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OVARIAN GRANULOSA CELL TUMORS: RETROSPECTIVE ANALYSIS OF 18 CASES

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Summary. ***Background.*** Granulosa cell tumors (GCTs) are rare neoplasms and they represent about 2 to 5% of all ovarian cancers. They are usually detected at an early stage and have a relatively favorable prognosis. ***Aim.*** The aim of this study was to investigate the clinical and pathological characteristics of GCT patients and to identify the prognostic factors. ***Methods.*** In a retrospective study, we have analyzed the medical data of 18 patients with newly diagnosed GCTs treated by the Department of Gynecology and Obstetrics in the University Hospital Centre Zagreb in the period from January 2011 until December 2017. We have investigated data for age, parity, symptoms, tumor size, stage of disease, radicality of surgery, pathological characteristics of the tumors (number of mitosis, presence of Call-Exner bodies), application of adjuvant chemotherapy, time to progression of disease and overall survival. ***Results.*** Data from 18 cases were obtained. The median age was 55 years. The mean parity was 1,39. The most common clinical manifestations of the disease were abdominal pain (44%) and abdominal distension (44%). The mean tumor size was 11 cm (range 2 – 30 cm). The majority of our patients were stage I (78%, N = 14), while (22%, N = 4) were stage III. 15 patients underwent radical surgery, while in 3 patients fertility-sparing surgery was performed. According to the tumor characteristics, the mitotic count was high (> 10 mitosis/10 HPFs) in 9 cases (50%) and 7 patients had presence of Call-Exner bodies. Four patients received 1–6 cycles of adjuvant chemotherapy. During the follow-up period (median 49 months), 3 patients relapsed and one patient died free of the primary disease, from myocardial infarction. ***Conclusion.*** The basis of therapy in GCTs is surgical removal of the disease, and platinum-based adjuvant chemotherapy is recommended for advanced-stage GCTs. A prolonged follow-up period is necessary because they progress slowly and have a specific tendency for late recurrences.

Introduction

Granulosa cell tumors (GCTs) are rare ovarian malignancies that represent 2–5% of all ovarian cancers. They were described for the first time in 1855 by Rokitansky (1). These tumors are part of ovarian sex-cord stromal tumors (SCST). They arise from hormonally active granulosa cells and secrete different substances such as estrogen, inhibin, anti-Müllerian hormone which are used as serum tumor markers. According to their clinical and histological features GCTs are divided into two subtypes: adult type (95%) and juvenile type (5%). Juvenile GCTs usually occur in women younger than 30 years, while the median age of diagnosis for the more common adult GCTs is between 50 and 54 years (2,3). The basis of therapy in GCTs is surgical removal of the disease. A total abdominal hysterectomy and bilateral salpingo-oophorectomy is recommended. In young patients with FIGO stage I disease, who wish to preserve fertility, a unilateral salpingo-oophorectomy can be an option. Adjuvant platinum-based chemotherapy or radiotherapy for limited disease is recommended in patients with advanced stages of disease (stage II-IV) and we can consider the use of the chemotherapy in patients with high risk stage IC disease. Prolonged surveillance is recommended because they can occur years later (even after 40 years) (4–6). The aim of our study presented here was to report clinical and pathological characteristics, treatment and outcomes of patients with ovarian GCTs treated at our hospital.

Methods

We have analyzed medical data of eighteen patients with adult type granulosa cell tumors of the ovary. All these patients were treated by the Department of Gynecology and Obstetrics in the University Hospital Center Zagreb in the period from January 2011 until December 2017. We have investigated data for age, parity, symptoms, tumor size, stage of disease, radicality of surgery, pathological characteristics of the tumors (number of mitosis, presence of Call-Exner bodies), application of adjuvant chemotherapy, time to progression of disease and overall survival. Patients were followed up until March 2018. Quantitative variables were expressed as mean and median values. Qualitative variables are expressed as absolute and relative frequencies.

