

Hypoxic isolated abdominal perfusion breaks through chemoresistance in recurrent FIGO stage IIIC and IV ovarian cancer

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Abstract. To overcome drug resistance in relapsed ovarian cancer, an isolated perfusion system was used to generate a higher local exposure to cytostatic drugs. In addition to cisplatin as the cytostatic agent of choice, the present study combined adriamycin and mitomycin in a three drugs regime due to their increased cytotoxicity under hypoxia. A total of 107 patients, including 87 patients with relapses after previous platinum-containing therapies, 46 stage IIIC and 41 stage IV cases, were enrolled in the present study. A total of 25 patients were chemonaive, including 20 stage IIIC. The systemically pretreated patients in stage IIIC survived a median of 12.8 months, and those in stage IV 10.9 months. The overall clinical response rate of stages IIIC and IV combined was 69%. A complete decrease in ascites was found in 43% of all patients, a significant reduction in 19%. Toxicity and side effects were very mild and the bone marrow suppression was mostly grade I and never exceeded grade II. The primary clinical symptom in patients with post-therapeutic tumor necrosis, which occurred in 10-15% of all cases, was fever, fatigue and poor performance. The isolated hypoxic abdominal perfusion treatment is a potent instrument to break an existing chemoresistance without significant side effects with a good quality of life and comparatively long survival time.

Introduction

Clinical research has noticeably improved progression-free survival and overall survival over the past few decades. Nevertheless, ovarian cancer is still the leading cause of death among all gynecological malignancies. The insidiousness of the disease is the early peritoneal spread, the rapid development of chemoresistance and the bypassing of the hosts immune response (1). The recommended therapy option is complete surgical cytoreduction and chemotherapy with a combination carboplatin and taxanes (2-4). Although a complete remission rate of ~80% is achieved, platinum-resistance often occurs within two years. The shorter the relapse-free interval, the less likely the tumor will respond again (5-7). A higher individual dose or dose-dense therapy could induce a new response, but are incompatible and too toxic for the patient (8-13). Even modified drug combinations or high-dose chemotherapy have not brought any real progress (14-17). Hyperthermic intraperitoneal chemotherapy has been of recent interest, particularly after surgical cytoreduction (18-20). Alternatively, new drugs or targeted substances can be considered (21-24). Because of responsiveness increases with an increased dose or concentration of cytostatics, we assume that isolated perfusion in a closed circuit is able to break through chemoresistance due to the increased exposure to cytostatic drugs.

In order to keep the systemic toxicity within acceptable limits, and to maintain the quality of life, chemofiltration was carried out directly after the therapy (25,26). We herein present a cohort study of 107 patients who underwent hypoxic abdominal perfusion. All pretreated patients had recurrent stage IIIC and IV epithelial ovarian cancers resistant to platinum-containing drug combinations.

Materials and methods

Patients. The study included 107 patients in the FIGO stages IIIC and IV, who were treated in one institution between 1997 and 2017. 87 patients were previously treated with platinum-containing combination chemotherapies, mostly taxanes and had recurrent epithelial ovarian cancers, resistant to platinum-based drug combination. 46 patients were stage FIGO IIIC and 41 were stage IV. An additional 20 patients who had refused prior therapies were all stage IIIC. 34 patients had G3 degree malignancies (Table I). All pretreated patients had

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Abbreviations: ECOG, Eastern Cooperative Oncology Group; CT, computed tomography; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; CA, carbohydrate antigen; PFS, progression-free survival; WHO, World Health Organization; OS, overall survival; LDH, lactate dehydrogenase; PCS, primary cytoreductive surgery; NACT, neoadjuvant chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; AUC, area under the curve; RCT, regional chemotherapy

Key words: isolated perfusion, ovarian cancer, quality of life, chemoresistance, platin-refractory tumors, hypoxic abdominal perfusion, recurrent ovarian cancer, intraarterial chemotherapy

received at least two prior lines of chemotherapy. 7 had undergone third-line and one patient fourth-line therapies. The median platinum-free interval in 46 stage IIIC patients was 7 months and in 41 patients in stage IV was 9 months (Table II). Performance status was mostly stage ECOG 2 and 3. The 20 patients who had refused prior systemic chemotherapy received the same isolated perfusion therapy as the 87 patients with recurrent disease. The possibility of debulking surgery after diagnosis of progression was not considered feasible in terms of patient's performance and advanced disease in all cases.

