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OPTIMIZIMG OF MANAGEMENT OF THE OVARIAN CANCER PATIENTS WITH PERITONEAL CARCINOMATOSIS

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Abstract. ***Objective:*** *At present, common forms of cancer of different localization can not be ignored. New approaches to the treatment of metastatic lesions have some success in clinical application. This study is devoted to the experience of using the technology of cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in practice, as well as the analysis of overall and relapse-free survival in the examined groups of patients.*

Patients and methods: *A total of 119 people were recruited from 2013 to 2020 inclusive. Patients were divided into two groups: the clinical control group (n = 53) consisted of individuals who underwent suboptimal cytoreduction; in the main group (n = 66) there were patients who performed optimal or complete cytoreductive volume and in some cases underwent intraoperative hyperthermic chemotherapy. Patients diagnosed with stage IIIC ovarian cancer were treated. In the initial analysis of these 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.*

Results: *The analysis showed an increase in relapse-free survival from 10 months in the control group to 13-19 months in the main group, also significantly increased (from 5 to 22%) the number of complications of class III-IV in HIPEC.*

Conclusion: *There was no statistical difference when comparing the median overall survival and progression-free survival in the study groups. It has also been shown that primary cytoreductive surgery with macroscopically visible residual masses, especially in suboptimal and suboptimal volume (CC 2-3), leads to a significant decrease in survival rates in patients with ovarian cancer. The expected results will be a significant discrepancy between overall and recurrence-free survival in the study groups.*

Key words: *Ovarian cancer, carcinomatosis, treatment, chemotherapy, HIPEC*

Introduction.

The problem of diagnosing and treating ovarian malignancies is one of the most challenging issues in oncology and gynaecology. The majority of patients with ovarian cancer (OC) are diagnosed at late stages, and treatment results remain disappointing. Despite the high sensitivity of many modern diagnostic methods, their specificity is insufficient to differentiate between benign and malignant processes in the ovaries [1-3]. 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 184799 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 [4-7].

Cytoreductive surgeries are mostly highly invasive procedures, during which total and partial peritoneectomies and multivisceral resections can be routinely performed

[8, 9]. The use of this approach to the treatment of patients with peritoneal carcinomatosis and other intra-abdominal metastases of various primary origins leads to improved oncological outcomes without worsening the general clinical outcomes. Such surgical interventions can be performed only with the participation of a multidisciplinary team in an oncological centre [10-12].

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.

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 aim of the study was 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.

Patients 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.

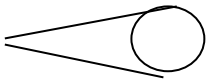
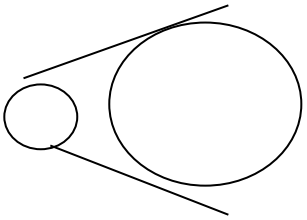
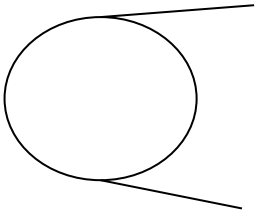
CC-0	***CC-1***	***CC-2***	***CC-3***
No one visual foci	0-2.5 mm	2.5 mm – 2.5 cm	More than 2.5 cm
			
Complete cytoreduction		***Incomplete cytoreduction***	

Fig. 1 Options for cytoreductive surgery

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

Clinical comparison group (hereinafter - control group (IInd group)): 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 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 (Ist 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).

