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Adult Granulosa Cell Tumor of the Ovary: A Retrospective Study of 40 Cases

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Authors' contributions

This work was carried out in collaboration among all authors. Author MSZ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author SHE managed the analyses of the study. Author WNA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Granulosa cell tumors (GCTs) are rare ovarian tumors represent only 5% of all ovarian cancers. GCTs are divided into an adult (AGCT) and juvenile (JGCT) types. The prognosis of these tumors is good when compared with other epithelial tumors. Radical surgery and adjuvant chemotherapy according to the presence of risk factors still the main line of treatment. Many Prognostic factors are suggested to affect the course of the disease like tumor stage and extend of surgery. But due to the small number of cases and indolent course of the disease, clinical characteristics and prognostic factors for this type of tumours still unclear.
Aim: To determine the clinical characteristics of cases with AGCT and the prognostic factors for disease relapse and survival.
Methods: This is a retrospective descriptive study. 40 patients with (AGCT) were recruited. Patient characteristics were collected. The disease-free interval and overall survival were determined.
Results: At the end of the study, the median disease-free survival DFS was 101.215 months (93.2-109.3) with statistically significant difference regarding the stage of the disease, extent of surgery, rupture of the tumor and presence of residual disease. The median overall survival OAS was 106.38 months (100.3-112.5) with statistically significant difference regarding stage of the disease, parity and presence of residual disease.

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Conclusion: (AGCT) are rare tumors with excellent survival. Stage of the disease and extent of surgery were significant prognostic factors affecting the course of the disease. Prospective studies are needed for better understanding of this disease.

Keywords: Granulosa cell tumors; surgical staging; recurrence; prognosis.

1. INTRODUCTION

Granulosa cell tumors (GCTs) are rare tumors accounts for only 5% of all ovarian cancers. but they represent 70% of ovarian sex-cord tumors [1]. They first were reported by Rokitanski in 1855 [2]. GCTs are divided into an adult (AGCT) and juvenile (JGCT) types based on differences in clinical and histopathologic features. AGCTs are seen in perimenopausal and postmenopausal women. A peak incidence is 50-55 years. The prognosis of these tumors is good when compared with other epithelial tumors [3]. The pathogenesis of these tumors is not clear. Many investigators suggest that they originate from early ovarian mesenchyma because of the presence of fibroblasts, granulosa cells and theca cells in its composition [4]. High estrogen levels detected in cases with GCT is related to the production of estrogens by the tumor tissue [5]. Radical surgery consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy is the main line of treatment. Adjuvant chemotherapy is indicated in cases with high risk factors like advanced stage and tumor rupture. Fertility-sparing surgery is an option for young patients wishing to maintain fertility. However, till now, the optimal treatment of AGCT is still controversy [6]. Many prognostic factors for GCTs have been determined previously and include age, tumor stage, tumor size, tumor rupture and presence of post-surgical residual tumor. However, clinical characteristics and prognostic factors related to recurrence and survival of this disease are still unclear due to a small number of cases and long course of the disease [7].

1.1 Aim of the Work

- To determine the prognostic factors affecting the course of this tumor either related to patients' characteristics or pathological findings.
- To report DFS and OAS for all cases and how they are affected by different prognostic factors.

2. PATIENTS AND METHODS

This is a retrospective descriptive study performed at clinical oncology and nuclear medicine department, Mansoura university hospital by reviewing outpatient and computerized medical records. 40 patients with adult-type granulosa cell ovarian tumor on histopathological reports who had undergone surgery between 2007 and 2015 were recruited. All data were collected regarding Patient characteristics, extent of surgery, whether received chemotherapy or not, developed recurrence or not, and follow-up status. The disease-free survival was reported from the date of surgery to the date of recurrence or the date of the last visit and overall survival was determined.

2.1 Statistical Analysis

Data were analyzed using the Statistical Package of Social Science (SPSS) (Standard version 24). The normality of data was first tested with one-sample Kolmogorov-Smirnov test.

Qualitative data were assessed using number and percent. Association between categorical variables was examined using Fischer exact test and monte carlo test when expected cell count less than 5. Continuous variables were reported as mean ± SD (standard deviation).

Kaplan- Meier test was used for survival analysis and statistical significance of differences among curves was determined by Log-Rank test.

3. RESULTS

A total of 40 patients with AGCT who presented to our institute from 2007 to 2015 were included in the study. Patients characteristics were collected from outpatients and computerised medical reports and showed in Table 1 where mean age was 51.35 years, 21 cases (52.5%) were premenopausal, and 19 cases (47.5%) were postmenopausal, 4 patients (10%) were nullipara and 36 patients (90%) were multipara. The most common presenting symptoms were bleeding in 19 cases (47.5%) followed by pain in

17 cases (42.5%). The most common presenting site of the tumor was the right ovary (21 cases-52.5%), compared to 14 cases (35%) in the left ovary and the disease presented bilaterally in 5 cases (12.5%). According to the stage; 23 cases (57.5%) presented in stage I, 9 cases (22.5%) in stage II, 4 cases (10%) in stage III and 4 cases (10%) in stage IV. The size of the tumor was more than 10 cm in 27 cases (67.5%) and less than 10 cm in 13 cases (32.5%). After surgery the pathology of the endometrium was assessed where 19 case (47.5%) showed endometrial hyperplasia, 9 cases (22.5%) showed endometrial proliferative disorder, 2 cases (5%) had endometrial cancer, 4 cases (10%) were normal and 6 cases were not assessed.

All cases were undergone surgical treatment with 28 patients (70%) underwent complete surgical staging including total abdominal hysterectomy, bilateral salpingo-oophorectomy, infra-colic omentectomy, pelvic lymphadenectomy with or without para-aortic lymphadenectomy, 12 patients (30%) operated with incomplete surgical staging. Rupture of the tumor was observed in 4 cases (10%) and post-operative radiological assessment showed residual disease in 6 cases (15%). 33 cases 82.5%) received adjuvant chemotherapy (18 cases received bleomycin-etoposide-cisplatin protocol and 15 cases received Taxol-Carboplatin protocol). During the period of follow up, only 7 cases (17.5%) developed relapse, 5 of them showed peritoneal relapse and 2 patients developed nodal (para-aortic and pelvic lymph nodes) relapse as showed in Table 2.

At the end of the study, only 4 patients died. It was noticed that all died patients developed relapse, all of them had a tumor more than 10 cm at presentation, 3 of them had advanced stage (III and IV). This data was statistically significant and indicate that development of relapse, large tumor size and advanced stage are independent predictors of mortality as showed in Tables 3 and 4.

Table 1. Patients characteristics among the studied group

Patients characteristics	Study group (n=40)
Age/ years	
Mean ± SD	51.35±9.54
Menopause	
Premenopause	21 (52.5%)
Post menopause	19 (47.5%)
Parity	
Nullipara	4 (10%)
Multipara	36 (90%)
Symptoms	
Menorrhagia	10 (25%)
Postmenopausal bleeding	9 (22.5%)
Pain	17 (42.5%)
Others	4 (10%)
Location	
Rt ovary	21 (52.5%)
Lt ovary	14 (35%)
Both	5 (12.5%)
Stage	
I	23 (57.5%)
II	9 (22.5%)
III	4 (10%)
IV	4 (10%)
Size	12.97 ± 5.85
≤10	13 (32.5%)
>10	27 (67.5%)
Endometrial pathology	
Endometrial hyperplasia	19 (47.5%)
Endometrial proliferative disorder	9 (22.5%)
Endometrial cancer	2 (5%)
Normal	4 (10%)
Not assessed	6 (15%)

Table 2. Treatment and survival among the studied group

Variables	Study group (n=40)
Surgery	
Complete surgical staging	28 (70%)
Incomplete surgical staging	12 (30%)
Residual	
yes	6 (15%)
No	34 (85%)
Rupture	
yes	4 (10%)
No	36 (90%)
Chemotherapy	
yes	33 (82.5%)
No	7 (17.5%)
Chemotherapy protocol	**n=33**
BEP protocol	18 (54.5%)
Taxol carboplatin	15 (45.5%)
Relapse	
yes	7 (17.5%)
No	33 (82.5%)
Relapse site	**n=7**
peritoneal	5 (71.5%)
nodal	2 (28.5%)

The median follow-up time was 9 years (49-154 months). The median DFS was 101.215 months (93.2-109.3) as showed in Table 5. There was statistically significant difference in the median DFS regarding stage of the disease, extent of surgery, rupture of the tumor and presence of residual but not the age, menopausal status, parity, site and size of the tumor and whether received adjuvant chemotherapy or not as showed in Table 5.

