

## Gynaecological Cancer

# Prognostic Factors of Granulosa Cell Tumors: A Retrospective Study in a Tertiary Care Cancer Centre of Eastern India

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## Abstract



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**Background and Aims** The main objective of this study was to analyze the clinico-pathological profile and prognostic factors of granulosa cell tumors (GCT).

**Method** All the cases of ovarian cancer which were seen at our institute between January 2000 and December 2017 were reviewed. Data were analyzed with failure-free survival (FFS) as the primary end point.

**Results** GCTs consisted of 2.66% of all ovarian cancers at our institute. The median age was 43 years. Majority of the patients (62.5%) were unstaged. Six patients (25%) had a fertility-preserving procedure. Forty two percent of the patients received adjuvant chemotherapy. Thirty eight percent of the patients developed recurrence. Considering tumor-related prognostic factors, there was a statistically significant decrease in FFS with the presence of hemorrhage ( $p = < 0.001$ ), larger tumors ( $p = 0.042$ ), and juvenile variant ( $p = 0.002$ ). On the contrary, when treatment-related factors were considered, there was no statistically significant improvement in FFS with the performance of lymphadenectomy ( $p = 0.218$ ), omentectomy ( $p = 0.453$ ), fertility sparing surgery ( $p = 0.152$ ), or administration of adjuvant chemotherapy ( $p = 0.45$ ).

**Conclusion** Inherent tumor-related biological factors tend to play a more important role compared with treatment-related factors in GCTs. Hence, the traditional practice of performance of extensive staging procedures and routine adjuvant chemotherapy should be reviewed. Fertility-preserving surgery appears safe to be offered in early stages when desired. Although it is common knowledge that GCTs tend to be hemorrhagic tumors, this factor has not been well recognized as a prognostic indicator till date. Our study sheds some light on this aspect. Since these tumors have a tendency toward late recurrences, a long follow-up is prudent.

## Keywords

- ▶ granulosa cell tumors
- ▶ GCT
- ▶ prognostic factors
- ▶ hemorrhage

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## Introduction

Granulosa cell tumors (GCTs) of the ovary are classified under sex cord-stromal tumors of the ovary and are the most common among them. They comprise 2 to 5% of all ovarian malignancies.<sup>1</sup> Majority patients (57%) are in stage I at diagnosis and have a relatively favorable outcome with a 90% survival rate.<sup>2</sup> However, the outcomes are less favorable as the disease progresses, with survival rates of 50 to 65% for stage II disease and 17 to 33% for stage III or IV disease.<sup>2</sup> There are two types of GCTs—adult variant and the juvenile variant. The peak age of incidence has been reported to be 50 to 55 years.<sup>3</sup> To this date there are no established risk factors for GCTs, although infertility and infertility treatments have been suggested.<sup>3,4</sup> These tumors are known to be hormonally active which often produce estrogen and inhibin. Also they have an indolent growth with tendencies to relapse very late.<sup>5</sup> Considering prognostic factors, other than the FIGO (International Federation of Gynecology and Obstetrics) stage, not many others have been cited in the literature.<sup>6</sup> In view of rarity of this disease and scarcity of large studies, we undertook this study to analyze the clinicopathological features of GCTs treated at our center with special reference to prognostic factors.

## Patients and Methods

We undertook a retrospective study at our institute (regional cancer center) after acceptance from the institutional ethics committee. We compiled the data between January 2000 and December 2017. We included all the cases of GCTs of the ovary that received any part of the treatment in our hospital in this study period. A detailed review of patient files and records was undertaken. The data were abstracted and analyzed. Clinicopathological profile was studied, treatment practices in our institute evaluated, and an attempt made to outline prognostic factors. Follow-up was once in 3 months for the first year, 6 monthly for the next 4 years, and annually thereafter. Failure-free survival (FFS) was taken as the primary end point for analytical purposes. The Kaplan–Meier method was used in this analysis. The log-rank test was applied in statistical testing.

## Results

There were 900 cases of ovarian carcinoma treated at our center in the study period. Twenty four (2.66%) cases were of GCT. The median age group of patients was 43 years with a range of 6 to 67 years. Premenopausal patients were majority comprising 54.16%. When parity was considered Majority of the patients were parous (37.5%). Six patients (25%) were nulliparous. Most common chief-presenting complaint was abdominal distension (41.6%), followed by abdominal pain (37.5%), and abnormal uterine bleeding (20.8%).

