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The results of personificated ovarian cancer patients with peritoneal carcinomatosis treatment

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The objective: **to analyse of the experience of cytoreductive surgery using and hypenermic intraperitoneal chemperfusion (HIPEC) in patients with ovarian cancer IIIC stage, as well as overall and relapse-free survival in such patients.**
***Materials and methods*. 119 patients with ovarian cancer of the IIIC stage were involved into the study from 2013 to 2020 and they were treated at the University Clinic of Odessa National Medical University. Patients were divided into two groups: the clinical control group (n=53) included persons after suboptimal cytoreduction; the patients of the main group (n=66) had optimal or complete cytoreduction, and in some cases with subsequent intraoperative hyperthermic intraperitoneal chemotherapy.**
During the initial analysis of these groups, time (preoperative period, duration of surgery, number of postoperative bed-days), as well as the presence of complications in the postoperative period were determined.
***Results*. In the main group there was an increase operation time due to large surgery volumes and the implementation of the HIPEC procedure with primary cytoreduction (p=0.001). In the postoperative period, an increase in the number of bed-days in the hospital in patients of the main group in relation to the control group was established, especially in those who had HIPEC (p=0.001). There was an increase in the number of surgical complications of class III-IV according to the Clavien-Dindo classification (from 5 % to 22.2 %) in patients after HIPEC.**
An increase in relapse-free survival from 10 months in the control group to 13-19 months in the main group was revealed. The recurrence median in the postoperative period in the control group was 10±1.3 months, and after interval cytoreduction and primary cytoreduction with HIPEC – 13±1.5 and 19±6.3 months, respectively. The index of relapse-free survival in the first 6 months in the control group was 63.2 %, in patients after optimal or complete cytoreduction – 88.0 %, in patients after optimal or complete cytoreduction and HIPEC – 90.4 %. One-year recurrence-free survival rate was 37.5 %, 63.2 % and 60.1 %, respectively, the average values of overall survival – 27.7±4.1 months versus 24.5±1.8 and 24.1±2.2 months, respectively.
***Conclusions*. Cytoreductive surgery and methods of intraoperative hyperthermic intraperitoneal chemotherapy are perspective options of treatment of patients with peritoneal carcinomatosis by ovarian cancer regarding recurrence of the disease and survival, although they are accompanied by more postoperative complications and number of bed-days in hospital.**
Keywords: *ovarian cancer, carcinomatosis, treatment, hyperthermic intraoperative intrperitoneal chemotherapy, cytoreduction.*

Результати персоніфікованого лікування раку яєчників у хворих з карциноматозом очеревини

А.І. Рибін

Мета дослідження: аналіз досвіду використання на практиці технології циторедуктивної хірургії та гіпертермічної інтраопераційної внутрішньочеревної хіміотерапії *(hyperthermic intraperitoneal chemoperfusion – HIPEC)* у хворих із раком яєчника IIIC стадії, а також загальної та безрецидивної виживаності у даних пацієнток.
Матеріали та методи. З 2013 до 2020 року включно проведено обстеження 119 хворих із раком яєчника IIIC стадії, які знаходились на лікуванні в Університетській клініці Одеського національного медичного університету. Пацієнтки були розподілені на дві групи: до групи клінічного контролю (n=53) увійшли особи, які зазнали субоптимальної циторедукції; пацієнткам основної групи (n=66) проводили оптимальний або повний об'єм циторедукції, а в окремих випадках – з подальшою інтраопераційною гіпертермічною внутрішньочеревною хіміотерапією.
Під час первинного аналізу даних цих груп ураховували часові показники (передопераційний період, тривалість операції, кількість післяопераційних ліжко-днів), а також наявність і характер ускладнень у післяопераційний період.
Результати. В основній групі відзначено збільшення часу операцій за рахунок великих операційних об'ємів та впровадження процедури HIPEC при первинній циторедукції (p=0,001). У післяопераційний період встановлено збільшення кількості ліжко-днів перебування у стаціонарі у пацієнток основної групи стосовно групи контролю, особливо у тих, яким проведено HIPEC (p=0,001). У хворих, яким проведено HIPEC, відзначено збільшення кількості ускладнень III-IV класу за класифікацією Clavien–Dindo (з 5 % до 22,2 %).
Виявлено збільшення безрецидивної виживаності з 10 міс у контрольній групі до 13–19 міс в основній групі. Медіана рецидиву у післяопераційний період у контрольній групі становила 10±1,3 місяця, а після інтервальної циторедукції та первинної циторедукції з HIPEC – 13±1,5 та 19±6,3 місяця відповідно.
Показник безрецидивної виживаності у перші 6 міс у контрольній групі становив 63,2 %, у пацієнток після оптимальної або повної циторедукції – 88,0 %, у хворих після оптимальної або повної циторедукції та HIPEC – 90,4 %. Річна безре-