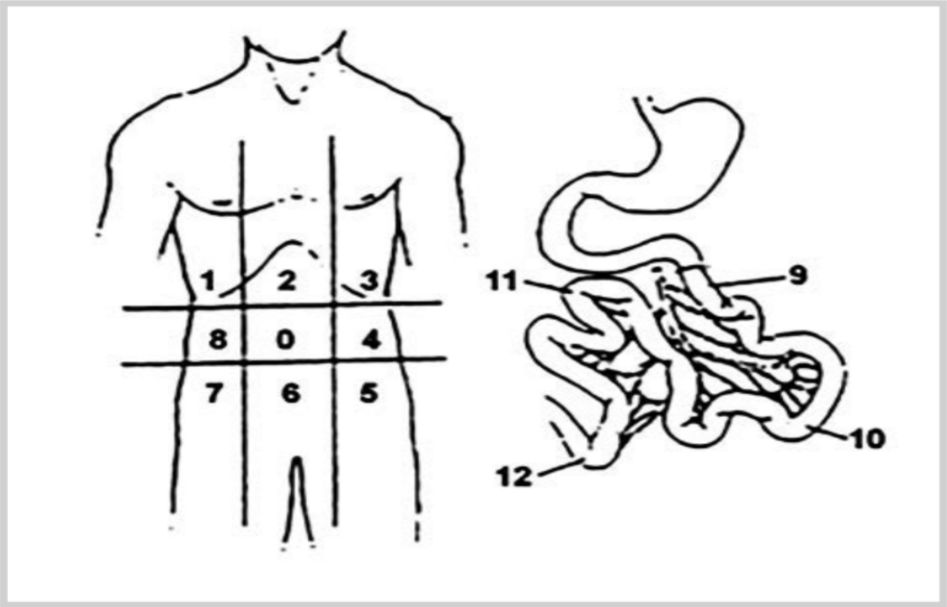


Fig2 Segments for calculating the peritoneal carcinoma index

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 / m2 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. 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 $p \leq 0.05$.

Results and discussion

All observed patients 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 (Table 3).

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

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.

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

Table 3 - Early postoperative complications

Complications	Group of patients, n (%)	
	Ist n=59	IInd n=66
Perforation of the small intestine	2 (3,4)	0 (0,0)
Intra-abdominal bleeding	1 (1,7)	1 (6,3)
Failure of the intestinal anastomosis	1 (1,7)	1 (6,3)
Relaparotomy	7 (11,9)	1 (6,3)
Evening surgery	2 (3,4)	0 (0,0)
Intestinal obstruction	2 (3,4)	0 (0,0)
Purulent and septic complications	4 (6,7)	2 (12,5)
Acute renal failure	2 (3,4)	1 (6,3)
Acute liver failure	1 (1,7)	0 (0,0)
Pleurisy	2 (3,4)	0 (0,0)
Pneumothorax	1 (1,7)	0 (0,0)
Thromboembolism of the pulmonary artery	1 (1,7)	0 (0,0)
Postoperative pneumonia	2 (3,4)	1 (6,3)
Deep vein thrombosis	0 (0,0)	1 (6,3)
Disorders of cerebral circulation	1 (1,7)	0 (0,0)
Anaemia in the postoperative period	21 (35,6)	3 (18,8)
Perforation of gastric ulcer	1 (1,7)	0 (0,0)
Bleeding from a stomach ulcer	1 (1,7)	0 (0,0)

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).