Investigations were performed in compliance with the principles of good clinical practice outlined in the Declaration of Helsinki and federal guidelines, and had approval by the Medias Institutional Review Committee. Informed consent was obtained from each participant or participant's guardian. Patients were required to have an ECOG performance status of 3 or less. Exclusion criteria included cardiovascular disease, uncontrolled diabetes and serious infections. The white blood count had to be no less than 2,500/ μ l, and should under no circumstances be in decline before starting therapy. The same applied to the platelet count with a limit of no less than 100,000/ μ l.

Isolated hypoxic abdominal perfusion. The procedure (Fig. 1) is carried out with heparinization at 150 IU/kg body weight under general anesthesia and takes a total of one and a half to two hours. The femoral vessels, artery and vein, are exposed through a short incision in the groin and cannulated with stop-flow balloon catheters (Dispomedica, Hamburg). Both thighs are blocked with inflatable pneumatic cuffs. The venous balloon is positioned in the vena cava between the confluence of the hepatic vein and the right atrium, the aortic balloon shortly above the diaphragm level. After the correct position of the balloons has been documented with contrast medium, they are unblocked again and after temporary hyperoxygenation, the cytostatic combination is injected as a bolus into the aorta and both balloons are blocked again immediately. To prevent an initial acidification of the system, the balloons are only blocked after a short prior hyperoxygenation and aortic bolus injection of the chemotherapeutic agents. The therapy itself is conducted for 15 min under hypoxic conditions. Mitomycin and adriamycin unlike other cytostatics exhibit an augmented tumoricidal effect under hypoxia. The pH value has no influence on the efficacy of cisplatin (27). In isolated hypoxic abdominal perfusion the average dose of cisplatin was 60 mg, the maximum safe intra-arterial total dose of cisplatin was 70 mg as a bolus-injection. The maximum dose of adriamycin was 50 mg and for mitomycin 20 mg totally at one shot into the aorta. These seemingly low doses of cisplatin and adriamycin develop high active concentrations when used intra-arterially in an isolated circuit. Due to the intra-arterial application, the chemotherapeutics were not dosed by bodyweight for these patients. Plasma levels of mitomycin and adriamycin are 50 times higher in the arterial vs. venous perfusion line for the first three minutes and then adjust (28). Leakage monitoring is not necessary during the 15 min isolated perfusion period because after the balloons and thigh pressure cuffs have been unblocked, chemofiltration via the perfusion catheters is started immediately. Chemofiltration is continued at a maximum blood flow rate of 500 ml per minute to a substitution volume of 4 liters. After completing chemofiltration, the catheters are removed and the vessels repaired with running sutures.

Table I. Patient characteristics (n=107).

| Variable | Value | |
|-------------------|-------------------|-----------------------|
| | Pretreated (n=87) | Non-pretreated (n=20) |
| Median age, years | 56.6 | |
| Stage, n (%) | | |
| FIGO IIIC | 46 (53) | 20 (100) |
| FIGO IV | 41 (47) | 0 (0) |
| Grading, n (%) | | |
| G3 | 34 (30) | |

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique.

Table II. Time interval between prior treatments and hypoxic abdominal perfusion with chemofiltration.

| Stage | No. | Median platinum-free interval before perfusion |
|--------------------------|-----|--|
| FIGO IIIC non-pretreated | 20 | No pretreatment |
| FIGO IIIC pretreated | 46 | 7 months |
| FIGO IV pretreated | 41 | 9 months |

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique.

The isolated hypoxic abdominal perfusion is conducted in four cycles in three to four weeks intervals each. The blood count is checked weekly, and, while approaching the lowest Nadir, controls are carried out every second day until the blood count starts to reemerge. The tumor marker CA12-5 is checked before each therapy and a CT monitoring was performed two weeks after the second and fourth perfusion each. The extent of the residual tumor load and the tumor response were assessed according to the course of the tumor marker, the amount of residual ascites and the CT findings as well as the general condition of the patient. In case of progressive peritoneal lesions or distant metastases the treatment was discontinued.

Statistical analysis. Statistics have been calculated with 95% confidence limits. Survival times were estimated using the Kaplan-Meier product limit estimator and follow up for the surviving patients was minimum 12 months. Statistical analyses were performed using MediasStat software, version 28.5.14.

Results

Endpoints of the study. The most important endpoints of the trial were quality of life and overall survival, followed by the response rates. The latter was derived from the clinical response rate in the form of the tumor marker CA 12-5, the computer tomographic control and not least, quality of life.

