

Granulosa Cell Tumors of the Ovary: Retrospective Analysis of 17 Cases

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Abstract

Background: Granulosa cell tumors (GCTs) are rare neoplasms with a relatively favorable prognosis. They are characterized by a prolonged history and a tendency to late recurrences. It is the most common type of sex cord-stromal tumors. **Aims:** To analyze, to report and to better understand the clinico-pathologic features and results of treatment, and prognostic factors of these tumors. **Materials and Methods:** A retrospective single-institutional review 17 cases of GCTs were treated in National Cancer Institute—Cairo University from January 2010 till December 2014. The clinical and pathological characteristics, treatment, and outcomes of patients with ovarian GCTs were analyzed. **Results:** Data from 17 patients were obtained. The median age was 54 years (range; 14 - 72). Abdominal pain was the most common presentation (64.7%). The mean tumor size was 14 cm (range; 7 - 23 cm). The majority of our patients were stage I (n = 11; 64.7%), while (n = 3; 17.6%) had stage III and (n = 2, 11.8%) were stage IV. Only one case (5.9%) had an unknown stage (explored outside NCI). The majority of cases were of adult type disease (n = 14) and low grade pathology (n = 10). In follow-up period (median = 42 months; ranging 9 - 60) three patients relapsed; the median overall survival time was not reached yet, however, the estimated 3-year survival was 72.5%. **Conclusion:** Granulosa cell tumors are rare neoplasms of the ovaries. They progress slowly and often are diagnosed in an early stage. Surgery is the main line of treatment. Prolonged post-therapeutic follow-up is necessary. Definition of proper prognostic factors is mandatory.

Keywords

Granulosa Cell Tumors, Ovary, Outcomes

1. Introduction

Granulosa cell tumors of the ovaries are very rare malignancies. They represent the most common sex cord stromal tumors accounting for about 5% of all ovarian neoplasms [1]. They are hormone active tumors, originating from granulosa cells which produce estradiol. Overproduction of estradiol is helpful in the diagnosis of the tumor because of its numerous symptoms. These are tumors with relatively a favorable prognosis compared to epithelial ovarian cancers. Pathologically, there are two subtypes: an adult type (95%) and a juvenile type (5%), the latter is characterized by an early age of onset; more pronounced malignant signs and increased risk of local and systemic failure [2]. These tumors have a particular clinical and histological profile, and may reoccur up to 40 years after diagnosis [3].

Complete surgical resection either with fertility preserving procedure or not together with formal staging is the mainstay of management especially for the early stages. For advanced disease, surgery has to be combined with platinum based chemotherapeutic agents [4].

2. Materials and Methods

A retrospective single-institutional review of cases of ovarian granulosa cell tumors were identified from the surgical pathology files of National Cancer Institute-Cairo University from January 2009 till December 2014. The clinical and pathological characteristics, treatment, and outcomes of patients with ovarian GCTs were analyzed.

3. Results

3.1. Clinical Features

During the period from January 2009 through December 2014, 17 patients underwent surgery for granulosa cell tumors. The median age of the patients was 54 years (range: 14 - 72). About 60% of the patients, the tumor occurred between the fifth and seventh decades and ten of the patients were menopausal.

The median duration of symptomatology was 6 months (range: 5 - 23). A total of 64.7% of the patients (n = 11) presented abdominal pain at diagnosis followed by abdominal distension (58.8%). Other symptomatology included vaginal bleeding either inter-menstrual (35.3%) or postmenopausal (29.4%) and secondary amenorrhea (12.5%). The mean tumor size was 14 cm (range: 7 - 23 cm).

Nulliparous patients were only 17.6% (n = 3). Fourteen cases were unilateral (82.4%). As regard tumor markers; AFP, B-HCG-LDH and CA125; none was specifically raised at presentation apart of CA125 which was elevated in only five cases (37 - 56 U/mL) and no recorded elevation at recurrence.

Table 1 summarizes patients' characteristics at presentation.

3.2. Treatment

Fourteen patients (82.4%) underwent pan-hysterectomy with bilateral salpingo-oophorectomy, while a fertility preserving procedure (unilateral salpingo-oophorectomy and standard surgical staging) was done only in three patients. Standard surgical staging consists of peritoneal washing, peritoneal biopsies infracolic omentectomy, and any suspicious lesion biopsy.

