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Research Article

To Study the Management and Outcome of Operated Cases of Germ Cell Tumors of Ovary

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ABSTRACT
Background: Worldwide ovarian cancer accounts for 225,000 new cases and 140,000 deaths every year. Ovarian germ cell tumors account for 15–20% of all ovarian malignancies and incidence of malignant ovarian germ cell tumors is 2–6%. These tumors typically occur in adolescent girls and young women. Ovarian germ cell tumors (OGCTs) are heterogeneous tumors that are derived from the primitive germ cells of the embryonic gonad, which accounts for about 2.6% of all ovarian malignancies. There are four main types of OGCTs, namely dysgerminomas, yolk sac tumor, teratoma, and choriocarcinoma.
Aim and Objectives: 1. To study the management and outcome of operated cases of Germ cell Tumours of Ovary.2. To Study the proportion of International Federation of Gynecology and Obstetrics (FIGO) Stage.3. Study the of various Types of ovarian germ cell tumor
Methodology: Study Design: A hospital-based retrospective, analytical study.
Study Setting: OBGY department of GGMC, Mumbai, Maharashtra.
Study Population: All Operable cases of Germ cell Tumours of Ovary attending OPD/IPD of OBGY department of GGMC Mumbai such cases were included in the study.
Study Period: 18months from 1 October 2018 to 30 June 2019.
Sample Size = 30
Results: Majority of the patients (30%) were in the age group of 31-40 years followed by 23.4% in the age group of 21-30 years.17 (56.7%) patients were unmarried while 13 (43.3%) patients were married. The most common symptom was abdominal mass and pain (86.7%) followed by irregular menstruation (16.7%).The most common histologic type was dysgerminoma (46.7%) followed by immature teratoma (26.7%). 19 (63.3%) and 6 (20%) patients had FIGO Stage I and II respectively while 4 (13.4%) and 1 (3.3%) patient had FIGO Stage III and IV respectively. All 5 incompletely staged patients with FIGO Stage I underwent FSS in the form of ovarian cystectomy. 7 (36.8%) patients were placed under active surveillance after surgery while 12 (63.2%) patients received adjuvant chemotherapy. 4 (36.4%) patients with FIGO Stage II-IV underwent primary debulking surgery (PDS) followed by adjuvant chemotherapy, whereas 7 (63.6%) patients with FIGO Stage II-IV received neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS). In PDS cohort, 3 (75%) patients underwent FSS, whereas in NAC cohort, all patients underwent FSS. In patients with FIGO Stage I, no recurrence was observed in all patients with complete staging surgery and 1 (5.3%) patient with incomplete staging. 3 (15.8%) patients with incomplete surgery showed recurrence and 1 (5.3%) patient with incomplete surgery died. There were no recurrence and no death in all patients with FIGO Stage II-IV.
Conclusions: Surgery has an important role in the management of germ cell tumours. Initial careful surgical staging is of great importance for appropriate subsequent therapy. Fertility sparing surgery is feasible in most cases. Malignant ovarian germ cell tumours have excellent for Stage I and for advanced stages.

Keywords: OGCT, FIGO, Clinical Features, Management, Treatment Outcome.

INTRODUCTION

Worldwide ovarian cancer accounts for 225,000 new cases and 140,000 deaths every year.[1] Ovarian germ cell tumors account for 15–20% of all ovarian malignancies and incidence of malignant ovarian germ cell tumors is 2–6%. These tumors typically occur in adolescent girls and young women.[2] Ovarian germ cell tumors (OGCTs) are heterogeneous tumors that are derived from the primitive germ cells of the embryonic gonad, which accounts for about 2.6% of all ovarian malignancies.[3] There are four main types of OGCTs, namely

dysgerminomas, yolk sac tumor, teratoma, and choriocarcinoma.[3]

Dygerminomas are the most common type and are particularly prominent in patients diagnosed with gonadal dysgenesis.[3] OGCTs are relatively difficult to detect and diagnose at an early stage because of the nonspecific histological characteristics.[3] Common symptoms of OGCT are bloating, abdominal distention, ascites, and dyspareunia[3] OGCT is caused mainly due to the formation of malignant cancer cells in the primordial germ cells of the ovary.[3]

Neoplasms presenting in the ovary can originate from any of the various cell types present. The tumor may be derived from the surface epithelium, the stroma, or the cellular elements of the follicle, where the latter may result in sex cord-stromal tumors (such as granulosa cell tumor or thecoma) or germ cell tumors (GCTs).[4,5] The most frequently occurring ovarian GCTs are benign, cystic mature teratomas (MTs) that may show highly differentiated tissue and high morphological heterogeneity.

