Hyperthermic intraperitoneal chemotherapy (HIPEC). Mechanisms of action and the role of HIPEC in the treatment of peritoneal carcinomatosis

Ann Ital Chir, 2018 89, 6: 513-527
pii: S0003469X18029287
free reading: www.annitalchir.com

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Hyperthermic intraperitoneal chemotherapy (HIPEC). Mechanisms of action and the role of HIPEC in the treatment of peritoneal carcinomatosis.

Peritoneal carcinomatosis represents the advanced, final stage of peritoneal malignancy, although it is often not accompanied by systemic neoplasia. The development of the pharmaceutical industry in combination with advanced surgery techniques has helped to improve the outcome of these patients, considered for a long time without radical resources. Tumoral cytoreduction followed by hypertermic intraperitoneal chemotherapy (HIPEC) is the treatment of choice for these patients, of course, this beeing done in a multimodal treatment, carefully chosen, following a multidisciplinary consensus. In this article we reviewed the main aspects of HIPEC procedure, describing the main chemotherapeutic agents used, highlighting the role that they play in this oncological treatment. Finally, we have pinpointed the main research lines in this field, which although have a well-established role in recent guidelines, have a great potential for development, with a maximum impact on the prognosis of patients with peritoneal metastases.

KEY WORDS: Cytoreductive surgery, Hyperthermia, Intraperitoneal chemotherapy, Pharmacology, Peritoneal metastasis

Introduction

Cancer treatment represents a challenge for contemporary medicine due to the growing rate of this disease[1]. The occurance of peritoneal carcinomatosis causes the infaust evolution of abdomino-pelvine cancers, placing them automatically into a final stage [2]. The development of new methods for treating cancer in general and especially for advanced cancer represents a goal for both clinicians and researchers.

One of the relatively new techniques and particularly controversial is cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC, associated with cytoreductive surgery, resulted in improved survival rate due to an enhanced action of cytotoxic agents on the microscopic residual peritoneal deposits.

Cytoreductive surgery and HIPEC are used both for the treatment of primary and secondary peritoneal tumors [3,4]. Although the favorable results after this approach were demonstrated by many studies from the literature [55,6]. this domain presents an extraordinary potential for devel-

Pervenuto in Redazione Agosto 2018. Accettato per la pubblicazione Settembre 2018
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ABBREVIATION

ATP	Adenosine triphosphate
BMI	Body Mass Index
CRS	Cytoreductive Surgery
CC	Cytoreduction score
DNA	Deoxyribonucleic acid
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
ICG	Indocyanin Green
MPM	Malignant Peritoneal Mezotelioma
MMC	Mitomycin C
NIRF	Near infrared field
PCI	Peritoneal Cancer Index Score
PSDSS	Peritoneal Surface Disease Severity Score
PIPAC	Pressurized intraperitoneal aerosol chemotherapy
RNA	Ribonucleic acid
TNM	Tumor-lymph nodes-metastasis staging system
5FU	5 Fluorouracil

oping [55]. Thus, the study of cytotoxic agents used for intraperitoneal chemotherapy and the development of new compounds with antitumoral properties represent an issue highly debated in the field of modern oncology. Through this article, we aim to review the chemotherapeutic agents used for the HIPEC procedure, highlighting its mechanism of action and its potential for development.

Definitions

Cytoreductive Surgery and CC Score.

Tumoral cytoreduction (CRS) represents the surgical removement of macroscopic tumoral tissue. The quantification of the success rate of cytoreduction is done at the end of surgery by setting the completeness of cytoreducion score (CC)[7]. Thus, we are talking about the CC-0 score in situations where there are no visible (macroscopic) tumoral deposits after cytoreduction. The CC-1 score is established when nodules with dimensions <2.5 mm remain in the peritoneal cavity, still considered HIPEC reactive nodules. The CC-2 score indicates the presence of overlapping tumor nodules between 2.5 mm and 2.5 cm. The CC-3 score is established in cases with remnant tumoral deposits larger than 2.5 cm or when there is an unresectable tumor confluence in the abdomen and pelvis. In the case of colorectal cancer with peritoneal carcinomatosis, complete CRS (CC-0), obtained with the cost of multiorgan resections and extended peritonectomy, is the only one able to provide optimal results, the CC score being the main prognostic factor [8-16].

Peritoneal Cancer Index Score (PCI)

The peritoneal carcinomatosis index (PCI) is a quantification score for the extent of peritoneal neoplastic lesions, first described by Sugarbaker [17]. The abdomen is divided into 13 regions (central, right hypochondrium, epigastrum, left hypochondrium, left flank, right flank, right iliac fossa, pelvis, left iliac fossa, proximal jejunum, distal jejunum, proximal ileum, distal ileon). Those 13 regions receive 0 points in the absence of neoplasia, 1 point for the presence of tumor nodules> 0.5 cm, 2 points for tumors with a size between 0.5-5 cm and 3 points for formations> 5 cm. Thus, PCI can reach values between 0 and 39, this score being designed to predict the likelihood of complete cytoreduction [18].

Peritoneal Surface Disease Severity Score (PSDSS)

PSDSS was introduced as a patient selection tool to improve the results obtained by applying PCI only. The stratification of patients using this method is based on the severity of the peritoneal disease and uses 3 parameters: the peritoneal carcinomatosis index (PCI), the patient's symptoms due to the peritoneal metastasis and the histological origin of the primary tumor. The impact of these parameters on the patient is classified into 4 degrees of severity (I-IV) as follows: grade I, PSDSS <4; grade II, PSDSS 4-7; grade III, PSDSS 8-10; grade IV, PSDSS> 10. There are studies that compared the outcomes of patients according to their PSDSS score and the used citotoxic agent. So, in the case of using cisplatin and paclitaxel the group of patients characterized by a PSDSS score grade III/IV presented significantly shorter survival rate (57 months for cisplatin group) than those with PSDSS score grade I/II (113 months for cisplatin group). Regarding the use of cisplatin associated with doxorubicin there was no significantly difference between the two groups. (P value 0,19) [19].

Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Intraperitoneal chemotherapy consists of lavaging the peritoneal cavity with cytotoxic substances. The great advantage of intraperitoneal administration of chemotherapeutic agents is low systemic toxicity that makes prolonged exposure and higher doses of intra-abdominal tumors to antineoplastic agents possible. Basically, the purpose of intraperitoneal chemotherapy is to obtain high concentrations of chemotherapeutic agents, especially in areas with peritoneal carcinomatosis, to eradicate the eventually microscopic deposits remnant after cytoreduction is performed.

HIPEC involves intraperitoneal administration of cytotoxic agents at a temperature above 41 °C. It has been shown that at above 41 °C, they have selective cytotox-

icity on tumor cells, acting by protein denaturation, inhibition of oxidative metabolism, increasing the pH, activation of lysosomes and activation of cellular apoptosis [20-22]. Moreover, temperatures above 41 °C increase the cytotoxic effect of cytotoxic agents as well as increase absorption and penetration into the tumoral tissue [20-22]. Hyperthermia has proven benefits in the treatment of primary or secondary tumors of the peritoneum by direct cytotoxic effect and by potentiating the action of administered chemotherapy. Mechanisms that help to achieve the direct cytotoxic effect of temperature on malignant cells are represented by damaging the DNA repairmen process, inhibition of aerobic metabolism and protein denaturation in the tumor cell. These phenomena lead to acidosis in the cellular environment, which causes lysosome activation and ultimately cellular apoptosis. Besides the direct cytotoxic effect, which in some cases can be reduced due to the increased expression of "heat-shock proteins", the application of hyperthermia potentiates cytotoxic action, which is possible due to damaging ATP transporters which leads to an increased accumulation of chemotherapeutic agents in the malignant cells. At the same time, hyperthermia conditions interfere with the metabolic pathways of the used drug and, last but not least, with the repairment process of the damaged DNA. Also, the increased intraperitoneal administration of chemotherapeutic agents leads to an increased penetration of these in the malignant tissue and affected lymph nodes [23].

The role of hyperthermia has been highlighted in studies that indicate the superiority of HIPEC vs. early postoperative intraperitoneal chemotherapy (EPIC) or sequential postoperative intraperitoneal chemotherapy (SPIC), which are both normothermic lavage methods [23,24]. The benefits of HIPEC have been translated through greater survival rate due to lower recurrence risk and a lower rate of postoperative complication [23,24]. Thus, the recommended temperature of the peritoneal lavage solution is between 41-43 °C, the exposure period being between 30 minutes (for Oxaliplatin) and 60-120 minutes (for MMC) [21,22,25]. Achieving optimal temperature and maintaining it is conditioned by the presence of increased flow of intraperitoneal lavage, which is possible due to modern dedicated devices [26] (Fig. 1a, b, Fig. 2)

Cytoreductive surgery causes extensive trauma to the tissues and has as a consequence the decrease of the central temperature of the patient and an important loss of fluids due to laparotomy. The effects of the hyperthermal phase are superposable to a hyperdynamic status associated with the acute increase of intraabdominal pressure with the occurrence of systemic vasodilation and the release of a large amount of cytokines [27]. These important hemodynamic changes were similar to those occurring in the septic shock; in both cases there is a circulation collapse, renal toxicity being more severe due to the hemodynamic impact than the toxicity of the chemical agents used, demonstrating also the improvement obtained by compensating the liquid losses and by using inotropic agents to compensate for circulatory collapse [28].

