Adult-type ovarian granulosa cell tumour: Treatment Outcomes from a Single Institutional Experience

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Abstract

Background: Ovarian granulosa cell tumour is rare. This study aim is to report the clinical characteristics and long-term outcomes of adult-type OGCT (AOGCT) at King Faisal Specialist Hospital and Research Centre (KFSH&RC) and to determine the prognostic factors affecting relapse and survival. we retrospectively reviewed patients with AOGCT, from 1988 to 2014, who were treated at our institution. Baseline characteristics, pathological findings, and outcomes were analysed, and reported.

RESULTS: Sixty-one patients with AOGCT were identified with a median age of 49 years. Median follow-up was 5.0 years (range 2.1 -8.2 years). 74% of patients were FIGO stage I, whereas 7% stage II, 5% stage III and unknown in 14%. The most common presenting symptoms included abdominal pain (43%) and vaginal bleeding (43%). The majority of patients (38 patients, 62%) were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Five (8%) patients received adjuvant chemotherapy. Sixteen patients (26%) relapsed with a median time to relapse of 5.5 years (0.7-8.1 years). Half of the recurrences (8 patients, 50%) occurred after 5 years of diagnosis. Five-year overall survival and disease-free survival were 93% and 84%, respectively. Factors associated with high risk of recurrence were presence of ascites ($p=0.000$) and elevated preoperative CA 125 level ($p=0.048$). The overall survival was significantly influenced by the menopausal status (premenopausal 100% vs. postmenopausal 84%; $p=0.02$), preoperative CA 125 (normal 100% vs. elevated 64%; $p=0.005$), Ascites (present 33% vs. absent 100%; $p=0.000$), and age (<55 years 100% vs. ≥ 55 years 77%; $p=0.002$).

CONCLUSION: This study confirms a good outcome of patients with AOGCT. They require long-term follow-up because the recurrence can occur many years post the definitive therapy. The presence of ascites and elevated preoperative CA 125 levels were associated with a higher risk of recurrence and poor prognosis. The outcome seems not to be affected by fertility-sparing surgery and/or adjuvant chemotherapy.

Introduction

Ovarian granulosa cell tumour (OGCT) are relatively rare malignancy, it is part of ovarian sex cord–stromal tumours, which are heterogenous group of malignancies arise from primitive sex cord cells. It accounts for 2–5% of all ovarian tumours.(1) It includes both adult and juvenile subtypes. The adult subtype (AOGCT) is more common and occurs in middle-aged and older women, representing 95% of all OGCTs.(2) Most of the patients have stage I at time of diagnosis with estimated five-year survival rate of more than 90%.(3–5) Women with OGCT may present with an asymptomatic mass or it can cause abdominal pain. Abnormal vaginal bleeding or precocious puberty may occur at the initial presentation due to hyper-estrogenic effects.(6–9)

Surgery is the main treatment of OGCT which includes hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. The performance of lymphadenectomy remains controversial due to low incidence of lymph node metastasis at initial diagnosis.(10) Fertility-sparing surgery can be an option for

premenopausal women.(11,12) The role of adjuvant therapy is uncertain due to rarity of the neoplasm which makes it difficult to conduct well-designed randomized studies. Patients can develop recurrence in 20% – 30% of cases, and have tendency for late relapse, usually after 5 years of follow up.(13,14)

There is no standard approach to the management of metastatic or recurrent disease. Complete surgical resection can provide long-term disease control. Radiation therapy has been shown to induce clinical response and occasional long-term remission.(15–18) Platinum-based chemotherapy such as bleomycin, etoposide, cisplatin (BEP) are active and produce an overall response rate of 58–84%.(19,20)

Due to the rarity of OGCT, indolent clinical course and relatively small sample size and/or short follow-up of the older studies, studies with larger sample size are needed to improve our understanding of OGCT. This study aimed to evaluate the clinicopathologic characteristics, treatment, and long-term survival for patients treated at King Faisal Specialist Hospital, Riyadh over the past 30 years and to determine the prognostic factors affecting the disease-free and overall survival.

Patients And Methods

Ethical consideration

This research project was conducted in accordance with the ethical principles contained in the declaration of Helsinki (2000), Good Clinical Practice Guidelines and the policies and guidelines of the Research advisory council (RAC) in KFSH&RC. and approved by the Medical Ethics Committee, under project number (RAC#2141 – 141). The identity of the patients studied remained anonymous since no identifying data or protected health information were recorded. All data were password secured to safeguard the confidentiality of the collected patient's data. This research has been consented for publication from the office of research affairs (ORA), according to internal regulation of KFSH&RC, all authors read and approved the final manuscript.

Study design and statistical consideration

The objective of this study was to report real world experience regarding managing AOGCT in our institute, to evaluate the clinicopathologic characteristics, treatment, long-term survival and to determine prognostic factors affecting the disease-free and overall survival.

