Journal of BUON **17:** 461-464, 2012

ORIGINAL ARTICLE

Granulosa cell tumors of the ovary: review of 43 cases

D. Oztekin[1], S. Kurt[1], H. Camuzcuoglu[1], D. Balsak[1], N. Dicle[2], S. Tinar[1]

[1]Department of Obstetrics and Gynecology and [2]Department of Pathology, Aegean Obstetrics and Gynecology Training and Research Hospital, Izmir, Turkey

Summary

Purpose: *Granulosa cell tumors of the ovary (OGCT) are rarely seen tumors and display a quite interesting behavior profile. The purpose of this study was to evaluate the impact of stage, histological type (juvenile or adult type) and treatment on the prognosis of this disease.*

Methods: *Forty-three females with OGCT operated between January 1990 and June 2007 were retrospectively evaluated. Radical surgery was performed to 37 patients (86%) without fertility desire, whereas conservative surgery was performed to 6 patients with early-stage disease and fertility desire.*

Results: *Thirty-nine (90.6%) patients had stage I disease, whereas 4 (9.4%) had advanced-disease stage (stage II 2 and stage III 2 patients). All of the patients were surgically treated, but conservative surgery was applied to only 6 cases. Postoperative chemotherapy was administered to 18 cases and the remaining 25 cases were put under follow-up without chemotherapy. Recurrence was observed in 8 cases and 1 of these cases was of juvenile type. Mean time to recurrence was 55.14±32.18 months (range 15-122). Tumor stage was the most important prognostic factor, with 5-year overall survival of 96.77% in local disease, and 66.67% in advanced-stage disease ($p<0.01$).*

Conclusion: *OGCT can recur many years after primary therapy. Consequently these patients must be followed-up for long periods of time. Disease stage at diagnosis was the most important factor affecting the recurrence rate and prognosis. The evaluation of all factors affecting survival needs further studies with larger numbers of patients.*

Key words: chemotherapy, granulosa cell tumor, ovarian tumor, radical surgery

Introduction

OGCT are rarely observed tumors (5%) and are divided into 2 subgroups, the juvenile and the adult type. As juvenile type is observed more commonly in the premenarchal period, it can lead to premature puberty because of estrogen secretion by the neoplastic cells. The adult type is observed in older ages and endometrial hyperplasia and/or endometrial carcinoma can accompany this type due to adult-type hormonal activity.

Although the most important factor affecting survival in cases with OGCT is the stage of the tumor, the therapeutic approach and histological tumor type are additional factors which may affect survival.

The objective of this study was to evaluate the impact of these prognostic factors on the survival of cases diagnosed with OGCT and treated at our clinic.

Methods

The medical records of patients with OGCT diagnosed and treated at the Oncology Department of the Aegean Obstetrics and Gynecology Training and Research Hospital between January 1990 and June 2007 were retrospectively evaluated.

The International Federation of Gynecologic Oncology (FIGO) staging system was used for disease staging. Radical surgery (type I hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, pelvic and paraaortic lymphadenectomy) was applied to women without desire for fertility, whereas conservative surgery (unilateral oophorectomy of the diseased ovary, abdominal washings and inspection of the contralateral ovary) was applied to women 6 cases with desire for fertility and diagnosed in early stages. Postoperative adjuvant chemotherapy was administered to some patients who accepted to undergo such a treatment. Chemotherapy regimens administered were VAC (vincristine, actinomycin-D, cyclophosphamide), BEP (bleomycin, etoposide, cisplatin) and VCD (vincristine, cyclophosphamide, doxorubicin).

Correspondence to: Deniz Oztekin, MD. Albayrak mavisehir evleri, Yali mahallesi, 6525 sok. no: 35 daire no: 31 Karsiyaka, Izmir, Turkey.
Tel: +90 5323330201, E-mail: dcoztekin@gmail.com

Received 15-12-2011; Accepted 24-01-2012

Statistical analysis

Statistical calculations were performed with SPSS 10.0 for Windows®. Survival rates of the cases were calculated by using Kaplan-Meier method and log-rank analysis. A p value<0.05 was accepted as statistically significant.

Results

Forty-three out of 483 cases (8.9%) with ovarian tumors were diagnosed as OGCT.

The mean patient age was 42.69 ± 12.42 years (range 15-73). Thirty-nine (90.6%) of the cases were diagnosed in stage I, whereas 4 (9.4%) were in more advanced stages (Table 1).

Thirty-seven (86%) patients were treated with radical surgery; conservative surgery was performed in only 6 (14%) patients with early-stage disease and desire for fertility. Adjuvant chemotherapy was administered to 18 (41.8%) cases, while the remaining 25 (58.2%) were put under follow-up without chemotherapy (Table 2). Only one patient underwent both radiotherapy and chemotherapy.

