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PERSONALISED TREATMENT OF PATIENTS WITH ADVANCED OVARIAN CANCER: COMPARATIVE ANALYSIS OF SURGICAL APPROACHES

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Abstract

The authors analysed the results of treatment of patients with advanced ovarian cancer depending on the surgical approach used and the results of NIRES application. The study was conducted at the University Clinic of Odessa National Medical University. The data of 104 patients with advanced ovarian cancer who underwent laparoscopic surgical access (L-CRS) (54 patients) and patients who underwent laparotomy access (O-CRS) (50 patients) were compared. It was shown that laparoscopic access reduced the incidence of postoperative complications of II–IV degrees according to Clavien-Dindo from 56.4% to 27.8% ($\chi 2=14.56$; $p < 0.001$), the duration of hospitalisation (on average (5.4 ± 1.2) days versus (10.1 ± 2.3) days ($t = 14.58$; $p < 0.001$) and the time to the start of adjuvant chemotherapy (4.1 ± 1.2) weeks and (7.2 ± 1.5) weeks, respectively ($t = 14.29$; $p < 0.001$) without a significant difference in postoperative mortality. The HIPEC technique has demonstrated its clinical safety in the treatment of peritoneal carcinomatosis of various primary localisations.

Keywords: ovarian cancer; treatment; cytoreduction; laparoscopy; HIPEC.

Резюме

Авторами проведений аналіз результатів лікування хворих на розповсюджений рак яєчників в залежності від виконаного хірургічного доступу та результатів використання HIPEC. Дослідження проводилось на базі Університетської клініки Одеського національного медичного університету. Порівняно дані 104 пацієнтів з РЯ, яким оперативне втручання було виконано лапароскопічним хірургічним доступом (L-CRS) (54 хворих) та хворих, яким було виконано операцію з лапаротомним доступом (O-CRS) (50 хворих). Показано, що лапароскопічний доступ дозволив зменшити частоту післяопераційних ускладнень II–IV ступеня за Clavien-Dindo з 56,4 % до 27,8 % ($\chi 2$=14,56; p < 0,001), тривалість стаціонарного лікування (в середньому (5,4 ± 1,2) дні проти (10,1 ± 2,3) дні (t = 14,58; p < 0,001) та термін до початку ад'ювантної хіміотерапії (4,1 ± 1,2) тижні і (7,2 ± 1,5) тижні відповідно (t = 14,29; p < 0,001) без істотної різниці у післяопераційній смертності. Техніка HIPEC продемонструвала свою клінічну безпеку при лікуванні перитонеального канцероматозу різних первинних локалізацій.

Ключові слова: рак яєчників; лікування; циторедукція; лапароскопія; HIPEC.

Ovarian cancer is one of the most aggressive and least controllable forms of malignant neoplasms of the female reproductive system. According to WHO data, more than 300,000 new cases are registered worldwide each year, with more than 70% of them already in stages III–IV of the disease. In Ukraine, ovarian cancer ranks fifth among gynaecological oncological pathologies in terms of frequency and second in terms of mortality, which indicates its significant socio-medical problem. The high mortality rate is associated with the asymptomatic onset of the disease, late referral, and significant difficulties in achieving complete resection of the tumour [1-3, 8, 11-13].

The gold standard for the treatment of epithelial ovarian cancer is a combination of cytoreductive surgery and platinum-based chemotherapy. However, there has been ongoing debate regarding the optimal surgical approach: primary debulking surgery (PDS) or interval debulking surgery (IDS) after neoadjuvant chemotherapy (NACT). Some studies demonstrate the advantages of PDS when complete cytoreduction is achieved, but in clinical practice this is

only possible in 30–50% of patients. In patients with advanced disease, complicated anatomy, or severe general condition, a strategy of NACT followed by IDS is more appropriate, as it is less traumatic with comparable oncological results [4, 5, 7-9, 17].

In this context, the method of hyperthermic intraperitoneal chemotherapy (HIPEC) is attracting increasing attention. The essence of this approach is the introduction of chemotherapy drugs heated to 41–43°C directly into the abdominal cavity after cytoreduction, which allows for high local drug concentration, enhances the cytotoxic effect, and overcomes chemoresistance. Data from recent randomised clinical trials indicate a potential improvement in recurrence-free and overall survival when HIPEC is used in combination with IDS, especially in patients with stage III disease after NACT [2, 3, 6, 10, 14].

