ORIGINAL ARTICLE

MALIGNANT OVARIAN GERM CELL TUMOURS – SURVIVAL OUTCOMES FROM A SINGLE INSTITUTION IN PAKISTAN

Kamran Saeed[1], Tabinda Sadaf[1], Neelam Siddiqui[2], Aamir Ali Syed[3], Arif Jamshed[1]

[1]Department of Radiation Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, [2]Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, [3]Department of Surgical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan

Received: 1 June 2015 / Accepted: 2 October 2015

Abstract

Objectives: Malignant ovarian germ cell tumours (MOGCTs) are rare, but aggressive tumours seen mostly in young women or adolescent girls. The aim of our study was to evaluate the survival outcomes of MOGCT patients treated at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan.

Materials and Methods: One hundred and nine females were retrospectively identified through hospital information system with MOGCT from 2007 to 2013. Histology was based on the WHO classification. Tumours were staged according to the Federation of Gynaecology and Obstetrics staging system. Overall survival (OS) and disease-free survival (DFS) were determined by the Kaplan–Meier method. All patients were included in the study. Patient who had been lost to follow-up was contacted through telephone.

Results: Mean presenting age was 20 years (range 4–54). 38% of patients had Stage I, 7% had Stage II, 25% had Stage III and 30% of patients had Stage IV disease. Based on histology, 42% had dysgerminoma, 25% had mixed germ cell tumours, 18% had yolk sac tumour, 13% had teratoma and 2% had embryonal carcinoma. Median follow-up time was 41 months. All patients underwent initial surgery, of which 86 (79%) had fertility-preserving surgery. 91 (84%) patients received adjuvant chemotherapy and 18 (16%) were kept on surveillance. The chemotherapy regimen used was a combination of bleomycin, etoposide and cisplatin. 89 patients had a complete remission, 14 had partial response and one had progressive disease. Five patients had relapsed disease, four distant and one local. The 5-year OS was 91% and DFS was 88%.

Conclusion: MOGCTs have a good prognosis. Fertility-sparing surgery was possible in the majority of cases. BEP regimen has excellent activity and acceptable toxicity in patients with MOGCT.

Key words: Disease-free survival, malignant ovarian germ cell tumours, overall survival

Introduction

Malignant ovarian germ cell tumours (MOGCTs) are rare, but aggressive tumours that comprise 2–6% of all ovarian cancers and mostly affect young women.[1-3] MOGCTs consist of a broad variety of tumour types histologically derived from primordial germ cells and sex-stromal derivatives that differ with regard to their clinical presentation, tumour biology and histology.[4] Although these tumours have a rapid growth and are characterised by a large tumour size, almost all MOGCTs are sensitive to BEP chemotherapy consisting of bleomycin, etoposide and cisplatin. The contralateral ovary or the uterus is rarely involved, and thus, it is feasible to preserve fertility by preservation of the contralateral ovary, fallopian tube and uterus, without compromising the chances of a cure. Fertility can even be preserved in extensive and metastatic disease.

The most commonly seen histology is dysgerminoma followed by immature teratoma and endodermal sinus

Correspondence: Dr. Kamran Saeed, Department of Radiation Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan.
Email: drsaeedkamran@gmail.com

tumour (EST).[5] Mixed varieties of these tumours are also present with dysgerminoma and EST combination being the most common.[6] The typical tumour markers of these MOGCT cases are lactate dehydrogenase, alpha-fetoprotein and beta-hCG that are elevated in dysgerminoma, EST and choriocarcinoma, respectively.[6]

Since the most commonly affected population is young women and these tumours have a good response to chemotherapy with BEP (bleomycin, etoposide and cisplatin) regimen, the standard treatment of MOGCT is fertility-sparing surgery followed by adjuvant chemotherapy. One exception is Stage IA dysgerminoma or Grade I immature teratoma in which only surveillance is required after surgery.[7] With this treatment, the 5-year overall survival (OS) rate in the early stage disease is 100% while 70% in the advanced stage disease.[6]

Most of the data regarding MOGCTs have come from the Western countries while Asian data regarding this disease are limited.

Therefore, we conducted a retrospective review of the patients with a diagnosis of MOGCTs to assess the treatment outcomes at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, a single centre in Pakistan.