цидивна виживаність становила 37,5 %, 63,2 % та 60,1 % відповідно, середній показник загальної виживаності – 27,7±4,1 місяця проти 24,5±1,8 і 24,1±2,2 місяця відповідно.
Висновки. Циторедуктивні операції та методи інтраопераційної гіпертермічної внутрішньочеревної хіміотерапії є перспективними шляхами лікування хворих на карциноматоз очеревини при раку яєчників щодо рецидиву захворювання та виживаності, хоча і супроводжується більшою кількістю післяопераційних ускладнень та днів перебування у стаціонарі.
Ключові слова: *рак яєчника, карциноматоз, лікування, гіпертермічна інтраопераційна внутрішньочеревна хіміотерапія, циторедукція.*

Common forms of cancer of different localizations have a significant frequency and, as a consequence, are of great importance for improving the principles of treatment and diagnosis. The most common tumors with peritoneal metastases are ovarian cancer and gastric cancer. The number of new cases of ovarian cancer in the world, according to previous years, per year is 295414 (6.6% of all forms of cancer in women). Mortality from ovarian cancer in the world is 184 799 cases (3.9% in the structure of cancer mortality in women). There has been a steady increase in the incidence in recent years, as well as a high percentage of patients with III–IV disease stages [1–3, 6–8, 15–17].

Unfortunately, all patients with common forms of ovarian cancer have thoroughly disappointing overall and relapse-free survival rates, even when prescribed treatment. One-year mortality after diagnosis is about 20%. Thus, according to a multicentric prospective study of the development of carcinomatosis EVOCAPE-1, the median overall survival of patients is 3.1 months, and the average life expectancy is 6 months. Despite the removal of the tumor, which can achieve complete or partial regression, more than 1/2 of patients in the first 2 years have a recurrence of the disease. According to some authors, the average time of disease progression after treatment is 18 months [5, 10, 11, 13, 19–22].

Ovarian cancer is also a common and socially significant problem, as surgical techniques include removal of the ovaries, which involves surgical castration of women who are often of childbearing age. Modern diagnostic approaches do not meet the requirements of oncology. Low informativeness of preventive examinations, erased course of the disease, as a result of which the diagnosis is made at the III–IV stages of the process, lead to an increase in the incidence of ovarian cancer. The reason for late and imperfect diagnosis is the presence in more than 75% of cases of primary tumors of small size, when the main tumor focus and subsequent peritoneal metastases are nodes of small size. In the future, such tumors are simply not detected during preventive gynecological examinations [9, 12, 14, 17, 18, 23, 25].

The main principle of treatment of all tumors of ovarian origin is the implementation of surgical interventions, which are the most complete removal of tumor nodes, in combination with the use of chemotherapeutics at different stages. At the revealed recurrences of a disease it is also accepted to consider as an optimum variant of the further tactics of appointment of courses of chemotherapeutic treatment. However, there is quite convincing evidence of more aggressive methods of surgical manipulation with the removal of all visually identifiable tumor nodes. Cytoreductive surgery with peritonectomy was first described by P. Sugarbaker in 1995. With small technical variations, it was later tested in clinics around the world. Optimal resection in metastatic disease is a powerful determinant of survival. The current strategy for the treatment of peritoneal carcinoma is based on the concept of regional impact: cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). The leading role is played by the implementation of an adequate amount of surgery, rather than the calculation to achieve regression of the disease on the background of chemotherapy. There is no definite certainty about the need for neoadjuvant chemotherapy (NACT) in the preoperative phase. Numerous studies have not shown significant differences in the median postoperative survival [13, 19, 21, 22, 24].

