Original Article-II

Granulosa Cell Tumours of Ovary: Variables Affecting Prognosis

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ABSTRACT

Background: **Granulosa cell tumours account for less than 5% of all ovarian malignancies. Limited data is available from India.**

Methods: 27 patients with diagnosis of granulosa cell tumour of the ovary were treated between 1991 and 2003 at our Institute. The surgical records were reviewed and the patients were staged according to the FIGO system. The clinical and histological findings are correlated with prognosis and survival.

Results: Mean age at diagnosis was 46.2 (2-64) years. The number of patients in various stages was I-19; II-1; III-5 and IV-2. Menstrual irregularity was diagnosed in 22%, and postmenopausal bleeding in 7.4% of women. Twenty-five patients were treated with primary surgery, 9 patients received adjuvant chemotherapy (CT) and only one patients received chemotherapy as primary treatment. Overall survival was 82% at 5 years. Overall survival for stage I was 100% after 5 and 10 years and in stage II-IV, was 56.4% after 5 and 10 years. Mean tumour size was 18cm (range 3-30 cm). Women with larger tumour diameter (>15cm) had significantly worse outcome than those with tumours of smaller diameter (P<0.05). The frequency of observed mitosis influenced the survival rate; with 0-3/10 HPF the survival was 100% in 5 years and with 4/10 HPF the survival was 2.6 years.

Conclusion: The tumour size, mitotic rate and stage of disease are well-defined variables and influence the survival significantly and should be considered as important prognostic factors for treatment planning.

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INTRODUCTION

Granulosa cell tumours comprise 5% of all malignant ovarian tumours and account for approximately 70% of malignant sex cord-stromal tumours.[1] Granulosa cell tumours have been diagnosed from infancy through the tenth decade of life, the peak incidence being perimenopausal decade. The malignant potential of these tumours is low and recurrences, are often late and found in 10-33%.[2] A variety of microscopic patterns have been described and different patterns can occur within the same tumour.[3] Many investigators have found that age, stage, mitotic index and size of tumour to be of prognostic importance. In poor risk patients the risk for metastases even after long delay, is substantial.[4]

We reviewed the care records of 27 patients diagnosed to have granulosa cell tumours at AIIMS from 1991 through 2003. The clinical and histological findings were correlated with prognosis and survival.

MATERIALS AND METHODS

During the 13 year period 1991-2003, 27 women with histologically verified granulosa cells tumour were treated at the Gynaecologic Tumour Clinic. All patients were staged according to FIGO. The patients were divided into subgroups according to age, stage, mitotic rate, tumour size and histological features. The individual and mean mitotic rates were calculated in the subgroup. Surgical treatment varied from total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy to unilateral ovariotomy(Table-1). Adjuvant chemotherapy was given to 2 patients using melphalan as a single agent therapy, and five patients received combination of cyclophosphomide and cisplatin (CP) therapy. One patient received combination of carboplatinum and cyclophosphomide (CE) and in one patients 2 cycles of CP and 4 cycles of CE combination was used as an adjuvant treatment. Only in one patient bleomycin, etoposide and cisplatin combination therapy was used as a primary treatment (Table -2).

The data has been censored on 31st December 2003, of the 27 patients 24 patients were evaluable for treatment and response as three patients after initial visit received treatment elsewhere. Statistical analysis was performed using the statistical package stata 8.0 (inter coiled version). Kaplan –Meier estimates of survival probabilities were calculated.

RESULTS

The age of patients at the time of diagnosis ranged from 2 to 64 years with a mean of 46.8 years. Twelve women (44%) were postmen-opausal at the time of diagnosis. Eleven patients (40%) were less than 40 years and one patient was in premenarchal age group. The symptomatology was similar in most cases and often related to hormonal activity. Most commonly the patients consulted a gynaecologist because of menstrual disturbances (29.6%) or bleeding postmenopausally (7.4%). Secondary amenorrhoea was a presenting symptom in two (7.4%) patients. Six patients (22.6%) had noticed a distended abdomen or painful resistance in the abdomen. Only four (14.8%) had symptoms from urinary tract (Table-1.)