Nine (37.5%) of these cases underwent a complete staging procedure which included ascitic fluid/peritoneal washings for cytology, thorough assessment of peritoneal cavity with biopsies if needed, total hysterectomy with b/l salpingo-

oophorectomy or unilateral adnexectomy (fertility sparing), infragastric omentectomy, and b/l pelvic and para aortic lymphadenectomy. Rest 15 cases (62.5%) did not undergo a comprehensive staging procedure. Eight cases (33.3%) underwent only a total hysterectomy with b/l salpingo-oophorectomy. Sixteen patients (66.66%) underwent an omentectomy, while 10 (41.66%) cases underwent additional lymphadenectomy. Fertility sparing staging procedures were done in six patients (25%). Of the nine cases which underwent a complete staging procedure, seven (77.7%) were stage I, and two cases (22.2%) were stage IIIC. For one of the cases, staging was not applicable since she was preoperatively wrongly diagnosed as serous papillary carcinoma on fine needle aspiration cytology and had received three cycles of neoadjuvant chemotherapy with paclitaxel and carboplatin.

On histopathology, 21 cases (87.5%) were diagnosed to be adult GCT, while three (12.5%) turned out to be of juvenile type. We also assessed the tumor size in these cases. Most of the tumors (66.6%) were more than 10 cm in size ranging from 4 to 30 cm. GCTs are known to be hemorrhagic tumors, thirteen (54.16%) cases had hemorrhage, including intratumoral and intraperitoneal. None of the cases had lymph node involvement.

In our study adjuvant chemotherapy was given to 10 (41.66%) patients. The indications for adjuvant chemotherapy included cases of stages IC and higher, and stage IA/IB with tumor size >10 cm. Four patients who had indications for adjuvant chemotherapy defaulted and were eventually lost to follow-up. One of the patients as elaborated earlier underwent neoadjuvant chemotherapy, surgery followed by adjuvant chemotherapy. This one particular patient received paclitaxel and carboplatin—six cycles in total, while the rest received four cycles of bleomycin, etoposide, and cisplatin.

Our median follow-up was for 30 months ranging between 2 and 72 months. Patients were followed up with serum inhibin B after 2007, and an imaging study was performed based on clinical suspicion or raised inhibin levels. Eleven (45.83%) remained disease free, nine (37.5%) had recurrence, and four (16.6%) were lost to follow-up. Among the six patients who underwent fertility sparing surgeries, four had relapses (66.6%), three of whom had juvenile GCT. Two (33.3%) had successful obstetric careers and underwent completion surgery later and remained disease free.

We then analyzed various factors to correlate with recurrence and FFS. There was a statistically significant difference in FFS with respect to tumor-related factors such as presence of hemorrhage (median time of recurrence: 31 vs. 53 months,  $p = < 0.001$ ), larger tumors of >10 cm (median time of recurrence: 43 vs. 62 months,  $p = 0.042$ ), and juvenile variant (median time of recurrence: 23 vs. 57 months,  $p = 0.002$ ). But on the contrary, when treatment-related prognostic factors were considered, there was no statistically significant improvement in FFS with the performance of lymphadenectomy (median time of recurrence: 43 vs. 60 months,  $p = 0.218$ ), omentectomy (median time of recurrence: 50 vs. 55 months,  $p = 0.453$ ), and fertility sparing surgery (median time of

**Table 1** Prognostic factors

Factor	Total No.	Percentage	Recurrences	Percentage	Median recurrence (mo) <sup>a</sup>	Log-rank (Mantel–Cox)
Hemorrhage, No.	11	(11/24) 45.83	0	(0/11) 0	53	
Yes	13	(13/24) 54.16	9	(9/13) 69.23	31	< 0.001
Size of tumor						
≤ 10 cm	8	(8/24) 33.3	1	(1/8) 12.5	62	0.042
> 10 cm	16	(16/24) 66.6	8	(8/16) 50	43	
Histopathology adult	21	(21/24) 87.5	6	(6/21) 28.5	57	
Juvenile	3	(3/24) 12.5	3	(3/3) 100	23	0.002
Lymphadenectomy						
No	14	(14/24) 58.33	4	(4/14) 28.57	60	0.218
Yes	10	(10/24) 41.66	5	(5/10) 50	43	
Omentectomy						
No	8	(8/24) 33.33	2	(2/9) 22.2	55	
Yes	16	(16/24) 66.6	7	(7/9) 77.7	50	0.453
Fertility sparing surgery						
No	18	(18/24) 75	5	(5/18) 27.77	58	
Yes	6	(6/24) 25	4	(4/6) 66.6	36	0.152
Adjuvant chemotherapy						
Defaulters	4	(4/24) 16.6				0.45
No	10	(10/24) 41.6	3	(3/10) 30	45	
Yes	10	(10/24) 41.6	6	(6/10) 60	41	

<sup>a</sup>Rounded off to the nearest round figure.

