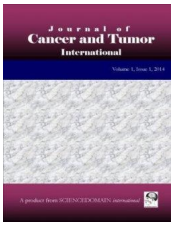

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Pediatric and Adolescent Malignant Ovarian Tumors: Mansoura 5 - Year Experience

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Authors' contributions

This work was carried out in collaboration between all authors. Author MS designed the study and shared in data collection. Author AH wrote the protocol, managed the literature searches and the first draft of the manuscript. Authors IE and TS revised and documented the surgical data of the cases who were operated upon in their hospital and shared in literature searches. Authors AEH and WEK revised the pathologic specimens. Author AEB revised the radiologic data. Authors HW and HEH shared in data collection, management of the literature searches and the writing of the manuscript. Author OF revised and documented the surgical data of the cases who were operated upon in his hospital. All authors read and approved the final manuscript.

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ABSTRACT

Background: Pediatric ovarian tumors are rare. The aim of this work is to study the epidemiological characteristics and treatment outcome of these tumors in our locality.
Methods: This retrospective study was performed in accordance with the ethical policies. Between January 2011 to December 2015, Thirteen cases of pediatric ovarian cancers were recorded in the Pediatric Oncology Unit of Oncology Center of Mansoura University and the Clinical Oncology & Nuclear Medicine Department of Mansoura University Hospital. The clinico-epidemiologic data and the treatment protocols were analyzed.
Results: The median age was 10 years (range: 2-17). Presenting symptoms were mainly lower abdominal pain (6; 46.2%) and palpable abdominal mass (4; 30.7). Through laparotomy all patients underwent unilateral salpingo-oophorectomy except one case for whom bilateral salpingio-oophorectomy was done. Six patients were stage I (46.2%), 2 patients were stage II (15.4%) and 5 patients were stage III tumors (38.4%). The majority had germ cell tumors (11; 85%). Adjuvant chemotherapy was given to all cases. Further chemotherapy was needed in 6 cases due to progression or recurrence. The median follow up was 35 months while the median overall survival was 40 months. Mortality rates were 90% in stages II and III together. The advanced stages and yolk sac pathology had the highest mortality. One of the survived cases got married and delivered a baby.
Conclusion: Germ cell tumors are the commonest pediatric malignant ovarian tumors. Multimodality treatment is essential. Fertility preservation should be respected. Our mortality rates are relatively high.

Keywords: Pediatric ovarian tumors; germ cell tumors; PEB protocol; JEB.

1. INTRODUCTION

Pediatric ovarian tumors account for less than 5% of all the childhood malignancies and less than 10% of all abdominal tumors in children. [1,2]. Tumors of the ovary may be benign like mature cystic teratomas or malignant like yolk sac tumors. Pediatric ovarian tumors mostly belong to the group of germ cell tumors [3].

1.1 Aim of the Work

The rarity of this disease cases encouraged the conduction of this study to explore the clinico-epidemiologic features of different malignant ovarian tumors in the pediatric age.

2. MATERIALS AND METHODS

This retrospective study was performed in accordance with the ethical policies. Inclusion criteria were: documented pathology of malignant ovarian tumor, age less than 19 years, no major comorbidities, no other malignancy, and ECOG performance status less than or equal to 2.

During the period from January 2011 to December 2015, 13 pediatric malignant ovarian tumors were recorded in Pediatric Oncology Unit of Oncology Center of Mansoura University and the Clinical Oncology & Nuclear Medicine Department of Mansoura University hospital. Hopefully they were in agreement with the inclusion criteria. Various aspects were analyzed in the records such as the epidemiology, the detailed history, the presentation, the examination, the investigations, the treatment details and the outcome. Radiologic investigations done as MRI of pelvis, CT scan of abdomen & pelvis, chest x ray, etc were revised by a radiologic consultant.

All H&E stained slides were retrieved from the archives of the Pathology Department, Faculty of medicine, Mansoura University and revised by a panel of senior pathologists. In 3 cases, the paraffin blocks were cut by ordinary microtome to sections of 3-5 μ thickness, mounted on glass slide and stained with H&E staining because of the bad quality of the available slides.