World Health Organization (1973) classified malignant germ cell tumors as dysgerminoma, endodermal sinus tumor (yolk sac tumor), and immature teratoma, non-gestational choriocarcinoma, embryonal carcinoma, and mixed germ cell type.[6] Malignant mixed germ cell tumor is a type of tumor that consists of two or more malignant germ cell components. These tumors are quite rare cancers, seen in 8% cases of germ cell tumors but are very aggressive in nature.[7] The most common combination reported is dysgerminoma and Endodermal Sinus Tumor (EST)[8] and the rarest combination has embryonal carcinoma and immature teratoma as its components. Embryonal carcinoma, although very rare, holds the most malignant potential.[9]

Pectasides D et al[10] found Prognostic factors include stage, amount of residual tumor, histologic type and raised tumor markers. For patients with early stage disease, cure rates approach 100%, while for those with advanced-stage disease are at least 75%. Appropriate surgical treatment for patients where fertility needs to be preserved consists in laparotomy with unilateral salpingo-oophorectomy (USO) and resection of all visible disease. For patients with advanced-stage disease, the role and the extent of debulking surgery remain controversial despite its routine use.

Malignant OGCTs are predominantly unilateral and chemosensitive, which means they are localized in only one side of the ovary.[11] Fertility-preserving surgery is primarily standardized to keep the contralateral ovary and fallopian tube intact, also known as unilateral salpingo-oophorectomy.[11] For Stage II patients with observable metastasis, cytoreductive surgery may be performed to debulk the volume of the tumor, such as hysterectomy (removal of all or part of the uterus) and bilateral salpingo-oophorectomy. A surgical incision at the abdominal cavity after the completion of adjuvant chemotherapy, called second look laparotomy, is best applicable for patients reported with teratomatous elements after previous cytoreductive surgery.[11]

Debulking surgery is the mainstay in treatment of ovarian cancer. Since these tumors affect young adolescent girls, preservation of fertility is a major concern. Fertility preserving surgery followed by combination chemotherapy is the preferred treatment modality followed worldwide.

In general, patients with OMGCT have a much better prognosis than do those with an ovarian malignant epithelial tumor, and, in many cases, fertility-preserving surgery (ie, unilateral salpingo-oophrectomy) may be performed with excellent results. Conservative, fertility-sparing surgery is the procedure of choice in young women with MOGCT confined to a single ovary. Advanced stages are not always accompanied by extensive pelvic disease and should not be a contraindication to preservation of the uterus and contralateral ovary. With the appropriate addition of postoperative adjuvant platinum-based combination chemotherapy, these young women have an excellent prognosis and can expect to maintain normal ovarian function and reproductive capacity. Hence the present study was done at GGMC Mumbai to study the management and outcome of operated cases of Germ cell Tumours of Ovary.

Aim and Objectives:

AIM: To study the management and outcome of operated cases of germ cell tumors of ovary

Objectives

1. To Study the proportion of International Federation of Gynecology and Obstetrics (FIGO) Stage.
2. To Study the of various Types of ovarian germ cell tumor.

Material and Methods

Study Design: A hospital-based retrospective, analytical study.

Study Setting: OBGY department of GGMC, Mumbai, Maharashtra.
Study Population: All Operable cases of Germ cell Tumours of Ovary attending OPD/IPD of OBGY department of GGMC Mumbai such cases were included in the study.
Study Period: 18months from 1 October 2018 to 30 June 2019.
Sample Size = 30
Sample size was calculated using the formula: $n= [z^2p(1-p)]/d^2$
Where: Z = table value of alpha error from Standard Normal Distribution table (0.95), Power (p) = 80%, Precision error of estimation (d) = 0.07, n= [0.95 x 0.95 x 0.8 (0.2)] / 0.07 x 0.07 = 29.46
Hence a sample size of 30 patients was considered adequate for our study.

Inclusion Criteria

- Age group < 75yrs, Operable cases of germ ovary, Performance status ECOG 0-3
- 50% LVEF, Hb-> 8 , TLC >4000, ANC >45%, Plt>1 lakh, creat<1.5