This research is a retrospective study. Patient characteristics, such as, age; symptoms; menopausal status; parity; presence of ascites at presentation; pretreatment Cancer antigen 125(CA125) level; FIGO staging at initial presentation; surgery; surgical outcome; uterine pathology; adjuvant therapy; response rate; disease progression, and survival outcome, were collected. The response was assessed retrospectively according to response evaluation criteria in solid tumours (RECIST) v1.1(21).The response in patients with non-measurable disease was categorized according to the decision made by the treating physician.

Disease-free survival (DFS) was calculated from the date of surgery till the date of recurrence, death or last follow up, Overall survival (OS) was calculated from the date of diagnosis till death or last follow up. Patients who were lost to follow up were censored at the date of their last follow up. Median follow up was calculated by reversing the codes for death or censoring using the Kaplan Meier method.

DFS and OS were analysed according to age (< 55 years vs $\geq$ 55 years), Menopausal status (pre vs post-menopausal), FIGO staging at initial presentation (stage I vs stages II and III), pretreatment CA 125 (Normal vs Elevated), presence of ascites and type of surgery (Conservative fertility sparing vs non conservative surgery).

Statistical analysis was done using the software package JMP- SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics for the continuous variables were reported as mean $\pm$ 95% CI and categorical variables were summarized as frequencies and percentages. Continuous variables were compared by Student's t-test or ANOVA as appropriate, while categorical variables were compared by Chi-square test. Kaplan-Meier method was used in survival tables and curves and the different subgroups were compared by the log-rank test. The level of statistical significance is set at $p < 0.05$.

Procedure and data collection:

The medical records of all patients with a known diagnosis of AOGCT at our institute between 1988 and 2014, were reviewed. Patients were identified through the hospital tumour registry software CNExT (C/NET Solutions, Berkeley, CA). Patients were considered eligible for this analysis if they had histologically confirmed AOGCT. Data of eligible 61 patients were analysed. All pathology specimens were reviewed by expert pathologists in gynaecologic oncology. The above-mentioned data have been collected in a pre-designed data collection file (DCF).

Results

Sixty-one female patients with AOGCT were identified, with a median age of 49 years and a median follow-up of 5.0 years (range 2.1–8.2 years). Twenty-five patients (41%) were post-menopausal. Nine patients were Nulliparous. The most common presenting symptoms included abdominal pain (43%) and vaginal bleeding (43%). Sixteen (26%) patients had secondary hyperplasia, with no endometrial carcinoma observed. Only 15 (24%) patients presented with high pre-treatment tumour marker CA 125 level, The majority were FIGO stage I (74%) at presentation, 38 patients (62%) were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO), 22 patients (36%) had Conservative fertility sparing surgery, 98% had optimal debulking. Mean tumour size 11.8 cm (5–27 cm), with 8 patients (13.1%) had their tumour size > 15 cm. No reported cases of spontaneous pre-operative tumour rupture, however Tumour ruptured intraoperatively in 3 (5%) patients. Fifty-five (90%) patients had no adjuvant therapy, only 5 (8%) patients received adjuvant chemotherapy (4 cycles of BEP chemo protocol). and 1 (2%) patient had adjuvant hormonal treatment (Megestrol Acetate). (Table 1).

Table 1
Patients' Characteristics

	No 61(%)
Age(years)	
Median	49
Range	(16–77)
Tumour size (cm)	
Mean	11.8
Presenting symptoms	
Abdominal pain	26 (43)
Vaginal bleeding	26 (43)
Abdominal/pelvic mass	12 (20)
Amenorrhea	4 (7)
Asymptomatic	
Menopausal status	
Pre-menopausal	31 (51)
Post-menopausal	25 (41)
Missing	5 (8)
Parity	
Nulliparous	9 (15)
Multiparous	34 (65)
Primiparous	1 (2)
NA	17 (28)
Pretreatment CA 125	
Normal	26 (43)
Elevated	15 (24)
NA	20 (33)

No: number; NA: not available; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; SO: salpingo-oophorectomy; FIGO: International Federation of Gynaecology and Obstetrics system.

	No 61(%)
Ascites	
Present	7 (11.5)
Absent	54 (88.5)
Surgery	
BSO+/-TAH	38 (62)
Unilateral SO	22 (36)
Cystectomy	1 (2)
Lymph node dissection	2 (3)
Omentectomy	8 (13)
Surgical outcome	
Optimal debulking	60 (98)
Residual disease	1 (2)
FIGO stage at presentation	
I	45 (74)
II	4 (7)
III	3 (5)
Unknown	9 (14)
Endometrial pathology	
Normal	27(44)
Hyperplasia	16 (26)
Polyp	1 (2)
NA	17 (28)
Adjuvant therapy	
No	55 (90)
Chemotherapy	5 (8)
Hormonal therapy	1 (2)
No: number; NA: not available; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; SO: salpingo-oophorectomy; FIGO: International Federation of Gynaecology and Obstetrics system.	

