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*Review paper*

# Hyperthermic intraperitoneal chemotherapy: a critical review

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**Simple Summary:** Patients with cancer of the digestive system or ovarian cancer are at risk of developing peritoneal metastases (PM). In some patients with PM, surgery followed by intraperitoneal (IP) chemotherapy has emerged as a valid treatment option. The addition of hyperthermia is thought to further enhance the efficacy of IP chemotherapy. However, the results of recent clinical trials in large bowel cancer have put into question the use of hyperthermic intraperitoneal chemotherapy (HIPEC). Here, we review the rationale and current results of HIPEC for PM, and propose a roadmap to further progress.

**Abstract:** With increasing awareness amongst physicians and improved radiological imaging techniques, the peritoneal cavity is increasingly recognized as an important metastatic site in various malignancies. Prognosis of these patients is usually poor as traditional treatment including surgical resection or systemic treatment is relatively ineffective. Intraperitoneal delivery of chemotherapeutic agents is thought to be an attractive alternative as this results in high tumor tissue concentrations with limited systemic exposure. The addition of hyperthermia aims to potentiate the anti-tumor effects of chemotherapy, resulting in the concept of heated intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal metastases as it was developed about 3 decades ago. With increasing experience, HIPEC has become a safe and accepted treatment offered in many centers around the world. However, standardization of the technique has been poor and results from clinical trials have been equivocal. As a result, the true value of HIPEC in the treatment of peritoneal metastases remains a matter of debate. The current review aims to provide a critical overview of the theoretical concept and preclinical and clinical study results, to outline areas of persisting uncertainty, and to propose a framework to better define the role of HIPEC in the treatment of peritoneal malignancies.

**Keywords:** peritoneal, HIPEC, intraperitoneal, drug transport

## 1. Introduction

Peritoneal metastases (PM) are a common manifestation of abdominal malignancies, most frequently occurring in patients with colorectal and ovarian cancer.[1-3] Although less often, primary solid tumors outside the peritoneal cavity may also metastasize to the peritoneum, such as malignant melanoma, lung cancer, and lobular breast cancer.[4,5] An increased awareness amongst physicians as well as the improvement of radiological techniques such as diffusion-weighted MRI have resulted in an increasing incidence of PM reported in population-based studies in recent years. When taking all the origins together, PM pose a significant burden on the current oncological care.

For long, it has been recognized that systemic treatment of PM appears to be less effective as compared to lung or liver metastases.[6] Poor vascularization of the peritoneal cavity may play a role, but the exact mechanisms underlying this phenomenon remain to be

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elucidated. As anticancer drugs are usually administered systemically exposing healthy tissue, their therapeutic index is limited. An attractive alternative may be locoregional drug delivery, targeted at the tissue or organ of interest. This may allow to increase treatment intensity while at the same time limiting systemic toxicity. Over the past decades, several methods of locoregional anticancer therapy have been clinically implemented. These include instillation in an anatomical cavity (intraperitoneal, intravesical, intrathecal, intrapleural) or selective infusion into a feeding blood vessel with or without vascular isolation of the target organ.

The peritoneal cavity, with its serosal exchange surface of approximately 1.5-2 square meters, is a well-established route of drug delivery. Examples include renal replacement using peritoneal dialysis and intraperitoneal (IP) instillation of analgesic compounds following laparoscopic surgery. The concept of IP therapy was first reported in 1744 by the English surgeon Christopher Warrick, who, apparently with great success, injected a mixture of 'Bristol water' and 'claret' (a Bordeaux wine) in the peritoneal cavity of a woman suffering from intractable ascites.[7] In the nineteen forties, interest arose in intraperitoneal administration of radionuclides. Intraperitoneal colloidal radioactive gold (Au-198) was used as adjuvant treatment or as palliation of ascites and pleural effusions in ovarian cancer patients. Although some success was reported, serious complications and treatment related deaths were also observed.[8] Similarly, adjuvant IP instillation of radioactive chromic phosphate ($^{32}P$) was associated with inadequate distribution and small bowel perforation in early stage ovarian cancer.[9]

