

PRELIMINARY RESULTS OF PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) FOR OVARIAN CANCER WITH PERITONEAL METASTASES IN TAJIKISTAN

M.M. HOJIEVA^{1,2}

¹State Institution "Republican Cancer Research Center" of the Ministry of Health and Social Protection of the Population, Dushanbe, Republic of Tajikistan;

²State educational institution "Institute of Postgraduate Education in Healthcare of the Republic of Tajikistan," Dushanbe, Republic of Tajikistan

ABSTRACT

Relevance: Ovarian cancer is the most aggressive form among all nosologies of the female reproductive system. More than 75% of women are diagnosed at advanced stages, and about 60% have metastases to other organs at diagnosis. Systemic chemotherapy has a limited effect on the peritoneum and a high incidence of side effects. There is a need for more effective approaches to prolong survival and preserve quality of life by reducing disease symptoms and treatment side effects, especially in countries with limited health resources.

The study aimed to evaluate the preliminary results of using pressurized intraperitoneal aerosol chemotherapy (PIPAC) in patients with ovarian cancer with peritoneal metastases.

Methods: 18 women with disease stage T3a-cN0M0 treated at the Republican Cancer Research Center for 2022-2023 were studied. The first group included six patients who underwent cytoreduction + PIPAC at the 1st stage, and the second group (12 women) underwent exploratory laparotomy + biopsy + PIPAC at the 1st stage. Patients in both groups received two courses of chemotherapy followed by a repeat of PIPAC. Taxanes + platinum-containing drugs were used in the PIPAC process – cisplatin or carboplatin with doxorubicin. Each patient received 2 PIPAC sessions and 4 to 6 chemotherapy courses with cytoreductive surgery. All patients underwent laparoscopic control with a reassessment of the Peritoneal Carcinomatosis Index (PCI) by Sugarbaker (2010) and repeated biopsy of the peritoneum.

Results: The use of cytoreductive surgery + PIPAC at the first stage made it possible to level the symptoms of peritoneal carcinomatosis, to achieve a complete radiological response in 12 (67%) cases, a complete morphological response in the form of complete regression in 44%, a moderate response in 39% of cases

Conclusion: Using PIPAC with a cytoreductive component at the first stage of combined treatment of ovarian cancer with peritoneal metastases improves immediate results and the patient's quality of life and reduces the hospital stay. The research is ongoing.

Keywords: PIPAC, ovarian cancer, peritoneal carcinomatosis.

Introduction: There is no need to remind that ovarian cancer (OC) is the most aggressive form among all nosologies of the female reproductive system. More than 75% of women are diagnosed at advanced stages, and about 60% have metastases to other organs at diagnosis [1, 2].

Usually, OC remains local; it metastasizes directly to neighboring organs or by transperitoneal dissemination of detached cancer cells to all intraperitoneal structures.

Secondary peritoneal cancer occurs due to metastasis and is the most common cancer of the abdomen. OC, gastric, and colorectal cancer metastases are associated with high recurrence and mortality rates [3].

The best approach to treating peritoneal cancer from ovarian cancer metastases is multimodal, includ-

ing surgical, chemotherapy components, and targeted therapy.

The effect of systemic chemotherapy (SCT) on the peritoneum remains limited due to poor vascularization and low penetration. The side effects after SCT of peritoneal metastases are relatively frequent. The quality of life of these patients is constantly deteriorating due to the disease itself and the drug therapy.

Therefore, there is a need for more effective approaches to prolong survival and preserve quality of life by reducing disease symptoms and treatment side effects, especially in countries with limited health resources.

One such approach is the pressurized intraperitoneal aerosol chemotherapy (PIPAC), proposed by German colleagues in 2011. Using the physical properties

of gas and pressure by creating an artificial pressure gradient contributes to increased absorption of cytostatics by tissues and their homogeneous distribution in the abdominal cavity.

Based on relevant experience and support of Russian colleagues in their use of PIPAC in recent years for gastric cancer, we also decided to introduce and test this technique in our institution for patients with OC [4, 5].

The PIPAC technique is implementable in practice and well tolerated, also stabilizes and improves the quality of life of patients even with terminal stages, and can cause severe therapeutic pathomorphosis with the use of significantly lower doses of cytotoxic drugs (up to 10% of the commonly used dose), which reduces toxicity, allows the patient to be discharged the next day after manipulation, and thereby reduce the economic costs. Besides, there is an opportunity for recurrent PIPAC implementation in contrast to cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy [6-11].

