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ORIGINAL ARTICLE

Granulosa Cell Tumours: A Study of 37 Cases

Nirmala C. · Dave Kalpana S. · Chauhan Anjana · Bhansali Ronak P. · Arora Ruchi

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Abstract
Objectives To evaluate the clinico-pathological features, surgical procedures and postoperative treatment and their relation to survival in women with granulosa cell tumours.
Methods Data of 37 women with granulosa cell tumours were collected and reviewed retrospectively. Mann–Whitney test, log rank test and Kaplan–Meier survival analysis were applied appropriately.
Results Thirty-seven women of median age 48.6 years were diagnosed in stage Ia (45.9 %), stage Ic (27 %), stage III (16.2 %) and unstaged (10.8 %). The median follow up was 5 years. Overall survival was 93 % at 5 years. Disease-free survival at 5 years was 63 %. Tumour stage and residual disease were associated with poor prognosis ($p < 0.001$). Mitotic rate and tumour grade were not of prognostic significance.
Conclusions Stage of disease and residual disease are valuable prognostic factors. Prospective studies with large sample sizes and long-term follow up are needed to confirm our findings.

Nirmala C., Fellow in Gynecologic Oncology · Dave K. S., Professor and Head of Department · Chauhan A., Associate Professor · Bhansali R. P., Assistant Professor · Arora R., Lecturer
Gujarat Cancer and Research Institute, New Civil Hospital Campus, Asarva, Ahmedabad 380016, India

Nirmala C. (✉), Fellow in Gynecologic Oncology
No. 91, III Cross, New Timber Yard Layout, Telecom Colony, Bangalore 560026, India
e-mail: nimc80@yahoo.com

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Introduction

Granulosa cell tumour of the ovary is an uncommon neoplasm that represents 2–5 % of all ovarian cancers. It accounts for 70 % of the sex cord stromal tumours [1]. Most commonly, patients present with abdominal distention and pain [2].

Approximately 75 % of the granulosa cell tumours are diagnosed in stage Ia–Ic with 10 year survival rate at 75–90 %. Mitotic rate, tumour stage and residual disease are prognostic factors for survival [3].

Primary treatment is surgical with total abdominal hysterectomy and bilateral salpingo oophorectomy alone in early stages, but adjunctive chemotherapy is needed for advanced stages. The role of retroperitoneal lymph node dissection is controversial [1]. BEP regimen appears to be an active combination for malignant tumours of the ovarian stroma [4]. Granulosa cell tumours have a tendency for late relapse, and hence long-term follow up is necessary [5].

Materials and methods

The clinical and pathological records of 37 patients with granulosa cell tumours from 1990 to 2006 were reviewed. All the patients were retrospectively staged according to

the International Federation of Gynecology and Obstetrics (FIGO) staging system for gynaecological cancers. The following data were obtained from the case files of the patients: age at initial diagnosis, menstrual history, parity, presenting symptoms, tumour markers (serum estradiol), sonological findings, size of the tumour (maximum diameter), surgery done, per operative findings, surgical stage, frozen section diagnosis, histopathological findings, chemotherapy given, duration of follow up, survival status, recurrence, treatment instituted and disease-free survival.

Results

The total number of retrospectively studied patients was 37. The median age of the patients with adult granulosa cell tumour was 48.6 years ($n = 35$) and that of juvenile granulosa cell tumour ($n = 2$) was 17.5 years. Five patients were of $\leq$30 years of age and ten were >30 years of age (premenopausal). Twenty-two were postmenopausal (59.4 %). The symptoms at presentation are shown in Table 1.

Surgery

All patients, except those who were unstaged, underwent infracolic omentectomy with retro peritoneal lymph node dissection: total abdominal hysterectomy ($n = 26$), unilateral salpingo oophorectomy ($n = 4$), bilateral salpingo oophorectomy ($n = 29$), unstaged ($n = 4$). 81 % of the patients underwent a complete surgical resection (Primary surgery = 28, completion surgery = 5). Patients who underwent incomplete surgery elsewhere were called unstaged. One amongst these unstaged patients had a fertility-preserving surgery. Residual disease was more than 2 cm (sub optimal debulking) in three patients (all with stage IIIc disease), less than 2 cm in four and nil in the rest of them. The number of patients with stage Ia was 17 (45.94 %), Ic was 10 (27.02 %), IIIc was six (16.21 %), unstaged was four (10.8 %). Three were operated on elsewhere and unstaged due to various reasons. Fertility-preserving surgery was done on four patients, three in our institute (10.8 %). The details of the four patients who underwent fertility-preserving surgery are shown in Table 2.

