Malignant ovarian germ cell tumors: the KK Hospital Experience

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Summary

Ovarian germ cell malignancies pose a therapeutic challenge especially amongst young patients. This is a retrospective review of 49 patients treated for such malignancies at KK Women's and Children's Hospital over a 13-year period. The relative proportion of such tumors was 6.2%. Age at presentation ranged from 14 to 51 years (mean 25.4 years). Forty-nine percent of tumors were immature teratomas and 81.6% had stage I disease. All patients had surgery initially and 67.3% required postoperative adjuvant chemotherapy. The patients were followed-up for one to 145 months (mean 51.6 months). All the 87.8% of patients on follow-up are alive and disease-free. There was one recurrence. Five patients had eight successful pregnancies, with no congenital anomalies. Mean duration when menstruation was resumed and regular was 2.5 and 3.5 months, respectively.

With combination chemotherapy and conservative surgery, the outlook for patients is excellent, with emphasis on preservation of ovarian function and fertility.

Key words: Germ cell tumor; Germ cell malignancy; Ovarian germ cell; Malignant ovarian germ cell tumor; Fertility sparing surgery; Menstrual function.

Introduction

Germ cell malignancies of the ovary are rare, accounting for less than 5% of all ovarian malignancies. However, they are more commonly seen amongst patients in the first two decades of life. This group of patients poses a therapeutic challenge since the issue of preservation of fertility has to be addressed. Fortunately, its previous dismal prognosis has improved dramatically with the use of combination chemotherapy, thus allowing for more conservative surgery in these young patients. The focus of recent papers has therefore shifted from survival to ovarian function after conservative surgery and combination chemotherapy. This is a retrospective review of 49 patients treated for malignant ovarian germ cell tumors at the Kandang Kerbau Women's and Children's Hospital in Singapore over a 13-year period.

Materials and Methods

The clinical records of 49 patients with malignant ovarian germ cell tumors who were managed between 1st January 1988 and 31st December 2000 were reviewed. Telephone interviews were conducted for patients lost to follow-up.

All cases underwent a central pathology review and diagnosis was classified according to WHO criteria. Immature teratomas were graded according to modified Serov *et al.* criteria [1].

Results

A. Clinical Presentation

Forty-nine patients were diagnosed with malignant ovarian germ cell tumours during the 13-year period between 1st January 1988 and 31st December 2000. During this period, a total of 786 cases of ovarian carcinoma were registered at our institution. Thus the relative proportion of malignant ovarian germ cell tumours during the study period was 6.2%.

The age distribution at presentation was from 14 to 51 years, with a mean of 25.4 years, and a median of 23 years. All the patients were postmenarchal and one was postmenopausal. The presenting symptoms are summarized in Table 1. The most common symptom was abdominal pain, and four of the 24 patients presented with an acute abdomen. A pelvi-abdominal mass was found in 63% of the patients at the time of presentation.

Tumour markers were measured in 39 of the patients. Of seven patients with pure yolk sac tumours, five patients who had tumour markers measured preoperatively expressed elevated levels of α-fetoprotein (AFP). The other two patients with pure yolk sac tumours did not

Table 1. — *Presenting signs and symptoms (n=49)*

Symptom / Sign	Number of patients	%
Pelvi-abdominal mass	31	63
Abdominal pain	24	49
Abdominal distension	17	35
Irregular menstruation	5	10
Abdominal pain with acute abdomen	4	8
Subfertility	2	4
Fever	2	4
Urinary symptoms	1	2
Loss of weight	1	2
Backache	1	2
Urinary symptoms	1	2

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Table 2. — *Tumour stage and histology (n=49)*

