Ovarıan Granulosa Cell Tumors: Evaluatıon of Clınıcal, Outcome and Reccurence Factors

T Şenol[1], MK Eken[1], EI Kaygusuz[2], M Polat[1], E Özkaya[1], GŞ Ersoy[3], A Karateke[1], D Kerkiloglu[1]

ABSTRACT

Objective: We aimed to determine the predictors for poor prognosis and to find out the effect of treatment strategies on survival functions

Methods: Thirty seven women with granulosa cell tumor were enrolled for the study between 2000 and 2013. All data was obtained from hospital prospectively collected databese.

Results: The mean age was 50.1±13.3 and the most common symptom was abdominal distansion (21.6%) . Mean follow up period was 67.9±33.6 months. During follow up period Disease specific mortality was observed in only 1 (2.7%) patient and recurrence was observed in 7 patients (18.9 %). Comparison of the groups with and without recurrence revealed significant differences in terms of stage, capsule involvement, mitotic index between groups ($p<0.05$). In multivariate regression analyses tumor differentiation was found to be significantly associated with the disease recurrence (OR:8.2,CI 95%: 0,019-0,771).

Conclusion: Tumor differentiation is found to be a significant confounder for the disease recurrence after adjustment for the stage.

Keywords: Granulosa cell tumor, outcome, ovary, recurrence

From: [1]Obstetric and Gynaecology Department, Zeynep Kamil Traning and Education Hospital, [2]Zeynep Kamil Traning and Education Hospital, Pathology, and [3]Obstetric and Gynaecology Department, Kartal Traning and Education Hospital, İstanbul ,Turkey.

Correspondence: Dr MK Eken, Obstetric and Gynaecology Department, Zeynep Kamil Traning and Education Hospital, Opr Dr Burhanettin Ustunel Cad. No 10, Uskudar, Istanbul, Turkey. E-mail: meryemkurek@yahoo.com

INTRODUCTION

Adult-type granulosa cell tumors (GCTs) of the ovary account for 1-2% of all ovarian tumors, and are derived from ovarian sex-cord stromal hormone-secreting tumors (1). Two types have been defined as adult and the juvenile forms. Adult type accounts 95 % of the all granulosa cell tumors and diagnosed in women with a mean age of 50-54 years. There is no symptom specific for this type of tumors, however most common ones are abdominal pain, distantion, palpable pelvic mass, and vaginal bleeding due to the increased levels of estrogen secreted by the tumor. Tumor, generally has low malignancy potential and characrerized by late recurrences (2).

In the literature, different prognostic factors have been proposed(3-5). Most of them supported the data that stage is the most important factor to predict prognosis and determine treatment strategies (6). Tumor diameter, high mitotic index, tumor rupture, age at diagnosis, nuclear atypia, residual tumor after surgery were shown to be other prognostic factors for survival. (2,5).

There has been no consensus for the treatment algorithm for this kind of tumors (5). Surgical management is the first choice as for the epithelial ovarian cancers (7). Clinical follow up for early stages, adjuvant chemo, hormono and radiotherapy for higher stages following an appropriate surgery are widely accepted treatment strategies for these kind of cases. (7-10).

In this study, we aimed to determine the predictors for poor prognosis and to find out the effect of treatment strategies on survival functions.

MATERIAL AND METHODS

Thirty seven women who had been diagnosed to have granulosa cell tumor and treated at gynecologic oncology depertment of Zeynep Kamil Women and Chilren's Health Training

and Research Hospital between 2000 to 2013 were enrolled for the study. Demographic data including age, gravidity, parity, menopausal status, major complaints, adjuvant treatments, recurrences, type of surgery and histopathological results of surgical specimens were all recorded from prospectively collected hospital databese. Patients were stratified into different stages according to the FIGO classification. Type of surgeries were classified into total abdominal hysterectomy with lymph node dissection and fertility preserving approaches. All participants were recalled and a detailed confirmation histories and disease status were obtained from each. Age, stage, preoperative CA125 level (U/ml), tumor diameter(cm), capsule involvement and mitotic indexes were analysed as prognostic factors.