Quality of life (QoL). QoL was in particular measured in the form of the decline or complete disappearance of ascites and especially, the substantial improvement in pain and the often described

Table III. Response rates of pretreated Fédération Internationale de Gynécologie et d'Obstétrique stage IIIC and IV patients with recurrent disease.

| Response | Stage IIIC, % | Stage IV, % | Stage IIIC/IV, % | Ascites, % |
|----------|---------------|-------------|------------------|------------|
| PD | 6.5 | 9.8 | 8.0 | 0.0 |
| SD | 26.1 | 19.5 | 23.0 | 0.0 |
| PR | 47.8 | 56.1 | 51.7 | 19.0 |
| CR | 19.6 | 14.6 | 17.3 | 43.0 |
| CR+PR | 67.4 | 70.7 | 69.0 | 62.0 |

PD, progressive disease; SD, stable disease; CR, complete response; PR, partial response.

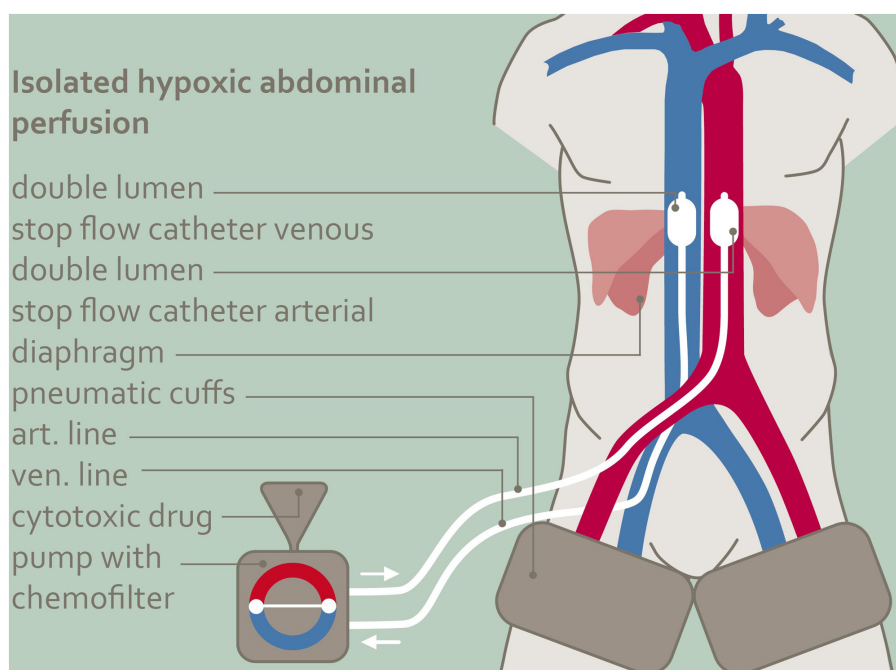


Figure 1. Schematic of isolated hypoxic abdominal perfusion through cannulation of the femoral artery and vein. The balloon catheters are positioned beneath the diaphragm and connected with an extracorporeal roller pump. Art., arterial; ven., venous.

general discomfort. Patients who had prior systemic followed by regional chemotherapy filled in questionnaires comparing the intensity of the most common side effects after the respective therapies in a scale from one to six. Patients perceived regional perfusion therapy less stressing than conventional chemotherapy.

Response rates. A positive influence on clinical response rates was noted among 69% of all patients in stage IIIC and IV. The rate of complete remissions was 19,6% in stage IIIC and 14,6% in stage IV, partial remissions 47,8 and 56,1% respectively. Complete disappearance of ascites was observed in 43% of patients after only two perfusions, and 19% of patients reported a 50% or more reduction of abdominal pressure and fluid volume (Table III). A considerable improvement in general wellbeing, with a reduction in abdominal symptoms and a substantial decrease in pain, was reported by 74% or 3/4 of patients with advanced ovarian carcinoma.

Survival. The median progression-free survival (PFS) of all 87 patients was 8 months, the median overall survival

11.9 months (Fig. 2). The median survival rate of pretreated platinum-refractory patients at FIGO IIIC stage was 12.8 months and at stage IV, 10.9 months (Fig. 3). In stage IIIC, overall survival in pretreated vs. non-pretreated patients at one year is 54 vs. 70%, respectively, at two years 25 vs. 40% at three years 19 vs. 30%, and at four years still 13 vs. 25% (Fig. 4). The response rates are summarized in Table III. The annual survival rates of 1-4 years for all patients together and selectively at FIGO IIIC and IV stage are summarized in Table IV.