Results

Eighteen cases with histologically confirmed GCTs of the ovary were identified during a period between January 2011 and December 2017. The median age was 55 years (range 26 – 84 years). For 89% of the patients (N=16), the tumor occurred between the fifth and ninth decade of life. The mean parity was 1.39, and 12 of the patients were menopausal. The most common clinical manifestations of the disease were abdominal pain (44%) and abdominal distension (44%). Other symptomatology included postmenopausal bleeding (27%) and secondary amenorrhea

Table 1. Characteristics of the patients

Characteristics (N=18)	N (%)
Age, median (years)	55
≤40	2 (11%)
>40	16 (89%)
Parity	
0	4 (22%)
1	5 (28%)
2	7 (39%)
3	2 (11%)
Symptoms	
Pelvic/abdominal pain	8 (44%)
Abdominal distension	8 (44%)
Postmenopausal bleeding	5 (28%)
Secondary amenorrhea	1 (6%)
FIGO stage of disease	
Stage I	14 (78%)
IA	9 (50%)
IC	5 (28%)
Stage III	4 (22%)
IIIA	1 (5,5%)
IIIB	1 (5,5%)
IIIC	2 (11%)

Table 2. Characteristics of the tumor

	N (%)
Size of the tumor	
≤10 cm	10 (56%)
>10 cm	8 (44%)
Mitotic count	
<5	9 (50%)
5–10	5 (28%)
>10	2 (11%)
unknown	2 (11%)
Presence of Call-Exner bodies	
Presence	7 (39%)
Absence	11 (61%)
Tumor rupture	
Yes	4 (22%)
– preoperatively	2 (11%)
– during the operative procedure	2 (11%)
No	14 (78%)
Peritoneal cytology	
Negative	12 (67%)
Positive	4 (22%)
Not measured	2 (11%)

(5,5%). Fractional curettage was performed before operation in 5 patients (one patient had an orderly pathohistological finding, two were diagnosed with endometrial polyps, and two with endometrial hyperplasia). Preoperative values of inhibin B were not studied in any of our patients. A summary of patients' characteristic is presented in *Table 1*.

The mean tumor size was 11 cm (range 2 – 30 cm). The majority of our patients were stage I (78%, N = 14), while (22%, N = 4) were stage III. The primary treatment was surgery in all cases. Out of 18 patients, 15 patients (83%) underwent a radical surgery which included hysterectomy with bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies and abdominal washout. Lymphadenectomy was done in three patients. Three patients underwent a conservative surgery, which included unilateral salpingo-oophorectomy in two patients (11%) and cystectomy in one patient (5%). Two patients had a rupture of the tumor in the intraoperative finding and two patients had a cystic rupture during the operative procedure. In four patients (22%) the presence of malignant cells was found in peritoneal fluid. Postoperatively, in one patient was found simultaneously endometrial adenocarcinoma, which was stage I, gradus I and did not require further therapy. According to the tumor characteristics, the mitotic count was high (> 5 mitosis/10 HPFs) in 9 cases (50%) and 7 patients had presence of Call-Exner bodies. A summary of tumor characteristic is presented in *Table 2*.

We recommended adjuvant chemotherapy for five patients (one with stage FIGO IC and four with stage III) and only four patients received 1–6 cycles of postoperative chemotherapy. Adjuvant chemotherapy was a platinum-based regimen: CEP (cyclophosphamide 600 mg/m^{2}D1, epirubicin 70 mg/m^2 D1 plus cisplatin 50 mg/m^2 D1 every 4 weeks) in 1 patient and PEB (cisplatin 20 mg/ m^2 D1-D3, bleomycin 20 mg/ m^2 (max 30 mg) D2,D9,D16 and etoposide 100 mg/ m^2 D1-D5 every 3 weeks) in 3 patients. No patient received adjuvant radiotherapy or hormonal therapy. The median follow-up period was 49 months. During this period, recurrence was observed in three patients (16%), and the mean time from initial surgery to recurrence was 47 months (range 30 to 70 months). The site of relapse was pelvis in all three patients, and one had also retroperitoneal lymph nodes involvements. In all patients a surgery was done and one patient received chemotherapy with PEB regimen, others refused administration of chemotherapy. They are still alive, two of them are without recurrence of the disease and one patient had second recurrence, also in the pelvis. She has had a surgery and now has received the second line chemotherapy with paclitaxel and carboplatin. One patient died free of the primary disease, from myocardial infarction**.** The median overall survival has not yet been reached. 5-year survival in our study is 94%. A summary of patients' characteristic with recurrent disease is presented in *Table 3*.

