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Clinicopathological Pattern and Survival Outcome of Malignant Ovarian Germ Cell Tumors: A Retrospective Study

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ABSTRACT

Objective: The objective of this study was to evaluate the clinicopathological pattern and survival outcome of Malignant Ovarian Germ Cell Tumors (MOGCTs).

Materials and methods: Thirty seven patients with MOGCTs were retrospectively identified through hospital information system from 2013 to 2018. Tumors were staged according to the International Federation of Gynecology and Obstetrics staging system and histology was based on the WHO classification. Clinicopathological characteristics and overall survival and progression free survival were determined by the Kaplan–Meier method. All patients were included in the study.

Results: The mean age of the patients was 19.9 ± 5.42 years. Most of them were unmarried ($n = 31$, 83.78%). The most common mode of presentation was pain abdomen and abdominal mass in 15 (40.54%) cases followed by abdominal pain alone in 12 (32.43%) cases, abdominal mass in four (10.81%) cases and incidental findings were in six (16.21%) cases. The most common histological type was immature teratoma in 14 (37.83%) followed by dysgerminoma in eight (21.62%), yolk sac tumor in seven (18.91%) and mixed germ cell tumor in seven (18.91%). Twenty seven (72.97%) patients presented in early stage of disease. The median follow up period was 36.75 (6-77) months. Progression free survival was 34.02 months and overall survival was 36.75 months and the overall survival rate was 94.59%. Five patients had disease relapse, two distant and three local recurrences.

Conclusion: MOGCTs are rare. They generally affect the young women and are diagnosed at an early stage. They have excellent prognosis with fertility sparing surgery and adjuvant chemotherapy even in advanced stage.

Keywords: Kaplan–Meier method, malignant ovarian germ cell tumors, teratoma, survival rate.

INTRODUCTION

Malignant Ovarian Germ Cell Tumors (MOGCTs) consist of a broad variety of tumor types histologically derived from primordial germ cells that differ with regard to their clinical presentation, tumor biology and histology.¹ MOGCTs account for less than 5% of all ovarian cancers in western countries,² however in Asian and Black Societies the incidence is as high as 15%.³

Eighty percent of MOGCTs are diagnosed before 30 years of age, and 70-75% of patients have stage I disease. MOGCTs constitute one-third of germ cell

origin tumors and two-thirds of all ovarian malignancy in this age-group. MOGCTs are also seen in the third decade, after that they become quite rare.^{4,5} The most common presenting symptom is rapidly progressive

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abdominal pain associated with a palpable abdominal and/or pelvic mass.^{6,7}

The current standard treatment regimen includes fertility sparing surgery whenever appropriate along with a thorough staging procedure, followed by adjuvant combination chemotherapy with bleomycin, etoposide and cisplatin (BEP). One exception is Stage IA pure dysgerminoma and Stage IA Grade 1 immature teratoma in which only surveillance is required after surgery. With this treatment, the 5-year overall survival (OS) rate in the early stage disease is 100% and as high as 70% in the advanced stage disease.⁸

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.⁹⁻¹¹ The recurrences of MOGCTs are also sensitive to chemotherapy.¹²

MATERIALS AND METHODS

This is a single hospital based retrospective study conducted at VPS Lakeshore Hospital, Kerala, India. All the patients diagnosed with MOGCTs between 2013 and 2018 were included in the study. Information regarding demographic, clinical, surgicopathological characteristics, management patterns and recurrence was collected retrospectively from electronic medical records and hospital based cancer registry. Histological classification was made according to the WHO classification and staging according to International Federation of Gynaecology and Obstetrics (FIGO) staging system.

A fertility sparing operation was defined as preservation of the uterus and at least part of one ovary to preserve fertility. Disease free survival (DFS) was defined as the time between completion of treatment and the date of the first recurrence and overall survival (OS) was defined as the time from diagnosis to date of death or last follow up which ever occurred first.

Depending upon the clinical, radiological and pathological findings, patient either underwent upfront surgery or got neoadjuvant chemotherapy (NACT). Before starting NACT pathological diagnosis of MOGCT was made by biopsy taken from the primary site or metastatic site. For NACT group, after two to three cycles of chemotherapy, patient was reassessed clinically

and radiologically for response to chemotherapy and then interval debulking surgery was done. For upfront surgery group, on the basis of surgical findings and final histopathological report adjuvant therapy was given. Complete surgical staging with unilateral salpingo-oophorectomy (USO), omentectomy, peritoneal biopsies, washings, bilateral pelvic and paraaortic lymphadenectomy were done whenever indicated. The chemotherapy regimen included the BEP regimen which was usually administered three to four cycles.

