

## Clinicopathological Study and Management of Malignant Ovarian Tumors in Children and Adolescents, A Three-Years Study

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### ABSTRACT

**Background:** Ovarian tumors true incidence in young females is not known. **Objective:** To review the incidence of ovarian tumors in children and adolescents and their clinical presentation in these patients in Aswan city and district as representative of Egypt. We also characterized the pathological features of these ovarian tumors and tailor the best management of these tumors in young females (less than 18 years old). **Patients and Methods:** Thirty-six malignant ovarian tumors in females <18 years were followed in Surgery Department, Aswan University hospital. Different aspects were analyzed regarding clinicopathological data, investigations and treatment. 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 follow up period for each case was calculated from end of the treatment to the last follow up visit. **Results:** Thirty-six young female patients with malignant ovarian tumors were recorded, which represented 18% of total pediatric malignancy throughout the 3 years of the study. All patients underwent primary surgical resection through laparotomy. Unilateral salpingo-oophorectomy (USO) was performed. AFP was the commonest elevated marker in 6 cases and CA125 in 4 cases. The most common symptom was abdominal mass in 14 cases and most common tumor was yolk sac tumor 14 cases. All cases received chemotherapy adjuvantly except the four cases stage 1. However, due to progression and recurrence, six cases required further chemotherapy lines. **Conclusion:** Yolk sac tumor and dysgerminoma are the commonest pediatric malignant ovarian tumors in this study. Multimodality treatment is essential. Fertility preservation should be respected. The advanced stages have the highest mortality.

**Keywords:** Ovarian tumors, Children and adolescents.

### INTRODUCTION

Only 0.9% of all malignancies in children and adolescents are malignant ovarian tumours. Malignant ovarian tumours may arise as primary tumours from healthy ovarian tissue or as metastases. 70% of all ovarian malignancies are epithelial ovarian carcinomas, which are primary ovarian tumours. Most of these cancers develop in the fallopian tubes <sup>(1,2)</sup>.

Less than 5% of juvenile malignancies and less than 10% of paediatric abdominal tumours are ovarian tumours in young female patients <sup>(1,2)</sup>. Most patients are detected at an advanced stage because the disease has few, vague, or even no symptoms <sup>(3)</sup>.

Germ-cell tumours (GCT), sex-cord stromal tumours (SCST), and various stromal tumours of the ovary are examples. Endometrial, breast, colon, stomach, and cervical tumours are among the tumour types that can metastasize to the ovaries. Malignant ovarian tumours are uncommon in young females, who typically have germ cell tumours, and their prognosis is better than that of adult females <sup>(4-7)</sup>.

### AIMS OF THE STUDY

To review the true incidence of ovarian tumors in children and adolescents, which is unknown, the clinical presentation of ovarian malignant tumors in young female patients in the city and district of Aswan as representative of Egypt. It's also to characterize the pathological features of these ovarian tumors and tailor the best management of these tumors in young females

(less than 18 years old) aiming to preserve fertility. Outcome of treatment also is recorded.

### PATIENTS AND METHODS

A prospective study was done during the period from May 2018 to May 2021, thirty-six malignant ovarian tumors in young females less than 18 years old were followed in Surgery Department of Aswan University Hospital.

#### Inclusion criteria included:

1. Pelvic ultrasonography is used to diagnose ovarian tumours. Unilocular cysts, smooth multilocular tumours, solid components smaller than 7 mm, the absence of an acoustic shadow, and a Doppler signal are ultrasonography indicators of a benign tumour. On the other hand, a solid, unregulated tumour, a multilocular solid mass with at least four papillary structures, ascites, and a strong doppler signal are signs of a malignant mass.
2. Pathologically-confirmed malignant ovarian mass, age less than 18 years.

Thirty-six malignant ovarian tumors were recorded in Surgery Department of Aswan University hospital. According to intraoperative results, the extent of gonad resection varied from total, in which case the whole gonad affected by the lesion was removed, to partial resection, in which case at least a small amount of ovarian tissue was spared. Comparing preservation rates was done while taking into account the surgical

technique, histology type, mass size, and ovarian torsion. Ascites cytology, omentectomy, peritoneal tumour debulking, pelvic and paraortic lymph node biopsy were all performed as part of the staging process.