The interest in intraperitoneal drug delivery (IPDD) was rekindled by the work of Robert Dedrick in the nineteen seventies, who proposed a theoretical framework for IP therapy based on the assumption that, since peritoneal clearance is much lower than plasma clearance, a regional pharmacokinetic (PK) advantage results in much higher IP drug concentrations with limited systemic exposure and toxicity.[10] The same author, however, was also one of the first to highlight the fact that, despite the PK advantage of IPDD, tissue penetration depth remains very limited.[11]

The use of hyperthermia to treat cancerous growths dates from several millennia ago and continues to find applications in modern medicine. The concept of combining IPDD with hyperthermia as a 'hyperthermic intraperitoneal chemoperfusion' (HIPEC) was first described in an animal model in 1974 by Euler.[12] The first clinical application of combined cytoreduction and HIPEC was reported in 1980 by Spratt and coworkers, who treated a young patient suffering from pseudomyxoma peritonei (PMP) with extensive surgery followed by IP chemoperfusion of Thiotepa under hyperthermic conditions using a delivery system consisting of a heat exchanger and pump.[13] After the procedure, the drains were left in place and 5 days later another HIPEC procedure with methotrexate was performed. In that publication, the authors stressed the importance of removing free floating cancer cells by the microfilters in the perfusion circuit. The advantage of intraoperative (as opposed to adjuvant) chemoperfusion is the possibility to achieve optimal chemotherapeutic exposure of all peritoneal surfaces at risk.

In the following decades, HIPEC was introduced in the treatment of peritoneal metastases from a variety of primary malignancies and in primary peritoneal malignancies including peritoneal mesothelioma. Long surrounded by skepticism, HIPEC is now offered at hundreds of treatment centers worldwide.[14] Nevertheless, the efficacy and safety of HIPEC remain under debate and hamper the universal acceptance by the oncology community. Proponents will argue that the addition of HIPEC was recently shown to prolong survival in ovarian cancer in a randomized clinical trial (RCT) but criticism was undoubtedly fueled by negative results of RCTs in patients with colorectal cancer (CRC) PM.[15]

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The aims of this review are to provide a critical overview of the theoretical concept and preclinical and clinical study results, to outline areas of persisting uncertainty, and to propose a framework to better define the role of HIPEC in the treatment of peritoneal malignancies.

## 2. Basic concepts

### 2.1. Pharmacokinetics and tissue transport after IP chemotherapy (Fig.1)

The pharmacokinetic rationale for IPDD is based mainly on the presence of the peritoneal-plasma barrier.[16] This barrier results in a peritoneal drug clearance that is much slower than the plasma clearance. The pharmacokinetic (PK) advantage associated with IP administration was expressed by Dedrick as the parameter $R_d$, calculated as $(C_P/C_B)IP/(C_P/C_B)IV$ with $C_P$ and $C_B$ the peritoneal and blood concentrations, respectively.[17] Theoretically, the regional advantage will be inversely proportional to the peritoneal clearance and proportional to the plasma clearance. The pharmacokinetic (PK) advantage of IPDD drug is usually expressed as the ratio of the area under the concentration versus time curve (AUC) in peritoneal perfusate versus plasma. The general kinetic behavior of IP chemotherapy can be described using a compartmental model, consisting of a systemic and a peritoneal compartment. Both compartments are separated by the peritoneal barrier, characterized by a permeability-area (PA) product. The PA product of the peritoneal barrier cannot be directly measured. However, from correlations of drug clearance with molecular properties, it was estimated that the PA decreases approximately with the square root of the molecular weight.[18]

