A 20 YEARS' EXPERIENCE ON GRANULOSA CELL TUMOUR

P. Jovita M. Martin[1], Kalaichelvi K[2], Lakshminarasimhan[3], Ramkumar[4], Dheenadhayalan[5]

[1]Assistant Professor, Department of Medical Oncology, SRMC, Chennai, Tamilnadu, India.
[2]Professor, Department of Medical Oncology, Madras Medical College, Chennai, Tamilnadu, India.
[3]Professor, Department of Medical Oncology, SRMC, Chennai, Tamilnadu, India.
[4]Associate Professor, Department of Medical Oncology, IOG, Egmore, Chennai, Tamilnadu, India.
[5]Resident, Department of Medical Oncology, Madras Medical College, Chennai, Tamilnadu, India.

ABSTRACT

BACKGROUND

The prognostic factors and the recurrent nature of Granulosa cell tumour is unclear. Chemotherapy has a compelling role in locally advanced cases, inoperable cases and metastatic cases. This retrospective study results elucidate the need for chemotherapy in advanced cases which then translates to a better overall survival benefit, increased disease free survival and delay in progression. The prognostic factors and the recurrent nature of Granulosa cell tumour is unclear and unpredictable added to the fact that these tumours are rare and have an indolent course. There is only a scarce data on the optimum treatment for this group of patient.

The aim of this study was to pursue the clinico-pathological features and prognostic factors for the recurrence patterns and the optimal management of these cases.

MATERIALS AND METHODS

This is a descriptive study with secondary data from records. A retrospective multi-institutional review of patients with GCTs of the ovary treated or referred were analysed. Surgical outcome, pathological details, chemotherapy details, follow-up details, relapse pattern and the treatment of the relapse disease were analysed. Kaplan-Meier survival analysis was used to determine the prognostic and predictive markers for survival.

RESULTS

This is an analysis of the survival rate and the treatment results of Granulosa cell tumour between 1995 and 2015 over a period of 20 years. We have analysed the results of 126 patients, of which 53 patients (42%) were premenopausal and 73 patients (58%) were postmenopausal. Out of the 126 patients 84 patients had complete surgical staging which constitutes transabdominal hysterectomy and bilateral salpingo-oophorectomy and a staging laparotomy, 35 patients had incomplete or suboptimal surgery, 7 patients had fertility sparing operation. The 67 patients who had complete surgery and early stage disease with no risk factors were on observation. These patients have not had relapse. A dataset of 34 relapsed granulosa cell tumour patients were analysed. Out of these, 19 patients have survived cancer. Out of 34 cases, 10 patients had complete surgery and 15 patients had incomplete surgery including fertility preserving surgery. Kaplan-Meier survival analysis results show that cancer was cured by complete surgery followed in chemotherapy wherever high-risk factors were present, whereas the survival rate drastically declined in the cases of incomplete surgery without adjuvant chemotherapy. For patient's stage of cancer size of the tumour, type of surgery done, tumour spill, histopathology and chemotherapy in positive high-risk parameters have relatively more effect on survival chance.

CONCLUSION

Granulosa cell tumours are known for their rarity. Chemotherapy has a compelling role in locally advanced cases, inoperable cases, metastatic cases, in cases with tumour spill or rupture, certain histopathological variants (such as juvenile granulosa cell tumour, yolk sac tumour) and tumours > 9 cm. Other factors which do contribute to the prognosis would be age at diagnosis, nuclear atypia, mitotic index, surgical method and presence of residual disease after initial surgery.

KEY WORDS

Granulosa Cell Tumour, Recurrence of Granulosa Cell Tumour.

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BACKGROUND

Ovarian sex cord stromal cells are known for their rarity comprising of 2 - 3% of all primary ovarian cancers.

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Corresponding Author:
P. Jovita M. Martin,
AG Alsa Deer Park,
#108, Velechery Main Road,
Huindy, Chennai-32,
Tamilnadu, India.
E-mail: jovimartin4@gmail.com
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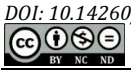


They are known for their heterogeneity as well. From benign to malignant subtypes, there are several varieties known. They develop from the proliferating cells which produce cells to support and surround oocytes, which includes the cells that produce ovarian hormones. The different types of sex cord stromal tumours include fibroma-thecoma, granulosa cell tumour (adult and juvenile, which differentiates into female characteristics), Sertoli-Leydig cell tumour (which differentiates into male characteristics). Granulosa cell tumour have the most common malignant potential among the sex cord stromal cell tumours as described by Rokitansky in 1855.[1]

The adult subtype is often seen in the middle aged and old aged women with a median age of 50 - 54 years. The juvenile

subtype comprises of only 5% of the total sex cord stromal tumours, typically develop before puberty, common in children and young women being highly proliferative but with a lower risk of recurrence.[2]

Malignant sex cord tumour cells are diagnosed at an earlier stage and are considered to be low-grade malignancies compared to the primary ovarian cancers. Granulosa cell tumour present with features of hyper-oestrogenism such as abnormal vaginal bleeding and precocious puberty.[3]

Complete surgery is the main stay of the management in early stages. Adjuvant platinum-based chemo is indicated in advanced stages. Though granulosa cell tumours have favourable prognosis, late relapses are known to occur due to the indolent nature of the disease. Advanced disease has a poor prognosis with 5-year survival rate of 0 - 20% in comparison to epithelial ovarian cancer.[4]

The most common prognostic factors known in granulosa tumours are age, tumour size, tumour stage, bilaterality, post-op residual tumour status and high mitotic index.[5-15]

The prognostic factors and the recurrent nature is unclear and unpredictable added to the fact that these tumours are rare and have an indolent course. There is only a scarce data on the optimum treatment for this group of patients. The present study is conducted to pursue the clinico-pathological features and prognostic factors for the recurrence patterns and the optimal management of these cases.