After completion of treatment, patients was kept on active surveillance with clinical examination, tumor markers and ultrasound. Additional radiological investigation like CT scan was utilized when clinically indicated or when recurrence was suspected. Patients were followed up every 3-4 months for first 2 years and every 6 months for next 3 years and then annually.

Data collection and entry was done in Microsoft Excel spreadsheet and was subsequently imported to Statistical Package for Social Sciences (SPSS TM) software version 20 for analysis. Continuous variables were presented in means and categorical variables were expressed as frequency and percentages.

RESULTS

During this study period, total of 37 patients were identified. The clinicopathological features of the study population have been mentioned in Table 1. The mean age of presentation was 19.9 years. Majority of them (37.80%) were in the age group of 16-20 years. The clinical characteristics, treatment and outcome of patients with recurrence have been mentioned in Table 2.

Most of them were unmarried [N=31/37 (83.78%)]. Only 6 (16.21%) patients were parous. The most common mode of presentation was abdominal pain and mass in 15(40.54%) cases followed by pain abdomen alone in 12 (32.43%) cases, and then incidental finding in 6 (16.21%) cases and mass per abdomen in 4 (10.81%) cases. The size of ovarian cyst was less than 10 cm in 6 (16.21%) patients, between 10-20 cm in 19 (51.35%) patients, and more than 20 cm in 12 (32.43%) patients.

The tumor subtypes included 14(37.83%) immature teratomas, 8 (21.62%) dysgerminomas, 7 (18.91%) yolk sac tumors, 7 (18.91%) mixed germ cell tumor and 1 (2.7%) embryonal carcinoma. Most of the patients i.e. 27 (72.97%) presented in early stage of disease.

Table 1
Clinicopathological features of the study population (n = 37)

Variables	Frequency (%)
Mean age at diagnosis (SD)	19.9 ± 5.42 (years)
Medial follow up period (IQR)	36.75 (6- 80 months)
Marital status	
Unmarried	31(83.78%)
Married	6(16.21%)
Parity	
Nulliparous	31(83.78%)
P1	5(13.51%)
P3	1(2.7%)
Initial presenting complains	
Pain and abdominal mass	15(40.54%)
Pain abdomen	12(32.43%)
Mass per abdomen	4(10.81%)
Incidental finding	6(16.21%)
Tumor size (cm)	
<10 cm	6(16.21%)
10-20 cm	19(51.35%)
>20 cm	12(32.43%)
Histological types	
Immature teratoma	14(37.83%)
Dysgerminoma	8(21.62%)
Yolk sac tumor	7(18.91%)
Mixed germ cell tumor	7(18.91%)
Embryonal carcinoma	1(2.7%)
FIGO stage	
I	27(72.97%)
II	1(2.7%)
III	8(21.62%)
IV	1(2.7%)

Fertility sparing surgery was performed in 35 (94.59%) patients. Only two patients who had completed their family underwent Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy (TAH + BSO) and staging (TAH + BSO), both were from early stage disease. In fertility sparing surgery, four patients (Stage IA disease) underwent unilateral salpingo-oophorectomy (USO) alone whereas USO and staging was done in 31 cases.

Nine patients with clinically suspicious and three patients with palpable pelvic lymph nodes underwent excision of nodes and final pathological reports showed no metastasis.

The median follow up period was 36.75 (6-80) months. Disease free survival was 34.02 months and overall survival was 36.75 months. The overall survival rate was 94.59%.

Among 27 cases of early stage diseases, three patients had incomplete surgery done outside that later underwent completion surgery (USO and staging) in our center. Two patients who completed their family and not desirous of further pregnancy underwent TAH+BSO and staging. The different methods of treatment received and outcomes (Flow charts 1 and 2).

DISCUSSION

MOGCTs are rare, aggressive but curable tumors accounting for approximately 1–2% of all ovarian malignancies.² The peak age of incidence is 15-19 years of age.⁸ In this study the incidence of MOGCTs was 8.52% among all the ovarian malignancies with mean age at occurrence of 19.9 ± 5.42 years and most patients were in the age group of 16-20 years (37.80%).

The most common presenting symptom in the present study was 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.^{6,7} In about 10% of women, the mass may grow rapidly, resulting in acute abdominal pain related to capsular distention, necrosis, hemorrhage, rupture or torsion of the ovarian tumor.

Most of the previous studies have shown the most common histological type of MOGCT as dysgerminoma,³ but in this study it is immature teratoma. However, the study done by Chan JK et al.,¹³ showed the similar pattern of histological type as in this study where the most common type was immature teratoma followed by dysgerminoma, yolk sac tumor and mixed germ cell tumor.