Exclusion Criteria

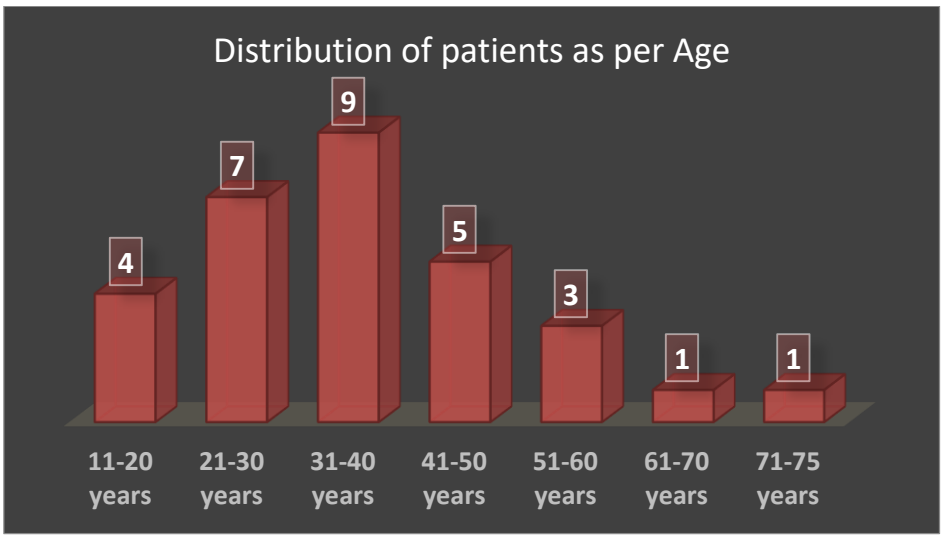
- Recurrence case of germ cell tumors, Inoperable cases of ca ovary
- Metastatic cases, Performance status ECOG ¾

Approval for the Study: Written approval from Institutional Ethics committee was obtained beforehand. Written approval of OBGY and another related department was obtained. After obtaining informed verbal consent from all patients coming to our institute during study period according to exclusion and inclusion criteria attended OBGY OPD/IPD of GGMC Mumbai such cases were included in the study.

Methods of Data Collection and Questionnaire: Predesigned and pretested questionnaire was used to record the necessary information. Questionnaires included general information, such as age, Place of residence, maternal education, occupation, Socioeconomical status, Religion, Medical history- chief complain, past history, general examination, systemic examination, Menstrual history. Demographic, clinical, surgicopathological characteristics, details of treatment, recurrence, and survival were collected from electronic medical records and hospital-based cancer registry. Staging in patients undergoing with NAC was based on clinical and radiological information. Epidemiological and clinical profile of patients was reviewed. Clinical stage of presentation and treatment received (neoadjuvant chemotherapy, surgery, and adjuvant treatment) was recorded. Patient follow-up was done to ascertain disease-free interval, treatment outcome, and the ability to conceive following fertility-preserving surgery.
Data Entry and Analysis: The data were entered in Microsoft Excel and data analysis was done by using SPSS demo version no 21 for windows. The analysis was performed by using percentages in frequency tables and p<.05. was considered as level of significance using the Chi-square test.

RESULT AND OBSERVATIONS

A hospital-based retrospective, analytical study was conducted with 30 patients to evaluate the outcome in operated cases of germ cell tumors of ovary.

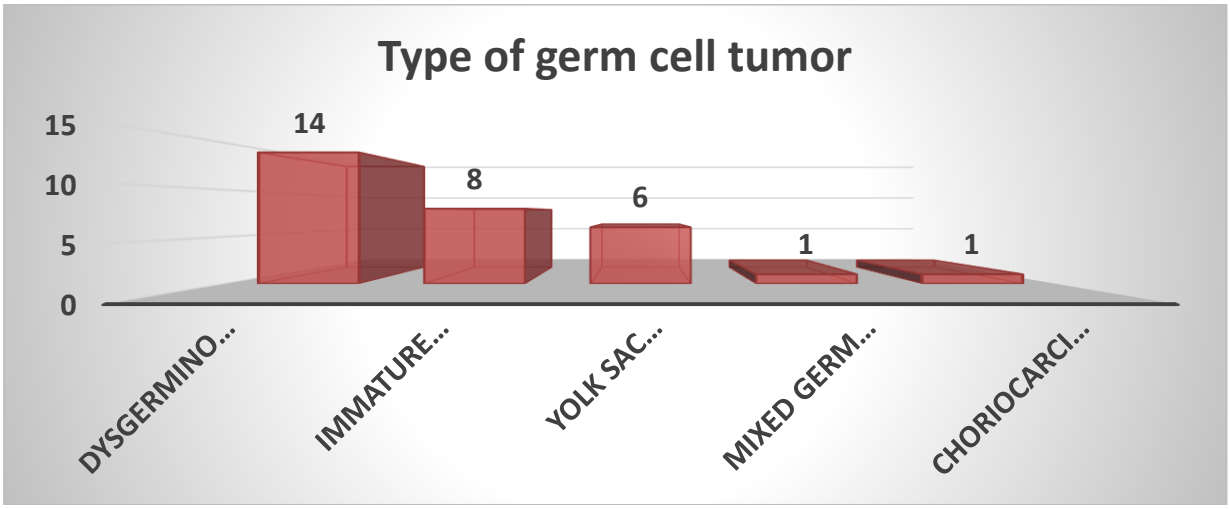


Above figure shows Majority of the patients (30%) were in the age group of 31-40 years followed by 23.4% in the age group of 21-30 years, 16.7% in the age group of 41-50 years, 13.3% in the age group of 11-20 years, 10% in the age group of 51-60 years and 3.3% in the age groups of 61-70 years and 71-75 years.