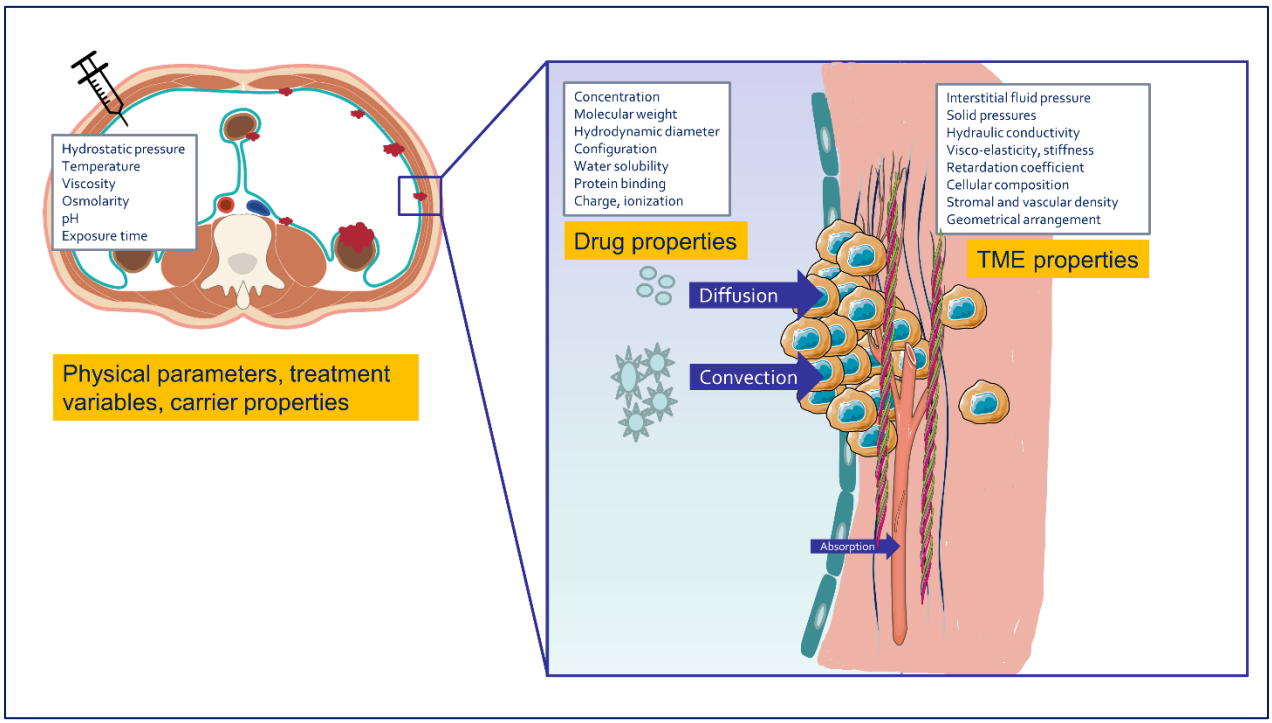


*Figure 1. Overview of relevant mechanisms and variables that affect tissue transport after intraperitoneal drug delivery. Drug transport is driven by convection (pressure gradient) and by diffusion (concentration gradient). The ratio of convective/diffusive transport is larger for large or nanosized compounds.*

While IPDD delivery results in a PK advantage, its anticancer efficacy is determined by tumor tissue concentrations. Therefore, adequate tissue transport is of paramount importance. The physiological study of drug transport usually considers tumor tissue as a homogeneous (isotropic) porous medium. Interstitial mass transport is driven by two

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main mechanisms: convection or bulk fluid flow, driven by a pressure gradient, and diffusion, which results from a concentration gradient. The ratio of convective versus diffusive transport is defined as the dimensionless Péclet number. The Péclet number is low for small molecules and higher for larger substances such as antibodies or nucleic acids.

#### 2.1.1. Convection

Convection describes the interstitial fluid flow resulting from a pressure gradient. Since tumor tissue is characterized by elevated solid and interstitial fluid pressure (IFP), which decreases sharply at the tumor periphery, a net outward convective flow results in 'oozing' from the tumor surface.[19] Interstitial fluid pressure ranges from 4-100 mm Hg, and this has to be balanced against the pressure exerted by the intraperitoneal fluid column (average of 10-20 cm $H_2O$ or 7.4-14.8 mm Hg) when IP chemotherapy is instilled. Solid tissue stress in tumors arises from three different sources.[20] *External* solid tissue stress is exerted on the tumor as it grows and compresses the surrounding tissue. *Swelling* solid tissue stress, on the other hand, results from electrostatic repulsive forces between negatively charged stromal components (hyaluronic acid), and from adaptive changes in cancer cell tonicity.[21] A third source of stress is residual solid tissue stress, which represents stored elastic energy and can be estimated by making cuts in the tissue leading to measurable bulging and deformation. The degree of convective drug transport depends on the hydraulic conductivity of the tissue, which is determined by the viscosity of the interstitial fluid and by the stromal architecture or mechanical 'stiffness'.[22] Since chemotherapy will interact with cellular and stromal structures, the velocity of the compound is always slower than that of the carrier fluid in which it is dissolved. The ratio of both velocities is termed the retardation or hindrance coefficient.

#### 2.1.2. Diffusion

The rate of drug diffusion is proportional to a concentration gradient, according to Fick's first law of diffusion. The rate of diffusion depends on temperature, the physicochemical drug properties, and on the stromal architecture.[23] The temperature dependence is explained by the Einstein-Stokes equation, which states that diffusion is proportional to temperature and inversely proportional to the viscosity of the medium. Relevant properties of the drug include molecular weight, size, charge, configuration. Important properties of the extracellular matrix (ECM) are cellular composition, density, stiffness, viscoelasticity, and geometrical arrangement).[24] Tumor tissue is characterized by increased deposition of collagen I, the most abundant ECM protein. As a result, tumor stroma is characterized by increased stiffness or rigidity compared to normal tissue. Also, tumors overexpress the collagen cross linking enzyme LOX (lysyl oxidase), which further contributes to increased stiffness.[25] In addition to the *density* of the collagen fibers, their *geometric arrangement* may affect drug diffusion. Fibers that are oriented tangentially from the tumor surface direct drug diffusion away from the tumor, while the opposite occurs when fibers are radially aligned.[26]

### 2.2. Penetration depth after IPDD

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An important limitation of IPDD is the very limited penetration distance in tumor tissue, which is a few millimeters at most, depending on drug, treatment, and tissue properties.[27] This is explained by the elevated pressure characterizing the biophysical TME, and by the very low hydraulic conductivity of tumor tissue, which is typically in the range of $10^{-15}$- $10^{-14}$ $m^2$/pa*s in colorectal PM as measured using modified Ussing chambers (unpublished data). Only limited clinical data are available on tissue penetration after IPDD. Several authors have reported drug concentrations in tissue homogenates after HIPEC, but this is a poor substitute for the actual penetration distance. Preliminary data from a study comparing normothermic versus hyperthermic chemoperfusion with cisplatin for ovarian cancer (NCT02567253) show that platinum penetrates normal stroma much easier than the cancer nodules (Fig.2, unpublished data). As a consequence, numerous physical, chemical, and pharmacological approaches have been tested preclinically in order to enhance drug penetration after IPDD, and the interested reader is referred to a recent review on this topic.[28] In clinical trials, several approaches are being tested that target matrix deposition, matrix remodeling, and cell - matrix interactions in solid cancers.[29] However, none of these trials use IPDD for PM.