16 patients (26%) relapsed; 6 (10%) had local recurrence, 10 (16.4%) developed systemic relapse, liver involvement was the most common site of systemic relapse. The median time to relapse was 5.5 years (0.7–8.1 years). Half of the recurrences (8 patients, 50%) occurred after 5 years of diagnosis. Five-year overall survival and disease-free survival were 93% and 84%, respectively. Figure 1&2.

Using univariate analysis; Factors associated with a high risk of recurrence were the presence of ascites ($p = 0.000$) and elevated preoperative tumour marker CA 125 level ($p = 0.048$). The overall survival was significantly influenced by the menopausal status (premenopausal 100% vs. postmenopausal 84%; $p = 0.02$), FIGO staging at presentation (stage I 100% Vs. II&III 64%), preoperative CA 125 (normal 100% vs. elevated 64%; $p = 0.005$), Ascites (present 33% vs. absent 100%; $p = 0.000$), and age (< 55 years 100% vs. ≥ 55 years 77%; $p = 0.002$). (Table 2.)

Table 2
Univariate analysis of different prognostic factors correlated with DFS and OS

Item	5-year DFS	p-value	5-year OS	p-value
Age				
< 55 years	90%	0.35	100%	0.002
≥ 55 years	70.5%		77%	
Menopausal status				
Pre-menopausal	92%	0.98	100%	0.028
Post-menopausal	79%		84%	
FIGO stage				
Stage I	90%	0.14	100%	0.005
Stages II and III	69%		64%	
Surgery				
Fertility sparing	100%	0.063	100%	0.063
Non-conservative	89%		89%	
Ascites				
Yes	0%	0.000	33%	0.000
No	92%		100%	
DFS: disease free survival; OS: overall survival; FIGO: International Federation of Gynecology and Obstetrics system.				
(Fig. 1) Kaplan-Meyer Overall Survival Curve				

While type of surgery whether fertility sparing versus TAH + BSO and age (< 55 , ≥ 55 years) did not show any significance for both DFS, OS. Tumour rupture, lymphadenectomy and use of adjuvant therapy were not analysed due to relatively small number of patients included in the study.

Discussion

Adult ovarian granulosa cell tumour is a slowly progressive rare ovarian tumour, with a better prognosis when compared to epithelial tumours, though 20–30% of them may recur late.(1,5,22)

Ovarian granulosa cell tumour has different clinical behavior and biology compared to epithelial ovarian tumors, with the sustained ability for Estrogen production, which Explains the prevalence of hormone dysfunction related symptoms. In our study Approximately half of the patients presented with either; vaginal bleeding (43%), or Amenorrhea (7%), which may explain the early diagnosis of the disease as 74% were diagnosed in stage I. This is of utmost importance, as it may lead to endometrial abnormalities with an incidence of 30–85% endometrial hyperplasia and 3–20% endometrial carcinoma.(9,23,24) In our study hyperplasia was documented in 26% of all group with no endometrial carcinoma found, which matches the international results.

The mean tumour size in our report was 11.8 cm, which is matched with the average value documented in most studies, Miller and his colleagues, (25) found that 33% of patients with recurrence had tumour larger than 15 cm, which was encountered in eight patients in our study. Other studies were unable to validate the prognostic significance of tumour size.(22,26,27) Impact of size on survival was not analysed in this report due to low number of tumour size above 15 cm.

The rarity of the disease and the small number of publications are the main reasons of absence of prognostic model for AOGCT. However, certain common factors published in the literature had an impact on local failure rate and overall survival, among them; Stage which was shown to be a prognostic factor for survival in many reports. (1,5,27) Five-year overall survival was reported to range between 75–95% in patients with stage I disease and 22–50% in higher stages.(28–30) Similarly, in the present study, stage was important factor predicting survival with 5-year OS was 100% in stage I disease, whereas it was 64% in stage II -III. Although there was a numerical difference in favoring better DFS for stage I but was not statistically significant in our report.

The prognostic value of age in AOGCT is controversial in the literature. Although Chan et al (31) reported that age younger than 50 years was a favorable prognostic factor, Zhang et al(22).

It has been demonstrated that women under the age of 50 years had a 10% survival advantage in a series of 376 women. but Lee and his colleagues (32) showed that the recurrence rate was higher at the age younger than 40 years. In this study age of 55 years chose as a cut of value for analysis; with survival reached 77% for the older group in contrary to 100% for the younger group, which may in light the impact of menopausal status as a co-prognostic factor in this study group at this age level. Which was found to be statistically significant, and 5-year OS of 84% for postmenopausal patients.

