RESEARCH ARTICLE

Ovarian Cancer in Children and Adolescents: Treatment and Reproductive Outcomes

Pattama Chaopotong*, Suwanit Therasakvichya, Chairat Leelapatanadit, Atthapon Jaishuen, Sompop Kuljarusnont

Abstract

Objective: To review ovarian cancer cases in children and adolescents in Siriraj Hospital and assess the prognosis, recurrence of disease, and reproductive outcomes after treatment. Materials and Methods: A retrospective descriptive study was conducted in ovarian cancer patients 21 years and younger who had been treated at Siriraj Hospital between January 1990 and December 2009. Medical records were reviewed and relevant data were recorded. Results: A total of 48 cases met the criteria; their mean age was 16.4 years. Abdominal distension was the major symptom. 91.6% were germ cell tumors and the remaining cases were sex cord-stromal and epithelial tumors. More than half (25/48 cases) presented with stage I disease. The most common used chemotherapy regimen for germ cell tumors was BEP (bloemycin, etoposide, cisplatin). Most of patients had favorable outcomes; 46/48 cases had complete remission and retained their good health at the time of the review. We had only one recurrent case and one dead case. Ten of contacted patients had married and 3 of them had successful full-term pregnancies. Conclusions: Ovarian malignancy in children and adolescents is a rare disease. The authors reported 48 cases in 20 year-period of work. Most of them have favorable outcomes. Return of ovarian function and fertility are the topics of interest.

Keywords: Adolescent - children - ovarian cancer - treatment - reproduction

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Introduction

Ovarian cancer is the most aggressive disease in female reproductive organs and two third of these patients presented in the advanced stages due to non-specific presenting symptoms and lack of effective screening methods. Ovarian cancer which occurs commonly in women more than 50 years old is the epithelial histological cell type. Standard treatment for these patients includes laparotomy for total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH, BSO) and comprehensive surgical staging; follow by adjuvant combination platinum-based chemotherapy, dependent on their stages.

Conversely, ovarian cancer in children and adolescent is rare. The incidence of ovarian cancer in these groups were 0.102 and 1.072 per 100,000 female populations per year in children less than 9 years old and girls between 10-19 years old, respectively (Brookfield et al., 2009). The common ovarian cancer histology differed from the older group; the majorities were germ cell tumors and sex cord-stromal tumors. In addition, most of patients presented in apparent early stage diseases with good prognosis. The aims of treatment are to eradicate the diseases, and restore the uterus and remaining ovarian function for future fertility. Thus, the recommended treatments in this group are conservative surgery with comprehensive staging to rule out occult diseases, following by adjuvant combination chemotherapy regimens which depended on histology and stages.

We have been working with and treating these young patients for years. The aims of this study are review ovarian cancer in children and adolescent at age 21 years and younger who have been treated at Siriraj Hospital, assess the prognosis of these patients in terms of 5-year, and 10-year disease specific survival, recurrence of disease and also their reproductive outcomes after treatment and use this database for clinical researches in the future.

Materials and Methods

A retrospective descriptive study was conducted including all ovarian cancer patients with the age of 21 years and younger who have been treated at Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital between January 1990 and December 2009 (20 years). The study protocol was approved by SIRB, Faculty of Medicine, Siriraj Hospital, Mahidol University.

Individual medical records for all patients were reviewed and all relevant data were recorded for the program, such as, age at diagnosis, presenting symptoms, type of surgery, tumor size, FIGO stage, tumor histology,

*Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand *For correspondence: chaopotong@yahoo.co.th*

adjuvant treatment, outcome of treatment and disease free interval.

Statistical analysis

The data were processed using SPSS for Windows (Statistical Package for the Social Science). Descriptive analysis was used to determine demographic and treatment characteristics of the patients. 5-year and 10-year disease specific survival were analyzed by Kaplan-Meier method. The survival was calculated from date of initial diagnosis to date of last follow up or death.

Results

66 medical records of the children and adolescent at age under 21 years old with ovarian cancer were reviewed. 48 cases met the criteria. Demographic data of the patients were shown in Table 1.