The study aimed to evaluate the preliminary results of using pressurized intraperitoneal aerosol chemotherapy (PIPAC) in ovarian cancer patients with peritoneal metastases (OCPM).

Materials and Methods: The study involved 18 women with OCPM at T3a-cN0M0 stage by FIGO classification examined and treated at the Republican Cancer Research Center from October 2022 to March 2023.

In the study, the patients' age averaged 55 years. The main complaints included pain, palpable abdomen swelling, enlargement, and dysuric disorders (Table 1).

Table 1 – Characteristics of patients with OCPM (n=18)

Parameters	Abs.	%
Median age	55.5±10.5	
ИМТ, кг/м ² (M±m)	27.7±6.5	
Complaints:		
- Increasing the abdomen volume	11	61.1
- Pain in the lower abdomen and lumbar region	18	100
- Palpable tumor	6	33.3
- Pain in the epigastric region	14	77.8
- Dysuric disorders	6	33.3
- Constipation	10	55.6
- Discharge from the genital tract	2	11.1
- Weight loss	6	44.4

During an ultrasound examination, 83% of patients had less than 5 L of free fluid in the abdominal cavity; in 61%, the ovarian tumor volume did not exceed 5 cm³; in 89%, the tumor was hyperechoic or had a mixed structure (Table 2).

In 78% of cases, the tumor histology represented a serous adenocarcinoma with moderate differentiation (Figure 1).

The tumor differentiation was G2 in 11 (61.1%) cases and G3 in 7 (38.9%) cases.

Table 2 – Results of ultrasound examination of the abdominal cavity and pelvic organs of patients with OCPM (n = 18)

Signs	Abs.	%
Ascites (amount of fluid, L):		
- up to 5 l	15	83.3
- up to 10 l	2	11.1
- more than 10 l	1	5.6
Tumor volume:		
- up to 5 cm	11	61.1
- up to 10 cm	3	16.7
- more than 10 cm	4	22.2
Tumor structure:		
- Tissue	9	50.0
- Liquid	2	11.1
- Mixed	7	38.9

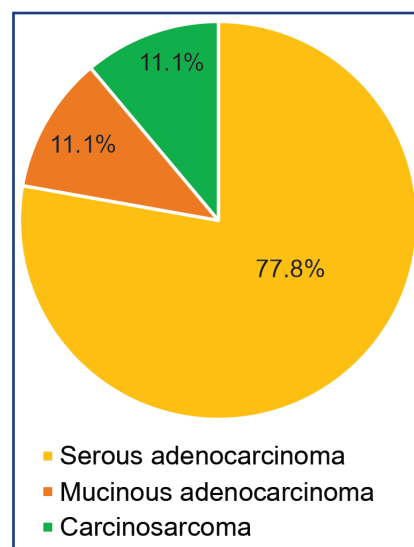


Figure 1 – Histological options of ovarian tumors in patients with OCPM (n=18)

Half of the patients had the T3aN0M0 stage, 33% had the T3cN0M0 stage, and the remaining proportion (16.7%) accounted for the T3bN0M0 stage by FIGO classification of the tumor extent.

Based on the study design, the patients were divided into two groups. The first group included six patients who received the CS + PIPAC at the 1st stage, and the second group received the exploratory laparotomy, biopsy + PIAC at the 1st stage. Subsequently, patients in both groups received two courses of SCT followed by a repetition of PIPAC. SCT scheme included taxanes + platinum-containing drugs, and PIPAC utilized cisplatin or carboplatin with doxorubicin. Overall, each patient received two sessions of PIPAC and from 4 to 6 courses of SCT with CS. All patients underwent a comprehensive laboratory (including tumor markers), cytological, histological, and instrumental examination, as well as laparoscopic control with a reassessment of the peritoneal carcinomatosis index (PCI) by Sugarbaker method (2010) [12] (Figures 2, 3).