In the case of improving the tactics of treatment of ovarian cancer, there is no systematic common treatment option. Most clinics use established treatment protocols for this group of patients based on their own experience.

The objective: of the study is to analyze the results of treatment of patients with stage IIIC ovarian cancer with different versions of the performed surgical manuals, as well as with the inclusion in the treatment format of the method HIPEC; identification of factors influencing the effectiveness of treatment, the duration of the recurrence-free period and overall survival. The development of a topical treatment program for this group of patients was also included in the study.

MATERIALS AND METHODS

The study included 119 patients diagnosed with stage IIIC ovarian cancer that have been treated in University Clinic of Odessa National Medical University. The principle of operation is a clinical comparison of parallel groups.

The classification of cytoreductive surgical interventions of the Russian Society of Oncology (2020) was used to divide patients into the study groups (Fig. 1).

Complete cytoreductive surgery (CC-0) – performing extirpation of the uterus with appendages, removal of the large omentum, as well as all visible manifestations of the tumor process without macroscopically determined residual tumor masses.

Optimal cytoreductive surgery (CC-1) – extirpation of the uterus with appendages, removal of the large omentum, as well as visible manifestations of the tumor process with macroscopically identified residual nodules of tumors, each with a diameter of not more than 10 mm.

Suboptimal cytoreductive surgery (CC-2; CC-3) – extirpation of the uterus with appendages, removal of the large omentum, manifestations of the tumor process with macroscopically defined residual nodes, of which at least one is more than 10 mm in diameter.

According to this classification, the patients included in the study were divided into two groups.

Clinical comparison group (hereinafter – control group (control)): 53 patients with a diagnosis of ovarian cancer stage IIIC, where the first stage was 3 courses of NAHT; then performed suboptimal cytoreductive surgery (CC-2; CC-3) in the amount of extirpation of the uterus

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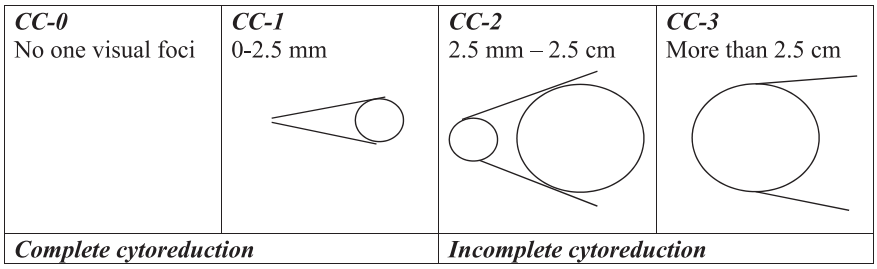

Fig. 1. Options for cytoreductive surgery

with appendages and resection of the large omentum. Then according to the same scheme in the postoperative period carried out 3 courses of adjuvant chemotherapy. This group was recruited from 2013 to 2016.

Main group: 66 patients diagnosed with stage IIIC ovarian cancer, where the obligatory component of the operation was cytoreductive intervention in the amount of complete or optimal cytoreduction (CC-0; CC-1), which includes not only extirpation of the uterus with appendages, omentectomy, but also removal of all organs involved in the tumor process. This group was recruited from 2016 to 2020.

The main group was divided into the main group 1 (hereinafter – CS (cytoreductive surgery)) and the main group 2 (hereinafter – HIPEC). The group of CS included 39 patients with a diagnosis of ovarian cancer stage IIIC, which used the scheme of interval cytoreduction: after 3 courses of NAHT performed surgery in the amount of complete or optimal cytoreduction (CC-0; CC-1), then the same scheme in the postoperative period conducted 3 courses of adjuvant chemotherapy. Group HIPEC consisted of 27 patients diagnosed with ovarian cancer stage IIIc, they carried out the scheme of primary cytoreduction: the first stage – cytoreductive surgery with HIPEC technology in the amount of complete or optimal cytoreduction (CC-0; CC-1), then, postoperative period, courses adjuvant chemotherapy.

