Ministry of Health
of Nizhny Novgorod region
State budgetary healthcare institution
of Nizhny Novgorod region
"Nizhny Novgorod Regional Clinical Oncological Dispensary"

It was approved by

the Chief Physician

PhD in Medical Sciences S. V. Gamayuov

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The Single-center randomized researcher-initiated phase II study «Comparison of safety and effectiveness of the first line of polychemotherapy (6 courses of FLOT) and polychemotherapy in combination with PIPAC sessions using intraperitoneal administration of docetaxel (3 courses of FLOT + (3 courses of mFLOT + dPIPAC) in case of the primary 4 stage gastric cancer with peritoneal carcinomatosis Cy+ and/ or PCI≤15».

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Content

The list of abbreviations and conventions

FLOT – drug therapy regimen: Docetaxel 50 mg/m^2 intravenously drip on the first day + Oxaliplatin 85 mg/m^2 on the first day + Calcium Folinate 200 mg/m^2 within 2 hours intravenously infusion on the first day + fluorouracil 2600 mg/m^2 intravenously infusion within 24 hours (the infusion of the same total dose of fluorouracil within 48 hours is acceptable) on the first day.

mFLOT drug therapy regimen (the abbreviation was introduced into the study taking into account the transfer of docetaxel to intraperitoneal pressurized aerosol administration): Oxaliplatin 85 mg/m^2 on the first day + Calcium Folinate 200 mg/m^2 within 2 hours intravenously infusion on the first day + fluorouracil 2600 mg/m^2 intravenously infusion within 24 hours (the infusion of the same total dose of fluorouracil within 48 hours is acceptable) on the first day.

HIPEC – Hyperthermic intraperitoneal chemotherapy

PIPAC – Pressurized intraperitoneal aerosol chemotherapy

dPIPAC – Pressurized intraperitoneal aerosol chemotherapy (the abbreviation was introduced into the study taking into account the transfer of docetaxel to intraperitoneal pressurized aerosol administration)

CTCAE – Common Terminology Criteria for Adverse Events

Cy – the designation of the peritoneal lavage cytology

PCI – Peritoneal carcinomatosis index

PAI – Peritoneal adhesion index

PRGS – Peritoneal regress grading score

EORTC – European Organisation for Research and Treatment of Cancer

QLQ – Quality of life questionnaire

IVC – informed voluntary consent

CRF – the case record form

AE – adverse events

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2. The relevance

Gastric cancer takes 5th place in the structure of morbidity and 3rd place in the structure of mortality among all the malignant neoplasms according to global statistics [1]. One of the most common manifestations of the dissemination of gastric cancer is the peritoneal dissemination. Early diagnosis of the peritoneal dissemination is possible using laparoscopy with the cytological examination of the peritoneal lavage [2, 3]. The absence of macroscopic manifestations of peritoneal carcinomatosis does not indicate the absence of tumor cells in the lavage, approximately 10% of patients have free tumor cells [4]. Systemic chemotherapy is the treatment method for the patients of this group. At the same time, the effectiveness of systemic chemotherapy in the disseminated gastric cancer remains low, the frequency of partial regressions does not exceed 25%, and the median survival varies between 8-12 months [5]. The fact remains unchanged that over the past 15 years there have been no significant changes and progress in the treatment of this group of patients and the median progression-free survival is currently 9.7 months (7.2 months in 1999 - 2001) [6]. Subsequently to improve these indicators, a method of intraperitoneal hyperthermic chemotherapy was proposed. So the meta-analysis of randomized trials of HIPEC in gastric cancer published in 2017, summarizing 30 years of experience with this technology, results in the median survival for the disseminated group of only 11.1 months. [7]. Currently, PIPAC is the preferred technique for the intraabdominal treatment of peritoneal metastases; with the introduction of a fine aerosol, a more uniform distribution of the chemotherapy drug is noted, as well as deeper penetration directly into the tumor tissue, compared to conventional intracavitary administration or HIPEC [8, 9]. In clinical trials, the most commonly used drug regimen in most centers identified the combination of cisplatin and doxorubicin, which has shown its advantage in reducing toxicity and improving the quality of life of patients in conjunction with increased survival [10–12]. Currently, the addition of PIPAC to the treatment of patients with oligometastatic peritoneal lesion is becoming an increasingly promising direction to increase resectability, morphological response of the tumor to treatment and overall and disease-free survival [13]. The question of optimal chemotherapy drugs for intraperitoneal use also remains relevant. Given the success of the 3-component FLOT regimen, it is advisable to continue research on the use of taxanes in the intraperitoneal component; such studies are already resonating in the professional community and tend to increase the effectiveness of the treatment of patients with peritoneal carcinomatosis [14]. Docetaxel remains the promising component for pressurized intraperitoneal aerosol chemotherapy because of its slow absorption through the lymphatic system due to its lipophilic structure and large molecular weight; thus the high concentration and long-term effect of the drug in the abdominal cavity is achieved; the absence of the need for augmentation by heating, as well as the absence of local abscess properties is the additional advantage of taxanes [15–17]. Despite encouraging results from the studies on pressurized intraperitoneal aerosol chemotherapy, to determine the optimal drugs for intraperitoneal spraying, to obtain an objective answer to the question of effectiveness, to resolve the issue of reducing the overall toxic effect due to local application, further clinical studies are required.

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3. The purpose and the objectives of the study

The purpose of the study: to research the effectiveness and safety of combined treatment in the first line (courses of polychemotherapy FLOT (3 courses) + mFLOT (3 courses) + dPIPAC using docetaxel) in case of the primary 4 stage gastric cancer with peritoneal carcinomatosis Cy+ and/ or PCI≤15 in comparison with separate therapy polychemotherapy FLOT (6 courses) treatment in the first line.

