ORIGINAL ARTICLE

MALIGNANT OVARIAN GERM CELL TUMORS AT A TERTIARY CARE SETTING IN PAKISTAN

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Background: Malignant Ovarian Germ Cell Tumours (MOGCT) are rare neoplasms and their behavior is unknown in South-East Asian population. **Methods:** Case records of 66 patients from 1994–2007 with MOGCT were reviewed. Histology was based on WHO classification. Tumours were staged according to International Federation of Gynecology and Obstetrics (FIGO) system. Data was collected on age, histopathology, stage, alpha-feto protein (AFP) and B-human chorionic gonadotropins (B-hCG) levels, treatment, time to recurrence (TTR) and overall survival (OS). OS was the interval in months between date of diagnosis and last encounter while TTR was between the date of diagnosis and recurrence. OS was determined by Kaplan-Meier method. **Results:** Median age of our patients was 18 years. Ninteen patients were in stage I, eight in II, twenty-one in III and eighteen in stage IV. Histologically, dysgerminoma was the most common diagnosis (22 patients) followed by teratoma in 16, yolk sac tumor in 15, mixed germ cell tumor in 12 while embryonal carcinoma was identified in only one patient. Median followup was 48 months (0.2-183). All patients underwent initial surgery. Fertility sparing procedures were performed in 75% patients. Thirty-four patients (57.62%) achieved complete remission while 16 (27.11%) had progressive disease. Seven (10.60%) patients relapsed, all within first 3 years. TTR was 11.2–32.5 months. OS for study population was 60 months. Sixteen (88%) of stage I while only 4 (26.6%) of stage IV patients were alive at median follow-up. **Conclusions:** MOGCT has good prognosis with conservative surgery and platinum chemotherapy. Fertility sparing surgery has become a standard in MOGCTs, so awareness should be raised amongst professionals for early referral to cancer care facility.

Keywords: Ovarian, Malignant, Germ cell tumors.

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INTRODUCTION

Malignant ovarian germ cell tumors (MOGCTs) are uncommon neoplasms constituting only 2–3% of ovarian malignancies in the west.[1–3] Incidence is reported to be higher (8–19%) among Asian population.[4–6] These tumors are commonly seen in young girls and adolescents.[7]

Due to the reproductive and younger age groups, fertility preservation has been an important consideration while treating these tumors. Practically this translates into preservation of at least one ovary, fallopian tube and uterus or doing a wedge resection of tumor from involved side. Recently, use of effective chemotherapy after initial surgery has improved the outcome for women in the case of advanced disease.[8] Aim of the current study was to know the behaviour, characteristics and to analyse the outcome of MOGCT in Pakistani population.

MATERIAL AND METHODS

This retrospective review included all patients with a diagnosis of MOGCTs at Shaukat Khanum Memorial Cancer Hopsital and Research Centre (SKMCH and RC) from 1994 to 2007. Medical records were reviewed to obtain details about patient's characteristics, treatment and follow up. Sixty-six patients were identified with MOGCTs. Patients were included in this study if, after their initial diagnosis surgical and chemotherapeutic management was carried out at our institution. Histology was reviewed and classified according to WHO classification. Tumors were staged with regard to clinical and pathlogical presentation according to International Federation of Gynecology and Obstetrics (FIGO) staging system. After treatment completion, patients were followed up 3 monthly with clinical examination and tumor markers in the first two years, 6 monthly in third and fourth years and then annualy in oncology outpatient department. Telephonic interviews were conducted for patients who had lost to follow up till the time of data collection., which was January 2011.

Descriptive statistics were used to characterize patient population. Age was taken in median and range while counts and percentages were obtained for categorical variables. Overall survival was the primary endpoint and calculated as the time from diagnosis to last visit or date of death. Time to recurrence (TTR) was calculated as time of diagnosis to first evidence of recurrence. Overall survival (OS) was calculated using Kaplan-Meier method. All analysis was performed using the SPSS-20.0

SKMCH and RC cater for patients who have already been diagnosed elsewhere.Primary surgeries performed included tumor resection with preservation of maximum possible ovarian tissue. Biopsies were taken from the contralateral side for suspicious lesions.