Stage	Histology								
	Immature Teratoma Grade 1	Grade 2	Grade 3	Dysgerminoma	Endodermal Sinus Tumour	Mixed Germ Cell Tumour	Others	Total	%
1A	5	4	3	4	3	3	4	26	53.1
1B	0	0	0	0	0	0	0	0	0
1C	2	3	3	3	2	0	1	14	28.6
2A	0	0	0	0	0	0	0	0	0
2B	1	0	0	0	0	0	0	1	2.0
2C	0	0	0	0	0	1	0	1	2.0
3A	0	1	0	0	1	0	0	2	4.1
3B	0	1	1	0	1	0	0	3	6.1
3C	0	0	0	0	0	1	1	2	4.1
4	0	0	0	0	0	0	0	0	0
Total	8	9	7	7	7	5	6	49	
%	16.3	18.4	14.3	14.3	14.3	10.2	10.2		100

have tumour markers assessed at the time of diagnosis. Four of the five patients with mixed germ cell tumours with yolk sac tumour elements had elevated AFP.

B. Histological Type and Staging of Tumours

Tumour stage and histology are summarized in Table 2. The majority of tumours were immature teratomas (49.0%), with dysgerminomas comprising 10.2%, yolk sac tumours 14.3%, mixed germ cell tumours 6.9%, and other tumours 12.2%. Distribution by stage is as follows: 40 (81.6%) had stage I disease, of which 26 were stage IA, two (4.1%) had stage II disease, seven (14.3%) had stage III disease, and none had stage IV disease. For the patients with immature teratomas, eight had grade 1 disease, nine had grade 2 disease, and seven had grade 3 disease.

Other tumours in the series include two cases of malignant struma ovarii, a benign cystic teratoma with malignant transformation to squamous cell carcinoma, and a non-gestational choriocarcinoma of the ovary.

C. Exploratory Findings

The mean size of the tumours was 16.3 cm (range: 3 to 33 cm). None of the tumours was macroscopically bilateral. However, one of the patients with dysgerminoma had a wedge biopsy of the contralateral ovary.

A review was made of the involvement of abdominal organs in the nine patients who were stage II and higher. Posterior uterine surface biopsies were positive for one patient with stage 3, grade 2 immature teratoma. There was involvement of the omentum in two cases. One had stage 3B yolk sac tumour, while the other had stage 3C non-gestational choriocarcinoma. Six patients had positive peritoneal seedings, but the size was not documented. One patient with stage 3 C mixed germ cell tumour had documented metastasis to the para-aortic lymph nodes.

D. Surgical Procedure

All the patients underwent surgery for their initial treatment. The operations performed are listed in Table 3. Conservative surgery was performed with preservation of the uterus and at least one ovary in 43 (87.8%) patients, 31 of whom underwent unilateral salpingo-oophorectomy, and seven of whom underwent unilateral cystectomy. The other six (12.2%) patients underwent total hysterectomy and bilateral salpingo-oophorectomy. A retrospective review was made as to whether such patients could have benefited from fertility preserving surgery, and two of these six patients in fact had not completed childbearing.

Omentectomy was performed in 15 patients, while lymphadenectomy or lymph node sampling was performed in 11 patients, one of whom had positive para-aortic nodal involvement. Three patients had peritoneal tumour excision. All the patients had optimal resection of macroscopic disease.

None of the patients underwent a second-look laparotomy. Six (12.2%) patients however had second operations subsequent to their primary operation. These second operations were performed at an interval of 6 to 55 months after the primary surgery and while one patient had surgery for recurrence, the others had no evidence of persistent or recurrent disease. One patient with immature teratoma stage 1C grade 3 was found to have mature glial implants at laparotomy 24 months after the first operation. The patient with recurrence was a 32-year-old patient with mixed germ cell tumor stage 1A. She underwent a unilateral salpingo-oophorectomy with a negative contralateral ovarian biopsy. No adjuvant therapy was given as the initial pathology showed a pure dysgerminoma. A subsequent review identified a small focus of yolk sac tumor. Seven months after the primary surgery, she recurred in the contralateral ovary. A laparotomy, ovarian cystectomy, with pelvic and para-aortic lymphadectomy was done. Histology confirmed recurrence of pure dysgerminoma with pelvic wall biopsies positive for malignancy. She was subsequently given 5 cycles of bleomycin, etoposide and cisplatinum (BEP) chemotherapy, and remained disease-free for 21 months at last follow-up.

