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ORIGINAL ARTICLE

DYNAMIC ASSESSMENT OF PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY IMPACT ON PERITONEAL CARCINOMATOSIS IN OVARIAN CANCER (PRELIMINARY RESULTS)

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ABSTRACT

Purpose of the study. Dynamic assessment of the direct impact of pressurized intraperitoneal aerosol chemotherapy (PIPAC) on peritoneal carcinomatosis in ovarian cancer.

Patients and methods. The study involved 164 people with visually detectable and morphologically verified ovarian cancer with peritoneal carcinomatosis of the peritoneum (IIIb-IIIc stages of ovarian cancer). All patients underwent combined treatment of ovarian cancer, which included primary cytoreduction and 6 courses of chemotherapy according to the TC scheme. In the main group, the standard treatment was supplemented with 3 PIPAC procedures. Statistical processing was carried out by analyzing the exact criterion of the Wilcoxon-Mann-Whitney sums, the distribution of patients in groups by age and peritoneal lesion was estimated. It was found that the distribution of the analyzed parameters was random. The distribution in the groups by stages of the disease was homogeneous, which is justified by the use of the Barnard criterion. The dynamics of the parameters of the study was evaluated by the methods of basic statistics. Used software packages: MedCals, Statistica.

Results. The results obtained demonstrate a distinct positive dynamics in the group of patients receiving PIPAC in addition to standard treatment of newly diagnosed ovarian cancer: a significant decrease in the peritoneal cancer index, therapeutic pathomorphosis in peritoneal samples during treatment, reduction of ascites.

Conclusion. The team of authors managed to establish that PIPAC simultaneously with standard combined treatment for primary ovarian cancer with peritoneal carcinomatosis makes it possible to achieve a dynamic regression effect of peritoneal carcinomatosis of the peritoneum, morphological regression of carcinomatosis and complete resorption of ascites in the vast majority of treated patients. The revealed therapeutic effect was prolonged and persistent with an objective assessment 6 months after the end of treatment.

Keywords:
ovarian cancer, ascites, peritoneal carcinomatosis, drug pathomorphosis, pressurized intraperitoneal aerosol chemotherapy, PIPAC

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The work followed the ethical principles set forth by the Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964, ed. 2013). The study was approved by the Committee on Biomedical Ethics at the National Medical Research Centre for Oncology (extract from the protocol of the meeting No. 660 dated 04/09/2021).
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ОРИГИНАЛЬНАЯ СТАТЬЯ

ДИНАМИЧЕСКАЯ ОЦЕНКА ВОЗДЕЙСТВИЯ ВНУТРИБРЮШНОЙ АЭРОЗОЛЬНОЙ ХИМИОТЕРАПИИ ПОД ДАВЛЕНИЕМ НА КАНЦЕРОМАТОЗ БРЮШИНЫ ПРИ РАКЕ ЯИЧНИКОВ (НЕПОСРЕДСТВЕННЫЕ РЕЗУЛЬТАТЫ)

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РЕЗЮМЕ

Цель исследования. Динамическая оценка непосредственного воздействия внутрибрюшной аэрозольной химиотерапии под давлением (ВАХД) на перитонеальный канцероматоз при раке яичников.

Пациенты и методы. В исследовании приняли участие 164 человека с визуально определяемым и морфологически верифицированным раком яичников с перитонеальным канцероматозом брюшины (III*b*-IIIc стадии рака яичников). Всем пациенткам проводилось комбинированное лечение рака яичников, включавшее первичную циторедукцию и 6 курсов системной полихимиотерапии (ПХТ) по схеме ТС. В основной группе стандартное лечение было дополнено 3-мя сеансами ВАХД. Статистическая обработка проведена посредством анализа точного критерия сумм Уилкоксона-Манна-Уитни произведена оценка распределения пациенток в группах по возрасту и поражению брюшины. Установлено, что распределение по анализируемым параметрам было случайным. Распределение в группах по стадиям заболевания было гомогенным, что обосновано использованием критерия Барнарда. Динамика параметров исследования оценена методами базовой статистики. Используемые пакеты программ: MedCalc, Statistika.

