Prognostic factors in adult granulosa cell tumor of the ovary

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ABSTRACT

الأهداف: من أجل تحديد عوامل التكهن المرضية السريرية في البالغات المصابات بورم الخلايا المحبب في المبيض (GCTs).

الطريقة: أجريت هذه الدراسة الإستعادية على مدى 10 سنوات خلال الفترة مابين 1995م وحتى 2005م، في قسم أمراض النساء – مستشفى تشنجق جينق – كلية طب الصين – تشينيانق – الصين. تم إدراج 46 مريضة تعاني من ورم الخلايا المحبب في المبيض (GCT) في هذه الدراسة. تمت مراجعة البيانات السكانية والنتائج المرضية والمعالجة ووقت النجاة والتحليل لعوامل التكهن الواضحة.

النتائج: تبين أن مرحلة الاتحاد الدولي للنساء والولادة (FIGO) (*p*=0.0003)، ووجود اللانمطية في النواة (*p*=0.036)، وزيادة الانقسام الفتيلي (*p*=0.002) كانت العوامل الثلاثة الملحوظة التي تؤثر على الناجيات. لم يكن للعمر، مرض بقايا الورم، النسل، وحجم الورم أثر ملحوظ على الناجيات. العامل الوحيد المصاحب لخطورة تكرار المرض هو تمزق الورم (*p*=0.038)، كان لدى المريضات اللواتي تلقين العلاج الكيميائي فترة نجاة متوسطة خالية من المرض أفضل من أولئك اللواتي لم يتلقين العلاج الكيميائي (105 مقابل 78 شهراً)، ولكن لم يصل هذا الفرق إلى أهمية إحصائية (*p*=0.080).

خاتمة: تعد مرحلة (FIGO)، وجود اللانمطية في النواة، وزيادة الانقسام الفتيلي عوامل تكهنية ملحوظة من الناحية الإحصائية، ويمكن استعمالها لاختيار المرضى من أجل العلاج المساعد. تعتبر المتابعة الطويلة أمر ضروري نتيجة لخطورة تكرار ومعاودة المرض لورم الخلايا المحبب في المبيض خاصة عندما يتمزق الورم قبل أو خلال إجراء العملية.

Objectives: To determine the clinicopathologic prognostic factors in adult granulosa cell tumors (GCTs) of the ovary.

Methods: This retrospective study was carried out over a period of 10 years (1995-2005) in the Gynecology Department of Shengjing Hospital, China Medical University, Shenyang, China. Forty-six patients with GCT were enrolled in this study. Demographic data, pathologic findings, treatments, and survival time were reviewed and analyzed for prognostic significance.

Results: It was found that International Federation of Gynecology and Obstetrics (FIGO) stage (*p*=0.0003), presence of nuclear atypia (*p*=0.036), and increased mitoses (*p*=0.002) were the 3 factors that impacted significantly on survival. Age, residual tumor disease, parity, and size of the tumor had no significant effect on survival. The only factor associated with risk of recurrence was rupture of the tumor (*p*=0.038). Patients who received chemotherapy had a better median disease-free survival than those who did not (105 versus 78 months), however, this did not reach statistical significance (*p*=0.080).

Conclusion: The FIGO stage, nuclear atypia, and increased mitoses are the statistically significant prognostic factors, and may be used for selecting patients for adjuvant therapy. A prolonged follow-up is necessary due to risk of recurrences, late, and exceptional for the adult ovarian GCT, especially when the tumor ruptured before, or at operation.

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Granulosa cell tumors (GCTs) constitute 2-5% of all ovarian neoplasms, but are the most common malignant neoplasms among the sex cord-stromal tumors, and occur in the perimenopausal age group.[1] Although infertility,[2] and infertility treatments[3] have been suggested to be associated with the disease, there are no known risk factors for GCTs. Granulosa cell tumors are characterized by a very indolent course, and late recurrences. Numerous clinical and pathological parameters have been implicated as prognostic factors for GCTs. However, besides the fact that stage is related to prognosis, other factors such as patient age, tumor size, and residual disease have not been identified as definite prognostic factors.[4-7] In this study, we aimed to evaluate clinicopathological findings, and to identify the clinical and pathologic prognostic factors by comparing disease-free and overall survivals.