MATERIALS AND METHODS

This is a descriptive study with secondary data from records. All cases of histologically proven and treated patients between 1993 and 2015 in the Department of Obstetrics and Gynaecology were analysed retrospectively with the medical records. Information on the patient's characteristics, clinical presentation, International Federation of Gynaecology and Obstetrics Staging (FIGO), surgical details, adjuvant details, recurrences, management of recurrences and follow-up until 2015 were analysed.

Size of the tumour was ascertained by preoperative ultrasound or computer tomography. All patients had surgery. The complete staging laparotomy included total abdominal hysterectomy + bilateral salpingo-oophorectomy with optimal resection (RO), omentectomy, +/- lymphadenectomy and multiple biopsies. All other surgeries constituted partial surgical staging. Fertility preserving surgery or fertility sparing surgery was defined as preservation of the uterus and at least one adnexa. In advanced stages, patient received chemotherapy. Other patients were put on active surveillance.

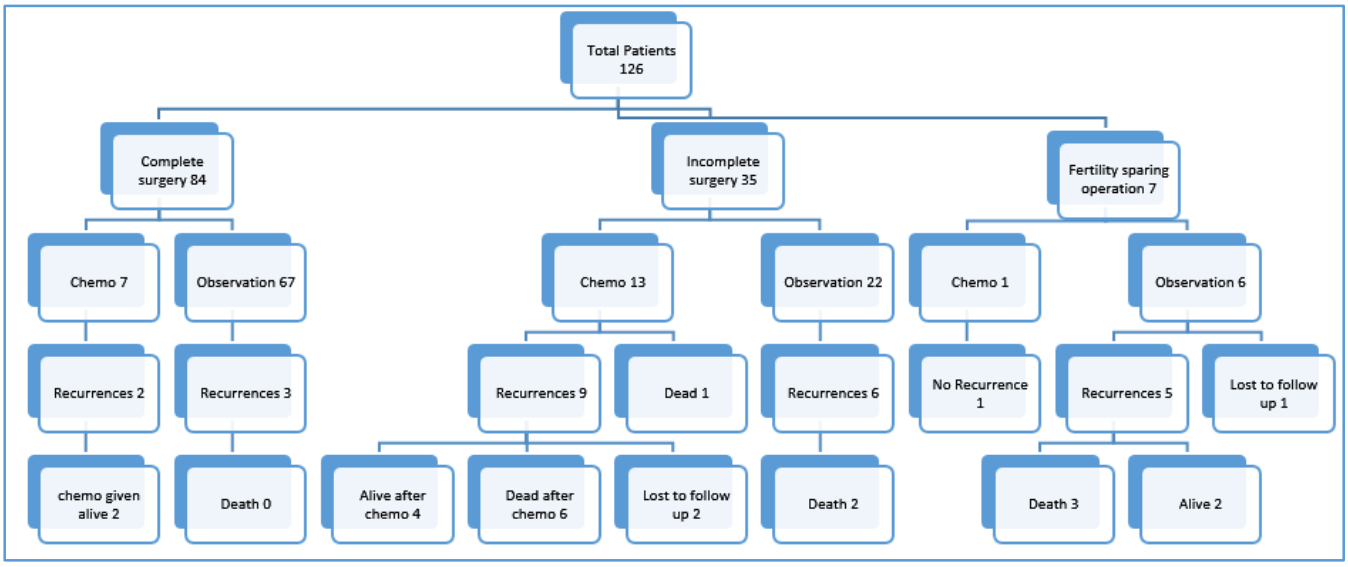
Characteristics

Age	Percentage
<10	3
10-19	3
20-29	17
30-39	20
40-49	28
50-59	28
60-70	26
>70	1
Median Age	

Total 126 patients- Premenopausal 58 patients and Postmenopausal 44 patients.

Symptoms	N%
Abdominal pain	40
Palpable mass	20
Abdominal distension	6
Precocious puberty	2
Virilisation	2
Mastalgia	1
Menorrhagia	33
Postmenopausal bleeding	24
Secondary amenorrhea	0
Constipation	0
Urinary tract symptoms	0

Surgical Approach: Laparotomy and Laparoscopy	126 (100%) n (%)
FIGO Stage	N (%)
Ia	79
Ib	14
Ic	11
IIa	1
IIb	1
IIc	2
IIIa	7
IIIb	4
IIIc	4
IV	3
Surgical staging	n(%)
Complete surgical staging	85
Incomplete surgical staging	41
PLND	n(%)
No	44
Yes	82
Fertility sparing surgery	n(%)
Yes	10
No	116
Postoperative residual tumour	n(%)
Yes	41
No	85
Intraoperative tumour rupture	n(%)
Yes	5
No	121



Flow Chart showing the number of patients who relapsed and their Treatment Results

Out of the 84 patients who had complete surgery, those who had chemotherapy did not show recurrence. Out of the 77 patients who were on observation, 3 patients had recurrences.

