Adult Granulosa Cell Tumors of the Ovary: A Clinicopathological Study of 34 Patients by the Hellenic Cooperative Oncology Group (HeCOG)

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Abstract. *Background: Granulosa cell tumors (GCT) are rare malignant neoplasms of the ovaries with, usually, indolent biological behavior. Patients and Methods: The epidemiological, clinical and pathological features of 34 patients with adult GCT, from the registry of the HeCOG, were analyzed retrospectively for their prognostic significance. Results: The median age was 51 years with post- to premenopausal ratio=1.8 and median size of the tumor 10 cm. Forty-seven % had a low mitotic index (1-3 mitoses/10 high-power fields, HPFs) and 48% had International Federation of Obstetrics and Gynecology (FIGO) stage IA. After 34.5 months of median follow-up, the estimated 5-year and 10-year progression-free survival (PFS) was 78% and 65% , respectively, while both the 5- and 10-year overall survival (OS) was 89% . The stage and the presence of residual disease after surgery had prognostic significance for OS in the univariate analysis. Out of 19 patients whose disease was completely resected, the median disease-free survival (DFS) was 11 months. Only rupture of the tumor during surgery had prognostic significance for DFS in the univariate analysis. Seven out of 13 evaluable patients with unresectable disease responded to first-line chemotherapy (CT), 6 of them completely, while three patients responded to second-line chemotherapy. All the responders were retreated with platinum-based CT and one of them was platinum-insensitive. All the patients receiving second-line non-platinum CT developed progressive disease (PD). Conclusion: The only curative treatment of GCT is complete surgical resection of all visible disease, while platinum-based CT is the most effective first-line, as well as second-line treatment.*

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Granulosa cell tumors (GCT) of the ovary are rare tumors, accounting for 2-5% of ovarian malignancies and more than 70% of the sex cord-stromal tumors (1). They are derived from the granulosa cell, a hormonally active component of the ovarian stroma, secreting estradiol. Usually, they are localized in the ovary and, less frequently, they spread locally. They behave with an indolent clinical course, late relapses and long survival. The optimal treatment is complete surgical resection, whereas the role of all other therapeutic modalities is palliative or adjunctive to surgery (2-4).

The aim of the present retrospective study was to illustrate the patient characteristics, describe the efficacy of the applied treatments and examine the prognostic significance of various clinical and histopathological features on survival.

Patients and Methods

Patient selection. From April 1983 to February 2007, among 1800 patients with ovarian tumors on the HeCOG registry, 34 (0.018%) patients were found to have adult GCT of the ovary. These patients were treated in five referral cancer centers of Greece. The patient data used in the study were derived from the medical records and the electronic tumor registry of the HeCOG. Patients were included in the study, if their diagnosis was confirmed by review of the pathological specimen from primary surgery by the expert pathologists of the participating centers in the HeCOG.

Staging procedures, study groups and response assessment. The patient's basic demographic, clinical and histopathological characteristics were recorded. All the patients were staged according to the International Federation of Obstetrics and Gynecology (FIGO)

Table I. *Basic patient characteristics.*

Patient characteristics	% of patients	Median
Age (range)		51 years (23-80)
Postmenopausal:Premenopausal ratio	1.8	
Age of menarche		12 years
Age of menopause		46.5 years
History of pregnancies		
Nulliparous	31%	
Number of births	69%	2
Symptoms		
Asymptomatic	23%	
Abdominal pain	61%	
Menstrual disturbances	38%	
Abdominal enlargement	31%	
Location of primary tumor		
Right ovary	73%	
Left ovary	23%	
Bilateral	4%	
Size of primary tumor		10 cm
Rupture of primary tumor	12%	
Mitotic index		
Low (1-3 mitoses per high-power field)	47%	
Intermediate (4-10 mitoses per HPF)	24%	
High (>10 mitoses per HPF)	29%	
FIGO Stage		
IA	48%	
IB-IC	11%	
II	8%	
III	22%	
IV	11%	
Type of surgery		
TAH-BSO	64%	
USO	24%	
BSO	8%	
TAH-USO	4%	
Macroscopic residual disease after surgery	24%	

TAH: total abdominal hysterectomy, BSO: bilateral salpingo-oophorectomy, USO: unilateral salpingo-oophorectomy.

classification used for epithelial ovarian cancer (5). The patients were grouped as those subjected to macroscopically complete resection of their disease, those with unresectable or incompletely resected tumors at presentation or following disease recurrence, treated with first-line chemotherapy (CT) and those with relapsed disease receiving second-line CT. The treatment applied and the objective response achieved, according to the World Health Organisation (WHO) criteria (6), were recorded separately for these groups of patients.