Research objectives:

1) To develop and implement a method of treating primary 4 stage gastric cancer with peritoneal carcinomatosis Cy+ and/ or PCI≤15 as part of the first line of polychemotherapy according to the schedule FLOT (3 courses) + mFLOT (3 courses) including sessions of pressurized intraperitoneal aerosol chemotherapy using docetaxel (dPIPAC).

2) To standardize the algorithm of administration and dosage of the chemotherapy drug for the dPIPAC session based on the three-component FLOT chemotherapy regimen (mFLOT).

3) To study and evaluate the immediate effectiveness of the first line of polychemotherapy according to the schedule FLOT (3 courses) + mFLOT (3 courses) including sessions of pressurized intraperitoneal aerosol chemotherapy using docetaxel (dPIPAC) of the criteria: median time without progression and overall survival, planned treatment completeness, conversion rate of patients to Cy- and/ or PCI-.

4) To study immediate results of treatment and possible complications of the criteria: frequency and severity of toxic reactions and postoperative complications according to generally accepted criteria CTCAE v5.0 and Clavien-Dindo.

5) To compare the quality of life of patients receiving polychemotherapy according to the schedule FLOT (3 courses) + mFLOT (3 courses) including dPIPAC sessions and polychemotherapy according to the FLOT regime (6 courses) without PIPAC using the scale EORTC QLQ-C30.

4. The study endpoints

Main endpoints:

1) The progression-free survival (the appearance of new metastases (excluding the PCI increase less than 25% of initial evaluation) confirmed histologically and/or according to PET-CT with 18-FDG; the increase in the PCI index by at least 25% of the initial evaluation (for cytological and/or histological verification); obvious progression according to the physician-researcher/ research team. Explanation of the term the progression-free survival – time interval from randomization to progression of disease, death from any cause or date of last observation in the absence of these events. Median progression-free survival is evaluated.

2) Complications from polychemotherapy (including intraperitoneal administration), evaluated according to CTCAE v5.0 (the proportion of patients with any adverse events); the proportion of patients with grade 3-5 adverse events).

Additional endpoints:

1) The overall survival. Explanation of the term the overall survival – time interval from randomization to death from any cause or date of last observation in the absence of these events.

2) The completeness of the planned therapy (the proportion of patients who received all the therapy planned in the study in each group).
3) Quality of life assessment (EORTC QLQ-C30) (the proportion of patients with clinically significant deterioration in quality of life relative to baseline indicators).
4) Percentage of patient conversions to Cy- and/or PCI- rate.
5) Surgical complications of operated patients (the evaluation by Clavien-Dindo classification) (the proportion of patients with surgical complications IIIb-V grade). Note – the evaluation of postoperative complications associated with laparoscopy +/- dPIPAC sessions will be made starting from grade IIIb (inclusive) due to the possible overlap of adverse events of polychemotherapy to be evaluated by CTCAE v.5.0.

5. The study description

5.1 The Research design:

Single-center prospective randomized research-initiated clinical phase II study with superiority design comparing the safety and effectiveness of the first line of polychemotherapy (6 courses of FLOT) and polychemotherapy in combination with PIPAC sessions using intraperitoneal administration of docetaxel (3 courses of FLOT + (3 courses of mFLOT + dPIPAC) in case of the primary gastric 4 stage cancer of the group of peritoneal carcinomatosis Cy+ and/ or PCI≤15. Zero hypothesis is that the medians of progression-free survival do not differ and are 6 months in both groups; the alternative hypothesis is that the median of progression-free survival will be 6 months in the control group and 8.5 months in the study group. The sample size is calculated with the following parameters. The acceptable probability of the first kind error is 5%, that is α=0,05. The probability of the second kind error is taken as 20%, that is β=0,2. The statistical power is 1-β=1-0,2=0,8. Normal distribution critical values corresponding to α=0,05 and 1-β=0,8 - $Z\alpha$ и $Z\beta$ accordingly were taken from normal distribution critical table and were $Z\alpha = Z0,05 = 1,6449$, $Z\beta = Z0,8 = 0,8416$. The clinical effectiveness of the active control method (the group No 1– 6 courses of FLOT) Pc were 36%. The clinical effectiveness of the proposed new treatment method (3 courses of FLOT + 3 courses of mFLOT + dPIPAC) PT were 51%. The border of "no-less effectiveness" was taken 10%, that is δ=0,1. The testable hypotheses: H0 : PT-Pc $\leq$ 0.1, the alternative hypothesis H1 : PT-Pc >0.1. The sample size in each group was calculated according to the formula: $n = (Z\alpha + Z\beta)2 * (Pc * (1-Pc) + PT * (1-PT))/(Pc - PT - \delta)2$. Thus to refute the null hypothesis and confirm the alternative one 53 patients in the control group and 53 patients in the study group must be included in the study, if and when included data is loss 10% of patients. So 106 patients will be included in the study in total. Evaluation of the results based on the criteria specified above. The analysis of the results of the study will be carried out in accordance with standard algorithms of variation statistics using an application package. The analysis will include data from all patients initiating therapy in this study.

5.2 Screening, randomization, stratification

Signing the informed consent to participate in the study. All the patients with suspected peritoneal carcinomatosis (according to the results of radiation diagnostics, as well as confirmed peritoneal carcinomatosis by puncture biopsy or by taking ascitic fluid) undergo diagnostic laparoscopy at the first stage. In addition, screening will include all the patients with locally advanced gastric cancer undergoing laparoscopy prior to planning combination treatment. If they have foci of carcinomatosis in the peritoneum PCI up to 15 inclusive and/or Su+ (as the only manifestation of M1), the patients of this group can be included in the study. The methodology for performing diagnostic laparoscopy is described below (excluding dPIPAC components). Note – the examination of the omental bursa as part of diagnostic laparoscopy is optional, depending on the clinical situation. Screening and examination of patients according to current clinical guidelines for nosology stomach cancer taking into account the examination criteria specified in this protocol. Performing initial diagnostic laparoscopy at the stationary stage according to the standard procedure (described above). If carcinomatosis is detected the evaluation of PCI is carried out by Sugarbaker. The patient randomization based on positive (Cy+) abdominal flushing and/or peritoneal dissemination with PCI index <16. The randomization will be carried out using an Internet resource https://www.sealedenvelope.com. Taking into account the planned set and heterogeneity of the groups, the patients will be stratified before randomization according to the following factors: microscopic carcinomatosis of Cy+ only, macroscopic carcinomatosis PCI up to 7 inclusive, macroscopic carcinomatosis PCI from 8 to 15 inclusive; accordingly, the patients within the strata will be randomized separately.

