects including tumor's grade, size, location, and also complications like relapse, rupture, and tumor residue. (Table 1).

Moreover, based on the pathology reports, 93.8% of the patients had adult tumors. The tumor's differentiation grade (well, moderate, poorly) was investigated and the results revealed that most adult type tumors had a well differentiated grade (53.1%).

The number of mitoses was also investigated based on the pathologic report and it was shown that 78.1% of the tumors (25 tumors) had less than 5 mitoses while 21.9% (7 tumors) had more than 5 mitoses in each microscopic field.

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**Table 1: Characteristics of the Tumor**

Tumor's Condition	Tumor's Grade			Tumor's Size		Tumor's Location		Complications		
Categories	Ia	Ic	IIIc	>10cm	<10cm	Rt.	Lt.	Relapse	Rupture	Remaining
Number (Percent)	28(87.7)	3(9.4)	1(3.1)	22(68.8)	10(31.2)	17(53.1)	15(46.9)	3(9.4)	3(9.0)	0(0)

Different clinical symptoms such as abdominal pain (75%), AUB (65.6%) and abdominal distension (40.6%) were reported. Furthermore, according to different conditions, different surgeries were performed on patients including omentectomy, bilateral salpingo-oophorectomy (BSO), left or right unilateral salpingo-oophorectomy, total abdominal hysterectomy (TAH), pelvic lymphadenectomy, and two or three types of these surgeries together. Some patients only underwent surgery; however, for 31.3% of them, in addition to the surgery, adjuvant treatment was applied (Table 2).

**Table 2: Treatment Modalities**

Number (Percentage)	Surgery Type	Characteristics
13(40.6)	TAH+BSO+ Omentectomy+ Pelvic Lymphadenectomy	Surgery Type
4(12.5)	TAH+BSO	
6(18.8)	RSO	
3(9.4)	LSO	
1(3.1)	TAH+RSO	
5(15.6)	TAH+LSO	

Comparison of the clinical symptoms of the two types of tumor, adult type and juvenile type, indicated that neither of them had no statistically significant relationship with abdominal pain and distension, and only Abnormal Uterine Bleeding (AUB) had a statistically significant relationship with adult type (Chi-square Test,  $p < 0.05$ ). Also, the two tumor types had no statistically significant relationship with tumor's stage, size, relapse, rupture, and number of mitoses in each microscopic field.

Comparison of the two types of tumors with patients' parity, menopause, and pre-menopause showed no significant relationship (Chi-square Test,  $p > 0.05$ ). Moreover, the age of patients had no statistically significant relationship with tumor's type (Chi-square,  $p > 0.05$ ).

The above-mentioned factors had also no statistically significant relationship with tumors' type, like differentiation grade. However, as to the menstruation conditions (menopause and pre-menopause), the difference was statistically significant, as 64.7% of the adult type tumors with well differentiated grade and 100% of those with moderate differentiation grade were related to the menopause women. On the other hand, 50% of the juvenile type tumors were related to menopause and 50% of them were related to the pre-menopause women (Chi-square Test,  $p < 0.05$ ).

Comparison of the patients' age indicated that in adult type tumors, the mean age in patients with moderate differentiation was significantly higher (Kruskal-Wallis,  $p < 0.05$ ).

On the other hand, the mean age in juvenile tumor patients with well and moderate differentiation grade tumors was  $47 \pm 14$  and in those with poorly differentiated tumors it was  $34 \pm 11$ .

The patients were followed about  $37 \pm 1$  months. The progression-free survival for 10 years and 5 years were observed among 90.6% and 93.5% of subjects, respectively.

Comparison of patients who had tumors with more than 5 mitoses and less 5 mitoses in each microscopic field indicated that survival rate is higher in the second group. However, the difference was not statistically significant. The progression-free survival was not statistically different in multiparous,

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uniparous, and nulliparous patients, while the highest and lowest survival rates were related to uniparous and nulliparous patients, respectively. Among 3 relapses, 2 were in Ia stage and one was in the Ic stage. The progression-free survival was not statistically significant among them.

The patients received adjuvant treatment showed no statistically significant difference with those without adjuvant treatment. The progression-free survival in patients with tumor's rupture was lower than those without tumor's rupture with a statistically significant difference ( $p=0.003$ ) (Table 1). In these patients, ruptures occurred prior to the surgery. The progression-free survival in patients having a tumor on the left side was higher than those with tumors on the right side. The difference between them was not statistically significant.