Different aspects were analyzed such as demographic data, detailed history, clinical presentation, clinical examination, laboratory investigations, treatment details and the outcome. Radiologic investigations were done as sonar pelvis, MRI of pelvis, CT scan of abdomen & pelvis, and chest X-ray. 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 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.

**Ethical consent:**

The academic and ethical committee at Aswan University approved the project. Each patient signed a written informed consent form to agree to participate in the study. The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of this work.

**Statistical analysis**

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were presented as frequency and percentage.

**RESULTS**

Thirty-six young female patients with malignant ovarian tumors were recorded, which represented 18% of total pediatric malignancy throughout the 3 years of the study. All patients underwent primary surgical resection through laparotomy.

Unilateral salpingo-oophrectomy (USO) was performed. Table 1, denotes the percentage distribution of our different pediatric malignancies, while table 2, showed the different malignant ovarian tumors recorded. These included 14 yolk sac tumors, 11 dysgerminoma, 7 cases of embryonal carcinoma and 4 cases of mixed germ cell tumor. The patients' age ranged from 5 to 15 years, table 3.

Complaints at presentation were lower abdominal pain in 4 cases, 14 cases with palpable abdominal mass, 7cases with weight loss, weakness,

nausea, vomiting and fever (general symptoms), and 11 cases with menstrual disturbance. Alpha-fetoprotein (AFP) had an upper reference limit of approximately 15 µg/L while the normal range of serum human chorionic gonadotropin (HCG) was up to ~5 U/L.

The reference range of CA 125 was 0-35units/mL (0-35 kU/L). At initial presentation, AFP was the commonest elevated marker in 6 cases and CA125 in 4 cases also. No cases of HCG elevation were reported. The right ovary was involved in 19 patients while the left one in 17 patients.

According to FIGO classification, four patients were stage I in two cases of dysgerminoma and two cases of embryonal carcinoma , nine patients of yolk sac tumor were stage II and five patients were stage III tumors, (table 3).

**Table (1):** Malignant diseases of 200 pediatric recorded within the 2- year period in Aswan-Egypt

Type of malignancy	No. (%)
Leukemia	62(31%)
Non-Hodgkin's Lymphoma	42 (21%)
Neuroblastoma	2(1%)
Wilms tumor	42(21%)
Rhabdomyosarcoma	2(1%)
Osteosarcoma	4(2%)
Ewing's sarcoma	2(1%)
Langerhans cell histiocytosis	2(1%)
Hepatoblastoma	2(1%)
Brain tumors	4(2%)
Ovarian cancers	36(18%)

**Table (2):** Pathologic types of the 36 ovarian tumors

Pathologic type	No. (%)
Yolk sac tumor	14 (38.9%)
Dysgerminoma	11(30.5%)
Embryonal carcinoma	7 (19.5%)
Mixed germ cell tumor	4 (11.1%)

All cases received chemotherapy adjuvantly except the four cases stage 1. 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 to the patients' characteristics, therapy given and the fate. Alopecia, nausea and vomiting of grade II were the commonest toxicities and were encountered in more than half of the cases. Neither major acute toxicity nor treatment-related death was reported. The median time of follow up was 36 months. The mortality rate was only in 3 cases (one of mixed germ cell tumor, one case of dysgerminoma & one case yolk sac tumor) all were stage 3.

**Table (3):** Characteristics of 36 malignant pediatric ovarian tumor

No. of patient	Age in years	Main presentation	Pathology	Stage	Laterality	AFP	HCG	CA 125	Drugs	Fate
14	5-7	Mass	Yolk sac tumor 14	9 stage II & 5 stage III	Right 8 Left 6	High in 2 cases	Normal	High in 2 cases	FEB	13 alive & 1 died
11	11-14	Menstrual irregularities	Dysgerminoma 11	2 stage I & 8 Stage II & 1 stage III	Right 7 Left 4	High in 2 cases	Normal	High in 2 cases	CEP + ICE	10 alive & 1 died
7	2-6	General symptom	Embryonal carcinoma 7	2 Stage I 3 stage II 2 stage III	Right 3 Left 4	Normal	Normal	Normal	CEP + ICE	Alive
4	8-15	Pain	Mixed germ cell tumor 4	3 stage II & 1 stage III	Right 1 Left 3	High in 2 cases	N	N	FEB	3 alive & 1 died