5.3 The Description of the treatment method

5.3.1 The Control group (the group No 1). Within 1-4 weeks after the initial diagnostic laparoscopy the group No 1 patients start polychemotherapy courses according to the FLOT scheme in the amount of 6 (six); the examination is carried out every 3 courses (after the 3rd and the 6th courses) with the control diagnostic laparoscopy after 6 courses of polychemotherapy for no more than 2 weeks with no obvious signs of progression (in this case, the patient switches to the 2nd line of chemotherapy). The evaluation of the therapeutic pathomorphosis of foci in the peritoneum is carried out according to the PRGS system (Peritoneal Regression Grading Score). As the result of the treatment: in the event of the complete regression of foci along the peritoneum and receiving Cy- in the peritoneal lavage, after the completion of the planned treatment, the patients switch to the dynamic observation or cytoreductive surgery is considered within 1 month after the completion of polychemotherapy (optionally, by decision of the local council); in case of the incomplete response (due to the immeasurable characteristics of the tumor and the impossibility of evaluation by RECIST), the dynamic observation is carried out until progression; in case of progression the 2nd line of chemotherapy (the scheme at the discretion of the attending physician) or the optimal palliative care options depending on the clinical situation is considered; accordingly the patient completes the therapy proposed by the study. The response criteria are specified separately. Shifting the timing of chemotherapy up to 10 days and the timing of control examinations up to 10 days due to objective circumstances is considered acceptable within the study.

5.3.2 The Study group (the group No 2). Within 1-4 weeks after the initial diagnostic laparoscopy the group No 2 patients start polychemotherapy courses according to the scheme FLOT (the 1st , the 3rd, the 5th courses) and mFLOT (the 2nd, the 4th, the 6th courses) in the amount of 6 (six, 3+3); the examination is carried out every 3 courses (after the 3rd and the 6th courses) with with dPIPAC sessions using docetaxel the examination is carried out every 3 courses (after the 3rd and 6th) with the performance of dPIPAC sessions using docetaxel (thus excluding it from the system administration) in

the 2nd , the 4th, the 6th courses of polychemotherapy (all the procedures are performed according to the method described in the protocol; the evaluation of the therapeutic pathomorphosis of lesions in the peritoneum is carried out according to the PRGS system (Peritoneal Regression Grading Score)). Control diagnostic laparoscopy is not performed in the group No 2, its function is performed by the revision at the PIPAC session of the 6th course of polychemotherapy, which corresponds to the time interval of the group No 1. As the result of the treatment: in the event of the complete regression of foci along the peritoneum and receiving Cy- in the peritoneal lavage, after the completion of the planned treatment, the patients switch to the dynamic observation or cytoreductive surgery is considered after the completion of polychemotherapy (optionally, by decision of the local council); in case of the incomplete response (due to the immeasurable characteristics of the tumor and the impossibility of evaluation by RECIST), the dynamic observation is carried out until progression; in case of progression the 2nd line of chemotherapy (the scheme at the discretion of the attending physician) or the optimal palliative care options depending on the clinical situation is considered; accordingly the patient completes the therapy proposed by the study. The method of performing the surgical manual is specified separately. The response criteria are specified separately. Shifting the timing of chemotherapy with dPIPAC sessions up to 10 days and the timing of control examinations up to 10 days due to objective circumstances is considered acceptable within the study.

5.3.3 The brief synopsis of the study:

After the initial diagnostic laparoscopy the Control group patients undergo 6 courses of polychemotherapy according to the FLOT scheme; the examination is carried out every 3 courses (after the 3rd and the 6th courses) with the control diagnostic laparoscopy after 6 courses of polychemotherapy. In the event of the complete regression of foci along the peritoneum and receiving Cy- in the peritoneal lavage, the dynamic observation or cytoreductive surgery is considered (optionally); in case of the incomplete response the dynamic observation is carried out until progression; in case of progression the 2nd line of chemotherapy or the optimal palliative care options depending on the clinical situation is considered.

After the initial diagnostic laparoscopy the Study group patients undergo courses of polychemotherapy according to the scheme FLOT (the 1st, the 3rd, the 5th courses) and mFLOT (the 2nd , the 4th, the 6th courses) in the amount of 6 (six, 3+3); the examination is carried out every 3 courses (after the 3rd and the 6th courses) with dPIPAC sessions using docetaxel (thus excluding it from the system administration) in the 2nd , the 4th, the 6th courses of polychemotherapy. Control diagnostic laparoscopy is not performed in the group No 2, its function is performed by the revision at the PIPAC session of the 6th course of polychemotherapy, which corresponds to the time interval of the Control group. In the event of the complete regression of foci along the peritoneum and receiving Cy- in the peritoneal lavage, the dynamic observation or cytoreductive surgery is considered (optionally); in case of the incomplete response the dynamic observation is carried out until progression; in case of progression the 2nd line of chemotherapy or the optimal palliative care options depending on the clinical situation is considered.