Результаты. Полученные результаты демонстрируют отчетливую положительную динамику в группе пациенток, получавших ВАХД в дополнение к стандартному лечению впервые выявленного рака яичников: достоверное уменьшение индекса перитонеального канцероматоза, терапевтический патоморфоз в образцах брюшины в процессе лечения, редукция асцита.

Заключение. Авторскому коллективу удалось установить, что проведение ВАХД совместно со стандартным комбинированным лечением по поводу впервые выявленного рака яичников с перитонеальным канцероматозом позволяет достичь нарастающего в динамике эффекта регрессии перитонеального канцероматоза брюшины, морфологической регрессии канцероматоза и полной резорбции асцита у подавляющего большинства пролеченных пациенток. Выявленный терапевтический эффект был пролонгированным и стойким при объективной оценке через 6 мес. по окончании лечения.

Ключевые слова:
рак яичников, асцит, перитонеальный канцероматоз, лекарственный патоморфоз, внутрибрюшная аэрозольная химиотерапия под давлением, ВАХД

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В работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при ФГБУ «НМИЦ онкологии» Минздрава России (выписка из протокола заседания № 660 от 09.04.2021 г.).
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INTRODUCTION

Unsatisfactory results of treatment of peritoneal carcinomatosis in ovarian cancer are one of the most actual problems of modern oncogynecology. Ovarian cancer is characterized by the latent nature of the disease in the early stages, the absence of pathognomonic symptoms, diagnostic difficulties in detecting early forms of the disease, recurrent nature and relatively low effectiveness of anti-relapse treatment [1]. Peritoneal carcinomatosis is one of the main obstacles to achieving high efficiency of primary and anti-recurrent treatment of ovarian cancer. The incidence of metastatic lesions of the peritoneum in newly diagnosed ovarian cancer is 65–70 % of cases according to worldwide data.

With the progression of ovarian cancer, the defeat of the peritoneum by metastases is noted in 65 % of cases according to various studies [2]. In the vast majority of cases, complete cytoreduction with widespread peritoneal carcinomatosis is technically impossible, and systemic drug treatment does not give a stable clinical effect, which makes peritoneal carcinomatosis an unfavorable prognostic sign in ovarian cancer [3].

Systemic intravenous cytostatic therapy of metastatic lesions of the peritoneum still does not have a high efficiency and a persistent clinical antitumor effect, due to the low bioavailability of cytostatics in metastases on the peritoneum. For many years, attempts have been made to increase the bioavailability of antitumor drugs to carcinomatous foci on the peritoneum. One of such options is locoregional application of cytostatics, a special case of which is intraperitoneal administration of chemotherapy drugs in the form of a normothermal solution of cytostatics [4].

Through intra-abdominal chemotherapy, it is possible to create a high concentration of chemotherapy drugs in tumor foci without resorptive effect and associated systemic toxic effects [5].

In 2000, a group of researchers led by M. Reymond proposed a new variant of intraperitoneal chemotherapy – intraperitoneal aerosol chemotherapy under pressure or PIPAC (Pressurized IntraPeritoneal Aerosol Chemotherapy) – which is the injection of a solution of cytostatics into the closed abdominal cavity in the form of a fine aerosol in the conditions of normothermal carboxyperitoneum [6]. The method ensures uniform distribution of the aerosol over the entire metastatic surface of the peritoneum, which determines its advantage over other types of peritoneal lavage, and increased intra-abdominal pressure increases the depth of penetration of drugs into the peritoneal tissue. With each PIPAC procedure, diagnostic laparoscopy and multifocal biopsy of the peritoneum are performed, which makes it possible to objectively assess the condition of the peritoneum in dynamics through repeated procedures.