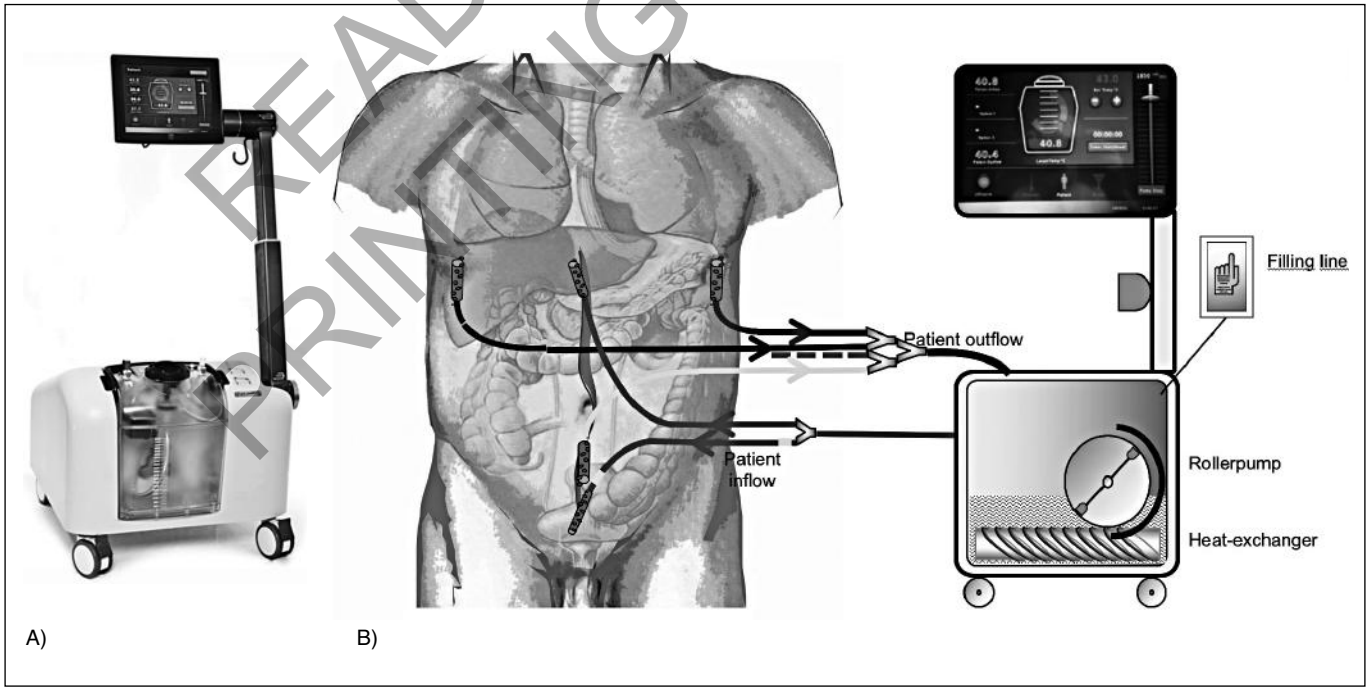

Fig.1: A) HIPEC machine (with kind permission of Eight Medical International B.V).
B) HIPEC "closed" circuit with inflow and outflow peritoneal drains. (with kind permission of Eight Medical International B.V).

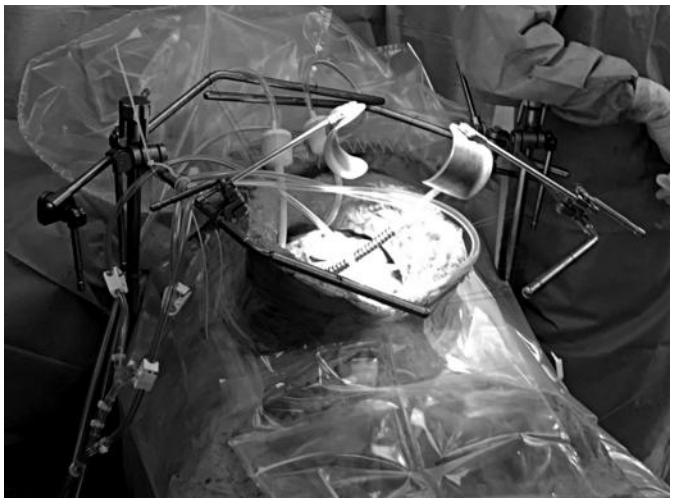

Fig. 2: "Open abdomen" HIPEC procedure; intraoperative aspect (from the personal files of the authors).

TABLE I - *Molecular weight and area-under-the-curve ratios of intraperitoneal exposure to systemic exposure of chemotherapeutic agents used to treat peritoneal carcinomatosis (after Der Speeten, et al [44]).*

Drug	Molecular Weight (Da)	Area unde the curve ratio
5 Fluorouracil	130.08	250
Carboplatin	371.25	10
Cisplatin	300.1	7.8
Docetaxel	861.9	552
Etoposide	588.58	65
Floxuridine	246.2	75
Gemcitabine	299.5	500
Irinotecan	677.19	No data available
Melphalan	305.2	93
Mitomycin C	334.3	23.5
Mitoxantrone	517.41	115-255
Oxaliplatin	397.3	16
Paclitaxel	853.9	1000
Pemetrexed	597.49	40.8

Indications of HIPEC. Current state.

In the past, the presence of peritoneal carcinomatosis staged the disease into an advanced stage, without any available radical treatment. Currently, cytoreductive surgery associated with HIPEC has become an increasingly used technique for the treatment of cancers with secondary peritoneal determinations as well as primary peritoneal tumors. The main neoplasms for which this technique is used are: ovarian cancer, colorectal cancer, and peritoneal pseudomixoma [4]. Currently there are centers that are using this treatment for gastric cancer and rare neoplasms [29,30].

Ovarian cancer accounts for 25% of the neoplasms affecting the female genital tract [31]. HIPEC-associated cytoreduction surgery can be applied in the treatment of ovarian cancer as well as the first line of treatment and in the case of peritoneal recurrence.

Starting with 2017, international guidelines recommend CRS + HIPEC also for cases with peritoneal carcinomatosis of colorectal origin [4], the favorable outcomes being highlighted by 1 randomized trial [32], 2 multicentric studies [8,33], several Phase II-III studies and numerous other literature reports [34].

Primary tumors (malignant peritoneal mezotelioma - MPM), if untreated, has a survival rate of less than 1 year. Together with the development of CRS and HIPEC the survival rate increased. At present, the first line of treatment for patients with MPM is represented by CRS and HIPEC, with median survival rates reported by different studies ranged between 38 and 92 months. CRS and HIPEC is also considered to be efficient in recurrent MPM [35].

In order to obtain optimal results, patient selection is a very important step and multiple exclusion criteria have been developed as follows: age over 70 years, multiple comorbidities, continuous evolution of neoplastic disease despite appropriate systemic treatment, the altered biological status of the patient, the presence of extra-abdominal or liver metastases, or any other contraindication of chemotherapy. In addition to these absolute exclusion criteria, some minor criteria have been developed in order to achieve a more rigorous selection. The minor criteria are: absence of decreasing tumor marker values despite optimal systemic chemotherapy, obesity with BMI> 40, history of pelvic radiotherapy, history of several surgeries (> 4) and presence of bowel occlusion [36,37]. As for the age of patients, there are studies that demonstrate that patients over 70 years have an increased risk of complications and postoperative deaths [38]. To support this study, there is data from other studies that shows that patients aged over 75 years which receive HIPEC associated with extensive surgery have no prognostic benefit compared to those who only benefit from optimal systemic therapy [39].

The optimal timing to perform HIPEC is immediately after the tumor cytoreduction and before any reconstruction of the digestive tract is done. If recurrence occurs after CRS / HIPEC, especially in patients with recurrence occurring over a considerable period of time, reassessment for a new CRS / HIPEC procedure should be considered. The reapeted CRS / HIPEC procedure has a postoperative morbidity and mortality rate similar to that encountered after the first procedure [40]. In order to achieve optimal results after the second CRS / HIPEC session, it is imperative that both patient selection and the timing for surgery are made with the utmost rigor. Also, a suboptimal initial cytoreduction (R2) is not an absolute contraindication for repeating the CRS / HIPEC procedure. The decision to repeat the procedure should

be taken only in cases where positive results (CC0 resections) can be obtained with a satisfactory quality of life. In some cases, repeating the procedure may even result in a free range of substantial disease [41].

The role of systemic chemotherapy

The role of systemic chemotherapy remains particularly important, contributing essentially to completing the treatment, by its neoadjuvant or adjuvant character, depending on each case. Moreover, for some pathologies (colorectal carcinomatosis), concomitant intra-operative administration of systemic cytotoxic agents leads to a potentiation of intraperitoneal cytotoxic effect by reaching a bidirectional diffusion gradient [22,42,43] (Fig. 3).
Typically, 5-fluorouracil and folinic acid are administered intravenously 30-60 minutes prior to starting HIPEC [22].

Cytotoxic drugs used in HIPEC procedure

5-Fulorouracil (5FU)

5 Fluorouracil is still the cornerstone of oncological therapy in colorectal cancer, despite the fact that it was discovered more than 40 years ago. (Fig. 4) This cytotoxic agent is part of the 5-fluoropyrimidine class and once inside the cell, it is transformed into various nucleotidic compounds with cytotoxic effect via several biochemical pathways [44]. 5FU has a cytotoxic effect by several mechanisms: inhibition of Thymydilat synthase, adhesion to RNA and DNA. The inhibition of Thymydilat Synthase is believed to cause the activation of programmed cell death and the induction of nuclear DNA fragmentation. The ability to produce Thymydilat synthetase inhibition gives to 5FU the advantage of potentiating the antitumoral action of the radiation. Over time, several mechanisms of cell resistance to the action of 5FU have been identified. The most important mechanism of resistance is the modification of the target enzyme, Thymydilat synthase. Numerous studies highlight that tumor cells with a much higher Thymylate Synthase activity are more resistant to 5FU treatment. Also, the structural changes of Thymydilat synthase leading to a poor binding of the antitumor agent determine resistance. The enhanced action of Dihydropirmidine dehydrogenase results in an accelerated metabolism of 5FU, thus inhibiting the antitumor effect [45].

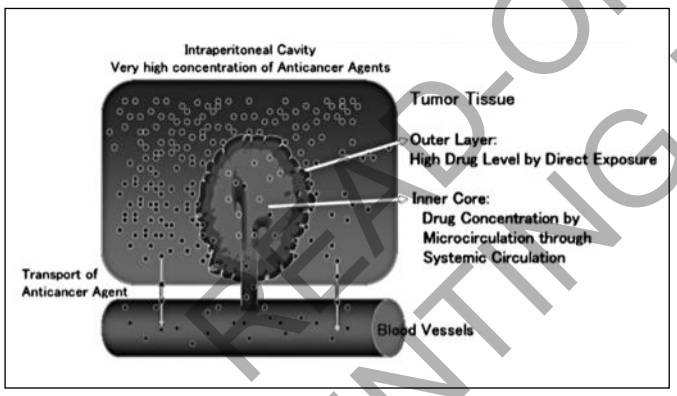

Fig. 3: Bidirectional i.v. and intraperitoneal delivery of chemotherapeutic drugs. (from Ref.22, Van der Speeten et al, 2012).

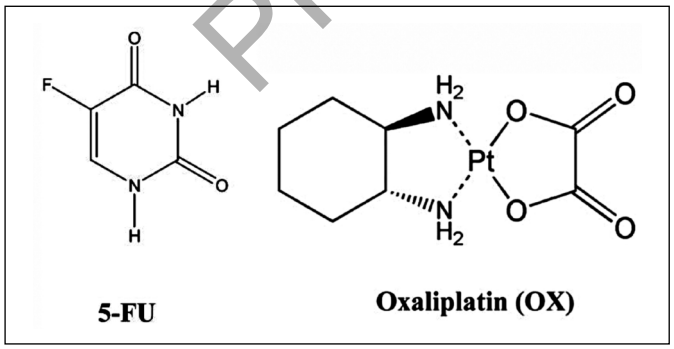

Fig. 4: Chemical structure of 5FU (left) and Oxaliplatine (right).

Mitomycin C

Mitomycin C is a chemotherapeutic agent with antibiotic and alkilant effect, extracted from Streptomyces species whose main mechanism of action is represented by cross-linking the DNA molecule. The drug undergoes transformation into the active form once it penetrates inside the malignant cell and is inactivated by microsomal enzymes in the liver. It is also metabolised to the spleen and kidney [46].
Mitomycin C is a widely used chemotherapeutic agent in HIPEC procedures, especially because of the large molecular weight which limitates the transperitoneal absorption, thus decreasing the amount of cytotoxic agent in the systemic circulation, which has the main consequence of decreasing the incidence of adverse reactions. Unlike systemic administration that provides low doses of peritoneal antitumor agent, intraperitoneal administration provides high doses of chemotherapeutic agents at the level of remnant microscopic deposits, and the cytotoxic effect obtained is highly improved. The increase of the cytotoxic effect is also due to the use of hyperthermia which increases both the direct cytotoxic capacity of Mitomycin C and the tissue depth at which it acts. Intraperitoneal administration is not without side effects, the most pronounced being neutropenia; female gender and the increased dose of Mitomycin C/m^2 represents the main risk factors for developing this adverse reaction [47]. This cytotoxic agent is used both for the treatment of peritoneal carcinoma secondary to colorectal, ovarian, gastric or appendicular cancer and for the treatment of malignant mesothelioma.

Cisplatin

Cisplatin is the first platinum-derived chemotherapeutic agent widely used in oncologic treatment schemes. The anti-tumor effect is due to the induction of cellular apoptosis by the formation of DNA adducts. This antitumor agent has been used for ovarian and gastric cancer but also for mesothelioma and round small cell desmoid tumors. Since its inception, it has been observed that its increased toxicity influences its effectiveness as an anti-tumor agent. Despite the fact that it is particularly effective for cancers, this chemotherapeutic agent has not proven its effectiveness in all the malignancies in which it was attempted [45]. Excretion is performed by the kidney, so Cisplatin-induced toxicity is the main adverse effect of administering this anti-tumor agent, due to both the toxicity exerted on the epithelial cells of the kidney and by lowering the blood flow at this level. Nephrotoxicity induced by the use of Cisplatin was observed in 28-36% of patients receiving a single 50 mg/m^2 dose. Most often, chronic kidney failure caused by Cisplatin occurs a few days later after administration and is manifested by increased creatine and serum urea levels with preserved diuresis. Some cases may even develop chronic kidney failure. Hypomagnesaemia is another marker of renal impairment caused by Cisplatin, and this can occur even in the presence of a preserved glomerular filtration rate. Concomitant use of other nephrotoxic agents leads to increased risk of developing renal impairment. There are other factors contributing to the appearance of renal impairment: low intraoperative diuresis and use of angiotensin II receptor blockers [48]. Low blood pressure was associated with an increased rate of kidney failure. Thus, stopping antihypertensive therapy in patients' oncologic treatment with Cisplatin should be considered if we try to reduce the renal toxic effect [49]. Cisplatin is an anti-tumor agent commonly used for performing HIPEC procedures, with little data on renal toxicity caused by intraperitoneal administration. Studying the pharmacokinetics of Cisplatin in HIPEC procedures has shown that the amount of cytotoxic agent that reaches the systemic circulation and can give the known adverse effects is much diminished, and the adverse effects that occur are caused by the extremely aggressive surgery [50]. Analysis of Cisplatin dosing resulted in the findings that a dose higher than 240 mg/m^2 was associated with poor postoperative outcomes and elevated serum creatinine.[51].

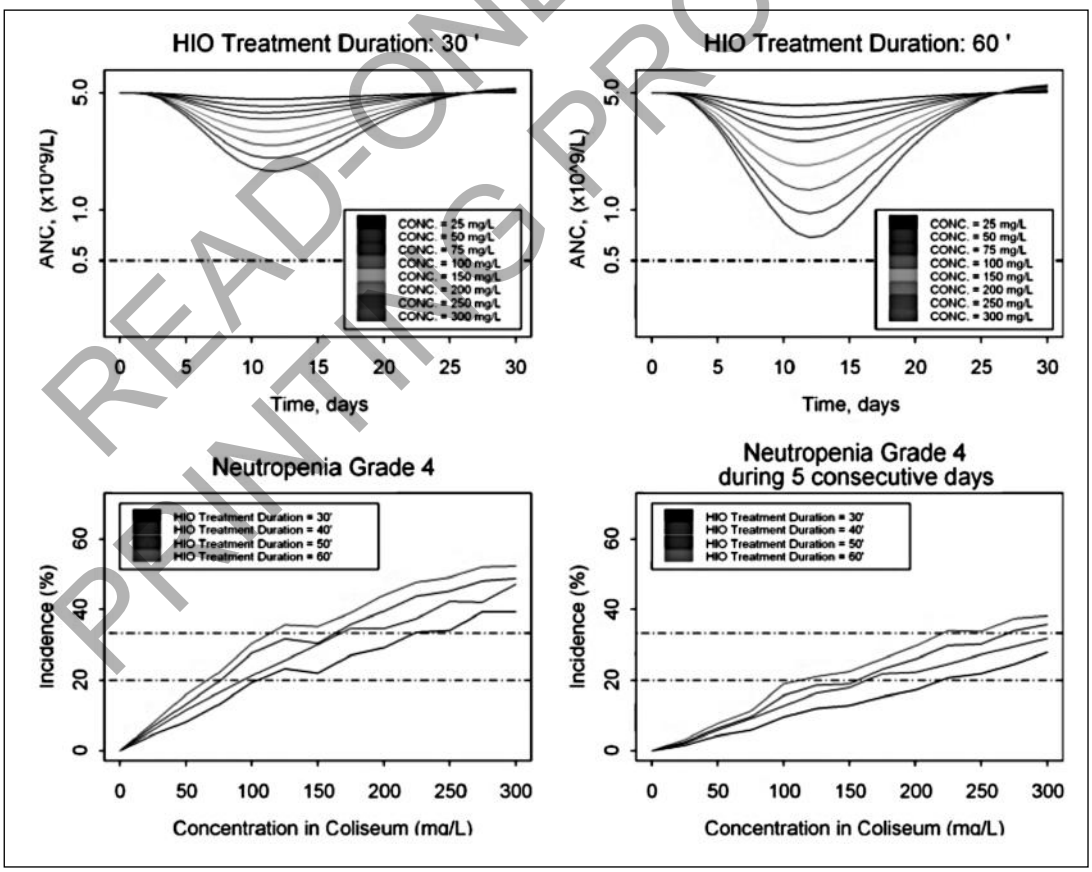

Fig. 5: Effect of initial oxaliplatin concentration in peritoneum and hipertermic intraperitoneal treatment (HIO) duration on the time course of neutrophil counts (upper panels) and on the incidence of neutropenia grade 4 and grade 4 lasting at least 5 days (lower panels) (from Ref 54, Valenzuela B et al, 2011).