Protocol for the patients who needed adjuvant chemotherapy was as follows: Bleomisin, Etoposide and Paclitaxel combination once for each 3 weeks, totally 3 times.

Statistical analyses: During analyses continuous variables were presented as means and the standart deviation, whereas frequencies were used for the categorical variables. For categorical variables Fisher's Exact test, for continuous variables Mann Whitney U test were used to compare groups. Binary lgistic regression test was used to show associations between the variables and the disease recurrence. For all the analyses SPSS version 17 was used. All statistical analyses were performed within the 95 % confidence interval and the alfa error of 0.05.

RESULTS

Among 37 women with granulosa cell tumor, recurrence was observed in 7 patients (18.9 %). All demographic charecteristics and the initial complaints at admission were all summarized in Table 1. Mean follow up period was 67.9±33.6 months. One of the patients with disease recurrence died within 6 th month of the recurrence due to the comorbidities(

Serebrovascular Disease). During follow up period 2 mortalities were observed one of which was disease specific (2.7%).

As for the prognostic factors age, stage, CA125, tumor, diameter, capsule involvement, and the mitotic index were all compared between groups with (n=7) and without recurrence (n=30). Results of these comparisons were summarized in Table 2.
Among 37 patients lymph node dissection was performed in 22 patients. Non of the lymph nodes showed metastatic involvement.

During follow up mean time for recurrence free survival 52.1 ± 43.9 months for group with recurrence while 65.9 ± 35.3 for the group without recurrence (p=0.380). For overall survival time comparison it was 76.2 ± 25.6 months in group with recurrence and it was 65.9 ± 35.3 months without recurrence (p=0.47).

Five years overall survival rate was 85 % in group with recurrence %85 and 100% in group without recurrence (p=0.02). 5 years disease free survival rate was %28.6 in group with recurrence while 100 % in group without recurrence (p<0.001). Comparison of the groups with and without recurrence revealed significant differences in terms of stage, capsule involvement, mitotic index between groups (p<0.05) (Table 2). Some clinical characteristics of the patients with recurrence were all summarized in Table 3.

Correlation analyses between the parameters that were found to be significantly different between groups and the disease recurrence revealed significant correlation with tumor differentiation (r=0.402; p<0.05), capsule involvement (r=0.402; p<0.05), stage (r=0.640; p<0,001) and disease recurrence. In multivariate regression analyses tumor differentiation was found to be significantly associated with the disease recurrence (OR:8.2, CI 95%: 0.019-0.771).

DISCUSSION

Adult type granulosa cell tumors accounts for 1-2 % of all ovarian tumors and may be hormonal active, also most of the time they are encountered in women within their perimenopausal or early postmenopausal years with a mean age of 46 to54years (1,2,5,7,11). Consistent with the literature in our study population, mean age was 50.1±13.3 years.

Abdominal distantion is frequently seen symptom. In our study population, women presented with a complaint of abdominal distantion (n=13, 35.1%), postmenopausal bleeding (n=11, 29.7 %), abnormal vaginal bleedings (n=10, 27 %), amenorrhea (n=2, 5.4 %). In the literature rate of abnormal bleedings was reported to be seen in 40-50 % of the patients on the other hand abdominal distantion was observed to be in 30-50 % of the women. (4,5,12-14). FIGO stage, mitotic index, patients age, residuel tumor after surgery, tumor spread out of the capsule, tumor rupture during surgery, tumor diameter, preoperative CA125 level, lymph node involvement, postoperative adjuvant treatment were found to be prognostic indicators in these type of tumor (15-18). In addition to the stage, CA125 level, age, capsule involvement, mitotic index, in our study, other indicators that had been assessed in the literature were tried to be analysed to predict prognosis.