6. Characteristics of the studied patients

6.1 Survey scope:

1) Clinical blood tests (general and biochemical) and urine, coagulogram (no more than 10 days by the date of screening)

2) CT scan of the chest, abdominal cavity with intravenous contrast (no more than 1.5 months by the date of screening)
3) Ultrasound (or CT) of the pelvic organs and peripheral lymph nodes (supraclavicular group) – availability is optional (no more than 1.5 months by the date of screening)
4) FGDS with biopsy (no more than 2 months by the date of screening)
5) Histological examination in the Joint pathoanatomical department of the State budgetary healthcare institution of Nizhny Novgorod region "Nizhny Novgorod Regional Clinical Oncological Dispensary" либо предоставление архивного материала для гистологического исследования (no more than 2 months by the date of screening)
6) HER2neu expression research (CISH performing with 2+ result HER2neu) (no more than 2 months by the date of screening)
7) Laparoscopy with cytological examination of abdominal lavage (standard), cytological prints from the serous membrane and lymph node biopsy (optional) (no more than 2 months by the date of screening)
8) PET-CT with 18-FDG and intravenous contrast (optional – if necessary, differentiate extra organic lessions that are doubtful about metastasis) (no more than 2 months by the date of screening; availability is optional)

6.2 The Primary Diagnosis – it is planned to include patients with primary gastric cancer with peritoneal carcinomatosis, taking into account the following criteria**:**

6.3 **Inclusion criteria:**

1) Availability of the signed informed voluntary consent of the patient
2) Age ≥18 years old and ≤75 years old
3) ECOG ≤1
4) Histological verification of gastric cancer and esophageal-gastric junction Siewert III (adenocarcinoma, cricoid cell carcinoma)
5) Her2neu negative tumor status
6) Availability of the preserved informative block of the primary tumor in the histological archive (biopsy and/or providing archival material - with the consent of the patient) of the State budgetary healthcare institution of Nizhny Novgorod region "Nizhny Novgorod Regional Clinical Oncological Dispensary"
7) Verified gastric cancer (adenocarcinoma, cricoid cell carcinoma) with the presence of M1 (with the single manifestation of M1 in the form of – Cy + in the initial peritoneal lavage and/or peritoneal dissemination PCI <16)
8) Peritoneal adhesion index PAI <16
9) Absence of active infectious, mental diseases, severe allergic conditions, as well as other comorbidities that may interfere with the therapeutic and diagnostic measures provided for by the protocol
10) Adequate organ function (evaluation by laboratory indicators at screening – evaluation of hemoglobin, neutrophils, platelets, ALT, AST, total bilirubin, urea, creatinine)
11) The consent of men and women with saved childbearing potential to use highly effective methods of contraception.

6.4 **Exclusion criteria:**

1) Lack of the informed voluntary consent of the patient
2) Age <18 years old and >75 years old
3) ECOG ≥2
4) Histological types other than adenocarcinoma and ring cell gastric carcinoma and oesophageal-gastric junction (Siewert III)
5) Her2neu positive tumor status

6) The absence of the preserved informative block of the primary tumor in the histological archive of the State budgetary healthcare institution of Nizhny Novgorod region "Nizhny Novgorod Regional Clinical Oncological Dispensary"
7) M1 except for Cy+ in the initial peritoneal lavage and/or and/or peritoneal dissemination PCI <16 (Distant metastases, including metastases to the supraclavicular, mediastinal, paraaortic lymph nodes (collector 16), metastases to the ovaries. Note – metastases to peripheral lymph nodes require fine needle biopsy with cytological examination for verification. In metastatic lesions of intracorporeal lymph nodes the criteria for metastases will be sizes larger than 15 mm along the short axis or and metastatic altered lymph node structure regardless of size; PCI ≥16)
8) Peritoneal adhesion index PAI ≥16
9) Contraindications to performing diagnostic laparoscopy
10) Complicated primary tumor (bleeding, decompensated stenosis, dysphagia III-IV) if complications were not corrugated.
11) Decompensated comorbidity
12) Primary multiple tumors (except basal cell skin cancer and cervical cancer in situ – provided there is no evidence of a relapse)
13) Any specific anti-tumor for gastric cancer and/ and/or other malignant tumor in in history (except basal cell skin cancer and cervical cancer in situ – provided there is no evidence of a relapse)
14) Previous specialized treatment for gastric cancer
15) Known individual intolerance to the drugs included in the protocol
16) Pregnancy, breastfeeding

6.5 **Research conclusion criteria:**

1) Unacceptable toxicity (≥ grade 4 by CTCAE v.5.0) (adverse events, laboratory abnormalities or comorbid conditions that according to the researchers make further therapy of the subject impossible, dangerous or impossible for the purposes of ensuring the welfare or safety of the subject)

2) Complications of the surgical component ≥ IV grade by Clavien-Dindo

3) Withdrawal of the informed voluntary consent of the patient

4) Obvious progression of the disease according to the research team

5) Pregnancy

6) Violation of compliance

7. The description of standard research procedures and data evaluation techniques

7.1 The description of the standard course of polychemotherapy according to the FLOT regime (FLOT 6 courses; FLOT 3 courses):

The informed voluntary consent to polychemotherapy. Premedication (omeprazole, dexamethasone, chloropyramine hydrochloride, ondansetron, nutritional support optional). FLOT regimen: Docetaxel 50 mg/m^2 intravenously drip on the first day + Oxaliplatin 85 mg/m^2 on the first day + Calcium Folinate 200 mg/m^2 within 2 hours intravenously infusion on the first day + fluorouracil 2600 mg/m^2 intravenously infusion within 24 hours (the infusion of the same total dose of fluorouracil within 48

hours is acceptable) on the first day. Postmedication (omeprazole, dexamethasone, colony-stimulating factors № 3-5). Repeat every 2 weeks. 6 courses.

7.2 The description of the course of polychemotherapy according to the mFLOT regime (the abbreviation was introduced into the study taking into account the transfer of docetaxel to intraperitoneal pressurized aerosol administration) (in the study group at the 2nd, 4th, 6th courses when using docetaxel in PIPAC):

The informed voluntary consent to polychemotherapy. Premedication (omeprazole, dexamethasone, chloropyramine hydrochloride, ondansetron, nutritional support optional). mFLOT regimen: Oxaliplatin 85 mg/m^2 on the first day + Calcium Folinate 200 mg/m^2 within 2 hours intravenously infusion on the first day + fluorouracil 2600 mg/m^2 intravenously infusion within 24 hours (the infusion of the same total dose of fluorouracil within 48 hours is acceptable) on the first day. Postmedication (omeprazole, dexamethasone, colony-stimulating factors № 3-5).

7.3 The description of the standard diagnostic laparoscopy procedure and the session of PIPAC (dPIPAC):

Required equipment used: The procedure will be carried out using a laparoscopic stand, an angiographic injector and the patented device for intracavity and intraorgan administration of drugs in the form of an aerosol «Mechanical nozzle» manufactured by «OTDEL INNOVATSIY» LLC (Russia).

The informed voluntary consent to for the surgery. The informed voluntary consent to polychemotherapy. Premedication – Enoxaparini 0.4 subcutaneously 12 hours before the surgery, Cefazolini 2 gr intravenously 30 minutes before the surgery. Preparation of the injector system. Connecting the syringe flask to the infusor, venting air from the syringe flask, taking the chemotherapy solution for spraying, connecting the syringe flask to the high pressure line connected to the nozzle. Access to the abdominal cavity by Hassen (3 trocars - paraumbilical the 1st (12mm), right and left mesogastric area the 2nd (12mm) and the 3rd (5mm). Carboxyperitoneum – 12 mm of water column – stable pressure maintenance throughout the operation. Additional sealing by stitching and laying wet gauze wipes on the area of the installed ports. Revision. Photo recording of 4 quadrants of the abdominal cavity from the paraumbilical port: 1 – right upper quadrant, 2 – left upper quadrant, 3 - left lower quadrant, 4 - right lower quadrant (the storage and safety of the photo protocol is provided by Klimin Sergey Andreevich, the responsible executor of the protocol). In the presence of ascites – the complete evacuation with the volume measurement and cytological examination. The evaluation of the PCI index. The evaluation of other distant dissemination. Standard peritoneal lavage of 300 ml Sol. NaCl 0.9 % (37 ºC), with the exposure of 3-5 minutes (with Trendelenburg and Fowler position alternately) and the lavage aspiration, the transfer of the lavage for the cytological examination (the material is delivered to the laboratory immediately , no more than 15 minutes). The pinch biopsy of the lesions suspicious for dissemination in the peritoneum. The separate transfer for the cytological and histological examination (indicating the localization of the biopsy according to the classification of zones by PCI), including the assessment of therapeutic pathomorphosis (by the PRGS classification) when the patient is pretreated and repeated dPIPAC sessions are performed. The drugs for PIPAC – Docetaxel 50 mg/ m^2 diluted with saline sodium chloride to a total volume of 200 ml. The description of the PIPAC session. The laparoscope is in the first trocar of 12 mm, the nozzle is in the second trocar of 12 mm. The nozzle and torch must be visually controlled during the entire manipulation. It is

necessary to fix the laparoscope and the nozzle with clamps to the surgical linen. The direction of the spray torch is the parietal peritoneum. The rate of administration is 30 ml per minute. The maximum pressure in the injector system is 250 PSI. During manipulation, the constant visual control is required. After the spray stage, the exposure is 30 minutes while maintaining the declared intraperitoneal pressure. After the exposure stage, only gas is removed from the abdominal cavity. The routine installation of the trap drains is not required except in cases of massive ascites or other reasons requiring the installation of drainage. The operation is completed as standard with the extraction of laparoports and suturing of laparoport wounds. Postmedication: Omeprazoli 40 mg one time per day orally or intravenously (n=3) + Paracetamoli 100 ml one time per day intravenously (n=3) + Cefazolini 2 gr one time per day intravenously (n=3) + intravenous infusion of Natrii Chloridi 0.9 % at the rate of 25ml/kg of the patient's body weight one time per day (n=3), sufficient volume of liquid received per os (at least 1500 ml per day). The control of daily diuresis for 3 days with stimulation by loop diuretics (intravenously or orally) when clinically necessary. The control of the general blood test and the biochemical blood test for the 1st and the 3rd days. Discharge from the hospital on the 3rd day at the scheduled course of hospitalization.

7.4 The assessment of the objective response after 3 and 6 courses of polychemotherapy:

The full response: the disappearance of all the manifestations of the disease according to the computed tomography (+ laparoscopy after the 6th course) (the group No 1) or computed tomography (+ laparoscopy with dPIPAC sessions) (the group No 2);

The uncomplete response (given the immeasurable tumor, partial response criteria and stabilization criteria are not applicable): the situations that do not correspond to the full response, the progression of the disease.

The progression of the disease (one or more criteria):

- the appearance of new metastases (excluding the PCI increase less than 25 % of initial evaluation) confirmed histologically and/or according to PET-CT with 18-FDG;
- the increase in the PCI index by at least 25 % of the initial evaluation (for cytological and/or histological verification);
- obvious progression according to the physician-researcher/ research team.

Notes (The Table “Response interpretation”. See Paragraph 11. Notes. The Table No 1):

1) Given the different number of visual assessments of the abdominal cavity (laparoscopy) in both groups and the absence of the need to artificially increase the number of diagnostic laparoscopies in the control group – in the absence of the clinical symptoms of the disease progression, the visual data of negative dynamics will not be regarded as the disease progression.
2) The RECIST criteria are not applicable given the immeasurable tumor.

7.5 The changes in the peritoneal index of carcinomatosis:

- The full response for peritoneal carcinomatosis. PCI is 0 or negative for two (optionally) biopsies (cytological and (if feasible) histological), the negative peritoneal lavage (Cy-)
- The partial response for peritoneal carcinomatosis. The decrease the PCI index by at least 25% of the initial evaluation.

