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Clinical Characteristics Of Patients With Clear Cell Ovarian Cancer And Mixed Malignant Epithelial Ovarian Tumors

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ABSTRACT

For the first time on a large clinical material, the results of the study of clinical and morphological features and prognostic factors of clear cell ovarian cancer and mixed malignant neoplasms of the ovaries with a mandatory clear cell component are presented.

Based on a comparative analysis of pure and mixed forms of clear cell neoplasms of the ovaries, their morphological signs and features of the clinical course of the disease were established.

The factors of prognosis of malignant clear-cell neoplasms of the ovaries were revealed: the stage of the disease, the volume of surgery, the degree of tumor differentiation and the degree of cellular anaplasia.

KEYWORDS

Clear cell ovarian cancer, clinical and morphological features, ovarian neoplasms

INTRODUCTION

According to various authors, the prevalence of clear cell adenocarcinoma is 2-6% of all

ovarian neoplasms and 5-6% of all malignant epithelial ovarian tumors [2,4,5].

Benign clear cell neoplasms of the ovaries are represented by adenofibromas and are extremely rare [7]. Border forms of clear cell neoplasms account for 1% of all borderline ovarian tumors.

Clear cell ovarian carcinoma is more common in women with an average age of 50-70 years [3,6] and is practically not observed under the age of 24.

Parker J. et al. observed a case of clear cell ovarian adenocarcinoma in a 19-year-old woman. It should be noted that this is the youngest patient in the literature to be diagnosed with clear cell carcinoma [1].

Most researchers find no relationship between the risk of clear cell adenocarcinoma and changes in the hormonal status of patients. However, the work done by Shevchuk M.M. et al. showed that 44% of patients with clear cell ovarian cancer had hormonal disorders, which indicates a hormonal activity or hormonal dependence of these tumors.

Other authors believe that estrogens and other steroid hormones are actively involved in the stimulation of proliferative processes in malignant neoplasms of the ovaries. One of the enzymes that play an important role in the synthesis of estrogens and androgens is steroid sulfatase. High expression of this enzyme, was found in clear cell neoplasms of the ovaries (71.1%), which suggests the hormonal nature of the origin of this tumor [8].

MATERIALS AND METHODS

The work is based on a retrospective analysis of the course of the disease and the results of treatment of 96 patients with clear-cell malignant ovarian tumors, who were examined and treated at the oncogynecological

department of the Andijan branch of the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology from 2000 to 2020.

In order to identify the features of the clinical and morphological course of clear-cell ovarian neoplasms and the development of prognostic factors to determine the further tactics of treatment of patients in the pathomorphology department of the Andijan branch of the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology of human tumors, histological micropreparations of 96 patients were revised according to the WHO international histological classification of clear-cell ovarian tumors: (Lyon, 2003).

We analyzed the clinical signs of the disease based on data from case histories. For the statistical analysis of the research results, we have compiled a codifier, of which 44 consisted of several parts. The first part contains the patient's passport data: life history, family history, previous and concomitant diseases.

Further, the codifier reflects obstetric and gynecological history. Patients suffering from clear cell ovarian cancer were followed up from the moment of diagnosis until the last examination, until the moment of death, or the last hospitalization at the Russian Oncology Center.

The last part of the codifier includes a number of questions reflecting the treatment, the clinical course of the disease.

At the initial stage of treatment of the primary tumor, all patients underwent surgical interventions of various sizes, depending on the prevalence of the blastomatous process, the patient's age, and concomitant somatic pathology. At the second stage of treatment,

in most cases, chemotherapy was carried out (various regimens with/without the inclusion of platinum drugs), much less often radiation therapy was used to the pelvic and/or abdominal cavity.

The volume of surgical intervention was assessed as optimal, suboptimal (residual tumor less than 2 cm) and non-radical or cytoreductive (residual tumor more than 2 cm), depending on the volume of tumor removal, as well as in relation to the adequate volume of surgical interventions for ovarian malignant neoplasms.

RESULTS AND DISCUSSION

We analyzed the clinical and morphological characteristics and course of the disease in 96 patients with clear cell ovarian cancer aged 21 to 75 years.

After revision of histological preparations according to the above diagnostic criteria, all patients were divided into two groups.

The first group (preparations revised according to the WHO classification in 1999, Geneva) consisted of 71 patients with a pure form of clear cell ovarian adenocarcinoma. The second group included 25 patients with mixed malignant ovarian tumors with the obligatory presence of a clear cell component in them.

Table 1

Distribution of patients depending on histological type tumors

Histological type of tumor	Group I	Group II
Clear cell ovarian cancer (CCOC) (pure form)	71	—
Mixed forms of malignant clear cell neoplasms of the ovaries (MFMCCNO)	—	25

The average age of patients in the first group was 52.2 ± 1.2 years, in the second group — 54.4 ± 1.8 years.

