

## REVIEW

# The Controversy of Intraperitoneal Hyperthermic Chemotherapy for Ovarian Cancer

Lucian ALECU<sup>1</sup>, Adrian TULIN<sup>1</sup>, Iulian SLAVU<sup>1\*</sup>, Cristina ORLOV-SLAVU<sup>2</sup>, Bogdan SOCEA<sup>3,4</sup>, Cornelia NITIPIR<sup>2,4</sup>

## Abstract

Although the standard treatment for ovarian carcinoma with peritoneal metastases is systemic chemotherapy alone or systemic chemotherapy with debulking surgery, a new technique gains more ground: a combination of hyperthermic intraperitoneal chemotherapy (HIPEC) and optimal cytoreduction surgery. The proof is mounting regarding the benefits of HIPEC for patients with metastatic ovarian carcinoma but it still lacks a standard protocol of use. It has increased costs, and incomplete data regarding its safety. Due to these reasons, it is still considered an alternative treatment. Our study aimed to evaluate the published literature regarding this technique from the point of view of safety and efficacy when compared with the standard of care treatment.

**Keywords:** HIPEC, ovarian cancer, peritoneal metastasis.

## Rezumat

Deși standardul de tratament actual în carcinomul ovarian cu determinări secundare peritoneale este chimioterapia sistemică sau chirurgia de citoreducție combinată cu chimioterapie intravenoasă, o nouă tehnică este de interes: chirurgia maximală urmată de chimioterapie intraperitoneală administrată la temperatură crescută. Dovezile care demonstrează eficiența acestei tehnici s-au acumulat în ultima perioadă, dar un protocol de administrare lipsește încă. Trebuie reținute costurile mai mari și datele incomplete legate de siguranța acestei proceduri. Din aceste motive, este considerat încă un tratament alternativ în această localizare. Prezenta lucrare își propune să evalueze literatura recentă care tratează aceste aspecte și să dea informații legate de comparația acestei proceduri cu standardul de tratament.

**Cuvinte cheie:** HIPEC, cancer ovarian, metastază peritoneală.

## INTRODUCTION

Surgery represents the mainstay treatment in early ovarian cancer. The standard of care when peritoneal metastases are involved is intravenous chemotherapy as unique treatment, in combination with cytoreduction/debulking surgery or palliative surgery<sup>1</sup>.

The lifetime risk to develop ovarian cancer is 1 of 70 women thus making it one of the most frequent causes of death due to malignancies in women. This high frequency coupled with a silent evolution has both drawn increased attention to the diagnosis and treatment in early and advanced stages<sup>2,3</sup>. This is very

<sup>1</sup> Clinic of General Surgery, „Agrippa Ionescu” Emergency Hospital, Bucharest, Romania

<sup>2</sup> Clinic of Oncology, Elias University Emergency Hospital, Bucharest, Romania

<sup>3</sup> Clinic of Surgery, „Sfantul Pantelimon” Emergency Hospital, Bucharest, Romania

<sup>4</sup> „Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

### Corresponding author:

Iulian SLAVU, 7<sup>th</sup> Architect Ion Mincu Street, 011356, Bucharest, Romania.

E-mail: iulian.slavu@yahoo.com

difficult due to the fact that ovarian carcinoma has non-specific signs and symptoms. Frequently these patients present with advanced disease and peritoneal metastasis<sup>4</sup>.

Due to the predominant development of these tumors in the peritoneal serosa, a coherent approach would try to treat at this level as the whole peritoneal cavity is accessible by surgery. With this principle in mind, intraperitoneal chemotherapy was developed<sup>4</sup>.

Recently the technique was upgraded by preheating the chemotherapy agent and then inserting it into the peritoneal cavity: a procedure known as HIPEC (hypertermic intraperitoneal chemotherapy). It involves the administration of various chemotherapy agents, in the case of ovarian cancer frequently used are: mitomycin C, oxaliplatin, 5-fluorouracil or cisplatin at a temperature of 42 degrees Celsius. The crucial threshold for the optimal efficacy of these agents is 40 degrees Celsius<sup>5,6</sup>.

Intraperitoneal chemotherapy is focused on the remnant microscopic malignant tissue following surgery involving maximum cytoreduction. HIPEC is most efficient in low-volume, weakly vascularised tumors for which systemic chemotherapy is inefficient<sup>7</sup>.

Also, the blood-peritoneum barrier limits the transport of large amounts of chemotherapeutic in the systemic circulation, therefore, high concentrations can be administered directly into the abdomen with low systemic toxicity<sup>8</sup>. The increased temperature has a direct cytotoxic effect and a synergistic one with various molecules as cisplatin, paclitaxel, oxaliplatin, and mitomycin. The synergy is explained by reducing the resistance of tumor cells when these molecules are used in high temperatures<sup>8</sup>.

Hyperthermia produced high lysosomal enzyme activity in malignant cells, resulting in cell apoptosis<sup>9</sup>.