Staging of the disease followed the FIGO Classification while chemotherapy toxicity assessment followed Common Terminology Criteria for Adverse Events version 3. The recorded chemotherapy protocols were PEB, JEB, and ICE. The BEP protocol consisted of Bleomycin 15 mg/m^2 over 24 hours days 1,2,3 plus Etoposide 80 mg/m^2 over 3 hours days 1,2,3 plus Cisplatinum 20 mg/m^2 over 1 hour days 4,5,6,7,8. JEB protocol consisted of Carboplatin

600 mg/m^2 over 1 hour day 2 plus Etoposide 120 mg/m^2 over 1 hour days 1,2,3 plus Bleomycin 15 mg/m^2 over 15 min day 3. Lastly, ICE protocol consisted of Carboplatin 600 mg/m^2 over 1 hour day 1 plus Etoposide 100 mg /m^2 over 3 hours days 1,2,3,22,23,24 plus Ifosfamide 1800 mg/m^2 over 3 hours days 22,23,24,25,26. Follow up by clinical examination, CT scan and laboratory profile was done every 3 months in the first year, then every 6 months in the second year and then yearly. The magnitude of statistical analysis was limited by the limited patient number. Quantitative data were presented as median and qualitative data as frequency and percentage. The follow up period for each case was calculated from the end of the treatment to the last follow up visit. The overall survival for each patient was calculated from the date of diagnosis till the date of death or the date of the last follow up visit.

3. RESULTS

Thirteen female patients with malignant ovarian germ cell (MOGT) and juvenile sex cord (JSCT) stromal tumors were recorded (1.5% of total pediatric malignancy throughout the 5 years of study). Table 1 demonstrated the percentage distribution of our different pediatric malignancies. None of the cases showed congenital anomalies.

The median age was 10 years (range: 2-17), with 7 cases being premenarchal (53.8%). Complaints at presentation were lower abdominal pain (6; 46.2%), palpable abdominal mass (4; 30.7), weight loss (4; 30.7), menstrual disturbance (2; 15.4%), and diffuse abdominal distension (1; 7.7%). Reporting of the significance of marker elevation was signed by a panel of clinical pathologists. AFP had an upper reference limit of approximately 15 µg/L while the normal range of serum HCG was up to ~5 U/L. The reference range of CA 125 was 0-35 units/mL (0-35 kU/L). At initial presentation, AFP was the commonest elevated marker (7; 53%) followed by CA125 (5; 38.5%). No cases of HCG elevation were reported. The right ovary was involved in 8 patients (62%) while the left one in 5 patients (38%). No bilaterality was reported. MRI pelvis of a case of MOGT and a case of JSCT are shown in Figs. 1 & 2 respectively. Surgeries were done in either Oncology Center of Mansoura University or Mansoura International hospital. All patients underwent primary surgical resection through laparotomy. Unilateral salpingio-oophorectomy (USO) was performed except in one case who underwent bilateral salpingio-oophorectomy (BSO) because of advanced stage. No cases of tumorectomy were done. One patient on exploration had multiple peritoneal deposits. According to FIGO classification, 6 patients were stage I (46.2%), 2 patients were stage II (15.4%) and 5 patients were stage III tumors (38.4%). MOGT represented 85% (11 cases) among which the yolk sac type was the commonest (4/13; 31%) (Figs. 3 & 4), followed by dysgerminoma (3/13; 23%) (Fig. 5 & 6). Two cases only were JSCT (15%). Table 2 showed the different malignant ovarian tumors recorded.