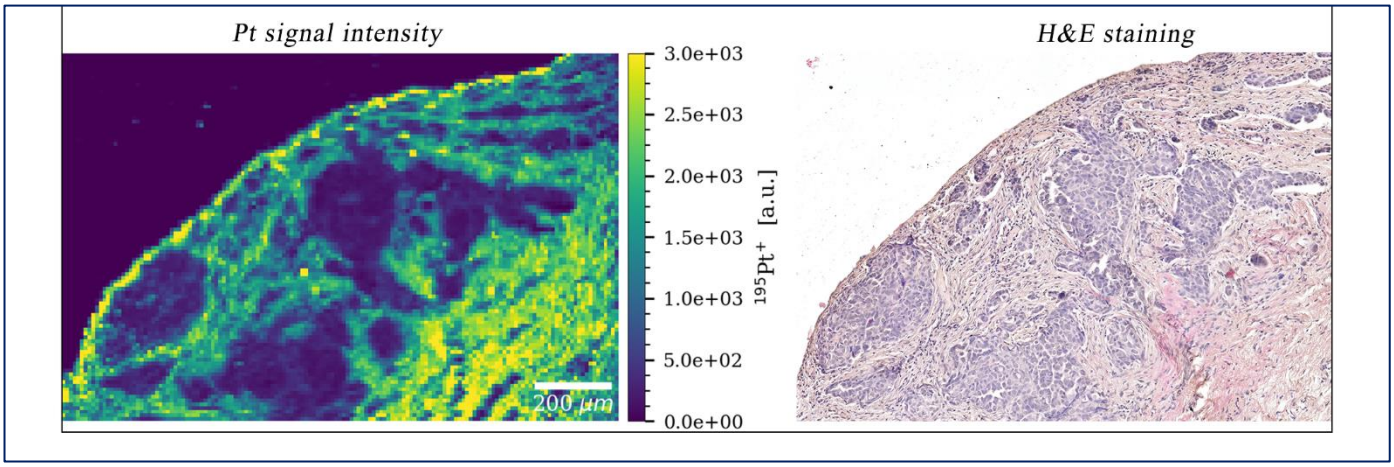


*Figure 2. Platinum (Pt) penetration after HIPEC using cisplatin in a patient with peritoneal metastases from ovarina cancer. When comparing Pt penetration with histology, it is obvious that Pt penetrates the stroma much more efficiently compared to the nests of cancer cells.*

### 2.3. Use of hyperthermia

The use of hyperthermia in oncology has a decades long history, and is based on several observations. First, hyperthermia is selectively cytotoxic for malignant cells.[30] Second, the effects of heat can be synergistic with those of other anticancer treatments, including chemotherapy and radiotherapy.[31] There is considerable heterogeneity in the extent, timing, and underlying mechanisms of thermal enhancement of chemotherapy. Synergism with heat is particularly evident for the platinum compounds and mitomycin C. However, other agents such as the taxanes and the antimetabolites do not show thermal enhancement. Third, hyperthermia enhances tissue perfusion and oxygenation, and may improve drug penetration. Los and coworkers demonstrated a significant increase in peritoneal tumour platinum concentrations when IP cisplatin therapy was combined with regional hyperthermia (41.5° C) in a rat colon cancer model.[32] Other drugs that were shown to exhibit increased tumor penetration under hyperthermic conditions are carboplatin, oxaliplatin, and doxorubicin.[33,34] Of note, many of the in vitro studies that have aimed to establish thermal enhancement of chemotherapy have used temperatures, exposure times, and drug concentrations that are not clinically relevant or achievable. Helderman and coworkers recently performed a series of in vitro experiments using clinically relevant conditions (38 - 43°C for 60 min) in several 2D and 3D human

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colorectal cancer cultures.[35] They showed that thermal enhancement of cytotoxicity is highly dependent on the cell line and on the drug used: thermal enhancement was evident for oxaliplatin and cisplatin, but not for mitomycin C, carboplatin, or 5-FU. Besides the choice of drug, also length of the exposure to hyperthermia might play a crucial role. This was recently investigated using patient-derived organoids from colorectal cancer PM. In this study by Forsythe, low dose heated oxaliplatin (200 mg/m$^2$) for 200 minutes appeared to be more effective in terms of cytotoxicity than a higher dose of oxaliplatin (460 mg/m$^2$) for only 30 minutes.[36]

The ideal target temperature of HIPEC is unknown. In vitro, DNA repair is inhibited at a temperature >41°C, but the relationship between temperature and anticancer efficacy in vivo is not known. Also, due to the heat sink effect of the tumor blood vessels, the actual tissue temperature that can be reached is lower than that of the heated IP solution. There are at present no clinical studies in patients comparing normothermic with hyperthermic chemoperfusion. However, hyperthermia elicits the expression of heat shock proteins (HSP's), which were shown to exert anti-apoptotic and proliferative effects, and to induce resistance to chemotherapy.[37,38] Also, temperatures above 41°C may cause scald injury to the peritoneum, which is already extensively damaged by the CRS.[39]

In the era of immune therapy, there is renewed interest in the potential immune stimulating effects of hyperthermia.[40] Hyperthermia leads to immunogenic cell death by secretion of damage associated molecular patterns (DAMPs) including calreticulin, ATP, high mobility group B1 (HMGB1), and heat shock proteins 90 and 70. These patterns may activate antigen presenting cells and mobilize an effective T cell mediated immune response. Also, hyperthermia may reverse the 'cold' tumor microenvironment (TME) observed in most PM to a highly immunogenic TME, which sensitizes tumors to immune checkpoint inhibition. In studies that combine radiotherapy with external hyperthermia, immune modulating effects were observed, leading to an abscopal therapy response.[41] Others have shown, however, potentially adverse effects of local heating on overall tumor immunity.[42] HSPs s can promote cancer growth and malignant behavior by the induction of extracellular matrix remodeling, resistance to apoptosis, epithelial to mesenchymal transition, tumor angiogenesis, and metastasis.[43] A recent fase-2 clinical trial investigated the potential additional value of autologous tumor antigen-loaded $\alpha$DC1 vaccine in patients undergoing CRS and HIPEC for peritoneal metastases. The therapy appeared to be well tolerated by patients but the effect of vaccination on median survival appeared to be limited and it was concluded that this was not a good strategy to pursue.[44]