Lymph node biopsy was done in eight patients (47.1%), while laterality was found in three patients (17.6%). The pathological subtype was juvenile in three patients, while the remaining was of adult type. Eleven patients had endometrial biopsies. The results were as follows: four were negative, five were hyperplastic and two were atrophic. Six patients received post-operative chemotherapy; starting from stage II disease.

In the current study all indicated cases were given BEP (bleomycin 30 U on days 2, 9, and 16, etoposide 100 mg/m²/day on days 1 - 5, and cisplatin 20 mg/m²/day on days 1 - 5) administered every 3 weeks for four courses.

Table 2 resumes different treatment modalities.

3.3. Staging

The staging breakdown was as follows: stage I (64.7%, n = 11), stage III (17.6%, n = 3) and stage IV (11.8%, n = 2). For the remaining patient (n = 1), the stage was unknown as it was explored outside NCI.

Table 1. Patients characteristics in our study.

Age	No (%)
≤18 years	3 (18.6%)
>18 years	14 (82.4%)
Symptomatology	
1) Abdominal pain	11 (64.7%)
2) Abdominal distension	10 (58.8%)
3) Intermenstrual bleeding	6 (35.3%)
4) Postmenopausal bleeding	5 (29.4%)
5) Secondary amenorrhea	2 (12.5%)
Size of the tumor	
≤14 cm	9 (52.9%)
>14 cm	8 (47.1%)
Staging	
Stage I	11 (64.7%)
Stage III	3 (17.6%)
Stage IV	2 (11.8%)
Improper staging	1 (5.9%)

Table 2. Different treatment modalities in our study.

Type of surgery	No (%)
Fertility preserving surgery	3 (17.6%)
TAH + BSO	14 (82.4%)
Post operative	
Follow up only	11 (64.7%)
Adjuvant CTH	6 (34.3%)

CTH: chemotherapy; TAH + BSO: total abdominal hysterectomy & bilateral salping-oopherctomy.

3.4. Survival

During the follow-up (median: 42 months, ranging 9 - 60), three patients was relapsed, and one of those patients died of the disease. Four other recorded death due to either unrelated or unknown causes. The median overall 5 years survival for all cases was not reached yet. The estimated 3 year survival was 72.5% (Figure 1 and Table 3).

4. Discussion

Granulosa cell tumors (GCT) of the ovary are classified as sex-cord stromal tumors and their occurrence is rare, representing approximately 5% of all ovarian tumors. There are two distinct types of GCT: adult (AGCT) and juvenile (JGCT) [5] [6]. AGCTs are more common and are usually seen in peri-menopausal and post-menopausal women, with a peak incidence at 50 - 55 years. JGCTs are rare tumors, representing 5% of all GCTs and occurring in pre-menarche girls and young women [7].

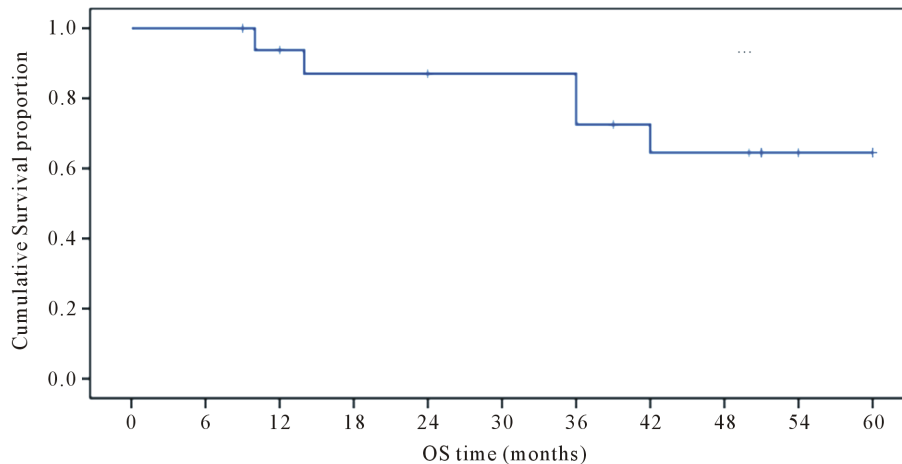


Figure 1. Overall survival of 17 cases of granulosa cell tumor.

Table 3. Shows characteristics of patients experienced recurrence.