- The stabilization of the process for peritoneal carcinomatosis. Все виды ответа, при которых нельзя говорить ни о частичном ответе, ни о прогрессировании заболевания (в соответствии с указанными выше критериями).
- The progression for peritoneal carcinomatosis. The increase in the PCI index by at least 25 % of the initial evaluation (for cytological and/or histological verification).

Note:

1) The evaluation of PCI is carried out by Sugarbaker.

2) The Table "Response interpretation". See Paragraph 11. Notes. The Table No 1.

7.6 The evaluation of adverse events:

All the adverse events that occur during the clinical trial (that is, from the moment the patient signs the informed consent) must be identified and documented (by the CTCAE v.5.0 classification, additionally for the postoperative patients – by Clavien-Dindo scale). Note – the evaluation of postoperative complications associated with laparoscopy +/- dPIPAC sessions will be made starting from grade IIIb (inclusive) due to the possible overlap of adverse events of polychemotherapy to be evaluated by CTCAE v.5.0.

An adverse event is any clinically unfavorable event that occurs in a patient included in a clinical trial and receiving treatment, whether or not it is recognized as being related to the use of that treatment technique.

A serious adverse event is any adverse event that results in death, an immediate life-threatening condition, permanent or significant impairment or incapacity, hospitalization of the patient or prolongation of hospitalization, or is considered serious for any other reason that reflects a significant risk to the condition of patient health, comparable to the above situations.

All adverse events, both serious and not related to this category, must be documented in detail in the relevant sections of the CRF. For each adverse event, the reseacher must report the start date, duration, intensity, treatment required, outcome and actions taken in relation to the treatment method under study.

7.7 The morphological response of lesions in the peritoneum will be assessed using the PRGS system (Peritoneal Regression Grading Score):

PRGS 1 – There are no tumor cells. Profuse fibrosis and/or acellular mucus lakes and/or infarct-like necrosis.

PRGS 2 – Regressive changes prevail over tumor cells. Foci of fibrosis and/or acellular mucin and/or infarct-like necrosis overlying tumor cells.

PRGS 3 – The predominance of tumor cells. Tumor cells predominate over fibrosis and/or acellular mucin lakes and/or infarct-like necrosis. There are no regressive changes.

PRGS 4 – Massive growth of tumor cells (visible at minimum magnification). Tumor cells predominate over fibrosis and/or acellular mucin lakes and/or infarct-like necrosis. There are no regressive changes.

Note (applies to the entire protocol). The lesion is considered metastatic in the case of the histologically positive and cytologically negative result of the peritoneal biopsy, as well as in the case of the histologically negative and cytologically positive result of the peritoneal biopsy.

8. The Schedule of visits

Signing the informed consent to participate in the study

VISIT No 1. Screening (within 14 days of the initial diagnostic laparoscopy)

Screening is carried out when patients have objective evidence of the presence of peritoneal carcinomatosis after diagnosis.

1. Obtaining the written consent before performing any of the procedures necessary to include the patient in the study;

2. Checking of the required patient inclusion/exclusion criteria, the registration of the results on the provided page of CRF;

3. The general examination (with the examination and palpation of peripheral lymph nodes - supraclavicular, axillary, inguinal);

4. The assessment of vital parameters (heart rate, blood pressure, temperature);

5. The anthropometric indicators (height, weight);

6. The general clinical blood test (hemoglobin, neutrophils, platelets) and urine (-10-0 days);

7. The biochemical blood test (ALT, AST, total bilirubin, urea, creatinine) (-10-0 days);

8. The coagulogram (international normalised ratio, fibrinogen, clotting time, bleeding time, prothrombin index) (-15-0 days);

9. The terapist's advisory opinion (-30-0 days);

10. The electrocardiogram (-60-0 days);

11. The esophagogastroduodenoscopy, the tumor biopsy (no time limit);

12. The pathological examination of biopsy material, performing the immunohistochemical study (HER2neu status, CISH if required). If there is no study by the date of screening, it may be performed by the date of randomization. At HER2neu positive status, the patient is excluded from the study.

13. In the presence of an ascitic fluid, a puncture is performed followed by cytological and/or immunocytochemical (optionally) examination (it is carried out during the initial diagnostic laparoscopy)**;**

14. The computed tomography of thoracic and abdominal organs with intravenous contrast (-60-0 days);

15. The quality of life (EORTC QLQ-C30);

16. The registration of all the adverse events that occurred after signing the informed consent.

Note – <u>The quality of life assessment by EORTC QLQ-C30.</u> It is planned:

1) Before the treatment based on diagnostic laparoscopy and randomization (the ^{1st} survey)
2) Before starting each course of the treatment (the 2^{nd} – 7^{th} visits)

3) After finishing the treatment (10th visit)
4) Follow-up visits

VISIT No 2. Patient randomization when included in the study (within 14 days of the initial diagnostic laparoscopy, not earlier than the day after screening)

1. The general examination (with the examination and palpation of peripheral lymph nodes - supraclavicular, axillary, inguinal);

2. The assessment of vital parameters (heart rate, blood pressure, temperature);

3. The general clinical blood test (hemoglobin, neutrophils, platelets) and urine (-10-0 days);

4. The biochemical blood test (ALT, AST, total bilirubin, urea, creatinine) (-10-0 days);

The group No 1 (control) – VISITS NoNo 3 – 8 (on the first day of the 1st – 6th courses of chemotherapy

1. The general examination (with the examination and palpation of peripheral lymph nodes - supraclavicular, axillary, inguinal);

2. The assessment of vital parameters (heart rate, blood pressure, temperature);

3. The general clinical blood test (hemoglobin, neutrophils, platelets) and urine (-10-0 days);

4. The biochemical blood test (ALT, AST, total bilirubin, urea, creatinine) (-15-0 days);

5. The coagulogram (international normalised ratio, fibrinogen, clotting time, bleeding time, prothrombin index) (-15-0 days);

6. Blood electrolytes (K, Na, Cl) (-15-0 days);

7. The terapist's advisory opinion (-30-0 days), the ENT doctor's advisory opinion (once before the 1st course) (-30-0 days), the neurologist's advisory opinion (once before the 1st course) (-30-0 days);