Most of the patients in this study were between 11-21 years old, mean age was 16.4, only 2 cases were below 10. The youngest one was 7 years old with mixed germ cell tumor stage IA, and the other one was 9 years old with juvenile granulosa cell tumor stage IA. Abdominal distension was the major symptom of these patients (44/48 cases), only one case had abnormal menstruation and she was 21 years old at diagnosis. This patient had mixed germ cell tumor stage IIIB, her initial β- hCG was 9,920 mIU/ml.

5 from 48 cases received emergency exploratory laparotomy from abdominal pain; this entire group received conservative surgery. However, none of these patients received comprehensive surgical staging, only unilateral salpingo-oophorectomy (uniSO), peritoneal washing for cytology and/or infracolic omentectomy had been performed. 13/48 cases (27.1%) underwent radical surgery (TAH, BSO and comprehensive surgical staging). The mean age of this subgroup was 19.3 years.

Tumor histology, size, stages, and treatment outcomes were shown in Table 2. Ovarian cancer histology could be classified into 2 major subcategories; epithelial cancer and non-epithelial cancer. In the non-epithelial group, there were 3 sub-classifications; germ cell, sex cord- stromal, and uncommon malignant tumors, such as lipoid tumors, sarcoma, and small cell carcinoma. Most of non-epithelial malignant tumors occurred in young patients as in our study population. 44/48 cases (91.6%) were germ cell tumors, 1 case (2.1%) was juvenile granulosa cell tumor, and the remaining 3 cases (6.3%) were epithelial tumors; 1 endometrioid carcinoma, and 2 mucinous carcinoma.

According to germ cell tumor histology in our study, the majority in this group was dysgerminoma (15/44 cases, 34.1%), followed by yolk sac tumor (12/44 cases, 27.3%), immature teratoma and mixed germ cell tumor (8 cases each, 18.2%). The remaining one case was embryonal carcinoma. More than half of this group presented in stage I disease (25/48 cases, 52.0%). The second most was stage III disease (17/48 cases, 35.4%). We had 2 cases of stage IV disease, one case of mixed germ cell tumor with lung and liver metastases; the other was yolk sac tumor with brain metastasis. These 2 severe cases have normal health at the present.

All of patients had the tumor size larger than 5 centimeters (cm.) in maximal diameter. The mean and maximum tumor diameters were 17 and 40 cm., respectively. 40/48 cases (83.3%) had tumor size of more than 10 cm. For adjuvant treatment after operation; 44/48 patients received adjuvant chemotherapy. The 3 cases who did not receive adjuvant treatment were in stage IA of the disease: 1 mucinous cystadenocarcinoma case, and 2 dysgerminoma cases. Another one case who did not receive chemotherapy died on the 19th day postoperatively before chemotherapy was started.

The most common used chemotherapy regimen for germ cell tumor was BEP (cisplatin 20 mg/m2 plus etoposide 100 mg/m2 plus bleomycin 10 U, all for 5 days per cycle every 4 weeks). Of total 41 germ cell tumor cases, 37 cases (90.2%) received this combined regimen; the other 4 germ cell tumor cases received VAC (vincristine, dactinomycin, and cyclophosphamide), MAC (methotrexate, actinomycin D, and cyclophosphamide), and EP regimens. The remaining 3 cases who received chemotherapy were one juvenile granulosa cell tumor case and 2 cases of epithelial carcinomas, these 3 cases had stage IC diseases and received CP regimen (platinum plus cyclophosphamide).