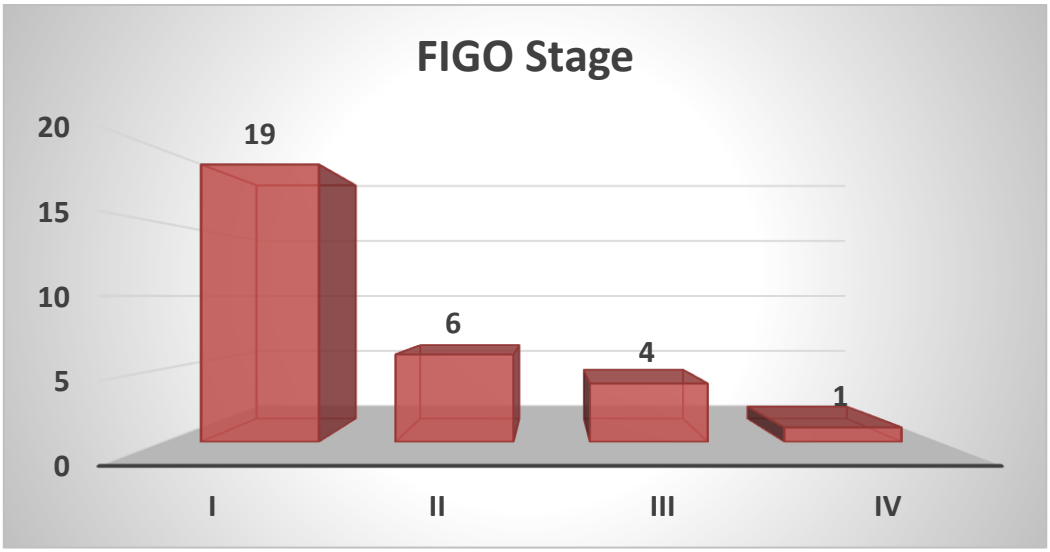
Table No.1: Distribution of Patients According to Symptoms

Symptoms	N	%
Abdominal mass and pain	26	86.7%
Irregular menstruation	5	16.7%
Acute abdominal pain	2	6.7%

The most common symptom was abdominal mass and pain (86.7%) followed by irregular menstruation (16.7%) and acute abdominal pain (6.7%).



The most common histologic type was dysgerminoma (46.7%) followed by immature teratoma (26.7%), yolk sac tumor (20%), mixed germ cell tumor (3.3%) and choriocarcinoma (3.3%).



19 (63.3%) and 6 (20%) patients had International Federation of Gynecology and Obstetrics (FIGO) Stage I and II respectively while 4 (13.4%) and 1 (3.3%) patient had FIGO Stage III and IV respectively.

Table No.2: Type of Surgery of Patients with FIGO Stage I (N=19)

Type of Surgery		N	%
Completely Staging Surgery	**Fertility Sparing Surgery**	13	68.4%
	Non-FSS	1	5.3%
Incomplete surgery		5	26.3%
Management of patients after surgery		**N**	%
Active surveillance		7	36.8%
Adjuvant chemotherapy		12	63.2%
Total		19	100%

Complete surgery represented the first approach for 14 (73.7%) Stage I patients while incomplete surgery was the first approach for 5 patients. Of 14 completely staged patients, 13/14 (92.8%) patients underwent Fertility sparing surgery (FSS) and 1 patient underwent Non-FSS. All 5 incompletely staged patients with FIGO Stage I underwent FSS in the form of ovarian cystectomy. 7 (36.8%) patients were placed under active surveillance after surgery while 12 (63.2%) patients received adjuvant chemotherapy.

