A long-term follow-up study of 176 Taiwanese women with adult-type ovarian granulosa cell tumors – from the Taiwanese Gynecologic Oncology Group (TGOG)

Hsu-Dong Sun, MD[1]; Hao Lin[2]; Mei-Shan Jao[3]; Kung-Liahng Wang[4]; Wen-Shiung Liou[5]; Yao-Ching Hung[6]; Ying-Cheng Chiang[7]; Chien-Hsing Lu[8]; Hung Cheng Lai[9]; Mu-Hsien Yu, MD, PhD[9].

[1] Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei and Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, Ban Ciao, New Taipei City, Taiwan

[2] Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung

[3] Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou

[4] Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei

[5] Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung

[6] Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung

[7] Department of Obstetrics and Gynecology, National Taiwan University Hospital, Taipei

[8] Department of Obstetrics and Gynecology, Taichung Veterans General Hospital, Taichung

[9] Department of Obstetrics and Gynecology, Tri-Service General Hospital, Taipei

Running title: adult type granulosa cell tumors of ovary

Address correspondence and reprint requests to: Mu-Hsien Yu, M.D., Ph.D.
Department of Obstetrics and Gynecology, Tri-Service General Hospital, Taipei, Taiwan
E-mail: bitalvox@hotmail.com

Abstract

Objective

Because of rarity, indolent clinical course, and of most importance, small sample size studies of previous adult-type ovarian granulosa cell tumors (GCTs), this study was conducted to report the clinical characteristics and long-term outcomes of 176 pathologically confirmed GCTs.

Patients and methods

Between 1984 and 2010, we retrospectively evaluated 176 Taiwanese patients from multiple medical centers in Taiwan (TGOG Study Group).

Results

The mean age at the diagnosis was 46 years (range, 15–83 years) and nearly half of the patients (45.7%) were in their fourth or fifth decades of life. The most common symptoms included abdominal pain (28.5%, n = 58), following by irregular menstruation (16.7%, n = 34). The mean tumor size was 10.4 cm (range, 0.2–40 cm). The stage distribution at diagnosis was stage I in 77.8% of patients, stage II in 5.1%, stage III–V in 6.1%, and unknown in 11% of patients. The median follow-up period was 60.7 months (range, 1–316 months). The recurrence rate was 21%. The overall 5- and 10-year survival rates were 96.5% and 94.1%, respectively. In univariate Cox-regression analysis, initial stage, presence of residual tumor after initial surgery,

need for adjuvant chemotherapy, and tumor size were associated with disease recurrence. In the multivariate Cox-regression analysis, only presence of residual tumor after initial surgery and tumor size were significantly associated with recurrence.

Conclusions

The outcomes of patients with GCTs were good, with nearly to 95% of patients surviving 5 and 10 years. The prognosis was related to initial tumor status, including initial stage, presence of residual tumor after initial surgery, and tumor size (> 13.5 cm), suggesting complete removal of the tumor during the initial operation is important; different surgical methods and/or adjuvant therapy appear not to affect the outcome.

Key words: characteristics of recurrence; granulosa cell tumors; outcomes

Introduction

Adult-type ovarian granulosa cell tumors (GCTs) are very rare neoplasms that arise from the sex cord stromal cells of the ovaries. These neoplasms have a long natural history and a relatively favorable prognosis.[1] There is no doubt that some patients with GCTs have recurrent disease and finally die of the disease.[2] Symptoms of GCTs are often non-specific, although abnormal vaginal bleeding or precocious puberty may be the initial presentation, because of estrogen-production by GCTs.[3,4] After diagnosis of a GCT, complete surgical excision is the mainstay of treatment,[1,4] and the majority of patients can be adequately controlled or frequently cured, especially patients with early-stage disease. The value of postoperative adjuvant therapy is uncertain,[1] although multi-agent chemotherapy is often administered to patients with high-risk or advanced disease. A handful papers address the topic of GCTs and some prognostic factors are proposed, including disease stage, tumor size, tumor rupture, age at diagnosis, nuclear atypia, mitotic index, and presence of residual tumor after initial surgery.[3–28] Some of these factors remain controversial. Nonetheless, because of their rarity, indolent clinical course, and of most importance, small sample sizes of these studies,[4–27] a larger sample size is needed to improve our understanding of GCTs. Thus, the purpose of this study was to characterize this rare tumor and identify the factors associated with its prognosis among Taiwanese women.