Most of patients in this study group had good favorable

Table 1. Demographic Data

Patients characteristics	Number	%
Age at diagnosis (years)		
≤ 10	2	4.2
11 to 21	46	95.8
Signs and symptoms at the time of diagnosis		
Abdominal distension	34	70.8
Abdominal pain	3	6.3
Abdominal distension with pain	10	20.8
Abnormal menstruation	1	2.1
Primary surgery		
Elective	43	89.6
Emergency	5	10.4
Type of surgery		
Conservative	35	72.9
Radical	13	27.1

Table 2. Disease and Treatment Characteristics

Disease characteristics	Number	%
Tumor Histology		
Germ cell tumor	44	91.6
Sex cord- stromal tumor	1	2.1
Epithelial tumor	3	6.3
FIGO stage		
I	25	52
II	4	8.4
III	17	35.4
IV	2	4.2
Tumor size (cm)		
<5	0	0
5 to 10	8	16.7
>10	40	83.3
Treatment outcomes		
Complete response	46	95.8
Recurrence	1	2.1
Death	1	2.1

outcomes. 46/48 cases (95.8%) had complete remission after initial treatment and retained their good health at the time of this review. We had one recurrent case and one dead case.

The recurrent case was a 19 year old girl with dysgerminoma stage IA, and conservative surgery was performed on March 2000. Due to her early stage of disease, she did not receive adjuvant chemotherapy. Nineteen months later, she developed dysgerminoma in the contralateral ovary. After the second operation for tumor radically, she received adjuvant combination chemotherapy (BEP regimen). On last follow up time, she still has good health.

We had one dead case; she was 15 years old girl with yolk sac tumor stage IIIc. She was referred to our hospital after tumor debulking surgery from other hospital. Postoperatively, she developed sepsis and acute renal failure, so the adjuvant chemotherapy was postponed. She died on the 19th day post-surgery.

Because this study population had only one dead case and only one recurrent case, the Kaplan-Meier method could not be used to analyze the survival of patients. Our study group had disease specific survival (times from initial diagnosis to times of last follow up or death) ranging from 19 days in the fatal case and 0.6-18.4 years in the surviving cases. In surviving group, the mean disease specific survival is 8.3 years. The treatment details of only one recurrent case were mentioned above. At the time of this review, she had disease free interval from last treatment of recurrence of 8.4 years.

At the time of this review, 42/47 cases are kept in touch with. 10 of these 42 patients have married, half of them do not have uterus from previous operation, 3 of them had successful full-term pregnancy without complication (ranging from 4-12 years after treatment), 3 babies of these patients had good Apgar score at birth without birth defect and all of them had a birth weight of more than 2500 grams. The remaining 2 cases in this married group have not got pregnant. None of patients who still have the uterus in the married group had a miscarriage.

Discussion

Ovarian malignancy is a very rare disease in children and adolescent. Due to its rare incidence, we have only 66 cases in our records in a 20-year period and only 48 cases had completed data. We used the SEER data (Surveillance, Epidemiology, and End Results) for reference in term of incidence and survival of cancer. SEER is the largest information program for cancer in the United States and has been used in many researches, especially in pediatric malignancies fields (Brookfield et al., 2009).

95.8% of cases in this review were more than 10 years old. In study of Brookfield et al. analyzed data from 1037 malignant ovarian tumors in the pediatric population reported 89.9% of cases were between 10-19 years old (Brookfield et al., 2009). Major et al. reported data from their 10-year review and also found only 2 from 16 cases were less than 10 years old (Major et al., 1995). However, the report from Karachi, Pakistan showed similar incidence rate of ovarian malignancies in girls between 1-14 and 15-19 years old, 3.3% and 3.9%, respectively (Bhurgri et al., 2011). These data showed that ovarian malignancy was extremely rare in children less than 10 years of age. Most of ovarian cancer in the young is non-epithelial type; they have specific characteristics that differed from the epithelial type in adults. Non-epithelial tumors especially germ cell tumors have very rapid growth properties, majority of patients have abdominal distension from mass effect, some have acute abdomen from capsular distension, hemorrhage or necrosis (Berek and Natarajan, 2007) and most of the patients had bulky tumor mass, same as our report, 91.6% had abdominal distension and more than one fourth of patients had abdominal pain.

