

Malignant Ovarian Germ Cell Tumors in Pediatric Age Group: A Clinicopathological Study over 21 Years in Eastern Rajasthan (India)

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To cite this article:

Rajendra Kumar Tanwar, Bharti Saxena, Shankar Lal Mohanpuria, Harsh Goyal, Laxmi Agarwal, Madhu Saxena, Man Mohan Agarwal. Malignant Ovarian Germ Cell Tumors in Pediatric Age Group: A Clinicopathological Study over 21 Years in Eastern Rajasthan (India). *Cancer Research Journal*. Vol. 8, No. 4, 2020, pp. 57-61. doi: 10.11648/j.crj.20200804.11

Received: August 18, 2020; Accepted: September 3, 2020; Published: October 27, 2020

Abstract: *Background:* The aim of this study is to analyze the clinicopathological features, diagnosis and treatment outcome of rare cases of malignant ovarian germ cell tumors in a government tertiary care hospital centre keeping fertility preservation surgery as a goal in young girls below 21 years of age. *Methods:* This is a retrospective study comprising of 24 patients diagnosed to have malignant ovarian germ cell tumors who attend the department of Radiation Oncology from 1998 to 2019 over 21 years period. The patients were evaluated on the basis of their age, obstetric history, investigations, and serum tumor markers estimation. All patients were staged according to FIGO, ECOG score were noted. Unilateral Salpingo oophorectomy (USO) with or without staging laparotomy surgery was done and BEP chemotherapy regimen was given. Response to treatment was evaluated by regular clinical examination, radiological and tumor marker studies. *Results:* In our study 17 patients were in FIGO stage III and 6 patients were in stage IV. The size of the primary tumor was 10-20 cm. in 15 patients. The various histology observed was-dysgerminoma -8, malignant teratoma-5, mixed germ cell tumor-5, yolk sac tumor-4 and embryonal carcinoma in 2 patients. Eighteen patients underwent fertility preservation surgery i.e. USO - 15, and 3 patients underwent USO with staging laparotomy. In 14 patients 3-4 cycles of adjuvant chemotherapy (BEP regimen) was administered and all of them achieved complete remission. *Conclusion:* Malignant ovarian germ cell tumors carries excellent prognosis in spite of advanced stage disease. Patients should be referred to oncology centre and to be operated by gynecologic oncologist/oncosurgeon. Adjuvant chemotherapy should be given to achieve complete remission.

Keywords: Germ Cell Tumor Ovary, Fertility Preserving Surgery, Neo-adjuvant Chemotherapy, BEP Regimen

1. Introduction

The pediatric age group includes adolescence i.e. up to 21 years now days. The malignant germ cell tumors of the ovary

account for 2-3% of all ovarian cancers and occur mostly in their early twenties. More over 10-30% of ovarian neoplasm's operated during childhood or adolescent girls are malignant. [1] Significant improvement in the management

of malignant ovarian germ cell tumors (MOGCT) has been achieved during past three decades because of major development in the area of proper histological diagnosis, clinical staging, tumor marker estimation, immunohistochemistry, facilities of oncosurgery and adjuvant chemotherapy. [2] Among MOGCT, the incidence of immature teratoma are most common 42-48%, followed by dysgerminoma 24-27%, mixed germ cell tumors (GCT) 14-20% and yolk sac tumor (YST) formally known as endodermal sinus tumor in 11-12%. [3, 4] The pure embryonal carcinoma and choriocarcinoma are rarely seen in ovary rather they are seen as a component of mixed GCT of ovary. The mixed GCT of the ovary contains two or more different types of germ cell neoplasms. The most frequent combination has been dysgerminoma and YST. [5] A good number of patients with MOGCTs are long term survivors and suffer minimum morbidity from treatment. Fertility preservation surgical procedures enable young women to preserve their reproducing potential. [2, 3] The better results are achieved due to team approach management including gynecologic oncology, medical oncology, pathology and radiology. Nogales FF *et al* described para neoplastic syndrome i.e. autoimmune encephalitis due to antibodies against the N-methyl-D-aspartate receptor has been reported most frequent autoimmune disorder associated with ovarian teratoma. [6]

2. Methods

A retrospective review of medical records of 24 patients of MOGCTs in pediatric age group from September 1998 to November 2019 over 21 years who attended department of