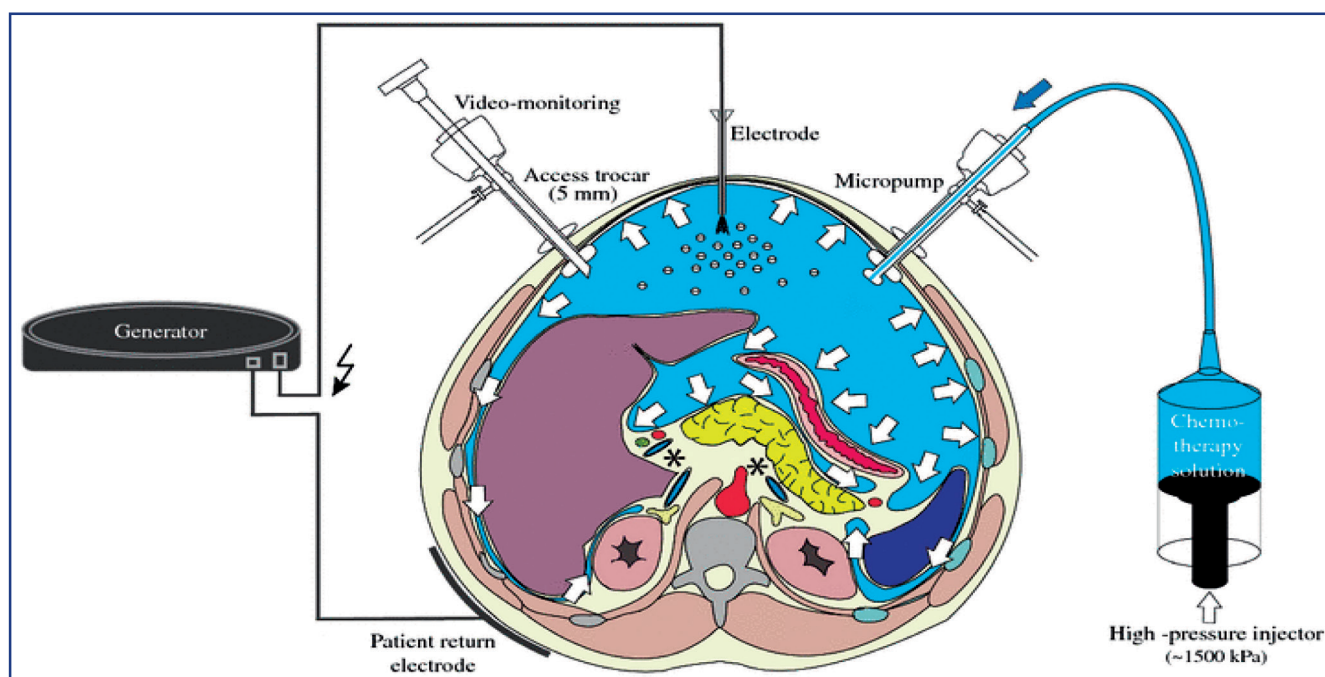


Figure 2 – Schematic illustration of the PIPAC methodology performance [12]