Table 1 Presenting symptoms

Symptoms	No.	%
Abd pain, distention, mass	28	75.6
PMB, irregular bleeding pv	8	21
Hirsutism, clitoromegaly	2	
Urinary symptoms	2	
Anorexia, fever	1	

Histopathology

The average maximum diameter of the tumour was 14.1 cm. The number of well-differentiated tumours was 17, moderate tumours was three and poor tumours was 13. Mitosis of <5/10 high power field (hpf) was present in 30 and $\geq$5/10 hpf in three patients. The number of adult granulosa cell tumours was 28, combined granulosa–theca cell tumours was 7, combined granulosa–sertoli cell tumour was 1 and juvenile granulosa cell tumours was two. Endometrial status obtained either by dilatation and curettage done for postmenopausal bleeding or by histopathological examination of the hysterectomy specimen was available in 14 patients; simple endometrial hyperplasia ($n = 6$), complex endometrial hyperplasia with atypia ($n = 1$) and adenocarcinoma of endometrium in situ (stage Ia) ($n = 2$). Specimens for frozen section diagnosis were sent in 11 patients, and they correlated with the final histopathological diagnosis in 7 patients (63.6 %) and false negative in 4 patients (36.3 %). Amongst the false negatives, two were diagnosed as malignant adenocarcinoma, one as papillary epithelial tumour and one as benign haemorrhagic cyst.

Chemotherapy was given postoperatively in 20 patients: cisplatin based chemotherapy in 12, BEP in 4, paclitaxol + etoposide in 3 and VAC regimen in 1 patient. Ten patients amongst stage Ia/Ic received chemotherapy as they had one or more of the risk factors for recurrence; poor differentiation, high mitotic counts (>5 hpf), large tumour diameter, intraoperative capsule rupture.

Follow up

The median follow up period was 5 years. There was no evidence of disease in 27 patients, 3 were alive with disease, 2 died due to disease. Seven patients were followed up for less than 6 months, 11 for a period of 6 months–1 year, 14 for more than 1–5 years and 5 were lost to follow up.

Survival

The overall survival and disease-free survival at 5 years are 93 and 63 %, respectively (Figs. 1, 2). Survival rates at 5 years for stage I, III and unstaged patients are 80, 50 and 25 %, respectively. The log rank test confirmed the significance of these differences (Fig. 3).

The mitotic counts were divided in two sets of <5/hpf and $\geq$5/hpf. Analysis between mitotic count and survival at 5 years was done and found to be insignificant ($p = 0.65$).

Tumour size and mitotic rates were compared and analysed. It was found that the larger the tumour size the higher the mitotic count. The Mann–Whitney test proved

Table 2 Fertility-preserving surgery

No.	Age (years)	Surgery	Histopathology	Rx given	DFS (months)
1	16	USO elsewhere	GCT, poor differentiation	3 cycles BEP	6
2	11	USO + ICO + RPLND	JGCT (Ia)	Obs	24
3	20	USO	GCT, well differentiation	Obs	6
4	24	USO	JGCT, mitosis of 9–14/10 hpf	Obs	12

USO unilateral salpingo oophorectomy, *ICO + RPLND* infracolic omentectomy + retroperitoneal lymph node dissection, *GCT* granulosa cell tumour, *JGCT* juvenile GCT