Radiation Oncology in our Institution was performed. The patients were operated in department of Obstetrics and Gynecology of our Institute as well as at other hospitals, were referred for further treatment. The records of these patients were evaluated for written informed consent, age, obstetric history, treatment received before coming to this institute. General physical examination, pelvico-abdominal examination, routine hematological, serological tests including tumor markers viz. alpha feto protein (AFP), beta human chorionic gonadotrophin (β -hCG), lactic dehydrogenase (LDH), CA-125, skiagram of the chest, USG of the abdomen and pelvis were done. Computerized tomography of the abdomen, pelvis and chest were done to evaluate clinical staging of the disease (Table 1). Eastern Cooperative Oncology Group (ECOG) Performance Score was noted.

All patients were evaluated for surgery. Neo-adjuvant chemotherapy was given in patients who were found to have extensive disease to make the tumor operable. BEP chemotherapy regimen as follows.

Inj. Bleomycin 20mg/M² I.V. Day 1, 8, 15

Inj. Etoposide 100 mg/M² I.V. Day 1-5

Inj. Cisplatin 20mg/M² I.V. D1-5

Every three weekly for 3-4 cycles with injection Filgrastim 5 mcg/kg S. C. day 6.

Treatment related toxicities were observed and managed appropriately.

Remission was considered when clinical, radiological and tumor marker levels were within normal limits. Patients were followed every monthly till one year with investigations every 3 monthly, then follow up every 3 monthly during 2nd year and every 6 monthly subsequently.

Table 1. Figo* staging of ovarian germ cell tumors.

Stage	Description
I	Tumor limited to ovaries (one or both).
IA	Tumor limited to one ovary, no ascites, intact capsule.
IB	Tumor limited to both ovaries, no ascites, intact capsule
IC	Tumor either Stage IA or IB, but with ascites present containing malignant cells or with ovarian capsule involvement or rupture or with positive peritoneal washings.
II	Tumor involving one or both ovaries with extension to the pelvis.
IIA	Extension to uterus or fallopian tubes.
IIB	Involvement of both ovaries with pelvic extension.
IIC	Tumor either Stage IIA or IIB, but with ascites present containing malignant cells or with ovarian capsule involvement or rupture or with positive peritoneal washings.
III	Tumor involving one or both ovaries with tumor implants outside the pelvis or with positive retro peritoneal or inguinal lymph nodes. Superficial liver metastases qualify as stage III
IIIA	Tumor limited to the pelvis with negative nodes but with microscopic seeding of the abdominal peritoneal surface.
IIIB	Negative nodes, tumor implants in the abdominal cavity less than 2 cm.
IIIC	Positive nodes, tumor implants in the abdominal cavity more than 2 cm.
IV	Distant metastasis present

* FIGO: International Federation of Gynecologists and Obstetricians

3. Results

3.1. Clinical Profile

A large number of our patients presented with advanced stage of disease due to a variety of reasons. Majority of these patients were illiterate and belonging to poor economic

backgrounds. They reach the oncology treatment centre quite late. The age ranges from 9-20 years (Mean age 16.17) (Table 2). In two patients the Hemoglobin was found below 10 Gm% at the time of presentation. One patient has extensive loco regional disease involving vulva, perineal mass, palpable inguinal lymph nodes, infiltration of vagina and rectum with retention of urine therefore supra pubic

cystostomy was done. All patients were presented with abdominal distension and pain. In 9 patients the tumor was found arising from left ovary and in 8 patients from right ovary where as in 7 patients, the laterality of the tumor could not be ascertained due to advanced disease. In 15 (62.5%) patients, the size of primary tumor was between 10-20 cm. Ascites was present in 10 patients. Four patients showed hydronephrotic changes radiologically however serum renal functions were found within normal range. We observed peritoneal carcinomatosis in 1, pleural effusion -2, hepatic metastasis -2, pulmonary metastasis -1 and associated tubercular lymphadenopathy of para aortic lymph nodes in one patient. The ECOG performance score revealed Score I in 5 patients, Score II -8, Score III in 6 and Score IV in 5 patients.

