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Clinical Characteristics and Treatment Outcomes of Patients with Malignant Ovarian Germ Cell Tumors: A Retrospective Monocentric Study

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Abstract

Background: Malignant Ovarian Germ Cell Tumors (MOGCTs) are rare and accounts for 2% to 3% of ovarian malignancies. The aim of this study was to describe characteristics in patients with MOGCTs and to analyze the treatment outcomes.

Methods: This was a retrospective study about 92 patients with MOGCTs treated in Salah Azaiez Institute in Tunisia between 1984 and 2012.

Results: The median age of diagnosis was 26 years (range, 8-76). The main clinical features were abdominal pain (81%) and abdominal distension (59%). Physical examination revealed an abdominal or pelvic mass in 68% of cases. The pathologic diagnoses were dysgerminoma in 29 patients, immature teratoma in 32, yolk sac tumor in 13, and mixed germ cell tumor in 12, embryonal carcinoma in 3 and choriocarcinoma in 3 patients. The majority presented with early-stage (I/II) disease (77%). Fifty eight patients (63%) underwent primary conservative surgery and 56% of patients were treated with cisplatin based chemotherapy. Six patients received adjuvant radiotherapy. The median follow-up period was 74 months (range 7 to 182). There were 13 cases of recurrence. The median time to relapse was 12 months (range 1 to 32). There were 8 cases of distant metastasis. The 5-year overall and disease-free survivals were 78% and 82%. Prognostic factors were age, stage, tumor size, optimal surgery and adjuvant chemotherapy. Four spontaneous pregnancies were achieved.

Conclusion: The Prognosis is closely related to disease stage. Fertility sparing surgery should be considered in early-staged young patients.

Keywords: Ovarian neoplasm; Germ cell and embryonal neoplasms; Surgery; Chemotherapy; Prognosis

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Introduction

Malignant Ovarian Germ Cell Tumors (MOGCTs) are rare and accounts for 2% to 3% of ovarian malignancies. They usually occur in young women and often diagnosed at an early stage of disease. These may include dysgerminomas and non dysgerminomas [1]. A multi modality approach with initial surgery followed by platinum-based chemotherapy is usually regarded as the standard of care [2]. The aim of this study was to describe characteristics in patients with MOGCTs and to analyze the treatment outcomes.

Materials and Methods

Study design and patients

We performed a monocentric retrospective study that included women diagnosed with MOGCTs between 1984 and 2012 at Salah Azaiez Institute in Tunisia. The hospital records of all patients were reviewed. Patient characteristics consisted of age, performance status, menarche, parity, menopausal status and medical history. Clinicopathologic information regarding histological diagnosis (dysgerminoma, non dysgerminoma), pelvic washing cytology, and spread of the disease to the peritoneum, contralateral ovary or distant organs were obtained. All patients were reclassified based on the 2014 FIGO staging guidelines. The non dysgerminomas tumor was subdivided into immature teratoma, Yolk sac tumor, embryonal carcinoma, Choriocarcinoma and mixed Germ cell tumors. Surgical data included the surgical modality (radical or Conservative), the performance

or not of a complete resection, an interval surgery and pelvic and/or para-aortic lymphadenectomy. Postsurgical treatment was recorded as observation, Chemotherapy and radiation therapy (whole pelvic radiotherapy). Adverse events were analyzed among different chemotherapy regimens and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v 4.0).

Statistical methodology

Overall Survival (OS), the time in months from diagnosis to death from any cause, and Disease Free Survival (DFS), the time in months from diagnosis to death directly caused by the primary malignant tumor were defined as the primary outcomes. The Kaplan-Meier method was used to calculate the OS and DFS rates. The log-rank test was used to formally test the differences. Univariate and multivariate Cox proportional hazards regression was performed. A p-value <0.05 was considered statistically significant in comparison between groups. Statistical analyses were carried out using SPSS statistics software package version 21.0 (IBM Corporation, Armonk, NY).