At the same time, questions remain about the effectiveness of HIPEC in different clinical scenarios (PDS vs IDS, primary or recurrent disease, complete or suboptimal cytoreduction). There is also a need for an objective analysis of complications associated with HIPEC, such as nephrotoxicity, risk of peritonitis, and haematological toxicity. Most of the available data has been obtained in multicentre Western studies, while in Ukraine, the experience of implementing HIPEC is relatively new and insufficiently systematised [2, 4, 8, 18].

Therefore, analysis of the results of treatment of patients with advanced ovarian cancer, taking into account the type of surgical access (PDS or IDS) and the use of HIPEC, is extremely relevant. This will allow assessing the feasibility and effectiveness of modern multidisciplinary approaches in real clinical conditions, contribute to improving individualized therapy planning and increasing oncological awareness among doctors.

The aim of the study was to conduct a comparative analysis of the results of treatment of patients with advanced ovarian cancer depending on the surgical approach used and the results of NIRES use.

Materials and methods. The study was conducted at the University Clinic of Odessa National Medical University. Data from 104 patients with OC who underwent laparoscopic surgical access (L-CRS) (54 patients) and patients who underwent laparotomy access (O-CRS) (50 patients) were compared. The selection criteria were the same. Postoperative and oncological outcomes were analysed. The clinical outcomes of treatment were also analysed in 57 patients with PC and peritoneal carcinomatosis who underwent cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC). Each patient with peritoneal carcinomatosis who underwent HIPEC was assessed preoperatively using the Eastern Cooperative Oncology Group (ECOG) scale, the Karnofsky scale, and the American Society of

Anesthesiologists (ASA) scale. In addition, 104 patients with peritoneal carcinomatosis caused by primary RCC were studied (57 patients who underwent CRS + adjuvant chemotherapy (ACT) and 57 patients who underwent CRS + HIPEC + ACT).

Research results. Laparoscopic surgery at the diagnostic stage is indicated for the exclusion of patients who cannot undergo optimal cytoreduction, and at the treatment stage – for patients with tumours accessible for laparoscopic removal and a peritoneal carcinomatosis index (PCI) ≤ 10.

In the L-CRS group, a shorter period of hospitalisation was determined (on average (5.4 ± 1.2) (3–15) days versus (10.1 ± 2.3) (4–35) days) ($p < 0.05$) and a shorter interval to the start of adjuvant chemotherapy (on average (4.1 ± 1.2) (3–7) weeks and on average (7.2 ± 1.5) (4–33) weeks, respectively) ($p < 0.05$) than in the O-CRS group. The study did not reveal any statistically significant differences in the parameters of operation duration, perioperative blood transfusion, and postoperative mortality. There were no early locoregional recurrences in the L-CRS group. Survival, assessed using the Kaplan-Meier method, did not differ statistically between the two groups ($p > 0.05$).

Laparoscopic access reduced the incidence of postoperative complications of II–IV degree according to Clavien-Dindo from 56.4% to 27.8% ($\chi2=14.56$; $p < 0.001$), the duration of hospitalisation (on average (5.4 ± 1.2) days versus (10.1 ± 2.3) days ($t = 14.58$; $p < 0.001$) and the time to the start of adjuvant chemotherapy (4.1 ± 1.2) weeks and (7.2 ± 1.5) weeks, respectively ($t = 14.29$; $p < 0.001$) without a significant difference in postoperative mortality.

Planning for NIRES after CRS begins at the preoperative stage, and the final decision on NIRES is made after the cytoreductive stage of the operation. However, there are currently no generally accepted recommendations for patient selection criteria for CRS + NIRES.

When planning treatment tactics, the determination of RSI in the preoperative period using intrascopic examination methods played a significant role. When comparing the incidence of postoperative complications of II–IV severity according to Clavien-Dindo among patients with ECOG 0, ECOG 1 and ECOG 2 statuses, $\chi2 = 6.295$, $p = 0.043$. When comparing the incidence of postoperative complications among patients with a Karnofsky score of 100–90%, 80–70% and 60–50%, $\chi2 = 6.988$; $p = 0.031$. When comparing the incidence of postoperative complications among patients with ASA I–IV, $\chi2 = 8.126$; $p = 0.044$. Therefore, assessment using the ECOG scale, the Karnofsky scale and the ASA scale can be recommended as one of the preoperative criteria for selecting patients for CRS + HIPEC. Patients with an ECOG score of 0–1, 100–70% on the Karnofsky scale, and ASA I–III are the best candidates for CRS + HIPEC, as their initial somatic status allows them to undergo such surgical

interventions with a lower probability of postoperative complications. Patient age < 65 years can also be included in the preoperative criteria for selecting patients for CRS + HIPEC ($p = 0.031$). However, this criterion cannot be considered absolute, and the somatic status of each elderly and senile patient must be assessed individually.