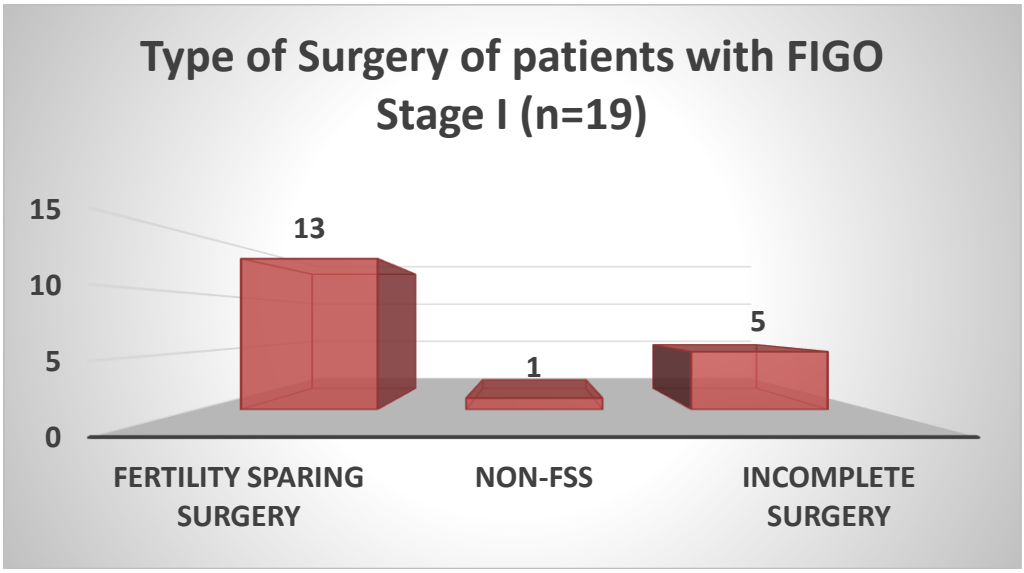


Table No.3: Management of Patients with FIGO Stage II-IV (N=11)

Management of patients with FIGO Stage II-IV (n=11)	N	%
PDS + adjuvant chemotherapy	4	36.4%
NAC + IDS	7	63.6%
Total	11	100%

4 (36.4%) patients with FIGO Stage II-IV underwent primary debulking surgery (PDS) followed by adjuvant chemotherapy, whereas 7 (63.6%) patients with FIGO Stage II-IV received neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS). In PDS cohort, 3 (75%) patients underwent FSS, whereas in NAC cohort, all patients underwent FSS.

Table No.4: Outcome of Patients with FIGO Stage I after Surgery (N=19)

Outcome of patients after surgery	N	%
No recurrence	15	78.9%
Recurrence	3	15.8%
Death	1	5.3%
Total	19	100%

In patients with FIGO Stage I, no recurrence was observed in all patients with complete staging surgery and 1 (5.3%) patient with incomplete staging. 3 (15.8%) patients with incomplete surgery showed recurrence and 1 (5.3%) patient with incomplete surgery died.

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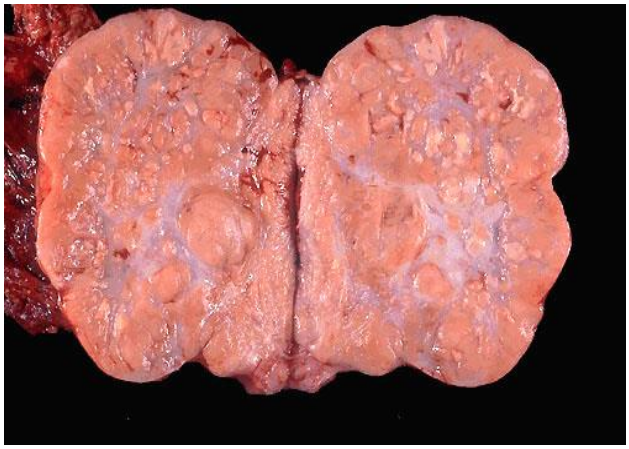

Image: Ovarian Dysgerminoma
This is an ovarian dysgerminoma that has been sectioned into two halves. Note the pale brown appearance of the parenchyma, along with some central collagenous scar.