Presence of Ascites, and high Tumour marker CA125 found to be the most important 2 independent factors for recurrence with an impact on survival as well. They are common presentation in epithelial ovarian tumors, and rarely reported among AOGCT.(33–36) Studies on Ascites and tumour marker CA125 among AOGCT are scarce, on the other hand, presence of ascites is a sign of higher stage, which was validated in literature as a strong prognostic factor for survival as mentioned above. While high CA125 reported in one study to be poor predictor of AOGCT.(37) To our knowledge this could be the first study to test ,the prognostic value of tumour marker CA125 in AOGCT, in contrary to serum inhibin ,which was extensively investigated.(38) This should be validated in larger studies.

performing of conservative surgical approach (Fertility-sparing surgery is appropriate for patients with stage I and stage II disease, because high survival and late disease recurrences.(39,40)In the present study, the performance of conservative surgery was not associated with recurrence failure and mortality, which confirm its role in fertility sparing age group without compromisation on survival.

There is no prospective, randomized, controlled study evaluating the effectiveness and necessity for adjuvant radiotherapy or chemotherapy in AOGCT.(41) Therefore, the role of adjuvant therapy is controversial. In our study, chemotherapy was applied as the adjuvant therapy in 8%, hormonal treatment in 2%, no one received adjuvant radiotherapy. This is due to the low numbers of patients presented with stage II-III (12%), low mean tumour size, and no presurgical tumour rupture documented. In addition to that optimal debulking achieved in 98% of the cases. Although high rate of late failure, indicate other poor risk features for investigation, Nevertheless, 90% of the patients with recurrence underwent resurgery.

The Prognostic effect of tumor cyst rupture time, spontaneously before the operation or iatrogenic rupture during the operation is also controversial. Tumour Cyst rupture was found to be associated with poor prognosis in some literature.(32,42)In the present study, presence of tumour cyst rupture was noted only intraoperatively in 3 patients. However, it was not tested against survival, due to low number of patients.

The retrospective nature of this study is one of its limitations. Nevertheless, the achievement of maximal debulking in all patients in this study is one of its advantages. In addition, relatively higher number of patients in comparison to international reports, long follow-up time (median, 97 months), involvement of patients from a single center, performance of staging surgery including lymphadenectomy in 76.6% of the patients, and performance of surgery in 90% of the patients who had recurrence are considered points of strengths in this study.

In summary, AGCT is diagnosed at earlier stages, Surgery is the standard treatment with a potential role for fertility preservation, and longer survival was achieved with maximal surgical resection. Stage of the disease was identified as the most important prognostic factor predicting local recurrence and overall survival.

Abbreviations

OGCT

Ovarian granulosa cell tumour
AOGCT
Adult-type ovarian granulosa cell tumour
KFSH&RC
King Faisal Specialist Hospital and Research Centre
FIGO
Fédération Internationale de Gynécologie et d'Obstétrique
CA 125
cancer antigen 125
BEP
bleomycin, etoposide, cisplatin chemo protocol
RAC
Research advisory council
ORA
office of research affairs
RECIST
response evaluation criteria in solid tumours
DFS
Disease-free survival
OS
Overall survival
DCF
data collection file
TAH + BSO
Total abdominal hysterectomy and bilateral salpingo-oophorectomy

Declarations

- **Ethics approval and consent to participate:**

This research project was conducted in accordance with the ethical principles contained in the declaration of Helsinki (2000), Good Clinical Practice Guidelines and the policies and guidelines of the Research advisory council (RAC) in KFSH&RC. and approved by the Medical Ethics Committee under project number (RAC#2141-141). The identity of the patients studied remained anonymous since no identifying data or protected health information were recorded. All data were password secured to safeguard the confidentiality of the collected patient's data. This research has been consented for publication from office of research affair (ORA), according to internal regulation of KFSH&RC, all authors read and approved the final manuscript.

- **Consent for publication**

Patients' consent to treatment is also approved for the use of their medical records in the research, The Research Advisory Council (RAC) has the right of access to the supporting records for all research at the KFSH&RC.

This research has granted approval by (RAC) in KFSH&RC, under project number (RAC#2141-141). and approved by the Institutional Review Board (IRB), which evaluates the ethical aspects of all research proposals that involve human subjects.

The RAC waiver consent includes access and use of patient files while maintaining the confidentiality of their data. The identity of the patients studied remained anonymous since no identifying data or protected health information were recorded. All data were password secured to safeguard the confidentiality of the collected patient's data.

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- **Availability of data and material**

All data generated or analyzed during this study are included in this published article [under excel sheet name: Database].

- **Competing Interests:**

All Authors declare that they have no competing interests.

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- **Authors contributions:**

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Not applicable

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Figures

Figure 1

Kaplan-Meier Overall Survival Curve

Figure 2

Kaplan-Meyer Disease Free Survival Curve