Oxaliplatin

Oxaliplatin (oxalate-1,2-diaminocyclohexane-platinum I) (Fig. 4) is a third-generation platinum derivative with a cytotoxic effect which is proven both in adjuvant therapy and palliative treatment of colorectal cancer, its efficacy being demonstrated in combination with 5-Fluorouracil. The efficacy of oxaliplatin has also been proven in other digestive cancers such as pancreatic cancer, gastric cancer and, most importantly, esophagus cancer [45]. The mechanism of action of oxaliplatin is similar to other platinum-class agents, formation of DNA adducts that induce cellular apoptosis. Its high molecular weight gives Oxaliplatin the ability of not passing the peritoneal barrier, thus reducing the degree of systemic toxicity. In vitro studies have demonstrated increased cytotoxicity of this chemotherapeutic agent in hyperthermia conditions, which led to its use for HIPEC procedures [52].

Starting from the premise that Oxaliplatin does not show stability in the carrier solutions based on chlor, in vitro studies have been conducted to analyze this hypothesis. Replacement of chlorine-based solution with Dextrose 5% leads to the occurrence of severe hyperglycemia and hydro-electrolytic equilibrium disorders, which have as a consequence an increased rate of postoperative morbidity and mortality. The instability of oxaliplatin in chlorine-based solutions has been predicted to be due to chlorine ions. This instability is also lowering the oncolytic capacity of oxaliplatin during HIPEC procedures. The in vitro study of the stability of Oxaliplatin in different carrier substances with different concentrations of chloride demonstrated a slight decrease in the active substance concentration, which was found to be directly proportional to the increase in chloride concentration. However, the decrease in oxaliplatin concentration was found to be limited, after 30 minutes 90% of the initial chemotherapeutic agent being present; at 120 minutes the concentration did not fall below 85%. It has also been observed that oxaliplatin degradation into 2 compounds is likely to even amplify the cytotoxic activity of the chemotherapeutic agent. Regarding side effects, it is known that extending the duration of the hipertermic administration, for a given initial oxaliplatin concentration in the peritoneum, will increase the severity and duration of the neutropenia as it is directly related to the oxaliplatin exposure in peritoneum (Fig. 5)[53,54]. In generally, compared to MMC, more pronounced haematological adverse reactions were found if oxaliplatin was used, but they were validated only in patients whose splenectomy was also necessary to achieve optimal cytoreduction.

Carboplatin

Carboplatin, or 1,1-cyclobutanedicarboxylatoplatin II, is a platinum-based chemotherapeutic agent that presents the same carrier amine as Cisplatin but has higher molecular weight, which gives it a reduced systemic absorption and also fewer side effects. The molecular modification of Cisplatin has led to the discovery of Carboplatin with reduced kidney toxicity. Studies conducted on laboratory animals have demonstrated this decrease in renal toxicity, but have shown an increased risk of haematological adverse effects, causing bone marrow suppression, through increased toxicity to the haematogenous bone marrow. Compared to Cisplatin, at effective doses, Carboplatin caused fewer side effects such as nausea, vomiting, renal or neurological toxicity [45]. The main mechanism of action is superposable to other platinum derivatives

Irinotecan. Hydroxycamptothecin

Irinotecan is a semisynthetic compound used as an antitumor agent and has its main mechanism of action the inhibition of topoisomerase 1. The irinotecan molecule suffers the action of carboxylesterase and thus gives rise to 7-methyl 10-hydroxycamptothecin, a compound with more pronounced cytotoxic activity. Topoisomerase 1 is a nuclear enzyme that plays an important role in DNA replication and transcription by creating a reversible breach in a helix chain and eliminating torsional stress, which facilitates the replication and transcription of nuclear DNA. By binding to Topoisomerase 1 and inhibiting the effect of this ubiquitous enzyme, Hydroxycamptothecin prevents the restoration of the brass and favors the final breakage of the helical DNA strand [45]. This chemotherapeutic agent is used for performing CRS / HIPEC in colon cancer in combination with oxaliplatin. Numerous studies reveal evidence of haematological toxicity, but it is considered by other authors that prescribing additional therapy is not necessary [55]. Hematologic toxicity of irinotecan is reported around 11% in the case of bidirectional chemotherapy schemes including intraperitoneal administration of Oxaliplatin and Irinotecan [56].

Diarrhea is a complication that occurs after the first 24 hours of drug administration and may even be life-threatening. The mechanism by which it is being established is not yet fully elucidated, but there are studies that reveal that action on the colon mucosal topoisomerase 1 induces apoptosis of epithelial cells at this level and thus alters hydroelectrolyte changes with the occurrence of an emphasized diarrhea syndrome. In addition to the mucosal changes, Irinotecan and its metabolites stimulate the production and release of various proinflammatory cytokines, which maintain diarrhea by secretory mechanisms [45].

Although oxaliplatin remains the major cytotoxic agent used for HIPEC in patients with advanced colorectal cancer, Irinotecan is an alternative to be considered in cases of neoplastic disease progression or development of intolerable adverse effects on oxaliplatin therapy [55].

Doxorubicin

Doxorubicin is a member of the anthracycline class, being one of the most used anticancer agents over the years. Anthracyclines show a flat molecule with hydrophobic properties. They maintain the oxido-reduction reactions and thus lead to the production of free radicals, which cause both the cytotoxic effect and the cardiovascular side effects that this class of drugs is responsible for. Anthracyclines also have a secondary mechanism of action inhibiting topoisomerase 2, a phenomenon that causes injury to tumor cell DNA. Over the years, research has been conducted to find pharmaceutical variants with fewer side effects, so the liposomal form of doxorubicin has been identified. Doxorubicin has been shown to be effective in the treatment of many types of neoplastic diseases such as lymphomas, nephroblastomas sarcomas and neuroblastomas but it can also be used in advanced stages of gastric, prostate or breast cancers. Neither this cytotoxic agent is free from side effects, most notably being: medullary suppression, nausea, vomiting and hair loss [45].

Results

Colorectal Cancer

The treatment of colorectal cancer with peritoneal carcinomatosis has made significant improvements with the development of systemic chemotherapy, but especially through the widespread application of CRS/HIPEC procedures. Overall survival of patients diagnosed with colorectal cancer with peritoneal carcinomatosis treated with CRS/HIPEC is reported by some studies as 50% at 5 years [57]. However, there are some more pragmatic studies that report the overall survival rate between 20 and 30%. The incidence of complications reported in patients receiving CRS/HIPEC for colorectal cancer with peritoneal carcinomatosis is reported in the literature around 40% with 24% grade III or more severe complications [58].

To improve the outcomes and to increase the overall survival rate, it is necessary to identify the patients who present risk factors for developing postoperative complications. Numerous patient-related risk factors have been incriminated in the development of postoperative complications. The most important of these are: age, hypoalbuminemia, low preoperative performance status and obesity [59].

In addition, there are a number of surgical risk factors: the peritoneal carcinomatosis index, the length of the resected segment of small bowel, diaphragm involvement in the neoplastic and resection process, the resection of the pancreas, hepatobiliary or urinary structures, iterative HIPEC procedures (reHIPEC), high-grade histology, perioperative systemic chemotherapy, and last but not least the surgeon's experience [60,61].

One of the most important individual predictive factors for morbidity and mortality is the peritoneal carcinomatosis index, which is explained by the need for extensive resections to obtain a cytoreduction score of 0 (CC0) [62].

Extensive resections involving important organs such as diaphragm, small intestine, pancreas, liver, gall bladder or urinary organs cause an increased risk of postoperative complications leading to a decrease in overall survival and worsening the outcomes of this procedure which is still under standardization. Furthermore, an increased index of carcinomatosis (> 16-20) is associated with the difficulty of obtaining a CC0 score, being shown that an incomplete cytoreduction leads to a decreased survival rate [9].

In addition to the influence of patient or surgeon-dependent factors, the properties of the used cytotoxic agent may lead to complications and thus influence the immediately or late prognosis. MMC used alone for HIPEC procedures leads to 28% of cases of medullary suppression; neutropenia can be fatal in 66% of cases where it is classified as grade IV. The use of platinum-derived agents such as Oxaliplatin is known to cause bleeding complications, which is reported by some studies as occurring in a proportion of 50% [59]. Recent studies suggest that the efficacy of MMC and oxaliplatin in patients diagnosed with colorectal cancer and peritoneal carcinomatosis is dependent on the severity of peritoneal carcinomatosis. Overall survival rate of patients was 32.7% for MMC and 31.4% for patients who received oxaliplatin. The same study obtained, by classifying patients into 2 groups according to the peritoneal carcinomatosis severity score, one with PSDSS I / II and one with PSDSS III / IV, a global survival of 54.3% versus 19.4% for the use of MMC and 31.4% versus 30.4% when using oxaliplatin [63].