In 1987, the pharmacokinetic advantage of intraperitoneal chemotherapy for cisplatin and etoposide was demonstrated. The intratumoral concentration of chemotherapy was far superior to intravenous ones. Since ovarian cancer metastasizes with peritoneal predilection, it was first investigated in this cancer site<sup>10</sup>.

The association of high temperature and chemotherapy is not always used. In 2006 the first major study was published regarding the role of just intraperitoneal chemotherapy in ovarian cancer, which included 415 patients with optimal cytoreduction surgery (remnant peritoneal lesions were below 1 cm in size). The patients were distributed in 2 arms. An arm that received intravenous paclitaxel (135 mg/m<sup>2</sup>) and intravenous cisplatin (75 mg/m<sup>2</sup>) and an arm that which received

paclitaxel through an IV line in a dose of 135 mg per square meter in the first day followed cisplatin in a dose of 100mg per square meter, intraperitoneally after two days and paclitaxel in a dose of 60 mg per square meter after eight days<sup>9</sup>. The patients had this treatment every 3 weeks for 8 cycles. Progression free survival at 5 months in the arm of intraperitoneal chemotherapy was improved by almost 5 months from 18.3 to 23.8 months,  $p = 0.05$ <sup>11</sup>.

Our study aims to confront and compare the recent data published in literature regarding the role of intraperitoneal chemotherapy in ovarian cancer with peritoneal metastasis.

## MATERIAL AND METHOD

We conducted a literature review to identify published articles between 2015 and 2020, with main topics including ovarian carcinoma and peritoneal metastasis. The abstract and full „HIPEC” and “ovarian peritoneal carcinomatosis” AND „intraperitoneal chemotherapy”. The evaluated variables of the selected trials were: the total number of patients included in the studies, clinical information, demographic information, tumor staging, the use of intraperitoneal chemotherapy, and chemotherapeutic agents used, tumor burden.

Through the research process, the PubMed database was consulted. The P.I.C.O.S concept (patient, intervention, comparator, outcome, study type) was used to construct the questions and topics to obtain clinical validity. The selected titles were evaluated with the PRISMA checklist (Preferred Reporting Items for Reviews and Meta-Analysis) Figure no. 1. We used the standard recommendation of 2 independent readers who executed the evaluation and selection.

## RESULTS

We identified 28 papers in one medical database. Four papers were excluded due to the fact they were duplicates resulting in 24 papers for analysis. From these, 3 papers were excluded based on the title and abstract, the full text could not be obtained. From the remaining 19 full-text articles another 4 were excluded due to the fact their subject was not of interest for this paper (Figure 1).

After this evaluation 15 full-text articles were used for our analysis. The P.I.C.O.S concept (patient, intervention, comparator, outcome, study type) was used to structure the questions and the research topic to attain clinical validity (Figure 1).

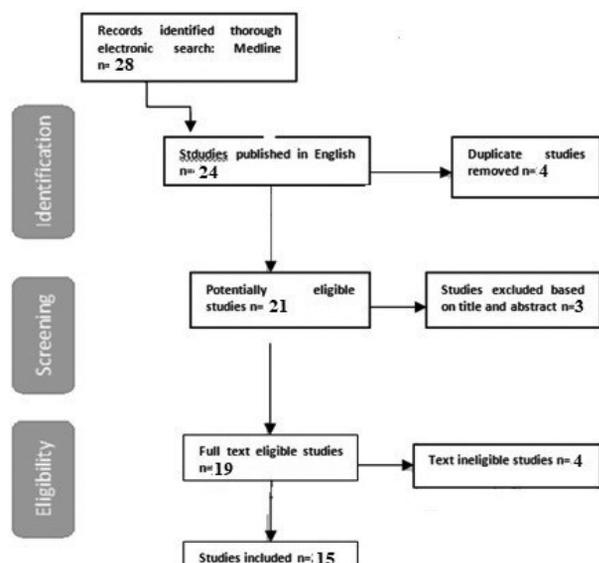


Figure 1. Analysis protocol under the PRISMA guidelines.

## DISCUSSION

### HIPEC in primary ovarian carcinoma and peritoneal carcinomatosis

In 2012 Ansaloni et al. published the results of one of the first phase II randomized prospective studies of the efficacy of HIPEC in advanced ovarian carcinoma<sup>12</sup>. This study was relatively small and involved 39 patients, 9 of whom received HIPEC during the initial surgical intervention. Overall survival was 14.4 months in the HIPEC group and patients with optimal cytoreduction surgery (tumor residue below 1cm) benefited most<sup>12</sup>.

