

Malignant germ cell tumors of the ovary: Diagnostic and therapeutic procedures

Lidija Tasic
Mladenko Vasiljevic
Zivko Perisic
Svetlana Jankovic

ABSTRACT

Objective: To determine the frequency of the malignant germ cell tumors within the group of all ovarian germ cell tumors and analyze the diagnostic and therapeutic procedures utilized in the treatment of the tumors.

Design: Prospective study

Setting: University Clinic of Gynaecology and Obstetrics

Patient: Ninety-six female inpatients in generative period who underwent surgery for germ cell tumors of the ovary.

Methods: The research was conducted in two phases, first using the general and anamnesis information, and second using the classical and special diagnostic methods. The suspicion of malignancy arose from the ultrasound finding. Therefore further diagnostic procedures undertaken included the Color Doppler ultrasound examination for measurement of additional parameters.

Results: We recruited 96 patients with germ cell tumors of the ovary. Eight of them had malignant germ cell tumor. The average size of the tumor was 12.9cm. Diffuse vascularization in capsule and in tumor was registered in all patients with malignant germ cell tumor. The average number of registered blood vessels was 3.5. Pourcelot's index of resistance was average 0.36; max. velocity flow was 12.47 cm/sec in tumor tissue. In all patients with malignant germ cell tumor, disease was diagnosed in stage Ia. In all cases of young patients who desire to preserve fertility and who had well-encapsulated unilateral tumors, conservative surgery consisting of unilateral salpingo-oophorectomy was performed. After surgical treatment, in all patients combined chemotherapy was administered.

Conclusions: All malignant germ cell tumors in our group were discovered in stage I by FIGO classification. Transvaginal color Doppler ultrasound gave significant information about tumor size and morphology and the characteristics of its vascularization. Adequate operative procedure was of prime importance for the determination of the stage of disease.

Key words: germ cell tumor, malignancy, ovary color, ultrasonography.

Clinic of Gynaecology and Obstetrics "Narodni Front"
Belgrade,
Yugoslavia

Correspondence:
Prof. Dr Mladenko Vasiljevic
Slobodana Penezica Krcuna No 33/III Street
Yugoslavia
E-mail: dmdnmvas@EUnet.yu

INTRODUCTION

In contrast with more common epithelial ovarian cancers that arise from the surface coelomic epithelium, ovarian germ cell malignancies are believed to originate from primordial germ cells that migrate into the gonadal ridge at 6 weeks of embryonic life¹. Consequently, ovarian germ cell tumors might exhibit a spectrum of histologic differentiation that

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mimics a primitive developing embryo. For example, dysgerminoma appears to be descended from relatively undifferentiated cells, whereas yolk sac tumors show malignant change in a cell line committed to extraembryonic differentiation¹. Immature teratomas are derived from cell predisposed to somatic (embryonic) differentiation and recapitulate tissue from all three primitive germ cell layers, ectoderm, endoderm, and mesoderm. When considered together, the dysgerminoma, yolk sac tumor, immature teratoma, and their hybrid-the mixed germ cell tumor-comprised more than 90% of malignant germ cell tumors². Nongestational choriocarcinoma, embryonal carcinoma, and polyembryoma manifest rarely as pure entities and comprise the remaining 5–10%.

Germ cell tumors constitute 20% of all ovarian tumors. In 95% of all cases they are benign, and in 5% are malignant³. 60% of all ovarian neoplasms discovered in women younger than 20 years belong to the germ cell tumors. In children younger than 10 years, 84% of germ cell tumors are malignant⁴. This type of malignant ovarian tumors mostly has good prognosis consisting disease-free survival of the patients. Germ cell tumors are diagnosed in FIGO Stage I in 60 to 70% of cases, and in the Stage III in 25 to 30%. Stages II and IV are rarely found. The surgical method depends on the operational finding. In young women who want to save their reproductive function, and who have a well-encapsulated unilateral tumor, the unilateral salpingo-oophorectomy and the biopsy of the contra lateral ovary are done⁵. Advanced-stage cases undergo radical surgical procedure. Malignant germ cell tumors are treated with combination chemotherapy after surgery⁶.