Chemotherapy toxicity assessment followed Common Terminology Criteria for Adverse Events version 3. The recorded chemotherapy protocols were BEP, CEB, and ICE. The BEP protocol consisted of Bleomycin 15 mg/m<sup>2</sup> over 24 hours days 1,2,3 plus Etoposide 80 mg/m<sup>2</sup> over 3 hours days 1,2,3 plus Cisplatin 20 mg/m<sup>2</sup> over 1 hour days 4,5,6,7,8. CEB protocol consisted of Carboplatin 600 mg/m<sup>2</sup> over 1 hour day 2 plus Etoposide 120mg/m<sup>2</sup> over 1 hour days 1,2,3 plus Bleomycin 15mg/m<sup>2</sup> over 15 min day 3. Lastly, ICE protocol consisted of Carboplatin 600 mg/m<sup>2</sup> over 1 hour day 1 plus Etoposide 100 mg /m<sup>2</sup> over 3 hours days 1,2,3,22,23,24 plus Ifosfamide 1800 mg/m<sup>2</sup> over 3 hours days 22,23,24,25,26.

## DISCUSSION

In our study, pediatric ovarian tumors represent 18% of 200 pediatric tumors in 3 years. In our work, yolk sac tumors (38.9%) more in incidence than to dysgerminomas (30.5%). **Mukhopadhyay et al.**<sup>(8)</sup> reported one case of non-Hodgkin lymphoma in his series of 49 pediatric ovarian neoplasms. However very few cases were reported in literatures<sup>(2-7)</sup>. Similarly, **Hassan et al.**<sup>(5)</sup> reported one among 57 cases.

Variable reports about the most common pathology exist. **Biswajit et al.**<sup>(7)</sup> discovered that mixed germ cell tumor was the commonest (32%). On the other hand, **Topaz et al.**<sup>(9)</sup> and **Mangle et al.**<sup>(10)</sup> found that dysgerminoma represented the majority of their cases (56% and 40% respectively). Lastly, **Ghosh et al.**<sup>(11)</sup> reported that dysgerminoma was equal in incidence to both yolk sac tumors and choriocarcinoma together. Bilaterality in malignant germ cell tumors is uncommon. **Zhao et al.**<sup>(12)</sup> diagnosed 8 out of 130 cases (6%) and **Siqismondi et al.**<sup>(13)</sup> diagnosed 8 cases among 145 (5.5%). No bilaterality exists in the present study. Our cases are characterized by mass and general symptoms at presentation higher than other cases

symptom series<sup>(2)</sup>. No documented emergent acute abdomen unlike some reports<sup>(23-26)</sup>. None of our 4 mixed germ cell tumors cases has precocious puberty.

As a whole, the general treatment policy adopted for our cases is in accordance with reported guidelines<sup>(8,14-16)</sup>. Stage I cases is to be managed with USO without chemotherapy. However, our cases of dysgerminoma were of higher stages so adjuvant chemotherapy was applied. The treatment for the rest of germ cell cases is USO plus chemotherapy, a policy which we applied<sup>(18)</sup>.

In parallel with literatures<sup>(17-21)</sup>, 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<sup>(16,21,22)</sup>. That policy had been respected in our series. However CEB protocol which is a less toxic carboplatin-based regimen<sup>(23)</sup> is used as well. Neoadjuvant chemotherapy could ameliorate surgical morbidity in cases of advanced disease and could increase the chance of fertility preservation<sup>(18-20)</sup>, however it is not a recommended policy in our institutions.

Yolk sac tumor 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<sup>(5-7,11,24-26)</sup>.

Alopecia, nausea and vomiting of grade II are the commonest toxicities similar to the review of **da Silva et al.**<sup>(27)</sup> who reported their retrospective study on management of 19 mixed germ cell tumor from April 2003 to July 2013. No documentation of chemotherapy-

related deaths in the present work. However, **da silva et al.**<sup>(27)</sup> reported one death from Bleomycin induced pneumonitis. The current management protocols for germ cell tumors can allow fertility preservation<sup>(28)</sup>.