Methods. During the 10-year period from 1995-2005, (duration of follow up ranges from 26-176.5 months) 50 patients with granulosa tumors of the ovary were treated at the Gynecology Department of Shengjing Hospital, China Medical University, Shenyang, China. The Ethics Committee of China Medical University approved the study protocol. The case records and the pathologic slides of these patients were reviewed. All patients underwent surgical resection, and were classified in stages according to the International Federation of Gynecology and Obstetrics (FIGO) criteria. The histological slides were re-evaluated by one of the researchers to confirm the diagnosis. Two cases with a diagnosis of juvenile GCT were excluded. The FIGO stage, age, menopausal status, parity, tumor size, residual disease, administration of adjuvant treatments, and tumor rupture were evaluated as prognostic factors. The following histopathological parameters were recorded: presence or absence of Call-Exner bodies (small cavities lined by granulosa tumor cells), the degree of atypia defined by hyperchromatism, pleomorphism, enlarged nucleoli, and was graded into the 3 categories: mild, moderate, and severe. The mitotic count was carried out according to the maximum and mean values in 10 high-power fields (HPFs), ≤4/10 HPFs was considered as low mitotic count, and >4/10 HPFs as high mitotic count. Cellular growth was categorized according to the predominant growth pattern into: microfollicular, macrofollicular, trabecular, and solid. The pattern was categorized as mixed, if more than one of these patterns were observed.

Statistical analyses were performed using Chi-square, Fisher's exact probability test, and the Mann-Whitney U-test for observed values. The Cox regression analysis, and the Kaplan-Meier method were used to calculate survival distributions. The log-rank test was used to compare the survival curves. Data were analyzed using SPSS 13.0 (SPSS Inc, Chicago, IL). A p-value of <0.05 was considered statistically significant.

Results. A total of 1416 patients received treatment for ovarian cancer at our institute during the period 1995-2005. During the same period, 50 patients were diagnosed to have histologically verified GCT. The incidence of adult GCT in our institution was 3.6%. Two of these patients were lost to follow-up after 2 years, and were excluded from the treatment and survival analysis. We enrolled 46 cases into statistics (excluding 2 cases of juvenile GCT). The age range of this cohort of patients varied from 10-68 years old. Approximately 69.6% of the patient population was more than 40 years of age. In terms of the menstrual status, 14 of the women were postmenopausal, and 40 of the women reviewed were primi/multiparous (**Table 1**). Symptomatically, most patients consulted a medical practitioner because of abdominal pain. Menstrual abnormalities also predominated, occurring in many patients, and being a natural consequence of the hormonally active tumor. Histopathologically, severe nuclear atypia was present in 12 of the valuable slides, and high mitotic count was observed in 13 of the slides. Nine tumors showed a single growth pattern: 3 microfollicular, 2 trabecular, and 4 solid. All others were mixed type. Presence of Call-Exner bodies is characteristic of GCT, but was detected in only 9 patients (**Table 1**). The stage distribution of the patient population did not correlate with the tumor size. Thirty-three patients were in stage I (FIGO staging), 7 patients in stage II, and 5 patients in stage III. There was only one patient with liver metastases. Forty of the 46 patients had complete surgical removal of the tumor, and complete response after primary treatment. In postmenopausal patients, omentectomy was carried out for 8 patients, and a complete surgical staging for one patient. In this patient, no nodal metastasis was detected. Twenty-eight patients received some form of adjuvant chemotherapy after surgery (**Table 2**). One patient with stage IV disease had residual disease after primary surgery and chemoresistant disease. She died of the disease 20 months after diagnosis.