Statistical methods. Progression-free survival (PFS) and overall survival (OS) was calculated for all patients. Disease-free survival (DFS) was calculated only for those patients subjected to curative surgery without macroscopic residual disease. PFS was determined as the time from the start of treatment to the date of disease progression or death from any cause. OS was considered as the time from the date of initial diagnosis to the date of death from any cause. DFS was defined as the time from the date of surgery to the date of disease relapse or death from any cause. Survival curves were plotted for the entire group of patients and separately for each group of patients described above. The median survival times were estimated according to the Kaplan-Meier method (7). Univariate analysis of prognostic factors was performed according to the log-rank test, whereas multivariate analysis was not conducted because of a very low number of events (only 3).

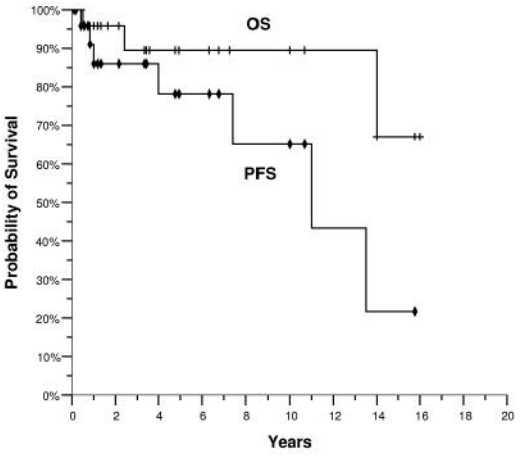

Figure 1. *PFS (progression-free survival) and OS (overall survival) curves of the 28 patients followed from initial diagnosis of their disease.*

Results

Patient characteristics. The basic characteristics of the patients are illustrated in Table I. The median age was 51 years and the majority of patients, 22, were postmenopausal while 12 were premenopausal. In 23% of patients, disease was found by chance or during routine examination, while the rest of them had symptoms at presentation (shown as percentages of the symptomatic patients, in Table I).

Survival analysis of the entire population. Twenty-eight patients were followed from their initial diagnosis, while for the remaining 6 patients data were available for the time after disease recurrence. The median time of follow-up for those observed from the initial disease diagnosis was 34.5 months (range 1-192). The median PFS was 11 years, while median OS had not yet been reached. The estimated 5-year and 10-year PFS was 78% and 65% , respectively, and estimated 5-year and 10-year OS were both 89% (Figure 1). In the univariate analysis, the presence of residual disease after surgery (p=0.009) and disease extension beyond the ovary, *i.e.* FIGO stage more than IA, (p=0.047) were associated with poorer OS (Figure 2).

Patients whose disease was completely resected. Nineteen patients were treated with debulking surgery, without macroscopic residual disease after operation. The majority of them (11 patients, 58%) were treated with total

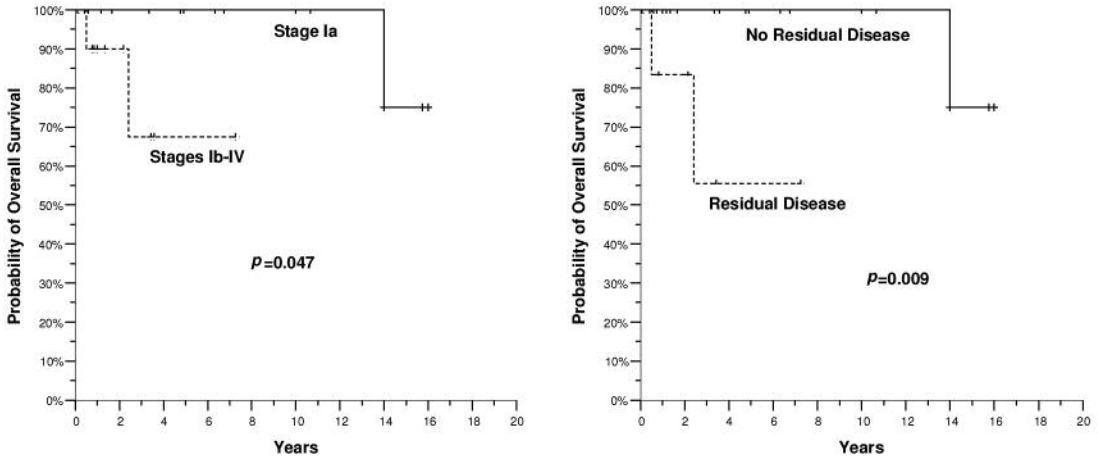

Figure 2. *Survival curves according to FIGO stage and the presence or not of residual disease after surgery in patients followed from initial diagnosis of disease.*