8. The quality of life (EORTC QLQ-C30);

9. The adverse events registration.

The group No 2 (study) – VISITS NoNo 3, 5, 7 (on the first day of the 1st, 3rd, 5th courses of chemotherapy

1. The general examination (with the examination and palpation of peripheral lymph nodes - supraclavicular, axillary, inguinal);

2. The assessment of vital parameters (heart rate, blood pressure, temperature);

3. The general clinical blood test (hemoglobin, neutrophils, platelets) and urine (-10-0 days);

4. The biochemical blood test (ALT, AST, total bilirubin, urea, creatinine) (-15-0 days);

5. The coagulogram (international normalised ratio, fibrinogen, clotting time, bleeding time, prothrombin index) (-15-0 days);

6. Blood electrolytes (K, Na, Cl) (-15-0 days);

7. The terapist's advisory opinion (-60-0 days), the ENT doctor's advisory opinion (once before the 1st course) (-60-0 days), the neurologist's advisory opinion (once before the 1st course) (-60-0 days);

8. The quality of life (EORTC QLQ-C30);

9. The adverse events registration.

The group No 2 (study) – VISITS NoNo 4, 6, 8 (on the first day of the 2nd, 4th, 6th courses of chemotherapy+ PIPAC)

1. The general examination (with the examination and palpation of peripheral lymph nodes - supraclavicular, axillary, inguinal);

2. The assessment of vital parameters (heart rate, blood pressure, temperature);

3. The general clinical blood test (hemoglobin, neutrophils, platelets) and urine (-10-0 days);

4. The biochemical blood test (ALT, AST, total bilirubin, urea, creatinine) (-15-0 days);

5. The coagulogram (international normalised ratio, fibrinogen, clotting time, bleeding time, prothrombin index) (-15-0 days);

6. Blood electrolytes (K, Na, Cl) (-15-0 days);

7. The echocardiography (once before the 1st PIPAC session) (-90-0 days);

8. The ultrasound dopplerography of the veins of the lower extremities (once before the 1st PIPAC session) (-90-0 days);

9. The terapist's advisory opinion (-60-0 days), the ENT doctor's advisory opinion (once before the 1st course) (-30-0 days), the neurologist's advisory opinion (once before the 1st course) (-30-0 days);

10. The quality of life (EORTC QLQ-C30);

11. The adverse events registration.

The group No 1 (control) – VISIT No 9 (on the day of control diagnostic laparoscopy (before surgery))

1. The general examination (with the examination and palpation of peripheral lymph nodes - supraclavicular, axillary, inguinal);

2. The assessment of vital parameters (heart rate, blood pressure, temperature);

3. The general clinical blood test (hemoglobin, neutrophils, platelets) and urine (-10-0 days);

4. The biochemical blood test (ALT, AST, total bilirubin, urea, creatinine) (-15-0 days);

5. The coagulogram (international normalised ratio, fibrinogen, clotting time, bleeding time, prothrombin index) (-15-0 days);

6. The echocardiography (-90-0 days);

7. The ultrasound dopplerography of the veins of the lower extremities (-90-0 days);

8. The quality of life (EORTC QLQ-C30);

9. The adverse events registration.

The group No 2 (study) – VISIT No 9 is not required

VISIT No 10. After 3 courses of the therapy in both groups (± 2 weeks)

1. The general examination (with the examination and palpation of peripheral lymph nodes - supraclavicular, axillary, inguinal);

2. The assessment of vital parameters (heart rate, blood pressure, temperature);

3. The anthropometric indicators (height, weight);

4. The general clinical blood test (hemoglobin, neutrophils, platelets) and urine (-10-0 days);

5. The biochemical blood test (ALT, AST, total bilirubin, urea, creatinine) (-15-0 days);

6. The coagulogram (international normalised ratio, fibrinogen, clotting time, bleeding time, prothrombin index) (-15-0 days);

7. The esophagogastroduodenoscopy, the tumor biopsy (-30-0 days);

8. The pathological examination of biopsy material (the assessment of the therapeutic pathomorphosis);

9. The computed tomography of thoracic and abdominal organs with intravenous contrast (-45-0 days)

10. The quality of life (EORTC QLQ-C30);

11. The registration of all the adverse events that occurred after signing the informed consent.

VISIT No 11. After 6 courses of the therapy in both groups – upon completion of all the planned therapy (± 2 weeks)

1. The general examination (with the examination and palpation of peripheral lymph nodes - supraclavicular, axillary, inguinal);

2. The assessment of vital parameters (heart rate, blood pressure, temperature);

3. The anthropometric indicators (height, weight);

4. The general clinical blood test (hemoglobin, neutrophils, platelets) and urine (-10-0 days);

5. The biochemical blood test (ALT, AST, total bilirubin, urea, creatinine) (-15-0 days);

6. The coagulogram (international normalised ratio, fibrinogen, clotting time, bleeding time, prothrombin index) (-15-0 days);

7. The esophagogastroduodenoscopy, the tumor biopsy (-30-0 days);

8. The pathological examination of biopsy material (the assessment of the therapeutic pathomorphosis);

9. The computed tomography of thoracic and abdominal organs with intravenous contrast (-45-0 days)

10. The quality of life (EORTC QLQ-C30);

11. The registration of all the adverse events that occurred after signing the informed consent.

VISIT No 12 and following steps. OBSERVATION VISIT (every 8 weeks ± 2 weeks during the first year after finishing the ***treatment and then 1 time every 16 ± 2 weeks). NOTE. When a patient leaves the study, the phone calls are made with the same frequency as observation visits to clarify the necessary data about the life and health of the patient.***

NOTE. The duration of the follow-up visit period is 3 years from the start of treatment (the 1st course of polychemotherapy). The occurrence of the event is a fatal outcome from any cause. The censorship in the case of absence of connection with the patient, the censor – the date of the last contact with the patient.