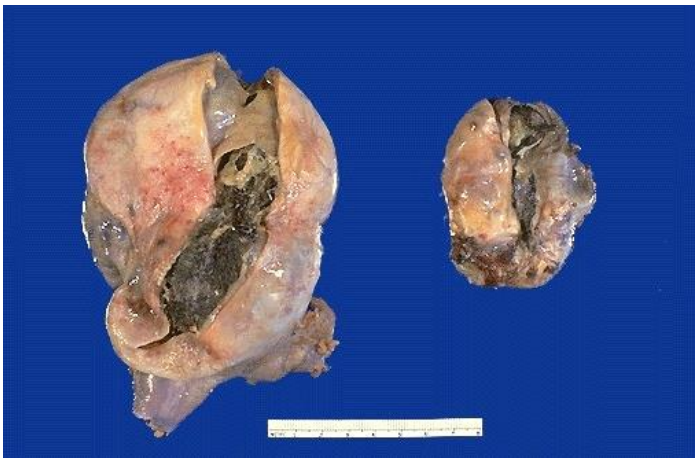

Image: Bilateral Mature Cystic Teratomas of the Ovaries

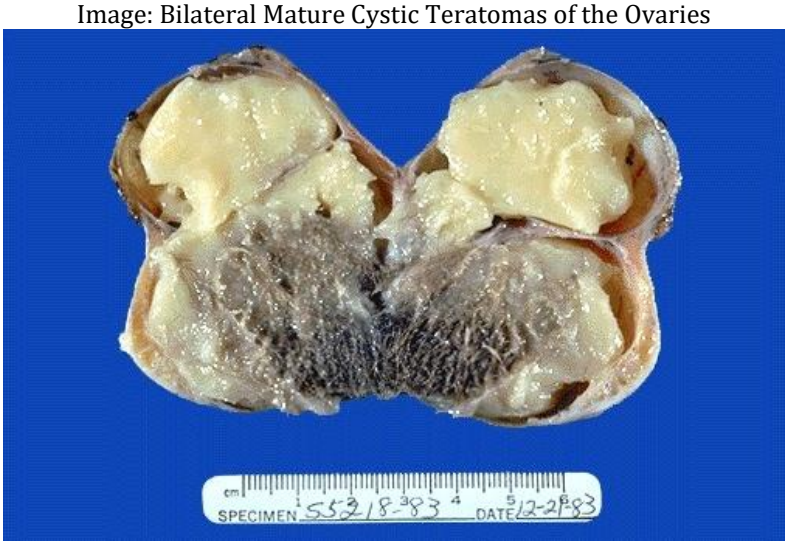

Image: Cystic Nature of a Mature Teratoma of Ovary

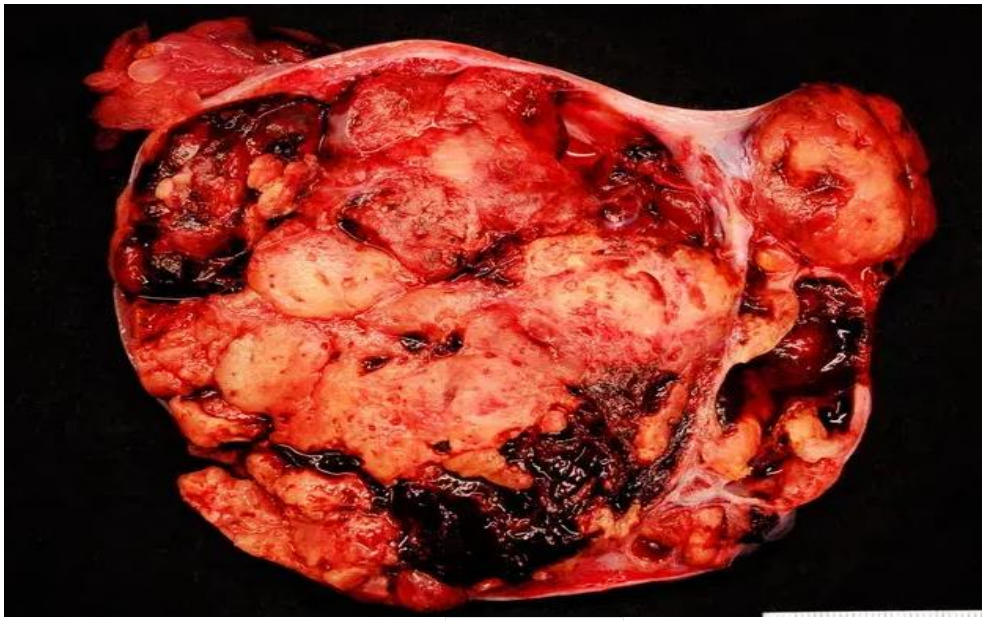

Image: Yolk Sac Tumor

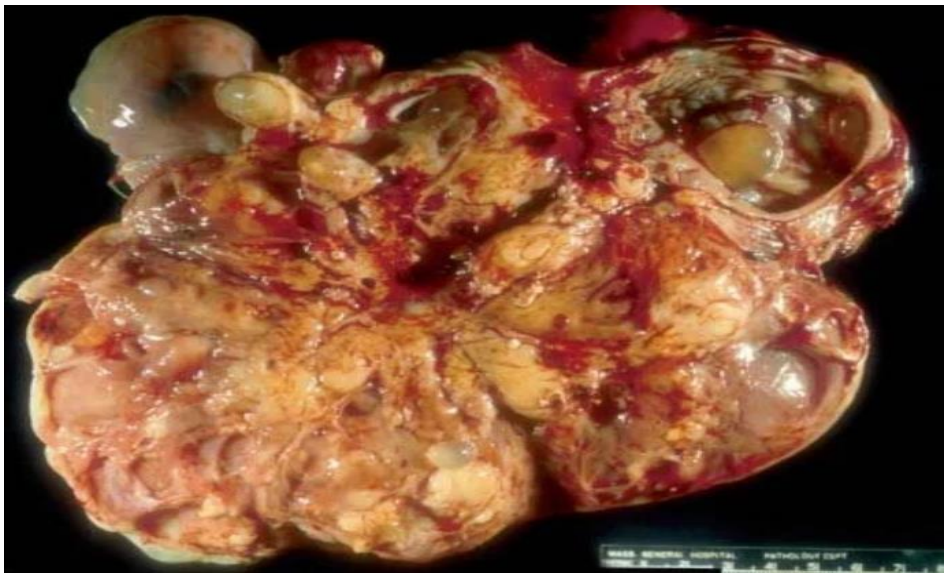

Image: Malignant Mixed Germ Tumor

DISCUSSION

A hospital-based retrospective, analytical study was conducted with 30 patients to evaluate the outcome in operated cases of germ cell tumors of ovary. In the present study, majority of the patients (30%) were in the age group of 31-40 years followed by 23.4% in the age group of 21-30 years, 16.7% in the age group of 41-50 years, 13.3% in the age group of 11-20 years, 10% in the age group of 51-60 years and 3.3% in the age groups of 61-70 years and 71-75 years. The mean age of the patients was 35.30 ± 14.30 years.

This is similar to the studies of Agarwal R et al[12] single-institution retrospective study evaluating the pattern of care and survival outcome in patients with malignant ovarian germ cell tumors found median age at diagnosis was 20.5 years (range: 8–45 years). Kumar RB et al[13] hospital based retrospective study evaluating the outcome of treatment in malignant germ cell tumours found age of the patients ranged between 14 years to 40 years, median age being 21 years. Median age at presentation was 21 years with age range between 14 and 40 years. Lakshmanan M et al[14] retrospective study assessing patients with ovarian germ cell tumors found median age of these patients was 22 years (11–65). 89.7% (n = 35) of these patients were premenopausal while three were postmenopausal and one was premenarche. Most of these patients (76.92% n = 30) were nulliparous.

The most common symptom in our study was abdominal mass and pain (86.7%) followed by irregular menstruation (16.7%) and acute