Table II. *Characteristics of patients who relapsed after curative surgery (without macroscopic residual disease after resection).*

Age	FIGO stage	Size of primary	Rupture during surgery	Mitoses per 10 HPFs	Type of surgery	CT (cycles)	DFS (mo)	OS (mo)
42	Ia	10	NO	UNK	USO	NO	89	168
36	Ia	7	NO	>10	USO	NO	132	+168
46	IIb	4	YES	1-3	TAH-USO	CBDCA-TX (6)	12	+43
51	Ia	8	NO	>10	BSO	CBDCA-CTX (4)	162	+192
62	Ic	10	NO	>10	TAH-BSO	CBDCA-CTX (8)	10	+20

USO: unilateral salpingo-oophorectomy, BSO: bilateral salpingo-oophorectomy, TAH-USO: total abdominal hysterectomy plus unilateral salpingo-oophorectomy, TAH-BSO: total abdominal hysterectomy plus bilateral salpingo-oophorectomy, HPFs: high-power fields, CT: chemotherapy, DFS: disease-free survival, OS: overall survival, mo: months, CBDCA: carboplatin, TX: paclitaxel, CTX: cyclophosphamide, UNK: unknown.

abdominal hysterectomy plus bilateral salpingo-oophorectomy (TAH-BSO), 5 patients (26%) with unilateral salpingo-oophorectomy (USO), 2 patients (11%) with total abdominal hysterectomy plus unilateral salpingo-oophorectomy (TAH-USO), and 1 patient (5%) with bilateral salpingo-oophorectomy (BSO). Among them, seven patients received adjuvant CT: 3 patients were treated with carboplatin plus cyclophosphamide, 2 with cisplatin, vinblastine and bleomycin (PVB), 1 with bleomycin, etoposide and cisplatin (BEP) and 1 with carboplatin plus paclitaxel. Seven out of 12 patients treated only with surgery and 4/7 patients treated with adjuvant CT, had stage IA disease. In total, 5 patients developed recurrence (26%); their characteristics are shown in Table II. Notably, 4 out of 8 patients treated with suboptimal surgery developed recurrence, in contrast to only 1/11 subjected to TAH-BSO. Also, 3 out of 5 patients with a mitotic rate >10 per 10 HPFs relapsed, in contrast to only 1/11 with a lower mitotic index. After a median time of follow-up of 50 months, the estimated median DFS was 11 years. Univariate analysis of prognostic factors for DFS revealed that the rupture of the tumor during surgery had a significant adverse effect (p=0.043), while the type of surgery or the mitotic rate did not have a significant effect.

Patients with incompletely resected or unresectable disease. Nine patients had metastatic (stage IV) or unresectable disease at presentation and 8 patients at relapse after surgical disease resection without adjuvant treatment (two of them included also in the previous paragraph before their relapse). Among them, 3 patients were subjected only to surgery, while the remaining 14 patients were treated with first-line chemotherapy. The majority of them (12 patients) received cyclophosphamide, doxorubicin or epirubicin and cisplatin (CAP or CEP), while 1 patient received BEP and one patient cisplatin, etoposide and epirubicin followed by cisplatin plus paclitaxel. Seven out of 13 evaluable patients responded to CT (6 completely), four patients had stable disease (SD) and

Table III. *Treatment results of patients receiving second line-treatment.*

Age	Disease status during 1st -line CT	1st line-CT	Response to 1st-line CT	PFS since 1st-line CT	2nd line-treatment	Response to 2nd line-treatment	PFS since 2nd line-treatment	OS since unresectable disease
46	Resected (st.IIb)	CBDCA-TX	NA	12 mo	CBDCA-TX	CR	+31 mo	+31 mo
51	Resected (st.Ia)	CBDCA-CTX	NA	162 mo	CBDCA-TX	CR	+30 mo	+30 mo
49	Relapsed	CAP	SD	5 mo	PVB	PR	+7 mo	+12 mo
53	Unresectable	CAP	CR	48 mo	Debulking Surgery+RT	CR	+39 mo	+87 mo
55	Relapsed	CAP	SD	5 mo	PVB+RT	PD	0	22 mo
62	Resected (st.Ic)	CBDCA-CTX	NA	10 mo	5FU	PD	0	+4 mo
52	Relapsed	CAP	SD	5 mo	5FU	PD	0	28 mo
51	Relapsed	CAP	PR	4 mo	MVF+RT	PD	0	60 mo
62	Unresectable	CEP	PD	0 mo	TX+RT	NE	0	29 mo