1	45	IIIc AGCT	> 10 cm	Incomplete Surgery	15 months	Pelvis and LN and Left adnexa	2 lines of chemo, CDDP + VCR, then CDDP + VP16 oral Endoxan	Alive with disease 90 months	Alive
2	55	IIIc AGCT	12 cm	Incomplete Surgery	5 months	Myometrial infiltration present upfront, relapsed in pelvis	2 lines of chemo, CDDP + VCR, then CDDP + VP16	Lost for follow-up by 16 months	LTFU
3	35	Ic SCST	9 cm	Complete Surgery	89 months	Omentum + Pelvis	CDDP + Ctx 6 cycles chemo, then CDDP + Etoposide	123 months alive	Alive
4	56	IIIc SCST	8.1 x 8.1 cm	Incomplete Surgery	3 months	Pelvis	BEP	at 3 months	Died
5	42	Ic AGCT	25 cm	Incomplete Surgery	11 months	Pelvis	Initially no chemo, Ctx + CDDP 6 cycles, then CDDP + Etoposide x 6 cycles	133 months on follow-up alive	Alive
6	65	Ia AGCT	8 x 9	Complete Surgery	12 months	Pelvis	No initial chemo, 4 cycles CDDP + CTx chemo	Alive 150 months	Alive
7	26	IV AGCT	20 cm	FSO	25 months	Pelvis	CDDP + Bleo + Vinb 3 cycles initially PR, then 2 years on Endoxan	Dead at 8 months	Died
8	25	IIIc AGCT	NA	Incomplete Surgery	24 months	Omentum + PAN	Initially no chemo, PEB; VAC; CDDP + Ctx each 6 cycles	Alive 132 months	Alive
9	42	IV SCST	10 cm	Incomplete surgery	26 months	Liver	3 cycles chemo initially, then 6 cycles EP	Dead at 35 months	Died
10	18	Ic SCST	9 cm	FSO	Progressed at 11 months	Pelvis	2 lines chemo	Dead at 23 months	Died
11	14	Ia JGCT	10 cm	FSO	Progressed at 7 months	Pelvis	EP	Dead at 7 months	Died
12	23	Ic androgen secreting	7 x 9 cm	FSO	8 months	Pelvis	PEB 4 cycles	Alive 85 months	Alive
13	40	Ia AGCT	9 x 9cm	Complete surgery	10 months	nil	CDDP + CT x 6 cycles alone	Alive 87 months	Alive
14	44	Ic AGCT	NA	FSO	26 months	Pelvis	No initial chemo, 6 cycles CDDP + Ctx	Alive 120 months	Alive
15	30	IV AGCT	NA	Incomplete surgery	Progressed	Pelvis	CDDP + VP16 4 cycles, then 3 cycles	Dead at 2nd month	Died
16	48	IIIa AGCT	NA	Complete surgery	At 76th month	Pelvis	No initial chemo, 6 cycles CDDP + Ctx	98 months alive	Alive
17	40	IIIc AGCT	18 x 20 cm	Incomplete surgery	Progressed	Omentum	6 cycles CDDP + Ctx	5 months dead	Died
18	60	IIIa AGCT	NA	Complete	No relapse	nil	6 cycles alone	43 months	Alive

				Surgery				Alive	
19	57	Ia AGCT	15 x 10 cm	Complete surgery	No relapse	nil	5 cycles alone	72 months alive	Alive
20	42	IIIc AGCT	NA	Incomplete surgery	Defaulted	Omentum, Pelvis	Defaulted	Dead at 3 months	Died
21	50	IIIc AGCT	NA	Complete surgery	No relapse	nil	6 cycles chemo alone	126 months Alive	Alive
22	58	IIIC AGCT	8 x 8 cm	Complete surgery	30th month	Pelvis	6 cycles chemo initially post-surgery after relapse CDDP + Etoposide; PVB	At 61 months alive	Alive
23	48	Ic AGCT	NA	Complete surgery	37th month	nil	6 cycles alone	Alive 148 months	Alive
24	21	IIIc JGCT	NA	FSO	Defaulted	Pelvis	2 cycles	Lost for follow-up	LTFU
25	38	IIa AGCT	10.6 x 11.94 cm	Optimal surgery	10 months	Pelvis, Omentum	6 cycles initially	83 months alive	Alive
26	21	Ia AGCT	10 cm	FSO	12 months	Liver	CDDP + Etoposide 6 cycles	Dead at 14 months	Died
27	52	Ia AGCT	NA	Incomplete Surgery	24 months	Omentum and PAN	Initially no chemo, 2 lines chemo	Alive at 140 months	Alive
28	55	Ia AGCT	6 cm	Incomplete surgery	24 months	Liver	Defaulted	Dead at 26 months	Died
29	19	Ia AGCT	10 cm	FSO	13 months	Omentum and Pelvis	Initially no chemo, 3 lines chemo	Alive 98 months	Alive
30	28	Ia AGCT	7 cm	Complete Surgery	75 months	Pelvis	Initially no chemo, 2 lines	Alive 75 months	Alive
31	44	Ic AGCT	11 x 12 cm	Incomplete Surgery	23 months	Pelvis	Initially no chemo, CDDP+ Ctx, then CDDP + Etop	Alive 85 months	Alive
32	54	IIIc AGCT	9 x 10 cm	Incomplete Surgery	16 months	Pelvis	Initially no chemo, CDDP+ Ctx, then CDDP + Etop then PVB	LTFU at 28 months	LTFU
33	60	IIIC AGCT	13 x 13	Incomplete Surgery	12 months	Pelvis	CDDP + CTx, then CDDP + Etop	Dead at 27 months	Died
34	67	IIC AGCT	10 x 10	Incomplete Surgery	24 months	Pelvis	CDDP + CTX 6 cycles, then CDDP + Etop	Dead at 33 months	Died
Details of Chemotherapy in the Patients									

Statistical Analysis

The collected data was analysed with IBM SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis was used. For survival analysis, the Kaplan-Meyer curve with log-rank method was used for the comparison of groups. In the above statistical tools, the probability value of .05 will be considered as significant level. Kaplan-Meier analysis is one of the best ways to measure the proportion of patients living for a certain amount of time after treatment. The time starting from a defined point to the occurrence of a given event, for example death is called as survival time and the analysis of group data as survival analysis. The effect of an intervention is assessed by measuring the number of patients survived after that intervention over a period of time.

The chance of occurrence of events over a period of time is computed and multiplying these successive probabilities by any earlier computed probabilities will give the final estimated values, which are used for plotting survival curves.