Very little is known on the effect of HIPEC on the TME of PM, and on the peritoneal immune environment. Franko and coworkers sampled peritoneal fluid during HIPEC procedures at different time intervals between 0 and 90 minutes.[45] They did not observe significant changes in the number of peritoneal NK cells, CD4/CD8 ratio, or granulocyte/lymphocyte ratio during the course of HIPEC.

## 3. Clinical implementation of hyperthermic intraperitoneal drug delivery

The basic setup used for HIPEC treatment consists of one or more inflow- and outflow tubes and temperature probes, one or more roller pumps, and a heating element. Several HIPEC devices are commercially available. There is considerable heterogeneity in the procedural parameters that are used to administer HIPEC: drug type and dose regimen, carrier solution, target temperature, treatment duration, and delivery technique all vary substantially according to local preference.[46] As a result, many different HIPEC-regimens are currently used and standardization is sparse, hampering pooling of outcome data.[47]

### 3.1. Choice and combination of chemotherapy

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Ideally, chemotherapy drugs for HIPEC should have the following properties: a favorable pharmacokinetic profile, no cell cycle specificity, and absence of local peritoneal toxicity. Unfortunately, all chemotherapeutics currently administered during HIPEC are used off label. In colorectal cancer, debate persists on the use of oxaliplatin versus mitomycin C for HIPEC. Results from retrospective studies are difficult to interpret due to differences in clinical and treatment parameters.[48] A prospective randomized trial in appendiceal cancer showed that compared to mitomycin C, the use of oxaliplatin for HIPEC was associated with a better safety and quality of life profile.[49,50] However, oxaliplatin as a HIPEC agent failed in recent randomized trials in colorectal cancer. Possibly, additional factors such as choice of carrier solution, target temperature, and treatment duration are important determinants of the efficacy of oxaliplatin, as recently demonstrated in organoid models.[36,51]

Although it seems intuitively appealing to combine drugs for HIPEC, several caveats should be taken into consideration. First, unsuspected chemical or physical incompatibilities may exist that preclude the administration of two or more drugs IP in the same solution. Second, when toxicity occurs, it will be problematic to find out which agent is responsible for which observed toxicity. Third, prospective clinical trials do not support the use of multi-agent HIPEC regimens. Quénet and coworkers showed that, compared to HIPEC with oxaliplatin alone, the addition of irinotecan significantly increased the complication rate, but did not benefit recurrence-free or overall survival.[52]

### 3.2. Open versus closed abdomen perfusion

Chemoperfusion with the skin and/or fascial layer closed theoretically prevents contamination of the OR environment and heat loss and may enhance convection driven tumor chemotherapy penetration due to increased IP pressure. The open technique ('coliseum'), on the other hand, allows to manually stir the abdominal contents in order to ensure homogeneous drug and temperature distribution. Prospective comparative studies are lacking, but retrospective data suggest that both techniques are comparable in terms of intraoperative hemodynamics and postoperative morbidity.[53,54] Recent developments include the use of $CO_2$ recirculation and laparoscopy assisted HIPEC.[55,56]

## 4. Clinical results of HIPEC

### 4.1. Ovarian cancer

The majority of epithelial ovarian cancer (EOC) patients presents with peritoneal metastases and around 75% will relapse in the peritoneal cavity after successful first line treatment. Therefore, EOC appears to be the ideal candidate for IPDD and remains the best studied indication. The multicenter randomized OVHIPEC trial investigated the additional benefit of cis-platin based HIPEC to cytoreduction after induction chemotherapy in patients with primary EOC that were initially not eligible for debulking due to extensive peritoneal involvement. It was found that the addition of HIPEC to interval CRS resulted in a significantly better progression free survival and improved the overall survival from 33.9 to 45.7 months.[57] Addition of HIPEC in these patients did not result in more postoperative complications, did not negatively affect the quality of life and appeared to be cost-effective.[58,59] A second smaller trial, published as abstract only, used a lower IP cisplatin dose, included both primary and interval CRS cases, and did not find a difference in PFS.[60] In recurrent EOC, the results of a small RCT showed a superior overall survival after CRS and HIPEC versus surgery alone (26.7 versus 13.4 months, P=0.006).[61] However, the methodological quality of that trial was only moderate.