On statistical analysis using the SPSS software, the median disease-free interval was 103 months (range 26-176.5 months), and the median overall survival was 126.3 months (range 20-176.5 months). Fifteen patients have died due to GCT. Of the 31 patients who were clinically disease-free after primary treatment, 6 patients (19.4%) eventually relapsed. Mean time to recurrence was 62 months. The shortest time to recurrence was 20 months, and the longest was 141 months. The results from the analysis of various histopathologic and clinical variables are presented in **Table 1**. The only factor

Table 1 - Clinical and histopathologic characteristics of the 46 ovarian granulosa cell tumors.

Characteristics	n (%)	Significance for risk of recurrence *P*-value
Age (years)		0.526
<40	14 (30.4)	
≥40	32 (69.6)	
Parity		0.748
Nulliparous	6 (13.0)	
Primi/multiparous	40 (87.0)	
Menopause		0.133
Pre-menopause	32 (69.6)	
Post-menopause	14 (30.4)	
Tumor size (cm)		0.652
<10	18 (39.1)	
≥10	28 (60.9)	
Residual disease		0.231
No	38 (82.6)	
Yes (≥2 cm)	8 (17.4)	
Tumor rupture		0.038
Yes (before or at operation)	6 (13.0)	
No	40 (87.0)	
FIGO Stage		0.553
I	33 (71.7)	
II-IV	13 (28.3)	
Adjuvant treatment		0.235
Yes	28 (60.9)	
No	18 (39.1)	
Number of mitosis		0.442
≤4/10HPFs	33 (71.7)	
>4/10HPFs	13 (28.3)	
Nuclear atypia		0.250
Mild/moderate	34 (73.9)	
Severe	12 (26.1)	
Call-Exner bodies		0.925
Yes	9 (19.6)	
No	37 (80.4)	
Tumor growth pattern		0.678
Microfollicular	3 (6.5)	
Trabecular	2 (4.3)	
Solid	4 (8.7)	
Mixed	37 (80.5)	

FIGO - International Federation of Gynecology and Obstetrics, HPFs - high-power fields

Table 2 - Patients adjuvant chemotherapy after surgery (n=28).

Treatment modalities	n (%)
TAH + USO + MPA	6 (21.4)
TAH + BSO + BEP	8 (28.6)
TAH + BSO + omentectomy + BVP	9 (32.1)
TAH + USO + APP + BEP	4 (14.3)
TAH + BSO + APP + omentectomy + BVP	1 (3.6)

TAH - total abdominal hysterectomy, USO - unilateral salpingo-oophorectomy, BSO - bilateral salpingo-oophorectomy, APP - appendectomy, MPA - medroxyprogesterone acetate, BEP - bleomycin, + etoposide + cisplatin, BVP - bleomycin + vincristine + cisplatin

associated with the risk of recurrence was rupture of the tumor (p=0.038). However, it was not associated with overall survival. Multivariate was performed by the Cox stepwise regression analysis to identify individual variables that were significant, in terms of survival (**Table 3**). Among 5 factors that were found to affect the outcome of patients by univariate analysis, FIGO stage, presence of nuclear atypia, and increased mitoses were judged as independent prognostic factors (**Table 3**, **Figures 1-3**). However, no other clinical or pathologic factor was found to be significant. Patients who received adjuvant chemotherapy had an improved survival, which however, did not reach statistical significance (p=0.080).

Discussion. We have studied survival, relapse, and prognostic factors of adult GCT of the ovary. In accordance with the literature, the age incidence of tumors in our study ranged from the very young to the elderly, with the peak incidence in the perimenopausal age group.[2] In our study, an increased incidence was found in the 40-50 year-age group. The mean age of occurrence was 45.3 years.