Peritoneal washings and ascitic fluid cytology was also taken at the time of surgery.

Chemotherapy protocols were as follows: BEP (Bleomycin 15 mg/m^2 Day 1, 8, 15, Etoposide 100 mg/m^2 D1 to D5, Cisplatin 20 mg/m^2 D1 to D5); EP (Etoposide 100 mg/m^2 D1 to D5, Cisplatin 20 mg/m^2 D1 to D5); ICE (Ifosfamide 2500 mg/m^2 D1 to D4,Carboplatin 375 mg/m^2 on D1 to D4, Etoposide 600 mg/m^2 D1 to D4); VeIP (Vinblastine 0.11 mg/kg, Cisplatin 20 mg/m^2, Ifosfamide 1200 mg/m^2); VIP (Etoposide 75 mg/m^2,Cisplatin 20 mg/m^2, Ifosfamide 1200 mg/m^2).

BEP and EP were the standard protocols used; except for those who already received chemotherapy. Salvage chemotherapy was given to those patients who did not show response to first line agents. Number of cycles administered depended on the tumor response, patient's tolerance, and physician preference.

Before each cycle, complete blood counts, renal and hepatic function tests were obtained. At the end of treatment patients were advised 2 monthly followup for the first year, 3 monthly for the second and 6 monthly for third to fifth years. Follow up visit consisted of clinical examinations, tumor markers and radiological studies. After 5 years patients were referred to primary physicians.

Patients were declared to have complete remission with complete normalization of tumor markers (AFP $\leq$5 IU/ml, BhCG$\leq$1.4 IU/L) and no residual masses on imaging. Stable disease was documented as normalization of tumor markers and stable residual masses on serial imaging. Partial response was defined as decreasing tumor mass and normalization of tumor markers whereas recurrence was documented as reappearance of tumor mass on imaging with rise in AFP or B-hCG levels after complete response earlier.

RESULTS

The study included sixty-six patients. Median age was 18 years (Range: 6–48). Median followup time was 48 months (0.2–183). Characteristics of patients at diagnosis are summarized in table-1.

At the time of presentation, 13 patients had already undergone non-fertility sparing procedures. At our hospital 32 patients underwent fertility sparing surgeries. Twenty patients underwent second look laparotomies which were inconclusive. Overall 50 patients had undergone fertility sparing procedures whereas 16 patients were operated with a non-fertility preserving approach. Individual detail of surgery procedures is given in table-2.

Sixty-four patients who had residual disease after surgery or advanced disease initially were candidates for chemotherapy. Frequency of chemotherapy combinations used is shown in table-3.

The disease status could not be evaluated in seven patients: 5 were lost to followup and did not complete treatment while two patients died (one due to renal failure and other due to Ifosfamide induced encephlopathy). Fifty-nine patients were able to complete planned treatment. Thirty four patients (57.62%) showed complete remission, two patients (3.38%) had partial response whereas 6 patients (10.16%) had stable disease.

Sixteen patients (27.11%) did not respond to any chemotherapy and had progressive disease (1 patient with stage 1,1 with stage II, 6 with stage III and 8 with stage IV). Seven patients (10.60%) experienced recurrences (TTR: 11.2–32.5 months) within first three years. All relapsed patients received salvage chemotherapy; however disease was not controlled in any of these.

Survival analysis was conducted using the Kaplan-Meier method and results were considered significant at alphalevel of 0.05. Of 66 patients, 7 patients with unknown final patient status or death were removed and the analysis was conducted on the remaining 59 patients. Of the 59 patients, 36 (61.01%) were alive and 23 (38.98%) had expired. Of the 18 in stage I, 2 had died; of the 8 in stage II, 1 had died; of the 18 in stage III, 9 had died; and of the 15 in stage IV, 11 had died. Stage wise comparison showed a statistically significant difference in the equality of survival distributions between stages I and III (Log rank chi-square=8.5, df=1, *p*-value=0.004) and stages I and IV (Log rank chi-square=12.7, df=1, *p*-value<0.001). The 8-year cumulative probability of survival was as follows: Stage I-0.88, stage II-0.84, stage III-0.42, and stage IV-0.40. For stage III disease, the median survival time was 78 months, whereas, for stage IV disease, it was 30 months (Figure-1).