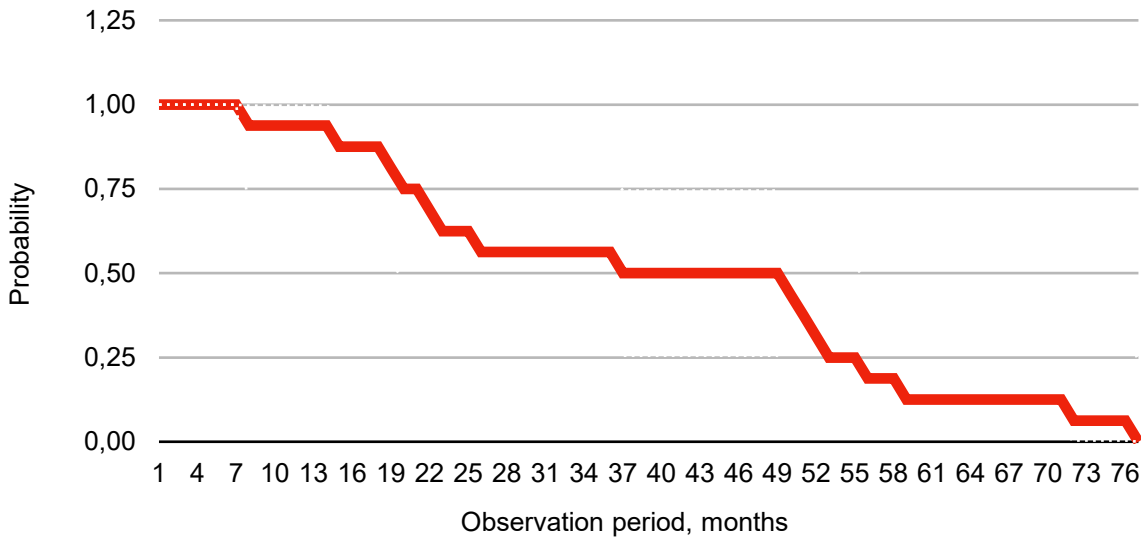


Fig.3 Recurrent survival (in months)

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. 4). 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 37.7 ± 4.1 months against 24.5 ± 1.8 and 24.1 ± 2.2 months in CS and HIPEC, respectively.

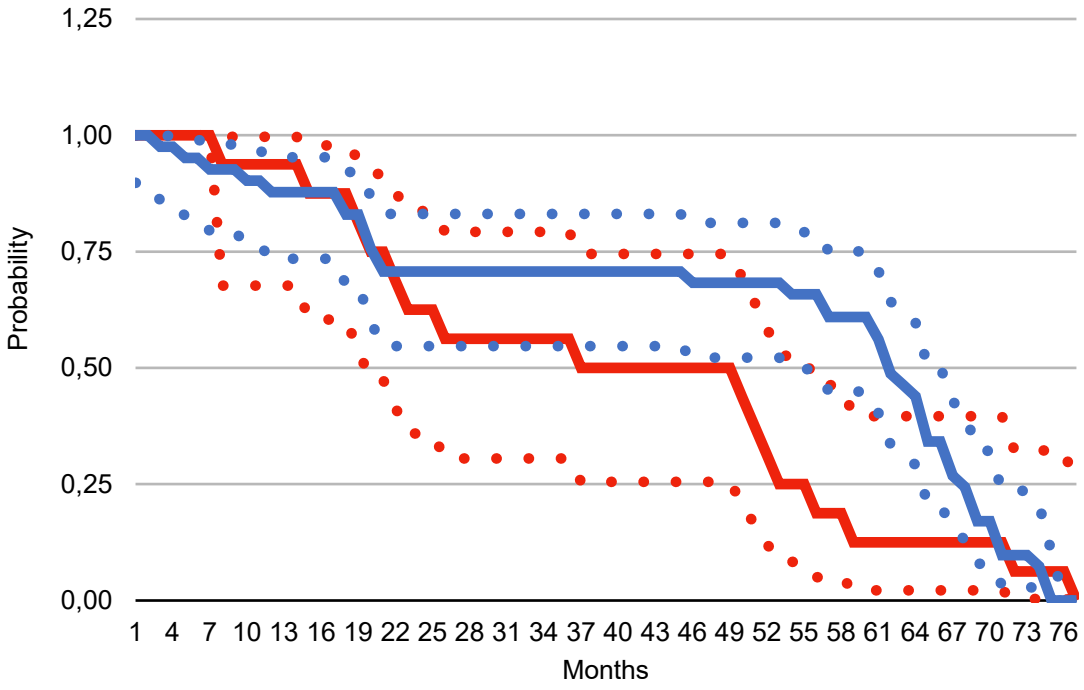


Fig4 Overall survival (per month)

Conclusions

There was no statistical difference when comparing the median overall survival and progression-free survival in the study groups. It has also been shown that primary cytoreductive surgery with macroscopically visible residual masses, especially in suboptimal and suboptimal volume (CC 2-3), leads to a significant decrease in survival rates in patients with ovarian cancer. 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.

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