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CORRELATION OF HEAVY METAL CONTENT IN THE BLOOD OF PATIENTS WITH OVARIAN CANCER BY PLACE OF RESIDENCE

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Abstract. **Introduction.** Malignant ovarian tumours are an urgent problem in oncology today. Ovarian cancer (OC) is in the top ten in terms of prevalence, ranking 7th, and in the top five in terms of mortality, ranking 4th. The asymptomatic course of the disease is explained by the progression of ovarian cancer mainly due to peritoneal dissemination; that is the reason why the disease is diagnosed at late stages. The prognosis of the disease depends on its stage, the degree of differentiation of the tumour, the recurrence-free period, the size of the residual tumour after surgical treatment. Taking into account the above factors, this disease is interesting for scientists in terms of finding new factors for predicting its course and trying to influence them.

The aim of the study is to increase the effectiveness of treatment of patients with ovarian cancer by individualizing supportive therapy taking into account the level of heavy metal salts in the blood.

Methods. The study is based on the results of observation of 127 patients with ovarian cancer of stages I-IV. The duration of recurrence-free survival was studied and evaluated depending on the place of residence of patients with ovarian cancer.

Results. The analysis of the recurrence-free survival of patients by the territorial principle was carried out: higher rates of cumulative survival of patients are recorded in virtually all studied intervals in patients living in Ivano-Frankivsk and Kalush districts (where a higher content of Zn in the blood of patients is recorded). Cox regressions in correlation with Zn variables were constructed for them.

The Cox regression was calculated in correlation with the variables of Zn in the blood of patients with OC living in the Ivano-Frankivsk and Kalush districts at minimal values of the metal content in the blood. For the Ivano-Frankivsk district, it is predicted that at the 16th month of observation, the recurrence-free survival rate will be 0%. For Kolomyia district, the projected recurrence-free survival rate is even lower, with no patients remaining at the 9th month of follow-up. The predicted recurrence-free survival in correlation with Zn variables in the blood of patients with OC living in Ivano-Frankivsk and Kalush districts at the maximum values of the metal in the blood was determined. For the Ivano-Frankivsk district, it is predicted that 97% of patients will remain under observation at month 36. For Kolomyia district, the predicted recurrence-free survival rate at the 36th month of observation is 99%.

Conclusions. A correlation was found between the zinc content in the blood of patients with OC and the place of residence in Ivano-Frankivsk region; according to the analysis of the obtained data set, the strongest correlation of recurrence-free survival of patients is observed with this element. Increased levels of zinc and copper in the blood of patients resulted in a longer duration of disease-free survival, so patients from Kalush and Ivano-Frankivsk regions have a more favourable prognosis.

For chromium and copper, the place of residence of patients doesn't play any role.

Key words: ovarian cancer, heavy metals, supportive therapy, prognostic factors, treatment.

Introduction. Malignant ovarian tumours are an urgent problem in oncology today. Ovarian cancer (OC) is in the top ten in terms of prevalence, ranking 7th, and in the top five in terms of mortality, ranking 4th. The International Agency for Research on Cancer (IARC) indicates that in 2018, 295,414 cases of malignant ovarian tumours were diagnosed and 184,799 deaths from this disease were recorded. It is predicted that in 2040, there will be 434,184 cases of ovarian cancer [5].

Among the known causes of ovarian cancer are mutations of the BRCA1 and BRCA2 genes (Norquist BM, Harrell 2016), obesity (Carmen Jochem, Inga Schlecht 2017), age, genetic factors (Norquist BM, Harrell 2016), Lynch syndrome (Wendy Kohlmann 2018), infertility, hormone replacement therapy (Reigstad MM, Storeng R, 2017), and polycystic ovaries. It is important to note the impact of the environment, especially heavy metals, on the occurrence of cancer. Heavy metals are released into