Table-1: Patient characteristics at start of treatment, n=66

Characteristic	Number of patients (n=66)	Percentage
Stage at presentation		
Stage I	19	28.78
Stage II	8	12.12
Stage III	21	31.18
Stage IV	18	27.27
Histological subtype		
Dysgerminoma	22	33
Malignant Teratoma	16	24
Yolk sac tumor	15	22
Mixed germ cell tumour	12	18
Embryonal Carcinoma	1	1.5
Laterality of Tumor		
Bilateral	9	13.6
Right Adnexal	33	50
Left Adnexal	13	19.7
Unknown	11	16.7
AFP Levels		
Elevated	29	43.93
Normal	25	37.87
Unknown	12	18
B-HCG levels		
Elevated	15	22
Normal	42	63.63
Unknown	9	13.6

Table-2: Surgery details of study population

	n=66	Percentage
Types of initial surgery		
Laparotomy + tumor excision	21	31.8
Unilateral salpingo-oophorectomy ± Omentectomy	29	43.93
TAH/BSO ± debulking	13	19.69
Biopsy only	3	4.5
Total	66	100
Fertility sparing procedure(s)		
Yes	50	75.75
No	16	24.24
Total	66	100

Table-3: Details of Chemotherapy Regimens

	Frequency	Percentage (%)
BEP	50	78.12
EP	4	6.25
VeIP	1	1.56
ICE	2	3.12
Others	7	10.93
Total	64	100

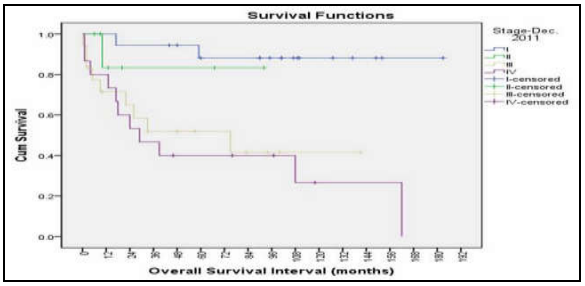

Figure-1: Kaplan-Meier survival analysis

DISCUSSION

Ovarian germ cell tumors have a high potential for cure with modern management. Very little data has been published on these tumors in South-East Asia. Their characteristics and properties might have been different in Asian females as compared to west. Median age of our patients at presentation was similar to most of the western and South East Asian data.[8–11] However the age range in our study was broader than west, in which it is around 10–39 years. The reason for this is unknown; genetics and environmental factors may have played some role.

MOGCT may be bilateral at times, Siriwan *et al* have shown a 7.7% incidence of bilaterality while other have shown a 10–15% incidence, similar to our results.[12] Low JJ and colleagues documented the lowest, 2.7% incidence in their series.[8] Clinically, it should be kept in mind that bilateral tumors are not always MOGCT, therefore a histopathological diagnosis must be obtained before any surgical procedure. Regarding histological subtypes, our results are similar to data presented by Low JJ et al.[8] Similarly a high incidence of dysgerminoma followed by the teratoma among MOGCTs has been reported by others.[13–15] No population based data have yet been published in Pakistan but few hospital based cancer reports confirm our findings.[7]