Most of the reports showed the most important prognostic factor to be the disease stage(1,3-5,17-20). Five years survival of early stage disease rate was reported to be 80-95 % while it was 88 % for ten years. On the other hand, it decreases to 25-40 % in progressive disease (1,3,4,5,7,9,17-20). Investigation of the mortal cases revealed that 40 % of these cases had tumor extension out of the ovary(21). Among our cases 13.5 % (n=5) of them had Stage 3C tumor. Again among these cases with progressive disease 80 % (n=4) of them experienced recurrences. For the cases with 1C2 stage disease ((27.1 %, n=10), recurrence was observed in 3 cases. Stage of the disease was found to be significant predictor for the disease recurrence ($p<0,001$). In a study by Huang et al on 30 cases, disease stage was found

to be higher in group with recurrences however difference was not shown to be statistically significant (22).

Capsule involvement is accepted to be other prognostic indicator. Capsule involvement was found to be significantly higher in group with recurrence (5/7 vs 7/30, P<0.025) in our study .

Granulosa cell tumors are fragile tumors and can be easily ruptured during surgical intervention. Like capsule involvement, tumor rupture lead to increase in disease stage and tumor spread to the whole abdomen. In our study tumor rupture was not found to be predictor fort he recurrence probably due to the small number of study population. Theorically, it is expected to see increased risk of residuel tumor among cases with tumor rupture and residuel tumor has been shown to be significant predictor fort he recurrence and the survival (7,15).

Among cases with disease recurrence, maximum tumor diameter was 9.9 ± 5.1cm, while it was 9.1 ± 5.1cm in cases without recurrence (P > 0.05). Malmström et al showed tumor diameter as a significant factor fort he prognosis(23). Futhermore Sun et al found mean diameter of the tumor to be 10.4 cm and a cut off to be 13.5 cm for poor prognostic indicator (7).

Analyses of the mitotic index revealed that among the 7 cases with disease recurrence 5 of them had high mitotic index on the other hand there were 7 cases with high mitotic index among patients without recurrence (p<0.025). High mitotic index has been found to be significant predicto in some previous studies (24- 28).

In some reports age of the patients was shown to be a prognostic indicator. However cut off value for the age varies among studies. In our study cut off value was accepted to be 60 years and the effect on prognosis was assessed. There was no significant difference interms of recurrence between groups with and without older age [5(17.2 %) vs. 25 (25 %), p>0.05]. In a study of multivariant analyses by Ayhan et al,age was not found to be a significant predictor(4). Recurrence rates were almost similar

with the rates in our cases. Furthermore Sun et al analysed cases startified to ages as 40, 50 and 60 yeasrs, study did not show any difference in terms of recurrence rates (7).

CA-125 levels were not found to be significantly different between groups with and without recurrence (24.2 ± 29.8U/mL vs. 43.5 ± 34.8U/mL) in our study which is consistent with the results of the study by Shembekar et al (29). Futhermore, Ayhan et al, did not found any difference between group with and without progressive disease in terms of CA-125 levels (4). There has been still a debade on necessity of total staging surgery and the systematic lymphadenectomy in the literature. The importance of total staging surgery and the the systematic lymphadenectomy fort he disease prognosis was emphasized in some previous studies (3,18). In our study total staging surgery was performed in 64.9 %(n=24) of the cases. Among cases with total staging surgery, there were 4 recurrences where as 3 cases in group with conservative surgery. Due to the small number of study population statistical analyses was performed. Among site of recurrences there were recurrences on intestinal wall in 5 cases with multiple implants on intestine and the peritoneal surface. In patients with peritoneal implants one has urinary bladder involvement with organ wall invasion. One of the patients with fertility preserving surgery developed disease recurrence on the ovary, in an other patient recurrence was observed in liver paranchyma. Total staging surgery may be a good alternative for the patients who do not need further fertility. Total surgical staging may be used to determine the need for adjuvant treatment and the know the real extend of the disease. There has been several unstandardized surgical approaches defined in the literature. However most of the authors reported high recurrences in cases with conservative surgery while better survival in cases with radical surgery (30). Ayhan et al analysed 80 cases, among them 11 cases were reoperated after 4 weeks due to the incomplete surgical intervention. Cases with appropriate surgical intervention in their first surgical approach showed better survival (151.9 - 67.0 months, p=0,003), however mortality rates were comparable (4). On the other hand Sun et al did not show any significant difference between groups