the atmosphere, after which they settle on soil and water, then enter plants and agricultural products, animals and humans. Toxic metals that enter the human body through the lungs and digestive tract after a few minutes appear in the blood plasma, pass into red blood cells, and then into organs and tissues, accumulating in the human body and causing pathological changes in metabolic processes of various nature (Sh.F. Misnyk, A.O. Lytvynenko 2016) [1,3]. Studies have been conducted on the impact of heavy metals on the risk of thyroid cancer (Tsymbaliuk S.N. 2017), breast cancer (Vivian Vu, Nina Navalkar &Yudan Wei 2019, Lindin M.S. 2014), endometrial cancer (Jane A. McElroy &Mark I Hunter, 2018), gastric cancer (Xufeng Fei, Zhaohan Lou, George Christakos 2018), ovarian cancer (Satarug S, Moore MR 2004), and colorectal cancer (Masoudreza Sohrabi, Ali Gholami 2018). In 2017, ovarian cancer caused by asbestos exposure was recognised as the first gynaecological occupational disease (Nowak D.) [2,8].

Chemical elements which can affect the gene expression of human cells that respond to estrogen are described. The effects are related to the physiological function of estrogen, since metalloestrogens can mimic estrogen and directly activate mammary receptors. The list of metalloestrogens includes aluminium, stibium, barium, cadmium, cobalt, copper, lead, mercury, and nickel [4,6]. The connection between the intake of heavy metals into the breast tumour and their accumulation in it has been described; it is reflected in the course of the malignant process. Affecting the morphological features of the tissue of infiltrative ductal breast cancer, heavy metals stimulate the progression of neoplasia, giving them more aggressive qualities, which determine both the sensitivity of tumours to therapy and prognosis of the course of the disease (Lyndin M.S., 2014) [7,10].

Epidemiological studies have shown evidence of an increase in ovarian cancer and mortality among women exposed to cadmium, but the mechanism of carcinogenesis in the ovaries is not known (Adams S.V., Newcomb P.A., 2012). The relationship between cadmium dietary intake and cancer risk was demonstrated in the Women's Health Initiative [6,9].

In the USA, studies have been conducted to find a connection between the emissions of several metals that disrupt the function of the endocrine system and the incidence of breast cancer. This group includes arsenic, lead, mercury, and cadmium. Among these metals, air emissions of lead showed the strongest association with breast cancer incidence. These results showed that exposure to heavy metals may be associated with an increased incidence of breast cancer in the United States [11,12].

The aim of the study is to increase the effectiveness of treatment of patients with ovarian cancer by individualizing supportive therapy taking into account the level of heavy metal salts in the blood.

Materials and methods

Patient characteristics. We analysed the follow-up data of 127 patients with ovarian cancer of stages I-IV. The duration of recurrence-free survival was studied and evaluated depending on the place of residence of patients with ovarian cancer treated at the municipal non-profit enterprise "Precarpathian Clinical Oncological Centre of the Ivano-Frankivsk Regional Council" in 2020-2021.

All patients were diagnosed with OC of stages I-IV, which was confirmed morphologically.

The recurrence-free survival of patients with ovarian cancer, depending on the place of residence and the content of heavy metals in the blood, was studied and evaluated.

The variational and statistical analysis of the study to assess the degree of reliability of the results was performed using a personal computer and Microsoft® Office Excel® 2007 and Statistica v.6 (Statsoft Inc., USA).

Criteria for inclusion in the study:

- patients' age (18 – 80 years);
- morphologically confirmed diagnosis of ovarian cancer;
- satisfactory ECOG status of patients 0 and 1;
- informed consent to participate in the study.

Exclusion criteria:

- HIV positive patients;
- metachronous cancer;
- decompensated other non-cancerous diseases.

Study results and discussion.

At the initial stage, the study patients were distributed according to the territorial principle (Table 1).

Table 1. Number of patients with ovarian cancer depending on place of residence

Place of residence	Number of patients studied
Ivano-Frankivsk	49
Kalush	36
Kolomyia	28
Nadvirna	14

According to the analysed data:

- the largest number of patients residing in Ivano-Frankivsk is 49, which is 38.6%;
- 36 and 28 patients live in Kalush and Kolomyia districts, respectively, which is 28.3% and 22%;
- the smallest number of patients studied (14) are residents of Nadvirna district, which is 11%.

The average content of the studied metals in the blood of patients with OC was calculated for each of the above territorial units.

The average **chromium** content in the blood of patients with OC in correlation with the place of residence was calculated and standard errors were determined (Table 2).