Candidates for cytoreductive surgery and DIIH:

1) verified ovarian cancer;
2) IIIC stage of the tumor process in the case of initially detected disease;
3) mandatory diagnostic laparoscopy with PCI assessment and establishment of process resectability (PCI value not more than 14);
4) the ability to perform only complete or optimal cytoreductive surgery;
5) age not more than 75 years;
6) general condition on the ECOG scale not more than 2 points, on the Karnowski scale – not less than 50%;
7) generally preserved patients, without gross concomitant pathology or with chronic diseases that are in the stage of compensation;
8) the absence of severe visceral carcinoma on the loops of the small intestine (with values of the PCI index of the corresponding loci slightly more than 1).

In the initial analysis of groups, time indicators (period before surgery, duration of surgery, number of postoperative bed-days), as well as the presence and nature of complications in the postoperative period were taken into account. The main tasks are to develop a modern topical algorithm for managing such patients as the most promising group, which performs complete and optimal cytoreductive interventions, as well as mastered and implemented in the practice of HIPEC. The procedure of intraoperative hyperthermic chemotherapy was performed using the device Performer HT (RAND, Italy).

Patients in the main group underwent diagnostic laparoscopy with mandatory calculation of the peritoneal cancer index (PCI). PCI was the main criterion for the distribution of patients in the main group by subgroups 1 and 2. To determine it, we calculated the maximum size of the tumor node for each of the 13 areas of parietal and visceral peritoneum (Fig. 2).

The method of calculating the index of peritoneal carcinoma is as follows: determine the maximum size of the implant and set the appropriate score: 0 – no tumor, 1 – implant 0.5 cm or less, 2 – implant 5 cm or less, 3 – implant more than 5 cm or implant fusion . The sum of scores suggests the resectability of the tumor at the initial stage (the maximum possible value of the carcinoma index is 39).

Ovarian cancer staging was performed according to the FIGO classification (International Federation of Obstetrics and Gynecology – FIGO (2014) and TNM (8th edition, 2017)).

The following regimens were used as neoadjuvant and adjuvant chemotherapy regimens: docetaxel 75 mg/m^2 intravenously for 1 h on day 1, cisplatin 75 mg/m^2 intravenously for 2 h on day 1 every 3 weeks.

After the comprehensive treatment, all patients were under dispensary supervision with mandatory control of the level of tumor markers in the dynamics, they performed the full range of necessary diagnostic procedures.

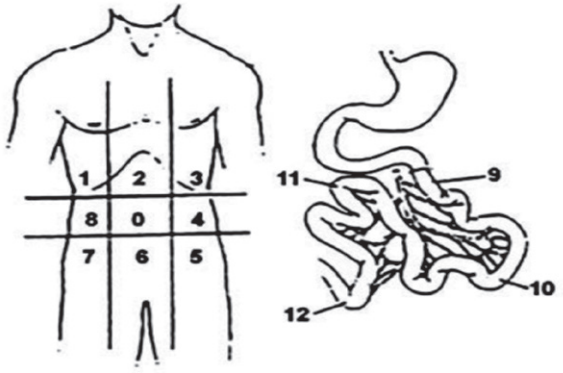

Fig.2. Segments for calculating the peritoneal carcinoma index

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The first follow-up examination in patients took place 4 weeks after the end of adjuvant chemotherapy. Subsequently, the frequency of examination was 1 time in 3 months during the 1st year after treatment, and the next 2 years – 1 time in 4 months.

Information was collected by analyzing medical histories and clinical cases during the examination period, conducting the main stage of treatment and subsequent dispensary observation.

Statistical processing of the results was performed using a personal computer and software package Microsoft Office Excel 2007, Microsoft Office Word 2007, IBM SPSS Statistics 17.0. Student's t-test was used to assess the reliability of differences in parametric quantities, and Mann-Whitney U-test was used in the analysis of nonparametric quantities. Differences between groups were taken into account in terms of asymptotic significance <0.05.

