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Original Article

Treatment and Survival of Malignant Ovarian Germ Cell Tumors: A Retrospective Single Institution Experience

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Abstract

Purpose of the Study: Malignant ovarian germ cell tumors (MOGCTs) are rare comprising <5% of ovarian tumors. We present our experience and data in MOGCT in government aided hospital, analyzing series of cases with respect to the patient characteristics, clinical profile, treatment, and survival. Since these tumors occur in young age, it affects the psychological status of the patients, but the outcome and significant disease free interval is unremarkable which is emphasized in this study as proven in similar studies.

Materials and Methods: We retrospectively analyzed the case records of patients diagnosed to have MOGCTs.

Results: Between 2012 and 2018, 41 patients were diagnosed with MOGCT. The median age was 20 years. The predominant pathology was dysgerminomas followed by yolk sac tumors, mixed germ cell tumors, and immature teratomas. Majority had either stage I or III disease. Most of the patients (n = 35) underwent conservative surgery, while six patients had total abdominal hysterectomy with bilateral oophorectomy. Thirty-one patients received adjuvant chemotherapy with Bleomycin, Etoposide, and Cisplatin (BEP) for three cycles. Surveillance was opted for stage I dysgerminoma and immature teratoma. Four patients had received neoadjuvant chemotherapy followed by fertility sparing surgery. After follow-up period of 24–84 (mean of 46 months), there was no evidence of disease in 37 patients. Three patients had recurrence or distant metastasis within 1 year and they were treated with second-line chemotherapy. One patient had progressive disease since she had defaulted after surgery. Disease-free survival was reasonably high and even in relapse, they are managed with salvage chemotherapy.

Conclusion: Germ cell tumor of the ovary is an adequately treatable disease and selected patients can be managed with fertility preserving surgery and adjuvant chemotherapy with BEP. Even recurrences can be managed with second-line chemotherapy resulting in good response.

Key words: Adjuvant chemotherapy, Fertility sparing surgery, Malignant ovarian germ cell tumors

INTRODUCTION

Malignant ovarian germ cell tumors (MOGCTs) arise from the primordial germ cell of the ovary and are rare comprising <5% of ovarian cancer.[1] The incidence is common in young females especially in the second and third decade.[1] MOGCT is classified into dysgerminoma and non-dysgerminomas which include yolk sac tumor (endodermal sinus tumor), immature teratoma, embryonal cell carcinoma, polyembryoma non-gestational choriocarcinomas, and mixed germ cell tumor (GCT).[2] Most MOGCT presents at earlier stage. Patients with Stage I have excellent prognosis with long-term disease-free status of more than 90%.[3] Even in advanced stage, the survival rates are considerable ranging from 60% to 80%. The presentation of MOGCTs may vary from pelvic pain which may be acute or subacute, menstrual irregularities, or abdominal mass. Evolution of management for MOGCT with conservative surgery and Cisplatin-based chemotherapy has dramatically improved the survival and preservation of fertility, especially in young patients.

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With Bleomycin, Etoposide, and Cisplatin (BEP), the 5-year survival has considerably increased to 100% for dysgerminoma and 85% for non-dysgerminomas.[4-6] Most of the patients resume their normal menstrual cycle and become pregnant after the entire treatment.[7,8] Stage Ia and grade 1 immature teratoma and Stage I a dysgerminoma do not require adjuvant chemotherapy after surgery[3] and can be kept under surveillance. In this paper, we have analyzed our experience of MOGCT including clinicopathological features, treatment, and outcomes.