Currently, the results of 16 foreign studies of the effectiveness of PIPAC in ovarian cancer with peritoneal carcinomatosis have been published. Pronounced therapeutic pathomorphosis and a decrease in the peritoneal cancer index (PCI) were noted in 69 % of cases [7–15].

At the same time, there are no references in the available literature to the simultaneous use of cytoreductive surgery and PIPAC in ovarian cancer, except for their own first experience of clinical use of the PIPAC method in combination with surgical cytoreduction in primary ovarian cancer with peritoneal carcinomatosis [4].

The authors created a "Method for the treatment of peritoneal carcinomatosis in ovarian cancer", which was the basis for the development of the world's first protocol of a prospective open randomized controlled phase II clinical trial "Intraperitoneal aerosol chemotherapy under pressure (PIPAC) in the treatment of primary ovarian cancer with peritoneal carcinomatosis", approved by the Independent Committee on Biomedical Ethics at the National Medical Research Centre for Oncology [16].

Purpose of the study: to evaluate the direct effect of intra-abdominal aerosol chemotherapy under pressure on metastatic altered peritoneum, carried out in addition to the standard combined treatment of ovarian cancer.

PATIENTS AND METHODS

The study included 164 patients with primary ovarian cancer with visually detectable and morphologically verified peritoneal carcinomatosis. Prior to inclusion in the study, informed consent was obtained from all patients to participate in the study and to conduct PIPAC on the condition of complete anonymity. The work followed the ethical principles

set forth by the Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964, ed. 2013). The study was approved by the Committee on Biomedical Ethics at the National Medical Research Centre for Oncology (extract from the protocol of the meeting No. 660 dated 04/09/2021).

Research stages and ongoing activities

Prior to inclusion in the study, patients were examined according to the recommendations of the AOR for patients suffering from ovarian cancer. The examination period did not exceed 7 days.

Upon completion of the examination, surgical intervention was performed in the following volume: extirpation of the uterus with appendages, omentectomy and multifocal biopsy from the 4 most altered areas of the peritoneum. The volume of cytoreduction in all cases was suboptimal.

Randomization was performed directly in the operating room after urgent morphological verification of metastatic peritoneal lesion by generating a random value of 0 or 1 on the site https://www.random.org/. Where the value 0 corresponded to the patient's getting into the control group, and 1 – into the main one.

In the control group, standard suturing of the anterior abdominal wall was performed. In the main group, after the completion of the organ-bearing stage of the operation, the patient underwent a PIPAC procedure.

In the postoperative period, a set of standard postoperative diagnostic and therapeutic measures was carried out in accordance with the clinical recommendations of the AOR, as well as taking into account the patient's condition and the specific clinical situation.

On the 8th day after cytoreductive surgery, patients of both groups underwent the 1st course of systemic polychemotherapy according to the TC scheme: paclitaxel 175 mg/m^2, carboplatin AUC 5–7. The first course of PCT was performed on the 2nd week of the study as part of a single hospitalization with a simultaneous organ-bearing stage and a PIPAC stage, the duration of systemic chemotherapeutic treatment was 1 day. The next (second course) intravenous chemo was performed after 21 days, and then 4 more courses (6 in total) were conducted with an interval of 21 days between them.

At the 3rd and 5th hospitalization, patients from the main group underwent the second and third PIPAC procedures, consistently and gradually performing diagnostic laparoscopy and pressurized intraperitoneal aerosol chemotherapy with an assessment of the peritoneal cancer index and multifocal biopsy of the peritoneum in the volume indicated earlier.

As part of the 3rd and 5th hospitalization, the activation of patients was performed the day after the PIPAC (2nd and 3rd procedures), and the day after activation, systemic intravenous PCT was performed according to the TC scheme.

6 months after the completion of the course of treatment, the patients from the main group, after a standard preoperative examination, underwent diagnostic laparoscopy with an assessment of the index of peritoneal carcinomatosis and a multipoint biopsy examination of the peritoneum.

At the same time, patients from the control group underwent a follow-up examination that corresponded to the recommendations of the AOR in terms of dispensary follow-up of patients who had undergone combined treatment for ovarian cancer.

Evaluation of the peritoneal carcinomatosis index

The scale of peritoneal metastasis lesion is estimated by calculating the index of peritoneal carcinomatosis in points for each PIPAC procedure. To do this, the parietal peritoneum and several sections of the visceral are conditionally divided into 13 zones: 0 – central, 1 – right dome of the diaphragm, 2 – epigastrium, 3 – left dome of the diaphragm, 4 – left lateral canal, 5 – left iliac region, 6 – pelvis, 7 – right iliac region, 8 – right lateral canal; additionally, 4 zones of the visceral peritoneum are evaluated: 9 – the proximal part of the jejunum, 10 – the distal part of the jejunum, 11 – the proximal part of the ileum, 12 – the distal part of the ileum. In the absence of a lesion in the selected zone, a score of 0 points is given, 1 point – the presence of formations up to 5 mm in size, 2 points – the presence of formations from 6 to 25 mm in size, 3 points – the presence of formations larger than 25 mm or drain formations.

The results of the calculation are entered into a standard form (Fig. 1). After that, all the scores are added, the result is an index of peritoneal carcinomatosis.

Histological assessment of tumor pathomorphosis

To assess the therapeutic effect directly in peritoneal metastases at the morphological level, we used the classification of G. A. Lavnikova, based on the assessment of the structure of both the tumor tissue as a whole and its individual cells. As a material for the study, 4 biopsies of the peritoneum were used, obtained during each PIPAC procedure and during control diagnostic laparoscopy 6 months after the end of treatment.

Within the framework of this classification, 4 degrees of pathomorphosis are distinguished:

- Grade I – more than 50 % of the tumor parenchyma is preserved;
- Grade II – 20–50 % of tumor parenchyma is preserved;
- Grade III – up to 20 % of the tumor parenchyma has been preserved as separate foci;
- Grade IV – complete absence of tumor parenchyma.

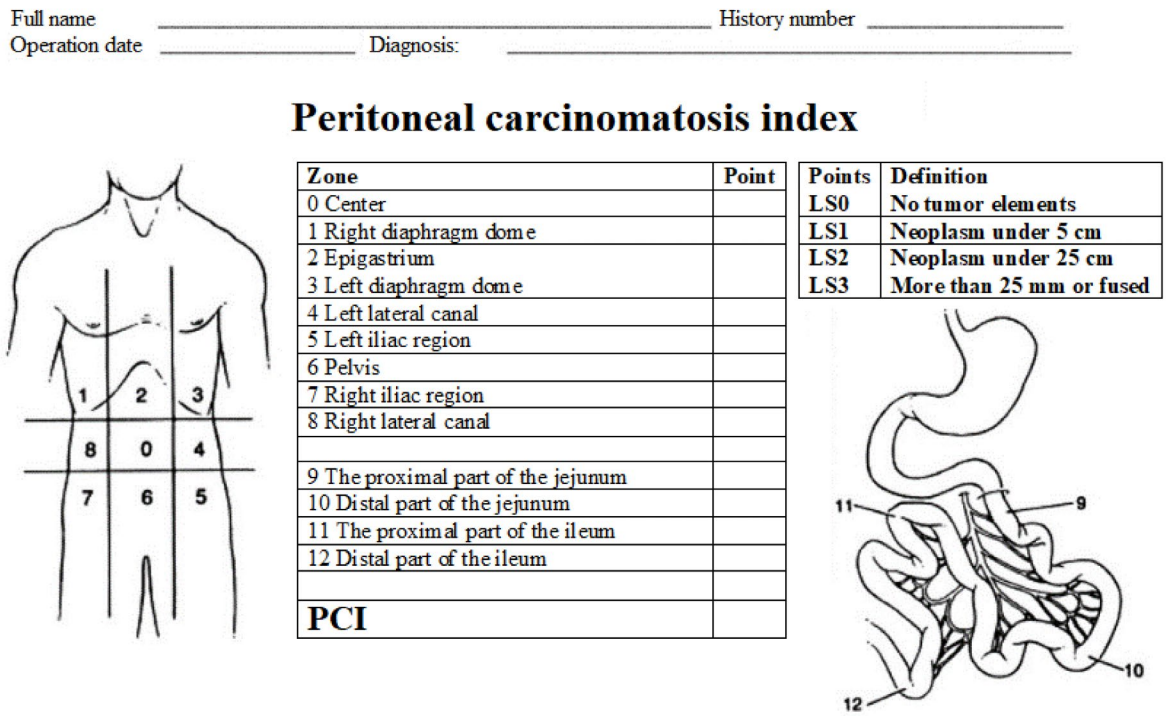
Clinical and demographic composition of the groups

The final sample included 164 patients, 79 of them in the main group, 85 in the control group. The average age of patients in the main group was 56.8 years, in the control group – 56.2 years. Analysis using the exact Wilcoxon-Mann-Whitney sum criterion showed a significance level of 0.779, which indicates a random distribution of patients between groups.

All the patients involved in the study were diagnosed with stage III serous ovarian cancer. In the main group, stage IIIb was established in 17 patients, and stage IIIc in 62. In the control group at 13 and 72, respectively. When evaluating the Barnard criterion, a significance level of $p = 0.364$ was obtained, hence the distribution among groups is homogeneous.

Also, peritoneal carcinomatosis was detected and verified in all patients at the time of initiation of treatment. After randomization, the lesion volume reflected in the PCI index varied in the range from 7 to 39 and from 5 to 39 points in the control and main groups, respectively. A more detailed distribution by the degree of peritoneal lesion is presented in Table 1.

The average PCI index in the main group was 23.1, and in the control group – 23.7 points. When compared using the exact Wilcoxon-Mann-Whitney sum criterion, the significance level was 0.642. Consequently, the distribution of patients between groups according to the degree of peritoneal lesion is random.


Full name _____ History number _____
Operation date _____ Diagnosis: _____

Peritoneal carcinomatosis index

Zone	Point
0 Center	
1 Right diaphragm dome	
2 Epigastrium 3 Left diaphragm dome	
4 Left lateral canal	
5 Left iliac region	
6 Pelvis	
7 Right iliac region	
8 Right lateral canal	
9 The proximal part of the jejunum	
10 Distal part of the jejunum	
11 The proximal part of the ileum	
12 Distal part of the ileum	
PCI	

Points	Definition
LS0	No tumor elements
LS1	Neoplasm under 5 cm
LS2	Neoplasm under 25 cm
LS3	More than 25 mm or fused

Fig. 1. Standard form for assessing the peritoneal carcinomatosis index.

The duration of hospitalization after treatment conducted at stage 1 of the study in the control and main groups averaged 7.2 days (range from 5 to 13 days) and 7.6 days (range from 6 to 12 days), respectively. There were no statistically significant differences between the groups for this indicator.

In the future, patients from both groups underwent 6 courses of systemic PCT according to the TC scheme. For patients from the control group, this therapy was the only one. In the main group, treatment was carried out in the mode of bidirectional chemotherapy with the addition of PIPAC sessions between courses of intravenous chemotherapy. Each of the patients had at least 1 PIPAC session, two sessions were conducted in 72 patients, three sessions each in 69 patients. Thus, a total of 220 PIPAC procedures were conducted in 79 patients, with an average of 2.8 sessions for each patient. The duration of each session ranged from 62 to 87 minutes, an average of 74 minutes. The duration of hospitalization after PIPAC varied from 2 to 5 days, on average 3 days. Also, 404 courses of systemic PCT were conducted in the main group, that is, an average of 5.6 courses per patient. In the control group, a total of 384 PCT sessions were conducted in 67 patients, which is 5.7 courses per person. The study of the direct effect of PIPAC on the metastatically altered peritoneum was carried out in the main group by assessing the dynamics of the PCI index, the morphological picture of drug pathomorphosis and the volume of ascitic fluid during diagnostic laparoscopy at the 2nd and 3rd PIPAC sessions.