Currently, the international OVHIPEC-2 consortium is investigating the role of HIPEC in patients with Figo stage-3 ovarian cancer that may be treated with primary debulking. In total, 538 patients will be randomized to primary debulking alone or primary

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debulking followed by HIPEC.[62] A French multicenter randomized trial (CHIPOR; ClinicalTrials.gov identifier: NCT01376752) was initiated in 2011 comparing cytoreduction alone with cytoreduction plus HIPEC in recurrent ovarian cancer.

### 4.2. Colorectal cancer

In 2003, a randomized clinical trial showed that CRS and HIPEC (90 minutes, mitomycin-C 35 mg/m$^2$) improved survival in patients with colorectal peritoneal metastases as compared to palliative surgery and systemic treatment alone (22 versus 12 months respectively).[63] Ever since, numerous non controlled studies have shown that long-term survival can be obtained with CRS and HIPEC with median survival ranging from 14.6 to 60.1 months in a recent review.[64] Although the treatment related mortality in the trial by Verwaal was as high a 8%, this has decreased significantly with increasing experience and is currently as low as 1-2% in most centers.[65]

A recently published French multicentre study compared CRS alone with CRS combined with short duration (30 minutes) oxaliplatin (460 mg/m$^2$) based HIPEC in colorectal PM (PRODIGE 7/ACCORD 15, NCT00769405).[15] Interestingly, the addition of HIPEC did not improve OS in this trial, but did increase 90 day morbidity. This raises the question concerning the value of HIPEC in addition to complete CRS in colorectal cancer PM. A possible explanation for the lack of efficacy of the oxaliplatin-based regimen in the PRODIGE 7 trial may be the selection of patients as these were only included after a minimum of 6 months of systemic therapy. Such therapy was oxaliplatin-based in the majority of patients and this may have resulted in an acquired resistance of the peritoneal metastases against IP oxaliplatin as was recently demonstrated in a pre-clinical study.[66] Also, patient-derived organoids from colorectal peritoneal metastases appear to be resistant to heated oxaliplatin in a dosage similar to the one used in the PRODIGE7 protocol.[67]

Another topic of debate is whether systemic treatment, either neo-adjuvant, adjuvant or both should be part of the initial treatment strategy. Although peri-operative treatment was part of the PRODIGE7 study protocol and is practised widely around the world, high-level evidence to support this practice is currently lacking.[68,69] In a recent retrospective comparative cohort study, no beneficial effect of peri-operative systemic therapy was shown after complete CRS and HIPEC.[70] In contrast, a large population based study including 393 patients undergoing CRS and HIPEC revealed a benefit of adjuvant systemic treatment as compared to standard follow up alone after propensity score matching. The value of perioperative chemotherapy is currently investigated in the international multicenter randomized CAIRO6-trial.[71]

Besides a role for HIPEC in the treatment of established PM, also the role of 'prophylactic' HIPEC with oxaliplatin was evaluated in patients at high risk of peritoneal recurrence (i.e., perforated tumors, pT4 tumors, minimal PM resected at the time of primary surgery, and ovarian (Krukenberg) metastases). Both the French ProphyloChip (NCT01226394) and the Dutch COLOPEC (NCT02231086) randomized trials were negative.[72,73] As also in these trials a short course (30 minutes) high-dosed oxaliplatin HIPEC regimen was used, this raises the questions on the efficacy of IP oxaliplatin.[51] A similar randomized study of 'prophylactic' HIPEC proposed by the National Cancer Institute (NCT01095523) has been withdrawn.[74]