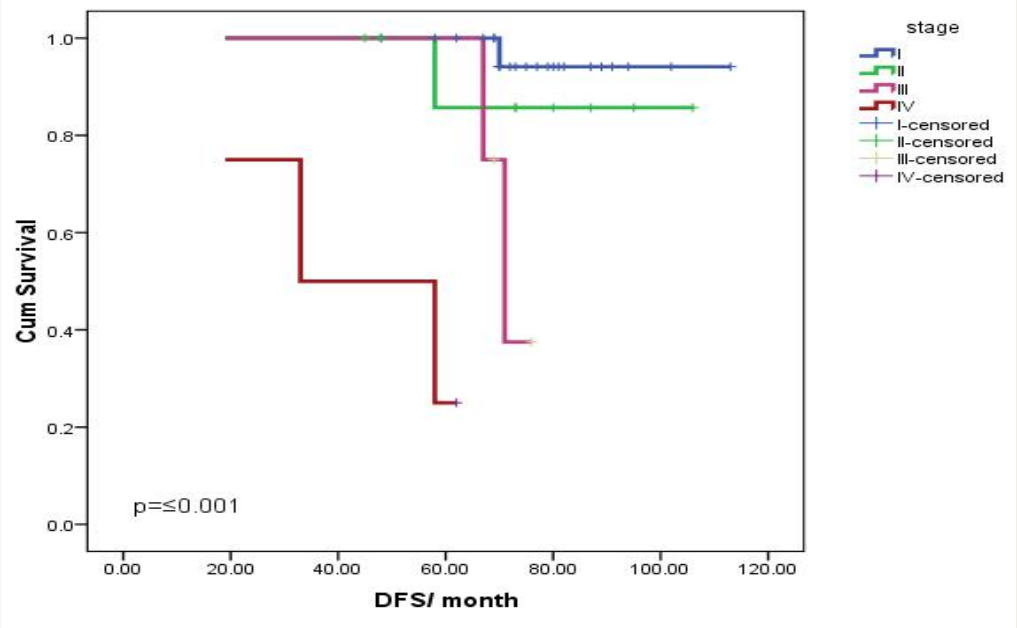

Fig. 1. Shows Kaplan−Meier plots of disease-free survival according to the stage. The 6 yeas DFS survival for stage I is 100% compared to 82% in stage II, 40% in stage III and 22% in stage IV

Table 3. Relation between mortality and patients' characteristics

Variables	Survived (n=36)	Died (n=4)	p-value
Age/ years			
≤50 y	19 (52.8%)	1 (25%)	0.605
>50 y	17 (47.2%)	3 (75%)	
Menopause			
Premenopause	20 (55.6%)	1 (25%)	0.331
Post menopause	16 (44.4%)	3 (75%)	
Parity			
Nullipara	3 (8.3%)	1 (25%)	0.355
Multipara	33 (91.7%)	3 (75%)	
Location			
Rt ovary	21 (58.3%)	0 (0%)	0.085
Lt ovary	11 (30.6%)	3 (75%)	
Both	4 (11.1%)	1 (25%)	
Stage			
I	23 (63.9%)	0 (0%)	0.014*
II	8 (22.2%)	1 (25%)	
III	3 (8.3%)	1 (25%)	
IV	2 (5.6%)	2 (50%)	
Size			
≤10	13 (36.1%)	0 (0%)	0.284
>10	23 (63.9%)	4 (100%)	
Endometrial pathology			
Endometrial hyper.	18 (50%)	1 (25%)	0.157
EPD	7 (19.4%)	2 (50%)	
Endometrial cancer	1 (2.8%)	1 (25%)	
Normal	4 (11.1%)	0 (0%)	
Surgery			
Complete	26 (72.2%)	2 (50%)	0.570
Incomplete	10 (27.8%)	2 (50%)	
Residual			
yes	4 (11.1%)	2 (50%)	0.1
No	32 (88.9%)	2 (50%)	
Rupture			
yes	3 (8.3%)	1 (25%)	0.355
No	33 (91.7%)	3 (75%)	
Chemotherapy			
yes	28 (77.8%)	3 (75%)	1.0
No	8 (22.2%)	1 (25%)	
Relapse			
yes	3 (8.3%)	4 (100%)	<0.001*
No	33 (91.7%)	0 (0%)	