Table 1. Distribution of 850 pediatric malignant diseases recorded within the 5- year period

Type of malignancy	No. (%)
Leukemias	382(45%)
NHL	102(12%)
HD	42(5%)
Neuroblastoma	110(13%)
Wilms tumor	34(4%)
Rhabdomyosarcoma	26(3%)
Osteosarcoma	26(3%)
Ewings sarcoma	18(2%)
Langerhans cell histocytosis	18(2%)
Hepatoblastoma	18(2%)
Brain tumors	26(3%)
Ovarian cancers	13(1.5%)
Soft tissue sarcoma	9(1%)
Adenocarcinomas	9(1%)
Peripheral neuroectodermal tumors	9(1%)

Table 2. Different pathologic types of the 13 ovarian malignancies

Pathologic type	No. (%)
Yolk sac tumor	4 (31%)
Dysgerminoma	3 (23%)
Embryonal cell carcinoma	2(15%)
Mixed germ cell tumor	1(8%)
Immature teratoma	1(8%)
Juvenile sex cord(granulosa cell) tumor	2(15%)

All cases received chemotherapy adjuvantly. However, due to progression and recurrence, six cases required further chemotherapy lines. The number of cycles received ranged from 2-6. Table 3 pointed out the patient characteristics, therapy given and the fate. Alopecia, nausea and vomiting of grade II were the commonest

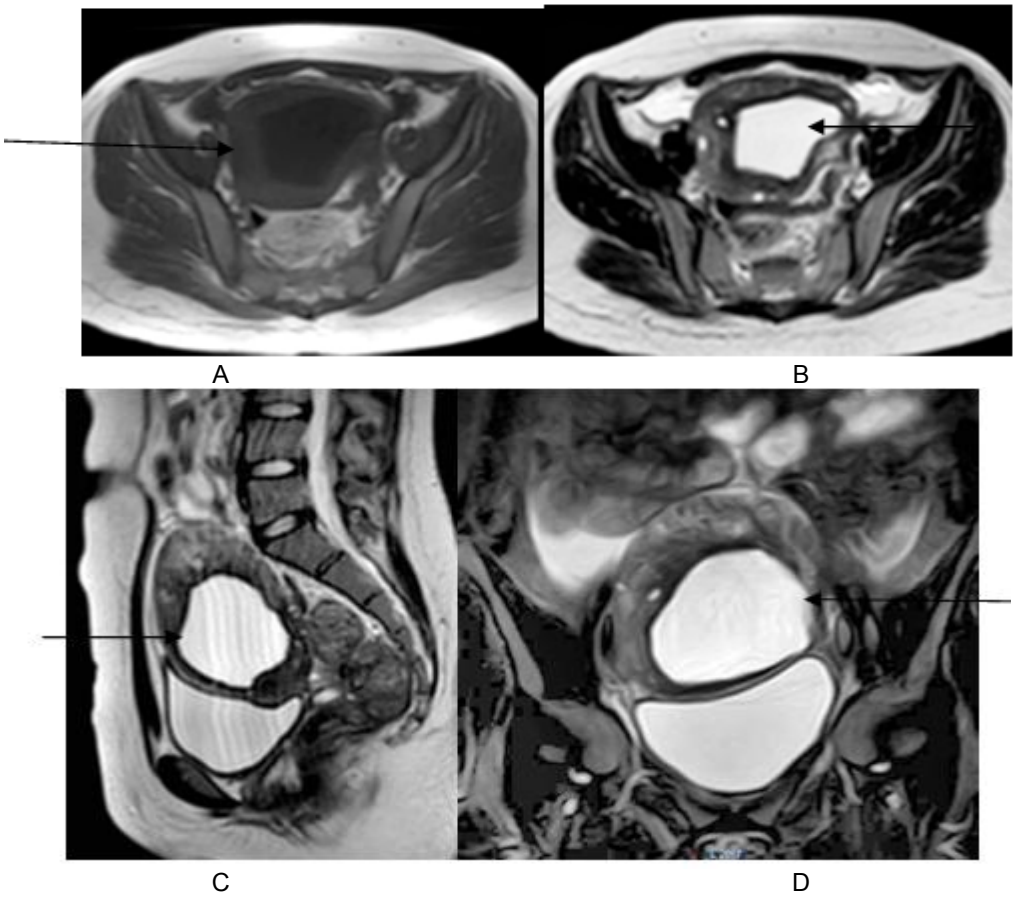

Fig. 1. 12 years-old female presented with abdominal pain and enlargement and underwent MRI examination. (A) Non-contrast axial T1 WI, (B) Axial T2 WI (C) Sagittal T2 without fat suppression and (D) Coronal T2 with fat suppression revealed heterogeneous pelvic mass with central necrosis and outer solid parts (arrows). This mass was pathologically- proved to be dysgerminoma