The stage of GCT is clearly the most important prognostic factor.[6,8,9] More than 75% of GCTs were diagnosed as FIGO stage I.[4] This is confirmed in the current data. However, similar to other reports,[10,11] 60.9% of GCTs' tumor size were greater than 10 cm, these cannot be considered as early diagnoses. Normally, tumors measuring 10 cm have already completed a long growth phase with a slow proliferative index, as demonstrated by flow cytometric analyses.[11] This may be the reason for tumor size not being a statistically significant factor, contrary to data from various studies.[12]

There is no consensus on whether these patients should undergo surgical staging including pelvic and para-aortic lymphadenectomy. In a study by Ayhan et al,[13] one out of 18 surgically-staged patients had lymph node metastasis, while in a retrospective study by Abu-Rustum et al,[14] 13 patients with GCT had pelvic and para-aortic lymphadenectomy, 3 patients had only pelvic lymphadenectomy, and no lymph node metastases were found. Of the 31 patients treated for recurrence, 4 had recurrence in the retroperitoneal lymph nodes. Both staging and complete gross resection cannot be achieved without an exploration of the pelvic and para-aortic retroperitoneum, to exclude disease in retroperitoneal nodal tissue. This reinforces the argument for upfront comprehensive surgical exploration and staging.

Adjuvant chemotherapy for treatment of patients with GCT confined to ovaries and tumors completely removed in surgery, also remains a subject of investigation and debate.[7] Previous studies have shown that there is no

Table 3 - Multivariate analysis with respect to overall survival in ovarian GCTs (Cox stepwise regression analysis).

Characteristics	Univariate analysis		Multivariate analysis			
	χ^2	*P*-value	χ^2	*P*-value	Risk ratio	95% Confidence interval
Residual disease						
No versus yes (≥2 cm)	8.891	0.003	3.844	0.878	1.496	0.040-1.262
Tumor rupture before or at operation						
No versus yes	4.314	0.038	2.405	0.666	0.224	0.240-9.337
FIGO Stage						
I versus II-IV	15.401	0.0009	14.019	0.0003	3.946	1.912-10.052
Nuclear atypia						
Mild/moderate versus severe	15.943	0.0007	4.405	0.036	3.811	1.077-18.434
Number of mitosis						
≤4/10 HPFs versus >4/10 HPFs	15.349	0.0005	13.155	0.002	7.461	2.474-27.094

GCT - granulosa cell tumor, FIGO - International Federation of Gynecology and Obstetrics, HPFs - high power fields

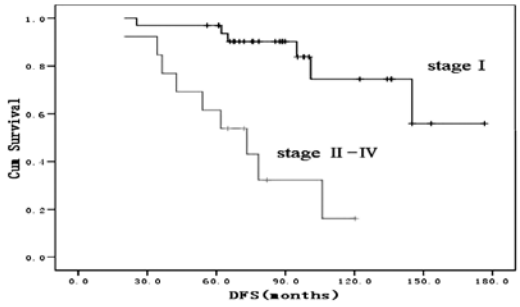

Figure 1 - Stage and disease-free survival.

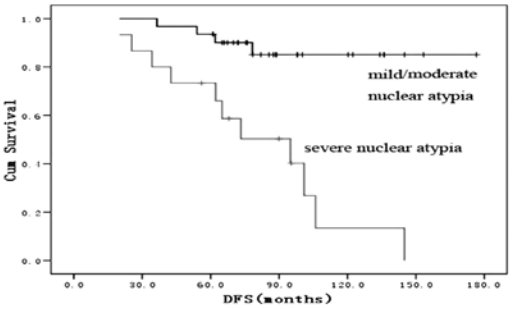

Figure 2 - Nuclear atypia and disease-free survival.

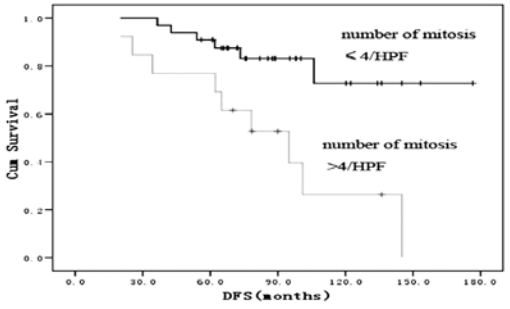

Figure 3 - Mitotic rate and disease-free survival.

statistical correlation between adjuvant chemotherapy and the risk of recurrence, or in overall survival.[13,15] In our study, patients who received chemotherapy had a better median disease-free survival than those who did not (105 versus 78 months), but this did not reach statistical significance (p=0.080), the risk of recurrence in the adjuvant treatment group was reduced by one-third when compared to the none treatment group. This risk reduction, however, was not significant.