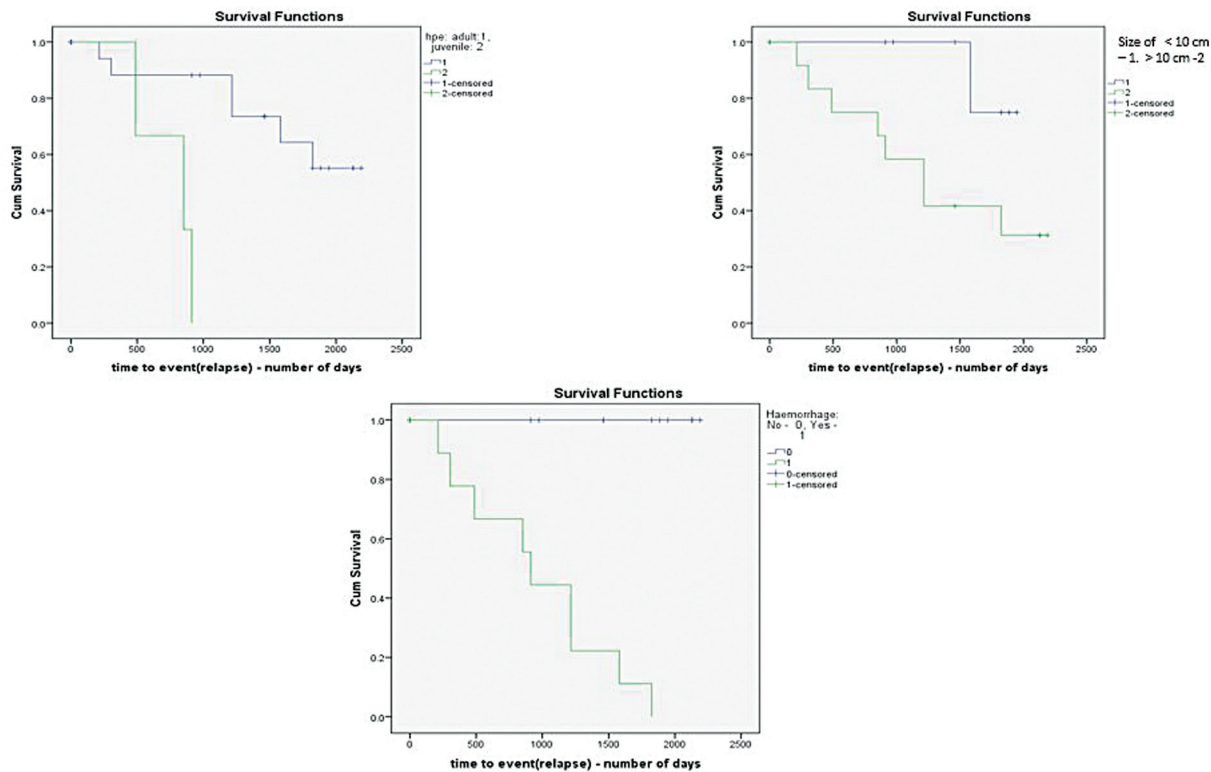
recurrence: 36 vs. 58 months,  $p = 0.152$ ). Considering adjuvant treatment, there were four defaulters, 10 who received and 10 who did not require adjuvant chemotherapy. There was no statistically significant difference noted between the two groups (median time of recurrence: 41 vs. 45 months,  $p = 0.45$ ). All the factors are tabulated in **Table 1** and Kaplan–Meier curves are depicted in **Figs. 1** and **2**.