Materials and Methods

The study was approved by the Institution Review Board of Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore. It is a specialist care hospital situated in the central part of Pakistan. The medical records of 109 patients who presented with MOGCT between January 2007 and September 2013 were reviewed. Hospital information system was used to identify the detailed records of these patients. The basic clinical data, histology, stage, type of surgery, chemotherapy regimen and the outcomes were identified. All pathologic specimens were examined by gynaecologic pathologists at our institute. Histological classification was made according to the WHO classification. The International Federation of Gynaecology and Obstetrics (FIGO) staging system was used to stage these tumours.

Statistical analysis of the data was carried out using the SPSS software version 20. Kaplan–Meier method was used to analyse overall and disease-free survival (DFS) of these patients [Figures 1 and 2].

All the patients were included in the study and those who were lost to follow-up were contacted through telephone. The contact numbers were taken from the online data present in hospital information system.

The types of the surgery used in this study were defined as the following: (i) Total abdominal hysterectomy and bilateral salpingo-oophorectomy and (ii) fertility-sparing surgery.

Response to chemotherapy was evaluated using the WHO criteria. Serum tumour markers for GCT were regularly checked preoperatively, before each course of

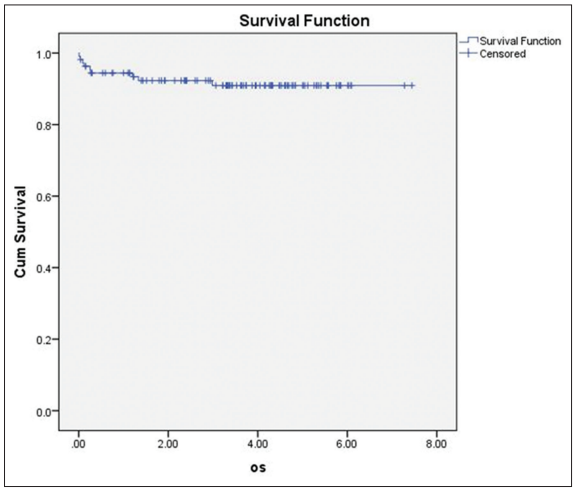

Figure 1: Overall survival (OS) of the patients

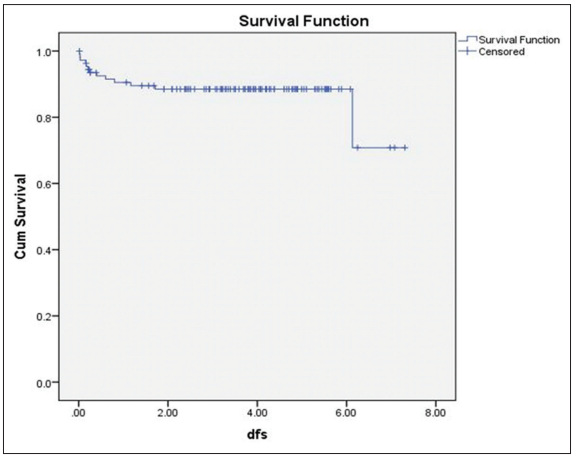

Figure 2: Disease-free survival (DFS) of the patients

chemotherapy, after the completion of the treatment and at follow-up visits.

After completion of treatment follow, visits were scheduled as follows: Every 3 months in the 1st year, every 4 months in the 2nd year and every 2 months in the 3rd–5th years and annually thereafter. Patients were examined by gynaecologic oncologists at every follow-up visit. Radiographic investigations pelvic ultrasound and CT scan were utilised when clinically indicated or in patients with rising tumour markers.

The OS was defined as the time between the diagnosis and date of last follow-up or death, whichever occurred first, whereas the DFS was defined as the time between completion of treatment and the date of the first relapse.

Results

The mean age of the patients at presentation was 20 years (range 4–54). Stage-wise distribution according to the FIGO staging system is shown in Table 1. Histologic distribution as per the WHO classification is shown in Table 2. Median follow-up time was 41 months. All patients underwent initial surgery, of which 86 (79%) had fertility-preserving surgery.

Postoperatively, 91 (84%) patients received chemotherapy and 18 (16%) were kept on surveillance. The chemotherapy regimen that was used consisted of three-drug combination: Bleomycin, etoposide and cisplatin. 89 patients were in complete remission, 14 had partial response and one had progressive disease. The response assessment was done biochemically as well as radiologically. Five deaths were reported, three due to chemotoxicity and one due to tumour lysis syndrome while one patient died due to encephalitis. A total of five patients developed disease relapse, of which four had distant metastasis and one patient had local recurrence as shown in Table 3. The 5-year OS was 91% and DFS was 88%. Earlier stage disease was associated with a better OS as compared to advanced stage disease [Figures 1-3].