Results

Patient characteristics

A total of 92 women met the study eligibility criteria. The demographic features are displayed in Table 1. Median age at diagnosis was 23 years (range, 8 to 76 years). Two of our patients older than 75 were treated for immature Teratoma.

Clinical features

The main clinical features were abdominal pain (81%) and abdominal distension (59%). Physical examination revealed an abdominal or pelvic mass in 68% of cases. An abdominal and pelvic echography was performed in 82 patients. Ultra sonographic examination showed a heterogeneous ovarian mass with a solid-cystic component in 17% of cases. The average radiologic tumor size was 15 cm (range, 1 to 35). An abdomino-pelvic MRI was performed in only three patients as part of the preoperative assessment. The clinical and radiological features are displayed in Table 2.

Pathological features

The pathologic diagnosis were dysgerminoma in 29 patients (31%) and non dysgerminoma in 63 patients (69%).Immature Teratoma was the most common histological subtype with 32 cases followed by yolk sac tumor and mixed germ cell tumors (Table 3). The average histological tumor size was 17 cm (range, 3-50). The majority presented with early-stage (I/II) disease (77%). The distribution of patients according to the FIGO 2014 classification is shown in Table 4. Three of our patients were metastatic (1 case of lung metastasis, 1 case of hepatic metastasis, 1 case of inguinal lymph node metastasis).

Therapeutic management

The decision on treatment was discussed at multidisciplinary consultative meetings.

Surgery: All patients underwent surgery. Fifty eight patients (63%) underwent primary conservative surgery. Eighty seven patients were operated by laparotomy and six patients by laparoscopy (4 patients had laparo-conversion). Seven of our patients, who had initially sub-optimal surgery, underwent an interval surgery. All of these patients had adjuvant chemotherapy. Pelvic and para-aortic lymphadenectomy were performed for dysgerminoma and non dysgerminoma respectively in 9 (31%) and 24 (38%) patients.

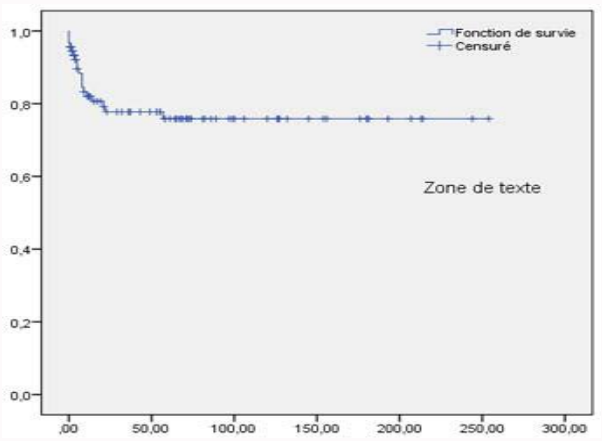

Figure 1: Overall Survival Plot.

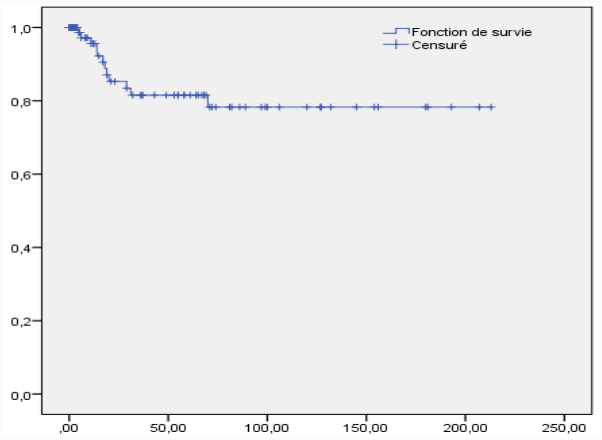

Figure 2: Disease free survival Plot.

Table 1: Characteristics of the study population.