toxicities and were encountered in more than half of the cases. Neither major acute toxicity nor treatment-related death was reported. The median follow up was 35 months (2-69 months) while the median overall survival was 40 months (3-72) The mortality rates were 17%, 50% and 40% in stages I, II, and III respectively. The mortality rate of our patients as a whole was 31%. The tumor pathology of the 4 cases who died were yolk sac tumors in 3 cases and mixed germ cell tumor in one case. Among the surviving patients, one got married and delivered a baby.

4. DISCUSSION

Publications concerning experiences in the classic malignant pediatric ovarian tumors and related case reports have not exceeded 80.

Our cases are characterized by common pre-menarchal germ cell tumors and common abdominal pain at presentation similar to other case series [4-9]. No documented emergent acute abdomen unlike some reports [10,11]. None of our 2 JSCT cases has precocious puberty, however Bhattacharyya et al. [2] in India found 2 cases with precocious puberty out of 3 in his series of 151 malignant pediatric ovarian tumor patients.

Bilaterality in malignant germ cell tumors is uncommon. Zhao et al. [12] diagnosed 8 out of 130 cases (6%) and Siqismondi et al. [13] diagnosed 8 cases among 145 (5.5%). No bilaterality exists in the present study.

In our work, yolk sac tumors exceed in incidence all other pathologies (31%) and are followed by dysgerminomas. Variable reports about the most