Majority of patients in our study presented with advanced stage in contrast to other Asian and western literature published. Low JJ *et al* had shown that approximately 79.8% patients present at early stage.[8,13,14] All recurrences in our study were experienced in advanced stage, however the recurrence rate in our population was comparable to Siriwan and colleagues who documented a 13.3% recurrence rate.[12] Poor socioeconomic status, lack of health facilities and health awareness are possible contributing factors in late presentation, which also play their role towards poor outcome. Patients in our study who completed treatment for early stage or advanced stage disease did well and had a prolonged survival. These results testify the good tumor sensitivity to upfront chemotherapy.[15] Low JJ *et al* showed a mean survival of 98.2% for stage I disease.[8] These results are better than our data which has 88% survival. In our results survival was 87% for stage II disease. However, due to unknown reasons it fell steeply below 50% for advanced stage, as compared to Low JJ *et al* who have shown 95% survival for advanced stage.[8] The results of our study are actually negatively skewed due to large number of advanced stage cases which has a poor prognosis. Other factors identified were delayed presentation, delay in chemotherapy after initial surgery and poor patient compliance to treatment.[5]

Our results show quite a few cases with chemotherapy unresponsiveness. Not much data is available; however Germa *et al* has reported only one case of chemotherapy resistance.[13] Exact mechanisms are unknown but patients partially treated at other hospitals may have developed resistant clones. This needs to be further evaluated in other studies.

Fertility sparing in MOGCT has now become a standard practice as evidenced by many authors and advanced disease is not considered a contraindication.[16–19] Many authors have shown a survival of 95–97% for stage I MOGCT treated with fertility sparing surgery with or without chemotherapy.[20–23] Siriwan *et al* concluded that approximately 73% patients may get conservative surgery initially.[12] Wu PC *et al* have concluded that preservation of fertility for young patients with ovarian germ cell tumors, regardless of the stage of the disease is a safe and practical procedure in the absence of involvement of the contralateral ovary.[11] We were able to preserve fertility in 75% cases as compared to this study. In their data primary surgery was performed by the gynecologist oncologist while our patients had surgery at outside facility with likley limited expertise in oncologic management. Thus it is emphasized that surgery should be done by experienced surgeons to preserve fertility.

Majority of second look surgeries in our cohort were for restaging as they were referred to us after initial incomplete surgery outside. There is no definite role of second look surgeries, if adequate initial surgery has

been done. However it may be performed in cases such as malignant teratoma, to resect mature teratomatous element. Culine and colleagues recommended only a limited benefit from restaging surgery except in a few patients, in whom there is a suspicion of recurrence or in case of development of another malignancy.[24]

Limitations of our study include missing information for a few patients. Results are also negatively skewed due to large number of advanced stage patients.

CONCLUSION

In conclusion, MOGCT have a good prognosis if diagnosed on time and treated at early stage. Fertility sparing surgery should be attempted in all cases. Surgery should always be attempted by experienced surgeons in gynecology oncology surgery as this has a major impact on future child bearing and prognosis. Prognosis is guarded for those who relapse with MOGCT. Moreover, awareness should be raised among practitioners in community for early referral to cancer care facility for optimal results.

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All authors significantly contributed in preparation of this manuscript according to ICMJE guidelines and final manuscript has been approved by all the authors.