Endometrial tissue was obtained shortly before or at the initial laparatomy from 19 patients. Simple hyperplasia was diagnosed in 31% of them, proliferative endometrium in 42%, secretory endometrium in 17% and atypia of endometrial cells in 10% of the cases. Surgical treatment was employed in all cases except two. Ten patients (37%) had unilateral salpingo-oophorectomy with or with out omentectomy. Fourteen patients (52%) underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. One patient underwent primary debulking surgery and one patients underwent secondary debulking surgery following chemotherapy. (Table –1)

Nineteen patients were in clinical stage I and only one had stage II disease. Seven patients had disease outside the pelvic region; 5 were in stage III and 2 were in stage IV (Table-1). In 13 patients the histological pattern was diffuse, 10 patients had trabecular pattern and in 4 patients there was a microfollicular pattern. Eighteen patients (66.6%) had a tumour size $\leq$ 15 cm in diameter and 9 (33.3%) patients had tumour size $>$ 15 cm in diameter. Mean tumour size was 10.5 cm (4-25cm), survival according to tumour size is shown in Fig. 1. Survival curves for patients with clinical stage I and II-IV disease are given in Fig. 2 the relative survival being significantly better in the former, $P<0.001$.

The mitotic rate was evaluated in 21 patients, in 8 (38%) patients the frequency was <4 mitosis / 10 HPF, in 13 (62%) patients it was $\geq$4 mitoses / 10 HPF. The overall mean mitotic rate per 10 HPF was 5.8 mitoses (range 0-15). The survival in patients with mitotic rate of <4 / 10HPF was 100% at 5 years. With the increase in mitotic rate the survival decreases,

Table:1. Patients Characteristics

Characteristics	No. of patients (n=27)	Percentage
Age (Years)		
• <20	1	3.7
• 21-30	3	11.1
• 31-40	7	25.9
• 41-50	12	44.4
• 51-60	2	7.4
• 61-70	2	7.4
Presenting symptoms		
Irregular Vaginal bleeding	8	29.6
Menorrhagia	4	14.8
Amenorrhoea	2	7.4
Post menopausal bleeding	2	7.4
Precocious puberty	1	3.7
Abdominal pain/ distension/ mass	6	22.6
Urinary Symptoms	4	14.8
Surgery performed		
Unilateral saplingo Ovariotomy	9	33.3
LSO + Rt ovarian cystectomy	1	3.7
TAH + USO	3	11.2
TAH + BSO	6	22.5
TAH + BSO + omentectomy	5	18.5
Primary debulking	1	3.7
Secondary debulking	1	3.7
None	1	3.7
Stage of disease		
I	19	70.4
II	1	3.7
III	5	18.5
IV	2	7.4

TAH – Total abdominal hysterectomy, USO – Unilateral salpingo – oophorectomy,

BSO – Bilateral salpingo – oophorectomy, LSO – Left salpingo – oophorectomy.

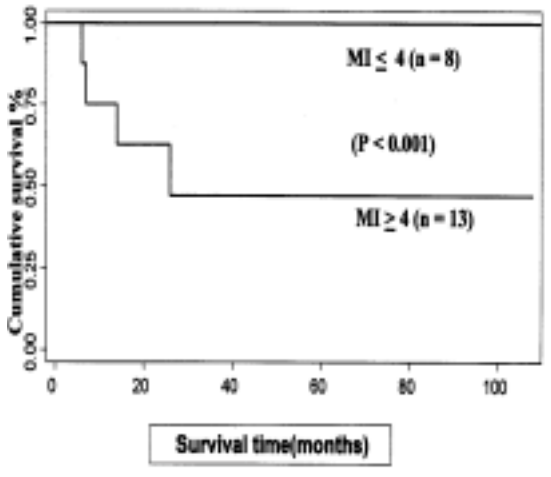
Table: 2 Chemotherapy for Granulosa cell tumours

S. No.	Disease status of patients	CT regimen	No. Of cycles	Current status of patient
1	S1 - HMA #	Melphalan	9	NED/9.4 Years
2	S3 - no RD*	Melphalan	9	NED/4 Years
3	S1 - HMA	CE++	6	NED/4 Years
4	S2 -	CP**	6	NED/8 Years
5	S3 - Minimal RD	CP+CE	2+4	NED/8 Months
6	S3 - no RD	CP	6	NED/1.5 Years
7	S3 - Gross RD	CP	6	alive with residual disease
8	S3 - Gross RD	CP	2	Died of progressive disease
9	S4 - Pleural effusion+/Liver metastasis	CP	3	Died of progressive disease
10	S4 - Lung metastasis	BEP***	4	Died due to post op complications