Patients and methods

The Institutional Review Boards of all medical centers in the Taiwanese Gynecologic Oncology Group Study Group (TGOG Study Group) approved the study. After excluding the overlapping patients between the different medical centers and the cases which loss of follow up, 176 Taiwanese women with pathologically confirmed GCTs diagnosed between 1984 and 2010 were analyzed. A retrospective review of patient medical records was conducted.

The characteristics recorded included age at diagnosis, height, weight, gravidity, parity, menopausal status, chief complaint, presence of endometrial pathology, surgical and adjuvant treatment, presence of recurrent disease and mortality, and survival in months.

The statistical analysis was conducted using SPSS ver. 18 (SPSS, Inc., Chicago, Illinois). $P < 0.05$ was defined as statistically significant; all tests were 2-tailed. The recurrence curves were calculated using the Kaplan-Meier method and the log-rank test was used to compare the recurrence curves. Univariate and multivariate analyses were performed using Cox's regression model. Pearson's chi-squared or Fisher's exact test was used to compare the differences of proportions.

Results

A total of 176 patients underwent surgical treatment for GCTs at the multiple medical centers in Taiwan (TGOG Study Group) during the period of 1984–2010.

The mean age of patients was 46 years (range, 15–83 years) and almost half of the cases (45.7%) occurred in the fourth and fifth decades of life. The mean gravidity was 3.0 and the mean parity was 2.1. The most common symptoms included abdominal pain (28.5%, n = 58), following by irregular menstruation (16.7%, n = 34). Other presenting symptoms were palpable mass, abdominal distention, and vaginal bleeding. Some 29 patients (14.3%) were asymptomatic and were diagnosed with GCTs during routine examinations such as ultrasonography or computerized tomography. The mean tumor size was 10.4 cm (range, 0.2–40 cm). The clinical characteristics of the patients are summarized in Table 1.

The type of initial surgery was conservative and staging surgery. Of the 176 patients, 98 underwent conservative surgery, which included unilateral oophorectomy, bilateral salpingo-oophorectomy, or total abdominal hysterectomy with bilateral salpingo-oophorectomy. Another 78 patients underwent staging surgery. Seven patients had residual tumors after surgery and 28 patients received postoperative adjuvant chemotherapy. Indications for chemotherapy and chemotherapeutic regimens were not standardized.

We found that the majority of patients had stage I disease (137 cases, 77.8%), while 5.1% had stage II, 6.1% had stage III–V, and in 11% of patients, the stage was unknown. The follow-up began with the initial surgery and the mean follow-up period was 60.7 months (range, 1–316 months).

There were 36 cases (21.0%) of recurrence during follow up, including five cases of disease-related death (Table 2). The median time to relapse was 57.6 months (range, 2–166 months). Among the cases of recurrence, peritoneal recurrence was the most common (77.4%). The clinical findings of patients with recurrent disease are summarized in Table 3. The overall 5-year survival and 10-year survival rates for all stages were 96.5% and 94.1%, respectively.

Kaplan-Meier curves illustrate the recurrence outcomes (Figs. 1). Following univariate Cox regression modeling, recurrence was associated with advanced stage ($P = 0.015$), residual tumor during surgery ($P < 0.001$), and adjuvant chemotherapy ($P = 0.017$, see below). After excluding interfering factors, in the multivariate analysis, residual tumor during surgery and tumor size (13.5 cm) were significantly associated with recurrence; tumor size and cutoff point were evaluated using the receiver operator characteristic curve. Age at diagnosis, menopausal status, body mass index, gravidity and parity, surgical method (conservative surgery or staging surgery), and type of adjuvant chemotherapy were not statistically significantly associated with

disease recurrence (Figs. 2).