with and without total staging surgery in terms of recurrence (7). In our literature search, pelvic-paraaortic lymph node dissection rate was found to be 10-30 %. Lymph node metastases rates were varying between 0 to 8.8 %. (4,7,18,31-37). In our study lymph node dissection was performed in 78.4 %(n=29) of cases. Non of the cases showed lymph node metastases. Lymph node dissection is not recommented by some authors due to the this low rate of lymph node metastases (7,18,34,36) . Further multicenter studies with high number of cases are needed to assess the necessity of lymph node dissesction in cases with these kind of tumors. Due to the lack of data for the prognostic variables there is no consensus fort he need fort he adjuvant therapy. In the literature high stage, residuel tumor, intraoperative tumor rupture, metastatic disease were shown to be indications for the need for adjuvant treatment. However effect of adjuvant treatment on the survival is not clear (5,38). In our study 10 cases received postoperative chemotherapy, 5 of them received chemotherapy due to recurrences.

In conclusion, tumor differentiation is found to be a significant confounder for the disease recurrence after adjustment for the stage.

Table 1: Clinical and Demographic Characteristics and Initial Complaints of Patients

	Min-Max	Median±Sd
Age	14-76	50,05±13,26
Gravidity	0-6	3,11±1,74 (3)
Parity	0-5	2,38±1,49 (2)
Menopause period (year)	2-22	9,47±5,98
Follow Up Period (day)	12-150	67,89±33,63
Tumor Diameter(cm)	2-22	9,46±5,08
CA 125(U/ml)	2,29-150	28,46±31,65
Mitosis count	1-22	3,42±4,31
Initial Complaints	% (n)	
Amenorrea	5.4(2)	
Intermenstruel bleeding	16.2(6)	
Abdominal Pain	8.1(3)	
Abdominal distansion	21.6(8)	
Abdominal distansion+ Pain	5.4(2)	
Abdominal distansion+Intermenstruel bleeding	5.4(2)	
Abdominal distansion+ Palpabl pelvic mass	2.7(1)	
Menometrorhagia	2.7(1)	
Oligomenorrea	2.7(1)	
Postmenoposal bleeding	27.0(10)	
Postmenoposal bleeding + Palpabl pelvic mass	2.7(1)	

Table 2: Comparison of Cases with and without disease recurrence

	Recurrence(n=7)	NoReccurence(n=30)	P value
Age (n)			
<60	5	24	0.631
≥60	2	6	
CA-125(U/ml) (Mean±SD)	24.2 ± 29.8	43.5 ± 34.8	0.081
Tumor Diameter(n)			
<10cm	4	17	1.000
≥10cm	3	13	
Stage(n)			
1A	0	21	
1C2	3	7	**<0.001**
2B	0	1	
3C	4	1	
Capsule invasion(n)			
Positive	5	7	
Negative	2	23	**0.025**
Mitotic Index (n)			
Low-modarate	2	23	
High	7	5	**0.025**
Operation Type (n)			
Cyctectomy	2	4	

TAH+BSO	0	6	
TAH+BSO+PLND	4	18	0.453
Debulking	1	2	

TAH+BSO: Total Abdominal Hysterectomy+ Bilateral Salphingooferectomi

PLND: Pelvic Lymph node dissection

Table-3: Some Clinical and Prognostic Features of Patients with Reccurence

Case	Ageat diagnosis	Primary Treatment	Stage	Time to relapse (month)	Recurrent site	Adj KT	Overall survive (month)	Mitotic İndex	Capsule İnvasion	Outcome
1	26	USO	1C2	59	Left Over	No	59	High	Yes	Alive
2	47	Tah+Bso+Plnd	3C	14	Liver	Yes	60	High	No	Alive
3	50	Tah+Bso+ Plnd	3C	10	Pelvic	Yes	52	High	Yes	Exitus (SVO)
4	58	Tah+Bso+ Plnd	1C2	9	Pelvic	Yes	90	High	Yes	Alive
5	69	Tah+Bso Plnd	3C	58	Pelvic	Yes	208	High	No	Alive
6	67	Tah Bso+Plnd	3C	120	Pelvic	Yes	120	Modarate	Yes	Exitus
7	14	USO	1C2	95	Pelvic	No	95	High	Yes	Alive