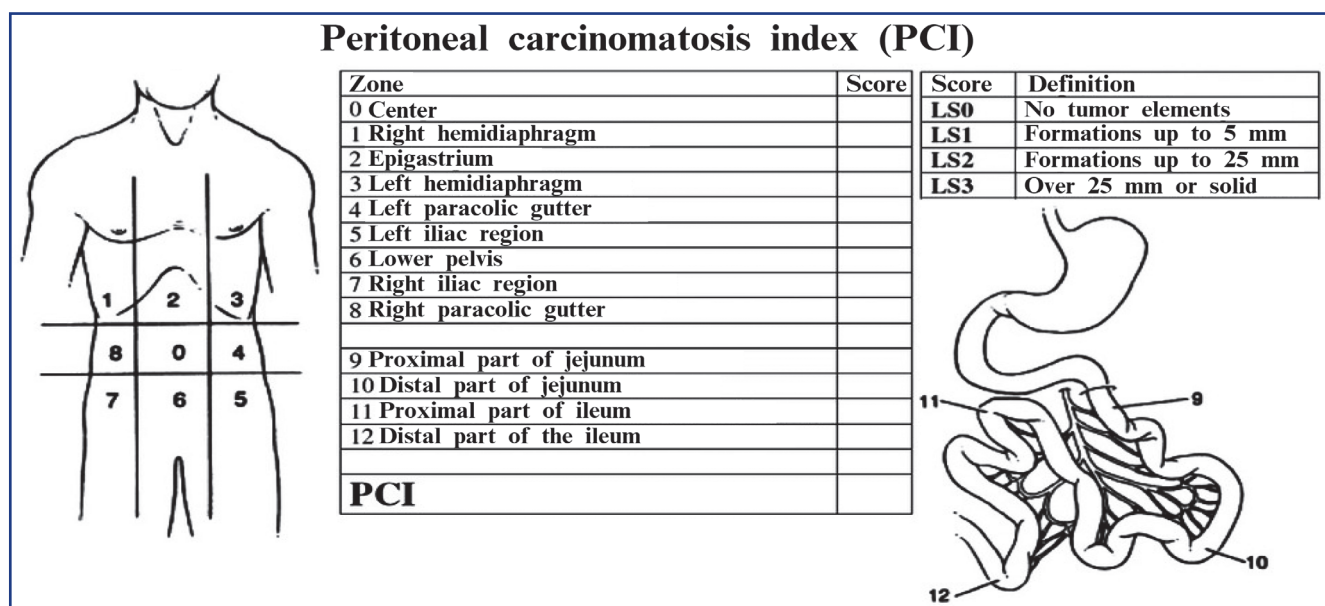


Figure 3 – PC index rating scale according to Sugarbaker P.H. (2010) [12]

Results: Within the study, during six months of 2022-2023, at stage 1, we performed CS with a simultaneous PIPAC in 9 (50%) cases. Due to the technical difficulties and the process prevalence, the remaining patients underwent only diagnostic laparotomy + biopsy + PIPAC at stage 1 (Table 3).

Table 3 – Results of surgical treatment of patients with OCPM

Surgical interventions	Abs.	%
Cytoreduction:		
- Optimal	9	50
- Suboptimal	5	27.8
- Nonoptimal	4	22.2

Subjective assessment of patients after combined treatment showed a leveling of symptoms associated with peritoneal carcinoma (Figure 4).

During an assessment of the effectiveness of treatment after 2 PIPAC sessions according to the RECIST system, a complete radiological response was achieved in 12 (67%) cases, and progression was noted in only one case.

Assessment of the morphological response showed that complete regression with an absence of cancer cells took place in 44%, a moderate response was obtained in 39% of cases, and a minor response in 17% of cases. No cases of lack of morphological response to therapy have been registered (Table 5).

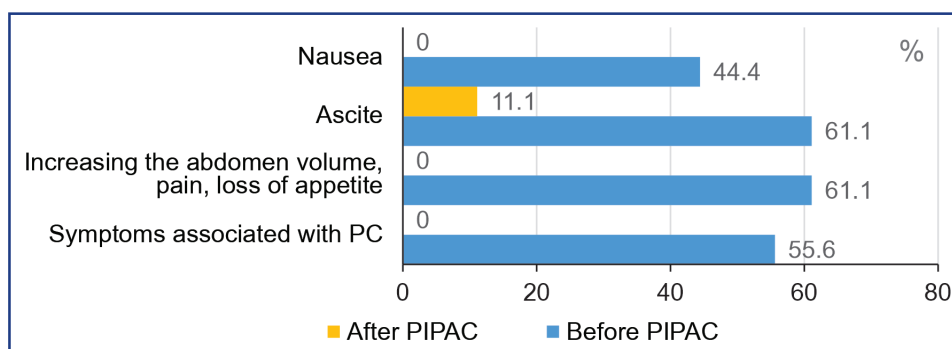


Figure 4 – Dynamics of the severity of symptoms of peritoneal carcinomatosis before and after PIPAC

Laboratory parameters also showed a marked decline of the tumor markers Ca-125 and HE4 (Table 4).

Table 4 – Laboratory parameters of the tumor markers Ca125 and HE4 before and after two PIPAC sessions

Parameters	Before PIPAC	After PIPAC
Ca125, Me(1q-3q)	595.58 (55-2000)	15.4 (12.9-59)
HE4, Me(1q-3q)	222.5 (46-372)	77.7 (44.9-153)

Table 5 – X-ray and morphological responses after two PIPAC sessions

Response according to the RECIST scale	Abs.	%
X-ray response:		
Complete response	12	66.7
Partial response	3	16.7
Stabilization	2	11.1
Progression	1	5.6
Morphological response:		
PRGS 1 (complete regression with absence of tumor cells)	8	44.4
PRGS 2 (moderate histological response with signs of regression, residual tumor cells predominate)	7	38.9
PRGS 3 (insignificant histological response with a predominance of residual tumor cells over regressive features)	3	16.7

Discussion: Our preliminary data showed PIPAC to be safe and effective in treating peritoneal cancer from OC metastases. This inspires to continue the study in our country.

Several studies also demonstrated a higher quality of life in patients treated by the new method than those who underwent a traditional multi-course SCT.