Table 1: Stage-wise distribution

FIGO stage	Number of patients
I	41
II	8
III	28
IV	32
Total	109

Table 2: Histologic classification

Histologic classification	Number of patients
Dysgerminoma	46
Yolk sac tumour	20
Mixed germ cell tumour	27
Immature teratoma	12
Mature teratoma	2
Embryonal carcinoma	2
Total	109

Table 3: Patterns of relapse

Patterns of failure	Number of patients
Distant	4
Local	1

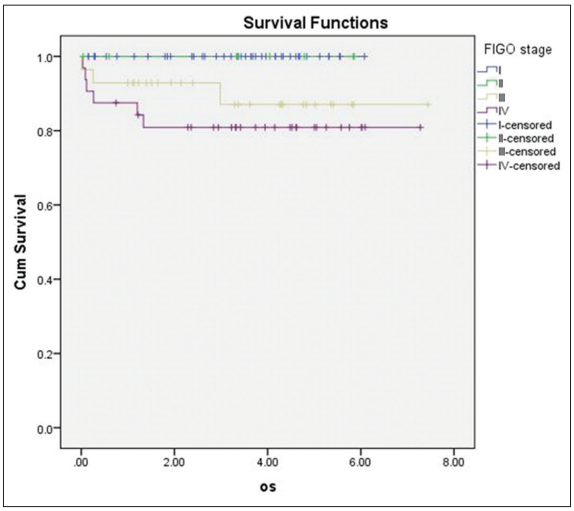

Figure 3: Overall survival (OS) according to disease stage

Discussion

The peak incidence of MOGCT is at the age of 15–19 years[6] which is close to the mean age of 20 years of the patients included in this study. However, we found two cases of age >50 years. MOGCTs in the fifth decade are quite rare.[8]

Solheim *et al*.[9] reviewed 351 Norwegian patients with MOGCT and found that patients over 50 years of age had a significantly poorer prognosis than younger patients contrary to the cases present in this study that showed a pathologic complete response to the chemotherapy.

The most common presenting symptoms in the present study were a pelvic mass and pelvic pain. This corresponds to a previous report in which over 80% of the MOGCT patients presented with pelvic mass and pain.[5,10] The most common type of MOGCT in literature review is dysgerminoma, a finding that is consistent with our study.[1,8]

As MOGCTs often present at a young reproductive age and are chemosensitive tumours, the conservative surgical i.e., unilateral adnexectomy, omentectomy, peritoneal washing, peritoneal biopsies and retroperitoneal lymphadenectomy followed by adjuvant chemotherapy (except in Stage I dysgerminoma and Grade 1 immature teratoma) is the standard of care.[8,10] Mahdi *et al*.[11] compared 493 MOGCT patients who underwent lymphadenectomy with 590 MOGCT patients who did not have lymphadenectomy and found that neither lymphadenectomy nor lymph node metastasis was an independent prognostic factor for survival. Furthermore, even in the advanced stage, a fertility-sparing surgery also yielded good outcomes.[12,13] In the present study, about 79% of the patients had fertility-sparing surgery and most of them were young adults.

Although MOGCTs are aggressive tumours, the 5-year survival of patients even in the advanced stages is 60–80%.[14,15]

The recurrences of MOGCTs are also sensitive to chemotherapy;[14] these recurrences rarely involve the contralateral ovary or uterus,[9] and thus, the removal of the contralateral ovary and uterus does not improve the prognosis.[16,17] Fertility-preserving surgery may be considered for patients with MOGCTs to improve the quality of life regardless of stage or pathological type.

Therefore, patients with MOGCTs who seek preservation of fertility are entitled to conservative surgery,[18] a decision that should not be affected by the pathological type or stage. In a retrospective study with a large sample size, Chan *et al*.[3] concluded that fertility-sparing surgery had no effect on the long-term survival of patients with MOGCTs. For further confirmation that surgery, chemotherapy and ovarian protection methods preserve fertility in the long-term prognosis;[19] more prospective, randomised controlled studies are needed.

The standard chemotherapy of MOGCT is a BEP regimen that consists of a combination of bleomycin, etoposide and cisplatin. A recent report from an Italian study showed a 5-year OS rate of 88.8% in 123 MOGCT patients.[1] This is almost similar to our study where the 5-year OS rate was 91%.