SVO: Serebrovascular disease TAH+BSO: Total Abdominal Hysterectomy + Bilateral salphingoopherectomy

PLND: Pelvic Lymph Node Dissection USO: Unilateral Salpingoopherectomy

REFERENCES

1. Colombo N, Parma G, Zanagnolo V et al. Management of ovarian stromal cell tumors. J Clin Oncol 2007;25: 2944-51.
2. Shim SH, Kim DY, Lee SW. et al. Laparoscopic management of early-stage malignant nonepithelial ovarian tumors: surgical and survival outcomes. Int J Gynecol Cancer 2013;23: 249-55.
3. Lee YK, Park NH, Kim JW et al. Characteristics of recurrence in adult-type granulose cell tumor. Int J Gynecol Cancer 2008; 18: 642–7.
4. Ayhan A, Salman MC, Velipasaoglu M et al. Prognostic factors in adult granulosa cell tumors of the ovary: a retrospective analysis of 80 cases. J Gynecol Oncol 2009;20:158–63.
5. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol 2003;21:1180-9.
6. Miller BE, Barron BA, Wan JY, et al. Prognostic factors in adult granulosa cell tumor of the ovary. Cancer 1997;79: 1951.
7. Sun HD, Lin H, Jao MS. et al. A longterm follow-up stu dy of 176 cases with adult-type ovarian granulosa cell tumors. Gynecol Oncol 2012;124:244-9.
8. Gershenson DM. Management of early ovarian cancer: germ cell and sex cord-stromal tumors. Gynecol Oncol 1994; 55:62.
9. Van Meurs HS, Buist MR, Westermann AM. et al. Effectiveness of chemotherapy in measurable granulosa cell tumors: a retrospective study and review of literature. Int J Gynecol Cancer Mar 2014;24:496–505.
10. Gurumurthy M, Bryant A, Shanbhag S. et al. Effectiveness of different treatment modalities for the management of adult-onset granulosa cell tumours of the ovary (primary and recurrent). Cochrane Database Syst Rev 2014;4:CD006912.

11. Healy DL, Burger HG, Mamers P. et al. Elevated serum inhibin concentrations in postmenopausal women with ovarian tumors. N Engl J Med 1993;329:1539-42.

12. Bompas E, Freyer G, Vitrey D. et al: Granulosa cell tumour: review of the literature. Bull Cancer 2000; 87:709–714.

13. Van Holsbeke C, Domali E, Holland TK et al. Imaging of gynecological disease (3): clinical and ultrasound characteristics of granulosa cell tumors of the ovary. Ultrasound Obstet Gynecol 2008; 31:450-6.

14. You XL, Yin RT, Li KM et al. Clinical and pathological analysis on ovarian granulosa cell tumors. Sichuan da Xue Xue Bao Bao Yi Xue Ban 2010; 41:467-70.

15. Auranen A, Sundstrom J, Ijas J. et al. Prognostic factors of ovarian granulosa cell tumor: a study of 35 patients and review of the literature. Int J Gynecol Cancer 2007; 17:1011-8.

16. Chua IS, Tan KT, Lim-Tan SK .et al. A clinical review of granulosa cell tumours of the ovary cases in KKH. Singapore Med J 2001; 42:203-7.