Table 4. Cox regression analysis of independent predictors of mortality

Independent predictors	β	P – value	HR (95%CI)
Stage I & II (r) III & IV	2.92	0.019*	18.6 (1.6-216)

HR: Hazard ratio, CI: confidence interval

The median OAS was 106.38 months (100.3-112.5) as showed in Table 6. There was statistically significant difference in the median OAS regarding stage of the disease, parity and presence of residual disease but not the age, menopausal status, extent of surgery and whether received adjuvant chemotherapy or not as showed in Table 6.

Table 5. Kaplan-Meier disease free survival/month

Patients characteristics	Disease free survival			
	Median	Std. Error	95% CI	P – value
Age/ years				
≤50 y	104.89	5.48	94.1-115.6	0.301
>50 y	92.91	5.17	82.7-103.1	
Menopause				0.752
Premenopause	102.12	5.83	90.7-113.6	
Post menopause	94.55	5.19	84.4-104.7	
Parity				0.338
Nullipara	62.500	12.557	37.8-87.1	
Multipara	102.818	3.811	95.3-110.3	
Location				0.115
Rt ovary	109.19	3.71	101.9-116.5	
Lt ovary	89.57	5.16	79.4-99.7	
Both	62.80	9.91	43.3-82.2	
Stage				
I	110.47	2.45	105.6-115.3	≤0.001*
II	99.14	6.34	86.7-11.6	
III	71.87	1.93	68.1-75.7	
IV	43.00	8.88	25.5-60.5	
Size				0.294
≤10	88.66	2.20	84.3-92.9	
>10	98.10	5.50	87.3-108.9	
Surgery				0.004*
Complete	108.64	2.949	102.8-114.4	
Incomplete	69.87	6.576	56.9-82.7	
Residual				≤0.001*
yes	59.50	7.66	44.5-74.5	
No	106.99	3.32	100.4-113.5	
Rupture				0.001*
yes	58.50	7.87	43.06-73.9	
No	105.35	3.67	98.14-112.5	
Chemotherapy				0.751
yes	101.31	4.30	92.9-109.7	
No	73.22	6.39	60.6-85.75	
Disease free survival/month	101.215	4.109	93.2-109.3	-

Log rank test was used

4. DISCUSSION

AGCTs are very rare tumors with a known good prognosis. Only 40 patients were included in our study from 2007 to 2015. Because of the rarity of this tumor, small data are available and more studies with larger numbers are needed for more standard results.

Bompas E et al. [8] reported that the most common presenting symptoms are abdominal pain and abdominal distension related to mass effect. Abnormal uterine bleeding such as irregular menstruation, intermenstrual bleeding, postmenopausal bleeding or amenorrhea is also frequently seen in these women as the result of the hormonally active tumor that leads to unopposed estrogen [8]. In our study, the most common presenting symptom was bleeding 47.5% followed by pain 42.5%.

According to endometrial abnormalities, it was reported that the incidence of endometrial hyperplasia ranges from 32-85% and endometrial carcinoma ranges from 3-22% [9]. Our study showed high rate of endometrial hyperplasia (47.5%) but low rate of endometrial cancer, only (5%).

Hysterectomy with bilateral salpingo-oophorectomy is the mainstay of treatment while the conservative measure is preserved in whom fertility function is needed.Complete surgery should includeinfra-colic omentectomy, pelvic lymphadenectomy with or without para-aortic lymphadenectomy [10].