Table 2. Study of Cr content in correlation with the territorial distribution of patients (μg/g)

Place of residence	Average metal content	Standard error
Ivano-Frankivsk	0.06	0.017
Kalush	0.06	0.018
Kolomyia	0.07	0.017
Nadvirna	0.07	0.02

Statistically ($p>0.05$), there is no differences in Cr content in correlation with the place of residence of patients.

The average **lead** content in the blood of patients with OC was calculated taking into account the territorial distribution of patients, and standard errors were calculated (Table 3).

Table 3. Study of Pb content in correlation with the territorial distribution of patients (μg/g)

Place of residence	Average metal content	Standard error
Ivano-Frankivsk	0.043	0.009
Kalush	0.042	0.009
Kolomyia	0.041	0.007
Nadvirna	0.04	0.01

According to the statistical analysis ($p>0.05$), there is no difference in lead content in correlation with the place of residence of patients.

The average **cadmium** content in the blood of patients with OC was calculated taking into account the territorial distribution of patients, and standard errors were calculated (Table 4).

Table 4. Study of Cd content in correlation with the territorial distribution of patients (μg/g)

Place of residence	Average metal content	Standard error
Ivano-Frankivsk	0.04	0.017
Kalush	0.04	0.016
Kolomyia	0.04	0.014
Nadvirna	0.04	0.02

According to the analysis ($p>0.05$), there is no significant difference depending on the place of residence of patients, and the average concentration of cadmium in the blood.

The content of **copper** in the blood of patients with OC was calculated taking into account the place of residence, and standard errors were calculated (Table 5).

Table 5. Study of Cu content in correlation with the territorial distribution of patients (μg/g)

Place of residence	Average metal content	Standard error
Ivano-Frankivsk	2.5	0.01
Kalush	2.16	0.74
Kolomyia	1.96	0.76
Nadvirna	2.08	0.66

According to the analysis ($p>0.05$), there is no significant difference depending on the place of residence of patients and the average concentration of copper in the blood.

The average **zinc** content in the blood of patients with OC was calculated taking into account the territorial distribution of patients, and standard errors were calculated (Table 6).

Table 6. Study of Zn content in correlation with the territorial distribution of patients (μg/g)

Place of residence	Average metal content	Standard error
Ivano-Frankivsk	4.943	1.677
Kalush	5.078	1.492
Kolomyia	4.904	1.573
Nadvirna	4.991	1.202

Statistically significant ($p<0.05$), differences in Zn content were found in correlation with the place of residence of patients.

The highest levels of zinc in the blood of patients with OC were found in Kalush (5.078 ± 1.492) and Ivano-Frankivsk (4.994 ± 1.492) districts.

The districts with the highest content of the studied metals were determined (Table 7, Fig. 1).

Table 7. Districts with the highest content of the studied metals in the blood of patients of group I (μg/g)

District	Metal				
	Cr	Pb	Cd	Cu	Zn
Ivano-Frankivsk	0.06	0.04	0.04	**2.5**	**4.994**
Kalush	0.06	0.04	0.04	2.2	**5.078**
Kolomyia	**0.07**	0.04	0.04	2.0	4.901
Nadvirna	**0.07**	0.04	0.04	2.1	4.882

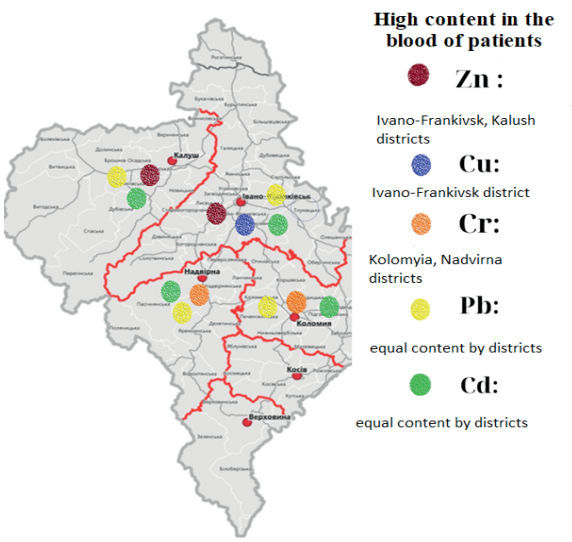

Fig. 1. Districts with the highest levels of heavy metals in the blood of OC patients.