- High mitotic activity * - Residual disease, + - Pleural effusion ** - Cyclophosphomide & cisplatinum *** - Bleomycin, etoposide & cisplatinum ++ carboplatinum, & cyclophosphomide

NED : No evidence of disease. S1 – Stage 1, S2 – Stage 2, S3 – Stage 3.

the median survival for patients with the mitotic rate of ≥4 / 10 HPF is about at 2 years (Fig. 3).



MI: Mitotic Index

Fig. 3. Survival curves according to mitotic rate in 21 of 27 patients with granulosa cell tumour of the ovary.

The recurrence rate was 11%, all patients who presented with recurrent disease had abdomino-pelvic metastases. The mean time from initial diagnosis to recurrence was 3 years and the mean tumour size in these patients was 16 cm and the mean mitotic rate was 8/10 HPF (Table-3). At the end of the study 12 patients are alive with no evidence of disease, 1 patients is alive with disease, 3 patients died of progressive disease, one died of postoperative complications and one died due to unrelated cause. Nine patients were lost to follow up (Table -4).

DISCUSSION

From this study and other previous reports it appears that granulosa cell tumours of the ovary is an uncommon gynaecological malignancy with a peak incidence in the first post menopausal decade. In our series an increased incidence is noted in the age group 41 to 50 years with a mean age of occurrence at 46.8 years, which is younger than those in several other reports.[5]

The main purpose of this study was to evaluate possible prognostic factors such as stage, size of tumour and frequency of mitosis on the survival rate. Age at diagnosis was not found to influence tumour mortality, whereas in other studies the prognosis was better for women under 40 years of age.[6,7] Majority of patients were diagnosed in stage I opposed to epithelial ovarian carcinoma which is usually diagnosed in stage III. This is due to the hormonal activity of these tumours causing bleeding disturbances as presenting symptoms parallel to the symptomatology in endometrial carcinoma.[8-10]

Factors shown in our study to be associated with better prognosis are consented mainly with the stage of disease, tumour size and mitotic activity of the tumour. There are some reports that tumour size is of prognostic value.[6,11] In the present series relative survival tend to be significantly better for women having small tumours compared with those having larger ones (Fig -1).

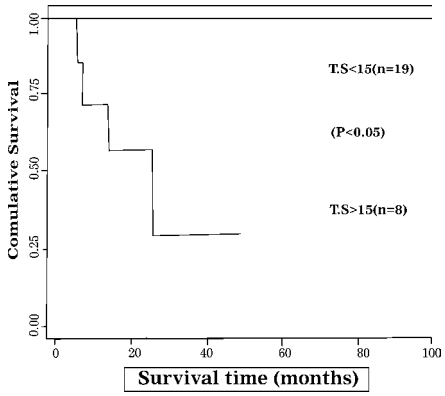


Fig 1. Survival curves according to tumor size in 24 of 27 patients with granulosa cell tumours of the ovary.

Note: T. S: Tumor size

The 5 year survival of our granulosa cell tumour patients was 100% when they were diagnosed at stage I, but this figure dropped to 56.4% for stages III and IV(Fig. 2). Other studies have also stressed on the major importance of the stage of disease on survival.[6,7,12] Histological appearance of tumour and its relation to prognosis has been discussed by various authors. Kottmeir[29] thought that a sarcomatoid pattern implied a worse prognosis but others do not agree.[14,15] In our study no significant correlation could be established between the histological type of tumour and survival. Of the different histological subtypes, the diffuse and the trabecular subtype seemed to be more aggressive on the basis of the higher mitotic rate observed in these tumours. Norris and Taylor[16] did not find any relation between the degree of atypia, mitotic activity, and prognosis, while others found that grading for mitotic activity is of some value, especially when the tumour had not spread beyond the ovary.[17,18] A positive relationship between atypia and mitotic index and recurrence rate has been reported.[13] In our study we found that four or more mitosis per 10 HPF indicated a higher risk and the mortality increased with the mitotic index (Fig 3).