The aim of our investigation was:

- To determine the frequency of the malignant germ cell tumors within the group of all ovarian germ cell tumors and
- To analyze the diagnostic and therapeutic procedures in the treatment of the malignant germ cell tumors

METHODS

The research was performed on 96 female inpatients in the reproductive period, who were treated for germ cell tumors of the ovary at the Clinic of Gynaecology and Obstetrics "Narodni Front" in Belgrade. The research was conducted in two phases, first using the general and anamnesis information, and second using the classical and special diagnostic methods. The protocol and the end of the treatment were specially analyzed. Among general and anamnesis information (recording of clinical data from patients), the age of women at the moment of hospitalization, the age of

menarche and the presence of subjective, as well as the time of the occurrence of the first symptom were analyzed.

Among special diagnostic methods used were: ultrasound, operative finding and histopathology as a definite diagnostic method.

The surgery technique and the adjuvant treatment methods were analyzed as part of therapeutic procedure.

The statistical analyzes included: Student's t-test to determine the differences between the probabilities, Kolmogorov-Smirnov test to determine the differences between the distributions of the probabilities, and Chi-square test to determine the correlation between single distributions of the probabilities.

RESULTS

Out of 96 female patients with germ cell tumors of the ovary who took part in the investigation, in 8 cases (8.33%) the malignant germ cell tumor was diagnosed. The youngest female patient with malignant tumor was 17, the oldest 29 years old. Most of these patients had menarche before the age of 12 years. Malignant germ cell tumors had usually larger dimensions than benign tumors of the same group. The average size of the malignant tumor was 12.8 cm, and of benign tumor 7.1 cm (52%). It is of special interest to determine which size of the tumor from this group is connected to pain as the main symptom. The data on the Table 1 show that whenever the tumor was larger than 8 cm, pain was present in 90% of cases.

The results of the anamnesis data analysis are shown in Table 2.

The suspicion of malignancy arose from the ultrasound finding and solid or solid-cystic morphology of the tumor, overall in 8 patients. Therefore further diagnostic procedure undertaken was Color Doppler ultrasound examination for measurement of additional parameters. The obtained values confirmed our previous suspicion of the malignant nature of the tumor. The diagnosis of malignancy was confirmed on histopathology after surgery in all cases.

Color Doppler criteria for the diagnosis of the malignancy were based on the following parameter:

- The presence of the "bizarre" vascular net located in situ
- Low values of the resistance index ($Ri < 0.4$) in the analyzed tissue

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- Extremely low values of the blood flow speed in the observed blood vessels of the tumor.

All values obtained investigating both malignant and benign germ cell tumors on Color Doppler ultrasound examination were compared.

The characteristics of malignant germ cell tumors obtained on Color Doppler ultrasound are shown in Table 3.

The type of vascularization in the malignant and benign germ cell tumors is shown on Table 4.

In 13 of 88 analyzed cases (14.77%) with benign tumors was found peripheral vascularization in the capsule, while diffuse vascularization in the capsule and in the tumor was present in all 8 cases with malignant tumors (100%).

The average number of the detected blood vessels in tumor is shown in Table 5.

There is statistically significant difference in the number of blood vessels between benign and malignant tumors of this group ($p < 0.001$).

Vascular resistance index (Pourcelot's index) in benign and malignant germ cell tumors is shown in Table 6.

There is statistically significant difference in the Pourcelot's index between benign and malignant tumors.

The treatment modality and the surgical techniques

The basic approach to the patients suspected from ovarian germ cell tumor is surgical and it includes both the diagnosis and the initial therapy. The adequate determination of the invasion of the disease was done by inspection and palpation. The type of the primary operative procedure depended on the operative finding. Finding and tumor staging determination during surgery was very important information, used to determine the invasion of the tumor that is very important for the prognosis and the selection of the postoperative treatment of the patients.

Table 7 shows the surgery technique in the investigated group of patients

Table 8 shows the results of the postoperative finding in malignant germ cell tumors.

The final diagnosis was based on the histopathological finding: in 8 cases with malignant germ cell tumor 7 patients has dysgerminoma, and 1 patient had mixed germ cell tumor containing 75% of the embryonal carcinoma and 25% of dysgerminoma.