## Discussion

GCT comprises 2.66% of all ovarian tumors in our institute which was less when compared with data published by Uygun et al, which was 4.9%.<sup>7</sup> The median age in our study (43 years) was relatively lesser compared with other studies, which were between 50 and 55 years.<sup>6,8,9</sup> Our cohort had 62.4% of the patients who were either unstaged or partially staged without lymphadenectomy, which was in concordance with 60.2% stated by Sakr et al in a SEER data review of 1,815 patients published in 2016.<sup>10</sup> When individual stages were considered, we had majority of the patients (29.16%) in stage I disease, which was in concordance with the review data. Although, histopathologically we had relatively more cases of juvenile GCT (12.5%) when compared with 1.15% of them in their data.<sup>10</sup> Fifty percent of our

patients received adjuvant chemotherapy which was comparable (51.42%) to that of Auranen et al.<sup>6</sup> But it was much higher when compared with a study of the role of adjuvant chemotherapy by Meisel et al,<sup>9</sup> which stood at 8.47%. We had a recurrence rate of 25% with a median follow-up period of 30 months, which was comparable with 21 and 27% stated in the previous two studies.<sup>6,9</sup>

Due to rarity of the disease, there has been little evidence which pointed out with certainty of any prognostic associations. Only recently, a National Cancer Database study by Seagle et al<sup>8</sup> with a cohort of 2,680 patients, a SEER data review of 1,815 patients by Sakr et al,<sup>10</sup> and a study on the role of adjuvant chemotherapy in GCT by Meisel et al<sup>9</sup> have shed some light on this aspect. The three aforementioned studies state the stage of the tumor as a statistically significant prognostic indicator. Our study indicates statistically significant results with respect to FFS when tumor-related factors like presence of hemorrhage ( $p < 0.001$ ), larger tumors ( $p = 0.042$ ), and juvenile variant ( $p = 0.002$ ) were considered. SEER review also supported this aspect, by revealing that patients with tumors greater than 5 cm had significantly worse 10-year overall survival (OS; 98.1 vs. 85.1%,  $p < 0.05$ ). Findings of National Cancer Database are in concordance with this. Although, one of the noteworthy



**Fig. 1** Kaplan Meir survival curves of tumor related factors.

highlights of our study is that hemorrhagic tumors have a remarkably poorer prognosis, making it a novel new prognostic factor to be studied into in further detail.

The surgical procedure for GCT remains enigmatic. There are a few studies quoted in the literature which recommend against lymphadenectomy<sup>11-13</sup> in view of low lymph-node positivity rates in these cases, to the tune of 3.1%.<sup>8</sup> However, in the recent SEER review data, lymphadenectomy in adult GCT was associated with significantly better OS (89.8 vs. 71.2%,  $p < 0.05$ ).<sup>10</sup> The National Cancer Database study states that lymphadenectomy in GCT is still debatable and that there may be a higher yield in advanced cases.<sup>8</sup> Lymphadenectomy in our cohort although did not prove to have any significant benefit in improving FFS. Likewise, our figures did not support omentectomy either. Having said that, Seagle et al<sup>8</sup> have stated that a complete surgical staging defined as hysterectomy with b/l salpingo-oophorectomy to have lesser hazard of death. At this point considering fertility sparing procedures, we had a recurrence rate of 66.6% and a conception rate of 33.3%. Both these figures stood much higher than that quoted in the literature, where the recurrence rate ranged between 9.8 and 27.4%, while the conception rate stood only at 10%.<sup>14</sup> With these figures, it is prudent to discuss the risks and benefits of fertility sparing surgeries with patients and offering completion surgery after completion of family.

Likewise there has been a debate about the benefits of adjuvant therapy, guidelines for indications, and the most effective agents. Currently, NCCN (National Comprehensive Cancer Network) recommends either paclitaxel and carbo-