MOGCTs usually present in Stage I.¹⁴ 72.97% of patients in this study presented in early stage of disease. As MOGCTs often present at a young reproductive age and are chemosensitive tumors, the conservative surgical, i.e. USO, 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.^{3,7}

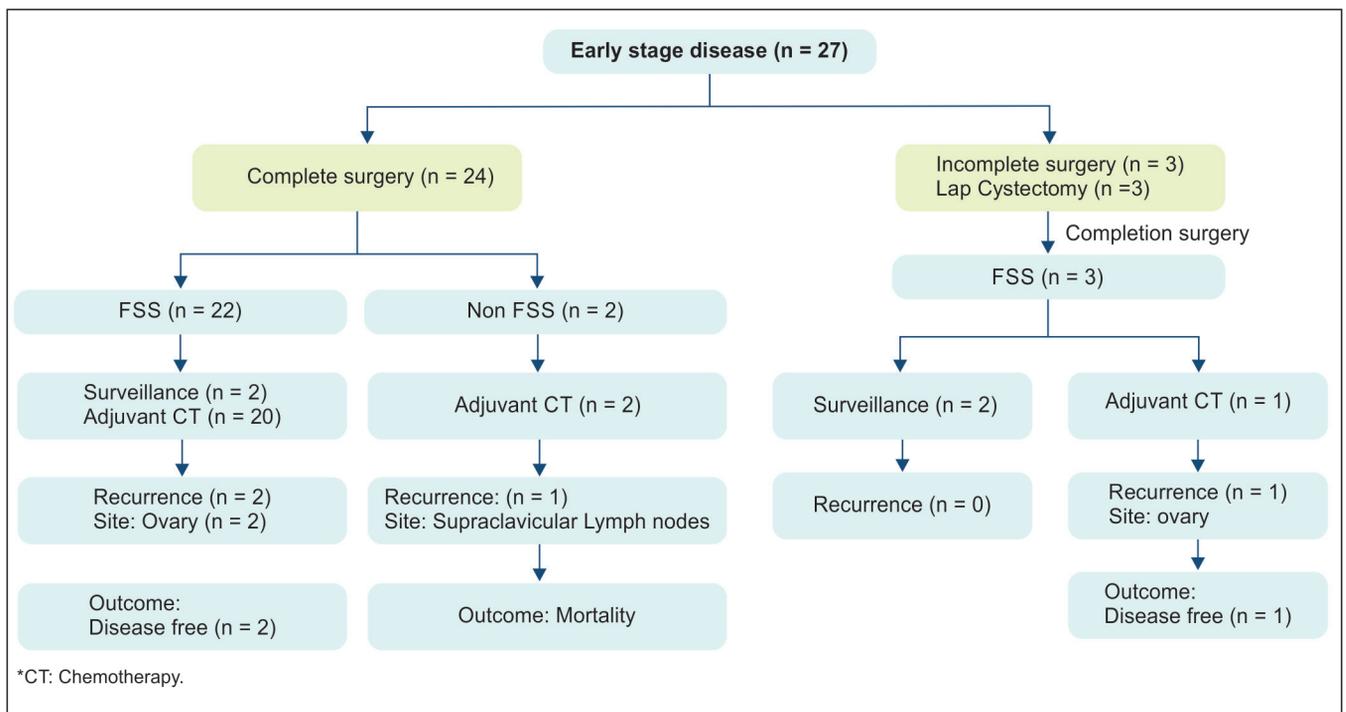
MOGCTs are potentially curable after fertility sparing surgeries followed by adjuvant therapy, with overall survival rates of at least 95% for stage I and 75% for higher stages of the disease.^{3,15} Fertility sparing procedures should be performed in combination with comprehensive surgical staging surgeries. Chan JK, et al.¹⁶ found that comprehensive surgical staging with lymphadenectomy