Immediate results

As indicated earlier in the main group, the distribution of patients by the degree of peritoneal lesion was as follows: from 1 to 10 points on the PCI scale in 6 patients (7.6 %); from 11 to 20 points – in 26 (32.9 %); from 21 to 30 points – in 29 (36.7 %) and 18 (22.8 %) of patients revealed the most massive lesion of the peritoneum 31–39 points. In other words, at the time of detection of the disease, total peritoneal metastasis was present in 92.4 % of patients. When re-evaluated during the 2nd PIPAC procedure, a significant decrease in PCI was noted in almost all patients. Thus, tumor elements were no longer detected in 31 patients (PCI 0 points), which is 43 % of cases; in one patient (1.3 %), PCI was 17 points. In the remaining 40 cases (50.6 %), the values of this indicator were in the range from 1 to 10 points. Thus, already at the 2nd session of the PIPAC, it was noted that complete regression of total carcinomatosis occurred in 43 % of cases, and in 50.6 % of cases total carcinomatosis transformed into limited, which corresponds to partial regression.

According to the results of histological examination of the biopsy material taken during the second session of the PIPAC, it was found that grade IV pathomorphosis (complete absence of viable tumor cells) was detected in 40 patients, which is 55.5 % of cases. This discrepancy with clinically determined pathomorphosis in favor of morphological pathomorphosis is due to the fact that metastases on the peritoneum at the stages of drug pathomorphosis initially underwent replacement with fibrous tissue, which looked like metastases during video endoscopic revision, and morphological examination recorded complete drug pathomorphosis with total replacement of metastasis with fibrous elements.

The III degree of pathomorphosis was detected

Table 1. PCI in the main and control groups

Peritoneal Carcinomatosis Index	Main group	Control group
1 to 10 points	6	4
11 to 20 points	26	30
21 to 30 points	29	35
31 to 39 points	18	16

in 17 cases (23.6 %), the II degree – in 13 cases (18.1 %), and the I degree in only 2 patients (2.8 %). In other words, complete morphological regression of peritoneal carcinomatosis took place in more than half of the patients (55.5 %), and partial regression in 41.7 %. The cumulative effective morphological response was 97.2 %.

When assessing the PCI index during the 3rd session of PIPAC (69 patients), visible lesions of the peritoneum were absent in 58 cases (84.0 %), in 11 (16.0 %) the index value did not exceed 6 points. Histologically, grade IV tumor pathomorphosis was detected in 50 cases (72.5 %), grade III – in 10 (14.5 %) cases, grade II – in 5 (7.2 %) cases and in 4 (5.8 %) patients, grade I pathomorphosis was detected. That is, complete clinical regression of peritoneal carcinomatosis at the 3rd session of PIPAC was 84.0 % versus 43 % at the 2nd session, and complete morphological regression was noted in 72.5 % at the 3rd session of PIPAC versus 55.5 % at the second session.

At the control diagnostic laparoscopy 6 months after the end of treatment, there were no signs of peritoneal lesion in all 47 patients (100 %). At the same time, 36 (76.6 %) of them had drug–induced tumor pathomorphosis of the IV grade, 9 (19.2 %) – of the III grade, and only two of the I and II grade (2.1 % each).