Statistical analysis of survival was performed by the method of constructing Kaplan-Meier curves. The Log rank criterion, the Breslow criterion, and the Tarone-Ware criterion were used to analyze survival curves. Differences between groups were considered significant at p≤0.05.

RESULTS AND DISCUSSION

119 patients from 3 groups underwent clinical observation: clinical comparison group (n=53), interval cytoreduction group (n=39) and primary cytoreduction group with GIIH (n=27).

The median age in the clinical comparison group was 54.6±1.5 years, in the 1st main group – 57.4±2.0 years, in the 2nd main group – 55.0±2.1 years.

During the period from 2013 to 2016, all patients underwent suboptimal volume of cytoreduction. Starting from 2016 and still any cytoreductive volume of the operation in the selected pathology is necessarily complete or optimal in its performance (Table 1).

Analysis of the peritoneal carcinoma index showed significant differences in this value in the study groups (p=0.001). Characteristics of PCI groups (average): control – 6.5±0.5; CH – 9.3±0.8; GIIX – 13.0±0.9. There is an increase in this indicator, respectively, in the groups of clinical comparison - interval cytoreduction - primary cytoreduction with HIPEC. This explains the conduct of NAHT in the preoperative phase, and, as a result, in a higher percentage of cases there is a stabilization of the process or a full / partial response to chemotherapy. Assessment of the possibility of tumor reduction was performed during a collegial discussion of a clinical case in the operating room during diagnostic laparoscopy.

The total time of the operation also tended to increase in these groups due to large operative volumes and the implementation of the HIPEC procedure in primary cytoreduction (p=0.001) (Table 2).

The characteristics of the performed resections by groups also differed strikingly. Cytoreductive operations in a large percentage of cases, in addition to the ordinary gynecological volume, also involve resection of the small and large intestine, as well as other affected organs.

In our practice, we focused on the fundamental essence of several variants of peritoneumectomy depending on the affected segments. The main clinically significant are the 4–8th segments, because they correspond to the lower floor of the abdominal cavity and primary metastasis occurs in these shallow places (Douglas space, ileocecal pockets, lateral canals of the abdominal cavity, inguinal and iliac fossae). The need for intervention in the upper floor of the abdominal cavity was noted in 20.5–66.6% of cases in the main group. Resection of the remaining segments (9–12th correspond to the visceral leaf of the peritoneum) involves resection of the small intestine in the affected areas – this is an infrequent situation, because the presence of miliary multiple carcinoma lesions often indicates the inability to perform optimal and complete cytoreductive volume.

Table 1

The volume of cytoreductive surgery

Group	CC-0	CC-1	CC-2; CC-3
Control	0	0	53 (100%)
CS	32 (82.1%)	7 (17.9%)	0
HIPEC	26 (96.3%)	1 (3.75%)	0

Table 2

The duration of surgery (min)

Group	Middle index	Minimum	Maximum
Control	82.8±3.5	35	159
CS	184.2±12.8	75	390
HIPEC	450.5±15.0	290	615

Table 3

The term of postoperative presence in clinic (days)

Group	Middle index	Minimum	Maximum
Control	6.8±0.4	5	14
CS	9.7±0.7	8	12
HIPEC	12.5±0.7	11	16

The magnitude of blood loss emphasizes the general aspects of the aggressive surgical concept of cytoreductive surgery and is directly proportional to the total volume of organ complexes in the main group (p = 0.001). Blood loss in the control group was 116.9±22.3 ml, CS group – 1106.4±160.3 ml, HIPEC group – 1005.5±110.0 ml.

In the postoperative period, there is a logical pattern in the increase in the number of beds in patients who have undergone large operative volumes, especially in combination with HIPEC (p=0.001) (Table 3).

In the analysis of postoperative complications of III-IV degree according to the Clavien-Dindo classification in the main group 2 (primary cytoreduction with HIPEC) in their total number was 22.2%. This indicator differs significantly from the clinical comparison group and the main group.