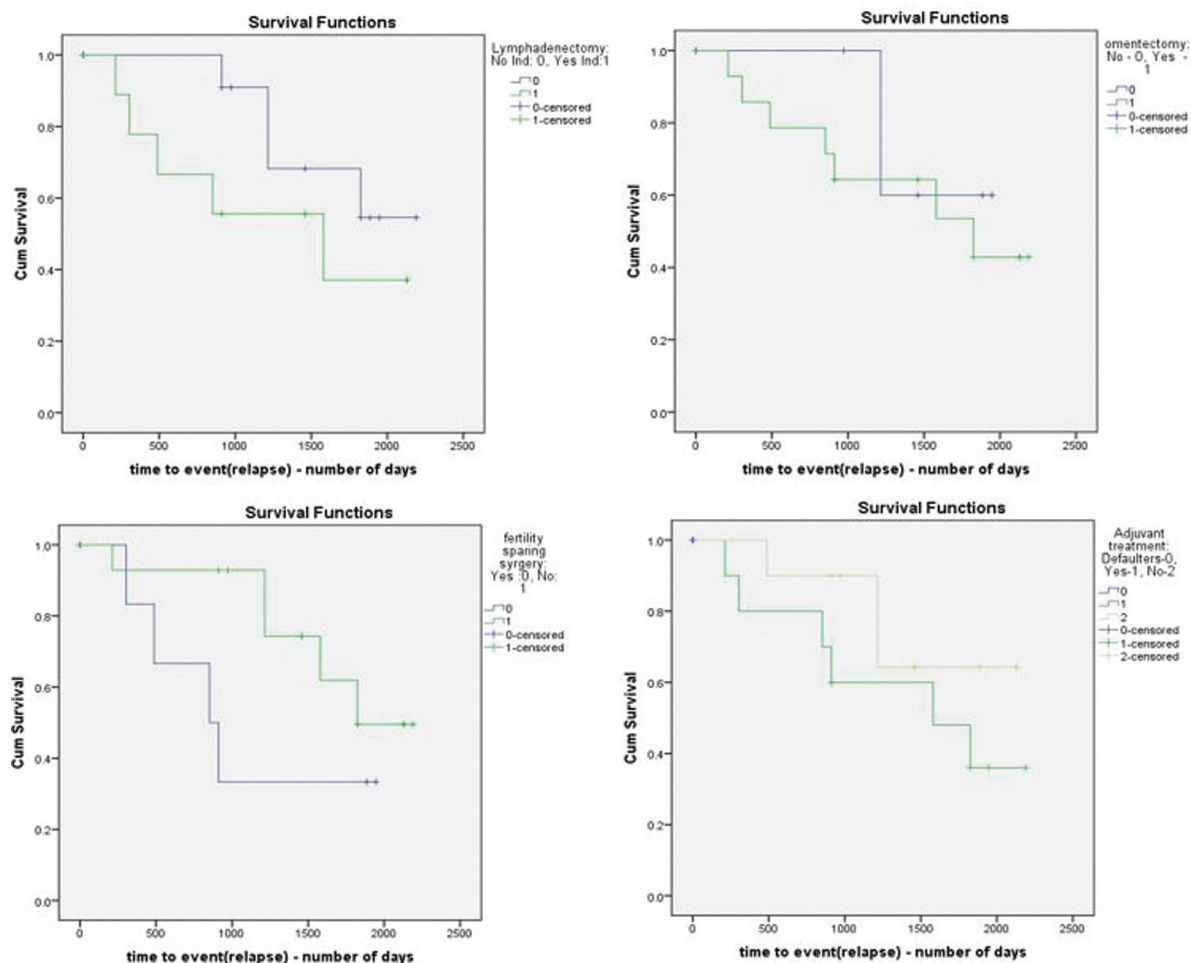
platin or bleomycin, etoposide, and cisplatin (malignant germ cell tumor) regimens for stage II to IV GCT.<sup>15</sup> There are multiple studies which show no clinical benefit from adjuvant chemotherapy,<sup>7,11,16-20</sup> while certain others have shown survival benefits.<sup>6,8-10,21-26</sup> Meisel et al<sup>9</sup> in turn reported a trend of earlier recurrence of patients who underwent adjuvant therapy. In concordance with the most recent evidence, our study also points toward no FFS benefits with adjuvant chemotherapy.

Late recurrences are a hallmark of GCT, to the tune of 3 to 4 decades after treatment completion has been reported. Literature quotes that approximately 47% of recurrences occur after 5 years.<sup>27</sup> Our study reported a median period of recurrence of 40 months (10-60 months).

Shortcomings of this study include an inadequately powered study with reference to small sample size, retrospective nature, and inhomogeneous cohort. Also notable is the relatively short follow-up time considering the tendency of these tumors to very late recurrences.

## Conclusion

Inherent tumor-related biological factors tend to play a more important role compared with treatment-related factors in GCTs. Hence, the traditional practice of performance of extensive staging procedures and routine adjuvant chemotherapy should be reviewed. Fertility preserving surgery appears safe to be offered in early stages when desired. Although it is common knowledge that GCTs tend to be hemorrhagic tumors, this factor has not been well



**Fig. 2** Kaplan Meir survival curves of treatment related factors.

recognized as a prognostic indicator till date. Our study sheds some light on this aspect. Since these tumors have a tendency toward late recurrences, a long follow-up is prudent.

#### Source of Support

None.

#### Conflict of Interest

None.

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