A similar dynamic was observed with respect to the volume of ascitic fluid in the abdominal cavity. At the beginning of the study in the main group, ascites was absent in only one patient (1.2 %), a volume of up to 1 liter was detected in 38 cases (48.1 %), from 1 to 2 liters – in 14 cases (17.7 %), 7 patients (8.9 %) had from 2 to 3 liters of free fluid in abdominal cavity, another 6 (7.6 %) – from 3 to 4 liters, and massive ascites with a volume of more than 4 liters were detected in 13 cases (16.5 %). During the second PIPAC session, ascites were no longer detected in the vast majority of cases (59 out of 72, i.e. 81.9 %), in the remaining 13 cases (18.1 %) its volume did not exceed 200 ml. During 3 sessions of PIPAC, only 3 patients out of 69 (4.4 %) had an insignificant amount of exudate (volume no more than 200 ml). Accordingly, ascites resorbed completely in 95.6 % of patients by the 3rd PIPAC session. During the control laparoscopy, 6 months after the end of therapy, only 1 (2.1 %) of 47 patients had an insignificant amount of exudate with a volume of no more than 100 ml. At the same time, there were no clinical manifestations of ascitic syndrome in all 47 cases (100 %).

CONCLUSION

Preliminary results of primary ovarian cancer with peritoneal carcinomatosis, supplemented with pressurized intraperitoneal aerosol chemotherapy. During the second PIPAC prosedure, 31 patients (43 %) revealed complete clinical regression of peritoneal carcinomatosis, and according to the results of histological examination of biopsy material, therapeutic pathomorphosis of the IV degree (complete morphological regression) was registered in 40 patients (55.5 %). During the 3rd PIPAC procedure, further development of the therapeutic effect was noted: complete regression of metastases on the peritoneum was registered in 58 patients (85.3 %), and morphologically determined pathomorphosis of the IV degree in 50 people (73.5 %). Later, during diagnostic laparoscopy, 6 months after the completion of treatment, complete clinical regression was detected in all patients (100 % of cases), and in 36 people (76.6 %), drug pathomorphosis of the IV degree was established, which corresponds to complete morphological regression of peritoneal carcinomatosis and the long-term effect of the treatment.

A similar positive trend was noted with respect to the frequency and severity of ascites. So at the beginning of the study, it was detected in all patients of the main group, except one, which was 98.8 %. At the same time, at the time of the second PIPAC procedure, complete resorption of ascites was noted in 59 patients (81.9 %). This trend was observed throughout the entire track of the study and persisted after the end of therapy (at the time of the control diagnostic laparoscopy, ascites syndrome was not registered in any case). This effect is clinically significant because it leads to a significant improvement in the general condition and, as a result, significantly improves the tolerability of the treatment and the quality of life of patients.

Our observations allow us to draw several conclusions.

1) pressurized intraperitoneal aerosol chemotherapy simultaneous with standard combined treatment for primary ovarian cancer with peritoneal carcinomatosis makes it possible to achieve complete clinical regression (PCI = 0) of peritoneal carcinomatosis in 85.3 % of patients by the 3rd session of PIPAC,

complete morphological regression of carcinomatosis (IV degree drug pathomorphosis according to Lavnikova) in 73.5 % patients, and complete resorption of ascites in 81.9 % of patients.

2) With laparoscopic control 6 months after the end of treatment, complete clinical regression was noted in 100 % of cases, complete morphological regression in 76.6 % of cases, ascites syndrome was absent in 100 % of patients. The revealed trend, in our opinion, indicates a prolonged and persistent therapeutic effect of PIPAC on peritoneal carcinomatosis accompanying primary ovarian cancer.

3) It seems promising to conduct a comparative assessment of the main and control groups of the study in terms of long-term treatment results by comparing the duration of the relapse-free period and overall survival.

4) The results obtained allow us to consider the possibility of expanding the indications for the use of PIPAC as a method of palliative and symptomatic care in patients at the terminal stage of the disease, accompanied by an intensive accumulation of ascites.

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Kostin A. A. – research idea, scientific guidance, research concept, methodology development;
Astashov V. L. – scientific management, research concept, methodology development, organizational and administrative activities;
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