It should be mentioned that all surgical interventions are performed by the same surgical team. All surgeons have the highest qualification category and many years of experience in dealing with gynecological pathology and in the abdominal area in the upper and lower floors of

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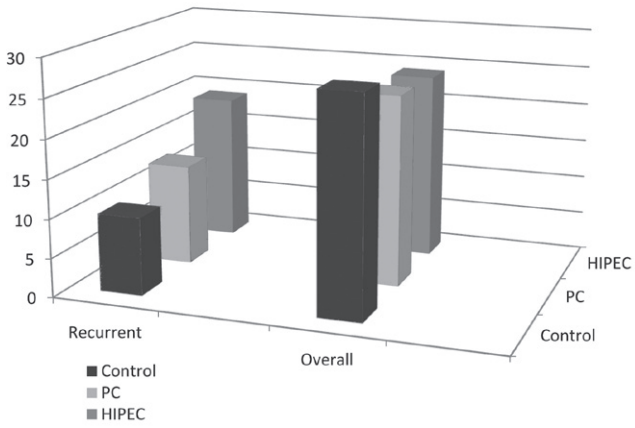

Fig. 3. Recurrent and oversll survival (per months)

the abdominal cavity. Only a multidisciplinary approach and teamwork is the main point for achieving success and quality implementation of these methods in practice.

At this stage, the median follow-up of the groups was as follows: control 23 months, group CH 11 months, group HIPEC 9 months. Kaplan-Meier curve methods were used to analyze recurrence-free survival (DFS) and overall survival (OS).

Based on the observations, it was found that the median recurrence in the postoperative period in the control group was 10±1.3 months, while in the groups after interval cytoreduction and primary cytoreduction with HIPEC – 13±1.5 and 19±6.3 months, respectively (Fig. 3). In pairwise analysis of the results obtained by the Breslow criterion (generalized Wilcoxon) obtained values that partially confirm the statistical significance of these differences and strive for it (p (counter/HIPEC) = 0.059 and p (counter / CS) = 0.046).

Analysis of the rate of relapse-free survival also showed that in the first 6 months in the control groups – CS – HIPEC was respectively 63.2–88.0–90.4%. One-year recurrence-free survival was 37.5–63.2–60.1%, respectively, which in absolute terms was 32 people with relapses in the control group (62.5% relapse occurred during the 1st year), 11 people in the CH group and 7 people in the HIPEC group.

At this stage of treatment there are no significant differences in overall survival in the study groups (Fig. 3). This is due to the short observation period in the main groups (recruitment has been conducted since 2016). The average values of overall survival in the control group are 27.7±4.1 months against 24.5±1.8 and 24.1±2.2 months in CS and HIPEC, respectively.

CONCLUSIONS

Cytoreductive operations and methods of intraoperative intra-abdominal hyperthermic chemotherapy are promising ways to treat patients with peritoneal carcinomatosis in ovarian cancer. Recurrence of the disease in most cases after standard treatment in the first 1–2 years occurs in 80% of cases. In the study, the median recurrence-free survival ranged from 13 to 19 months in the main group. The peritoneal carcinoma index is an important indicator that determines the treatment tactics and prognosis for advanced ovarian cancer. In our opinion, at the first stage of complex treatment of ovarian cancer, complete cytoreduction with the use of the HIPEC procedure and subsequent adjuvant chemotherapy is justified.

Optimal, and preferably complete cytoreduction allows to reduce the amount of resistant tumor mass with weak blood flow and minimize it, then carry out the first course of therapeutic treatment with chemotherapy on the remaining tumor cells, directly during surgery. Incomplete cytoreduction significantly increases the number of recurrences of the disease: 62.5% in the 1st year of follow-up compared with 36.8–39.9% when performing complete or optimal cytoreduction. However, the percentage of postoperative complications and the number of bed days significantly increase during primary cytoreduction.

Prospects for further research

The study HIPEC usage results in ovarin cancer patients is part of a comprehensive study of the effectiveness of treatment of patients with oncological ovarian pathology.

Conflict of interests. The author of the manuscript consciously certify the absence of actual or potential conflict of interests regarding the results of this work with pharmaceutical companies, manufacturers of biomedical devices, other organizations whose products, services, financial support may be related to the subject of materials or sponsored by the research.

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