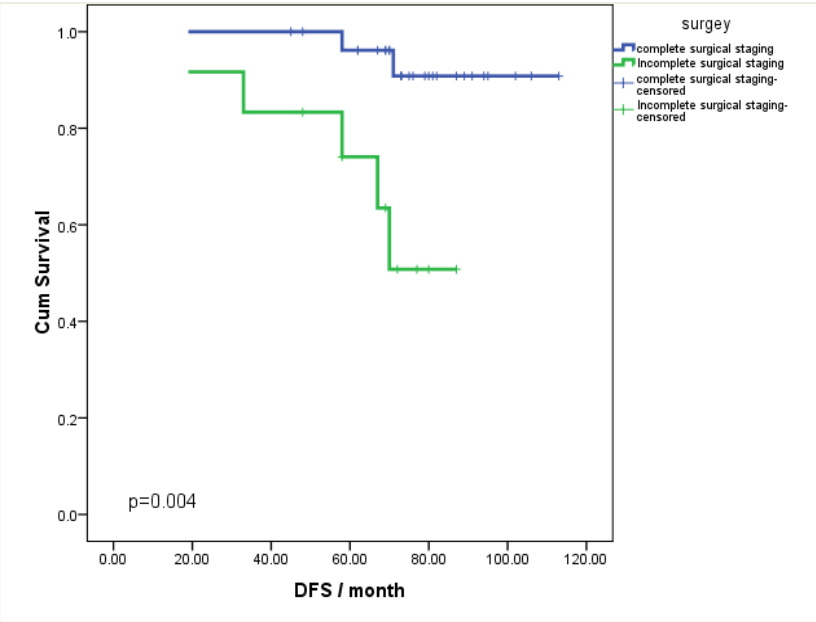

Fig. 2. Shows Kaplan−Meier plots of disease-free survival according to extent of surgery. The 6 years survival for cases who were underwent complete surgical staging was 98% compared to 50% for cases who were underwent incomplete surgery

Table 6. Kaplan-Meier overall survival/month

Patients characteristics	Overall survival			
	Median	Std. Error	95% CI	P – value
Age/ years				
≤50 y	110.0	2.89	104.3-115.6	0.443
>50 y	98.6	3.79	91.2-106.1	
Menopause				
Premenopause	110.18	2.72	104.8-115.5	0.430
Post menopause	98.67	3.79	91.2-112.51	
Parity	72.50	3.18	66.2-78.7	
Nullipara	107.44	3.04	101.5-113.4	0.049*
Multipara				
Stage				
I & II	111.10	1.86	107.4-114.7	0.002*
III & IV	80.42	3.95	72.7-88.18	
Surgery				
Complete	108.0	3.35	101.4-114.6	0.291
Incomplete	87.02	3.11	80.9-93.1	
Residual	81.86	5.34	71.3-92.3	
yes	108.61	2.98	102.7-114.5	0.029*
No				
Rupture	87.00	4.33	78.5-95.5	
yes	107.25	3.17	101-113.5	0.427
No				
Chemotherapy	107.04	3.21	100.7-113.4	
yes	78.00	1.82	74.4-81.6	0.466
No				
Overall survival/month	106.38	3.12	100.3-112.5	-