At the next stage of the study, the duration of recurrence-free survival was studied taking into account the place of residence of patients with OC (Fig. 2, Table 8).

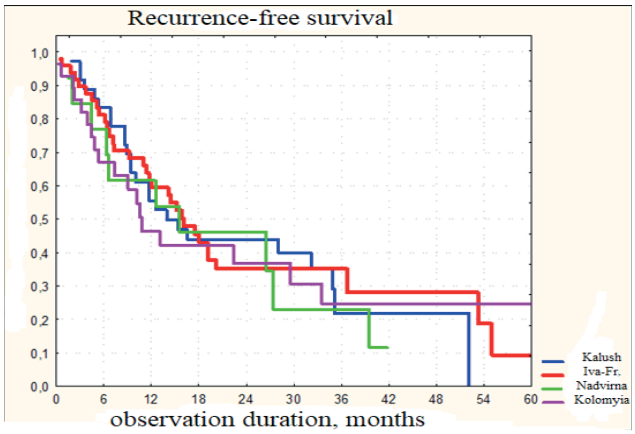

Fig. 2. Recurrence-free survival of patients with OC depending on the place of residence.

Table 8. Recurrence-free survival of patients with OC

Observation duration, (months)	Cumulative survival (%) depending on the place of residence of patients (district)			
	Ivano-Frankivsk	Kalush	Nadvirna	Kolomyia
6	**81.3**	**83.3**	76.9	66.9
12	**59.4**	**55.6**	57.7	46.2
18	**45.4**	**44.0**	43.3	39.8
24	**33.6**	**40.7**	36.4	32,4
30	**29.8**	**35.2**	19.4	24.8
36	**24.8**	**19.6**	10.9	17.3

After the 36 months of observation, it is incorrect to compare the recurrence-free survival of patients due to insufficient number of patients under observation (a total of 10 patients from the four study districts).

According to the data presented here, higher rates of cumulative recurrence-free survival are recorded in all study intervals in patients living in Ivano-Frankivsk and Kalush districts (where a higher blood Zn content was recorded). Cox regressions in correlation with Zn variables were constructed for them.

Cox regression was calculated in correlation with Zn variables in the blood of patients with OC living in Ivano-Frankivsk and Kalush districts with minimal values of the metal in the blood. For Ivano-Frankivsk district, it is predicted that at the 16th month of follow-up, the recurrence-free survival rate will be 0% (Fig. 5.3). For Kolomyia district, the predicted recurrence-free survival rate is even lower: at the 9th month of follow-up, there will be no patients left (Fig. 4).

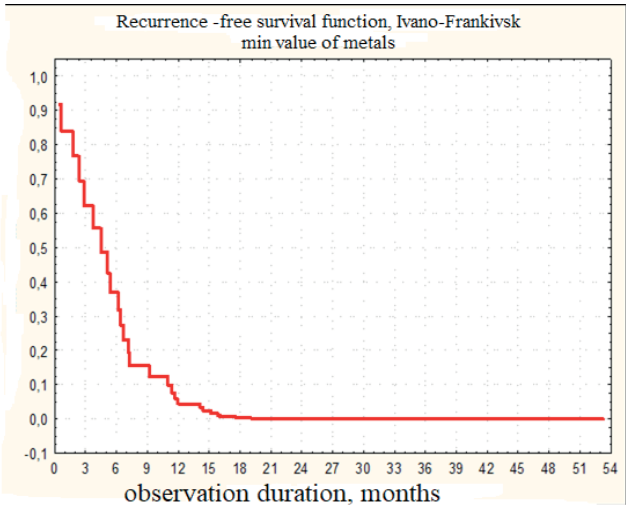

Fig. 3. Recurrence-free survival of patients living in Ivano-Frankivsk district with minimal Zn in the blood.