In the first two decades of life, germ cell tumors account for two thirds of the ovarian malignancies in this age group (Berek and Natarajan, 2007). We reported malignant germ cell tumor for 91.6% of total cases, the three most common subtypes were dysgerminoma for 34.1%, yolk sac tumor for 27.3%, and immature teratoma for 18.2%. Our study presented different percentages from other studies; Brookfield et al. reported 77.4% of 1037 cases (Brookfield et al., 2009) and Deprest et al. demonstrated 62.2% of 1364 patients were germ cell malignancies (Deprest et al., 1992). In contrast, we found only one from 48 cases (2.1%) which had sex cord- stromal tumor, whereas the report by Brookfield et al. showed 5.7% (Brookfield et al., 2009) and another study by Hassan et al. showed 12.3% of 57 cases (Hassan et al., 1999). In Asia, Haroon et al. from Pakistan reported 39 cases of ovarian sex cord- stromal tumor in children and young girls from their 20 year-experience (Haroon et al., 2014). These discrepancies may derive from the limitation of our data and the large number of patients in other studies may be deviated from the percentages of outcomes.

Concerning fertility in the future, since our patients were of young, the proper treatments for these patients who had germ cell tumors were conservative surgery, which consisted of midline incision, careful evaluation of all peritoneal surfaces, peritoneal washings for cytology, infracolic omentectomy, selected pelvic and para-aortic lymphadenectomy, biopsy and/or resection of any suspicious lesions, masses and any adhesions, random blind biopsies of normal peritoneal surfaces and unilateral salpingo-oophorectomy on the lesion side. The uterus should be left intact and examination of the opposite ovary performed without wedge biopsy (Billmire et al., 2004; von Allmen, 2005; Kavanagh et al., 2006; Aletti et al., 2007). Wedge biopsy of a normal ovary is not recommended as it could produce adhesion and scar which could possibly cause infertility. However, at least 18 cases in our study did not receive appropriate surgical intervention; maybe from emergency situation, limitation of information, and inadequate counseling to patients and their families. As well as germ cell tumors; sex cord-stromal tumors in children and women in reproductive age had the same treatment with germ cell tumors since the nature of disease is bilateral in only 2% of cases (Berek and Natarajan, 2007). Germ cell tumors are staged the same as epithelial ovarian cancer.

The outcomes of treatment are not dependent only on stage, because combination chemotherapeutic agents

have made highly curable outcomes common for germ cell tumor patients, even in advanced stage diseases or when there are a large number of residual tumors after surgery. These germ cell tumors are chemotherapy sensitive. The aggressiveness of the disease is dependent on the type; the most aggressive tumor is choriocarcinoma, but with chemotherapy, it is also highly curable. Dysgerminoma is highly radiosensitive tumor and radiotherapy may be useful in patients who have contraindication to chemotherapy. As chemotherapy can cure the majority of patients even with advanced disease, conservative surgery follow by combination chemotherapy is standard in all stages of all germ cell tumors (Kavanagh et al., 2006).

As BEP chemotherapy is associated with a lower relapse rate and shorter treatment time, it is preferred when compared to an older regimen, VAC. Other tested chemotherapy regimens include the following: combinations of ifosfamide and doxorubicin; vinblastine, ifosfamide and cisplatin; cyclophosphamide, doxorubicin and cisplatin and POMB-ACE; a combination of cisplatin, vincristine, bleomycin, methotrexate, actinomycin D, cyclophosphamide and etoposide (Kavanagh et al., 2006; Berek and Natarajan, 2007). In this review, 90.2% of our germ cell tumor cases received BEP regimen, as well as other regimens in 4 cases; all these patients including 2 cases of stage IV disease had good treatment outcomes and remain in remission at the time of this study.

All of patients have to be followed after their treatment; about 75% of recurrences occur within the first year and 90% within the second year after initial treatment (Berek & Natarajan, 2007). The recommended follow up time is every 1-2 months for year 1, every 2 months for year 2, every 3 months for year 3, every 4 months for year 4, every 6 months for year 5, and once a year subsequently (Kavanagh et al., 2006). Each visit should include history taking, physical examination and tumor markers measurement in cases whose tests showed elevated level before. Because our patients are of a younger age, and most of tumors secrete tumor markers, pelvic examination may be omitted.