Log rank test was used

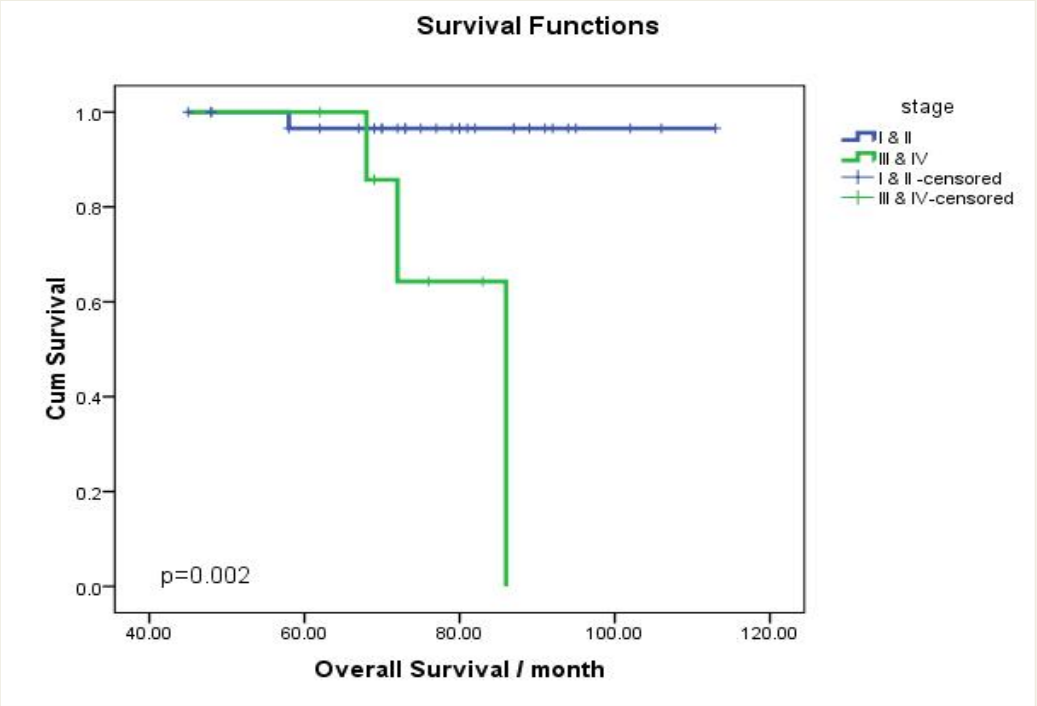

Fig. 3. Shows Kaplan−Meier plots of over-all survival according to the stage. The 6 years survival for stage I and II is 98% compared to 62% in stage III and IV

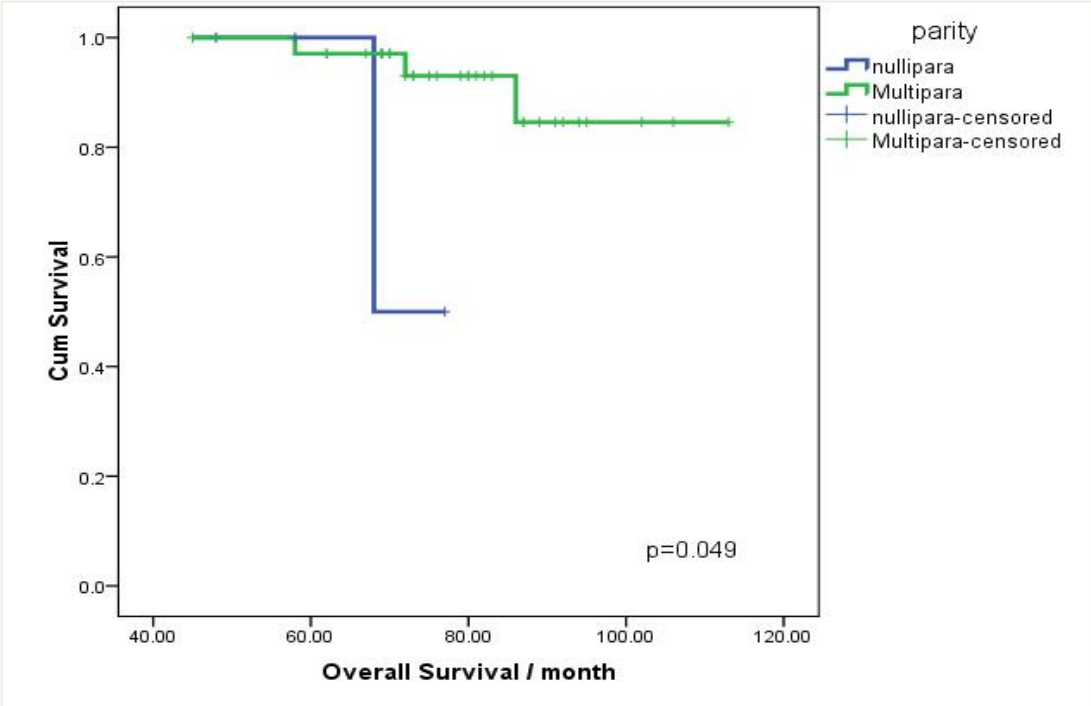

Fig. 4. Shows Kaplan−Meier plots of over-all survival according to parity. The 6 years survival for multipara cases was 98% compared to 50% for nullipara cases