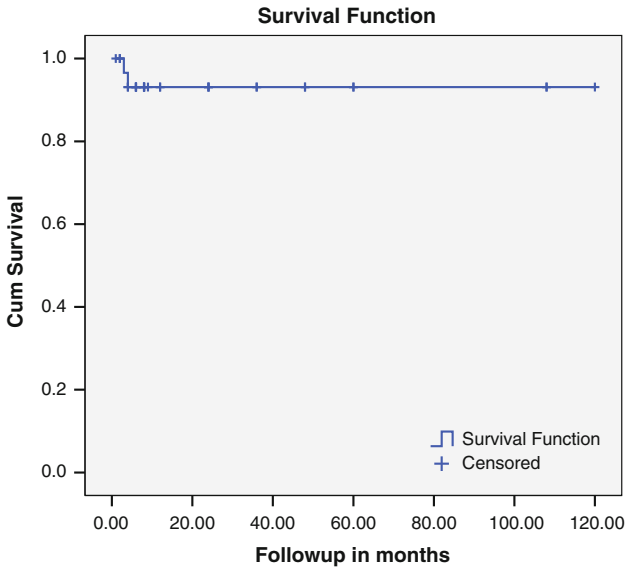

Fig. 1 Overall survival at 5 years

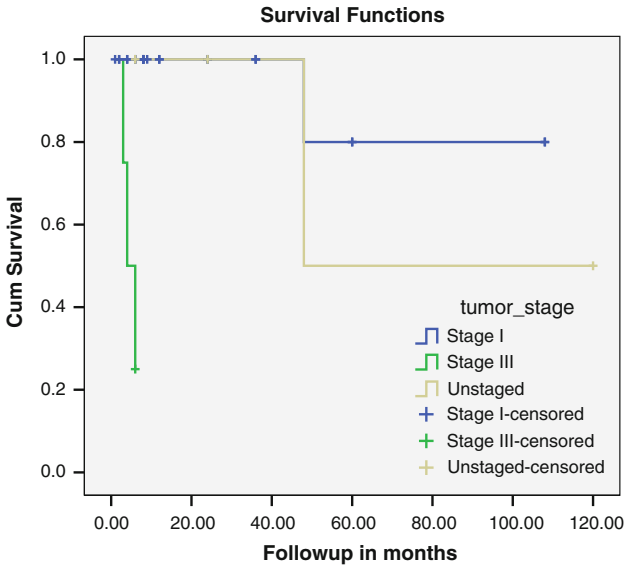

Fig. 3 Survival in stage I, III, unstaged

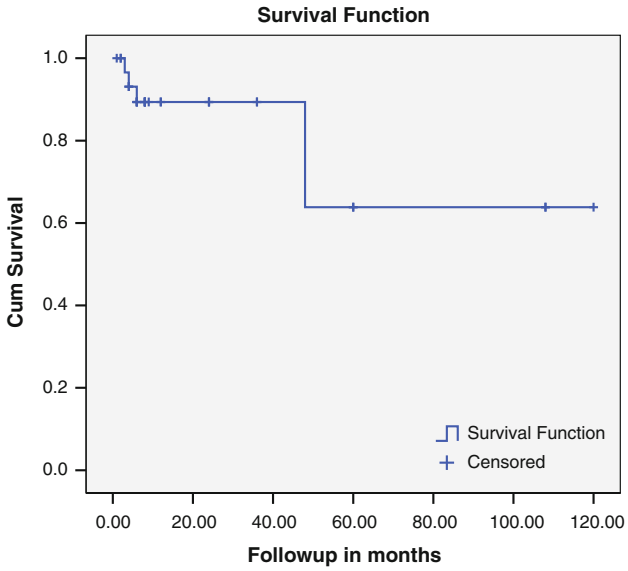

Fig. 2 Disease-free survival at 5 years

the significance. As mitotic rates and survival were not of statistical significance, tumour size in itself had no prognostic value.

Analysis between survival and postoperative residual disease showed a significant difference in survival of 76 and 60 % in those with and without residual disease. The log rank test showed a p value of 0.036 ($p < 0.05$) (Fig. 4).

The details of the five patients who developed recurrence are given in Table 3.

Discussion

Granulosa cell tumours constituted 6.44 % of all ovarian tumours. This corroborates with various studies which have 5–10 % incidence of granulosa cell tumours [6]. The median age of the patients in our study was 48.6 years, which is lower than that stated by Zambeth et al. [7].

Most of the patients (60 %) were postmenopausal, though postmenopausal bleeding was present in only 21 % of the patients. 70 % of the patients presented with

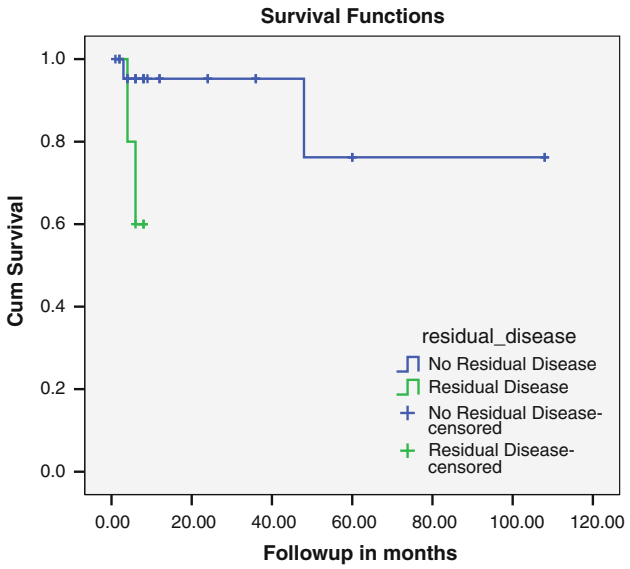

Fig. 4 Survival and postoperative residual tumour mass

abdominal pain, distension or mass per abdomen. Abdominal pain could be hypothesized due to distension of the capsule, intracystic haemorrhage ($n = 5$), torsion of the tumour ($n = 1$).

In the current study, the average maximum diameter of the tumour was not a prognostic factor. Sehouli et al. observed an average tumour diameter of 10.6 cm. 80 % of these were diagnosed in FIGO stage I disease. Therefore, the tumour diameter is not a valid prognostic factor for these tumours [3].

We observed that the vast majority (72.9 %) presented with FIGO stage I disease. Piura et al. [6] found that 78 % of the patients presented with stage I disease.