The analysis of patients with clear cell ovarian cancer and mixed forms of ovarian malignant tumors, taking into account age, revealed that most often these diseases occur at the age of 51 to 60 years (the data obtained in group I are reliable: $p < 0.005$) (Table 2). Equally, it is

often found in the age groups 41-50 years old and over 60 years old with a pure form of SRF (25.4 and 25.4%, respectively), and with mixed forms, 1/3 of patients (32%) were over the age of 60 years. The youngest patient in our study was 21 years old, and the oldest was 75 years old.

Table 2

Distribution of patients depending on histological type tumors and age

Histological type of tumor	Patient age (years)							
	21-40		41-50		51-60		Over 60	
	Abs.	%	Abs.	%	Abs..	%	Abs.	%
Group I CCOC	10	14,1%	18	25,4%	25	35,1%	18	25,4%
Group II MFMCCNO	4	16%	2	8%	11	44%	8	32%

The detection rate of synchronous and metachronous cancer is low and amounted to 4% and 1.4%.

Table 3

Distribution of patients depending on the presence of malignant tumors in blood relatives

Malignant tumor	Group I CCOC		Group II MFMCCNO	
	Abs.	%	Abs.	%
Yes	13	18,3	8	32
No	58	81,6	17	68
Total	71	100	25	100

As a result of the study, it was found that an oncological hereditary history is more often burdened in patients with mixed malignant ovarian tumors (32%). This indicator among

patients with clear cell ovarian cancer was (18.3%). (table 3).

In blood relatives of patients of group, I, tumors of the gastrointestinal tract were most often encountered (8.4%).

Table 4
Distribution of patients depending on tumor localization in blood relatives

Tumor localization	Group I		Group II	
	Abs.	%	Abs.	%
Hemoblastosis	-	-	1	4
Genital tract	3	4,2	3	12
Gastrointestinal tract	6	8,4	-	-
Mammary gland	2	2,8	3	12
Other localizations	2	2,8	1	4
No	58	81,6	17	68
Total	71	100	25	100

However, in the blood relatives of the II group, in the same number of observations, both genital tract cancer (4.2%) and breast cancer (4.2%) were diagnosed (Table 4).

Obstetric and gynecological history

When analyzing the distribution of patients depending on the age of the onset of menarche, it turned out that among patients with pure forms of clear cell ovarian cancer, patients in whom the age of onset of menarche was 11-14 years (66.2%) prevailed.

Table 5
Distribution of patients depending on the age of onset of menarche

Age menarche (years old) (лет)	Group I		Group II	
	Abs.	%	Abs.	%
11-14 years old	47	66,2	12	48
> 15 years old	24	33,8	13	52
Total	71	100	25	100

However, no fundamental differences were found in the age of menarche onset among patients with mixed malignant neoplasms of the ovaries (Table 5).

When assessing sexual function, it should be noted that only 3 (4.2%) patients in the group of clear cell ovarian cancer and 2 (8%) in the group of mixed tumors were Virgo.

At the time of diagnosis, the majority of patients in both groups were in menopause - 44 (61.9%) patients in group I and 16 (64%) in group II.

Menstrual dysfunction occurred significantly more often in patients with mixed forms of ovarian cancer than among patients with clear cell cancer (20% and 2.8%, respectively) (Table 6).

Table 6

Distribution of patients depending on the state of the menstrual function

The nature of menstruation	Group I		Group II	
	Abs.	%	Abs.	%
Amenorrhea	0	0	1	4
Dysmenorrhea	2	2,8	4	16
Menopause	44	61,9	16	64
Normal	25	35,2	4	16
Total	71	100	25	100

When assessing the generative function of patients with clear cell and mixed ovarian tumors, it turned out that in patients of both groups I and II, 2-4 pregnancies were most often observed.

Thus, the number of patients with a history of 2-4 pregnancies was 30 (42.3%) in group I and 13 (52%) in group II (Table 7).

Table 7

Distribution of patients depending on the number of pregnancies

Pregnancy number	Group I		Group II	
	Abs.	%	Abs.	%
0	19	26,7	5	20
<2	15	21,3	5	20
2-4	30	42,3	13	52
>4	7	9,9	2	8
Total:	71	100	25	100

Primary and secondary infertility occurred with the same frequency both among patients with clear cell ovarian cancer and in the group of mixed tumors. Primary infertility was observed in 19 (26.8%) patients in group I and

in 5 (20%) in group II. Secondary infertility was detected in 18 (25.4%) patients with pure forms of clear cell ovarian adenocarcinoma and in 5 (20%) patients with mixed forms of ovarian cancer.

Hormonal drugs for various gynecological diseases were taken by 6 (8.5%) patients in group I and 4 (16%) in group II.

It is assumed that endometriosis plays an important role in the pathogenesis of malignant clear cell neoplasms of the ovaries. This hypothesis is based on the frequent (up to 54% of cases) finding of concomitant

endometriosis in patients with clear cell ovarian adenocarcinoma [3].

In our study, endometriosis in patients with pure forms of clear cell ovarian cancer was detected as often as in mixed tumors (30.9% and 36%, respectively), which exceeds the frequency of this pathology in other histological types of ovarian malignant neoplasms (Table 8).