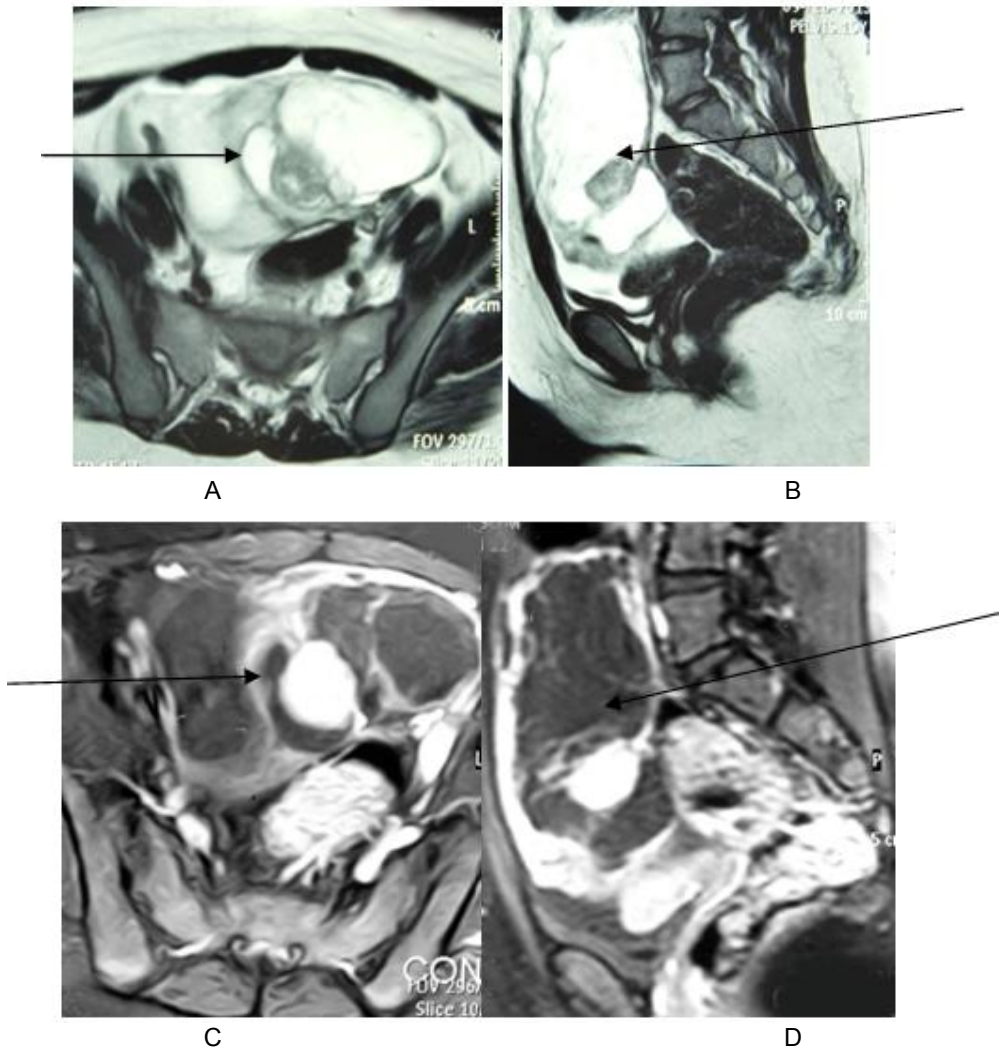

Fig. 2. 15-years-old female presented with abdominal pain and distension. Magnetic resonance imaging (MRI) of the abdomen was done. (A) Axial T2 and (B) Sagittal T2 weighted images revealed soft tissue mass(arrows) with multiple cystic components and central solid part. (C) Post-contrast axial T1 and (D) sagittal T1 with fat suppression revealed enhancement of the central solid part and septations. This mass was pathologically proved to be JSCT.

common pathology exist. Biswajit et al. [14] discovered that mixed germ cell tumor was the commonest (32%). On the other hand Topuz et al. [15] and Mangili et al. [16] found that dysgerminoma represented the majority of their cases (56% and 40% respectively). Lastly, Ghosh et al. [17] reported that dysgerminoma was equal in incidence to both yolk sac tumors and choriocarcinoma together.

In the review of *Karaman and his colleagues* [18], epithelial ovarian tumors were unusual in adolescent girls and extremely rare before menarche. No epithelial tumors are reported in the present work unlike the study of Rathore, et al. [11]. However, *Rathore* included patients with a wider age range. We have no records about Non –Hodgkin lymphoma cases, however very few cases were reported in literature. Mukhopadhyay et al. [10] reported one case in his series of 47 pediatric ovarian neoplasms. Similarly, Hassan et al. [19] reported one among 57 cases.

As a whole, the general treatment policy adopted for our cases is in accordance with

Table 3. Characteristics of 13 malignant ovarian cases

Age in years	Main presentation	Laterality	Stage	Pathology	AFP	HCG	CA125	Drug	Fate
3	Mass	Left	2	Yolk sac tumor	High	Normal	High	PEB	Alive
17	Menestrual irregularities	Left	2	Yolk sac tumor	High	Normal	High	PEB+JEP +ICE	Died
2	Distention	Right	3	Yolk sac tumor	Normal	Normal	Normal	JEB+ICE	Died
13	Pain	Right	3	Yolk sac tumor	High	Normal	High	PEB+JEB	Died
16	Pain	Left	1	Dysgerminoma	Normal	Normal	Normal	PEB	Alive
4.5	Mass	Left	1	Dysgerminoma	High	Normal	Normal	JEB	Alive
12	Pain	Left	1	Dysgerminoma	Normal	Normal	Normal	JEB	Alive
8	Pain	Right	1	Embryonal carcinoma	High	Normal	High	PEB	Alive
7	Mass	Right	3	Embryonal carcinoma	High	Normal	High	PEB+ICE	Alive
2.5	Mass	Right	1	Juvenile sex cord	Normal	Normal	Normal	JEB	Alive
15	Menestrual irregularities	Right	3	Juvenile sex cord	Normal	Normal	Normal	JEB	Alive
10	Pain	Right	1	Immature teratoma	High	Normal	Normal	PEB+JEB	Alive
13	Pain	Right	3	Mixed germ cell tumor	Normal	Normal	Normal	PEB+ICE	Died