abdominal pain (6.7%). This is comparable to the studies of Agarwal R et al[12] single-institution retrospective study observed most common presenting symptom was abdominal mass and pain in 85.4% patients. Kumar RB et al[13] hospital based retrospective study observed abdominal pain was the most common clinical presentation seen in 14 patients (66%) and 3 patients (14%) presented with abdominal mass. Other symptomatology included irregular menstruation, gastrointestinal disturbances and urinary symptoms. 3 patients with germ cell tumour complicating pregnancy had abdominal mass detected on ultrasound abdomen done during antenatal check-up.

The most common histologic type in the present study was dysgerminoma (46.7%) followed by immature teratoma (26.7%), yolk sac tumor (20%), mixed germ cell tumor (3.3%) and choriocarcinoma (3.3%). Agarwal R et al[12] single-institution retrospective study found common histologic type was mixed germ cell tumor in 37.5% of patients. Of 31 Stage I MOGCT patients, 8 (25.8%) had dysgerminoma, 13 (41.9%) had immature teratoma (6 [46.2%] – Grade 1, 2 (15.4%) – Grade 2, and 5 (38.4%) – Grade 3), 9 (29%) had mixed germ cell tumor, and 1 (3.2%) had yolk sac tumor (YST). Of 17 Stage II–IV MOGCT patients, 3 (17.6%) had dysgerminoma, 3 (17.6%) had immature teratoma (1 [33.3%] – Grade 1 and 2 [66.7%] – Grade 2), 9 (52.9%) had mixed germ cell tumor, and 2 (11.8%) had YST. Kumar RB et al[13] hospital based retrospective study found 9 patients (43%) presented with mixed germ cell tumour, 6 patients (29%) with dysgerminoma, 3 patients (14%) with yolk sac tumour and 3 patients (14%)with mature cystic teratoma. Lakshmanan M et al[14] retrospective study found Dysgerminoma was the most common histological type seen followed by teratoma and mixed germ cell tumors.

It was observed in the present study that 21 (70%) and 7 (23.4%) patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 1 respectively while 1 (3.3%) patient each had ECOG performance status of 2 and 3.Evidence form large studies on recommendations of the Fertility Task Force of the European Society of Gynecologic Oncology about the conservative management of ovarian malignant tumors suggest that unilateral salpingo-oophorectomy of involved ovary is the standard of care and removal or biopsy of contralateral ovary is not associated with survival benefit[15,16]. The issue of conservative surgery of involved ovary is still unanswered.