Conclusion: The newly developed approaches in diagnosing and combined treatment of OCPM using PIPAC with CS at the first stage will allow determining the effectiveness of radiation methods depending on the tumor prevalence degree, as well as improve the immediate and long-term treatment outcome in this category of patients and their quality of life and reducing the hospital stay. The research is ongoing.

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АНДАТПА

ТӘЖІКСТАНДА АНАЛЫҚ БЕЗ ҚАТЕРЛІ ІСІГІ КЕЗІНДЕ ІШПЕРДЕГЕ ТАРАҒАН МЕТАСТАЗДАРҒА ҚҰРСАҚШІЛІК ҚЫСЫМ АРҚЫЛЫ АЭРОЗОЛЬДІ ХИМИОТЕРАПИЯНЫ (PIPAC) ҚОЛДАНУДЫҢ АЛДЫН АЛА НӘТИЖЕЛЕРІ

М.М. Ходжиева^{1,2}

¹«Денсаулық сақтау және халықты әлеуметтік қорғау министрлігінің «Республикалық онкологиялық ғылыми орталығы» ММ, Душанбе, Тәжікстан Республикасы;

²«Тәжікстан Республикасының Денсаулық сақтау саласындағы жоғары оқу орнынан кейінгі білім беру институты» ММ, Душанбе, Тәжікстан Республикасы

Өзектілігі: Аналық без қатерлі ісігі – әйелдердің ұрпақты болу жүйесі мүшелерінің барлық нозологияларының ішіндегі ең агрессивті түрі. Бұл сырқат әйелдердің 75%-дан астамында кеш сатысында анықталады және диагноз қойылған кезде шамамен 60% басқа органдарға метастаз беріп үлгереді. Жүйелік химиотерапия құрсаққа шектеулі әсер етеді және жанама әсерлердің жоғары жиілігіне иелік етеді. Аурудың белгілері мен терапияның жанама әсерлерін азайту арқылы өмір сүруді ұзарту және өмір сүру сапасын сақтау үшін, әсіресе денсаулық сақтау ресурстары шектеулі елдерге тиімді тәсілдер қолдану қажет.

Зерттеудің мақсаты аналық без қатерлі ісігі кезінде ішпердеге тараған метастаздарға құрсақшылқ қысым арқылы аэрозольді химиотерапияны (PIPAC) қолданудың алдын ала нәтижелерін бағалау.

Әдістері: 2022-2023 жылдары T3a-cN0M0 (FIGO) ауру сатысы бар республикалық онкологиялық ғылыми орталықта тексеріліп, емделіп жатқан перитонеальді метастаздары бар аналық без обырымен ауыратын 18 әйел зерттелді. Пациенттер 2 топқа бөлінді: бірінші топтағы 6 пациентке 1-ші кезеңде + PIPAC циторедукциясын орындалды, ал екінші топ (12 әйел) – 1-ші кезеңде эксплоративті лапаротомия + биопсия + PIPAC орындалды. Екі топтың пациенттері де жүйелік химиотерапияның 2 курсы алды, содан кейін PIPAC-ты қайталады. Жүйелік химиотерапия ретінде таксандар + платинасы бар препараттар схемасы қолданылса, PIPAC процесінде цисплатин немесе карбоплатин доксорубицинмен қолданылды. Жалпы алғанда, әрбір пациент 2 PIPAC сеансын және циторедуктивті операциямен 4-тен 6-ға дейін жүйелік химиотерапия курсы алды. Барлық науқастарға Sugarbaker P.H. (2010) әдісі бойынша перитонеальді канцероматоз индексі (PCI) қайта баалаумен және перитонеальді биопсия алу арқылы кешенді зертханалық, цитологиялық, гистологиялық және аспаптық әдістер тексеру, сондай-ақ лапароскопиялық бақылау жүргізілді.

Нәтижелері: Бірінші кезеңде ЦО+PIPAC қолдану перитонеальді канцероматоздың белгілерін нивелирлеуге, 12 (67%) жағдайда толық рентгенологиялық жауапқа, 44% толық регрессия түрінде толық морфологиялық жауапқа, 39% жағдайда орташа жауапқа қол жеткізуге мүмкіндік берді.

Қорытынды: Бірінші кезеңде циторедуктивті компоненті бар PIPAC-ты жедел нәтижелерді жақсарту, олардың өмір сүру сапасын жақсарту, стационарда болу уақытын қысқарту түрінде біріктірілген емдеуде қолдану тиімділігі көрсетілген. Зерттеу жалғасуда.