E. Adjuvant Therapy

Details of adjuvant therapy administered are listed in Table 3. Thirty-three patients (67.3%) were given adjuvant chemotherapy postoperatively. The majority (32) received BEP, with a mean of 3.6 cycles and a range of 2 to 6 cycles administered. One patient with cystic teratoma with malignant transformation to squamous cell carcinoma received 6 cycles of a platinum and cyclophosphamide (CP) regime. None of the patients were given adjuvant radiotherapy.

Toxicity seen in the patients receiving chemotherapy was acceptable, and included nausea, vomiting, alopecia, leukopaenia, and electrolyte imbalance. Four patients displayed impaired lung function, two after the 4th cycle of BEP, and two after the 2nd cycle. These patients required interruption of their chemotherapy.

Sixteen patients were not given adjuvant therapy: five patients with immature teratoma stage 1A grade 1, one

Table 3. — *Summary of patients*

Patient	Age	Histology	Stage/Grade	Primary Therapy	Adjuvant Therapy	Current Status (months)
1	15	IT	1A/G1	USO		NED 40
2	17	IT	1A/G1	Cystectomy		NED 10
3	19	IT	1A/G1	Cystectomy		NED 24
4	25	IT	1A/G1	USO, Oment, Appx, LN		NED 8. Lost to F/U
5	33	IT	1A/G1	Cystectomy, USO		NED 68
6	20	IT	1A/G2	USO, Oment	BEP*3	NED 24
7	22	IT	1A/G2	USO	BEP*4	NED 30
8	27	IT	1A/G2	USO	BEP*4, VAC*1	NED 143
9	35	IT	1A/G2	USO	BEP*3	NED 9
10	15	IT	1A/G3	USO, Omet, LN	BEP*3	NED 24
11	20	IT	1A/G3	USO, Oment	BEP*4	NED 20
12	21	IT	1A/G3	USO, Oment	BEP*3	NED 81. Lost to F/U
13	18	IT	1C/G1	USO, Oment	BEP*3	NED 10. Lost to F/U
14	23	IT	1C/G1	Cystectomy	(Pregnant)	NED 13
15	18	IT	1C/G2	USO, Oment	PBE*4	NED 67
16	19	IT	1C/G2	USO, Oment	BEP*4	NED 74
17	36	IT	1C/G2	THBSO	BEP*4	NED 29
18	22	IT	1C/G3	USO, Appx	BEP*4	NED 42
19	28	IT	1C/G3	USO	BEP*4	NED 55
20	30	IT	1C/G3	THBSO, Oment	BEP*4	NED 70
21	15	IT	2B/G1	USO, Oment, ex Per Tu		,ED 86
22	23	IT	3A/G2	Cystectomy	Defaulted	NED 1. Lost to F/U
23	23	IT	3B/G2	USO	BEP*3	NED 145
24	16	IT	3B:G3	USO, Ex Per Tu	BEP*4	NED 94
25	17	DYS	1A	USO		NED 47
26	22	DYS	1A	USO, Oment, LN		NED 41
27	26	DYS	1A	USO		NED 143
28	29	DYS	1A	USO		NED 18
29	22	DYS	1C	USO	BEP*3	NED 128
30	27	DYS	1C	USO	BEP*3	NED 56
31	28	DYS	1C	USO, Oment	BEP*4	NED 41
32	22	EST	1A	USO, Oment, LN	BEP*3	NED 25
33	24	EST	1A	USO, Oment, LN	Defaulted	NED 7
34	37	EST	1A	THBSO, Oment	Defaulted	NED1. Lost to F/U
35	20	EST	1C	USO	BEP*4	NED 107
36	35	EST	1C	USO	BEP*3	NED 8. Lost to F/U
37	22	EST	3A	USO, Oment, LN	BEP*2, VIP*4	NED 36
38	19	EST	3B	USO, Oment, LN	BEP*5	NED 70
39	17	MGCT	1A	Cystectomy	BEP*3	NED 36
40	31	MGCT	1A	USO, Oment	BEP*3	NED 32
41	32	MGCT	1A	USO, Contralat Ov Bx	BEP*3	Recurrence 7.
42	37	MGCT	2C	THBSO, Oment, ex Per Tu	BEP*4	NED 47
43	14	MGCT	3C	USO, Oment	BEP*6	NED 95
44	41	MSO	1A	THBSO		NED 131
45	33	MSO	1A	Cystectomy		NED 3
46	51	Ter, SCC	1A	THBSO, Oment	CP*6	NED 114
47	31	Ter, SCC	1C	USO	Defaulted	NED 18
48	30	ChorioCA	1A	Cystectomy	BEP*3	NED 11
49	41	ChorioCA	3C	USO, Oment	BEP*4	NED 120

Legend: IT, Immature Teratoma; DYS, Dysgerminoma; EST, Endodermal Sinus Tumour; MGCT, Mixed Germ Cell Tumour; MSO, Malignant Struma Ovarii (Follicular Carcinoma); ChorioCA, Non-gestational Choriocarcinoma; THBSO, Total Hysterectomy, Bilateral Salpingo-oophorectomy; BEP, Bleomycin, Etoposide, Cisplatinum; VAC, Vincristin, Actinomycin-D, Cyclophospamide; VIP, Vinblastine, Ifosfamide, Cisplatinum; CP, Cyclophosphamide, platinum; NED, No Evidence of Disease; F/U, Follow up; USO, Unilateral Salpingo-oophorectomy; Oment, Omentectomy; Appx, Appendectomy; LN, Lymphadenectomy; Ex Per Tu, Excision of Peritoneal Tumours; Contralat Ov Bx, Contralateral Ovarian wedge Biopsy.

with immature teratoma stage 2B grade 1, four patients with dysgerminoma stage 1A, and two patients with malignant struma ovarii. Four patients defaulted on chemotherapy and further follow-up, one of whom was pregnant at the time of surgery.

F. Survival and Outcome

The current status of the patients is represented in Table 3. Follow-up of patients ranged from one to 145 months, with a mean of 51.6 months. Seventeen (34.7%) of the patients were followed-up for more than five years. Six

Table 4. — *Reproductive outcome of patients attempting conception after chemotherapy*

Patient	Age (years)	Tumor	Stage/Grade	Chemotherapy	PregnacnciesDuration from chemotherapy (months)		Oucome
12	21	Immature Teratoma	1A/G3	BEP*3	1	64	N
16	19	Immature Teratoma	1C/G2	BEP*4	2	36	2N
23	23	Immature Teratoma	3B/G2	CX*3	3	60	3N
30	27	Dysgerminoma	1C	BEP*3	1	13	N
38	19	Endodermal Sinus Tumour	3B	BEP*5	1	13	N
29	22	Dysgerminoma	1C	BEP*3	Male factor subfertility		

N= Normal liver births

(12.2%) patients were lost to follow-up. All the patients on follow-up were alive and free of disease at their last follow-up. There was only one (2.9%) recurrence. Forty-eight patients (98.0%) are recurrence-free.

G. Menstrual and Reproductive Outcome

Six of the patients who were treated with fertility-preserving surgery and adjuvant chemotherapy attempted conception. Five patients had successful pregnancies following chemotherapy, with no documented congenital anomalies in the offspring. The outcome has been tabulated in Table 4. One patient was being investigated for subfertility, and preliminary results showed male factor subfertility, after which she defaulted on further investigations.

The mean time to resumption of menstruation after completion of chemotherapy was 2.5 months, with a range of 1 to 6 months. Except for a patient who had irregular periods secondary to pre-existing polycystic ovarian disease, the mean duration when menstruation became regular was 3.5 months, with a range of 1 to 6 months.

Discussion

Marked improvement in the management of ovarian germ cell malignancies has been seen over the last two decades. The contribution of effective combination platinum-based chemotherapy has been most significant in changing these previously lethal malignancies into highly curable ones.

The overall survival of patients diagnosed with malignant ovarian germ cell tumours is now excellent, and the rate of long-term morbidity is low. It has also been demonstrated that fertility, an important issue as most of the patients are diagnosed early in life, may be preserved in most patients without any adverse effect, despite adjuvant chemotherapy [2].

The treatment policy in our unit consists of surgery alone for surgically staged and histologically confirmed Stage 1A pure dysgerminomas and low-grade immature teratomas. All other patients received adjuvant bleomycin, etoposide, and platinum (BEP) chemotherapy [3]. Surgical staging includes assessment of peritoneal fluid cytology, biopsy of suspicious areas on the peritoneal surfaces, retroperitoneal lymph node sampling including the pelvic and high para-aortic nodes, as well as an infracolic omentectomy. Patients referred to the hospital with an incompletely staged dysgerminoma or low grade immature teratoma apparently confined to the ovary have their histology reviewed, are evaluated with tumour markers (LDH, AFP and HCG) to detect non-dysgerminomatous elements, and have a CT scan to detect any unsuspected residual tumor. If these studies are normal, the patient is not restaged and is followed up with tumor markers and CT scans or ultrasonography.

Fertility preserving surgery is an important consideration in young patients, and previous studies have shown that unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is adequate and appropriate in patients with early stage ovarian germ cell malignancies and selected patients with advanced disease [4-6]. However, as dysgerminomas have been known to occur bilaterally in approximately 10 to 15% [7, 8] of the cases, Schwartz *et al.* suggested that a wedge biopsy should be performed at the time of the staging laparotomy [6]. Unnecessary biopsy, however, may result in future infertility in about 14% of cases due to peritoneal adhesions or ovarian failure [4, 9].

Laparoscopic operations were performed in four of the patients in this series, with subsequent follow-up showing no evidence of disease. Maiman *et al.* [10] found that attempted laparoscopic excision of adnexal masses which are subsequently found to be malignant are not uncommon. Potential problems with this approach include inappropriate surgical procedures, incomplete surgical staging, inadequate patient preparation, and delay in definitive therapy. He suggested that if there is suspicion of ovarian malignancy upon laparoscopic evaluation, the ovarian capsule should not be violated, and laparotomy should be initiated.

Adjuvant combination chemotherapy is offered to all patients, except patients who have stage 1A pure dysgerminoma or immature teratoma, grade 1 [3]. It offers several advantages when compared to radiotherapy: preservation of reproductive function, lack of abnormal bone growth associated with radiotherapy, and the ability of systemic control beyond the boundaries of the radiotherapy field [11]. The introduction of cisplatin-containing drug regimens, notably the bleomycin, etoposide, and platinum (BEP) regime since the 1980s, has resulted in a 5-year survival rate of up to 100% for dysgerminomas, and 85% for nondysgerminomatous malignant germ cell

tumours [12-14]. Similarly, in this study, the BEP regimen has been highly successful.

Many germ cell tumours possess the unique property of producing biologic markers, which can be detected in the serum [16-20]. The availability of specific and sensitive radioimmunoassay techniques for measuring hCG and AFP facilitate diagnosis, monitoring of the response to treatment, and follow-up.

Second-look laparotomy has generally not been recommended in the management of such patients [21]. However, in dysgerminomas and immature teratomas that have macroscopic residual disease at the start of chemotherapy, second-look laparotomy may be useful as such patients are at higher risk of failure, there are no reliable markers for immature teratomas, and second-line chemotherapy is available. Furthermore, in immature teratoma, if only mature teratoma elements are found at second-look, chemotherapy should be discontinued [22]. In this series, none of the patients had a second-look laparotomy. However, six patients underwent further surgery, one of which had recurrent disease. The low recurrence rate of 2% and 100% survival in this series reiterates the excellent overall prognosis of malignant ovarian germ cell tumours.

There have been some previous studies looking at the effect of fertility-conserving surgery and adjuvant chemotherapy on menstrual function and pregnancy outcome. In this series, there were five patients with a total of eight successful pregnancies amongst them. All the offspring were healthy with no evidence of fetal anomalies. Only one patient experienced infertility, and investigations revealed this to be due to male factor. Low *et al.* demonstrated 14 healthy live births amongst patients who had received chemotherapy, with documented infertility at 5% [23]. Gershenson [24] documented a 10% infertility rate, corresponding to the background incidence of infertility in the normal population. Papers by Schwartz [6, 25], Fishman [26], Creasman [27] and Sessa [28] also reported healthy pregnancies after chemotherapy. In our cohort, menstrual function resumed within seven months of completion of chemotherapy, showing that normal ovarian function was maintained after conservative surgery and chemotherapy. In a study from the M. D. Anderson Institute, 68% of patients maintained regular menses after completing chemotherapy, and 83% had regular periods at the time of follow-up [24]. In Low *et al.'s* series, 62% of those undergoing chemotherapy were amenorrhoeic during treatment, but 92% resumed regular menses on completing chemotherapy [23].

Conclusion

With modern management, the outlook of patients with malignant ovarian germ cell tumors is excellent. In the young patient, fertility-sparing surgery is the procedure of choice, even in the face of advanced disease. Prompt initiation of platinum-based combination chemotherapy is the cornerstone of management. This and other papers have demonstrated that ovarian function is preserved after chemotherapy, and normal fertility can be anticipated. Longer follow-up and meta-analyses of data are required to ascertain the impact on fetal anomaly and long-term development of offspring. Attention should also be focused on the reduction of toxicity from chemotherapy.

References

[1] Serov S. F., Scully R. E., Sobin L. J.: "Histological typing of ovarian tumors". In: World Health Organization. International histological classification of tumors. Geneva: The World Health Organization. 1973, *no. 9.*

[2] Wu P. C., Huang R. L., Lang J. H. *et al.*: "Treatment of malignant ovarian germ cell tumours with preservation of fertility: A report of 28 cases". *Gynecol. Oncol.*, 1991; *40*, 2.

[3] National Institutes of Health Consensus Development Panel on Ovarian Cancer. NIH consensus conference. Ovarian cancer. Screening, treatment and follow-up. *JAMA*, 1995; *8*, 491.

[4] Gershenson D. M.: "Management of early ovarian cancer: germ cell and sex cord-stromal tumors". *Gynecol. Oncol.*, 1994, *55*, S62-72.

[5] Gershenson D. M.: "Update on malignant ovarian germ cell tumors". *Cancer*, 1993, *71*, 1581.

[6] Schwartz P. E., Chambers S. K., Chamber J. T., Kohorn E., Mcintosh S.: "Ovarian germ cell malignancies: the Yale University experience". *Gynecol. Oncol.*, 1992, *45*, 26.

[7] Asadourian L. A., Taylor H. B.: "Dysgerminoma: an analysis of 105 cases". *Obstet. Gynecol.*, 1969, *33*, 370.

[8] De Palo G., Pilotti S., Kenda R.: "Natural history of dysgerminoma". *Am. J. Obstet. Gynecol.*, 1982, *143*, 799.

[9] Weinstein D., Polishuk W. Z.: "The role of wedge resection of the ovary as a cause for mechanical sterilty". *Surg. Obstet. Gynecol.*, 1975, *141*, 417.

[10] Maiman M., Seltzer V., Boyce J.: "Laparoscopic excision of ovarian neoplasms subsequently found to be malignant". *Obstet. Gynecol.*, 1991, 77, 563-565.

[11] Bjorkholm E., Lundell M., Gyftodimos A., Silfversward C. : "Dysgerminoma. The Radiumhemmet series 1927-1984", *Cancer*, 1990, *65*, 38.

[12] Segelov E., Campbell J., Ng M., Tattersall M., Rome R., Free K. *et al.*: "Cisplatin-based chemotherapy for ovarian germ cell malignancies: the Australian experience". *J. Clin. Oncol.*, 1994, *12*, 378.

[13] Dimopoulos M. A., Papdopoulou M., Andreopoulou E., Papadimitriou C., Pavlidid N., Aravantinos G. *et al.*: "Favourable outcome of germ cell malignancies treated with cisplatin or carboplatin-based chemotherapy: a Hellenic Cooperative Oncology Group Study". *Gynecol. Oncol.*, 1998, *70*, 70.

[14] Williams S. D., Birch R., Einhorn L. H., Irwin L., Greco F. A., Loehrer P. J:. "Treatment of disseminated germ-cell tumours with cisplatin, bleomycin, and either vinblastine or etoposide". *N. Engl. J. Med.*, 1987, *316*, 1435.

[15] Gershenson D. M., Morris M., Cangir A., Kavanagh J. J., Stringer C. A., Edwards C. L.: "Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide, and cisplatin". *J. Clin. Oncol.*, 1990, *8*, 715.

[16] Kawai M., Kano T., Kikkawa F. *et al.*: "Seven tumor markers in benign and malignant germ cell tumors of the ovary". *Gynecol. Oncol.*, 1992, *45*, 248.

[17] Pressley R. H., Muntz H. G., Falkenberry S., Rice L. W.: "Serum lactic dehydrogenase as a tumor marker in dysgerminoma". *Gynecol. Oncol.*, 1992, *44*, 281.

[18] Kawai M., Furuhashi Y., Kano T. *et al.*: "Alpha-fetoprotein in malignant germ cell tumors of the ovary". *Gynecol. Oncol.*, 1990, *39*, 160.

[19] Bonazzi C., Colombo N., Lissoni A. *et al.*: "Alpha-fetoprotein in the management of germ cell tumors of the ovary". *J. Nucl. Med. Allied. Sci.*, 1989, *33* (3 suppl), 53.

[20] Dgani R., Shoham Z., Czernobilsky B. *et al.*: "The content of lactic dehydrogenase, alkaline phosphatase and human chorionic gonadotropin in a pure ovarian dysgerminoma". *Gynecol. Oncol.*, 1988, *30*, 44.
[21] Williams S. D., Blessing J. A., DiSaia P. J., Major F. J., Ball H. G. 3rd, Liao S. Y.: "Second-look laparotomy in ovarian germ cell tumors: the Gynecologic Oncology Group experience". *Gynecol. Oncol.*, 1994, *52:3*, 287.
[22] Berek J. S, Hacker N. F.: "Non-epithelial ovarian and fallopian tube cancers. In: Berek S, Hacker NF, eds." *Practical gynecologic oncology.*, 3rd ed., Philadelphia, Lippincott Williams and Wilkins, 2000, 523.
[23] Low J. J. H., Perrin L. C., Crandon A. J., Hacker N. F.: "Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors". *Cancer*, 2000, *89*, 391.
[24] Gershenson D. M.: "Menstrual and reproductive function after treatment with combination chemotherapy for malignant ovarian germ cell tumours". *J. Clin. Oncol.*, 1988, *6*, 270.
[25] Schartz P.: "Combination chemotherapy in the management of ovarian germ cell malignancies". *Obstet. Gynecol.*, 1984, *64*, 564.
[26] Fishman D. A., Schwartz P. E.: "Current approach to diagnosis and treatment of ovarian germ cell malignancies". *Curr. Opin. Obstet. Gynecol.*, 1994, *6*, 98.
[27] Creasman W. T., Soper J.T.: "Assessment of the contemporary management of germ cell malignancies of the ovary". *Am. J. Obstet. Gynecol.*, 1985, *153*, 828.
[28] Sessa C., Bonazzi C., Landoni F., Pecorelli S., Sartori E., Mangioni C.: "Cisplatin, vinblastine and bleomycin combination chemotherapy in endodermal sinus tumor of the ovary". *Obstet. Gynecol.*, 1987, *70*, 220.

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