	N	%
	(Total=92)	
Median age (years)		
Dysgerminoma	18 (range, 10-61)	-
Non dysgerminoma	24 (range, 8-76)	-
Family history of cancer	12	13
Epithelial Ovarian Cancer	5	5
Breast Cancer	7	8
Medical History		
Swyer Syndrome	1	1
Mature Teratoma	1	1
Obstetric and Gynaecological History		
Menarche(age, years) prepubescent Parity Menopausal status	13 9 1 (0-6) 8	10 - 9

Biopsy of contralateral ovary was performed in 7 patients (24%) with dysgerminoma and 8 patients (13%) with non dysgerminoma. Twenty seven patients (93%) with dysgerminoma underwent a pelvic washing cytology versus 57 patients (90%) with non-dysgerminomas.

Chemotherapy: Chemotherapy was indicated for 52 women (56%) with 18 cases of dysgerminoma and 34 cases of non

Table 2: Clinical and radiological features in patients with MOGCTs.

	N (Total=92)	%
Clinical features		
Abdominal pain	75	81
Abdominal distension Acute surgical abdomen Deterioration of general status	55 6 12	59 6 13
Abdominal or pelvic mass	63	68
Ascites	18	19
Pleural effusion	2	2
Ultrasonography examination		
Heterogeneous ovarian mass	16	17
Liquid effusion Hepatic metastasis	4 1	4 1
CT scan Study		

Table 3: Histological subtype of MOGCTS.

	N (Total=92)	%
Dysgerminoma	29	31
Immature Teratoma	32	51
Yolk sac Tumor	13	20
Choriocarcinoma	3	5
Embryonnal Carcinoma	3	5
Mixed germ cell tumor	12	19

Table 4: FiGO classification.

Stage	N (Total=91)	%
Stage I	66	73
Stage II	4	4
Stage III	18	20
Stage IV	3	3

Table 5: Chemotherapy adverse event.

Adverse Events	Grade	Number of patients (N)
Gastro-intestinal	GI-GII	19
	GIII-GIV	5
Hematological	GI-GII	7
	GIII-GIV	3
Renal	GI-GII	3
	GIII-GIV	1
Neurological	GI-GII	1
	GIII-GIV	0
Pulmonary	GI-GII	1
	GIII-GIV	0

dysgerminomas. Different regimens were administered as shown in Table 5. The median number of cycles was 3.5 (range, 1-6 cycles). Adverse events included grade 3-4 toxicity was observed in 9 cases. No toxicity related death was reported (Table 5).

Radiotherapy: Adjuvant Radiotherapy (external beam radiotherapy) was delivered in 6 cases (7%) (5 dysgerminoma and 1 non-dysgerminoma) .The median intended radiation dose was 44 Gray (range, 20-40 Gy). These patient was treated during the period [1984-1993].

Table 6: OS and DFS according to Prognostic factors.

Prognostic Factor	OS	DFS
Age	p=0.012	p=0.248
Tumor size	p = 0.005	p=0.6
FIGO Stage	p<0.001	P= 0.1
Histological and subhistological types	p= 0.1 p=0.08	p=0.241 p=0.797
Adjuvant Chemotherapy Chemotherapy Regimens	p=0.001 p=0.24	p=0.81 -
Surgical modality	p=0.8	p=0.81
Lymphadenectomy	p=0.9	p= 0.83
Residual tumor	p=0.072	p=0.038

There was no statistically significant difference between subgroup in multivariate Cox regression analysis.

Survival outcomes and prognostic factors

After a median follow-up of 74 months (range, 7 to 182), we observed 13 recurrences with a median time to relapse of 12 months (range, 1 to 32). These recurrences were locoregional, metastatic or both in 2, 8 and 3 cases respectively. The 5-year DFS was 82% and the 5-year OS was 78% (Figure 1,2). The 5-year OS has improved over time. It was 52%, 76% and 95% respectively during the periods [1984-1993], [1994-2003] and [2004-2012]. Prognostic factors were age, stage, tumor size, optimal surgery and adjuvant chemotherapy (Table 6). Four spontaneous pregnancies were achieved.