RESULTS

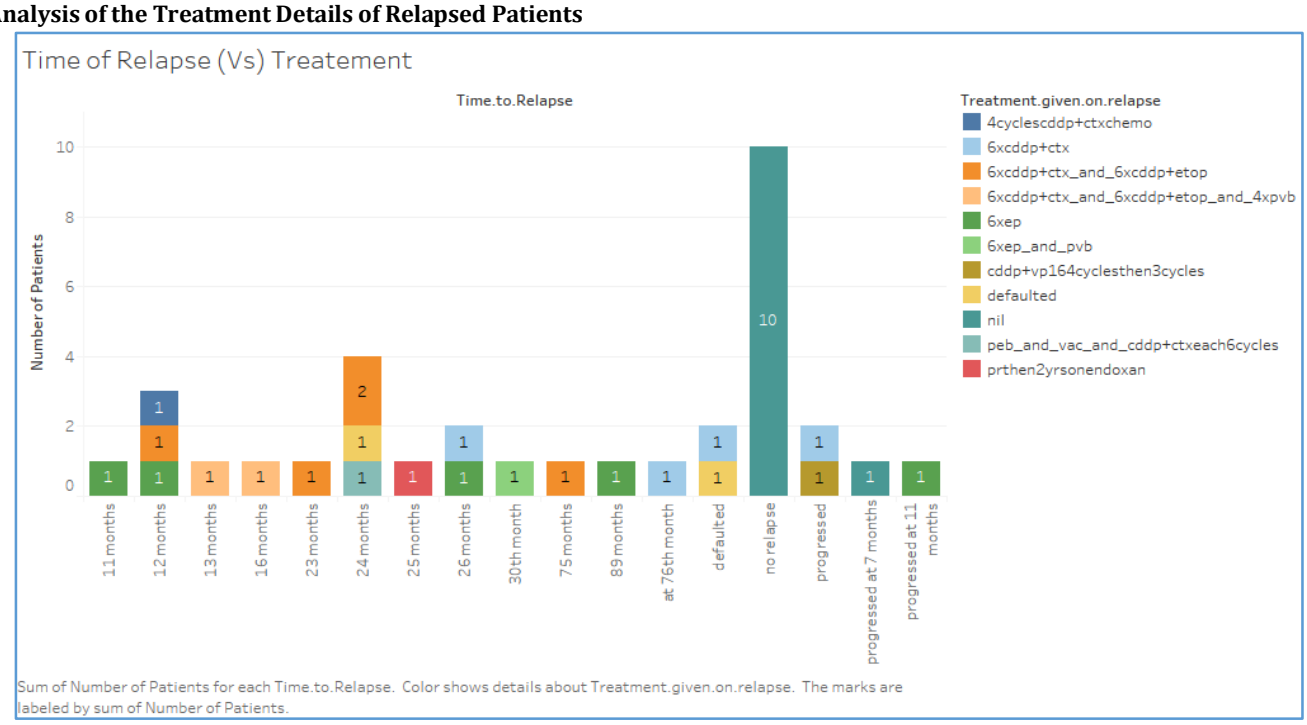
This is an analysis of the survival rate and the treatment results of Granulosa cell tumour between 1995 and 2015 over a period of 20 years. We have analysed the results of 126 patients, of which 53 patients (42%) were premenopausal and 73 patients (58 %) were postmenopausal. Out of the 126 patients, 84 patients had complete surgical staging which constitutes transabdominal hysterectomy and bilateral salpingo-oophorectomy and a staging laparotomy, 35 patients had incomplete or suboptimal surgery, 7 patients had fertility sparing operation. The 67 patients who had complete surgery and early stage disease with no risk factors were on observation. These patients have not had relapse. 7 patients after complete surgical staging had chemotherapy with Cisplatin and Cyclophosphamide. Amongst them 2 patients had recurrence and were given chemo with good response surviving. Out of the 35 patients who had incomplete surgery, 13 patients had adjuvant chemo with Cisplatin and Cyclophosphamide and 22 patients were on observation. Amongst the 22 patients who were on observation 6 patients recurred and were treated with 2 - 3 lines of chemo. Out of the 6 patients, 4 patients are alive, and 2 patients died due to progressive treatment. In the 13 patients who had chemo, one relapsed and died without any 2nd line chemo. 9 patients recurred were given 2nd line chemo with Cisplatin and Etoposide and 3rd line with Cisplatin, Vinblastine and Bleomycin or Bleomycin, Etoposide and Cisplatin. 7 patients had fertility sparing surgery and one of them had adjuvant chemo with no relapse. The 6 patients who did not have adjuvant chemo recurred. Amongst, the 6 patients 1 was lost for follow-up, 3 patients died after 2nd line chemo and 2 patients are alive.