Discussion

Granulosa cell tumors (GCTs) are rare malignancies with a good prognosis. In our study we included only eighteen patients in the period from January 2011 until December 2017. GTCs are the most common type of ovarian sex-cord stromal tumors. They are divided into two subtypes: adult type and juvenile type. Adult type GCTs are more common and usually occur in peri-menopausal and post-menopausal women (the median age 50–55 years). Juvenile GCTs are less common and they comprise 5 percent of all GCTs. This type usually occurs in pre-menarche girls

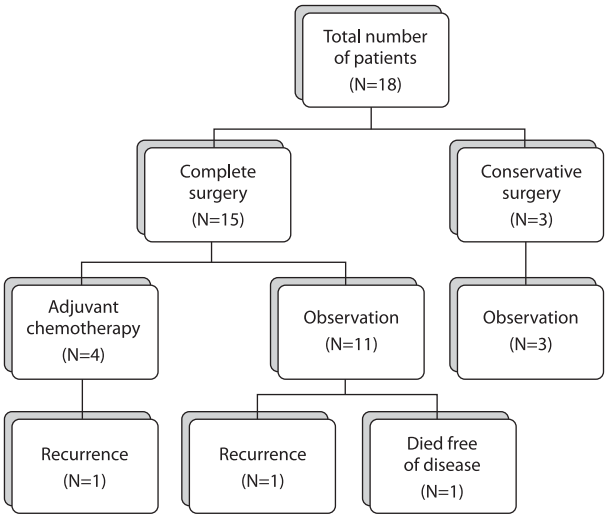

Figure 1. Treatment modalities in our patients

adenocarcinoma can be found simultaneously in 5–10% of patients with granulosa cell tumor and are often well-differentiated and in an early stage with a favorable prognosis (15). Fractional curettage was performed before operation in 5 of our patients. One patient had an orderly pathohistological finding, two were diagnosed with endometrial polyps and two with endometrial hyperplasia. Preoperatively, none of the patients was diagnosed with endometrial cancer.

The average size usually reported in literature is more than 10 cm (11–14). The average tumor size of our patients was 11 cm (range 2–30 cm).

Diagnosis of the GCTs is made by histology at the time of surgical excision. Preoperatively, ultrasound evaluation usually reveals a large solid ovarian mass with variable number of cysts and absent papillary projections. They arise from hormonally active granulosa cells and secrete different substances such as estrogen, inhibin, anti-Müllerian hormone which are used as serum tumor markers (16).

Table 3. Characteristics of patients with recurrent disease

Case	Age (years)	Stage (FIGO)	Size of tumor (cm)	Primary treatment	PFI (months)	Site of relapse	Treatment of relapse
1	82	IIIC2	4	Surgery + CTH (1xCEP)	40	Retroperitoneal + pelvic	surgery (refused postoperative CTH)
2	63	IC	7	surgery	30	pelvic	Surgery + CTH
3	69	IIIB	16	surgery (refused CTH)	70	pelvic	Surgery (refused postoperative CTH)

CTH=chemotherapy, PFI= progression free interval

and young women (2,3). The distinction between these two subtypes is further aided by the presence of a specific somatic missense mutation in FOXL2 gene in adult GCTs, which is typically absent in juvenile GCTs. FOXL2 gene encodes a transcription factor necessary for normal granulosa-cell development (7). In our study, the median age of patients was 55 years.

They are different from the epithelial ovarian cancer because they produce estrogen and/or progesterone and have a different nature of presentation and clinical behavior (8). Compared to epithelial ovarian cancers, the clinical course of GCTs is more indolent (slower peritoneal spread) leading to a large tumor size at the time of diagnosis confined to the ovary. The most reported signs are abdominal pain and abdominal distension but menstruation problems can also occur like intermenstrual bleeding or other menstrual irregularities, postmenopausal bleeding or amenorrhea (9–14). In our study, the most common symptoms were abdominal pain (44%) and abdominal distension (44%) and then postmenopausal bleeding (27%) and secondary amenorrhea (5.5%).

Abnormal uterine bleeding is caused by the exposure of the endometrium to tumor-derived estrogen (9,10). This excessive and prolonged exposure to estrogen may cause endometrial hyperplasia and endometrial carcinoma. For this reason, preoperative endometrial biopsy is suggested in all women with abnormal uterine bleeding. Endometrial

Preoperative values of inhibin B were not studied in any of our patients. Serum CA-125 is not correlated to this tumor.

The mainstay of initial management is a surgery which includes hysterectomy, bilateral salpingo-oophorectomy and removal of all gross disease (17). Nodal dissection is not recommended in surgical staging of GCT (18). GCTs are staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) staging system (19). The majority of patients initially present with stage I disease (65–80%) (11–13, 20). Similar results were obtained in our study, 78% (N=14) of our patients were FIGO stage I, while 22% (N=4) were FIGO stage III.a.