Four patients (9.3%) had juvenile type of OGCT, with mean age 19.25±3.77 years (range 15-24). Conservative surgery was performed to 3 of these cases. Radical surgery was carried out to only one case with stage III and 4 courses of BEP chemotherapy were administered postoperatively. Recurrence was observed 15 months later, and the patient died during the first course of second-line chemotherapy. No recurrence was observed in any of the other cases.

The remaining 39 cases had adult type OGCT. Radical surgery was performed in all of them, except 3 cases with stage Ia disease who had fertility desire. One patient with conservative surgery delivered a healthy baby with caesarian section 2 years later. She had normal abdominal washings and remains disease-free for 8 years.

Recurrence was observed in 8 (18.6%) cases and in one of them the disease was of the juvenile type. The mean time to recurrence was 55.14±32.18 months for all cases. Two of the recurrent cases had been treated with conservative surgery. The first case had been operated 10 years ago and had not been administered any adjuvant therapy. The recurrence of the second case occurred 2 years postoperatively, to whom adjuvant chemotherapy had been administered because of tumor rupture before the operation.

Six of the recurrent cases had central recurrence. The other 2 cases had distant metastasis (one case in the liver and the other one in the lung). Surgery and chemotherapy were applied to 7 of the recurrent cases and the last one had radiotherapy in addition to surgery and chemotherapy. Three patients with recurrent disease died after chemotherapy.

Five-year disease-free survival was 89.62% in stage I, whereas this rate dropped to 50% in advanced-stage (p<0.01).

Five year overall survival rate was 96.77% in local disease, whereas this rate was 66.67% in advanced-stage disease (p=0.02; Figure 1).

Five-year overall survival was 86% in the adjuvant chemotherapy-administered group, whereas it was 100%

Table 1. Distribution of cases with granulosa cell tumor of ovary according to stage

Stage	*Patients, N*	*%*
Ia	26	60.5
Ib	1	2.3
Ic	12	27.9
II	2	4.7
III	2	4.7
IV	0	0
Total	43	100

Table 2. Treatment methods

Treatment	*Patients, N*	*%*
Conservative surgery	4	9.3
Conservative surgery + CT	2	4.6
Radical surgery	21	48.8
Radical surgery + CT	15	34.8
Radical surgery + CT + RT	1	2.3
Total	43	100

CT: chemotherapy, RT: radiotherapy

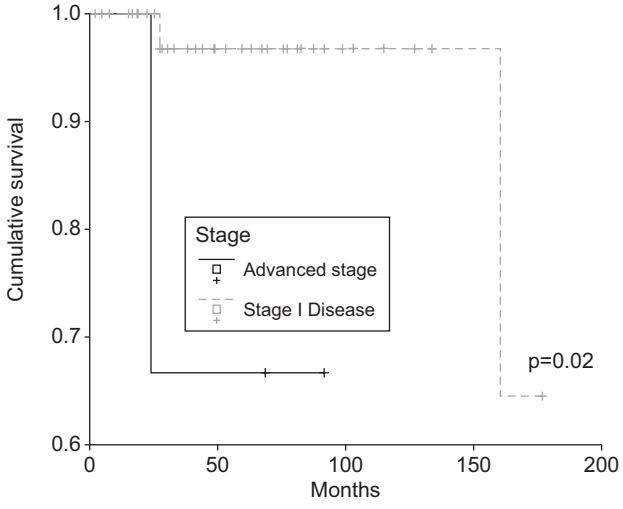

Figure 1. Overall survival rates of cases with according to disease stage.

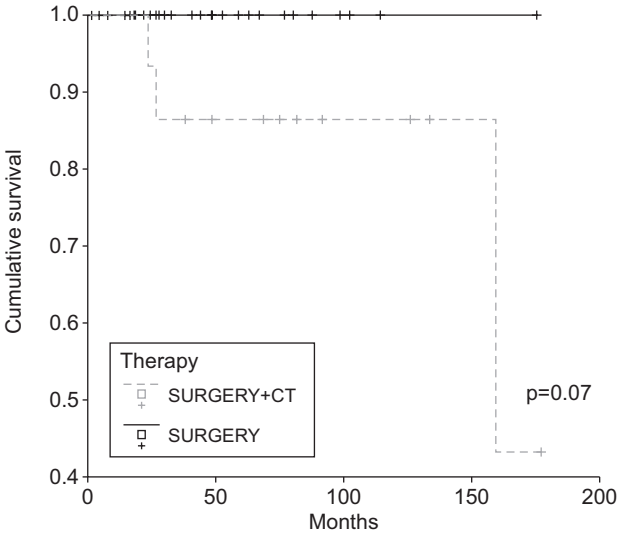

Figure 2. Overall survival rates of cases with and without postoperative adjuvant chemotherapy.

in patients treated with surgery alone (p=0.07; Figure 2). Although the difference was not statistically significant, the improved survival rate in patients treated with surgery alone could be possibly attributed to the advanced-stage patients who were administered chemotherapy.