Discussion

GCTs of the ovary are very rare sex cord stromal tumors. They are low-grade malignancies with relatively favorable prognoses compared to more commonly encountered epithelial ovarian tumors.[1,2] Nonetheless, some patients diagnosed with GCTs still suffer from late recurrence or disease-related mortality after treatment.[23] Additionally, the rarity of GCT and its slow progression make it difficult to clearly understand its clinical course, provide adequate treatment, and recognize its prognostic factors. Most patients with GCTs have mass effects, such as abdominal pain and distension or hormone-related symptoms such as vaginal bleeding or irregular menstruation, and these findings are considered nonspecific findings for ovarian tumors. Estradiol, inhibin, and anti-Müllerian hormone are reported as GCT tumor markers, [1–3] but routine tumor markers such asCA-125 are not correlated with the progression of the disease. Indolent growth, lack of specific symptoms, and the absence of specific tumor markers make it difficult to diagnose GCT before surgery and lead to large tumors at diagnosis.

Most studies report that the leading prognostic factors of GCTs include stage of the disease, tumor size, tumor rupture, age at diagnosis, nuclear atypia, mitotic index,

and presence or absence of residual tumor after initial surgery. [3–28] The currently available data on these tumors, including at least 30 cases with prognostic factors, are summarized in Table 4. From another point of view, there are too few studies on GCTs to identify the prognostic factors clearly. Therefore, prediction of the prognostic factors of these rare tumors is important.

In our study, age at diagnosis, stage of disease, presence or absence of macroscopic residual disease, tumor size, surgical method, and use of adjuvant chemotherapy modalities were investigated in order to determine their prognostic significance. Disease stage is the most widely accepted GCT prognostic factor (Table 4.[3–28] Many studies show a relationship between stage and survival rate. Five-year survival is reported to be 80%–95%% [3–28]for patients with early stage disease and survival declined to 25%–40%[3–28] in patients with advanced disease. Our results also indicated that the disease stage was significantly related to GCT recurrence ($P = 0.011$, Fig. 1).

In our study, the Kaplan-Meier curves illustrate that the most significant prognostic factor is the presence of residual tumor after initial resection ($P < 0.001$, Fig. 1). Theoretically, presence of residual tumor after initial surgery means the tumor will progress over time, and almost all patients who had residual tumor after their initial resection ended up with advanced-stage disease. [3–10] In our study, seven patients had

179 residual tumor after their initial resection and six (85.7%) of them had tumor
180 recurrence during follow up.

181 Adjuvant chemotherapy for high risk ovarian cancer is commonly accepted.
182 Additionally, it is usually recommended for treatment of adult type GCTs.[5] Among
183 our patients, adjuvant chemotherapy was associated with a greater probability of GCT
184 recurrence (P = 0.014, Fig. 1). At first glance, this is illogical, but patients who
185 received adjuvant chemotherapy had the greatest numbers of risk factors for
186 recurrence. Adjuvant chemotherapy is especially recommended for patients with
187 residual tumor after initial surgery.[5,8,12] Adjuvant chemotherapy using multiple
188 modalities is currently used and most regimens are platinum-containing protocols.[15]
189 Due to the rarity of GCTs, there is no standard regimen for postoperative adjuvant
190 chemotherapy. In our study different regimens were used for postoperative adjuvant
191 chemotherapy. Regardless of the regimen used, the results showed greater recurrence
192 in the adjuvant chemotherapy group than in the group without adjuvant chemotherapy.
193 In certain special conditions such as advanced age or multiple medical problems,
194 adjuvant chemotherapy might not be considered at all.

195 In our study, most patients (82.9%) were diagnosed in the early stage of their
196 disease and mean tumor size at diagnosis was 10.4 cm. Nonetheless, a tumor size of
197 10.4 cm is not considered to be associated with an early diagnosis. In the statistical

198 analyses, tumor sizes greater than 13.5 cm were associated with more recurrence
199 (95% CI 1.10–5.41, P = 0.028). Tumors as large as 10.4 cm had a long indolent
200 growth phase and already existed for a long time before discovery and diagnosis. We
201 believe this is the main reason why large tumors are poor prognostic factors in our
202 study.

203 Other parameters such as age at diagnosis, menopausal status, gravidity and parity,
204 and type of surgery (conservative surgery or staging surgery) were not significantly
205 associated with relapse of GCT (all P > 0.05).

206 Patient age is reported as a prognostic factor in some studies, but there is no
207 standardized age recognized and it is highly variable.[5] The patient age in our study
208 ranged from the very young to elderly (7–83 years), with the peak incidence in the
209 perimenopausal age group (fifth decade of life, 25.4%) and mean age of 46 years.
210 These data are compatible with those of other authors.[4,24] When patients were
211 categorized by age ($\leqq$40 or >40, $\leqq$50 or >50, $\leqq$60 or >60) the results did not differ
212 significantly. The recurrence rates were similar among the groups.

