MALIGNANT OVARIAN GERM CELL TUMOURS (MOGCT); SURVIVAL OUTCOMES FROM A SINGLE INSTITUTION IN PAKISTAN.

Kamran Saeed¹, Tabinda Sadaf¹, Neelam Siddiqui ², Aamir Ali Syed³, Arif Jamshed ¹
Department of Radiation Oncology¹, Medical Oncology², Surgical Oncology ³, 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 (MOGCT) are rare but aggressive tumours, seen mostly in young women or adolescent girls. The aim of our study was to evaluate survival outcomes of MOGCT patients treated at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan.

Methods: One hundred and nine females were retrospectively identified via hospital information system with MOGCT from 2007 to 2013. Histology was based on WHO classification. Tumours were staged according to FIGO 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, were contacted via telephone.

Results: Mean presenting age was 20 years (range 4-54). 38% patients had stage I, 7% had stage II, 25% had stage III and 30% 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 out of which 86(79%) had fertility preserving surgery. Ninety one (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 1 had progressive disease. 5 patients had relapsed disease, 4 distant and 1 local. The 5 years overall survival (OS) was 91% and disease free survival (DFS) was 88%.

Conclusion: Malignant ovarian germ cell tumours 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: Malignant ovarian germ cell tumours, overall survival, disease free survival

Introduction:
Malignant ovarian germ cell tumours (MOGCT) are rare but aggressive tumours that comprise 2-6% of all ovarian cancers and mostly affect young women¹,²,³. 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 histology⁴. Although these tumours have a rapid growth and are characterized 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 tumour (EST)⁵. Mixed varieties of these tumours are also present with dysgerminoma and EST combination being the most common⁶. The typical tumour markers of these MOGCT cases are

Corresponding author: Dr. Kamran Saeed MBBS, Radiation Oncology Department, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. Email: drsaeedkamran@gmail.com
lactate dehydrogenase (LDH), alfa-fetoprotein (AFP), and beta-hCG that are elevated in dysgerminoma, EST, and choriocarcinoma, respectively. 

Since the most commonly affected population is young women and these tumours have a good response to chemotherapy with BEP (bleomycin, etoposide, 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. With this treatment, the 5-year overall survival rate in the early stage disease is 100% while 70% in the advanced stage disease.

Most of the data regarding MOGCTs have come from the Western countries while Asian data regarding this disease is limited. Therefore, we conducted a retrospective review of the patients with a diagnosis of Malignant ovarian germ cell tumours to assess the treatment outcomes at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, a single centre in Pakistan.

Methods and Materials:

The study was approved by the Institution review board of Shaukat Khanum Memorial Cancer Hospital & 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. 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 of these patients.

All the patients were included in the study and those who were lost to follow up were contacted via 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, ii) Fertility sparing surgery.

Response to chemotherapy was evaluated by using WHO criteria. Serum tumour markers for GCT were regularly checked preoperatively, prior to each course of chemotherapy, after the completion of the treatment and at follow up visits.

After completion of treatment follow visits were scheduled as following: every three month in the first year, every four months in the second year, and every six months in the third to fifth year and annually thereafter. Patients were examined by gynaecologic oncologists at every follow up visit. Radiographic investigations pelvic ultrasound and CT-scan were utilized when clinically indicated or in patients with rising tumour markers.

The overall survival (OS) was defined as the time between the diagnosis and date of last follow up or death, whichever occurred first whereas the disease free survival (DFS) was defined as the time between completion of treatment and the date of 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 the table 1. Histologic distribution as per WHO classification is shown in the table 2. Median follow up time was 41 months. All patients underwent initial surgery out of which 86 (79%) had fertility preserving surgery. Post-operatively, 91(84%) patients received chemotherapy and 18(16%) were kept on surveillance. The chemotherapy regimen that was used consisted of 3 drug combination: Bleomycin,
Etoposide and Cisplatin. Eighty nine patients were in complete remission; 14 had partial response and 1 had progressive disease. The response assessment was done biochemically as well as radiologically. 5 deaths were reported, 3 due to chemo toxicity, 1 due to tumour lysis syndrome while 1 patient died due to encephalitis. A total of 5 patients developed disease relapse out of which 4 had distant metastasis and 1 patient had local recurrence as shown in table 3. The 5 years overall survival (OS) was 91% and disease free survival (DFS) was 88%. Earlier stage disease was associated with a better OS as compared to advanced stage disease as shown in figure 3.

Table 1: Stage wise distribution

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>41</td>
</tr>
<tr>
<td>II</td>
<td>8</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
</tr>
<tr>
<td>IV</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
</tr>
</tbody>
</table>

Table 2: Histologic classification

<table>
<thead>
<tr>
<th>Histologic classification</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>46</td>
</tr>
<tr>
<td>Yolk Sac tumour</td>
<td>20</td>
</tr>
<tr>
<td>Mixed Germ Cell Tumour</td>
<td>27</td>
</tr>
<tr>
<td>Immature Teratoma</td>
<td>12</td>
</tr>
<tr>
<td>Mature Teratoma</td>
<td>2</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
</tr>
</tbody>
</table>

Table 3: Patterns of Relapse

<table>
<thead>
<tr>
<th>Patterns of failure</th>
<th>Number of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant</td>
<td>4</td>
</tr>
<tr>
<td>Local</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig 1: Overall survival of the patient

Fig 2: Disease free survival of the patients

Fig 3: Overall Survival according to disease stage
Discussion:

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

Solheim et al 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 eighty percent of the MOGCT patients presented with pelvic mass and pain. The most common type of MOGCT in the literature review is dysgerminoma, a finding that is consistent with our study.

As MOGCTs often present at a young reproductive age and are chemosensitive tumors, 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 I immature teratoma) is the standard of care. Mahdi et al, 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. In the present study, about 79% of the patients had fertility sparing surgery and most of them were young adults.

Although MOGCTs are aggressive tumors, the 5-year survival of patients even in the advanced stages is 60–80%.

The recurrences of MOGCTs are also sensitive to chemotherapy; these recurrences rarely involve the contralateral ovary or uterus, and thus the removal of the contralateral ovary and uterus does not improve the prognosis. 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, 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 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, more prospective, randomized 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 five year overall survival rate of 88.8% in 123 MOGCT patients. This is almost similar to our study where the five year overall survival rate was 91%.

Majority of the patients were able to complete their chemotherapy as it was quite well tolerated. A total of 9 deaths were reported; 4 due to chemotoxicity and 1 death due to tumour lysis syndrome, acute myelogenous leukaemia, encephalitis, growing teratoma syndrome and progressive disease each. Among 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:

In conclusion, MOGCTs often occurs in the young reproductive age with successful outcomes by 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, overall survival and disease free survival. The BEP chemotherapy is well tolerated with limited toxicity.

References: