Survival and fertility of patients with malignant ovarian germ cell tumours

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Summary

Disease-free survival (DFS), overall survival (OS) and fertility of patients treated for malignant ovarian germ cell tumours at the Institute of Oncology Ljubljana from 1990-2000 were assessed. Twenty-three patients with a median age of 25 (15-67) years were treated. Five had pure dysgerminoma, three endodermal sinus tumour, ten immature teratoma and five had mixed germ cell tumours. Eleven patients had FIGO Stage I and the others advanced stage disease. All patients underwent initial surgery; in 13 of 15 patients under 35 years unilateral salpingo-oophorectomy was performed. Twenty-one patients received adjuvant cisplatin-based chemotherapy. At the median follow-up of 68 (11-140) months DFS was 74% and OS 87%. Six patients (two did not receive adjuvant chemotherapy) relapsed at a median of 16 (3-63) months after surgery. At relapse four were treated with surgery and chemotherapy, one with chemotherapy only and one with palliative radiotherapy only: two are still in complete remission, one has residual disease and three died of disease. Ten of 13 patients with fertility-preserving surgery regained menstrual cycles and one gave birth to a normal child. DFS and OS in our group of patients (over 15 years of age) are comparable to other institution's experience. Fertility in young patients can be preserved without compromising outcome.

Key words: Malignant ovarian germ cell tumours; Fertility preserving surgery; Cisplatin-based chemotherapy; Menstrual function; Survival.

Introduction

Malignant ovarian germ cell tumours are rare tumours. They account for less than five percent of all ovarian malignancies. However, in contrast to epithelial ovarian tumours, which occur mostly in postmenopausal women, their peak incidence is between 10 and 30, in the childbearing years. These tumours grow rapidly and patients often present as an abdominal emergency with incorrect diagnoses (acute appendicitis, extra-uterine pregnancy, bowel perforation, etc.). Vaginal bleeding or precocious puberty, the latter presumably due to human chorionic gonadotropin (HCG) production, are less common initial signs. Histologic types of malignant ovarian germ cell tumours include pure dysgerminoma, immature teratoma, endodermal sinus tumour, embrional carcinoma, choriocarcinoma and mixed cell tumours [1]. Depending on the histologic type of the ovarian tumour, serum levels of HCG (dysgerminoma), alpha-fetoprotein (AFP; endodermal sinus tumour), and/or lactic dehydrogenase (LDH) are increased. Malignant ovarian germ cell tumours are staged according to the International Federation of Gynecologists and Obstetricians (FIGO) staging system for epithelial ovarian cancer [2]. Studies in the past have shown that patients with completely resected malignant ovarian germ cell tumours had a very high risk of recurrence after surgery only. Since the introduction of cisplatin-based chemotherapy in the 1970s and 1980s, the prognosis of patients with malignant ovarian germ cell tumours has improved dramatically. Current treatment of malignant ovarian germ cell tumours consists of initial surgery and adjuvant cisplatin-based chemotherapy. Several trials have shown that the majority of patients with malignant ovarian germ cell tumours will be long-term survivors after three to four courses of bleomycin/etoposide/cisplatin (BEP) adjuvant chemotherapy following initial surgery [3-8]. Adjuvant chemotherapy is indicated in FIGO Stage Ic and all stages of FIGO II, III and IV.

The data from the literature show that the type of primary operative procedure should depend on the surgical findings. Since bilateral ovarian involvment with tumour is rare (except in pure dysgerminoma or Stage IV disease) surgery should consist of unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus, thus preserving the potential for fertility. If the contralateral ovary appears grossly normal on careful inspection it should be left undisturbed; however in the case of pure dysgerminoma, biopsy may be considered. If the contralateral ovary appears abnormally enlarged, a biopsy or ovarian cystectomy should be performed. If frozen section should reveal a dysgenetic gonad, then bilateral salpingo-oophorectomy is indicated [9]. Since the majority of patients with malignant ovarian germ cell tumours are in their childbearing age, attention has been focused on preserving fertility. Bilateral salphingo-oophorectomy and total hysterectomy as well as radiation therapy were the important causes of infertility after treatment for ovarian germ cell malignancy in the past. Currently unilateral salpingo-oophorectomy, which preserves the uterus and contralateral ovary with tuba is the standard surgical procedure in young patients. However, in postmenopausal patients, total hysterectomy and bilateral salpingo-oophorectomy are performed.

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In patients with extensive intra-abdominal disease whose clinical condition precludes debulking surgery, chemotherapy can be considered prior to surgery; after maximal surgical debulking, three to four courses of cis-platin-based combination chemotherapy are indicated [3, 6, 8].

The present paper is a retrospective review of patients treated for malignant ovarian germ cell tumours at the Institute of Oncology Ljubljana from 1990 to 2000. We assessed disease-free survival (DFS), overall survival (OS) and fertility.

Materials and Methods

The clinical records of 23 patients who were treated at the Institute of Oncology Ljubljana for malignant ovarian germ cell tumours between January 1990 and December 2000 were reviewed. The histologic types of tumours were classified according to WHO criteria [1]. Staging was performed according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system and classification was based on both the surgical and pathologic report [2].

Disease-free survival was defined as the time from diagnosis to the first relapse. Overall survival was defined as the time from diagnosis to the last follow-up. For the patients lost in follow-up the current status (alive or dead) was checked at the Registry of Cancer of the Republic of Slovenia. Statistical analysis was performed with the SPSS program - Version 10. Overall survival and disease-free survival were estimated according to the Kaplan-Meier method. For comparison between groups the two-sided Pearson chi-square test and Student's t-test were used.

Results

A. Clinical presentation

Twenty-three patients were treated for malignant ovarian germ cell tumours during the 11-year period. Median age of patients at presentation was 25 years, with the age distribution from 15 to 67 years. Eighteen patients were postmenarchal, four were postmenopausal, and one patient aged 15 years had Klinefelter Syndrome (47, XXY). Tumour markers AFP, HCG and CA-125 were measured preoperatively in 12, 7 and 16 patients, respectively. AFP was increased in three out of three patients with endodermal sinus tumours, three out of three patients with immature teratomas (in 6 patients it was not measured), and in three out of four patients with mixed germ cell tumours (in one it was not measured). HCG was increased in two out of two evaluable patients with dysgerminomas. CA-125 was increased in all two out of two, three out of three, six out of seven and two out of three patients evaluable for this marker, in dysgerminoma, endodermal sinus tumour, immature teratoma and mixed cell germ tumours, respectively (Table 1).

B. Histology type and staging of tumours

The most common histologic type of tumour was immature teratoma (43.4%). Dysgerminoma and mixed germ cell tumours each accounted for 21.7% and the endodermal sinus tumour was the least common with 13%. All endodermal sinus tumours and two-thirds of immature teratoma were in Stage I. All mixed germ cell tumours were in advanced stage (III and IV), whereas dysgerminomas were in all stages (Table 2.). Overall, 11 tumours were in Stage I, Stage Ia was present only in two tumours, both being dysgerminomas. Twelve tumours were in advanced stage (II, III and IV). Grade of the tumour was determined only in eight of 23 tumours.

Table 1. — *Tumour markers at presentation according to different histological types of malignant ovarian germ cell tumours.*

Histology	All patients	Increased/ Evaluated AFP	Increased/ Evaluated βHCG	Increased/ Evaluated CA-125
DYS	5	0/1	2/2	2/2
EST	3	3/3	0/1	3/3
IT	10	3/3	3/9	6/7
MCGT	5	3/4	1/2	2/3

AFP, α-fetoprotein; β-HCG, β-horiogonadotropin; DYS, Dysgerminoma; EST, Endodermal Sinus Tumour; IT, Immature Teratoma; MGCT, Mixed Germ Cell Tumour.

Table 2. — *Tumour histology and pathological stage.*

Histology	FIGO Stage I	II	III	IV	Total
Immature teratoma	6	1	2	1	10
Dysgerminoma	2	1	1	1	5
Mixed cell germ tumour	0	0	1	4	5
Endodermal sinus tumour	3	0	0	0	3
Total	11	2	4	6	23

C. Surgical procedure

Surgery was the initial treatment in all patients. A detailed description of the surgical procedures is shown in Table 3. In 13 of 15 patients younger then 39 years (86.7% of child-bearing patients) unilateral salpingo-oophorectomy with the preservation of the contralateral ovary and the uterus was performed. Bilateral salpingo-oophorectomy was performed in a patient aged 15 years due to Klinefelter Syndrome (47, XXY), and in a patient aged 25 with Stage IIc disease; both had mixed germ cell tumours. Eight patients were aged 39 years or older; seven of them underwent initial surgery that consisted of total hysterectomy and bilateral salpingo-oophorectomy and one had bilateral salpingo-oophorectomy with preservation of the uterus. Altogether, fertility-preserving operations were performed in 56.5% of all patients treated in our institution. None of the patients underwent second-look surgery after completion of adjuvant chemotherapy. Omentectomy was performed in all patients with Stage II, III and IV, except in one patient with Stage IIIc and in one patient with Stage IV disease; in the latter omentectomy was performed at the recurrence. Omentectomy was also performed in one patient with Stage Ia (49 years), one patient with Stage Ib (41 years) and two patients with Stage Ic disease (40 and 24 years).

Table 3. — *Summary of patients' record.*

Patient	Age	Hist	FIGO Stage/ Grade	Primary Therapy	Adjuvant Therapy	Recurrence/ Months/ Localisation/Therapy	Menses/ Child	Current Status (months)
1	16	IT	Ic/G1	USO	BEP*2	None	Unknown	NED 93+
2	18	DYS	IIIc/unknown	USO, Oment	BEP*4	None	Regular/None	NED 65+
3	21	IT	Ic/G2-3	USO	BEP*3	None	Irregular/None	NED 59+
4	27	DYS	Ia/ unknown	USO	None	Yes /63/Retroperiton/ BEP*4, Surg Oment	Regular/ None	NED 103+
5	25	MGCT	IIc/ unknown	BSO, Oment	BEP*5	None	Unknown	NED 42+
6	59	IT	Ic/ unknown	THBSO	BEP*3	None	None	NED 80+
7	67	IT	IIc/unknown	THBSO, Oment	BEP*2, RT	Yes /15 /Vagina/RT	None	D 15
8	16	MCGT	III?b/unknown	USO, Oment	BEP*4, VIP*2	Yes/9/Pelvis/Surg Cisplatin IP	Unknown	D 11
9	28	IT	IIIb/G 1	USO, Oment	BEP*3	None	Regular/None	NED 68+
10	67	MCGT	IIIc/G2-3	THBSO, Oment, Appx	EP*1, BEP*5	Yes /16/Vagina/P*7	None	ED 32+
11	15	DYS	IV/unknown	USO, Oment	BEP*2, EP*2, RT scl	None	Irregular/None	NED 18+
12	24	EST	Ic/unknown	USO, Oment, LN, Appx	BEP*4	None	Unknown	NED 48+
13	41	IT	Ib?/G3	THBSO, Oment	BEP*2, EP*1	None	None	NED 38+
14	26	IT?	IV/unknown	USO	None	Yes /3/Abdomen/ THBSO, Oment, Musc, BEPO*6	None	NED 104+
15	22	IT	Ic/G 2	USO	BEP*3	None	Regular/None	Lost-FU
16	65	IT	IIIc?/G3	THBSO, Oment, Appx	CP*5	Yes /19/Abdomen/ Surg, BEP*6	None	D 35
17	25	EST	Ic/unknown	USO-Ex	BEP*5	None	Regular/None	NED 111+
18	15	MGCT#	IIIc/unknown	BSO, Oment	BEP*6	None	Regular/None	NED 127+
19	40	EST	Ic/G 3	THBSO, Oment, Appx	CP*1, BEP*5	None	None	NED 115+
20	19	DYS	IIb?/unknown	USO, LN	EP*3	None	Regular/1 child	NED 130+
21	47	DYS	Ia/unknown	THBSO, Oment, Appx	BVP*3	None	None	NED 114+
22	39	MGCT	IIIc/unknown	BSO	BVP*2	None	None	Lost-FU
23	15	IT	Ic/unknown	USO	BEP*4	None	Regular/None	NED 127+

IT, Immature teratoma; T, Mature teratoma; DYS, Dysgerminoma; EST, Endodermal sinus tumour; MGCT, Mixed germ cell tumour; THSBO, Total hysterectomy, Bilateral salpingo-oophorectomy; USO, Unilateral salpingo-oophorectomy; Appx, Appendectomy, Oment. Omentectomy; LN, Lymphadenectomy; Surg, Surgical extirpation, BEP, Bleomycin, Etoposide, Cisplatin; EP, Etoposide, Cisplatin; BVP, Bleomycin, Vinblastine, Cisplatin; CP, Cyclophosphamide, Cisplatin; P, Cisplatin; BEPO, Bleomycin, Etoposide, Cisplatin, Oncovin; IP, intraperitoneal; RT, Radiation therapy; D, Dead; NED, No evidence of disease. Lost-FU, lost in follow-up.

D. Adjuvant therapy

A detailed description of adjuvant treatment is presented in Table 3. Twenty-one of 23 patients were treated with adjuvant chemotherapy. Seventeen patients (81%) received the bleomycin/etoposide/cisplatin (BEP) regimen (2-6 cycles, median 4 cycles), one etoposide/cisplatin (EP), two bleomycin/vinblastine/cisplatin (BVP) and one the cyclophosphamide/cisplatin (CP) chemotherapy regimen. Only two patients did not receive adjuvant chemotherapy; one patient aged 27 with dysgerminoma Stage Ia of unknown grade, and one patient aged 26 with immature teratoma Stage IV of unknown grade.

Two patients received adjuvant radiotherapy; one patient aged 67 with Stage IIc immature teratoma received radiotherapy to the pelvis (after 2 cycles of BEP chemotherapy), as well as one patient aged 15 with Stage IV dysgerminoma, who received radiotherapy to the unilateral supraclavicular region after complete response to chemotherapy.

E. Survival and outcome

The current status of the patients is presented in Table 3. At the median follow-up of 68 (11-140) months DFS was 74% (Figure 1) and OS 87% (Figure 2). Two patients were lost in follow-up. Six patients relapsed at a median of 16 (3-63) months after surgery; two did not receive adjuvant chemotherapy. At relapse four patients were treated with surgery followed by cisplatin-based chemotherapy, one was treated with chemotherapy only, and another received palliative radiotherapy only. Two patients are still in complete remission; one patient is still alive with residual disease and three died of disease.

One patient aged 27 with Stage Ia dysgerminoma of unknown grade, who was treated initially with surgery (unilateral salpingo-oophorectomy) only, relapsed after 63 months in the retroperitoneal lymph nodes. At relapse she was treated with four cycles of BEP chemotherapy followed by surgery (lymphadenectomy, omentectomy and biopsy of residual ovary). Surgery revealed only necrosis after chemotherapy in suspicious lymph nodes

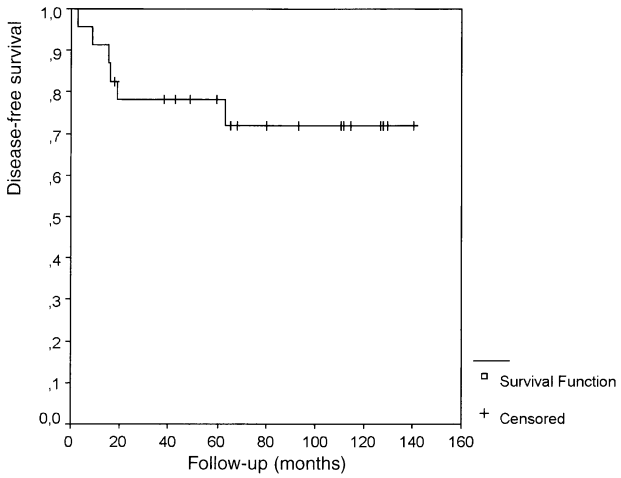

Figure 1. — Disease-free survival (DFS) of patients with malignant ovarian germ cell tumours (MOGCT).

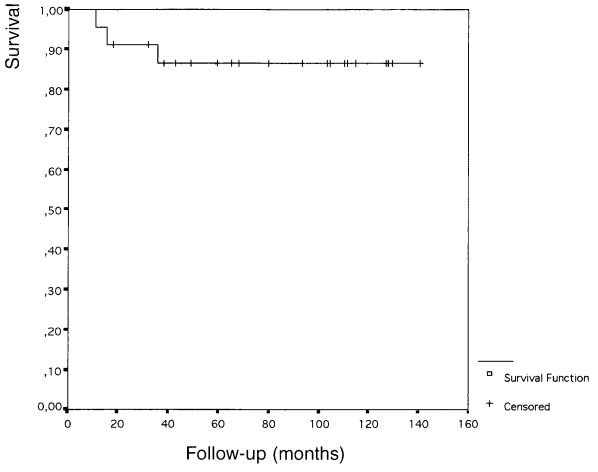

Figure 2. — Overall survival (OS) of patients with malignant ovarian germ cell tumours (MOGCT).

complete remission has been achieved which has now lasted for 26 months. One patient aged 26 with Stage IV immature teratoma, of unknown grade, was treated with initial unilateral salpingo-oophorectomy only. Three months after initial surgery relapse in the abdomen was diagnosed. At relapse she underwent surgery (total hysterectomy with bilateral oophorectomy, omentectomy, resection of abdominal muscle wall) followed by six cycles of the bleomycin/etoposide/cisplatin/oncovin (BEPO) chemotherapy regimen. At present, 87 months after achieving a complete response, she has no evidence of disease.

F. Fertility

Fertility preserving operations (unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus) were performed in 86.7% of patients in childbearing age. Ten of 13 (76.9%) patients with fertility-preserving surgery regained ovarian function (menstrual cycles) and one (7.7%) gave birth to a normal child.

Discussion

Like the data from the literature our results show that the majority of patients with malignant ovarian germ cell tumours can be cured with surgery followed by cisplatin-based chemotherapy. Since the majority of patients are in childbearing age, the surgery should consist of unilateral salpingo-oophorectomy to preserve fertility without compromising survival.

When comparing our results to results from the literature we have to consider the differences between the age of patients, histologic types and stage of the disease – these factors can contribute to different treatment options and therefore differences in survival and fertility. The median age of our patients was lower [10], similar [11,12] and higher [13-15] when compared to data from the literature. In our review immature teratoma, dysgerminoma, mixed germ cell tumours and endodermal sinus tumours accounted for 43%, 22%, 22% and 13%, respectively. On the contrary, dysgerminoma was the most common histological presentation in two reports [13,14], whereas in one report dysgerminoma and teratoma appeared at the same frequency [10]. Some authors evaluated only patients with pure dysgerminoma [12] or only non-dysgerminatous ovarian germ cell tumours [15].

Regarding FIGO stage, in our review only 11 of 23 (48%) tumours were in Stage I (Stage Ia only in 2 patients) whereas other authors have reported Stage I disease at presentation in much higher percentages: 78% [10], 82% [11], 60% [13] and 76 % [14].

Bilateral salpingo-oophorectomy was performed in one patient aged 15 years due to Klinefelter Syndrome (47, XXY). This is in concordance with recommendations [9], where in cases of dysgerminoma frozen section of the contralateral gonad is recomended and if dysgenetic, bilateral salpingo-oophorectomy is indicated. In another patient aged 25 with Stage IIc mixed cell germ cell tumour, bilateral salphingo-oophorectomy was probably unnecessary.

Ninety-one percent of patients were treated with adjuvant chemotherapy, 85% received cisplatin-based chemotherapy; 85% the BEP regimen (2-6 cycles, median 4 cycles), one EP only, two BVP and one CP. Only two patients did not receive adjuvant chemotherapy: one patient aged 27 with Stage Ia dysgerminoma and one patient aged 26 with Stage IV immature teratoma.

We think that disease-free survival and overall survival of 74% and 87% at the median follow-up of 68 (11-130) months is comparable to the results from the literature where the overall survival ranged from 80% to almost 100% [10-15]. In our study we had a higher number of patients with advanced stage of disease at presentation when compared to other studies.

Fertility preserving operations were performed in 87% of patients in childbearing age. With adjuvant chemother-

apy survival in the fertility-preserving group was comparable to the radical surgery group. Ten of 13 (77%) patients with fertility-preserving surgery regained ovarian function (menstrual cycles) and one (8%) gave birth to a normal child. Preserving ovarian function in such young women is important for their social, mental and medical well being.

Although the number of patients included in our study was small, our results were similar to data published in the literature, which have demonstrated that unilateral salpingo-oophorectomy followed by cisplatin-based chemotherapy is the preferred treatment when fertility is to be preserved without compromising the outcome (survival). The surgeon has to keep in mind that these patients are generally young and that bilateral salpingo-oophorectomy with hysterectomy is not needed for classical staging and treatment of malignant ovarian germ cell tumours as is the case in epithelial ovarian cancer.

Conclusion

Patients treated for malignant ovarian germ cell tumours at the Institute of Oncology Ljubljana from 1990-2000 had a high cure rate, similar to results from the literature. Unilateral salpingo-oophorectomy followed by cisplatin-based chemotherapy is the recommended treatment of choice since it preserves potential for fertility without compromising the survival of these patients. It should be performed in all patients who wish to preserve ovarian function and even fertility regardless of the stage of disease.

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