213 There was no significant difference in recurrence between patients who underwent
214 conservative surgery and those who underwent staging surgery in our study. Many
215 studies proved that there was no survival or recurrence advantage with standard
216 surgery compared to conservative surgery.[12–14] Complete resection of the tumor,

without any residual tumor, is the most important achievement for prevention of recurrence. For some special conditions such as fertility preservation or poor medical condition, complete staging surgery may not necessary.

The rarity of GCTs, make it hard to conduct prospective and well-controlled studies. Including our study, most of the previous studies have this weak point. Another weak point in this study is that it included patients without identical interventions and some data were incomplete due to loss of follow up. Other possible inevitable factors that could affect the study outcomes include the patient age, experience of the primary surgeons, different hospitals, and new and evolving regimens of combination chemotherapy.[6] The rarity of this disease leads to the need for a very long time period for the accumulation of cases. Conversely, the strongest aspects of our study include 1) its long-term follow-up period of up to 26 years and highly complete information; 2) each GCT case was handled or supervised by gynecologic oncologists (TGOG); 3) our study of 176 cases of adult type ovarian GCT represents one of the largest scale studies reported.

Conclusions

The most important prognostic factor in adult type ovarian GCT is initial disease stage. It is also very important to achieve complete resection of the tumor, without any

macroscopic residual tumor, since any residual tumor is a poor prognostic factor for recurrence. Tumor size greater than 13.5 cm is another poor prognostic factor. Nevertheless, complete staging surgery or adjuvant chemotherapy dose does not influence recurrence. In some cases, fertility preserving surgery can be performed. Due to the rarity of ovarian GCTs, we suggest prospective, randomized, well-controlled, multi-center studies are needed to accumulate greater case numbers with well-established standard treatment modalities to clarify other possible prognostic factors of GCTs.

Conflict of Interest Statement

Dr. Sun, Dr. Lin, Dr. Jao, Dr. Wang, Dr. Liou, Dr. Hung, Dr. Chiang, Dr. Lu, Dr. Lai, and Dr. Yu have no conflict of interest.

255 References

256 1. Rey RA, Lhommé C, Marcillac I, Lahlou N, Duvillard P, Josso N, Bidart JM.
257 Antimullerian hormone as a serum marker of granulosa cell tumors of the
258 ovary: comparative study with serum alpha-inhibin and estradiol. Am J Obstet
259 Gynecol 1996;174:958-65.
260 2. Healy DL, Burger HG, Mamers P, Jobling T, Bangah M, Quinn M, Grant P,
261 Day AJ, Rome R, Campbell JJ. Elevated serum inhibin concentrations in
262 postmenopausal women with ovarian tumors. N Engl J Med
263 1993;329:1539-42.
264 3. Zhang M, Cheung MK, Shin JY, Kapp DS, Husain A, Teng NN, Berek JS,
265 Osann K, Chan JK. Prognostic factors responsible for survival in sex cord
266 stromal tumors of the ovary: an analysis of 376 women. Gynecol Oncol
267 2007;104:396–400.
268 4. Lee YK, Park NH, Kim JW, Song YS, Kang SB, Lee HP. Characteristics of
269 recurrence in adult-type granulose cell tumor. Int J Gynecol Cancer 2008, 18,
270 642–647
271 5. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol
272 2003;21:1180–9.
273 6. Zanagnolo V, Pasinetti B, Sartori E. Clinical review of 63 cases of sex cord

stromal tumors. Eur J Gynaecol Oncol 2004;25:431–8.

7. Ayhan A, Salman M.C, Velipasaoglu M, Sakinci M, Yuce K. Prognostic factors in adult granulosa cell tumors of the ovary: a retrospective analysis of 80 cases. J Gynecol Oncol Vol. 20, No. 3:158–163

8. Malmstrom H, Hogberg T, Risberg B, Simonsen E. Granulosa cell tumors of the ovary: prognostic factors and outcome. Gynecol Oncol 1994; 52: 50-5.