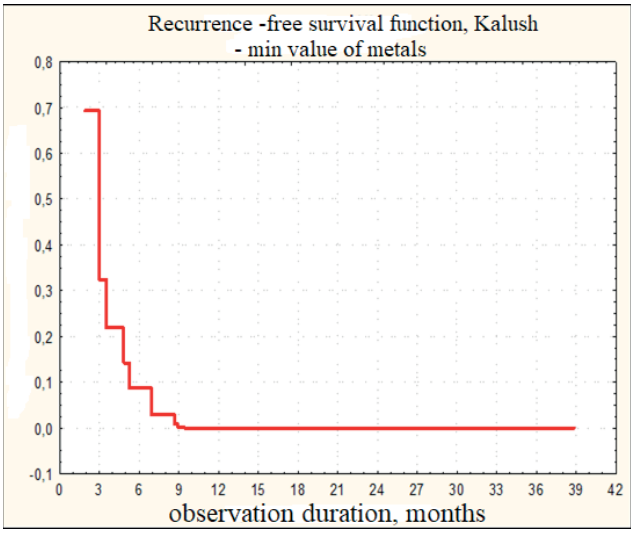

Fig. 4. Recurrence-free survival of patients living in Kalush district with minimal Zn values in the blood.

The predicted recurrence-free survival in correlation with Zn variables in the blood of patients with OC living in Ivano-Frankivsk and Kalush districts at the maximum

values of the metal in the blood was determined. For Ivano-Frankivsk district, it is predicted that 97% of patients will remain in follow-up at month 36 (Fig. 5). For Kolomyia district, the predicted recurrence-free survival rate at month 36 of follow-up is 99% (Fig. 6).

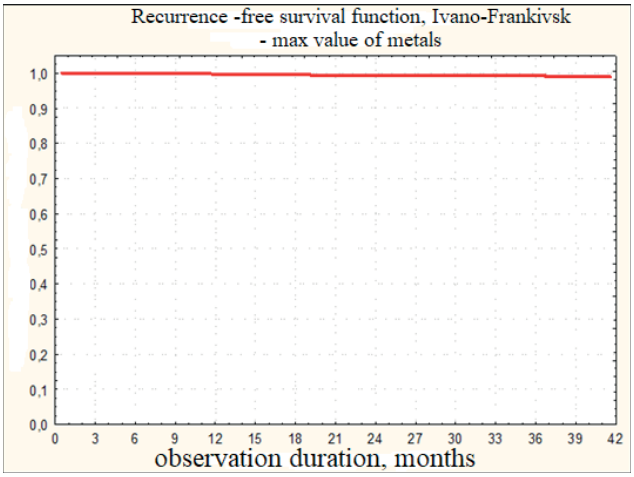

Fig. 5. Recurrence-free survival of patients living in Ivano-Frankivsk district with the maximum value of Zn in the blood.

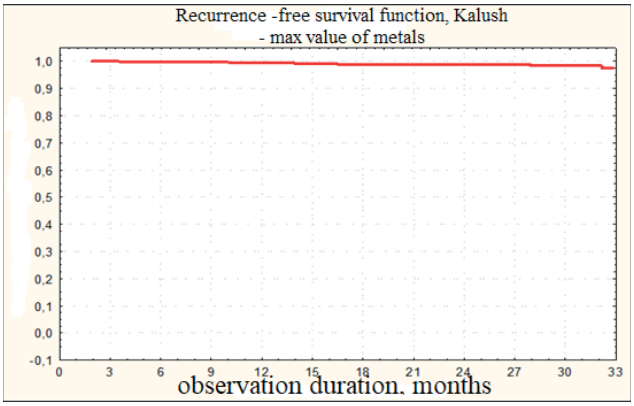

Fig. 6. Recurrence-free survival of patients living in Kalush district with the maximum value of Zn in the blood.

Conclusions. A correlation was found between the zinc content in the blood of patients with ovarian cancer and the place of residence in Ivano-Frankivsk region; according to the analysis of the obtained data, the strongest correlation of recurrence-free survival of patients is observed with this element. Increased levels of zinc and copper in the blood of patients resulted in a longer duration of recurrence-free survival, so patients from Kalush and Ivano-Frankivsk districts have a more favourable prognosis. For chromium and copper contents, the place of residence of patients doesn't play any role.

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