MATERIALS AND METHODS

All patients with malignant ovarian cell tumors registered in our medical oncology department from January 2012 to December 2018 for 6 years were included and retrospectively reviewed. The data were retrieved from the medical record books and hospital-based cancer registry. The data collected included the age, presenting symptoms, details of investigations including imaging, tumor markers, treatment received (neo-adjuvant chemotherapy, surgery and adjuvant chemotherapy, and histopathological diagnosis were documented. The tumors were staged according to the Federation of Gynecology and Obstetrics staging system. The follow-up details were analyzed to record the data regarding resumption of menstrual cycles, ability to conceive in the patients who were eager for the same following fertility sparing surgery. The disease-free interval was derived. Five patients who had lost for follow-up were contacted through phone. Out of them one patient could not be contacted for recent updates. In majority of the patients, surgical procedure done was staging Laparotomy and unilateral salpingo-oophorectomy or total abdominal hysterectomy with bilateral salpingo-oopherectomy in patients who had advanced disease at presentation or completed their family due to the patient's preference. Peritoneal biopsies, omentectomy, and peritoneal washings were performed in those patients, where disease extended to the abdomen. The adjuvant chemotherapy offered was BEP given every 3 weeks with Inj. Bleomycin 30 units IV bolus given on days 1, 8, and 15, Inj. Etoposide 100 mg/m^2 IV infusion on days 1–5 and Inj Cisplatin 20 mg/m^2 IV infusion on days 1–5 with appropriate prehydration, premedications, and posthydration for 3–4 cycles depending on the risk stratification. Neoadjuvant chemotherapy with BEP was offered in few patients who were that the disease was inoperable or extensive/bulky disease. Salvage chemotherapy was administered with VIP every 3 weeks with Etoposide 75 mg/m^2 IV infusion, Ifosphamide 1500 mg/m^2 IV infusion with mesna days 1–5, and Cisplatin 20 mg/m^2 IV infusion days 1–5. All statistical analysis were performed using the Statistical Package for the Social Science, version 17 for Microsoft windows. Descriptive statistics was presented as numbers and percentages. The data were expressed as mean and standard deviation. A Chi-square test was used for comparison between two attributes. Kaplan–Meier survival analysis was used for analysis of disease-free interval and overall survival (OS). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Patient's Characteristics

The patient's age ranged between 9 and 65 years with a median age of 20 years. There was only one patient who was 65 years and post-menopausal. Two patients were in prepubertal age. With regard to the clinical features, abdominal pain was the most common symptom which was either acute or chronic. One patient aged 17 years presented with the primary amenorrhea and she was found to be syndrome 45,X. Four patients (9.8%) were incidentally diagnosed to have ovarian masses during pregnancy. Two patients (4.9%) presented with secondary infertility. Twenty-eight patients were unmarried (68.3%). Of the 13 women (31%) who were married, nine patients (22%) had completed their family. The patients' characteristics are enumerated in Table 1.

Disease characteristics

The most predominant pathology was dysgerminoma followed by equal distribution of yolk sac tumors and mixed GCT's. Immature teratoma was less observed. Most of the patients had unilateral disease, but three patients with dysgerminoma had bilateral disease. Majority were documented as Stage I followed by Stage III. Moreover, only two of them had Stage IV at presentation. Disease characteristics are enlisted in Table 2. Two patients had ascites and abdominal nodes diagnosed in the initial imaging and one patient had pleural effusion at presentation. All the ten cases of yolk sac tumors had significantly elevated serum Alphafetoprotein (AFP) levels (levels varying from 380 ng/ml to 190,000 ng/ml. 5/10 patients with

Table 1: Characteristics of patients with malignant ovarian germ cell tumors

Patient characteristics	No. of patients (%)
Total	41 (100)
Median age (range) years	20 (9–65)
Presentation	
Acute or subacute abdominal pain	19 (46.3)
Abdominal distention	9 (22)
Amenorrhea	2 (4.9)
Pregnancy	4 (9.8)
Infertility	2 (4.9)
Menstrual irregularity	5 (12.2)

mixed GCT also had raised S.AFP. 11/15 patients with dysgerminoma had raised serum lactate dehydrogenase.

Treatment Characteristics

Majority of them (n = 35, 85.4%) underwent unilateral salpingo-oopherectomy, conservative surgery with preservation of opposite ovary and uterus. Rest had total abdominal hysterectomy with bilateral oopherectomy. Thirty-one patients (75.6%) received adjuvant chemotherapy with BEP for three cycles. The patients who had Stage IA dysgerminoma and grade 1 and Stage IA immature teratoma did not receive chemotherapy and were kept under surveillance. Four patients had received neoadjuvant chemotherapy with three cycles of BEP due to advanced disease and then were amenable to fertility-preserving surgery, and postoperatively, there was no residual disease in the pathological specimen. The treatment details are given in Table 3.