3.2. Treatment Given

Only one patient had stage I disease, while remaining patients were presented with advanced stage disease - Stage

III - 17 (70.83%) and stage IV - 6 (25.0%). Eighteen patients underwent surgery -Unilateral salphingo oophorectomy (USO) -15 and staging laparotomy in 3 patients. Six patients were found to be inoperable so diagnosis was made by FNAC only. The final histopathological diagnosis arrived was Dysgerminoma in 8 (33.33%), Malignant Teratoma - 5 (20.83%) and Mixed Germ cell Tumor - 5 (20.83%), Yok Sac Tumor - 4 (16.66%) and Embryonal Carcinoma - 2 (8.33%). All patients were planned BEP chemotherapy regimen. Four patients (16.66%) completed 3 cycles and 10 patients (41.66%) completed 4 cycles of BEP chemotherapy.

During treatment, 2 patients developed neutropenia grade IV after administration of 1st cycle chemotherapy, were recovered after treatment. All fourteen patients who completed post operative chemotherapy achieved complete remission and cured. One patient died of intestinal obstruction. In this study, only one patient was married before treatment, achieved complete remission and conceived 2 years after treatment and delivered a healthy child.

Table 2. Clinical characteristics of patients with MOGCT.

Clinical Characteristics		Number of patients	Percentage
Age (Years)	Range 9-20 Years, Mean Age 16.17		
Laterality of Tumor	Left side	9	37.50
	Right Side	8	33.33
	Side could not be ascertained	7	29.16
Primary Tumor Size	Less than 5 cm.	1	4.16
	5-10 cm	3	12.50
	10-15 cm	10	41.66
	15-20 cm	5	20.83
	More than 20 cm	5	20.83
Tissue Diagnosis by	FNAC	6	25.00
	Biopsy	18	75.00
FIGO Staging	Stage I	1	4.16
	Stage III	17	70.83
	Stage IV	6	25.00
Surgical treatment	USO	15	62.50
	Staging Laparotomy	3	12.50
	Inoperable	6	25.00
Radiation Therapy	Palliative	1	4.16
Histopathology	Dysgerminoma	8	33.33
	Malignant Teratoma	5	20.83
	Mixed Germ cell Tumor	5	20.83
	Yok Sac Tumor	4	16.66
	Embryonal Carcinoma	2	8.33
Performance Score	ECOG -I	5	20.83
	ECOG -II	8	33.33
	ECOG -III	6	25.00
	ECOG - IV	5	20.83
Number of BEP Cycles given	1	7	29.16
	2	2	8.33
	3	4	16.66
	4	10	41.66

Table 3. The serum tumor markers in malignant germ cell tumors of ovary. [5].

Histopathology	AFP	B-hCG
Dysgerminoma	-	±
Yok Sac Tumor (EST)	+	-
Malignant Teratoma	±	-
Mixed Germ cell Tumor	±	±
Choriocarcinoma	-	+
Embryonal Carcinoma	±	+

Table 4. Good outcomes to fertility preservation surgery have been documented in many series.

Author	Total no. of patients in the study	Number of patients underwent fertility preservation surgery	No. of patients who became pregnant	Percentage
Gershensen 1988 [15]	230	40	11	27.50
Perrin 1999 [16]	45	45	7	15.5
Ezzat 1999 [17]	67	44	16	36.36
Brewer 1999 [18]	26	16	5	31.25
Lakshmanan 2018 [11]	39	14	1	7.1
Present Series 2020	24	18	1	5.55

4. Discussion

The MOGCTs are derived from primordial germ cells which undergo defective mitosis. Karyotypic abnormalities are common and include aneuploidy or chromosomal rearrangements. [7] The MOGCT occurs in girls and young women with a median age between 16-20 years depending on histological subtypes. [8] The majority of patients presents with abdominal pain associated with palpable pelvicoabdominal mass. Other symptoms are acute abdominal pain misdiagnosed as acute appendicitis or torsion of the ovary, abdominal distension, fever or vaginal bleeding. A few patients exhibit isosexual precocity (precocious puberty) because of β -hCG production by tumor cells. [9] Many germ cell tumors possess the unique property of producing biomarkers [5, 9]. These markers (if initially raised) are helpful in diagnosis, response to treatment and detection of subclinical recurrent disease in follow up. (Table 3) Interestingly serum CA-125 level can also be nonspecifically elevated in patients with ovarian GCTs. [10] In the present study dysgerminoma was most common histological subtype followed by malignant teratoma, mixed GCT, yolk sac tumor and embryonal carcinoma. This is similar to other reports from India. [11, 12] In the USA, there was a different distribution of various histological subtypes reported. Smith et al (2006) analyzed SEER data of 30 years (1973-2002) and identified 1262 patients of ovarian GCT, out of which 38.5% were teratomas and 32.8% dysgerminomas. [13] The peak incidence of GCT in their series was 15-19 years age group [13], whereas in our series the median age was 16.17 years.