17. Ohel G, Kaneti H, Schenker JG. Granulosa cell tumors in Israel: a study of 172 cases. Gynecol Oncol 1983;15: 278-86.

18. Park JY, Jin KL, Kim DY, et al. Surgical staging and adjuvant chemotherapy in the management of patients with adult granulosa cell tumors of the ovary. Gynecol Oncol 2012; 125:80-6.

19. Pankratz E, Boyes DA, White GW, et al. Granulosa cell tumors. A clinical review of 61 cases. Obstet Gynecol 1978; 52:718-23.

20. Schwartz PE, Smith JP. Treatment of ovarian stromal tumors. Am J Obstet Gynecol 1976;125:402-11.

21. 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: 400-3.

22. Huang BS, Sun HD, Hsu YM, Chang WH, et al. Clinical presentation and outcome of adult-type granulosa cell tumors: A retrospective study of 30 patients in a single institute. JCMA 2014;77:21-25

23. Malmström H, Högbreg T, Risberg B, et al. Granulosa cell tumors of the ovary: prognostic factors and outcome. Gynecol Oncol 1994;52:50–5.

24. Fujimoto T, Sakuragi N, Okuyama K, et al: Histopathological prognostic factors of adult granulosa cell tumors of the ovary. Acta Obstet Gynecol Scand 2001;80:1069–1074.

25. Björkholm E, Silfverswärd C: Prognostic factors in granulosa-cell tumors. Gynecol Oncol 1981; 11:261–274.

26. Fox H. Pathologic prognostic factors in early stage adult-type granulosa cell tumors of the ovary. Int J Gynecol Cancer 2003;13:1–4.

27. Miller BE, Barron BA, Wan JY et al: Prognostic factors in adult granulosa cell tumor of the ovary. Cancer. 1997; 79:1951-5

28. Fujimoto T, Sakuragi N, Okuyama K et al: Histopathological prognostic factors of adult granulosa cell tumors of the ovary. Acta Obstet Gynecol Scand 2001;80:1069-74

29. Shembekar M, Casaclang D, Keen E. Granulosa cell tumours of the ovary express inhibin but not CA 125. J Obstet Gynecol 1998; 4:355-8.

30. Pautier P, Lhomme C, Culine S, et al. Adult granulosa-cell tumor of the ovary: a retrospective study of 45 cases. Int J Gynecol Cancer 1997; 7: 58-65.

31. Ertaş IE, Güngördük K, Taşkın S,et al. Prognostic predictors and spread patterns in adult ovarian granulosa cell tumors: a multicenter long-term follow-up study of 108 patients. Int J Clin Oncol 2014; 19:912–920

32. Lee IH, Choi CH, Hong DG. Clinicopathologic characteristics of granulosa cell tumors of the ovary: a multicenter retrospective study. J Gynecol Oncol 2011; 22:188–195

33. Ayhan A, Tuncer ZS, Tuncer R Granulosa cell tumor of the ovary. A clinicopathological evaluation of 60 cases. Eur J Gynaecol Oncol 1994; 15: 320–324

34. Fotopoulou C, Savvatis K, Braicu El. Adult granulosa cell tumors of the ovary: tumor dissemination pattern at primary and recurrent situation, surgical outcome. Gynecol Oncol 2010; 119:285–290

35. Iyibozkurt AC, Topuz S, Gungor F. Factors affecting recurrence and disease-free survival in granulosa cell tumors of the ovary. Eur J Gynaecol Oncol 2010;31: 667–671.

36. Brown J, Sood AK, Deavers MT, et al. Patterns of metastasis in sex cord-stromal tumors of the ovary: can routine staging lymphadenectomy be omitted? Gynecol Oncol 2009;113 :86.

37. Abu-Rustum NR, Restivo A, Ivy J, et al. Retroperitoneal nodal metastasis in primary and recurrent granulosa cell tumors of the ovary. Gynecol Oncol 2006; 103:31.

38. Cronje HS, Niemand I, Bam RH, et al. Review of the granulosa-theca cell tumors from the emil Novak ovarian tumor registry. Am J Obstet Gynecol 1999;180: 323-7.