Table 8

Distribution of patients depending on the history of concomitant endometriosis

The presence of endometriosis	Group I		Group II	
	Abs.	%	Abs.	%
Yes	22	30,9	9	36
No	49	69,1	16	64
Total	71	100	25	100

For concomitant endometriosis, all patients received conservative treatment (biphasic oral contraceptives).

Inflammation of the parovarium occurred with the same frequency both in the 1st and in the IIth group - 52.1% and 48%, respectively (Table 9).

Table 9

Distribution of patients depending on the presence in anamnesis inflammation of the parovarium

Inflammation of the parovarium	Group I		Group II	
	Abs.	%	Abs.	%
Yes	37	52,1	12	48
No	34	47,9	13	52
Total	71	100	25	100

However, ovarian dysfunction was more often associated with mixed ovarian tumors with a clear cell component.

So, this disease was diagnosed in 20 (28.2%) patients in group I and 12 (48%) in group II (Table 10).

An interesting fact is that with mixed malignant ovarian tumors in 9 (36%) patients, pathological processes in the uterus were revealed, while in clear cell ovarian cancer this figure was 12 (16.9%) patients (Table 11).

Table 10
Distribution of patients depending on the presence in the anamnesis ovarian dysfunction

Dysfunction of parovarium	Group I		Group II	
	Abs.	%	Abs.	%
Yes	20	28,2	12	48
No	51	71,8	13	52
Total	71	100	25	100

Table 11 **Distribution of patients depending on comorbidities in a history of internal genitalia**

Endometrial condition	Group I ccoc		Group II MFMCCNO	
	Abs.	%	Abs.	%
Hyperplasia	4	33,3	5	55,5
Polyposis	8	66,6	4	44,4

A similar trend was obtained by us when analyzing the frequency of detection of uterine fibroids: 16 (22.5%) patients - in group I and 13 (52%) - in group II.

Adenomyosis was detected in 5 (7.04%) patients in group I and in 3 (12%) patients in group II.

The high incidence of endometrial and uterine pathology in malignant clear-cell neoplasms of

the ovaries testifies in favor of the theory of the hormone-dependent nature of the origin of this type of neoplasm.

Breast diseases were also more common in the group of mixed tumors - in 9 (36%) patients versus 7 (9.9%) patients with pure forms of clear cell ovarian adenocarcinoma.

Diseases of the thyroid gland were 4 times more common in history in patients with mixed

ovarian tumors. So, thyroid diseases glands were observed in 3 (4.2%) patients in group I and in 4 (16%) patients in group II.

Table 12

Distribution of patients depending on the transferred history of gynecological operations

The volume of the transferred operations	I group		II group	
	Abs.	%	Abs.	%
Conservative myomectomy	1	1,41	1	4
US + OUP unilateral removal of uterine parovarium	0		1	4
US with parovarium	1	1,41	-	-
Unilateral removal of uterine parovarium	6	8,45	-	-
Electrocoagulation of the cervix uterus	13	18,3	6	24
Not carried out	50	70,42	17	68
Total	71	100	25	100

Surgical interventions for these gynecological diseases before treatment at the State Institution of the Russian Oncology Center named after N.N. Blokhin Russian Academy of Medical Sciences, 21 (29.6%) patients in group I and 8 (32%) patients in group II were performed (Table 12.)

Most often, patients with cervical erosion underwent electrocoagulation of the cervix - 13 (18.3%) patients in group I and 6 (24%) patients in group II.

CONCLUSION

The average age of patients in the first group was 52.8 + 1.2 years, in the second group - 54.4 + 1.8 years, which does not contradict the data of world literature.

When analyzing the age composition of patients with clear cell ovarian cancer and mixed forms of malignant ovarian tumors, it turned out that most often these diseases

occur at the age of 50-60 years (the data obtained in group I are reliable: $p < 0.005$).

One of the most important prognosis factors is the stage of the disease. According to world literature, clear cell ovarian tumors are

predominantly diagnosed in the early stages of the disease - in 59-66% of cases. However, in our study, most of the malignant clear-cell neoplasms of the ovaries were represented by stages III and IV according to the FIGO classification - in 69.9% of cases in group I and in 68% of cases in group II.

The analysis of the distribution of patients depending on the age of menarche onset showed that among patients with pure forms of clear cell ovarian cancer, patients with age menarche was 11-14 years old (66.2%). However, no fundamental differences were found in the age of menarche onset among patients with mixed malignant neoplasms of the ovaries.

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Thus, malignant clear cell neoplasms ovaries have some features of the clinical course. It the disease most often occurs in older age groups - from 51 up to 60 years old. For clear-cell neoplasms of the ovaries is not typical family hereditary history. Unlike other tumors histotypes, patients with malignant clear cell neoplasms have a history of a greater number of pregnancies - from 2 to 4. However, about 20% of patients suffered from primary or secondary infertility. In almost half of the cases, the disease was preceded by inflammation of the parovarium, pathological processes in the endometrium, uterine

myoma, and in 1/3 of cases, clear cell neoplasms were accompanied by endometriosis.

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