Most patients were operated by gynecologists and do not undergo comprehensive staging. In such cases, post operative CT scan of the abdomen and pelvis are recommended. If histopathology and available information from first surgery clearly indicates ovarian GCT, re exploration is not advisable. [2] These tumors are highly sensitive to chemotherapy therefore systemic chemotherapy should be instituted. [2] The re exploration for comprehensive staging is advisable in patients to confirm FIGO stage I, grade 1 immature teratoma or dysgerminoma who would undergo surveillance and forego chemotherapy in the event of negative comprehensive staging. [4, 14]

Unlike epithelial ovarian cancers, germ cell tumors are amenable to fertility preservation and hence conservative surgery should be standard of care whenever possible. Gershenson [15], Perrin [16], Ezzat [17], Brewer [18] and

Lakshmanan [11] in their series described fertility preservation surgery and delivered healthy babies (Table 4). There is very little Indian data available. [11] In our study only one patient was married before treatment who became mother. This number may be less as all patients except one were unmarried prior to diagnosis and due to social taboo continue to remain unmarried long after completing treatment. The most common effective chemotherapy regimen is BEP. [14] The chemotherapy dose reduction or delay in administration is not recommended even in the setting of neutropenia to achieve maximum tumor control.

For residual or recurrent disease high dose chemotherapy or additional chemotherapy is to be given. TIP (Paclitaxel, Ifosfamide and cisplatin), VIP (Etoposide, Ifosfamide and cisplatin), VeIP (Vinblastine, Ifosfamide and cisplatin), Cisplatin/ Etoposide, Docetaxel/Carboplatin, Paclitaxel/Carboplatin, Paclitaxel/Gemcitabine, Paclitaxel/Ifosfamide, Paclitaxel, Docetaxel [14], Radiotherapy or supportive care is to be given. Referral of these patients to a tertiary care centre for stem cell transplant consultation and potentially curative therapy is strongly recommended. [14] Several case reports suggest these patients who have received chemotherapy for GCT may later present with growing teratoma syndrome. [19] In these patients consider either surgical resection or observe with monitoring. If fertility is not an issue, metastatic disease may be treated with radiation therapy because these tumors are extremely radiosensitive. Newer drugs like Olaparib, Palbociclib, Pembrolizumab, Avelumab, Durvalumab, Tremelimumab are molecular targeted therapy are under trial. [14]

5. Conclusion

Malignant GCT of ovary has an excellent prognosis if detected in early stage. High index of suspicion in young females presenting with ovarian mass and timely diagnosis and referral may result in high cure rates. The tumor marker level estimation plays a key role in the diagnosis, treatment and follow up of these patients. It is recommended that these patients should be treated by a tertiary care center where they will receive specialized care which has a direct impact on survival, quality of life and fertility preservation. The introduction of BEP chemotherapy regimen has made this disease curable. After appropriate treatment, 5 year survival is more than 85%. Survival after fertility preserving surgery is quite high and patients return to their reproductive functions shortly (3-4 months) after completing

chemotherapy. BEP chemotherapy is effective first line chemotherapy regime and recurrence can be managed effectively with second line chemotherapy regimen. Women who retain one ovary might avoid sterility and premature ovarian failure and the attendant risk of accelerated cardiovascular disease and osteoporosis. Oocyte cryopreservation could be proposed to all adolescent patients and to all those who have not yet planned a pregnancy and a controlled ovarian hyperstimulation could also be considered after 12 months from chemotherapy treatment. Very little Indian studies had been published in literature. We hereby present rare cases of MOGCT at our institute.

Conflict of Interest

The authors declare that they have no competing interests.

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