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

10. Sehouli J, Drescher FS, Mustea A, Elling D, Friedmann W, Kühn W, Nehmzow M, Opri F, Klare P, Dietel M, Lichtenegger W. Granulosa cell tumor of the ovary: 10 years follow-up data of 65 patients. Anticancer Res 2004;24:1223–9.

11. Uygun K, Aydiner A, Saip P, Basaran M, Tas F, Kocak Z, Dincer M, Topuz E. Granulosa cell tumor of the ovary: retrospective analysis of 45 cases. Am J Clin Oncol 2003;26: 517–21.

12. Evans AT 3rd, Gaffey TA, Malkasian GD Jr, Annegers JF. Clinicopathologic review of 118 granulosa and 82 theca cell tumors. Obstet Gynecol 1980; 55:231-8.

13. Colombo N, Parma G, Zanagnolo V, Insinga A. Management of ovarian

293 stromal cell tumors. J Clin Oncol 2007; 25:2944–2951.
294 14. Bjorkholm E, Silfversward C. Prognostic factors in granulosa-cell tumors.
295 Gynecol Oncol 1981;11:261–74.
296 15. Bjorkholm E, Petterson F. Granulosa cell and theca cell tumors: the clinical
297 picture and long-term outcome for the Radiumhemmet series. Acta Obstet
298 Gynecol Scand 1980;59:361–5.
299 16. Mehta H, Trivedi P, Parikh B, Shukla K. Clinicopathological prognostic
300 factors of adult granulosa cell tumors of the ovary—a study of 37 cases. Indian
301 J Pathol Microbiol 2005;48:439–43.
302 17. Zanagnolo V, Pasinetti B, Sartori E. Clinical review of 63 cases of ovarian sex
303 cord stromal tumors. Eur J Gynaecol Oncol 2004;25:431–8.
304 18. Vimla N, Kumar L, Kumar S, Vijayaraghavan M, Bhatla N, Roopa H.
305 Granulosa cell tumors of the ovary: factors affecting prognosis. Indian J Med
306 Pediatr Oncol 2005;26:12–20.
307 19. Al-Badawi IA, Brasher PM, Ghatage P, Nation JG, Schepansky A, Stuart GC.
308 Post operative chemotherapy in advanced granulosa cell tumors. Int J Gynecol
309 Cancer 2002;12:119–23.
310 20. Fujimoto T, Sakuragi N, Okuyama K, Fujino T, Yamashita K, Yamashiro S,
311 Shimizu M, Fujimoto S. Histopathologic prognostic factors of adult granulose

cell tumors of the ovary. Acta Obstet Gynecol Scand 2001;80:1069–74.

21. Mehta H, Trivedi P, Parikh B, Shukla K. Clinicopathological prognostic factors of adult granulosa cell tumors of the ovary—a study of 37 cases. Indian J Pathol Microbiol 2005;48:439–43.

22. Fontanelli R, Stefanon B, Raspagliesi F, Kenda R. Adult granulosa cell tumor of the ovary: clinicopathologic study of 35 cases. Tumori 1998;84:60–4.

23. Ranganath R, Sridevi V, Shurkey S.S, Shantha V. Clinical and pathologic prognostic factors in adult granulosa cell tumors of the ovary: Int J Gynecol Cancer 2008, 18, 929–933

24. 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;81:456–60.

25. Pankratz E, Boyes DA, White GW, Galliford BW, Fairey RN, Benedet JL. Granulosa cell tumors. A clinical review of 61 cases. Obstet Gynecol 1978;52:718–23.

26. Miller BE, Barron BA, Wan JY, Delmore JE, Silva EG, Gershenson DM. Prognostic factors in adult granulosa cell tumor of the ovary. Cancer 1997;79:1951–5.

27. 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;7:136–52.

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

336 **FIGURE AND TABLE LEGENDS**

337 Figure 1. Relations between each prognostic factor and recurrence. C/T

338 chemotherapy

339

340 Figure 2. Univariate and multivariate Cox regression analyses.

341

342 Table 1. Characteristics of the patients with adult-type ovarian granulosa cell tumors.

343

344 Table 2. Flow chart of managements and outcomes.

345

346 Table3. Clinical findings of patients with adult-type GCTs who had recurrent disease

347

348 Table 4. Prognostic factors of more than thirty cases of adult type GCTs.

349