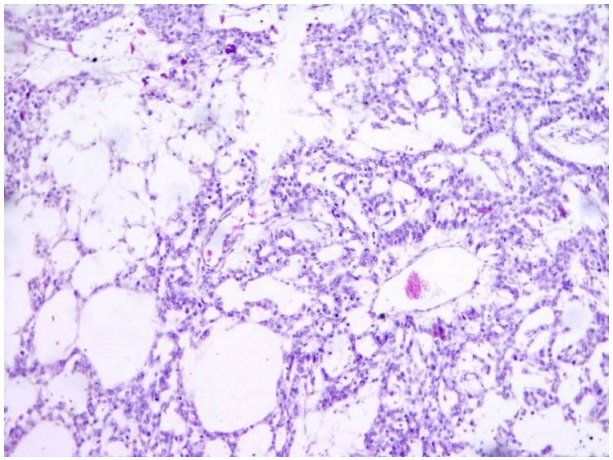

Fig. 3. Yolk sac tumor. Thin cords and microcysts of neoplastic cells separated by loose stroma. Schiller–Duval body is also present (H&E x100)

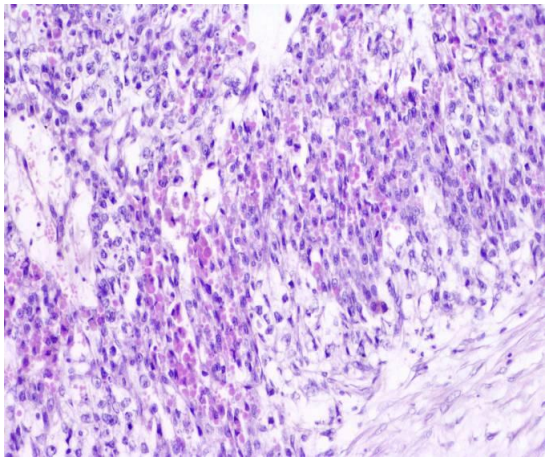

Fig. 4. Yolk sac tumor with hyaline globules (H&E x200)

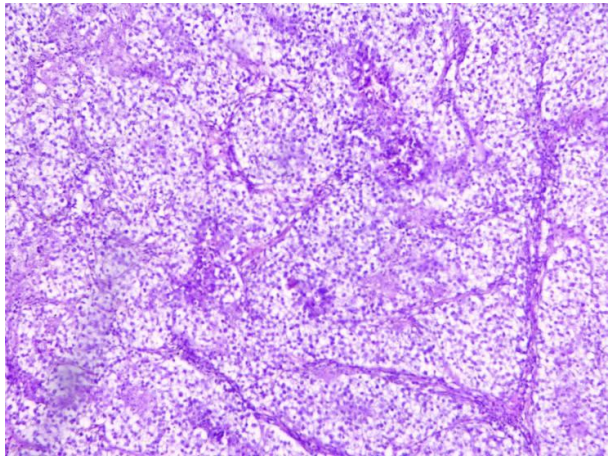

Fig. 5. Dysgerminoma. Nests of tumor cells separated by fibrous septa containing numerous lymphocytes (H&Ex100)

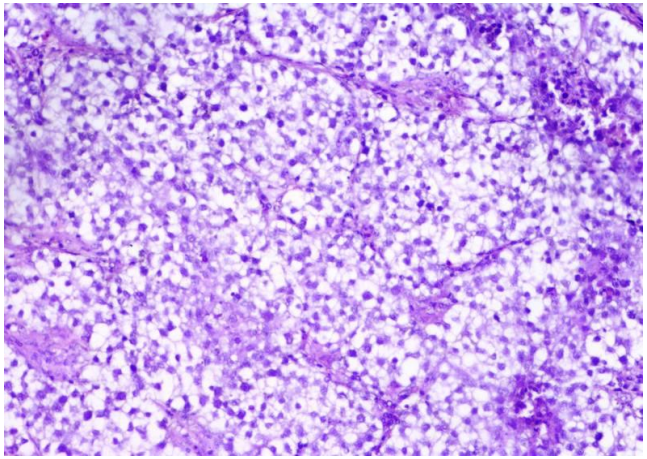

Fig. 6. Dysgerminoma. The neoplastic cells have abundant clear cytoplasm and large central nuclei (H&Ex200)