Importantly, literature indicates that intraperitoneal chemotherapy does not significantly affect morbidity and mortality compared to the situation in which only surgical resection is performed [59]. A review published in 2015, which compares the morbidity, mortality and duration of hospitalization of patients with cytoreduction alone with the results of those who were associated with the HIPEC procedure, does not reveal statistically significant values between the two groups (morbidity 41% versus 45% mortality - 1.1% vs. 2.5%, hospitalization - 11 versus 12 days) [64].

Ovarian Cancer

In the case of ovarian cancer, the development of CRS / HIPEC radically changed the oncologic treatment regimens and the prognosis of these patients. Studies published in the literature encourage CRS / HIPEC in patients diagnosed with advanced ovarian cancer with peritoneal secondary metastasis. An important concern is the ongoing study and improvement of staging systems in order to achieve a better stratification of patients and to be able to

identify with high precision the cases that are suitable for the different types of oncological treatment.
The mean survival rate reported by some authors in CRC / HIPEC-treated women with ovarian cancer was 51 months, with 1-year survival of 85.4%, 2 years of 63.3%, and 5 years of age 56,3% [65]. An American study reports overall survival rates of 73.4 months, which provides more confidence for this procedure [19].
Currently, two randomized trials aim to study the overall survival rate and the disease-free interval and are ongoing in patients undergoing optimal cytoreduction associated with HIPEC procedure performed with cisplatin in doses of 75 mg / m^2 [66]. These two trials are considered useful for optimizing the CRS / HIPEC procedure but also for reassessing the feasibility of this procedure.
A particular category of patients is represented by those with tumor recurrence after radical interventions. In their case, CRS/HIPEC procedure records promising results, but randomized prospective trials are needed to identify the optimal oncologic treatment protocol that generates the highest survival rate. Existing literature data provide overall survival rates ranging from 26.7 to 35 months with a disease-free interval between 8.5 and 48 months [66]. The benefit of HIPEC is illustrated by doubling the overall survival rate of patients with recurrent disease from 13.7 months for systemic chemotherapy associated with surgery to 26.7 months for CRS / HIPEC [67].
CRS / HIPEC associated morbidity is variable in the literature, ranging from 13.6% to 100%, but does not show significantly elevated values compared to cases receiving only surgical treatment followed by systemic chemotherapy [66].

Gastric Cancer

The prognosis of advanced gastric cancer with peritoneal carcinomatosis is reserved with an average survival rate of less than 5 months [29]. Performing CRS / HIPEC can significantly improve this prognosis; there is data from prospective studies currently showing that the median of survival may reach 11 months in patients receiving CRS / HIPEC.
Prognostic factors have been studied in numerous trials. The following were identified as independent prognostic factors: cytoreduction, association of systemic chemotherapy, peritoneal carcinomatosis index, TNM staging, presence of ascites, patient performance status, postoperative complications, and tumor histology [68]. From the point of view of postoperative complications, the most representative are: anastomosic fistula, systemic sepsis, wound infections, ileus and hypoalbuminemia [29].
Even if the so far published results are encouraging, there is still a lack of high-randomized trials. There are two trials (GASTRIPEC and GASTRICHIP) which are conducted in centers of excellence in Germany and France that aim to compare the association of neoadjuvant chemotherapy, CRS / HIPEC and adjuvant chemotherapy with the combination of neoadjuvant chemotherapy, conventional oncologic surgery followed by adjuvant chemotherapy (GASTRIPEC) and survival rates at 5 years and the disease-free interval for CRS / HIPEC patients compared to those undergoing conventional oncology surgery only [69].
The procedures safety, assessed into GASTRICHIP trial did not reveal significant differences between the two groups (CRS / HIPEC vs. conventional curative surgery) with severe morbidity rates of 28.4% vs. 26.2% [29].
In conclusion, the standardized implementation of the CRS / HIPEC technique for patients diagnosed with gastric cancer with peritoneal carcinomatosis is still controversial and to implement this technique into oncologic treatment protocols, prospective studies conducted on large groups of patients are needed. However, introducing CRS / HIPEC into current practice and performing this procedure in experienced centers, for carefully selected patients, is an alternative that improves prognosis and provides greater overall survival than other oncologic therapies.

Perspectives

Fluorescence

Nowadays there are a lot of options for diagnosing tumoral cells inside the abdomen during surgical procedures. One of the most promising tool is represented by Near infrared florescence (NIRF) which can guide the surgeon to spot more precisely the tumoral deposits spreaded on the peritoneal surface. When performing peritonectomies, preserving the uretherus is one of the most important objective. So, by using NIRF the surgeon may visualize the uretherus through the surrounding fat tissue [70]. Another important objective of using NIRF is a better visualization of peritoneal spreading by using tumor-specific fluorescent compounds. In the field of ovarian cancer, this technique requires a specific dye which binds to the folate receptors who has an overexpression in most tumoral cells. There is some evidence of using ICG for surgical practice. This technique is waited to become a very useful tool for surgeons in performing a more appropriate citoreduction [36]. Researchers are conducting new trials in order to improve peritoneal carcinomatosis detection in various cancers (NCT02032485, NCT01982227) [71]. Other fluorescent markers, such as 5-aminolevulinic acid have been studied for performing fluorescent maping of tumoral deposits. 5- aminolevulinic acid was used when performing staging laparoscopies and an improved peritoneal carcinomatsis detection was obtained in 21 % of the patients without any macroscopic signs of peritoneal metastases [72,73]. The authors of a phase I clinical trial

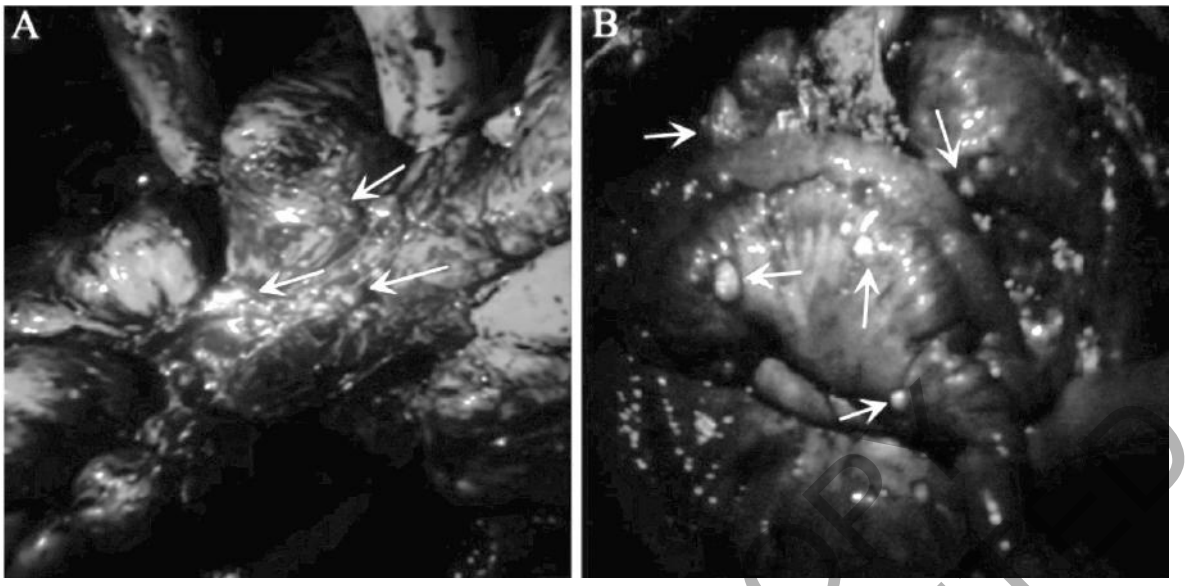

Fig. 6: Peritoneal carcinomatosis from ovarian cancer and primary peritoneal carcinoma emitted strong red fluorescence under irradiation of blue light. Arrows indicate peritoneal disseminated tumor emitting strong red fluorescence. a Peritoneal disseminated tumors from ovarian cancer; b peritoneal disseminated tumors from primary peritoneal carcinoma (from Ref 73, Liu Y et al).

report a 95% rate of detecting peritoneal cancer spreading by using aminolevulinic acid for fluorescent purpose, in cases of ovarian cancer and primary peritoneal cancer, when performing CRS/HIPEC (Fig. 6). The specifity of the method is reported as 100% [73].
It is possible that in the near future this new developed technique will help the surgeons to improve the citoreduction performed during CRS/HIPEC procedures.

Prophylactic HIPEC

A topical concept is to perform HIPEC for prophylactic purposes. This is a promising approach that aims to prevent neoplastic recurrence in patients with high risk of developing peritoneal carcinomatosis. This is supported by literature studies that indicate that 4-19% of patients operated radically for colorectal tumors will develop metacrone peritoneal tumor deposits [9]. Moreover, for locally advanced colorectal tumors, the risk of peritoneal carcinomatosis after radical interventions is 50-60% at 6 months [9].
Patient selection is a very important step and should be done with the utmost rigor. There are several studies evaluating this prophylactic procedure, but in order to be implemented in a standardized way, prospective studies are needed on large groups of carefully selected patients. Existing studies provide confident data on morbidity and perioperative mortality when prophylactic HIPEC is performed, but the obtained results are not significantly improved compared to conventional resections [74,75].
Furthermore, the application of hyperthermic intraperitoneal chemotherapy for prophylactic purposes resulted in statistically superior results in terms of peritoneal carcinomatosis occurrence and long-term survival. Thus, comparing 2 patient groups, one consisting of 25 patients who received profilactic HIPEC associated with surgical resection with another of 50 patients who underwent only conventional oncological resection, the authors provided encouraging results for the first technique, resulting in a decreased peritoneal carcinomatosis incidence from 28% to 4%, with a prolonged long-term survival rate [76].

Presurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

PIPAC is a minimally invasive technique used for treating patients with peritoneal carcinomatosis or primary peritoneal tumors which is still under study. With the onset of intraperitoneal chemotherapy, the major concern was to improve the penetrance of cytotoxic substances into the tumor tissue, something that has been achieved in someway for HIPEC procedures. PIPAC is a new technique designed to improve the results obtained by conventional intraperitoneal chemotherapy and consists in the intraperitoneal administration of cytotoxic aerosols via capnoperitoneum. Instead of practicing intraperitoneal lavage with cytotoxic substances (HIPEC), in the case of PIPAC, the antitumor agent is distributed into the peritoneal cavity by mixing with carbon dioxide, thus forming aerosols with cytotoxic properties. Aerosols are composed of 2 phases: a liquid phase and a gaseous one and if the liquid component is of very

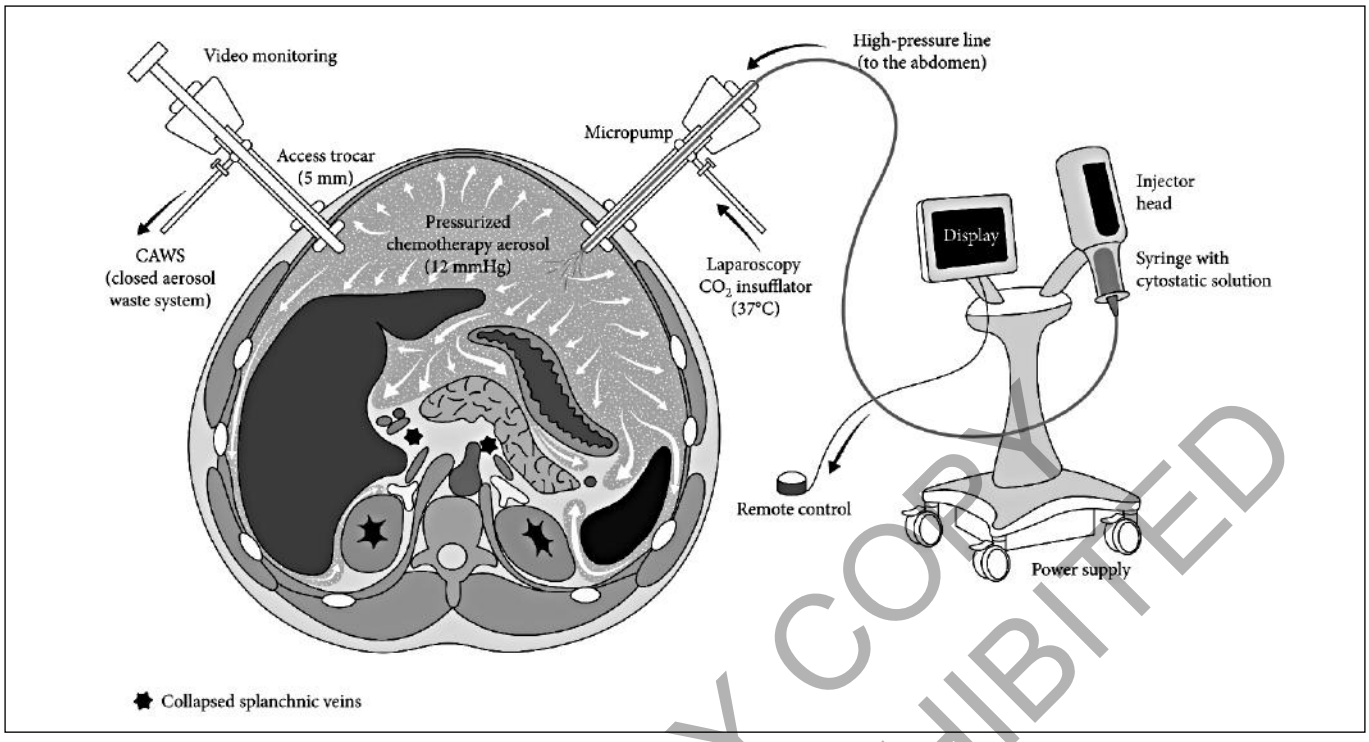

Fig. 7: Pressurized intraperitoneal aerosol chemotherapy (PIPAC). The abdominal cavity is accessed with 2 balloon trocars allowing hermetic seal. Liquid chemotherapy is dispersed as aerosol by use of a standard injector and a specific nebulizer. (from Ref 79, Hubner M et al)

small size, aerosols behave like a gas. The physical property of gas spreading uniformly in a closed cavity gives this technique the advantage of homogeneously distributing the cytotoxic substance in the peritoneal cavity. At a theoretical level, better intraperitoneal proliferation of antitumor agents and increased penetrance to tumor tissue give this new technique valuable advantages in the treatment of peritoneal carcinoma [77,78].

There is evidence of PIPAC used as a neoadjuvant treatment for CRS / HIPEC. This method can be applied in cases where CRS / HIPEC can not be performed primarily, due to the presence of contraindications. The most common reason why patients are not optimal candidates for CRS / HIPEC is the presence of extensive peritoneal carcinomatosis on the small intestine, which makes it impossible to achieve a cytoreductive score that allows intraperitoneal chemotherapy to be performed according to existing indications. In these cases, performing one or more PIPAC sessions can lead to regression of peritoneal carcinoma, which can make CRS / HIPEC possible in a later time. In conclusion, PIPAC associated or not with systemic neoadjuvant chemotherapy may be a feasible alternative for patients who are not eligible for CRS / HIPEC, but randomized prospective studies are needed to postulate this and to be able to introduce PIPAC as a standard technique in oncologic treatment protocols [79] (Fig. 7).

Discussions and Conclusions

Although peritoneal carcinomatosis has been considered for a long time the final stage of abdominal neoplasia, it is clear now that the situation has changed, recent studies from the literature showing that CRS and HIPEC may represent the radical treatment with an important impact on the outcome of these patients. This treatment should be part of a multidisciplinary management, systemic chemotherapy often having an additive role in enhancing the cytotoxic effect. Even though the role of chemotherapeutic agents is well established, the continued development of the pharmaceutical industry has the potential role to improve the treatment of these patients, the main goal being to lower the incidence of adverse effects and to increase the survival period.

In addition to conventional systemic chemotherapy, HIPEC offers the possibility of increased doses of chemotherapeutic agents, with low hematological toxicity, all of these beeing possible due to the physiochemical properties of the peritoneal complex.

Although nowadays, based on the experience of high volume centers, there are some guidelines related to the dosages and the optimal concentration of chemotherapeutic agents used intraperitoneally, a standardization based on pharmacodynamic and pharmacokinetic studies is still needed, this subject being in the attention of specialized research teams.

Unfortunately, results from CRS and HIPEC, although optimistic, are often limited by the late diagnosis and the high rate of relapse after treatment. Therefore, the most important research lines should primarily target the improvement of the chemotherapeutic agents used, nanomedicine being able to play an important role in the development of teranosic nanobioconjugates, both in diagnosis and targeted treatment. Regarding pre and intraoperative diagnosis of carcinomatosis, current diagnostic methods (fluorescence, NIR, etc.), by providing an accurate mapping of malignant implants could lead to increased operability rates (a better patient selection) and to a higher incidence of complete cytoreductive treatment (CC0).

Riassunto

La carcinosi peritoneale rappresenta lo stadio avanzato e finale dell'impegno neoplastico del peritoneo, sebbene spesso non sia accompagnata da diffusione sistemica delle neoplasie. Lo sviluppo dell'industria farmaceutica in combinazione con tecniche chirurgiche avanzate ha contribuito a migliorare l'esito di questi pazienti, considerati a lungo senza risorse risolutive. La citoriduzione tumorale seguita da chemioterapia intraperitoneale ipertermica (HIPEC) è naturalmente il trattamento di scelta per questi pazienti, eseguito con impegno multimodale, scelto con cura, seguendo un consenso multidisciplinare.
In questo articolo abbiamo esaminato i principali aspetti della procedura HIPEC, descrivendo i principali agenti chemioterapici utilizzati, evidenziando il ruolo che svolgono in questo trattamento oncologico. Infine, abbiamo individuato le principali linee di ricerca in questo campo, che sebbene abbiano un ruolo consolidato nelle recenti linee guida, hanno un grande potenziale di sviluppo, con un impatto massimo sulla prognosi dei pazienti con metastasi peritoneali.

Acknowledgement

Bartos Adrian, Dana Bartos, Andrei Herdean, Bianca Szabo equally contributed to this article (see below the contributions) so for that, they area all main authors: conception and design of the article and the acquisition of data; drafting the article; final approval of the version to be published.
Claudia Militaru and Stoian Raluca had substantial contributions to conception, design of the review and acquisition of data.
Mitre Calin and Cornel Iancu had substantial contributions in regard with drafting the article and revising it critically.
Caius Breazu had substantial contributions in regard with review design, acquisition of data and final approval of the version to be published.

References

1. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al.: *Colorectal cancer statistics, 2017*. CA: *A cancer journal for clinicians.* 2017; 67(3):177-93.

2. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al.: *The Eighth Edition AJCC Cancer Staging Manual*. CA: A cancer journal for clinicians, 2017; 67(2):93-9.