Majority of the patients were able to complete their chemotherapy as it was quite well tolerated. A total of nine deaths were reported; four due to chemotoxicity and one death due to tumour lysis syndrome, acute myelogenous leukaemia, encephalitis, growing teratoma syndrome and progressive disease each. Amongst the patients who received chemotherapy, two developed leukaemia as the second primary, one had acute myelogenous leukaemia and the other had acute lymphogenous leukaemia.

The strengths of our study are that it was done in a single institute that might decrease the variation of surgical technique and the types of chemotherapy regimens.

The limitations of the study were its retrospective nature and a limited number of patients due to the rarity of the disease.

Conclusion

MOGCTs often occur in the young reproductive age with successful outcomes using a combination of conservative surgery and adjuvant chemotherapy. Majority of the patient can be treated with fertility preservation surgery. These tumours tend to have a very good prognosis, OS and DFS. The BEP chemotherapy is well tolerated with limited toxicity.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Bhurgri Y, Shaheen Y, Kayani N, *et al.* Incidence, trends and morphology of ovarian cancer in Karachi (1995-2002). Asian Pac J Cancer Prev 2011;12:1567-71.

2. Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. Cancer Treat Rev 2008;34:427-41.
3. Chan JK, Tewari KS, Waller S, *et al.* The influence of conservative surgical practices for malignant ovarian germ cell tumors. J Surg Oncol 2008;98:111-6.
4. Sviracević B, Sedlar S, Malobabić D, *et al*. Mixed malignant germ cell tumor of ovary. Med Pregl 2011;64:93-5.
5. Bilici A, Inanc M, Ulas A, *et al.* Clinical and pathologic features of patients with rare ovarian tumors: Multi-center review of 167 patients by the anatolian society of medical oncology. Asian Pac J Cancer Prev 2014;14:6493-9.
6. Parkinson CA, Hatcher HM, Ajithkumar TV. Management of malignant ovarian germ cell tumors. Obstet Gynecol Surv 2011;66:507-14.
7. Gershenson DM. Treatment of ovarian cancer in young women. Clin Obstet Gynecol 2012;55:65-74.
8. Low JJ, Ilancheran A, Ng JS. Malignant ovarian germ-cell tumours. Best Pract Res Clin Obstet Gynaecol 2012;26:347-55.
9. Solheim O, Kærn J, Tropé CG, *et al.* Malignant ovarian germ cell tumors: Presentation, survival and second cancer in a population based Norwegian cohort (1953-2009). Gynecol Oncol 2013;131:330-5.
10. Matei D, Brown J, Frazier L. Updates in the management of ovarian germ cell tumors. Am Soc Clin Oncol Educ Book 2013;2013:210-6.
11. Mahdi H, Swensen RE, Hanna R, *et al.* Prognostic impact of lymphadenectomy in clinically early stage malignant germ cell tumour of the ovary. Br J Cancer 2011;105:493-7.
12. Vazquez I, Rustin GJ. Current controversies in the management of germ cell ovarian tumours. Curr Opin Oncol 2013;25:539-45.
13. Billmire D, Vinocur C, Rescorla F, *et al*. Outcome and staging evaluation in malignant germ cell tumours of the ovary in children and adolescents: An intergroup study. J Pediatr Surg 2004;39:424-9.
14. Kondagunta GV, Bacik J, Donadio A, *et al.* Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 2005;23:6549-55.
15. Lee KH, Lee IH, Kim BG, *et al*. Clinicopathologic characteristics of malignant germ cell tumors in the ovaries of Korean women: A Korean gynecologic oncology group study. Int J Gynecol Cancer 2009;19:84-7.
16. Alcazar JL, Guerriero S, Pascual MA, *et al*. Clinical and sonographic features of uncommon primary ovarian malignancies. J Clin Ultrasound 2012;40:323-9.
17. Shen K. Problems of fertility preservation treatment in gynecologic oncology. Zhonghua Fu Chan Ke Za Zhi 2006;41:219-21.
18. Abdel-Hady ES, Abdel-Hady Hemida R, Gamal A, *et al*. Fertility sparing surgery for ovarian tumors in children and young adults. Arch Gynecol Obstet 2012;285:469-71.
19. Matsushita H, Arai K, Fukase M, *et al*. Growing teratoma syndrome of the ovary after fertility-sparing surgery and successful pregnancy. Gynecol Obstet Invest 2010;69:221-3.