## **Discussions and Conclusion**

Investigation of prognostic factors in GCT patients can improve the quality of treatments and follow-ups. Several studies have investigated these factors (Ayhan *et al.*, 2009 and Auranen *et al.*, 2007). The present study was in the same line with previous ones regarding methodology, research population, and the studied prognostic factors.

One of the most important characteristics of GCT tumors mentioned in different studies is that these tumor may relapse after a while (Hopkins *et al.*, 2004 and Suri *et al.*, 2013), in a way that some studies have reported up to 23 years for this relapse (Crew *et al.*, 2005). Thus, long-term follow-ups are essential to investigate such patients. In the present study, the survival of patients started from 6 months after diagnosis and the treatment took up to 120 months after that, which shows an appropriate follow-up time compared with other studies. Hence, longer follow-ups are suggested.

GCTs may appear with different symptoms which are mostly in early stages at the time of diagnosis. Patients in this research were referred with different presentations varying from AUB, abdominal pain, and distension and the majority of them were in the Ia stage at the time of diagnosis. However, one patient was in the IIIC stage. These criteria suggest consistency between the results of the present study and those of previous ones.

Different studies, such as one conducted by Li *et al.*, (2009), have mentioned that age, parity, and the size of tumor have no statistically significant impact on the patients' survival rate. Moreover, chemotherapy had no effect on the survival rate of patients.

In the present study, none of the factors like age, parity, tumor's size, and adjuvant treatment had a statistically significant impact on the patients' survival rate without relapse. This result corresponds with those of previous studies.

Among the studied factors, only tumor's rupture had a statistically significant effect on the progression-free survival. In previous studies, Auranen *et al.*, (2007) reported tumor rupture as the only factor in relation to the tumor's relapse; this corresponds with the present study findings. However, they mentioned the tumors' stage as an important factor in patients' survival rate, which is not consistent with this study results. Probably, one reason for this difference is the fewer relapses in the present study (3 cases) as compared with their study (7 cases).

In the present study, none of the pathological factors such as tumors' differentiation grade and number of mitoses had a statistically significant effect on the survival rate of the patients without relapse. Other researchers like Lauszus *et al.*, (2001) also reported the same results (Lauszus *et al.*, 2001). However, in another study conducted by Li *et al.*, (2009), it was mentioned that pathological factors have a statistically significant effect on patients' survival rate. The reported factors were atypia and increased number of mitoses. In the present study, the number of mitoses was investigated which showed no statistically significant effect on the patients' survival rate.

The important point in the present study is that none of the patients showed remaining tumors while many studies have indicated remaining tumors and investigated their effects on the patients' survival rate (Ayhan *et al.*, 2009; Lee *et al.*, 2011; Kholsa *et al.*, 2014; Sun *et al.*, 2012). These studies have reported that existence of tumor has a statistically significant effect on the tumor's relapse. These results are not consistent with the findings of the present study. However, it is a positive point for the treatments applied for the patients in the present study.



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The present study findings showed no statistically significant difference between patients under the adjuvant treatment and other patients in terms of progression-free survival. However, some other studies such as Hauspy *et al.*, (2011) and Park *et al.*, (2012) reported such a difference between patients who received adjuvant treatment and those who did not receive it. Maybe this difference between the results of those studies and the present study is because of shorter follow-up time in the present study; actually, longer follow-ups may lead to a statistically significant difference between these two groups.

In the present study, in addition to the effect of different factors on the patients' progression-free survival, the relationship between clinical factors and patients' conditions was investigated. For example, with respect to AUB, the tumor's type had a statistically significant relationship with AUB, in a way that in the adult type it was more than the juvenile type.

Tumor's rupture is another important factor affecting the patients' progressive-free survival. Ruptures can occur before or during surgery, when the surgeon's role is crucial.

Few studies have been conducted in Iran on patients' survival rate and different prognostic factors. Regional and ethnic factors may affect these tumors. Thus, conducting more research on the related field can be helpful in identification of the factors affecting these tumors and patients' survival rate. The important point in this study is that most of the patients were in the stage I without chemotherapy.

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