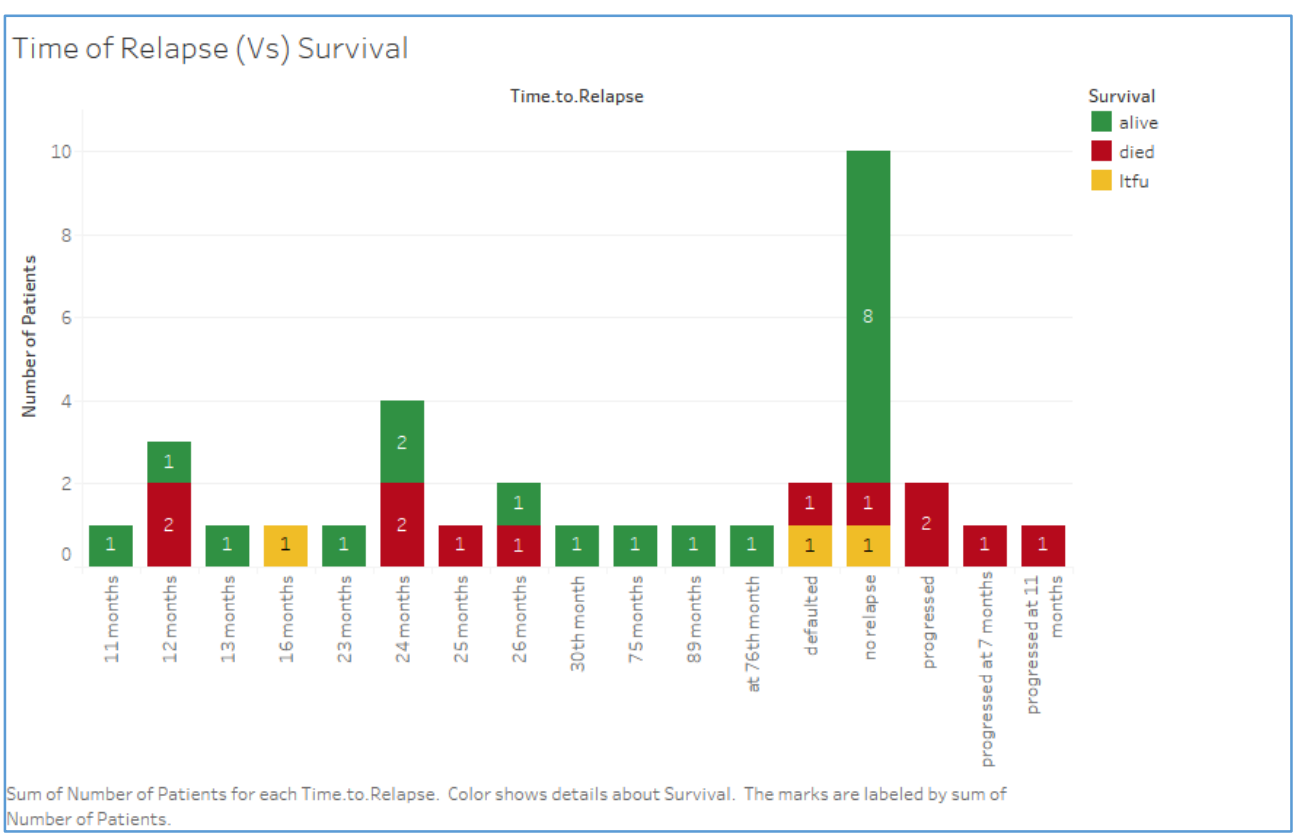
On analysing the chemotherapy details and the pattern of failure, there were few points which were clear. In the

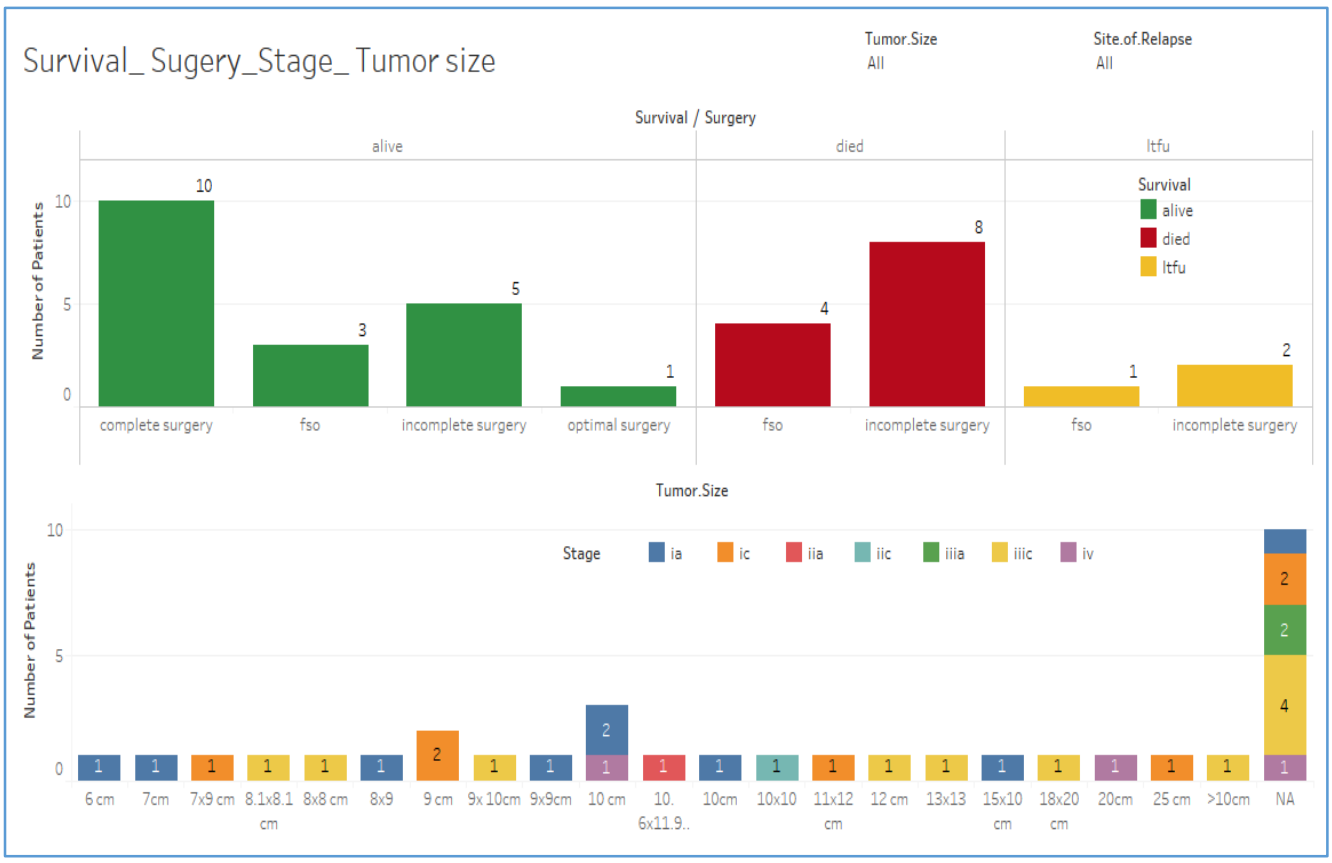
complete surgery group, those with adjuvant chemo did not relapse. Those who relapsed were treated with chemo and had good response to treatment and survived. Those with incomplete surgery had increased risk of recurrence, especially when the size of the tumour was > 9 cm, when there was tumour spill and when the stage was advanced. In the fertility sparing group also, those with lower stage with chemo did better than those with late stage disease, those without chemo or with increased risk factors.