Toxicity. Bone marrow depression ranged between WHO grade 1 and 2. Only patients with a reduced bone marrow reserve after stressful third and fourth-line therapy had leucopenia and thrombocytopenia grade 3 even after perfusion therapy with chemofiltration. WHO grade 4 toxicity and neutropenic fever as well as neuropathy in terms of hand-foot-syndrome were never observed. In the event of rapid tumor necrosis, which can occur during the first three post-therapeutic days, the patient report tiredness and fatigue with a simultaneous increase in LDH and tumor marker, which falls below the initial value

Table IV. Annual survival rates of 1-4 years of all pretreated FIGO stage IIIC and IV patients (n=87) with recurrent disease.

| Stage | 1-year OS, % | 2-year OS, % | 3-year OS, % | 4-year OS, % | 13-year OS, % |
|---------------------|--------------|--------------|--------------|--------------|---------------|
| FIGO IIIC/IV (n=87) | 47.1 | 23.8 | 16.4 | 9.8 | - |
| FIGO IIIC (n=46) | 54.3 | 25.2 | 19.2 | 12.8 | 3.1 |
| FIGO IV (n=41) | 39.0 | 22.0 | 13.2 | 9.5 | - |

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; OS, overall survival.

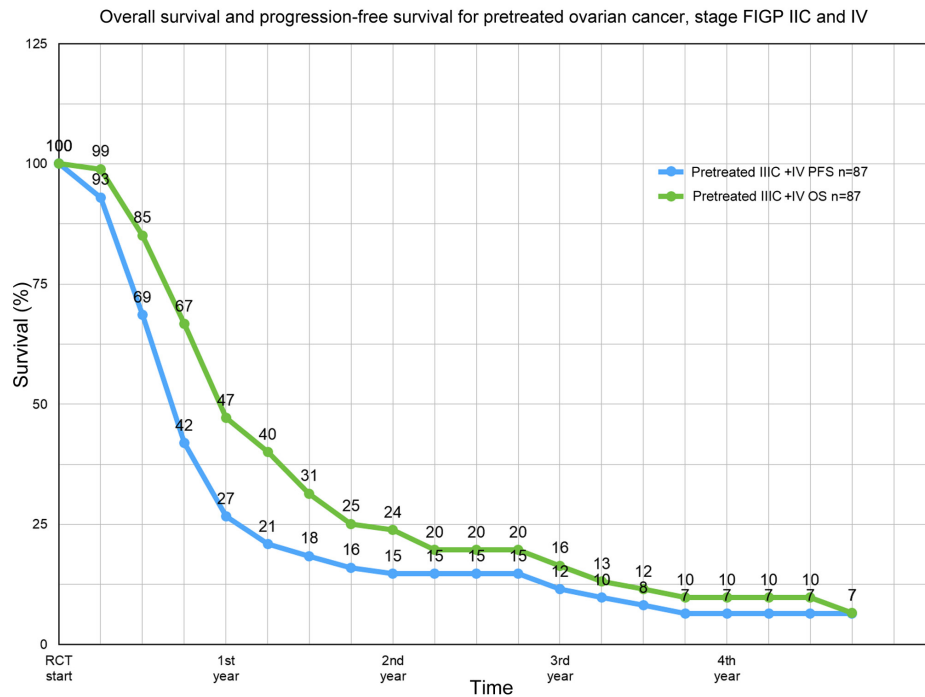


Figure 2. PFS and OS of all pretreated patients (n=87) in FIGO stage IIIC and IV. PFS, progression-free survival; OS, overall survival; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; RCT, regional chemotherapy.

within a few days. The syndrome occurs in 10-15% of patients, accompanied by fever and lassitude (Table V). In general, the performance of patients improves after perfusion therapy with chemofiltration from therapy to therapy (29).

Discussion

Ovarian cancer is the leading cause of death, and cure rates between 12-14% have changed little over the past few decades. Debulking operations in terms of complete cytoreduction and platinum-based chemotherapy are considered the cornerstones of current therapy.