In the literature, patients with early and advanced stages showed cure rates approaching 100% and 75% respectively<sup>[26]</sup> and yolk sac tumors behaved aggressively<sup>(20)</sup>. In the present study, advanced stages mixed germ cell tumor, yolk sac tumor & dysgerminoma with mortality rates are 8.3%. **Topaz et al.**<sup>(10)</sup> reported a recurrence rate of 17% among 41 mixed germ cell tumor patients, of whom 56% were dysgerminomas. Similarly, **Mangili et al.**<sup>(20)</sup>, announced a recurrence rate of 18% in a study of 123 patients of mixed germ cell tumor among whom dysgerminoma was 40% and stage I was 71%. Recurrence in our study in 6 cases (16.6%).

Additionally, **Neeyalavira & Suprasert**<sup>(14)</sup> (76patients) reported 12 recurrent cases (15.8%). Dysgerminoma constituted only 25%, however, stage I in their series represented 67%. Dysgerminoma and mature teratomas were more than one third in **Hannan et al. study**<sup>(29)</sup> (66 patients) that showed 7 relapses (11%). The 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<sup>(30)</sup>.

Turner Syndrome and hormone consumed by women during pregnancy are correlated with the development of germ cell cancers<sup>(17-20,31)</sup>. In our limited study, however, it was not possible to examine these connections.

**Limitation of the study:** The limited patient number restricted the magnitude of statistical analysis.

## CONCLUSION

Yolk sac tumor and dysgerminoma are the commonest pediatric malignant ovarian tumors in this study. Multimodality treatment is essential. Fertility preservation should be respected. The advanced stages has the highest mortality.

**Conflict of interest:** The authors declare no conflict of interest.

**Sources of funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Author contribution:** Authors contributed equally in the study.

## REFERENCES

1. **Alobaid A (2008):** Mucinous cystadenoma of the ovary in a 12-year-old girl. *Saudi Med J.*, 29:126–8.
2. **Bhattacharyya N, De A, Bera P et al. (2010):** Ovarian tumors in pediatric age group-A clinicopathologic study of 10 years' cases in West Bengal, India. *Indian J Med Paediatr Oncol.*, 31:54–7.
3. **Auersperg N, Wong A, Choi K et al. (2001):** Ovarian

surface epithelium: biology, endocrinology, and pathology. *Endocr Rev.*, 22:255–88.