Taking into account the possible depth of penetration of cytostatics according to other studies, the performance of NIRES is pathogenetically justified when achieving CR 0 and CR 1 cytoreduction. Therefore, in the final assessment of the completeness of cytoreduction after removal of all resectable tumour mass, the advisability of performing NIRES becomes clear. Thus, the absolute criterion for selecting patients for NIRES is the achievement of CR 0–1. An important criterion for deciding on the advisability of performing NIRES is the patient's PCI, since a high PCI is associated with a lower percentage of CR 0–CR 1 cytoreductions. When comparing the frequency of achieving CR 0–1 in patients with PCI < 10, 10 < PCI < 20 and PCI > 20, $\chi 2 = 7.359$; $p = 0.026$.

The average length of hospital stay among patients who underwent CRS + HIPEC + ACT was (12.4 ± 5.1) days, which is longer than among patients who underwent CRS + ACT, (9.7 ± 5.9) days ($p < 0.01$). Postoperative complications of Clavien-Dindo grades II–IV occurred in 50.2% of patients without HIPEC and in 56.1% of patients who underwent HIPEC ($p > 0.05$ ($\varphi^*emp = 0.653$), i.e., no statistically significant difference was obtained). When analysing early postoperative complications in patients after HIPEC, hyperthermia and acute renal failure were more common than in patients without HIPEC (for both complications $p < 0.05$), which was probably caused by the effect of chemotherapeutic drugs and prolonged exposure to hyperthermic solutions in the abdominal cavity. The overall mortality rate was 2.0% among patients without HIPEC and 0% among patients after HIPEC ($p > 0.05$ ($\varphi^*emp. = 0.626$), i.e., no statistically significant difference was obtained).

he use of HIPEC contributed to a deterioration in the recovery of intestinal function in the postoperative period (recovery of peristalsis in (1.9 ± 0.5) (1–4) days without HIPEC versus (3.5 ± 1.0) (1–6) days after HIPEC and defecation in (3.4 ± 0.8) (2–8) days versus (5.6 ± 1.2) (3–10) days, respectively ($p < 0.01$).

When studying the quality of life in patients with RAS and peritoneal carcinomatosis according to SF-36, there was no significant difference in the parameters of physical and mental health indicators in patients without NIRES and after NIRES at all stages of the questionnaire (before special treatment, 3 days after surgery, 20 days after surgery, before the fourth cycle of chemotherapy, and 1 month after completion of chemotherapy) ($p > 0.05$) (Fig. 1).

Similarly, patients were surveyed using QLQ-C30, and the data obtained were analysed in accordance with the recommendations of the EORTC group. There was no statistically significant difference between the indicators of functional and symptomatic scales and the indicator of overall quality of life before the start of special treatment among patients ($p > 0.05$).