Discussion

MOGCTs are a heterogeneous group of rare disease with a different biological behavior and clinical presentation. These may include dysgerminomas and non dysgerminomas. Dysgerminomas the most frequent (48%) of MOGCTs [1]. This retrospective study is one of the few large studies of this rare tumor. They usually occur in young patients of reproductive age. The median age at diagnosis is16 to 20 years (range, 6-60 years) [2]. In our cohort the median age was 23 (range, 8 to 76). No genetic susceptibility has been identified related to the development of MOGCTs [3]. The presence of gonadal dysgenesis (Swyer Syndrome) is the most important risk factor for the development of MOGCTs (a dysgerminoma) [4]. We reported a case in our study with Swyer syndrome. No specific symptoms exist for MOGCTs, but the diagnosis should be suspected when patients are younger and tumor is larger. Abdominal pain associated or not with a palpable pelvic mass are the most frequent presenting symptom (85%). Ten percent of patients may present with acute abdominal pain [3]. In our Cohort, The main clinical features were abdominal pain (81%) and abdominal distension (59%). Physical examination revealed an abdominal or pelvic mass in 68% of cases. Abdominal and pelvic echography and magnetic resonance imaging are the preferred imaging modalities for the evaluation of the pelvic mass. Most of MOGCTs are solid. The evaluation of a spreading disease may be facilitated by Computed Tomography (CT) [5]. In our cases, Ultra sonographic examination showed an heterogeneous ovarian mass with a solid-cystic component in 17% of cases. The average radiologic tumor size was 15 cm (range, 1-35). An abdomino-pelvic MRI was performed in only three patients as part of the preoperative assessment. Human Chorionic Gonadotropin (HCG) and Alpha Fetoprotein (AFP) are frequently secreted by MOGCTs (non-dysgerminomas). Alpha fetoprotein evaluation is an important prognostic factor any malignant germ cell tumors treatment protocols and it is also used in follow-up of thosin me patients. Additionally, it is a characteristic marker of yolk sac tumor [6].

The treatment must be done in expert center and discussed in multidisciplinary meeting board. The Outcomes appears to be superior when patients are treated in a large cancer center, likely due to the rare nature and infrequent presentation of these tumors [2].

Surgery is the first step to do for the diagnosis and to treat the patients. Fertility-sparing surgery appears to be the standard of care for these young patients [7].

The improvement in testicular germ cell tumor outcomes over the last several decades has prompted similar successes in MOGCTs. Cisplatin-based chemotherapy with Bleomycin, Etoposide, and Cisplatin (BEP) leads to cure most patients with MOGCTs. BEP is the standard of care for MOGCTs with 3 cycles for patients with completely resected disease and 4 cycles for patients with macro scopic residual disease. Patients with FIGO stage I dysgerminoma and stage IA grade 1 immature teratoma maybe observed [2]. The 5-year OS (78%) and DFS (82%) rate were excellent with a median follow-up of 74 months. The 5-year OS has improved over time. It was 52%, 76% and 95% respectively during the periods [1984-1993], [1994-2003] and [2004-2012]. Prognostic factors were age, stage, tumor size, optimal surgery and adjuvant chemotherapy.

Conclusion

The clinico-pathological features and survival outcomes of our cohort are conforming to literature. The main limitation of this study is that is a retrospective data set and firm conclusions cannot be made. A multimodality approach is the standard of care in MOGCTs. Despite the rarity of this tumor, the treatment must be done in expert center and discussed in multidisciplinary meeting board to provide the best outcomes. The prognosis is closely related to disease stage. Fertility sparing surgery should be considered in early-staged young patients.

Consent for Publication

In Tunisian law, patients consent is not mandatory for retrospective studies.

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