Several studies aim at correlating prognosis with pathological factors like nuclear atypia, mitotic count, Call-Exner bodies, and growth pattern. Nuclear atypia has been reported to be one of the most significant prognostic factor in GCTs.[5,11] In the present study, those patients whose tumors showed only slight nuclear atypia had a 10-year survival rate of 76%, while only 42% survival rate for those whose tumors showed more marked atypia. Similar result has been reported by Miller et al,[10] a single pathologist using strict criteria evaluated all the histopathologic slides in the present study for nuclear atypia, and so the assessments were precise. Furthermore, several studies have reported an association between the mitotic count of GCTs and survival, or recurrence.[16,17] The disease-free survival rate of 80% for patients with tumors containing <4 mitoses/10 HPFs, compared with 25% for patients whose tumors showed ≥4 mitoses/10 HPFs (p<0.0005).[1] Because nuclear atypia is an indication of malignancy, the current findings that mitotic rate correlates well with nuclear atypia also confirms mitotic rate as an important prognostic factor. While Call-Exner bodies and growth pattern remains inconclusive with respect to prognosis,[8] in this study Call-Exner bodies, and tumor growth pattern were not correlated with tumor recurrence and overall survival.

Tumor rupture before, or at operation was the only factor associated with risk of recurrence. Recurrences occurred after a mean of 62 months from the primary therapy. Most recurrences in patients with GCT are intra-abdominal, the liver was the most common extra-pelvic metastatic site followed by the intestine.[18,19] Retroperitoneum and bone metastasis has also been reported.[14,20] In this study, all patients with recurrent disease had intra-abdominal recurrences, and one patient had also hepatic metastasis. There are no standard guidelines for the treatment of recurrent GCT. Moreover, most patients experience several relapses, and are subjected to various treatment modalities. Therefore, multiple modalities such as surgery, radiotherapy, chemotherapy, gonadotropin-releasing hormone (GnRH) agonists,[1,7] and aromatase inhibitors[21] have been proposed. Despite the lack of evidence of large randomized studies, many clinicians agree that pelvic or abdominal recurrent mass should be removed by surgical resection. Patients with recurrent GCT show good survival if they undergo optimal debulking surgery with, or without adjuvant chemotherapy.[22] In our study, 2 patients experienced 3 or more relapses, and were successfully treated with the above mentioned treatments. The survival rate for stage I patients was 93.6% (5-year) and 74.5% (10-year), whereas for stages II-IV, survival rate was 53.8% (5-year), and 16.2% (10-year).

At a molecular level, various cytogenetic abnormalities have been discovered in adult GCT. Trisomy 12 and 14, and monosomy 22 are among the more prevalent ones. Aneuploidy has been correlated with a poorer survival. In addition, germ line p53 mutations have also been reported in these tumors. The prognostic significance of this mutation is, however, not known. Further research is needed before a definite conclusion is drawn regarding the clinical significance of these cytogenetic markers.[23,24]

Due to the rarity of this disease particularly advanced stage presentation, and the nature of delayed recurrences had limited our studies. Small sample size, as well as relatively short follow-up period could also limit our results.

The evaluation of the benefit of adjuvant treatment is complicated by the fact that, several different treatment modalities were used for adjuvant treatment. Further studies with larger series, and/or longer follow-up are needed to verify these results.

In summary, we find many important points that emerged from our study and from a review of the literature. After statistical analysis, FIGO stage, nuclear atypia, and mitotic rate remain statistically significant. These are markers of the invasive nature of the tumor, its proliferative index and metastatic potential. These could probably be used in the future to identify patients who would benefit from adjuvant therapy. A prolonged post therapeutic follow-up is necessary because of the risk of recurrences, late, and exceptional for the adult ovarian GCT, especially when the tumor ruptured before, or at operation.

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