While in women who are done with childbearing total abdominal hysterectomy and bilateral salpingo-oophorectomy are typically performed, in younger women wishing to preserve fertility a unilateral salpingo-oophorectomy with careful staging should be performed. In the early stages of the disease (FIGO IA), retrospective studies suggest a similar cure rate whether treated by a fertility-preserving surgery or a complete surgery (20). In these patients where fertility-preserving surgery is performed, endometrial biopsy is recommended to rule out concomitant uterine disease. Out of 18 of our patients, 15 patients underwent radical surgery. Lymphadenectomy was done in three patients. Three patients underwent a conservative surgery, which included unilateral salpingo-oophorectomy in two patients and cystectomy in one patient (she refused

more radical surgery). Postoperatively, in one of the patients was found simultaneously endometrial adenocarcinoma, which was in an early stage with a favorable prognosis and did not require further therapy. The percentage of simultaneous occurrence of endometrial carcinomas in our study is 6 %, which is similar to the occurrence in other studies (15).

Although the survival of patients with GCTs is generally excellent as they mostly present at an early-stage disease, certain patients at high risk of recurrence and disease-related death may be identified. For most patients with an early stage of disease, surgery alone is an acceptable treatment. Although, the benefit of postoperative treatment for women with stage IC to IV disease is unclear, adjuvant platinum-based chemotherapy or radiotherapy for limited disease is recommended in patients with advanced stages of disease (stage II-IV) and we can consider the use of the chemotherapy in patients with a high risk stage IC disease (whose tumor has ruptured, has nuclear atypia, or a high mitotic index) (15, 21). Regimens used for GCTs are mainly platinum-based with combinations of other agents such as bleomycin, cisplatin, etoposide, vinblastine, doxorubicin and cyclophosphamide (22). The most preferred regimen is a combination of bleomycin, etoposide, and cisplatin (BEP), but alternative chemotherapy regimens are bleomycin, vinblastine and cisplatin (BVP), etoposide and cisplatin (EP), cyclophosphamide, doxorubicin and cisplatin (CAP), and lately paclitaxel and carboplatin (PC). The reported response rates to these chemotherapy regimens have varied significantly from 20–100% (23–25). We recommended adjuvant chemotherapy for five patients and only four patients received 1–6 cycles of postoperative chemotherapy. Adjuvant chemotherapy was a platinum-based regimen: CEP regimen in one patient and three patients received chemotherapy per PEB regimen. No patient received adjuvant radiotherapy.

The role of adjuvant chemotherapy is still unclear. Some retrospective studies showed longer progression free interval (PFI) and overall survival (OS) in patients with advanced stage GCTs, who received adjuvant chemotherapy (26), and other studies did not show the same benefit (24).

The prognosis of patients with GCTs depends primarily on the stage of disease and the presence of residual disease after surgery (24,27,28). The others potential prognostic factors are age, tumor size, absence of lymph nodes invasion (20,28,29), but their significance has not been demonstrated in all studies. Cellular atypia, mitotic rate and the absence of Call-Exner bodies are identified like the only pathologic prognostic factors (29,30). According to the tumor characteristics, the mitotic count was high (> 5 mitosis/10 HPFs) in 9 cases and 11 patients had absence of Call-Exner bodies, but because of a small number of patients and a short time of follow-up period, we have not analyzed the effect of these factors on PFI and OS.

Around a quarter to third of all patients develop recurrent tumors and require further treatment (11). One third of recurrences occur more than 5 years following the initial treatment, and one fifth after 10 years, but occasionally they can also occur after more than 25 years (5,6). A common place for the tumor to recur is the pelvis with 30–45% of patients having local pelvic recurrence only. In 55–70% of patients, however, at the time of diagnosis the tumor has already spread extrapelvically and usually involves peritoneal surface. Distant metastases are generally rare (29). Stage is the only clinical factor unequivocally related to recurrence with a higher risk of relapse shown in stages II to IV of the disease (24,27–29). There is no standard treatment of recurrent disease. If it is possible, a complete tumor resection should be done. In patients with a metastatic or suboptimally cytoreduced disease, a platinum-based chemotherapy is an option. Platinum-based chemotherapy is also an option in postoperative settings. Regimens used for recurrent GCTs are the same like in adjuvant setting, but the choice of chemotherapy depends on ECOG performance status and comorbidities of patients, prior therapy and patient's wishes. If a patient is chemotherapy naive, PEB is the regimen of choice. If a patient has received PEB in adjuvant setting, some other chemotherapy regimen is recommended because of the pulmonary toxicity of the bleomycin (31). Other options for patients with recurrent GCTs are a radiation therapy or a hormonal therapy (tamoxifen, progesterone, combination of tamoxifen and progesterone or aromatase inhibitors). Antiangiogenic therapy (bevacizumab) also has a promising role in the treatment of the recurrent GCTs (32). In our study, recurrence was observed in three patients (16%) in the mean follow-up period of 49 months. In all patients with recurrence, a surgery has been done and one patient received chemotherapy with PEB regimen. They are still alive, one of them had a second recurrence and she has undergone a complete tumor resection and now has received the second line chemotherapy with paclitaxel and carboplatin.