TABLE 1

The distribution of the probabilities of sizes of tumor that cause pain

Diameter of tumor in cm	Total	Less than 5		6–8		9–11		11–14		Larger than 15	
	N	N	%	N	%	N	%	N	%	N	%
Symptoms	52	10	50	16	30.8	20	90.9	4	100	2	100
TOTAL	100	20		52		22		4		2	

TABLE 2

Characteristics of patients presenting with malignant germ cell tumors

	Min	Max	Average	Description
Age (years)	17	29	22.6	75% – younger than 25 (6 of 8)
Menarche (age)	11	14	12.5	75% – before 12 years (6 of 8)
Tumor size (cm)	10	17	12.8	75% – size 12 cm and larger (6 of 8)
Symptoms	8 cases (100%) dominant abdominal pain			
First symptom	7 cases (87%) the time of occurrence – up to one month			

TABLE 3

Color Doppler analysis of the malignant germ cell tumors

Diffuse vascularization	8 (100%)
Average number of the detected blood vessels	3.5
Average value of Resistance index	Ri = 0.36 (up to 25 years of age around 0.44)
Average maximal flow speed in the tumor tissue (V_{max})	12.47 cm/sec

TABLE 4

Type of vascularization

Diffuse vascularization (malignant tumors)	N = 8	100%
Peripheral vascularization (benign tumors)	N = 13	22%

TABLE 5

The number of the detected blood vessels in benign and malignant germ cell tumors.

Average number of blood vessels	BENIGN tumors	MALIGNANT tumors*
Average	1.13	3.5
SD	±0.35	±1.37

* Statistically significant difference in number of blood vessels between benign and malignant groups ($P < 0.001$)

TABLE 6

Pourcelot's index of the vascular resistance (Ri)

	BENIGN tumors	MALIGNANT tumors*
Ri	0.62	0.36
SD	±0.15	±0.06

* Statistically significant difference in Pourcelot's index between benign and malignant tumors ($P < 0.01$)

TABLE 7

Surgery technique performed in patients with malignant germ cell tumor

VERTICAL CUT	In all cases
ADNEXECTOMY (SALPINGO-OOFORECTOMY)	In all cases
OMENTUM RESECTION	In all cases
BIOPSY OF THE OTHER OVARY	In all cases
BIOPSY OR EXTIRPATION OF THE LYMPH NODES	In all cases
PELVIC LAVAGE	In all cases

TABLE 8

Results of the postoperative finding in malignant tumors.

Tumor morphology	Solid (7), solid-cystic (1)
Tumor capsule	Smooth, intact in 100%
Unilateral presence	100%
Infiltration into surrounding organs	0%
Infiltration into distant organs	0%
Presence of the free liquid	0%
FIGO Staging	Stage I in 100% of cases

DISCUSSION

Germ cell tumors of the ovary constitute one fifth of all ovarian tumors, and are characterized by the variety of histological types. A smaller group of these tumors, about 5%, consists of malignant tumors³. In our investigation group malignant tumors accounted for 8.4% of cases that minimally differentiates from the other reported data⁷. Dysgerminoma is the most common malignant germ cell tumor of the ovary, accounting for approximately 2% of all ovarian malignancies. Mean age of patients with dysgerminoma in our group was 22 years. Ovarian germ cell tumors occur in young women in whom fertility preservation is of great concern⁵. Rapid growth and early occurrence of first symptoms are characteristic for malignant germ cell tumors. About 85% of women had abdominal pain associated with palpable adnexal mass. Pain was present in all patients of the investigated group, and the mean period from the occurrence of first symptoms until histological verification was about one month.

Malignant tumors of this group are defined on the ultrasound as solid or solid-cystic masses. The size of tumors was 12.8 cm. All tumors were unilateral, had smooth capsule and on the contra lateral ovary no pathological finding was observed. Echography was the most used diagnostic method⁸.

On color Doppler ultrasound examination in all cases of malignant tumors a diffuse vascularization was registered in tumor capsule and tumor itself. On the contrary, in benign tumors of the same group only the peripheral vascularization in the capsule was observed. The average number of the detected blood vessels in malignant tumors was 3.5, and in benign tumors 1.37. Vascular resistance index was significantly lower in malignant tumors and was 0.36 ± 0.06 , while in benign tumors 0.62 ± 0.15 .