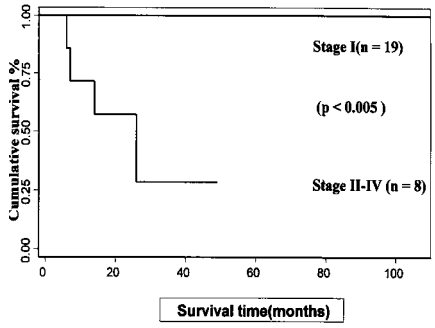


Fig.2 : Survival curves according to clinical staging in 24 of 27 patients with granulosa cell tumor of the ovary

A special feature of granulosa cell tumours is the appearance of recurrences long after treatment of the primary tumour, mean time for recurrence after diagnosis was 5.6 years.[6] Recurrences after more than 10 years are reported by several authors.[16,17,19] In our series the mean time until recurrence was 3 years (rage 1.5-9.4 years). All recurrences occurred in both pelvis and abdomen (Table 3).

The treatment of granulosa cell tumour patients is not well established. Some authors have reported improved outcome in patients treated with adjuvant radiation therapy, other investigators have found no clear value in the use of adjuvant radiation therapy.[20-22] Alkylating agent chemotherapy has been used in patients with granulosa cell tumours with responses

Table: 3. Recurrences

Age S. No.	Initial	MI*	Primary Rx	Time until replace (month)	Recurrent Site	Treatment Given	Outcome (months)
35	I	H**	USO	28	Abdomen+Pelvis	Surgery	alive
23	I	M***	USO	48	Abdomen+Pelvis	Surgery +CP (6)	NED^{+} 16mon
32	I	H	BSO	32	Abdomen + Pelvis	Surgery +CP (2)	DOD^{++}

Note: * - Mitotic Index , ** - High MI, *** - Moderate MI
Ned No evidence of disease, Nod died of progressive disease

Table:4. Follow up of Patients with Granulosa Cell Tumours

Patient status	Follow – up – period (years)			Total (n = 24)
	< 2	2 - 5	6 – 10	
Alive and well	2	5	6	13
Alive with disease	1	-	-	1
Died due to disease	3	-	-	3
Died due to post op Complications	1	-	-	1
Died due to unrelated cause	-	1	-	1
Lost to follow – up	2	3	-	5

* - Residual disease

noted in various reports.[23,24] Doxorubicin plus bleomycin as well as combination of dactinomycin, cyclophosphomide and 5-fluorouracil have yielded at least two complete responses.[15,26] The most promising report of a platinum based regimen included 9 responders to the combination of cisplatinum, vinblastine and bleomycin, in 11 previously untreated patients with advanced disease.[27] In our series 6 patients received combination of cyclophosphomide and cisplatinum as an adjuvant chemotherapy. Of them 3 showed complete response and one patient had partial response with a median follow up of 2.7 years (Table –5). We found that patients with gross residual disease at the time of initial surgery were relatively poor responders than the patients with either minimal or no residual disease.

Recently, Gynaecologic Oncology Group have reported the largest series of women with ovarian sex cord stromal tumours treated with chemotherapy. They used four cycles of cisplatinum, bleomycin and etoposide.[28] This chemotherapy combination was considered active with 11 of 16 primary disease patients and 21 of 41 recurrent disease patients remaining progression free at a median follow up of 3 years. In our study only one patient with stage IV disease had been treated with BEP regimen, showed partial response but she died due to postoperative complications following interval debulking surgery.

In summary, granulosa cell tumours must be regarded as ovarian tumours with a malignant potential that is only slightly less than that of the more common ovarian carcinomas. Early stage tumours with strong adverse prognostic factors should be treated with adjuvant chemotherapy. In selecting patient for adjuvant treatment one should take into account not only tumour stage but also tumour size and mitotic rate. An accurate surgical staging is also important in the treatment planning of these tumours. Recurrence is common and can occur late. Treatment of recurrences with combination chemotherapy is worth while. In these cases of stage III and IV disease treatment is individualized, but consists mainly of chemotherapy.

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