The reported 5-year survival for patients with stage I is greater than 90%, while for patients with stage II tumors 5-year survival is reduced to 55–75% and for patients with stage III/IV to 22–50%. More than 70% of women with recurrent disease die from their disease. (30,33,34)

Only one of our patients died free of the primary disease, from myocardial infarction**.** The median overall survival has not yet been reached and a 5-year survival is 94%.

For treatment response assessment and follow-up different tumor markers have been in use, with inhibin and anti-Müllerian hormone found to be more reliable markers of disease activity than estradiol. Inhibin as a polypeptide hormone produced by granulosa cells is secreted mostly in follicular phase of the menstrual cycle, while in postmenopausal women inhibin levels should be low. Anti-Müllerian hormone is also secreted during the reproductive period and becomes undetectable in postmenopausal women. Reported studies show elevated levels of both inhibin and anti-Müllerian hormone in women with active GCTs. The clinical utility of these markers is still, however, under debate due to a high risk of bias in these studies (35).

After primary therapy, a prolonged surveillance is indicated. Usually it is a recommendation to control tumor

markers and to do a clinical examination. Radiographic imaging is performed only if clinically indicated.

Conclusion

The basis of therapy in GCTs is a surgical removal of the disease, and platinum-based adjuvant chemotherapy is recommended for advanced-stage GCTs. A prolonged follow-up period is necessary because they progress slowly and have a specific tendency for late recurrences.

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GRANULOZA STANIČNI TUMORI JAJNIKA: RETROSPEKTIVNA ANALIZA 18 SLUČAJEVA

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Stručni članak

Ključne riječi: rak jajnika, granuloza stanični tumori, ishodi, liječenje

Sažetak. ***Uvod.*** Granulozna stanični tumori (GST) rijetke su neoplazme i predstavljaju oko 2 – 5% svih karcinoma jajnika. Uobičajeno se otkrivaju u ranoj fazi bolesti i imaju relativno povoljnu prognozu. ***Cilj*** ovog istraživanja bio je opisati kliničke i patološke karakteristike pacijentica s GST-ovima i utvrditi prognostičke čimbenike. ***Metode.*** Retrospektivnim istraživanjem analizirali smo medicinske podatke 18 bolesnica s novootkrivenim GST-ovima liječenih u Klinici za ženske bolesti i porode KBC-a Zagreb u razdoblju od siječnja 2011. do prosinca 2017. godine. Analizirani su dob, paritet, simptomi, veličina tumora, stadij bolesti, opsežnost operativnog zahvata, patološke karakteristike tumora (broj mitoza, prisutnost Call-Exnerovih tjelašaca), primjena adjuvantne kemoterapije, vrijeme do progresije bolesti i preživljenje. ***Rezultati.*** Dobiveni su podatci od 18 bolesnica. Srednja dob uključenih bolesnica bila je 55 godina. Medijan broja porođaja bio je 1,39. Najčešće kliničke manifestacije bolesti bile su abdominalna bol (44%) i abdominalna napetost (44%). Prosječna veličina tumora bila je 11 cm (raspon 2–30 cm). Većina naših bolesnica bila u I. stadiju bolesti (78%, N = 14), dok ih je manji dio (22%, N = 4) bio III. stadija bolesti. Od svih, 15 bolesnica podvrgnuto je radikalnoj operaciji, dok je u tri bolesnice izvršena poštedna operacija s ciljem očuvanja plodnosti. Prema karakteristikama tumora, broj mitoza bio je visok (> 10 mitoza / 10 HPF) u 9 slučajeva (50%), a 7 bolesnica imalo je prisutnost Call-Exnerovih tjelešaca. Četiri bolesnice primile su 1–6 ciklusa adjuvantne kemoterapije. Tijekom perioda praćenja (medijan 49 mjeseci), 3 bolesnice imale su recidiv bolesti, a jedna bolesnica umrla je nevezano uz osnovnu bolest, od infarkta miokarda. ***Zaključak.*** Temelj terapije GST-ova kirurško je odstranjenje bolesti, a u uznapredovalim stadijima i primjena adjuvantne kemoterapije na bazi platine. Potrebno je dugotrajno praćenje bolesnica jer bolest obično napreduje sporo i ima tendenciju pojave kasnih recidiva.