



Reproductive outcomes of fertility sparing surgeries in germ cell tumours

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Abstract: The main aim of the study is to observe the reproductive outcome in patient of germ cell tumour after fertility preserving surgery. In which retrospective records of patients diagnosed with malignant GCT in young patients treated with fertility sparing surgery and chemotherapy for ten years from 2000 to 2009. From the careful observations concluded the overall survival with the patients treated with fertility sparing surgery is excellent and the reproductive outcome is more or less equivalent to the general population of same age group.

Key words: Germ Cell Tumour; fertility; young patients

Introduction

Ovarian cancer accounts for approximately 26000 cases in US. While majority of the ovarian cancer are of advanced stage and occur in the post-menopausal women; approximately 15% of ovarian cancer is of malignant T germ cell. Ovarian tumour which occur in girl or younger women. Subcategory of this malignant germ cell tumour includes: Sex cord stromal tumour, low malignant potential. Malignant ovarian germ cell tumour comparison approximately 1 to 2 % of all ovarian malignancies. They typically occur in pre-pubertal girl & young women with an average of teenage years with the exception of dysgerminomas unilateral in 15% of cases. They are almost always unilateral furthermore 60% of the tumour is (unilateral) stage I confirmed to ovary. In about 10% of the cases benign cystic teratome is present in the ipsilateral or contralateral ovary.

Table:

Sr. No.	Author	No. of Pattern	No. of normal menses	No. of pregnancies
1	Gershinosis 1998	40	27/48(68%)	22 in 11
2	Brewer 1999	16	13/14(93%)	5 in 3
3	Low 2000	74	43/47(92%)	14 in 19
4	Zanetta 2001	138	80/81(99%)	16 in 41
5	Tangir 2003	64	28/40(69%)	29 in 47
6	Gershinso 2002	133	59/77(77%)	35 in 37

Multimodality therapy includes surgery and chemotherapy or initial chemotherapy followed by surgery. Even advance stage disease has a great outcome. Before the introduction of platinum base chemo therapy for malignant ovarian germ cell tumour before 1980 resulted in-fertility amongst the prepubertal and young age group female patient. With platinum based chemotherapy in the last two decades most of the patients can expect complete cure. The cause of in-fertility in early 1985 and before 1980 to patient receiving chemotherapy revealed that primary lesion was follicle destructions and ovarian stromal fibrosis. Factors such as cumulative drug dose, duration of chemotherapy age of the patient at the time of treatment were thought to be the most influential factors for ovarian dysfunction.

In addition, several studies to indicate that prepubertal ovary are more resistant to adverse effect of chemotherapy. During last two decades, several reports suggest successful

pregnancies after treatment not only of malignant germ cell tumour but also other malignancies of childhood which includes Hodgkin's lymphomas, breast cancer, malignant melanoma and others. However, there is significant risk of premature menopause in young women receiving chemotherapy. These were associated with the drug administered. The risk occurs in women of age 25 to 35. Several reports have documented successful pregnancies in young patient who underwent fertility sparing surgeries and combination of chemotherapy for malignant ovarian germ cell tumours.

Gershenon reports successful pregnancies in young patient who previously underwent fertility sparing surgeries followed by combination chemotherapy. At the time analysis, out of the 40-patient studied 33 had normal menses (88%). 16 patient who attempted pregnancies 11 delivered 22 healthy infants. None of whom has birth defects.

Brewer *et al.*, reported their experience with 26 patients treated with surgery and platinum based chemotherapy for ovarian dysgerminomas, of the patient who underwent fertility sparing surgeries and chemotherapy 71% has maintain normal menstrual function and 93% has return to their pre-chemotherapy menstrual pattern several life births in each of their series.

The prognostic factors for malignant ovarian germ cell tumours includes the pathology of the tumour FOGO system staging of the tumour, histological grade type and elevation of tumour markers. Few patients may not be suitable candidates for fertility sparing surgeries this patient with advance disease needs maximal cyto-reductive surgeries which compromises their fertility. This study has tried to establish the fertility outcomes in patients with early reproductive age group.