CT: chemotherapy, PFS: progression-free survival, OS: overall survival, mo: months, CBDCA: carboplatin, TX: paclitaxel, CTX: cyclophosphamide, MVF: mitomycin, vinblastine, 5FU: 5-fluorouracil, RT: radiotherapy, CAP: cyclophosphamide, doxorubicin, cisplatin, CEP: cyclophosphamide, epirubicin, cisplatin, PVB: cisplatin, vinblastine, bleomycin, NE: not evaluable, SD: stable disease, CR: complete response, PR: partial response, PD: progressive disease.

two patients developed disease progression (PD). After 21 months of median follow-up, seven patients had died (estimated median OS was 5 years).

In total, nine patients, treated with CT, developed disease recurrence and received second-line treatment (Table III). The main treatment modality chosen in the vast majority of them was CT, while 1 patient was subjected to debulking surgery followed by radiotherapy. Two patients received five-day continuous infusion of 5-fluorouracil (5-FU), 1 patient the combination of 5-FU, mitomycin-C and vinblastine plus radiotherapy, 2 patients carboplatin plus paclitaxel, 1 patient paclitaxel followed by radiotherapy to bone metastases and two patients the PVB regimen. Among the seven patients evaluable for response, 2 patients achieved a complete response (CR) and 1 patient a partial response (PR), while 4 patients had PD. After 23 months of median follow-up, 5 patients experienced PD and four succumbed to their disease. The estimated median OS was 4.6 months. As shown inTable III, all the responders had received platinum-based CT, whereas all the patients treated with non-platinum-based regimens had PD. Moreover, platinum-based CT was effective in the patients also pretreated with another platinum-based schedule, even if they had not responded or remained progression-free for only a few months.

Discussion

The characteristics of our study population were similar to those reported in the literature (2-4, 8-22). Postmenopausal women are affected more commonly and the median age ranges between 44-58 years. The commonest symptoms are menstrual disturbances, abdominal pain and distention. The size of primary tumor at presentation varies between a few and more than 30 cm, but the reported median values are quite similar (10-11.5 cm). Nevertheless, 45-87% of patients have stage I disease at diagnosis. These features are consistent with the observation that these tumors have an indolent biological behavior with late recurrences and long overall survival.

The 5-year OS reported in the literature ranges between 77-92% , the 10-year OS between 76-85% , whereas longer OS estimations have given lower survival rates down to 50% . This late decline in survival rates is attributed mainly to the long natural history of the disease. Indeed, Bjorkholm (23) in a comparative study confirmed that women with GCT have a 2.2 times higher mortality rate than their normal controls. Furthermore, relapses have been reported 15 to 30 years after initial diagnosis (24-26). The median PFS reported in some studies ranges between 44-50 months (13, 21), whereas, in the study of Savage *et al*. (15), patients with stage I disease were progression-free for a median of 76 months. Due to this uncommon biological behavior, in combination with the rarity of the disease, several unanswered questions remain concerning about the optimal treatment of these patients. The most important is which group has high preponderance for relapse and probably would benefit from a more aggressive treatment.

Several studies, mainly retrospective, have investigated the prognostic significance of various clinical and laboratory features. The most important, globally accepted, prognostic factor is the FIGO stage (4, 10, 14, 17-19, 22, 27, 28). Patients with stage I disease have a very favorable outcome, with reported survival rates of 93-100% at 5 years, 75-88% at 10 years, 75% at 15 years and 62% at 20 years (10, 11,14, 16), while patients with more advanced disease have a much worse prognosis (5-year survival rate ranges between

33-44%) (10, 11). Malmstrom *et al*. (10) have observed that GCT patients did not have essentially different survival rates than their epithelial ovarian cancer counterparts, if stage by stage comparisons were made. Many pathological and biological characteristics of the tumor have been investigated, but only the mitotic index has demonstrated prognostic significance in many studies (2, 10, 12, 13, 17, 22, 29), however, it was not confirmed by others (18, 27). This could be attributed to different estimations of the histological slides between pathologists. Other characteristics of prognostic significance published in some studies are advanced age, the presence of symptoms at presentation, a large primary tumor, lymphovascular space invasion, residual disease after surgery and tumor rupture (2, 4, 17, 28, 22, 30), but most of them were not confirmed in our study. The FIGO stage and resectability of disease were the only prognostic factors in the present group of patients. Those with stage IA disease or completely resected disease had excellent (100%) estimated 5-year and 10-year OS, with only 1 death noted 14 years after diagnosis, whereas patients with more advanced stages and those with unresectable or incompletely resected disease had 67% and 55% 5-year OS, respectively. Nevertheless, longer follow-up and a higher number of patients are probably required to draw definitive conclusions.