Discussion

OGCT are very rarely observed tumors [1,2]. In the literature the observed frequency of OGCT ranges from 5 to 12%, and in our series this rate was 8.9%. Their behavior is quite variable and difficult to estimate beforehand. Recurrences may develop many years after the first therapeutic approach. Consequently, these cases must be followed up for long periods of time [1,3].

OGCT can be distinguished into 2 subgroups: the juvenile type, which is generally observed in children and young adults, and the adult type which is observed mainly in the reproductive and the postmenopausal period of life.

OGCT are macroscopically solid, lobulated, non encapsulated tumors, sometimes with cystic areas. Microscopic characteristics are different in the adult and juvenile types. Typical microfollicular (Call-Exner bodies) pattern together with macrofollicular, trabecular and insular-trabecular patterns are observed in the adult type OGCT. Nuclear clefts called coffee-beans are very characteristic of this condition.

Diffuse and macrofollicular appearance is typical in the juvenile type of OGCT. Cells with nuclear clefts are less and luteinized cells are more, while atypia and high mitotic activity are more prominent compared with the adult type [4].

The juvenile type constitutes 5% of the OGCT cases [5] whereas only 4 cases (9.3%) were of the juvenile type in our series. We did not observe any case with premature puberty as reported in the literature [6,7].

Recurrence was observed in 7 patients with adult type OGCT. Two of them with distant metastasis had undergone conservative surgery. Liver metastasis was observed 21 months postoperatively in the first case, and BEP chemotherapy was administered after the complementary operation, but the patient died 3 months after the completion of chemotherapy. In the second case lung metastasis occurred 10 years postoperatively. The patient was subjected to complementary surgery and 6 courses of vincristine+cyclophosphamide+doxorubicin and she remains disease-free for approximately 5 years. The other 5 cases with locally recurrent disease occurred after radical surgery. All of them underwent a second operation and were rendered disease-free; however, one of them died 160 months later due to a new recurrence.

In the literature, late recurrences are attributed to spared genital organs after surgery. Consequently, radical surgery is suggested after conservative surgery for cases completing their fertility or in premenopausal cases [8-10].

Seven of our patients with adult type OGCT had endometrial hyperplasia, with 4 showing also atypia. It is believed that this pathology is due to estrogen secretion from the OGCT. Since invasive endometrial cancers accompanying OGCT have been reported by several authors [3,8,11], evaluation of the endometrium with dilatation and curettage is essential before conservative surgery is performed [3,8,11]. Measurement of serum estradiol levels for long-term follow-up can be used, as well as serum inhibin levels [12,13].

Surgery applied in 2 of our patients was due to rupture of ovarial cyst. Postoperative chemotherapy was applied in both of these cases. One of these 2 cases died 27 months after the operation because of recurrence. No recurrence was observed in the other case. In the literature, no effect on recurrence and survival of preoperative cyst rupture has been reported [14,15].

It has been reported that the chemosensitivity of OGCT is lower than that of other ovarian tumors. The effectiveness of adjuvant chemotherapy and/or radiotherapy after primary surgery to positively impact survival is still controversial according to some studies [16,17]. In our series chemotherapy and radiotherapy in addition to primary surgery were applied in only one with advanced-stage disease. Fourteen of the cases had stage I disease. The remaining cased with stage I underwent surgery but denied postoperative chemotherapy. No significant difference (p=0.07) was observed between surgery alone vs. surgery plus postoperative

chemotherapy. Also 17 cases were administered only chemotherapy after surgery.

According to many studies, stage of disease at diagnosis is the most important factor affecting the recurrence rate and prognosis [2,14,18,19]. Five-year disease-free survival and overall survival of stage I cases of our series were 89.62% and 96.77%, respectively. The corresponding figures were 50% and 66.67%, respectively, in advanced-disease stages, similar with those reported in the literature [3,17,20].

Recurrences observed in different time periods after the primary operation are difficult to explain based only to stage of disease, and it could be speculated that other factors are also implicated. Presence of residual tumor, size of the tumor, histological type and mitotic index could represent other probable prognostic factors [2,14,16]. Establishing a relationship between overexpression of p53, c-erbB-2, and Ki-67 genes and clinicopathological behavior could possibly explain the differences observed in OGCT [21].