4. **Breen J, Maxson W (1977):** Ovarian tumors in children and adolescents. *Clin Obstet Gynecol.*, 20: 607–23.
5. **Hassana E, Creatsas G, Deligeorolou E et al. (1999):** Ovarian tumors during childhood and adolescence. A clinicopathological study. *Eur J Gynaecol Oncol.*, 20:124–6.
6. **Berger-Chen S, Herzog T, Lewin S et al. (2012):** Access to conservative surgical therapy for adolescents with benign ovarian masses. *Obstet Gynecol.*, 119:270–5.
7. **Biswajit D, Patil C, Sagar T (2010):** Clinical presentation and outcome of pediatric ovarian germ cell tumor: a study of 40 patients. *J Pediatr Hematol Oncol.*, 32: 54–6.
8. **Mukhopadhyay M, Shukla R, Mukhopadhyay B et al. (2013):** Ovarian cysts and tumors in infancy and childhood. *J Indian Assoc Pediatr Surg.*, 18: 16-20.
9. **Topuz S, Iyibozkurt A, Akhan S et al. (2008):** Malignant germ cell tumors of the ovary: a review of 41 cases and risk factors for recurrence. *Eur J Gynaecol Oncol.*, 29:635–7.
10. **Mangili G, Sigismondi C, Gadducci A et al. (2011):** Outcome and risk factors for recurrence in malignant ovarian germ cell tumors: a MITO-9 retrospective study. *Int J Gynecol Cancer*, 21(8):1414-21.
11. **Ghosh A, Ghartimagar D, Thapa S et al. (2016):** Ovarian tumors: pattern of histomorphological types-a 10 years study in a tertiary referral center and review of literature. *Kathmandu Univ Med J.*, 14:153–8.
12. **Zhao T, Liu Y, Jiang H et al. (2016):** Management of bilateral malignant ovarian germ cell tumors: Experience of a single institute. *Mol Clin Oncol.*, 5:383–7.
13. **Mangili G, Sigismondi C, Scollo P et al. (2015):** Management of bilateral malignant ovarian germ cell tumors: a MITO-9 retrospective study. *Int J Gynecol Cancer*, 25: 203-207.
14. **Neeyalavira V, Suprasert P (2014):** Outcomes of malignant ovarian germ-cell tumors treated in Chiang Mai University Hospital over a nine year period. *Asian Pacific J Cancer Prev.*, 15:4909–13.
15. **Park J, Kim D, Suh D et al. (2015):** Outcomes of pediatric and adolescent girls with malignant ovarian germ cell tumors. *Gynecol Oncol.*, 137:418–22.
16. **Pectasides D, Pectasides E, Kassanos D (2008):** Germ cell tumors of the ovary. *Cancer Treat Rev.*, 34:427–41.
17. **Kim T, Kim D, Cho M et al. (2011):** Use of laparoscopic surgical resection for pediatric malignant solid tumors: a case series. *Surg Endosc.*, 25:1484–8.
18. **Li J, Wu X (2016):** Current strategy for the treatment of ovarian germ cell tumors: role of extensive surgery. *Curr Treat Options Oncol.*, 17: 1–12.
19. **Liu H, Wang X, Lu D et al. (2013):** Ovarian masses in children and adolescents in China: analysis of 203 cases. *J Ovarian Res.*, 6:1–6.
20. **Mangili G, Sigismondi C, Lorusso D et al. (2017):** The role of staging and adjuvant chemotherapy in stage I malignant ovarian germ cell tumors (MOGTs): the MITO-9 study. *Ann Oncol.*, 28:333–8.
21. **Zhao Q, Yang J, Cao D et al. (2016):** Tailored therapy and long-term surveillance of malignant germ cell

- tumors in the female genital system: 10-year experience. *J Gynecol Oncol.*, 27(3):e26. doi: 10.3802/jgo.2016.27
22. **Rathore R, Sharma S, Arora D (2016):** Spectrum of childhood and adolescent ovarian tumors in India: 25 years experience at a single institution. Open access Maced J Med Sci., 4:551-55.
  23. **Baranzelli M, Kramar A, Bouffet E et al. (1999):** Prognostic factors in children with localized malignant nonseminomatous germ cell tumors. *J Clin Oncol.*, 17: 1212. doi: 10.1200/JCO.1999.17.4.1212
  24. **Chaopotong P, Therasakvichya S, Leelapatanadit C et al. (2015):** Ovarian cancer in children and adolescents: treatment and reproductive outcomes. *Asian Pacific J Cancer Prev.*, 16:4787–90.
  25. **Fresneau B, Orbach D, Faure-Contier C et al. (2015):** Sex-cord stromal tumors in children and teenagers: results of the TGM-95 study. *Pediatr Blood Cancer*, 62:2114–9.
  26. **Gershenson D (2007):** Management of ovarian germ cell tumors. *J Clin Oncol.*, 25:2938–43.
  27. **da Silva L, Renna N, Paulino E et al. (2015):** Outcomes of ovarian germ cell tumors: ten years of experience at the Brazilian National Cancer Institute. *Int J Gynecol Cancer*, 25(5):786-91.
  28. **Chaopotong P, Therasakvichya S, Leelapatanadit C et al. (2015):** Ovarian cancer in children and adolescents: treatment and reproductive outcomes. *Asian Pacific J Cancer Prev.*, 16:4787–90.
  29. **Hannan A, Malik M, Fasih S et al. (2015):** Malignant ovarian germ cell tumors at a tertiary care setting in Pakistan. *J Ayub Med Coll Abbottabad*, 27:624–7.
  30. **Hinchcliff E, Rauh-Hain J, Clemmer J et al. (2016):** Racial disparities in survival in malignant germ cell tumors of the ovary. *Gynecol Oncol.*, 140:463–9.
  31. **Ki E, Byun S, Choi Y et al. (2013):** Clinicopathologic review of ovarian masses in Korean premenarchal girls. *Int J Med Sci.*, 10:1061-67.