reported guidelines [20]. Stage IA dysgerminoma is to be managed with USO without chemotherapy. However our cases of dysgerminoma were of higher stages so adjuvant chemotherapy was applied. USO alone is enough for stage IA immature teratoma grade 1 but our case was of higher grade and so chemotherapy was given. The treatment for the rest of germ cell cases is USO plus chemotherapy, a policy which we applied.

In parallel with literature [21,22], excessive debulking is not the policy applied for our cases and the role of minimally invasive surgery (laparoscopy) remains debatable. Laparoscopy was not applied in any of our cases. Regarding the type and number of chemotherapy regimens, three courses of Bleomycin, Etoposide and Cisplatin (BEP) is the current recommended standard adjuvant chemotherapy and four courses are recommended in case of bulky residual tumor after surgery [23]. That policy had been respected in our series. However JEB protocol which is a less toxic carboplatin-based regimen [24] is used as well. Neoadjuvant chemotherapy could ameliorate surgical morbidity in cases of advanced disease and could increase the chance of fertility preservation [25,26], however it is not a recommended policy in our institutions.

JSCT of the ovary usually carry favorable prognosis. Non-mutilating surgery is usually possible. Adjuvant chemotherapy should only be applied to prevent recurrences in cases of tumor rupture [27,28]. It seems that our 2 cases of JSCT were over treated as both were given adjuvant chemotherapy without tumor rupture.

Alopecia, nausea and vomiting of grade II are the commonest toxicities similar to the review of Lopes da Silva et al. [29] who reported their retrospective study on management of 19 MGCT from April 2003 to July 2013. No documentation of chemotherapy-related deaths in the present work. However, Lopes da silva reported one death from Bleomycin induced pneumonitis.

The current management protocols for germ cell tumors can allow fertility preservation [5]. One of our patients with dysgerminoma got married and delivered a baby.

In the literature, patients with early and advanced stages showed cure rates approaching 100% and 75% respectively [30] and yolk sac tumors behaved aggressively [31]. In the present study, advanced stages and yolk sac tumors rates are 53% and 31% respectively. Moreover, recurrence /refractory cases and mortality rates are 46% and 31% respectively. These figures are much worse than other published reports. Topuz et al. [16] reported a recurrence rate of 17% among 41 MOGT patients, of whom 56% were dysgerminomas. Similarly, Mangili et al. [17], announced a recurrence rate of 18% in a study of 123 patients of MOGT among whom dysgerminoma was 40% and stage I was 71%. Additionally, Neeyalavira & Suprasert [32] (76 patients) reported 12 recurrent cases (15.8%). Dysgerminoma constituted only 25%, however, stage 1 in their series represented 67%. Dysgerminoma and mature teratomas were more than one third in Hannan et al. study [33] (66 patients) that showed 7 relapses (11%). The poor prognosis in our study could be, in addition to the common existence of unfavorable pathology and stage, attributed to racial effect as it was proved that white girls had better survival than Africans [34].

Correlation between development of germ cell tumors and each of hormonal intake by mothers during pregnancy and Turner Syndrome was addressed in literature [35,36]. However, it was not possible to study these correlations in our small study.

5. CONCLUSION

Germ cell tumors are the commonest pediatric malignant ovarian tumors. Multimodality treastment is essential. Fertility preservation should be respected. The advanced stages and yolk sac pathology has the highest mortality. Our mortality figures are relatively high.

CONSENT

All authors declare that written informed consent was obtained from the patients parents for publication.

ETHICAL APPROVAL

Authors have obtained ethical approval from the Institutional Ethical Committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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