Conclusion

OGCT constitute a heterogeneous group of tumors with a wide range of clinical behaviors. Cases of OGCT should be followed frequently and for long periods of time.

Tumor stage is the most important prognostic factor for disease-free and overall survival.

Other factors affecting prognosis should be evaluated in future studies.

References

1. Martellotto G, Frede S, Ortiz S, Hliba E. Granulosa cell tumors: structural and ultrastructural analysis. Rev Fac Cien Med Univ Nac Cordoba 2001; 58: 117-123.
2. Li W, Wu X, Fang C, Yao J, Guo Y, Zhang S. Prognostic factors in adult granulosa cell tumor of the ovary. Saudi Med 2009; 30: 247-252.
3. Lauszus FF, Petersen AC, Greisen J, Jakobsen A. Granulosa cell tumor of the ovary: a population-based study of 37 women with stage I disease. Gynecol Oncol 2001; 81: 456-460.
4. Kurman R J (Ed). Blaustein's Pathology of the Female Genital Tract (5th Edn). Springer-Verlag, New York, USA, 2002.
5. Rishi M, Howard LN, Bratthauer GL, Tavassoli FA. Use of monoclonal antibody against human inhibin as a marker for sex cord-stromal tumors of the ovary. Am J Surg Pathol 1997; 215: 583-589.
6. Gittleman AM, Price AP, Coren C, Akhtar M, Donovan V, Katz DS. Juvenile granulosa cell tumor. Clin Imaging 2003; 27: 221-224.
7. Isguven P, Yoruk A, Adal E, Arslanoglu I, Ilvan S, Yildiz M. Adult type granulosa cell tumor causing precocious pseudopuberty in a 6 years-old girl. J Pediatr Endocrinol Metab 2003; 16: 571-573.
8. Vesco KK, Carney ME. Granulosa cell tumor of the ovary: extensive late recurrence after initial occult microscopic disease. Obstet Gynecol 2002; 99: 888-891.
9. Hines JF, Khalafia MA, Moore JL. Recurrent granulosa cell tumor of the ovary 37 years after initial diagnosis: a case report and review of the literature. Gynecol Oncol 1996; 60: 484.
10. Kietlinska Z, Pietrzak K, Drabik M. The management of granulosa cell tumors of the ovary based on long-term follow-up. Eur J Gynaecol Oncol 1993; 14: 118-127.
11. Nakamura S, Nakashima N, Ito M et al. A case of ovarian granulosa cell tumor with invasive adenocarcinoma of the endometrium. Acta Pathol Jpn 1988; 38: 947-951.
12. Chudecka-Głaz A, Rzepka-Górska I, Błogowska A, Zielińska D. Granulosa cell tumor in different periods of women's life. Ginecol Pol 2003; 74: 689-694.
13. Vihko KK, Bläuer M, Puistola U, Tuohimaa P. Activin B in patients with granulosa cell tumors: serum levels in comparison to inhibin. Acta Obstet Gynecol Scand 2003; 82: 570-574.
14. Sehouli J, Drescher FS Mustea A, et al. Granulosa cell tumor of the ovary: 10 years follow-up data of 65 patients. Anticancer Res 2004; 24: 1223-1229.
15. Balat O, Aydin A, Kutlar I, Camci C. Ruptured granulosa cell tumor of the left ovary and mature cystic teratoma of the right ovary: a case report of unusual acute abdominal syndrome. Eur J Gynaecol Oncol 2001; 22: 350-351.
16. Uygun K, Aydiner A, Saip P et al. Clinical parameters and treatment results in recurrent granulosa cell tumor of the ovary. Gynecol Oncol 2003; 88: 400-403.
17. Al-Badawi IA, Brasher PM, Ghatage P, Nation JG, Schepansky A, Stuart GC. Postoperative chemotherapy in advanced ovarian granulosa cell tumors. Int J Gynecol Cancer 2002; 12: 119-123.
18. Fontanelli R, Stefanon B, Raspagliesi F et al. Adult granulosa cell tumor of the ovary: a clinico pathologic study of 35 cases. Tumori 1998; 84: 60-64.
19. Evans AT 3rd, Gaffey TA, Malkasian GD Jr, Annegers JF. Clinicopathological review of 118 granulosa and 82 theca cell tumors. Obstet Gynecol 1980; 55: 231-238.
20. Stenwig JT, Hazekamp JT, Beecham JB. Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up. Gynecol Oncol 1979; 7: 136-152.
21. Kusamura S, Derchain S, Alvarenga M, Gomes CP, Syrjänen KJ, Andrade LA. Expression of p 53, c-erbB-2, Ki-67, and CD34 in granulosa cell tumor of the ovary. Int J Gynecol Cancer 2003; 13: 450-457.