1. The general examination (with the examination and palpation of peripheral lymph nodes - supraclavicular, axillary, inguinal);

2. The assessment of vital parameters (heart rate, blood pressure, temperature);

3. The anthropometric indicators (height, weight);

4. The general clinical blood test (hemoglobin, neutrophils, platelets) and urine (-10-0 days);

5. The biochemical blood test (ALT, AST, total bilirubin, urea, creatinine) (-15-0 days);

6. The esophagogastroduodenoscopy, the tumor biopsy (optionally) (-45-0 days);

7. The pathological examination of the biopsy material (the assessment of the therapeutic pathomorphosis – only if the esophagogastroduodenoscopy with the tumor biopsy is repeated) (optionally);

9. The computed tomography of thoracic and abdominal organs with intravenous contrast (-45-0 days);

10. The registration of all the adverse events that occurred after signing the informed consent;

11. The quality of life (EORTC QLQ-C30).

9. Withdrawal of patients from the study

The patients have the right to withdraw the consent at any time and stop participating in the study without prejudice to further treatment. The patient's participation in the study may be terminated at any time by the decision of the researcher. In case of discontinuation of the therapy for reasons not

related to the progression of the disease, the patient is invited to continue observation in the framework of this clinical study.

Possible reasons for the discontinuation of the patient's participation in the study by the decision of the researcher:

- Contraindication to chemotherapy in this patient.
- Diagnosis of the concomitant disease that does not allow to continue participating in the study.
- The patient refusal to continue the participation in the study.
- The intolerable adverse events that may or may not be related to the ongoing study.
- The decision of the local council to perform the cytoreductive surgery in the patient before the completion of the intended treatment.
- Progression of the disease according to the research team. At the same time, the growth and appearance of new lesions in the peritoneum, detected during the control laparoscopy in the PIPAC group in the absence of other signs of the disease progression (the computed tomography, esophagogastroduodenoscopy, clinically significant accumulation of ascites) outside the above criteria for peritoneal progression, will not be considered a reason for withdrawal from the study. In this case, the patient continues to be observed in order to obtain data on overall survival.
- Any other reasons according to the researcher

If the patient decides to discontinue participation in the study, the attending physician fill in the section "Completion of the Study / Premature termination of participation" of the CRF with an indication of the reason for the withdrawal.

Note. In case of withdrawal of the patient from the study, the researcher may make periodic phone calls, with the consent of the patient, to clarify the patient's health condition.

10. Recording of the study

10.1 The documentation (CRF and IVC):

Prior to participation in this study, the written informed consent must be obtained from each patient, drawn up in accordance with the requirements of state regulatory authorities and the legal norms of the Russian Federation. Each signature must be dated by the signer. Each informed consent and all the additional information for the patient should be kept by the researcher as the part of the study documentation. A signed copy of the informed consent and all the additional information intended for the patient must be given to the patient. The patient should be informed that clinical trial quality assurance auditors and regulatory inspectors may review his medical records. If the protocol is amended, it may be necessary to revise the patient consent form and the Patient Information accordingly. It is the reseacher's responsibility to ensure that the modified consent form is reviewed by the ethics committee, that approval is obtained, and, if necessary, that the modified consent form is signed by all patients who will be included in the study or already included in it.

The Case Record form (**CRF**) for each patient will be kept by the researcher as the official document. CRFs are used to record clinical study data. They are an integral part of this study and subsequent reports on its results. The primary documentation is the evidence of the reality of the existence of a particular patient and confirms the reliability of the data obtained. The primary documentation is filled in at the research center.

The primary documentation should contain the following data, which are recorded in the CRF:

- patient identification data (initials, sex, date of birth);
- indications of the participation in the study (the study number, the patient number, the date of the informed consent);
- patient visit dates;
- the medical history (history of life, diseases, clinical diagnosis);
- the information about the previous treatment;
- the adverse event information (the start date, duration, intensity, treatment required, outcome and actions taken in relation to the treatment method under study);
- the serious adverse event information (the start date, duration, intensity, treatment required, outcome and actions taken in relation to the treatment method under study);
- originals or copies of laboratory test results;
- originals or copies of X-ray or ultrasound data, endoscopic examinations and histoprotocol, results of electrophysiological functional studies;
- conclusion on the results of the patient's participation in this study.

The Information about the study for the patient includes: the description of the study, the risks and inconveniences caused by the participation in the study, the benefits of participating in the study, the voluntariness and confidentiality of the study.

10.2 The ethical issues:

The clinical study materials are submitted to the local ethical committee. The clinical study will be conducted in accordance with the Protocol approved by the Ethics Committee. All the amendments to the Protocol and Patient Information will be submitted to the Ethics Committee for approval. Informed consent will be obtained from the prospective study participants prior to the study. The Patient Information will contain all the information about the planned clinical study. The rights, safety, and well-being of research participants will be a priority and prevail over the interests of science and society. If necessary, the information on the procedure for obtaining informed consent from the volunteer patients can be submitted to the ethical committee. The confidentiality of the volunteer patients information and research results will be respected. The researchers will be familiarized with the study materials in advance of its start. The qualifications of the researchers will meet the requirements for quality clinical trials. The patient is informed in detail of the treatment to be provided, the possible side effects and complications, The patient is informed in detail of the treatment to be provided, the possible side effects and complications, the expected effectiveness based on the results of the previous studies, as well as about his or her participation in the study.

10.3 The study timeline:

The research planning, the meeting of the Local Ethics Committee – 2023

Patient recruitment – 2023-2026

Preliminary analysis will be carried out upon the recruitment of 50 (+/-5) patients.

The duration of the follow-up visit period is 3 years from the start of treatment (the 1st course of polychemotherapy). The occurrence of the event is a fatal outcome from any cause. The censorship in the case of absence of connection with the patient, the censor – the date of the last contact with the patient.