Түйінді сөздер: интраперитонеальді қысымды аэрозольді химиотерапия (PIPAC), аналық без обыры, перитонеальді канцероматоз.

АННОТАЦИЯ

ПРЕДВАРИТЕЛЬНЫЕ РЕЗУЛЬТАТЫ ВНУТРИБРЮШИННОЙ АЭРОЗОЛЬНОЙ ХИМИОТЕРАПИИ ПОД ДАВЛЕНИЕМ (PIPAC) ПРИ РАКЕ ЯИЧНИКОВ С ПЕРИТОНЕАЛЬНЫМИ МЕТАСТАЗАМИ В ТАДЖИКИСТАНЕ

М.М. Ходжиева^{1,2}

¹ГУ «Республиканский онкологический научный центр» Министерства здравоохранения и социальной защиты населения, Душанбе, Республика Таджикистан;

²ГОУ «Институт последипломного образования в сфере здравоохранения Республики Таджикистан», Душанбе, Республика Таджикистан

Актуальность: Рак яичников (РЯ) является самой агрессивной формой среди всех пазологий органов женской репродуктивной системы. Более чем 75% женщин выявляются на поздних стадиях, и около 60% на момент постановки диагноза имеют

метастазы в другие органы. Системная химиотерапия (СХТ) имеет ограниченное влияние на брюшину и высокую частоту побочных эффектов. Существует потребность в более эффективных подходах для продления выживаемости и сохранения качества жизни за счет уменьшения симптомов заболевания и побочных эффектов терапии, особенно для стран с ограниченными ресурсами здравоохранения.

Цель исследования – оценить предварительные результаты применения внутрибрюшинной аэрозольной химиотерапии под давлением (РПАС) у больных раком яичников с перитонеальными метастазами (РЯПМ).

Методы: Исследованы 18 женщин с РЯПМ, находившихся на обследовании и лечении в Республиканском онкологическом научном центре в 2022-2023гг. со стадией заболевания T3a-cN0M0 (FIGO). Пациентки были распределены на 2 группы: первая группа – 6 пациенток, которым на первом этапе удалось выполнить циторедукцию + РПАС, и вторая группа – 12 пациенток, которым на 1м этапе была проведена эксплоративная лапаротомия + биопсия + РПАС. Пациентки обеих групп получали по 2 курса СХТ с последующим повторением РПАС. В качестве СХТ применялась схема таксаны+латиносодержащие препараты, в процессе РПАС – цисплатин или карбоплатин с доксорубицином. В целом каждая пациентка получила по 2 сеанса РПАС и от 4 до 6 курсов СХТ с циторедуктивной операцией (ЦО). Всем больным проведено комплексное лабораторное, цитологическое, гистологическое и инструментальные методы обследование, а также лапароскопический контроль с переоценкой индекса перитонеального канцероматоза (PCI) по методу Sugarbaker P.H. (2010) и повторной биопсией брюшины.

Результаты: Применение ЦО+РПАС на первом этапе позволило нивелировать симптомы перитонеального канцероматоза (ПК), добиться полного рентгенологического ответа в 12(67%) случаях, полного морфологического ответа в виде полной регрессии в 44%, умеренного ответа в 39% случаев.

Заключение: Показана эффективность применения РПАС с циторедуктивным компонентом на первом этапе в комбинированном лечении РЯПМ, в виде улучшения непосредственных результатов, повышения качества их жизни, сокращения времени пребывания в стационаре. Исследование продолжается.

Ключевые слова: внутрибрюшинная аэрозольная химиотерапия под давлением (РПАС), рак яичников (РЯ), перитонеальный канцероматоз.

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The author's data:

Hojjeva Matluba Muzafarovna (corresponding author) – Candidate of Medical Sciences, Head of the Department of Tumors of Female Reproductive System, State Institution "Republican Cancer Research Center" MHSP RT, Dushanbe, the Republic of Tajikistan; Assistant at the Oncology Department of State Educational Institution "Institute of Postgraduate Education in Healthcare of the Republic of Tajikistan," Dushanbe, the Republic of Tajikistan, tel. +992918752100, e-mail: 1983mat@mail.ru, ORCID ID: 0009-0005-9648-9596.

Address for correspondence: Hojjeva M.M., State Institution "Republican Cancer Research Center" MHSP RT, Ismoil Somoni Ave. 59A, Dushanbe 734026, the Republic of Tajikistan.