3. El-Nakeep S, Rashad N, Oweira H, Schmidt J, Helbling D, Giryes A, et al.: *Intraperitoneal chemotherapy and cytoreductive surgery for peritoneal metastases coupled with curative treatment of colorectal liver metastases: An updated systematic review*. Expert review of gastroenterology & hepatolog, 2017; 11(3):249-58.

4. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al.: *ESMO consensus guidelines for the management of patients with metastatic colorectal cancer.* Annals of oncology: Official journal of the European Society for Medical Oncology / ESMO. 2016;27(8):1386-422.

5. Bartos A, Bartos D, Szabo B, Breazu C, Opincariu I, Mironiuc A, et al.: *Recent achievements in colorectal cancer diagnostic and therapy by the use of nanoparticles.* Drug Metab Rev, 2016; 48(1):27-46.

6. Bartos A, Bartos DM, Breazu C, Hosu M, Stoian R, Iancu C: *Cytoreductive surgery (CR) followed by hyperthermic intraperitoneal chemotherapy (HIPEC): a chance of survival for patients with advanced colorectal cancer*. Journal of gastrointestinal and liver diseases: JGLD, 2015; 24(3):392-93.

7. *Current indications for cytoreductive surgery and intraperitoneal chemotherapy 2017* [Available from: http://www.surgicaloncology.com/gpmindic.htm.

8. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al.: *Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study*. J Clin Oncol, 2010; 28(1):63-8.

9. Weber T, Roitman M, Link KH: *Current status of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer.* Clinical colorectal cancer, 2012; 11(3):167-76.

10. Araújo R, Lopes G, Aisen M: *Role of cytoreduction surgery with hipec in the management of peritoneal carcinomatosis from colorectal cancer and pseudomyxoma peritonei.* Curr Colorectal Cancer Rep, 2015:1-6.

11. Glehen O, Cotte E, Schreiber V, Sayag-Beaujard AC, Vignal J, Gilly FN: *Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin.* Br J Surg, 2004; 91(6):747-54.

12. Kecmanovic DM, Pavlov MJ, Ceranic MS, Sepetkovski AV, Kovacevic PA, Stamenkovic AB: *Treatment of peritoneal carcinomatosis from colorectal cancer by cytoreductive surgery and hyperthermic perioperative intraperitoneal chemotherapy.* Eur J Surg Oncol, 2005; 31(2):147-52.

13. Yan TD, Morris DL: *Cytoreductive surgery and perioperative intraperitoneal chemotherapy for isolated colorectal peritoneal carcinomatosis: experimental therapy or standard of care?* Annals of surgery, 2008; 248(5):829-35.

14. Vaira M, Cioppa T, D'Amico S, de Marco G, D'Alessandro M, Fiorentini G, et al.: Treat*ment of peritoneal carcinomatosis from colonic cancer by cytoreduction, peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC). Experience of ten years*. In vivo, 2010; 24(1):79-84.

15. Cavaliere F, De Simone M, Virzi S, Deraco M, Rossi CR, Garofalo A, et al.: *Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: Italian multicenter study S.I.T.I.L.O.* Eur J Surg Oncol, 2011; 37(2):148-54.

16. Chua TC, Morris DL, Saxena A, Esquivel J, Liauw W, Doerfer J, et al.: I*nfluence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: A multicenter study*. Ann Surg Oncol, 2011; 18(6):1560-567.

17. Sugarbaker PH: *Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis*. Seminars in surgical oncology, 1998; 14(3):254-61.

18. Edge SB, Compton CC: *The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM*. Ann Surg Oncol, 2010; 17(6):1471-474.

19. Sleightholm R, Foster JM, Smith L, Ceelen W, Deraco M, Yildirim Y, et al.: *The american society of peritoneal surface malignancies multi-institution evaluation of 1,051 advanced ovarian cancer patients undergoing cytoreductive surgery and HIPEC: An introduction of the peritoneal surface disease severity score.* Journal of surgical oncology, 2016; 114(7):779-84.

20. Rettenmaier MA, Mendivil AA, Gray CM, Chapman AP, Stone MK, Tinnerman EJ, et al.: *Intra-abdominal temperature distribution during consolidation hyperthermic intraperitoneal chemotherapy with carboplatin in the treatment of advanced stage ovarian carcinoma*. International journal of hyperthermia: the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group, 2015:1-7.

21. Kulu Y, Muller-Stich B, Buchler MW, Ulrich A: *Surgical treatment of peritoneal carcinomatosis: current treatment modalities*. Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie, 2014; 399(1):41-53.

22. Van der Speeten K, Stuart OA, Sugarbaker PH: *Pharmacology of perioperative intraperitoneal and intravenous chemotherapy in patients with peritoneal surface malignancy*. Surgical oncology clinics of North America, 2012; 21(4):577-97.

23. Elias D, Benizri E, Di Pietrantonio D, Menegon P, Malka D, Raynard B: *Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis*. Annals of surgical oncology. 2007; 14(2):509-14.

24. Cashin PH, Graf W, Nygren P, Mahteme H: *Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: Prognosis and treatment of recurrences in a cohort study.* Eur J Surg Oncol, 2012; 38(6):509-15.

25. Kitayama J: *Intraperitoneal chemotherapy against peritoneal carcinomatosis: Current status and future perspective.* Surgical oncology, 2014; 23(2):99-106.

26. Furman MJ, Picotte RJ, Wante MJ, Rajeshkumar BR, Whalen GF, Lambert L: *Higher flow rates improve heating during hyperthermic intraperitoneal chemoperfusion*. Journal of surgical oncology-2014; 110(8):970-75.

27. Vlaeminck-Guillem V, Bienvenu J, Isaac S, Grangier B, Golfier F, Passot G, et al.: *Intraperitoneal cytokine level in patients with peritoneal surface malignancies. A study of the RENAPE (French Network for Rare Peritoneal Malignancies).* Annals of surgical oncology, 2013; 20(8):2655-662.

28. Coccolini F, Corbella D, Finazzi P, Brambillasca P, Benigni A, Prussiani V, et al.: *Time course of cytokines, hemodynamic and metabolic parameters during hyperthermic intraperitoneal chemotherapy*. Minerva Anestesiol, 2015.

29. Ji ZH, Peng KW, Yu Y, Li XB, Yonemura Y, Liu Y, et al.: *Current status and future prospects of clinical trials on CRS + HIPEC for gastric cancer peritoneal metastases. International journal of hyperthermia: the official journal of European Society for Hyperthermic Oncology.* North American Hyperthermia Group, 2017;33(5):562-70.

30. Brandl A, Zielinski CB, Raue W, Pratschke J, Rau B: *Peritoneal metastases of rare carcinomas treated with cytoreductive surgery and HIPEC. A single center case series*. Ann Med Surg (Lond), 2017; 22:7-11.

31. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: *Global cancer statistics. CA: a cancer journal for clinicians.* 2011; 61(2):69-90.

32. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al.: *Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer.* Journal of clinical oncology: Official journal of the American Society of Clinical Oncology, 2003; 21(20):3737-743.

33. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al.: *Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: A multi-institutional study*. J Clin Oncol, 2004; 22(16):3284-qq92.

34. Cao C, Yan TD, Black D, Morris DL: *A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin*. Annals of surgical oncology, 2009; 16(8):2152-65.

35. Kim J, Bhagwandin S, Labow DM: *Malignant peritoneal mesothelioma: A review.* Ann Transl Med, 2017; 5(11):236.

36. Polom K, Roviello G, Generali D, Marano L, Petrioli R, Marsili S, et al.: *Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for treatment of ovarian cancer*. Int J Hyperthermia, 2016; 32(3):298-310.

37. Dube P, Sideris L, Law C: *Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms.* Curr Oncol, 2015; 22:100-12.

38. Votanopoulos KI, Newman NA, Russell G, Ihemelandu C, Shen P, Stewart JH, et al.: *Outcomes of Cytoreductive Surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients older than 70 years; survival benefit at considerable morbidity and mortality.* Annals of surgical oncolog, 2013; 20(11):3497-503.

39. Cascales-Campos P, Gil J, Gil E, Feliciangeli E, Lopez V, Gonzalez AG, et al.: *Cytoreduction and HIPEC after neoadjuvant*

chemotherapy in stage IIIC-IV ovarian cancer. Critical analysis in elderly patients. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2014; 179:88-93.

40. Mogal H, Chouliaras K, Levine EA, Shen P, Votanopoulos KI: *Repeat cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: Review of indications and outcomes.* J Gastrointest Oncol, 2016; 7(1):129-42.

41. Votanopoulos KI, Ihemelandu C, Shen P, Stewart JH, Russell GB, Levine EA: *Outcomes of repeat cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal surface malignancy*. Journal of the American College of Surgeon, 2012; 215(3):412, 7.

42. Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S, El OA, et al.: *Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution.* Annals of oncology: official journal of the European Society for Medical Oncology / ESMO, 2002; 13(2):267-72.

43. Fujiwara K, Armstrong D, Morgan M, Markman M: *Principles and practice of intraperitoneal chemotherapy for ovarian cancer.* International journal of gynecological cancer: official journal of the International Gynecological Cancer Society, 2007; 17(1):1-20.

44. Van der Speeten K, Stuart OA, Sugarbaker PH: *Using pharmacologic data to plan clinical treatments for patients with peritoneal surface malignancy.* Current drug discovery technologies, 2009; 6(1):72-81.