Material and Methods

Retrospective study

Patients enrolled in cancer institute from Jan 2000 to Dec. 2010 were included in the study patients who were diagnose as malignant ovarian germ cell tumour with surgery outside reported to the institute after surgery were also included. The present study describes 67 patients treated with fertility

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preservations. Patient had completed the family were not included in fertility preservation and underwent complete cyto-reductive surgery. In patients who appeared operable upfront were considered for surgery first followed by adjuvant chemotherapy. Patients who were referred to our institution after surgery using single ovarian procedure without staging surgery. In such cases, surgical restaging was considered upfront, residual disease was documented carefully in terms of size and extent of initial surgery then they were considered for adjuvant chemotherapy. Most of the patient who was referred with single ovarian procedure with tumour spill or peritoneal disease was considered for initial chemotherapy followed by completion surgery. Chemotherapy included four cycles of Bleomycin, etoposides and cisplatin.

Surgery upfront included diagnostic laparoscopy with complete assessment of upper abdomen disease, peritoneal disease, disease over the small and large bowel mesentery and pelvic disease. Then proceeded with laparotomy unilateral salpingo ovairectomy, infra colic omentectomy and multiple peritoneal biopsies of upper abdomen. Ipsilateral pelvic nodal dissection +/- para-aortic nodal sampling. According to the pathological staging they were subjected to adjuvant chemotherapy.

The patient with poor performance status or ascites, elevated tumour markers who were deemed unfit for surgery were given neo adjuvant chemotherapy four cycles BEP. These patients were then re-assessed radiologically and by tumour markers for the response of chemotherapy, after careful evaluation they were subjected to the fertility sparing surgery. Pathological assessment of the tumour included histological type of tumour grade of the tumour and present of metastatic disease. These patients were kept under close surveillance. They were followed up every three months for three years, 6 months for next two years and then annually up-to 10 years. During follow up at each visit serum tumour markers and periodical radiological scan were done to assess any relapse. Their menstrual function was monitored if they had issues related to infertility they were referred to reproductive medicine group after one year of completion of treatment. Patient was counsel to have natural pregnancy after two years of completion of treatment. Those who conceived naturally were offered antenatal care and delivery at hospital at local place. These patients resumed surveillance after 6 months of child birth. Information concern to all patients was obstructed from the medical records, their menstrual status marital history reproductive history was noted if available on the record. If unavailable it was requested on telephonic questionnaire for patients who were not followed up at institute. The fertility rate, pregnancy outcome and ovarian functions were analyzed. Overall survival was the primary end point, and reproductive outcome was secondary end point. Overall survival was defined as the time from the date of diagnosis to the date of death.

Table 1:

Sr. no.	Characteristics	No. and Percentage
1	Median age	20.5yrs
2	Prepubertal	6
3	Post menarche	61
4	Regular menses	58
5	Irregular menses	9
6	Obstetrics history -Nulliparous	5
7	Multipara	4
8	Detection of disease by abdominal pain	53
9	By abdominal distention	34
10	With ascites	14
11	Without ascites	52

Table 2:

Sr. no.	Characteristics	No. Percentage
1	Upfront surgery only	9
2	Chemotherapy followed by surgery	24
3	Surgery followed by chemotherapy	34
4	Secondary cyto-reductive surgery	2
5	Second line chemo for relapse	2

Table 3:

Sr. no.	Characteristic	No. Percentage
1	Primary infertility	4
2	Potentially fertile	63
3	Not attempting conception	8
4	Previous children	8
5	Attempting conception	6
6	Failure	
7	Tubal sterility	2
8	Multiple uterine myoma	1
9	Premature ovarian failure	2
10	Primary amenorrhea	3
11	Secondary amenorrhea	4

Table 4:

Sr. no.	Characteristic	No. Percentage
1	Pregnancy with stage-1	26
2	Pregnancy with stage-2	4
3	Total no. pregnancies	30
4	Normal pregnancies	24
5	Miscarriage	3
6	Pregnancy after ART treatment	3
7	Ectopic pregnancy	1
8	Unfavorable outcome	1

Table 5:

Sr. no.	Characteristic	No. Percentage
1	Dysgerminoma	17
2	Yolk sac tumour	6
3	Immature teratoma	7
4	Dermoid cyst	4
5	Polyembryoma	3
6	Mixed germ cell tumour	22
7	Undifferentiated	8

Results

Total number of patients who were enrolled for the study was 67. The age at the time of presentation to hospital with disease varied from 6 years to 36 yrs with median of 20.5 yrs. Patients with prepuberty were 6 (9%) and post menarchal were 61 (91%). The number of patients Results For germ cell tumour Fertility preservation. with menstrual abnormalities were 9(14%). And with normal menses were 58(86%). Out of the 67 patients 4 patients had completed their family and not keen on child bearing, 8 (12%) were not attempting conception due to various reasons.

All these patients presented with either lump in abdomen or abdominal distension for 1-2 months 14 patients (20%) presented with ascities. No of patients who were operated with fertility sparing surgery was 9 (13%). On histopathological diagnosis, they were stage as Stage I A with low grade tumour. 4 were dermoid cyst and 4 were dysgerminoma. patient who received adjuvant chemotherapy after surgery were 34 (52%). Patient who received neoadjuvant chemotherapy in form Of BEP for 3-4 cycles and followed by surgery were 24 (35%), all these patients were followed up every 3 months at hospital with clinical examination and tumour markers. and radiological examination as indicated. majority of patients resumed their menstrual cycles within 3-4 months after completion of chemotherapy. Patient with only surgical management resumed menses immediately.

Patients who were diagnosed histopathological dysgerminoma (25.3%), yolk sac tumour (8.7%). Immature teratoma 7(10%), dermoid cyst 6(8%). Polyembryoma 3 (4.5%) mixed germ cell

tumour (32.5%) and undifferentiated tumour 8 (11%). Out of these patients 2 patients had relapsed within 2 years of completion of treatment and were salvaged by second line chemotherapy followed by cyto reductive surgery, in both cases the contralateral ovary was involved & the cyto reductive surgery included the Hysterectomy with salpingo-oophorectomy.

Patients who attempted pregnancy 49 (73.1%). Out of these patients after evaluation 4(8%) patients had primary amenorrhea and 4(8%) patients had secondary amenorrhea after chemotherapy treatment. 2 patient were detected to have premature ovarian failure, one patient had tubal block and one had multiple leiomyoma of uterus.

Patients who attempted pregnancy 24 (48.9%) patients were able to have normal pregnancy, 3(6%) had miscarriage out of the three one patient had congenital malformation & underwent medical termination of pregnancy.

Discussion

This is the first kind of study to our knowledge in India that specifically addresses the fertility issues in malignant ovarian germ cell tumour. Patient characteristics in our studies are comparable with those of previous studies. First five-year overall survival rate was 98.5% and progression free survival was 97%. The result was much better with the group of patients with upfront surgery followed by chemotherapy with high cure rates, as most of our patients were young and multi-gravida fertility preservation is advocated for all nulliparous women, and those who desire fertility preservation. The advent of effective chemotherapy for malignant germ cell tumour once again raises the question whether fertility preserving surgery should be carried out in every patient.

Gershenson was the first to show that majority of women cured with this treatment recover normal menstruation and that patient attempting conception frequently succeeded. Pregnancies are possible after fertility sparing surgery and chemotherapy in patients presenting with advanced disease. In agreement with results of previous studies the median duration of amenorrhea after chemotherapy was 160 days was comparable with previous studies. One patient with intra-uterine death of foetus, one patient underwent medical termination for congenital anomaly of foetus which was comparable with standard population of the same age group. In our series two patients relapse after the treatment although they had achieved a persistent complete response after chemotherapy. As there are no guidelines for relapse cases secondary cyto-reduction was done for the patient.

Conclusion

Overall survival with the patients treated with fertility sparing surgery is excellent. The reproductive outcome is more or less equivalent to the general population of same age group. First

five-year overall survival rate was 98.5% and progression free survival was 97%. Total no of patients who attempted and had successful reproductive outcome was 30, (44.7%) with unfavorable outcome (miscarriage) was 6.7%; three patients had pregnancy after treatment for infertility. Which is comparable with normal population.

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