On the remaining options, an increase in dose in systemic chemotherapy is limited by the increasing toxicity (8,9). Because of the angiogenic properties of ovarian cancer, targeted therapies appeared to be a logical and generally accepted option (21). On the one hand, they were complicated by not inconsiderable collateral damage such as perforations in the intestine due to microcirculation disorders in the intestinal wall, bleedings, proteinuria and high blood pressure. On the other hand, the clinical results with bevacizumab were not necessarily convincing; the median survival of 6.9 months in a

group of 32 multiple chemically pretreated patients after treatment with bevacizumab was rated as good, but did not reach the 11.3 months of a comparable group after isolated perfusion therapy which corresponds to an increase of over 60% (23). Due to the large difference in survival, this may indicate a trend towards isolated perfusion, but is of limited importance due to the small number of cases, not necessarily comparable patient groups and the lack of randomization. In spite of all restrictions, in addition to the good survival times, the minor side effects with mostly rapid improvement in the quality of life through 'segmental' limited chemotherapy with subsequent detoxification are of primary importance. The basic prerequisite for any cancer treatment should be the prolongation of life while maintaining and if possible improving the quality of life. No other fundamental necessity for any treatment to be recommended should actually apply (24). Side effects scales in patients who were progressive after systemic therapies of different tumor entities and then received regional chemotherapy (RCT) showed significantly fewer side effects and better quality of life after regional chemotherapy (29). The reduction or removal of all tumor masses is a prerequisite for thorough treatment of advanced ovarian cancer. Debulking

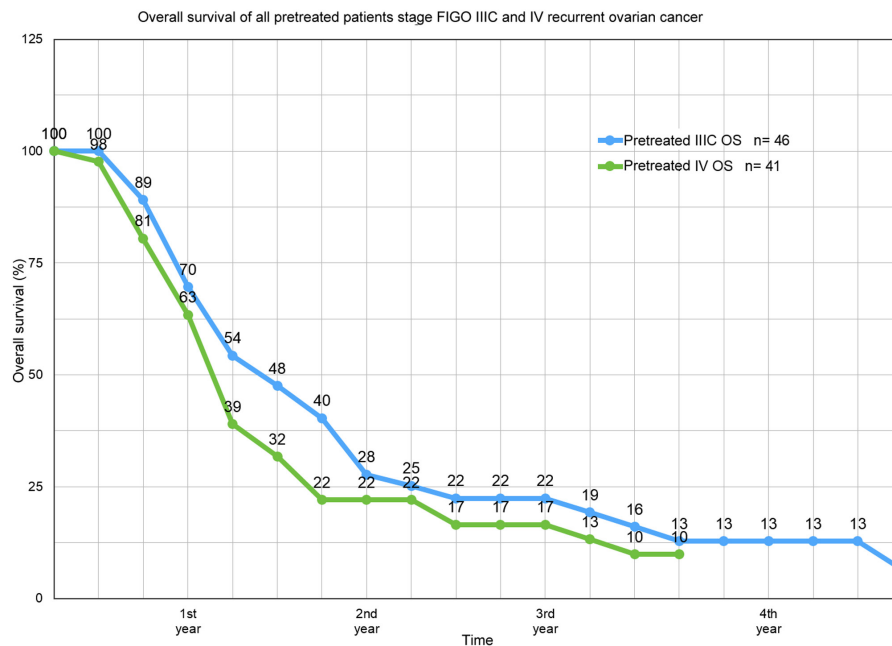


Figure 3. Overall survival of all pretreated patients in FIGO stage IIIC and IV. OS, overall survival; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique.

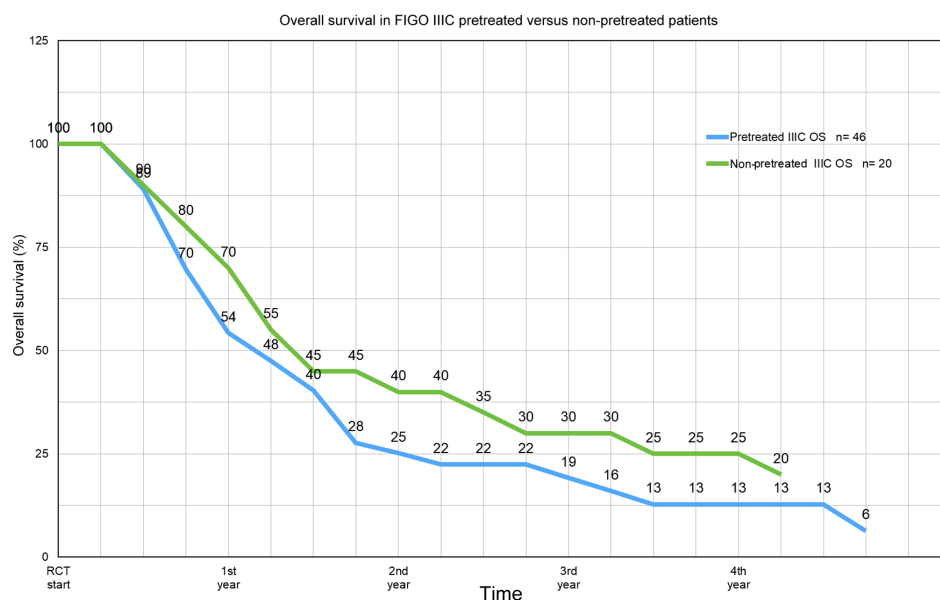


Figure 4. Overall survival in FIGO stage IIIC pretreated vs. non-pretreated patients. OS, overall survival; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; RCT, regional chemotherapy.