45. Rosenberg S, DeVita V, Lawrence T: *Devita, Hellman, and Rosenberg's cancer: principles & practice of oncology.* 10 ed: Philadelphia: Wolters Kluwer; 2015.

46. Kwakman R, de Cuba EM, de Winter JP, de Hingh IH, Delisvan Diemen PM, Tijssen M, et al.: *Tailoring heated intraperitoneal mitomycin C for peritoneal metastases originating from colorectal carcinoma: a translational approach to improve survival.* British journal of cancer, 2015; 112(5):851-56.

47. Abel ML, Kokosis G, Blazer DG: *Pulmonary toxicity after intraperitoneal mitomycin C: A case report of a rare complication of HIPEC*. World journal of surgical oncology.

48. Hakeam HA, Breakiet M, Azzam A, Nadeem A, Amin T: *The incidence of cisplatin nephrotoxicity post hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery.* Ren Fail, 2014; 36(10):1486-491.

49. Komaki K, Kusaba T, Tanaka M, Kado H, Shiotsu Y, Matsui M, et al.: *Lower blood pressure and risk of cisplatin nephrotoxicity: A retrospective cohort study.* BMC cancer, 2017; 17(1):144.

50. Ansaloni L, Coccolini F, Morosi L, Ballerini A, Ceresoli M, Grosso G, et al.: *Pharmacokinetics of concomitant cisplatin and paclitaxel administered by hyperthermic intraperitoneal chemotherapy to patients with peritoneal carcinomatosis from epithelial ovarian cancer.* British journal of cancer, 2015; 112(2):306-12.

51. Webb CA, Weyker PD, Moitra VK, Raker RK: *An overview of cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion for the anesthesiologist*. Anesth Analg, 2013; 116(4):924-31.

52. Piche N, Leblond FA, Sideris L, Pichette V, Drolet P, Fortier LP, et al:. *Rationale for heating oxaliplatin for the intraperitoneal treatment of peritoneal carcinomatosis: A study of the effect of heat on intraperitoneal oxaliplatin using a murine model.* Annals of surgery, 2011; 254(1):138-44.

53. Mehta AM, Van den Hoven JM, Rosing H, Hillebrand MJ, Nuijen B, Huitema AD, et al.: *Stability of oxaliplatin in chloride-containing carrier solutions used in hyperthermic intraperitoneal chemotherapy*. International journal of pharmaceutics, 2015; 479(1):23-7.

54. Valenzuela B, Nalda-Molina R, Bretcha-Boix P, Escudero-Ortíz V, Duart MJ, Carbonell V, et al.: *Pharmacokinetic and pharmacodynamic analysis of hyperthermic intraperitoneal oxaliplatin-induced neutropenia in subjects with peritoneal carcinomatosis.* The AAPS journal, 2011; 13(1):72-82.

55. Glockzin G, Gerken M, Lang SA, Klinkhammer-Schalke M, Piso P, Schlitt HJ: O*xaliplatin-based versus irinotecan-based hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastasis from appendiceal and colorectal cancer: A retrospective analysis*. BMC cance, 2014; 14:807.

56. Elias D, Goere D, Blot F, Billard V, Pocard M, Kohneh-Shahri N, et al.: *Optimization of hyperthermic intraperitoneal chemotherapy with oxaliplatin plus irinotecan at 43 degrees C after compete cytoreductive surgery: Mortality and morbidity in 106 consecutive patients*. Annals of surgical oncology, 2007; 14(6):1818-24.

57. Lin EK, Hsieh MC, Chen CH, Lu YJ, Wu SY: *Outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer with peritoneal metastasis.* Medicine (Baltimore), 2016; 95(52):e5522.

58. Lee L, Alie-Cusson F, Dube P, Sideris L: *Postoperative complications affect long-term outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis.* Journal of surgical oncolog, 2017; 116(2):236-43.

59. Newton AD, Bartlett EK, Karakousis GC: *Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: A review of factors contributing to morbidity and mortality.* J Gastrointest Oncol, 2016; 7(1):99-111.

60. Bartlett EK, Meise C, Roses RE, Fraker DL, Kelz RR, Karakousis GC: *Morbidity and mortality of cytoreduction with intraperitoneal chemotherapy: Outcomes from the ACS NSQIP database.* Annals of surgical oncology. 2014; 21(5):1494-500.

61. Randle RW, Ahmed S, Levine EA, Fino NF, Swett KR, Stewart JH, et al.: *Significance of diabetes on morbidity and mortality following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.* Journal of surgical oncology, 2015; 111(6):740-45.

62. Simkens GA, van Oudheusden TR, Luyer MD, Nienhuijs SW, Nieuwenhuijzen GA, Rutten HJ, et al.: *Predictors of severe morbidity after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis.* Annals of surgical oncology, 2016; 23(3):833-41.

63. Prada-Villaverde A, Esquivel J, Lowy AM, Markman M, Chua T, Pelz J, et al.: *The American Society of Peritoneal surface malignancies evaluation of HIPEC with mitomycin c versus oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery.* Journal of surgical oncology, 2014; 110(7):779-85.

64. Bartlett EK, Choudhury RA, Roses RE, Fraker DL, Kelz RR, Karakousis GC: *Intraperitoneal chemotherapy at the time of surgery is not associated with increased 30-day morbidity and mortality following colorectal resection.* Annals of surgical oncology, 2015; 22(5):1664-672.

65. Kocic M, Nikolic S, Zegarac M, Djurisic I, Soldatovic I, Milenkovic P, et al.: *Prognostic factors and outcomes of cytoreductive*

surgery combined with hyperthermic intraperitoneal chemotherapy in patients with advanced ovarian cancer. A single tertiary institution experience. Journal of BUON: official journal of the Balkan Union of Oncology, 2016; 21(5):1176-83.

66. Hotouras A, Desai D, Bhan C, Murphy J, Lampe B, Sugarbaker PH: *Heated Intra Peritoneal Chemotherapy (HIPEC) for patients with recurrent ovarian cancer: A systematic literature review*. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society, 2016; 26(4):661-70.

67. Spiliotis J, Halkia E, Lianos E, Kalantzi N, Grivas A, Efstathiou E, et al.: *Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: A prospective randomized phase III study*. Annals of surgical oncology. 2015; 22(5):1570-75.

68. Neuwirth MG, Alexander HR, Karakousis GC: *Then and now: cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC), a historical perspective.* J Gastrointest Oncol, 2016; 7(1):18-28.

69. Desiderio J, Chao J, Melstrom L, Warner S, Tozzi F, Fong Y, et al.: *The 30-year experience-A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer*. Eur J Cancer, 2017; 79:1-14.

70. Polom W, Markuszewski M, Rho YS, Matuszewski M: *Use of invisible near infrared light fluorescence with indocyanine green and methylene blue in urology*. Part 2. Central European journal of urology, 2014; 67(3):310-13.

71. Tipirneni KE, Warram JM, Moore LS, Prince AC, de Boer E, Jani AH, et al.: *Oncologic Procedures Amenable to Fluorescence-guided Surgery*. Annals of surgery, 2017; 266(1):36-47.

72. Kishi K, Fujiwara Y, Yano M, Motoori M, Sugimura K, Ohue M, et al.: *Diagnostic laparoscopy with 5-aminolevulinic-acid-mediated photodynamic diagnosis enhances the detection of peritoneal micrometastases in advanced gastric cancer.* Oncology, 2014; 87(5):257-65.

73. Liu Y, Endo Y, Fujita T, Ishibashi H, Nishioka T, Canbay E, et al.: C*ytoreductive surgery under aminolevulinic acid-mediated photodynamic diagnosis plus hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from ovarian cancer and primary peritoneal carcinoma: Results of a phase i trial*. Annals of surgical oncology,2014; 21(13):4256-262.

74. Sugarbaker PH: *Update on the prevention of local recurrence and peritoneal metastases in patients with colorectal cancer*. World J Gastroenterol, 2014; 20(28):9286-91.

75. Tuvin D, Berger Y, Aycart SN, Shtilbans T, Hiotis S, Labow DM, et al.: *Prophylactic hyperthermic intraperitoneal chemotherapy in patients with epithelial appendiceal neoplasms. International journal of hyperthermia : The official journal of European Society for Hyperthermic Oncology*. North American Hyperthermia Group. 2016; 32(3):311-15.

76. Sammartino P, Sibio S, Biacchi D, Cardi M, Accarpio F, Mingazzini P, et al.: *Prevention of peritoneal metastases from colon cancer in high-risk patients: Preliminary results of surgery plus prophylactic hipec*. Gastroenterol Res Pract, 2012; 2012:141585.

77. Solass W, Giger-Pabst U, Zieren J, Reymond MA: *Pressurized intraperitoneal aerosol chemotherapy (PIPAC): Occupational health and safety aspects.* Annals of surgical oncology, 2013; 20(11):3504-11.

78. Girshally R, Demtroder C, Albayrak N, Zieren J, Tempfer C, Reymond MA: *Pressurized intraperitoneal aerosol chemotherapy (PIPAC) as a neoadjuvant therapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.* World journal of surgical oncology, 2016; 14(1):253.

79. Hubner M, Teixeira Farinha H, Grass F, Wolfer A, Mathevet P, Hahnloser D, et al.: *Feasibility and safety of pressurized intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis: A retrospective cohort study.* Gastroenterol Res Pract, 2017; 2017:6852749.