Chemotherapy is recommended for patients with advanced stage and recurrent disease. In early stage AGCTs, chemotherapy is only indicated when there are high risk factors like large size or tumor rupture [11]. In our study, 33 patients received adjuvant chemotherapy due to advanced stage or high- risk factors.

The major factors suspected to affect the prognosis of the disease in several studies were age, type of surgery, tumor size, stage of the disease and tumor rupture. The effect of age on prognosis has been controversial. Sehouli J et al study illustrated that the age less than 40 years was preferably associated with better prognosis [10]. The previous study illustrated also that young ageis an independent prognostic factor for better survival, and those whose age less than 50 had a 10% survival advantage compared to patients more than 50 [12]. In our study, there was no significant difference in survival between patients more and less than 50 years.

It was noted in many studies that stage of the tumor is the strongest prognostic factor as regards the survival of cases. But prospective studies with large number of cases are needed to confirm that [11]. Wu et al. reported, in a study of 100 cases of GCT that 5-year survival was 98%- and 10-year survival was 96% for stage I.for stage II, it was 70% and 60%, respectively [13]. Park et al also found the 5-yearsurvival was 99% and 10-year survival was 90% in early stages (stage I and II), while in advanced stage (stages III and IV) they were 80% and 67%, respectively [14]. Data from our study also indicated that stage of the disease is the main factor affecting disease-free survival (6 yeas DFS for stage I was 100% compared to 82% in stage II, 40% in stage III and 22% in stage IV) and over-all survival (6 years OAS was 98% for stage I and II and 62% for stage III and IV) with statistically significant difference.

Many investigators found that tumors more than 10 cm are associated with lower survival [12]. In a study done by Tomakos et al, they found that for every 1 cm increase in the tumor size, there is 13% increase in the rate of recurrence. In our study, 4 patients died during the period of follow up, all of them had tumor larger than 10 cm at presentation.

It was noticed that recurrence rate was lower in patients underwentcomplete surgery compared with othersoperated with incomplete surgery (12.5% vs 22.5%) [15]. In our study, 70 % of patients underwent complete staging surgery and 30% underwent incomplete surgical staging. Cases who were operated by complete surgery had better DFS compared to cases underwent incomplete surgery (108.64 vs 69.87 months) with statistically significant difference. Complete surgery is associated with better OAS too, but without significant difference.

Residual tumor after surgery is also another important prognosticfactor. Al-Badawi et al. [16] reported that survival rate was significantly lower for patients with the postoperative residual disease. Our study also confirms that finding as regards DFS and OAS with statistically significant difference.

In our study, intra-operative tumor rupture was associated with significantly decreased DFS (58.5 vs 105.35 months), also associated with decreased OAS, however with no significant difference (87 vs 107.25 months). This is matched with the study done by G. V. Koukourakis et al who recorded marked decrease in DFS in cases where intra-operative tumor rupture occurred [7].

Our study showed multipara as significant prognostic factor for better OAS, however, due to small number of nullipara (only 4 cases), this finding should be confirmed in more studies with larger numbers.

5. CONCLUSION

Granulosa cell tumors of the ovary are rare tumors with a tendency for late relapses. Our study showed thatstage of the disease, tumor size, extent of surgery, intra-operative tumor rupture, and presence of residual disease were found to be strong prognostic factors affecting the course of the disease. Due to small number of cases in our study (only 40 cases), Prospective studies with larger numbers are needed for better understanding of the clinical course of the disease and to confirm our results.

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

This study protocol had ethical approval from Medical Research Ethics Committee, Faculty of Medicine, Mansoura University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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