REFERENCES

1. Gershenson DM. Management of ovarian germ cell tumors. J Clin Oncol 2007;25(20):2938–43.
2. Gershenson DM: Update on malignant ovarian germ cell tumors. Cancer 1993;71(4 Suppl): 1581–90.
3. Segelov E, Campbell J, Ng M, Tattersall M, Rome R, Free K, *et al*. Cisplatin-based chemotherapy for ovarian germ cell malignancies: the Australian experience. J Clin Oncol 1994;12(2):378–84.
4. Lim FK, Chanrachakul B, Chong SM, Ratnam SS. Malignant ovarian germ cell tumours: experience in the National University Hospital of Singapore. Ann Acad Med Singapore 1998;27(5):657–61.
5. Sarwar CM, Siddiqui N, Khokhar RA, Badar F. Epithelial ovarian cancer at a cancer hospital in a developing country. Asian Pac J Cancer Prev 2006;7(4):595–8.
6. Gilani MM, Behnamfar F, Zamani F, Zamani N. Frequency of different types of ovarian cancerin Vali-e-Asr hospital . (Tehran University of Medical Sciences) 2001-2003. Pak J Biol Sci 2007;10(17):3026–8.
7. Ahmad Z, Kayani N, Hasan SH, Muzaffar S, Gill MS. Histological pattern of ovarian neoplasma. J Pak Med Assoc 2000;50(12):416–9.
8. Low JJ, Perrin LC, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors. A review of 74 cases. Cancer 2000;89(2):391–8.
9. Gatphoh ED, Darnal HK. Pattern of ovarian neoplasm in Manipur. J Indian Med Assoc 1990;88(12):338–9.
10. Williams S, Blessing JA, Liao SY, Ball H, Hanjani P. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the Gynecologic Oncology Group. J Clin Oncol 1994;12(4):701–6.
11. Wu PC, Huang RL, Lang JH, Huang HF, Lian LJ, Tang MY. Treatment of malignant ovarian germ cell tumors with preservation of fertility: a report of 28 cases. Gynecol Oncol 1991;40(1):2–6.
12. Tangittagomal S, Hanprasertpong J, Manusirivithaya S, Wootipoom V, Thavaramara T, Buhachat R. Malignant ovarian germ cell tumors: clinico-pathological presentation and survival outcomes. Acta Obstet Gynecol Scand 2010;89(2):182–9.
13. Germá JR, Izquierdo MA, Seguí MA, Climent MA, Ojeda B, Alonso C. Malignant ovarian germ cell tumors: the experience at the Hospital de la Santa Creu i Sant Pau. Gynecol Oncol 1992;45(2):153–9.
14. Grischke EM, Wallwiener D, Bastert G. Characteristics of rare ovarian tumors-possibilities of organ preservation. Zentralbl Gynakol 1996;118(6):322–5.
15. El-Lamie IK, Shehata NA, Abou-Loz SK, El-Lamie KI. Conservative surgical management of malignant ovarian germ cell tumors: the experience of the Gynecologic Oncology Unit at Ain Shams University. Eur J Gynaecol Oncol 2000;21(6):605–9.
16. Perrin LC, Low J, Nicklin JL, Ward BG, Crandon AJ. Fertility and ovarian function after conservative surgery for germ cell tumours of the ovary. Aust N Z J Obstet Gynaecol 1999;39(2):243–5.
17. Ayhan A, Celik H, Taskiran C, Bozdag G, Aksu T. Oncologic and reproductive outcome after fertility-saving surgery in ovarian cancer. Eur J Gynaecol Oncol 2003;24(3-4):223–32.
18. Dark GG, Bower M, Newlands ES, Paradinas F, Rustin GJ. Surveillance policy for stage I ovarian germ cell tumors. J Clin Oncol 1997;15(2):620–4.
19. Zhang R, Sun YC, Zhang GY, Wu LY, Zou J. Treatmnent of malignant ovarian germ cell tumors and preservation of fertility. Eur J Gynaecol Oncol 2012;33(5):489–92.
20. Skof E, Grasic Kuhar C, Cerar O, Zakotnik B. Survival and fertility of patients with malignant ovarian germ cell tumours. Eur J Gynaecol Oncol 2004;25(6):702–6.
21. Peccatori F, Bonazzi C, Chiari S, Landoni F, Colombo N, Mangioni C. Surgical management of malignant ovarian germ-cell tumors: 10 years' experience of 129 patients. Obstet Gynecol 1995;86(3):367–72.
22. Al-Sayed MM, El-Sayed AA, El-Barbary TM, Hamad O. Conservative surgery in patients with malignant ovarian germ cell tumours. J Egypt Soc Parasitol 2011;41(3):737–44.
23. Weinberg LE, Lurain JR, Singh DK, Schink JC. Survival and reproductive outcomes in women treated for malignant ovarian germ cell tumors. Gynecol Oncol 2011;121(2):285–9.
24. Culine S, Lhomme C, Kattan J, Michel G, Duvillard P, Droz JP. Pure malignant immature teratoma of the ovary: the role of chemotherapy and second-look surgery. Int J Gynecol Cancer 1995;5(6):432–7.

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