It was observed in our study that 19 (63.3%) and 6 (20%) patients had International Federation of Gynecology and Obstetrics (FIGO) Stage I and II respectively while 4 (13.4%) and 1 (3.3%) patient had FIGO Stage III and IV respectively. This is in concordance to the studies of Agarwal R et al[12] single-institution retrospective study showed nearly 64.6% patients were Stage I at the time of diagnosis. The Federation of Gynecology and Obstetrics (FIGO) stage was IA in 11 (35.5%) and IC in 13 (41.9%), whereas remaining 7 (22.6%) were apparently Stage IA at presentation but upstaged to IC due to intraoperative rupture of tumor and its piecemeal removal. The FIGO stage was II in 2 (11.8%), III in 12 (70.6%), and IV in 3 (17.6%) patients. Lakshmanan M et al[14] retrospective study assessing patients with ovarian germ cell tumors found majority of the patients (82.1%) were diagnosed to have stage II and stage III disease.

In the present study, complete surgery represented the first approach for 14 (73.7%) Stage I patients while incomplete surgery was the first approach for 5 patients. Of 14 completely staged patients, 13/14 (92.8%) patients underwent Fertility sparing surgery (FSS) and 1 patient underwent Non-FSS. All 5 incompletely staged patients with FIGO Stage I underwent FSS in the form of ovarian cystectomy. 7 (36.8%) patients were placed under active surveillance after surgery while 12 (63.2%) patients received adjuvant chemotherapy. Similar observations were noted in the studies of Lakshmanan M et al[14] retrospective study reported one patient presented with metastatic disease and was treated with palliative chemotherapy. Among the rest (n =38), majority received neoadjuvant chemotherapy (71.1%, n = 27/38) with weekly bleomycin and bleomycin, etoposide, and cisplatin (BEP) combination three weekly.

In our study, 4 (36.4%) patients with FIGO Stage II-IV underwent primary debulking surgery (PDS) followed by adjuvant chemotherapy, whereas 7 (63.6%) patients with FIGO Stage II-IV received neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS). In PDS cohort, 3 (75%) patients underwent FSS, whereas in NAC cohort, all patients underwent FSS. This is in concordance to the studies of Agarwal R et al[12] single-institution retrospective study reported of 17 Stage II–IV MOGCT patients Six (35.3%)

patients underwent primary debulking surgery (PDS) followed by adjuvant chemotherapy, whereas 11 (64.7%) patients received NAC followed by interval debulking surgery (IDS). Patients with poor performance status or not suitable for optimal cytoreduction were chosen for NAC. In NAC cohort, 8 (72.7%) achieved complete pathological response. In PDS cohort, 4 (66.7%) patients underwent FSS, whereas in NAC cohort, all 11 (100%) patients underwent FSS.

It was observed in the present study that in patients with FIGO Stage I, no recurrence was observed in all patients with complete staging surgery and 1 (5.3%) patient with incomplete staging. 3 (15.8%) patients with incomplete surgery showed recurrence and 1 (5.3%) patient with incomplete surgery died. This is similar to the studies of Agarwal R et al[12] single-institution retrospective study observed median follow-up period was 34 months (range: 1–241 months). Total 5 of 8 (62.5%) incomplete surgery Stage I patients had disease recurrence, with a median time to recurrence of 6 months (range: 3–9 months). There was piecemeal removal of cyst and intraoperative spillage of tumor in all. Three out of five patients were wrongly diagnosed as benign mature cystic teratoma initially and presented to our center only on recurrence. Original slides were reviewed and confirmed as immature teratoma. Of these, two died of disease within 4 and 9 months of recurrence.

It was observed in our study that there was no recurrence and no death in all patients with FIGO Stage II-IV. Similar observations were noted in the studies of Agarwal R et al[12] reported DFS and OS of Stage II–IV MOGCT patients were 100%. There was no survival difference in the patients with NAC + IDS and PDS group (DFS and OS 100% in both). All 35 (72.9%) patients who underwent FSS resumed normal menstruation within 1 year of completing treatment. Of the 12 (25%) nulliparous patients desirous of pregnancy, 10/12 (83.3%) achieved pregnancy and delivered healthy full-term babies.

CONCLUSION

Surgery has an important role in the management of germ cell tumours. Initial careful surgical staging is of great importance for appropriate subsequent therapy. Fertility sparing surgery is feasible in most cases. Malignant ovarian germ cell tumours have excellent for Stage I and for advanced stages. Fertility preservation is a concern as these patients are usually young adolescent girls but fertility sparing treatment must be individualized on the basis of tumor type, surgical staging, and availability of combination chemotherapy. Considering high recurrence rate and mortality, total hysterectomy with complete surgical staging followed by combination chemotherapy should be performed at advanced stage and aggressive tumor biology. Preservation of fertility must be held secondary.

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