It is generally accepted that patients with a FIGO stage more than IA should receive optimal surgical treatment, *i.e*. TAH-BSO, plus adjuvant CT (7, 31, 32). In contrast, the role of aggressive surgery in patients with stage IA disease is controversial. Lauszus *et al*. (16) have studied 37 women with stage I disease (76% of them with stage IA) and reported an increased relapse rate in those treated with more conservative surgery. In contrast, other studies were inconclusive about the optimal extent of surgery (3, 4, 8). This question is of major importance in premenopausal women with stage IA disease who would like to preserve their fertility. On the other hand, adjuvant CT does not seem to confer any benefit in this group of patients (3, 28, 33). However this is difficult to prove, as no randomized trials can be conducted because of the rarity of the disease. The present study confirmed these results, as the type of surgery did not seem to offer better DFS. In contrast, the rupture of the tumor during surgery had a significant effect, but the number of patients was too low to draw definitive conclusions. Therefore, a larger series of patients with early disease would be necessary to investigate the role of radical surgery in the group of patients with possible adverse prognostic factors, such as large tumor size, high mitotic index or lymphovascular space invasion and other suspected biological features.

When the disease could not be completely resected or recurred after surgical resection, prognosis was poorer (4, 8, 22). These patients had usually been treated with CT with or without radiotherapy, with the intent to achieve disease remission and make the tumor resectable. The most studied and effective regimens were those with platinum-based combinations, with a response rate in most cases exceeding 60%. However, definitive conclusions about the efficacy of these regimens could not be made, because these studies included either a very small number of patients (34-39) or different chemotherapeutic regimens (15). The largest prospective phase II trial involving 75 patients with unresectable or recurrent disease treated with BEP was conducted by the Gynecologic Oncology Group (40). Among 25 patients evaluable for clinical response, 10 responded (RR=40%) and 14 (56%) achieved stable disease. A clinical complete response was shown in 24% of them, whereas a pathological complete response at the time of second-look laparotomy was found in 37% (14 out of 38 patients). After 3 years of median follow-up, 44% of patients had a recurrence and 17% had died of disease, including 3 pathologically complete responders (at 15.4, 20.1 and 68.7 months). In addition, the EORTC Gynecological Cancer Cooperative Group, in a phase II study (38), treated 38 patients with advanced or recurrent disease with PVB. Among 25 patients receiving first-line CT, 52% responded, 16% achieved a SD, while the median OS was 25.4 months. The figures in the present study (RR=54%, SD=31%) were not essentially different, although the patients had received different platinum-based regimens (mostly CAP). This confirmed that platinum-based CT is highly effective in patients with unresectable disease, patients with residual disease after surgery or patients with recurrent disease, in whom the resectability of the tumor could be increased and prolonged remissions be achieved. However, the optimal chemotherapeutic regimen has not been found yet.

Although several reports have been published concerning the treatment of CT-naïve patients, data concerning second-line CT are very scarce and comprise mainly case reports (41-43). The largest published series (43) included four patients treated with first-line CAP and second-line cisplatin plus cyclophosphamide and one patient who followed the reverse sequence. Among the four responders (response rate 80%), 2 patients achieved a CR and were free of disease for 33-43 months, whereas the other 3 patients died, two of disease after 35-38 months and one, partial responder, of another cause after 73 months. The present study confirmed that patients treated with first-line platinum-based CT could be "sensitive" to retreatment with other platinum-based regimens, while the duration of response could exceed two years. In contrast to epithelial ovarian cancer, retreatment with other platinum-based schedules would probably be of worth even in "resistant" cases (no response to first-line CT or very short duration of response). Unfortunately, these cases are extremely rare to enroll in prospective trials and, until now, evidence is based only on case reports.

Conclusion

The features of GCT make the inclusion and follow-up of patients in prospective studies very difficult. Therefore, all patients should be treated in referral centers with experience in these tumors and, if possible, enrolled in prospective carefully designed studies, including correlations with biological markers.

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