This study does not mention about return of the ovarian function after treatment. El-Lamie IK et al. reported 47 germ cell malignancies patients treated with combination chemotherapy, 91.5% resumed normal menstruation, and there were 14 healthy live births without birth defects (El-Lamie et al., 2000). Some authors reported assessment techniques for ovarian reserve in the survivor of childhood cancer (Johnston & Wallace, 2009). Another concern for the survivors who received etoposide more than 2,000 mg/m2 is that they have a chance of developing treatment-related leukemia of as high as 5% (336-fold increased likelihood) (Nichols et al., 1993; Haddy et al., 2004). This risk-benefit should be discussed with patients and their parents as well as being monitored in these patients in the long term period.

In conclusion, ovarian malignancy in children and adolescence is very rare disease. We reported 48 cases in our 20 year-period of work. The most common histological type is germ cell tumor which carries a high curable rate even in advanced stage. The standard treatment is conservative surgery followed by combination chemotherapy, depending on stage and aggressiveness of tumor. Return of ovarian function and fertility outcome are the topics of interest and future research should be encouraged on these.

References

Aletti GD, Gallenberg MM, Cliby WA, et al (2007). Current management strategies for ovarian cancer. *Mayo Clin Proc*, **82**, 751-70.

Berek JS, Natarajan S (2007). Ovarian and fallopian tube cancer. in 'Berek & Novak's Gynecology, 14th ed', Ed Berek JS. Lippincott Williams & Wilkins, p.1457-549.

Bhurgri Y, Shaheen Y, Kayani N, et al (2011). Incidence, trends and morphology of ovarian cancer in Karachi (1995-2002). *Asian Pac J Cancer Prev*, **12**, 1567-71.

Billmire D, Vinocur C, Rescorla F, et al (2004). Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. *J Pediatr Surg*, **39**, 424-9.

Brookfield KF, Cheung MC, Koniaris LG, et al (2009). A population-based analysis of 1037 malignant ovarian tumors in the pediatric population. *J Surg Res*, **156**, 45-9.

Deprest J, Moerman P, Corneillie P, et al (1992). Ovarian borderline mucinous tumor in a premenarchal girl: review on ovarian epithelial cancer in young girls. *Gynecol Oncol*, **45**, 219-24.

El-Lamie IK, Shehata NA, Abou-Loz SK, et al (2000). Conservative surgical management of malignant ovarian germ cell tumors: the experience of the Gynecologic Oncology Unit at Ain Shams University. *Eur J Gynaecol Oncol*, **21**, 605-9.

Haddy TB, Mosher RB, Dinndorf PA, et al (2004). Second neoplasms in survivors of childhood and adolescent cancer are often treatable. *J Adolesc Health*, **34**, 324-9.

Haroon S, Idrees R, Zia A, et al (2014). Ovarian sex cord stromal tumours in children and young girls-a more than two decade clinicopathological experience in a developing country, Pakistan. *Asian Pac J Cancer Prev*, **15**, 1351-5.

Hassan E, Creatsas G, Deligeorolgou E, et al (1999). Ovarian tumors during childhood and adolescence. A clinicopathological study. *Eur J Gynaecol Oncol*, **20**, 124-6.

Johnston RJ, Wallace WH (2009). Normal ovarian function and assessment of ovarian reserve in the survivor of childhood cancer. *Pediatr Blood Cancer*, **53**, 296-302.

Kavanagh JJ, Pecorelli S, Benedet J, et al (2006). Cancer of the ovary. in 'staging classifications and clinical practice guidelines for gynaecological cancers', Eds. Benedet J, Pecorelli S, Ngan HY, Hacker NF. Elsevier, p.95-121.

Major T, Borsos A, Lampe L, et al (1995). Ovarian malignancies in childhood and adolescence. *Eur J Obstet Gynecol Reprod Biol*, **63**, 65-8.

Nichols CR, Breeden ES, Loehrer PJ, et al (1993). Secondary leukemia associated with a conventional dose of etoposide: review of serial germ cell tumor protocols. *J Natl Cancer Inst*, **85**, 36-40.

von Allmen D (2005). Malignant lesions of the ovary in childhood. *Semin Pediatr Surg*, **14**, 100-5.