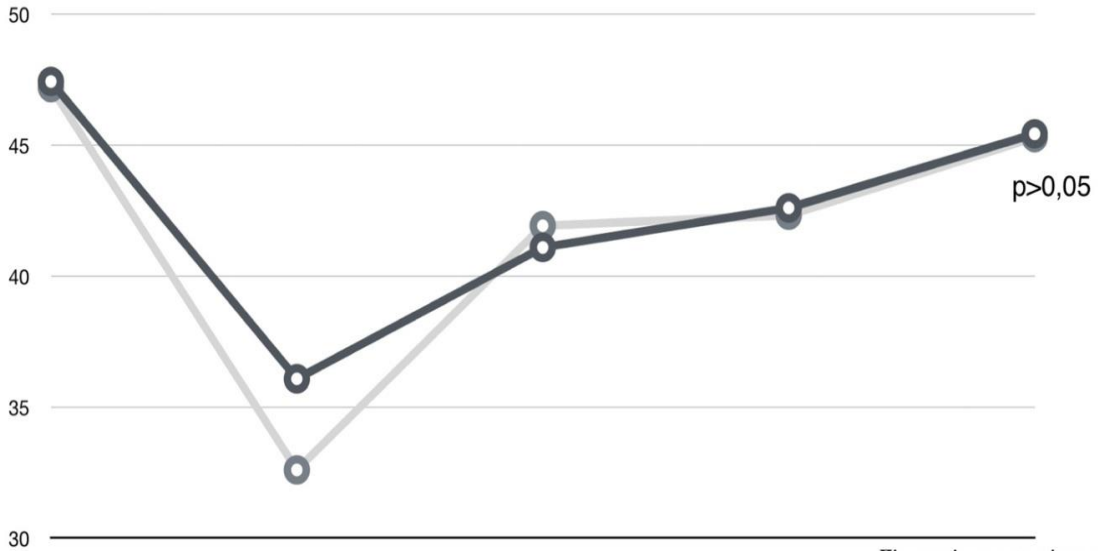

Fig. 1. Values of the physical component of health SF-36 in patients of the CRS + ACT group – dark grey colour and the CRS + HIPEC + ACT group – light grey colour at all stages of treatment (before treatment; 3 days after treatment; 20 days after treatment; after 3-rd course of ACT; after treatment finishing).

In the early postoperative period, there was a significant increase in the scores on the pain scale ($p < 0.05$), nausea and vomiting scale ($p < 0.05$), and constipation scale ($p < 0.05$) in patients who underwent NIRES. When comparing the parameters of functional scales, other symptom scales, and overall quality of life, the difference between patients who underwent NIRES and patients without NIRES was statistically insignificant ($p > 0.05$). When comparing patients, there is no significant difference between functional and symptom scales and overall quality of life in the late postoperative period, after the fourth course of ACT and 1 month after ACT ($p > 0.05$).

The results of the study indicate the importance of choosing the optimal surgical approach and the feasibility of using HIPEC in the treatment of patients with advanced ovarian cancer. A comparison of the effectiveness of different surgical approaches (traditional laparotomy and minimally invasive surgery) showed that with adequate patient selection, laparoscopic intervention can provide results comparable to open surgery, with less invasiveness and a shorter postoperative period. However, in cases of massive tumour

involvement, traditional laparotomy remains the method of choice for achieving optimal cytoreductive effect.

It is important to emphasise that the addition of HIPEC to cytoreductive surgery has improved recurrence-free survival and reduced the incidence of intra-abdominal recurrence in patients who have achieved complete or suboptimal cytoreduction. This is consistent with the results of international studies (van Driel et al., 2018; Spiliotis et al., 2015), which demonstrate the benefits of HIPEC in patients with stage III ovarian cancer. In our cohort of patients who underwent HIPEC, a statistically significant prolongation of the median recurrence-free period and overall survival was observed compared to those who did not receive this therapy.

However, the use of HIPEC is accompanied by increased requirements for the qualifications of the surgical team, as well as for material and technical support. Some patients experienced temporary complications associated with chemoperfusion (neutropenia, diarrhoea, transient renal failure), but the overall safety profile was acceptable.

The results also confirm that the degree of cytoreduction remains the most important prognostic factor. Patients with no macroscopic tumour residues had significantly better outcomes regardless of the type of surgical access or the use of HIPEC. This once again emphasises the need for a multidisciplinary approach and careful preoperative assessment to plan aggressive but justified surgery.

In the future, it would be advisable to further study a personalised approach to selecting candidates for HIPEC, taking into account tumour molecular subtypes, BRCA status and the peritoneal carcinomatosis index (PCI). Quality of life after treatment also deserves attention, as intensification of therapy should not worsen the functional status of patients.

Conclusions

1. Laparoscopic access reduced the incidence of postoperative complications of Clavien-Dindo grades II–IV from 56.4% to 27.8% ($\chi 2=14.56$; $p < 0.001$), the duration of hospitalisation (on average (5.4 ± 1.2) days versus (10.1 ± 2.3) days ($t = 14.58$; $p < 0.001$) and the time to the start of adjuvant chemotherapy (4.1 ± 1.2) weeks and (7.2 ± 1.5) weeks, respectively ($t = 14.29$; $p < 0.001$) without a significant difference in postoperative mortality.

2. A deterioration in the quality of life of patients who underwent HIPEC due to increased pain, nausea and vomiting, constipation and gastrointestinal symptoms was observed only in the early postoperative period. In the subsequent stages of specialised treatment and after its completion, no deterioration in quality of life was observed among patients who underwent HIPEC compared to the control group.

3. The HIPEC technique has demonstrated its clinical safety in the treatment of peritoneal carcinomatosis of various primary localisations.

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