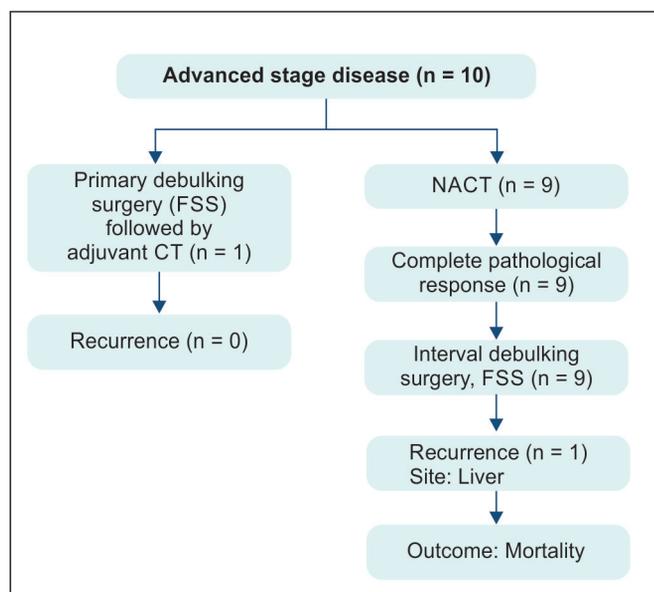
Table 2

Clinical characteristics, treatment and outcome of patients with recurrence (n = 5)

Variables	Frequency (%)
Median time of recurrence (range) in months	18.8 months (5-35 months)
Stage	
Stage IA	2(40%)
Stage IC	2(40%)
Stage IV	1(20%)
Histological types	
Immature teratoma, Grade 2	1(20%)
Immature teratoma, Grade 3	3(60%)
Embryonal carcinoma	1(20%)
Site of recurrence	
Localized	3(60%)
Disseminated	2(40%)
Initial treatment	
Primary surgery followed by active surveillance	2(40%)
Primary surgery followed by adjuvant chemotherapy	1(20%)
Incomplete surgery followed by completion surgery and adjuvant chemotherapy	1(20%)
Interval debulking surgery	1(20%)
Treatment of recurrence	
Secondary cytoreductive surgery with chemotherapy (all were fertility sparing surgery)	3(60%)
Excision of metastatic lesion and chemotherapy	2(40%)
Outcome	
Disease free	3(60%)
Mortality	2(40%)

Flow chart 1: Treatment and outcome pattern in early stage MGCOTs



Flow chart 2: Treatment and outcome pattern in advanced stage MGCOTs

is associated with an improved outcome. Furthermore, even in the advanced stage, a fertility-sparing surgery also yielded good outcomes.^{17,18} In the present study, about 79% of the patients had fertility-sparing surgery and most of them were young adults.

A study of the Pediatric Oncology Groups/Children's Cancer Group (POG/CCG) with MOGCTs suggested that an intraoperative clinical assessment of grossly normal lymph nodes is accurate in ruling out metastasis.¹⁸ In another POG/CCG intergroup, Roger et al.¹⁹ didn't find any histological evidence of lymphatic metastasis in any of the lymph node samples resected, even in macroscopically suspicious nodes. In this study also nine patients with clinically suspicious and three patients with palpable pelvic lymph nodes underwent excision of nodes and there were no metastasis.

Before the emergence of cisplatin-based chemotherapy, stage I nondysgerminomatous germ cell tumors had actuarial survival rates of around 50–60% even with complete surgical staging.²⁰ With the use of adjuvant chemotherapy in all nondysgerminomatous germ cell tumor patients (except for Grade I immature teratoma) the cure rate is as high as 98%.²¹ In one study the relapse rate of Grade 3 immature rate with active surveillance was 70% and hence the author strongly recommended adjuvant chemotherapy.²⁰ Billmire et al.²² showed the recurrence rate of 48% in yolk sac and mixed tumor with 4-year survival rate of 96% in active surveillance group.

Recurrence was observed in five (6.8%) patients and was influenced by the histological subtype and grade of tumor. The median period for recurrence was 14.75 months. Among five recurrences, three patients had local recurrence and underwent secondary cytoreduction surgery and chemotherapy. Two patients had distant metastasis and expired. First patient had metastatic left supraclavicular lymphnode after 14 months of primary surgery; lymph node dissection followed by second line chemotherapy was given to her but she expired after 5 months of recurrence. Second patient had isolated metastatic liver lesion which was diagnosed after 5 months of primary surgery. She underwent liver metastatectomy and chemotherapy; however, patient expired 4 months after the second surgery.

For recurrent disease there is a possible role of secondary cytoreductive surgery only in selected patients; those with an isolated focus or limited foci of recurrence.^{23,24} In this study also secondary reductive surgery was beneficial only for those patients with disease limited to pelvis. Munkarah et al.²⁴ reported improved survival only in immature teratoma with secondary surgery.

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

CONCLUSION

MOGCTs are rare ovarian tumors which often occur in young age in early stage of disease. With conservative surgery and adjuvant chemotherapy the prognosis is excellent.

Source of Support

Nil

Conflict of Interest

There are no conflict of interest.

Financial Disclosure

None

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