Follow-Up

The follow-up period ranged from 24 to 84 (mean of 46 months), there was no evidence of disease in 37 patients. Three patients had recurrence within 1 year and they had advanced disease at presentation. One patient with yolk sac tumor presented with mediastinal and mesenteric lymphnodes after 9 months. The next patient who had mixed GCT presented with pericardial effusion. One patient with mixed GCT presented with metastases in the lung. The patients with recurrent disease received salvage chemotherapy with VIP regimen. Of them, one of the patient lost for follow-up and two were alive in their last follow-up. One patient with immature teratoma had residual disease postoperatively and finally had progressive disease since she had delayedly presented for adjuvant chemotherapy. She was started on salvage chemotherapy with VIP regimen. She lost for follow-up and died due to progressive disease. The follow-up and outcome data are enumerated in Table 4.

In our study, 34 patients resumed their regular menstruation. The mean time to resume their periods was 4 months from the time of their last chemotherapy. Excluding the six patients who had total abdominal hysterectomy, and 20 who were still unmarried on follow-up, 15 patients who were planning for pregnancy had conceived. One of the two patients who were in the pre pubertal age attained their menarche. Out of the four patients who were pregnant in their first trimester, three patients completed their treatment and delivered normal healthy babies after completing their gestation period. The other patients had preterm delivery at 26 weeks and the baby succumbed to death.

Survival Analysis

Disease-free survival (DFS) and OS were analyzed and the Kaplan–Meier survival curves were plotted. The

Table 2: Disease characteristics in the patients

Pathology	No. of patients (%)
Dysgerminoma	15 (36.6)
Yolk sac tumor	10 (24.4)
Immature teratoma	6 (14.6)
Mixed GCT	10 (24.4)
Stage	
I	21 (51.2)
II	5 (12.2)
III	13 (31.7)
IV	2 (4.9)

Table 3: Treatment given to the patients

Treatment received	No. of patients (%)
Surgical treatment	
Fertility sparing surgery	35 (85.4)
TAH/BSO	6 (14.6)
Chemotherapy	
Adjuvant chemotherapy/BEP	31 (75.6)
Neo adjuvant chemotherapy/BEP	4 (9.8)
No chemotherapy/surveillance	6 (10.6)
Salvage chemotherapy in recurrence	4/4

Table 4: Treatment outcome on follow-up

Outcome	No. of patients (%)
No evidence of disease	37 (90.2)
Disease Recurrence/metastatic disease	3 (7.3)
Disease, progression/delayed chemotherapy	1 (2.4)

OS rate for the entire cohort is 95.3% [Figure 1] and the DFS for 2 years is 92.5%. There was no significant difference in survival between patients who had fertility sparing surgery versus TAH/BSO (P = 0.361). The survival rate for dysgerminoma, yolk sac tumor, immature teratoma, and mixed GCT was 100%, 100%, 90%, and 90%, respectively, but there was no significant survival difference between the various histologies (P = 0.276). This survival curve is illustrated in Figure 2. The survival for Stages I, II, III, and IV was 100%, 87%, 84%, and 82%, respectively.

DISCUSSION

MOGCTs comprise a minor spectrum among the ovarian malignancies, their immense response after surgery and chemotherapy better long-term survival rates soars their importance. In our retrospective study, for 6 years from January 2012 to December 2018 which includes 41 patients, we have analyzed the epidemiological, disease, treatment characteristics, and their impact on disease-free and OS. At our hospital, the annual incidence of MOGCTs was approximately on average six cases per annum constituting 3–4% of the all ovarian tumors which

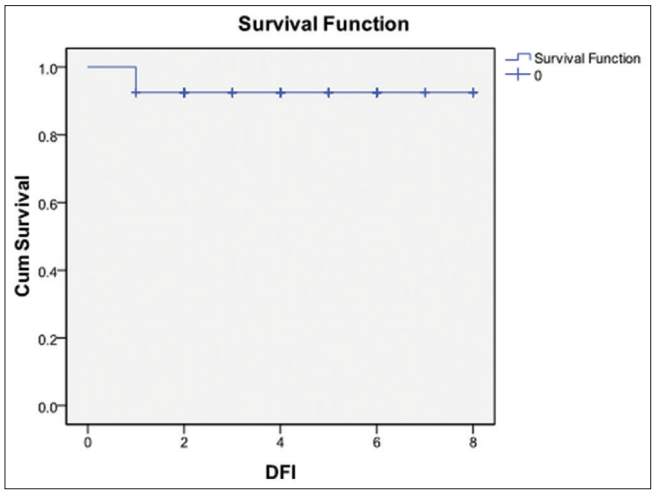

Figure 1: Disease-free survival for 2 years of our patients

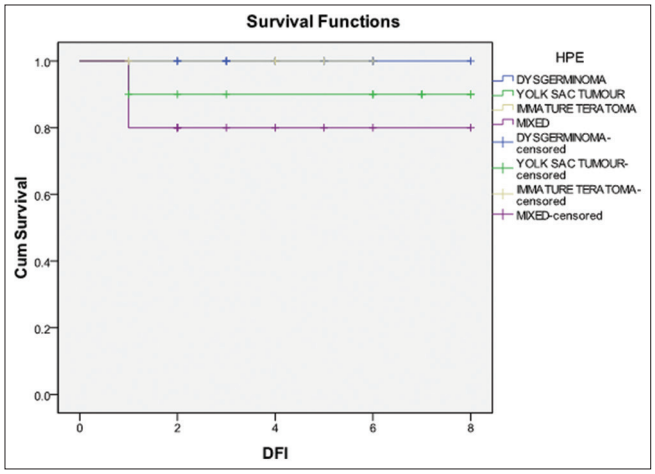

Figure 2: Disease-free survival for various histologies

are almost in par with the data given by Smith *et al*.[1] In our series, the median age is 20 years and most of the patients are in the second and third decade.[9] In this study, dysgerminoma comprises about 36.6 % (n = 15) which coincides with the Indian data. The predominant stage grouping in our retrospective cohort was stage I (n = 21, 51.2%). Out of this, there were six patients who did not receive chemotherapy. They were diagnosed as Stage I dysgerminoma and Stage I grade 1 immature teratoma and it is well established that surveillance is the management for the same. ESMO and NCCN also advocate that Stage IA pure dysgerminoma can be treated with surgery only. Recurrence rate following only surgery in the early stage is low (15–25%) and can be treated at the time of relapse with a high probability of cure.[3] In our series of patients, 35 (85.4%) had fertility sparing surgery that is unilateral salpingo-oopherectomy. Evidence is already there that conservative surgery does not increase risk of progression or any events.[10] Three out of four patients who had received neoadjuvant chemotherapy for advanced disease have also undergone conservative surgery. In view of the incidental age group of MOGCTs and established evidence of chances of fertility after treatment, emphasis should done for conservative surgery.[11] Adjuvant chemotherapy with BEP was administered in 31 patients (75.6%) which has been established earlier in number of trials.[4-6] Thirty-four of 35 patients resumed normal menstrual cycles after chemotherapy in a median period of 4 months. Recent studies have also reported that 80–90% of patients achieved a normal menses after fertility sparing surgery followed by chemotherapy.[12-14] Thirteen out of 15 patients who were eager to conceive were able to become pregnant. Many of our patients who were in second decade were still unmarried on follow-up. Recurrence occurred in only three patients which suggest its good prognosis.

Due to its rare incidence, the sample size in this study is also small to analyze the survival among our patients.

CONCLUSION

GCTs are typically occurring in younger girls and women with definite longevity of life after appropriate and adequate treatment with revival of fertility and menstrual functions in most of the individuals. Emphasis should be suggested to the patients on long-term follow-up also.

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