A dataset of 34 patients is analysed, out of these 19 patients have survived cancer. Out of 34 cases, 10 patients had complete surgery and 15 patients had incomplete surgery. Kaplan-Meier survival analysis results show that cancer was cured by complete surgery followed by chemotherapy wherever high-risk factors were present, whereas the survival rate drastically declined in the cases of incomplete surgery without adjuvant chemotherapy. For patients, stage of cancer, size of the tumour, type of surgery done, tumour spill, histopathology, chemotherapy in positive high-risk parameters, has relatively more effect on survival chance.

Analysis of the Treatment Details of Relapsed Patients



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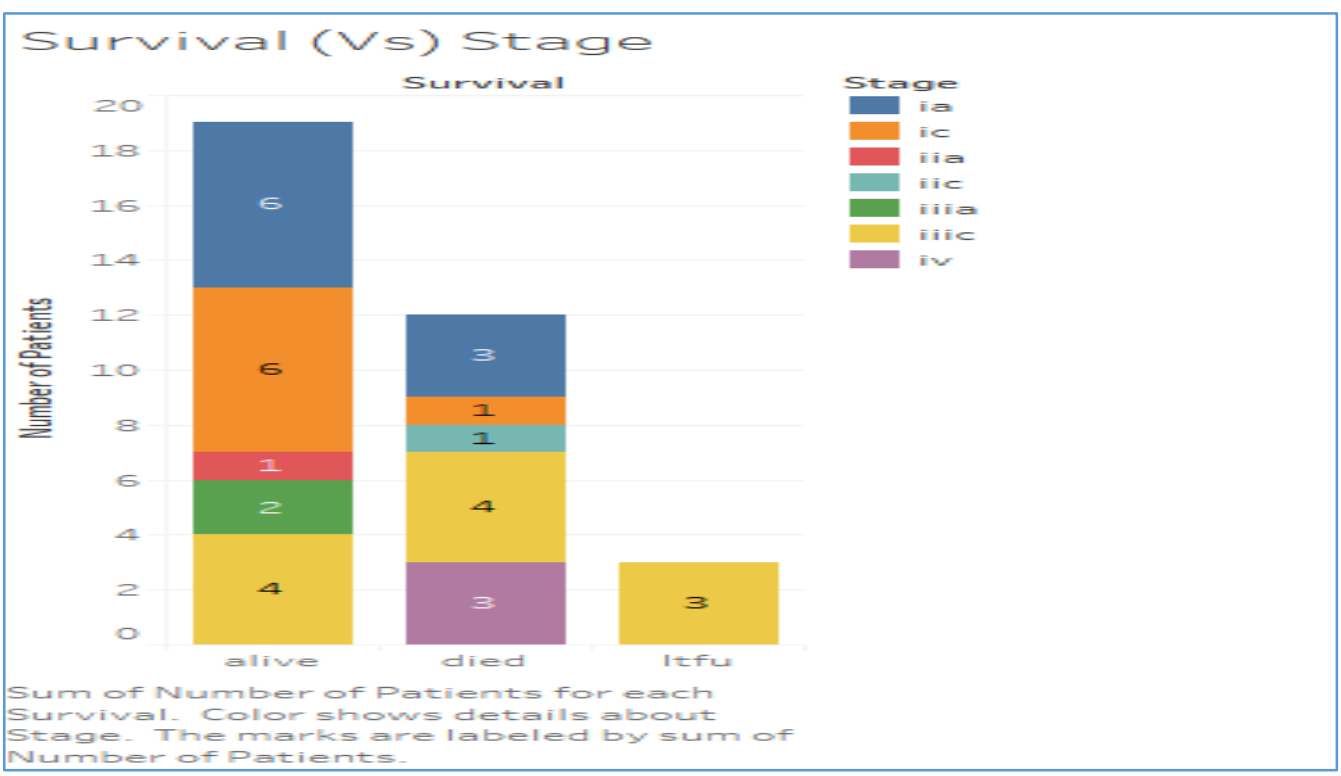
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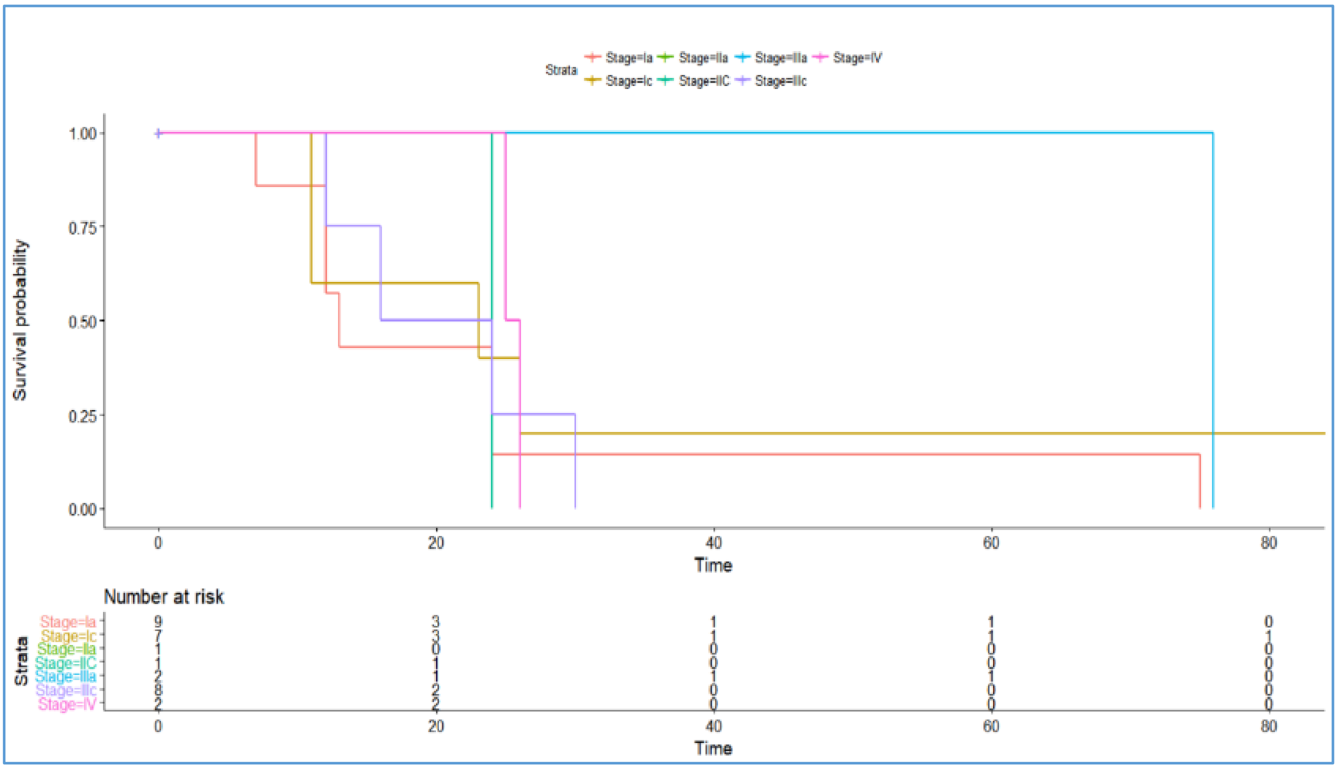
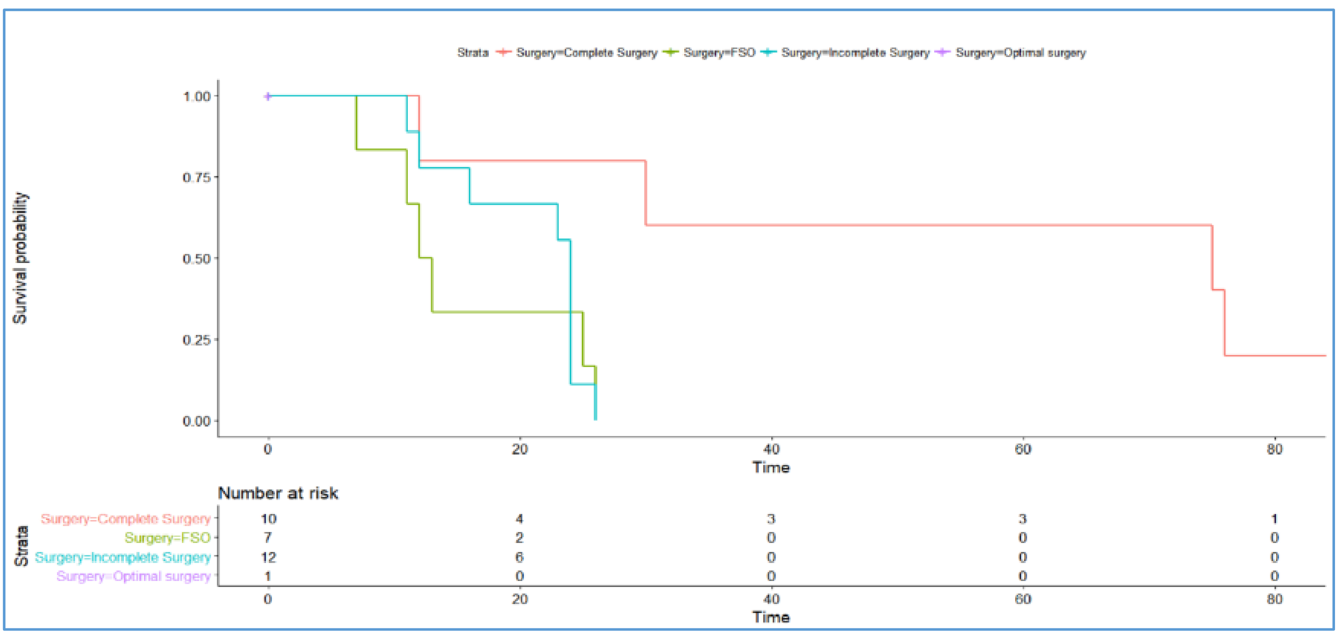
Sum of Number of Patients for each Survival. Color shows details about Stage. The marks are labeled by sum of Number of Patients.