Table V. Toxicity profile after isolated hypoxic abdominal perfusion with cisplatin, adriamycin and mitomycin for advanced ovarian cancer.

| Adverse event | Extent |
|----------------------------------|----------------|
| Bone marrow suppression | WHO grade I/II |
| Fatigue syndrome | 15-20% |
| Transient elevation of creatinin | 15% |
| Neutropenic fever | 0% |
| Hand-foot-syndrome | 0% |

WHO, World Health Organization.

surgery with no or less than 1 cm residual tumor is also considered a decisive factor for the long-term prognosis. Basically, the aim is to achieve this, but the greater the tumor mass, the more difficult it is to achieve.

Primary surgery for complete cytoreduction is not possible in advanced stage IV ovarian cancers; these patients can only be treated with chemotherapy.

The DESKTOP III study, comparing chemotherapy and tumor debulking surgery vs. chemotherapy alone was the first prospectively randomized trial showing an overall survival benefit of debulking surgery in recurrent ovarian cancer (30). In other studies with secondary cytoreduction combined with platinum-based chemotherapy in relapsed

ovarian cancer, no differences were found in progression-free survival and overall survival, which may be due to different clinical expertise in the radicality of cytoreduction, but also in biological criteria and medication, including the role of bevacizumab in combination therapy is still unclear (31-34). The preoperative tumor load also influences survival, just as solitary recurrent disease is associated with a much better life expectancy (35).

HIPEC pursues the purpose of increased exposure to all peritoneal surfaces after debulking surgery and the best results are expected after debulking to zero or at least less than 1 cm residual disease because the depth of penetration of cytostatics under hyperthermic peritoneal irrigation is at most 2 mm (36). Although survival benefits have been shown in randomized studies (4,18,19), the HIPEC procedure is not regarded as the standard of care for first-line therapy of ovarian cancer, not least because of its high toxicity (37-39).

On the other hand, novel methodologies are under investigation, such as PIPAC, pressurized intraperitoneal aerosol chemotherapy (40) and precision chemotherapy using liquid biopsies for chemosensitivity and tumors gene expression assays (41).

The goal of all efforts in the treatment of ovarian cancer, and especially advanced ovarian cancer, is to increase the efficiency of the therapy used without affecting the quality of life due to unacceptable toxicity. It is a well-known rule that a higher local active drug concentration causes a better response. The limiting factor in higher exposure to cytostatics that may be effective is toxicity. With high-dose therapy limited to one region of the body only (28), the tumor can be permanently damaged with good long-term results. A further prolongation of progression-free and overall survival after initial isolated perfusion according to recent data (42-44) might be maintenance therapy with PARP-inhibitors.

Hypoxic abdominal perfusion with chemofiltration on the other hand, is relatively uncomplicated with some vascular surgery experience (28), without the need for follow-up treatment in an intensive care unit. Patients report little or very rarely about relevant side effects, while a decrease in tumor markers and stressful symptoms such as ascites or general discomfort is observed very often. The most striking feature of the isolated perfusion therapy is the high effectiveness with quick onset of tumor response with hardly any side effects and preserved, often improved quality of life.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KRA, SG and KA conceived the study. KRA and SG developed the methodology and assessed the authenticity of the data. KRA, SG and KA validated the data. KRA and KA performed formal analysis. KRA and SG performed the investigation. KRA and KA provided resources. KRA, SG and KA curated the data. KRA wrote the original draft. KRA and KA reviewed and edited the manuscript. KRA was involved in visualization. KRA supervised the study. KRA was responsible for project administration. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Investigations were performed in compliance with the principles of good clinical practice outlined in the Declaration of Helsinki and federal guidelines, and had approval by the Medias Institutional Review Committee (permit number MIRB20200515; Burghausen, Germany). Written informed consent was obtained from each participant or participant's guardian.

Patient consent for publication

Consent for publication was obtained from any individual person whose data are included in this manuscript.

Competing interests

The authors declare that they have no competing interests.

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