In the current study, no correlation was found between cell differentiation and high mitotic counts with survival. This has been supported by Lauszus et al. [5]. Newer diagnostic methods like flow cytometry of DNA content, ploidy and morphometry have been applied with no clear conclusion [8].

Endometrial hyperplasia on histopathological examination of the curretage specimen or specimen of uterus was found only in 14 patients. Endometroid adenocarcinoma of the endometrium was found in two patients, both in stage Ia. Co malignancy with carcinoma of the endometrium has an incidence of 3.4 %: one was well and the other poor in differentiation. Endometroid adenocarcinoma of the endometrium was found to be detected at an earlier stage and mostly well differentiated in patients with granulosa cell tumours [8]. Lauszus et al. [5] found no co malignancy in his study.

Although serum estradiol may be helpful in monitoring the status of some patients, it is not always sensitive enough to serve as a reliable tumour marker [1].

Frozen section diagnosis correlated with final histopathology only in 63.6 % patients. Hence, frozen section diagnosis may not be reliable in fertility-preserving surgery done in granulosa cell tumours.

Residual disease postoperatively was a highly significant prognostic factor ($p < 0.05$) in our study. This has been similarly proved by Sehouli et al. [3].

In the current study, survival in the early stage of the disease is significantly higher than in stage III of the disease ($p < 0.001$). The survival in stage I and III was 80 and 50 %, respectively.

Sehouli et al. observed that the survival rates after 10 years were 87.2, 75, 20 and 0 % for stage I, II, III and IV tumours, respectively. The estimated, average survival was 113 and 67 months for stage I and advanced stage tumours, respectively [3, 9].

The median time of recurrence was 8 months, and recurrence rate in the current study was 13.5 %. The risk of recurrence in stage I disease after complete resection with staging was 5.8 %. Lauszus et al. [5] observed a recurrence rate of 35 % in stage I, but it remains inconclusive with respect to whether premenopausal patients should have extensive surgery. In the present study, recurrence was noted in five patients with Ia ($n = 1$), IIIc ($n = 3$), unstaged ($n = 1$). Recurrence was, interestingly,

Table 3 Clinical data and outcome in patients with advanced/recurrent disease

No.	Age (years)	Stage/ differentiation	Sx	R D (cm)	CT (No.)	Response	PFI (months)	Site of recurrence	Further Rx	Survival status
1	65	IIIc/poor	Sx	≤2	4 (P + E)	PD	5	Abdomen	VAC	AWD
2	46	IIIc/moderate	Sx	>2	VAC	PD	4	Abdomen	–	DDD
3	20	Relapse/poor	Complete	Nil	P + E	PD	3	Lung mets	Pacli + Epi	AWD (metastasis in thyroid)
4	36	IIIc	Sx	Nil	P + A + C	PD	3	Abdomen	-ss	DDD
5	60	Ia	Complete	Nil		CR	24	Abdomen	C	NED (1y)

Sx TAH + BSO + BLND + ICO, *RD* residual disease, *CT* chemotherapy, *P + E* cisplatin + etoposide, *VAC* vincristine + adriamycin + cyclophosphamide, *PD* progressive disease, *CR* complete response, *PFI* progression free interval, *DDD* died due to disease, *NED* no evidence of disease, *AWD* alive with disease

noted earlier of about 2 years in stage Ia disease and with in 6 months in the rest of them. Two amongst them (stage IIIc) died due to progressive disease before institution of chemotherapy. The patient with stage Ia responded well to salvage chemotherapy and is alive with no evidence of disease.

According to Sehouli et al. [3], the recurrence rate was 43 % after 10 years. Piura et al. [6] observed recurrence in three patients (one with stage Ic and two with advanced disease), who succumbed to progressive disease despite vigorous surgery, RT and chemotherapy.

Hence, these patients should have long-term follow up to detect recurrence. Completion surgery is advised once child bearing has been completed in those who underwent fertility-preserving surgery.

Old age, advanced stage of disease at presentation, residual disease after initial surgery and poor performance status prior to institution of treatment were probably factors that caused early recurrence in patients in the present study.

In the current study, two patients had juvenile granulosa cell tumour and both were well differentiated with one in stage Ia and the other with stage Ic. The outcome correlated with both stages and histological differentiation. There was no relapse in both patients. However, the sample size is less to derive conclusion from the study, our data correlated with the observation of Schneider DT et al. Two of the three patients with poorly differentiated juvenile granulosa tumours relapsed, but none of them with intermediate or high differentiation [10].

Conclusions

The peak incidence of granulosa cell tumours is in women older than 50 years of age, but a significant proportion occurs in premenopausal women. Surgery remains the cornerstone of treatment for these patients. The stage of disease and residual disease are valuable prognostic factors. Prospective studies with large sample sizes and long-term follow up are needed to confirm our findings.

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