Various reports describe the use of Doppler to detect the characteristically high flow in blood vessels of a malignant tumor⁹.

This type of malignant tumors of the ovary has generally good prognosis considering life survival of the patients. Germ cell tumors are most often diagnosed in the Ia Stage (FIGO) (in 60–70%). The next most frequent diagnosed was Stage III, while Stage II and IV are relatively rare¹⁰.

The type of surgery method depended on the operative finding⁵. In cases of young women who wanted to preserve their reproductive functions, and have a well-encapsulated unilateral tumor, the most conservative operating method was performed – unilateral salpingo-oophorectomy with obligatory biopsy of the second

ovary¹¹. In advanced stage of the disease a radical operation procedure was absolutely necessary. All our patients with malignant tumor were treated surgically. The surgery procedure was more conservative than usually in cases of other ovarian malignant tumors. In all patients a unilateral adnexectomy and biopsy of the other ovary were performed, including omentum resection and pelvic lavage. In one patient retroperitoneal and paraaortal lymph nodes were removed.

Based on the recommendation of the GOG (Gynecologic Oncology Group), malignant germ cell tumors are postoperatively treated with combination chemotherapy, in three to four cycles with the interval of 21 days (Tewari et al., 2000; David et al., 2002.). This treatment can lead to complete remission even in patients in advanced stage of the disease.

Fertility-preserving treatment for malignant germ cell tumors of the ovary, even in advanced stages, allowed these young women to conceive and have children.

Brewer et al¹² reported a series of 16 patients with dysgerminoma who underwent conservative treatment. Three of the 16 who attempted to conceive were successful. All of them had been treated with bleomycin, etoposide, and cisplatin. About the untoward side effect of chemotherapeutic agents, alkylating agents such as cyclophosphamide have been associated with gonadal failure in women¹³. It is important to note that premature menopause has also been associated with chemotherapy in young women, especially with alkylating agents. Byrne et al¹⁴ showed that treatment with alkylating agents carried a relative risk of premature menopause of 9.3. Results in the literature, however, have not been consistent. In one of the largest series recently reported, Chiarelli et al¹⁵ studied the risk of early menopause and infertility after treatment for childhood cancer in Ontario. In series of 719 patients they found no increased risk for either early menopause or infertility in women treated with combinations of several alkylating chemotherapeutic agents including cyclophosphamide. Unfortunately, in this study they also included patients who received carboplatin and cisplatin, described as “alkylating agents.” These two agents are not alkylating agents, and they are not known to affect gonadal function¹⁶. The grouping of drugs from different categories might have masked the potential adverse effect of alkylating agents like cyclophosphamide.

Interestingly, in the study by Chiarelli as well as in others, it was found that women treated before puberty have a reduced risk of developing gonadal damage relative to those treated after menarche^{15,17}. In one report from The M.D. Anderson Cancer Centre, patients who developed menstrual dysfunction after

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completion of chemotherapy were significantly older at diagnosis than those who had normal menses (mean ages 17.7 and 13.6, respectively)¹⁸. Premenarcheal ovaries may be more resistant to the toxicity from the chemotherapy than postmenarcheal ovaries because of the relatively larger amount of oocytes in reserve¹⁶. This information is extremely important to parents of young girls diagnosed with malignant germ cell tumors of the ovary who are concerned about their daughters' future reproductive function.

CONCLUSION

Based on our investigation the following was concluded:

- All patients belong to a group of young women in reproductive period.
- In all patients pain was the first and basic symptom; when the tumor was larger than 8 cm pain was present in 90% of cases.
- On classical bimanual gynecologic examination a presence of adnexal mass was observed, but a transvaginal ultrasound gave significant information about tumor size and morphology and the characteristics of its vascularization.
- Adequate operative procedure was of prime importance for the dertermination of the clinical stage of disease.
- All malignant germ cell tumors in our investigated group were discovered in Stage I by FIGO.
- Considering the fact that in all cases we had young women who still did not fulfil their reproductive function, and in fact that the disease was discovered in Stage I, the most conservative operation procedure was conducted, and that was unilateral adnexectomy.
- Obligatory final therapy was combined chemotherapy.

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