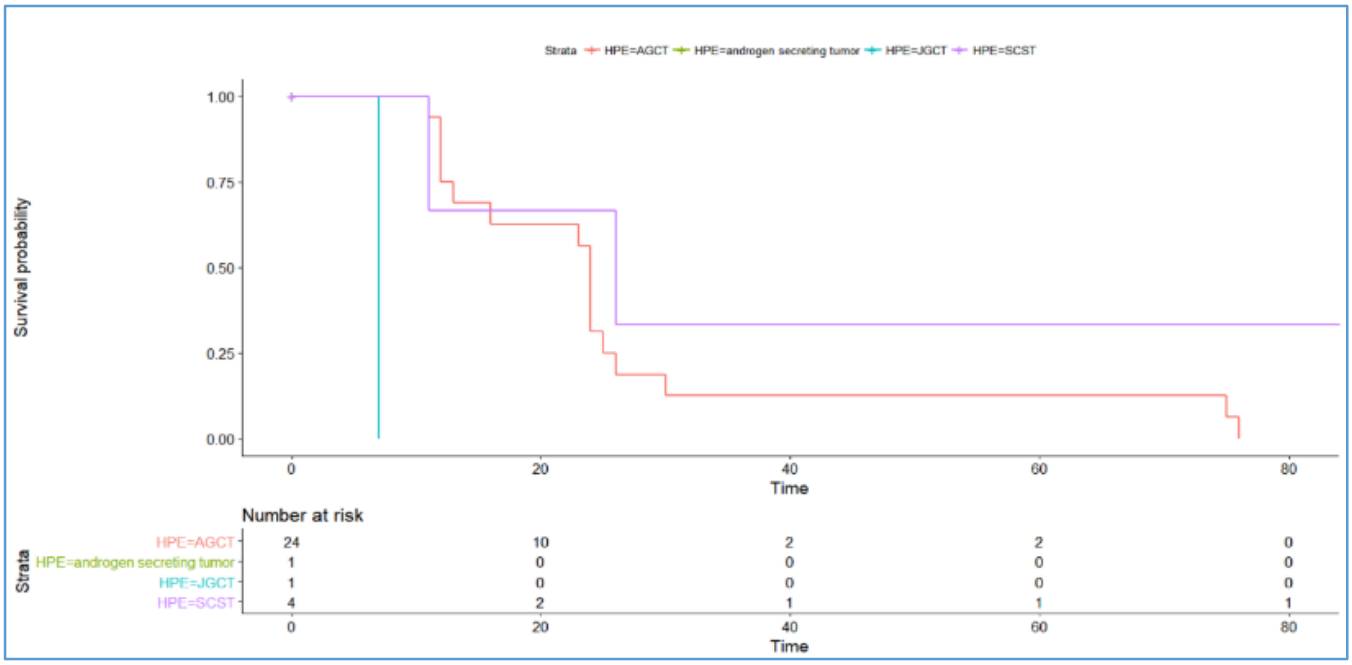
Survival Plot with Respect to Stage



Survival Plot with Respect to Surgery



Survival Plot with Respect to Histopathology



DISCUSSION

Granulosa cell tumours are a subtype of malignant sex cord stromal tumours. It has two histological types, namely adult 95% and juvenile 5%. Adult type occurs in postmenopausal women in the 5th decade with favourable prognosis. Juvenile type occurs in younger age with severe symptoms and signs and increased risk of recurrence implicating poorer prognosis. Hyperoestrogenic symptoms have been reported in a retrospective study of 118 patients with abnormal uterine bleeding, hyperplastic endometrium. It can also produce precocious puberty, mastalgia and galactorrhoea.[4]

Granulosa cell tumours radiologically presents as a solid tumour with cystic component with a median size of 12 cm.[5] Diagnosis of granulosa cell tumour is through histopathology. The adult form has 5 subtypes the most common is microfollicular with call exner bodies. The Juvenile form is with macrofollicular with lobulated architecture and few call-exner bodies. The common immunohistochemical markers expressed by these cells are alpha inhibin, CD 99, Vimentin; serum tumour markers are inhibin, estradiol, anti-Mullerian hormone.[6] Serum CA-125 are not of any significance in this tumour variety.[7] FOXL2 gene mutation has been identified in 97% of adult granulosa cell tumour and 10% of juvenile type. The common differential diagnosis with this entity are stromal sarcoma, carcinoid tumour, endometrial cancer and adenocarcinoma. The main modality of treatment here is complete staging laparotomy with transabdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node resection. For women who would like to preserve the fertility in stage I unilateral salpingo-oophorectomy with uterine preservation is done. In majority of the cases, where the tumour is limited to one ovary the patients are just kept of close follow-up with observation. In case, the stage is IC (Tumour size > 10 - 15 cm) or there are high risk features such as tumour rupture or poorly differentiated tumour or advanced stages (Stage III or IV). The outcome is unfavourable, therefore in such cases adjuvant chemotherapy is given.[11] However, the value-add and the significance of the use of the adjuvant chemo is yet to be validated given the rarity of the disease and the difficulty in conducting randomised trial in such rarity. The recommended chemotherapy options available are Paclitaxel + Carboplatin, Bleomycin + Etoposide + Cisplatin (BEP) Etoposide + Cisplatin (EP), Cyclophosphamide + Doxorubicin + Cisplatin (CAP) and platin alone.[10]

In children with juvenile granulosa cell tumour, the usage of adjuvant chemo yields complete and a long-lasting response which is usually given in Stage Ic with a high mitotic index (> 20 per high power field). Long surveillance is recommended in granulosa cell tumour, as these tumours have an indolent course. The median time to relapse ranges from 4 years to 30 years.[12] The sites of recurrence commonly are pelvis, retroperitoneum and upper abdomen. Local relapse is managed with complete resection when feasible. The other chemo regimens in inoperable tumours or the recurrent tumours would be Docetaxel, Paclitaxel + Ifosfamide, Paclitaxel + Carboplatin and VAC.[13] The hormonal treatment used are Tamoxifen alone, Megestrol or in combination which does produce sustained long-term clinical response. The investigational agents in relapse cases includes anti-angiogenic therapy, LHRH antagonist and mTOR inhibitors.[14] Large tumour size > 10 cm is associated with poor prognosis. In Sehouili's trial, survival was lower with suboptimal surgery or residual tumour or tumour rupture.[15,16,17]

CONCLUSION

Granulosa cell tumours are known for their rarity. They occur both in premenopausal and postmenopausal women. Patients who had tumour size of > 10 cm seem to have more recurrence. Juvenile granulosa cell tumour and sex cord stromal tumours have poorer prognosis as compared to adult granulosa tumour. The role of chemotherapy is explicit in operated cases, as adjuvant in high risk group decreasing the recurrence rates. Chemotherapy has a compelling role in locally advanced cases, inoperable cases, metastatic cases, in

cases with tumour spill or rupture, certain histopathological variants (such as juvenile granulosa cell tumour, yolk sac tumour), tumours > 10 cm. Other factors which do contribute to the prognosis would be age at diagnosis, nuclear atypia, mitotic index, surgical method and presence of residual disease after initial surgery.[18,19,20]

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