Age (years)	Stage	Initial Size (cm)	Relapse time (months)	Site of relapse
61	IV	15	25	lung
15	I	12	49	Retroperitoneal
68	IV	8	54	Retroperitoneal

What makes them different from the epithelial ovarian cancers is the nature of presentation and clinical behavior. They occur in a younger age group, are usually detected in an early stage and usually have features of hyperestrogenism. They are more readily cured by surgery alone. Generally they have a better prognosis than epithelial ovarian tumors and follow an indolent course. They are characterized by a long natural history and 25% may recur years after apparent clinical cure of the primary tumor [7].

In our study the median age was 54 years old and nearly 60% of patients presented between the fifth and seventh decades. Three patients only were of the juvenile type and were younger than 18 years. These data were matching with Sekkate *et al.* 2013 [3] and Bompas *et al.* 2000 [8].

Patients may present with abdominal pain, abdominal distension related to mass effects, and hormonal events such as; menstrual irregularities, postmenopausal bleeding or amenorrhea, as reported in our patients [7] [9] [10].

Endocrinal manifestation due to estrogen secretion by the tumor may be occurring as frequent as 65% of cases. This explains the frequent association between these rare tumors and hyperplasia of the endometrium (25% - 50%) and even endometrial adenocarcinoma (5% - 10%). Therefore, endometrial and cervical biopsies are essential [11]-[13]. None of our patients suffered adenocarcinoma of the endometrium and five had endometrial hyperplasia.

Granulosa cell tumors usually present as a unilateral mass, with both cystic and solid components that ranges in size in most studies from (5 - 40 cm) with a mean diameter of 14 cm [14]-[17]. Results were matching to our work; mean size was 14 cm and 82.4% were unilateral.

Stromal sarcoma, endometrioid carcinoma, carcinoid tumors and adenocarcinoma are among the commonest differential diagnosis [7] [14].

The diagnosis was confirmed by immunohisto-chemistry. This tumor expresses vimentin, CD 99 and alpha inhibin markers [7] [18].

Serum CA-125 is not correlated to this tumor, instead serum estradiol, inhibin [19], Mullerian Inhibiting Substances (MIS) and anti-Mullerian hormone (AMH) are useful serum markers at diagnosis, recurrence or disease progression which may be evaluated in further studies [7].

Only five cases had raised CA125 at presentation (range: 37 - 56) and no recorded elevation at recurrence. The normal value is less than 35 U/mL. Serum Ca 125 is therefore a non-specific marker [20].

Multi factors are determining the prognosis. The most important are stage, age, tumor size, type of surgery and tumor rupture [19]-[24]. Unfortunately; we didn't report any due small numbers of cases to be evaluated statistically.

In the majority of publications, patients usually present early i.e. stage I disease (70% - 90%), thus having a very favorable outcome [7] [23] [24]. Nearly 65% of patients in our study had stage I disease.

Complete tumor resection is the mainstay of treatment with staging for early disease and debulking for advanced disease [7] [25] [26]. There is no standard regimen concerning adjuvant treatment for granulosa cell tumors but it is usually recommended for the adult type and high risk patients. Chemotherapy typically includes a combination of platinum based chemotherapy, the most common of which is BEP regimen [7] [26] [27].

The role of adjuvant radiation therapy is still unclear. The radiation therapy dose when administrated was in the form of 50 Gy divided on 25 fractions over a period of 5 - 6 weeks [7] [17].

The median follow-up period was 42 months. 17.6% of patients suffered disease relapse which was mainly retroperitoneal. Recurrence in our patients occurred after a median period of 49 months (range; 25 - 54) in this study, which is in concordance to Mangili *et al.* [28]; Sehoul *et al.* [29] and Abu-Rustum *et al.* [30].

The evolution of granulosa cell tumors is slow and recurrences are rare and often delayed. These tumors can reoccur after a free interval of 6 to 23 years [7] [28]-[30].

There is a controversy regarding management of relapsed disease. Surgery may provide long-term control in localized recurrence with hyperthermic intraperitoneal chemoperfusion therapy. Distant organ failure may still need a second line therapy which is usually single agent chemotherapy or hormone therapy [31]-[33]. Radiation therapy either pelvic or whole abdominal can result in a good response in patients with persistent or recurrent disease [34].

5. Conclusion

Granulosa cell tumors of the ovary are rare neoplasms and have a tendency for late relapses. Several publications are still needed to set up a consensus for optimum prognostic factors, serum markers and natural behavior of the tumor.

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