The first multicenter phase III, randomized, prospective study was published by Dreel et al. in 2018 and was composed of 245 patients diagnosed as stage III ovarian neoplasms which received neoadjuvant system-

mic chemotherapy with carboplatin (Area Under the Curve - 5) and paclitaxel 175 mg/m<sup>2</sup> for 3 courses<sup>13</sup>. If ideal cytoreduction could be obtained after the surgical intervention they were distributed in one group with HIPEC and another without. Postoperatively, three more cycles of intravenous chemotherapy were administered. The HIPEC group demonstrated a 4-month progression-free survival benefit and total 12 month increased overall survival<sup>13</sup> (Table 1).

In 2017 Lim et al. published a study that included 184 patients with stage 3 and 4 ovarian cancer who were randomized into two groups with and without HIPEC and optimal cytoreduction surgery. The drug used for HIPEC was cisplatin (75 mg/m<sup>2</sup>). No differences in progression free survival were observed after 2 years and 5 years between the two groups<sup>14</sup>. Also, overall survival at 5 years was similar (Table 1).

In terms of the ideal time to administer HIPEC - good results were obtained both at the time of first surgery, but also at the time of interval cytoreduction surgery after neoadjuvant IV chemotherapy. The NCCN Guidelines currently recommend the use of HIPEC at the time of interval cytoreduction. The most used chemotherapy in HIPEC is cisplatin with a dose of 100 mg/m<sup>2</sup> administered at a temperature of 42°C.

At the moment the utility of HIPEC is questioned given the benefit of new and emerging treatments such as bevacizumab or PARP inhibitors.

### Evidence for HIPEC in relapsed ovarian cancer

At the moment, experience with HIPEC in the treatment of relapsed ovarian cancer is limited to single-institution or retrospective studies, which is why there is no consensus on the chemotherapy regimen to be used, the protocol of administration, or the postoperative evolution.

Table 1

<b>Lim 2017-Level I<sup>14</sup></b>	Type of study: Randomized controlled for stage III and IV (2 arms)	Survival without disease relapse at 5 years	5-year overall survival
	HIPEC with cytoreductive surgery followed by systemic chemotherapy	20.9%	51%
	Cytoreductive surgery and systemic chemotherapy	16%	49.4%
<b>Van Driel 2018-Level I<sup>13</sup></b>	Type of study: multicenter prospective for stages III and IV of ovarian neoplasms	Progression-free survival	Median overall survival
	HIPEC and Cytoreductive surgery	14.2 months	45.7 months
	Cytoreductive surgery alone	10.1 months	33.9 months

Bakrin et al. published in 2012 a study of 246 patients diagnosed with relapsed ovarian cancer,  $n=184$  being platinum-sensitive tumors and  $n=62$  platinum-resistant<sup>15</sup>. The purpose of this trial was to establish the efficacy of HIPEC in platinum resistant versus sensitive tumors. The chemotherapeutic agent was administered intraperitoneally when the surgical reintervention was performed and was represented by cisplatin in 95.5% of the patients as monotherapy or together with doxorubicin or mitomycin. The procedure lasted 90 minutes<sup>15</sup>. The temperatures had a range from 44 to 46° C. 92.2% of patients received optimal cytoreduction. OS was 48.9 months in the platinum-resistant group and 52 months in the platinum-sensitive group. The overall survival of the studied patients was 86% in the first year of follow-up, 60% at 3 years, and 35% at 5 years<sup>15</sup>.

Spiliotis et al. in 2015 published the first randomized study on the impact of HIPEC in patients with relapsed ovarian cancer. A number of 120 patients with stage IIIc and IV of relapsed ovarian cancer were included<sup>16</sup>. The patients were divided into 2 groups: a group that benefited from secondary cytoreduction surgery plus HIPEC and systemic chemotherapy and a group with maximum cytoreduction surgery and systemic chemotherapy<sup>16</sup>. Chemotherapy agents administered with HIPEC varied as follows: cisplatin 100 mg/m<sup>2</sup>, paclitaxel 60 mg/m<sup>2</sup>, doxorubicin 35 mg/m<sup>2</sup> for 60 minutes at 42.5° C. OS in the intraperitoneal chemotherapy group was increased to 26.7 months from 13.4

months in the group which did not receive intraperitoneal chemotherapy ( $p=0.006$ ). The patients diagnosed with stage IIIc ovarian carcinoma had an OS of 26.4 months and 11.9 months, thus the overall survival increased by almost 14 months in the group with HIPEC. Additional data regarding PFS for each intraperitoneal chemotherapy regimen was not provided.

In conclusion, it seems that for selected cases of patients with ovarian carcinoma and peritoneal carcinomatosis, HIPEC and optimal cytoreductive surgery may result in increased overall survival when compared to systemic chemotherapy and surgery. Despite the benefits, this technique has yet to achieve wide acceptance due to increased costs and prolonged operative time. The principle of administering chemotherapy directly in the peritoneal cavity to increase the local dose of the agent has to be further studied. Based on current data and the evolution of technology, new techniques, more cost-efficient and less time-consuming need to be implemented.

**Compliance with ethics requirements:** The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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