### 4.4. Pseudomyxoma peritonei

Appendiceal mucinous neoplasms represent a rare, histologically heterogeneous entity encompassing low-grade appendicular neoplasm (LAMN), high-grade appendicular neoplasm (HAMN) and true mucinous appendicular adenocarcinoma.[75-77] When ruptured, low grade tumors may cause accumulation of mucinous ascites, giving rise to the

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'pseudomyxoma peritonei' (PMP) syndrome, a clinical or radiological descriptor rather than a histopathological diagnosis.[78] Impressive long term survival results have been achieved in patients with PMP using CRS and HIPEC.[79-81] Results from a recent international registry including over 2000 patients showed a median survival of 16.3 years and a 10 year survival of 63% following cytoreductive surgery and HIPEC for PMP.[82]

Recently, an international cohort study was published including 1924 patients with PMP, investigating the outcome after CRS with or without HIPEC.[83] It was found that the addition of HIPEC after CRS was associated with a significantly better overall survival as compared to HIPEC alone with a 5-year overall survival of 58% versus 46.2% respectively. The addition of HIPEC did not result in more post-operative complications. Therefore, this approach has been proposed as the standard of care in patients with low grade appendiceal tumours associated with PMP.[84] Others have argued that the outcome achieved in these patients is mainly resulting from a favorable tumour biology and that, given the proven prognostic impact of complete surgical cytoreduction, the contribution of IP chemoperfusion remains uncertain.[85]

### 4.5. Gastric cancer

The risk of peritoneal metastasis in gastric cancer is approximately 40%, with almost 30% of patients presenting with peritoneal metastases at the time of diagnosis.[2] In the Far East (primarily Japan), promising results have been obtained with prolonged IP taxane based chemotherapy in gastric cancer patients with PM.[86,87]

Meta-analyses of small RCT's and non-controlled trials suggest a potential benefit of HIPEC in gastric cancer, specifically in patients with positive cytology and without extensive nodal disease.[88,89] A recent propensity score adjusted comparison of CRS alone versus CRS with HIPEC in gastric cancer with PM suggested that the addition of HIPEC results in a significant improvement of both recurrence free and overall survival.[89] Randomized trials are currently exploring the efficacy of HIPEC in gastric cancer with PM in the Netherlands (PERISCOPE II, NCT03348150), France (GASTRICHIP, NCT01882933), and China (NCT02356276). The initial results of the PERISCOPE-trial aimed at dose-finding were recently published. Although the amount of serious adverse events in the trial was high (17 out of 25 patients), it was shown that HIPEC with a dose of 50 mg/m$^2$ intraperitoneal docetaxel appeared to be feasible.[90] Survival data from that trial are currently awaited.

### 4.6. Other intra-abdominal cancers

Promising results have been obtained using CRS and HIPEC in patients with malignant peritoneal mesothelioma, a condition for which very few other effective therapy options are available. A systematic review of six published series totaling 240 patients showed a median survival ranging from 34 to 92 months.[91]

Other peritoneal cancers that were treated with IP chemotherapy in small numbers of patients include small bowel adenocarcinoma, sarcomatosis, and desmoplastic small round cell tumors.[92,93]

## 5. Addressing current limitations of HIPEC: the road to progress

### 5.1. Development of novel anticancer compounds and carriers

The main current limitation of HIPEC is that none of the currently used drugs were developed for intraperitoneal administration. Toxic effects of chemotherapy or the carrier solution on mesothelial integrity may offset anticancer efficacy. Also, HIPEC is performed only once, and treatment duration is typically short. Emerging approaches are

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the development of nanoparticles and prolonged delivery formulations such as hydrogels and drug loaded textiles.[94] While these may not be easily administered as a hyperthermic chemoperfusion, they may be combined with external sources of hyperthermia such as radiofrequency or with photothermal activation.[95,96]

### 5.2. Improved heat delivery methods

Homogeneous tissue heating is impeded by insufficient and preferential fluid flow and heat sink effects. Recently, studies based on computational fluid dynamics (CFD) were used to simulate fluid flow, temperature, and drug distribution to predict the influence of location and number of catheters, flow alternations, and flow rate.[97] The results of these studies, combined with adequate thermometry methods, may allow to improve spatial homogeneity of heat and drug in the peritoneal cavity.

### 5.3. Clinically relevant preclinical models

HIPEC treatment was introduced in clinical practice in the absence of solid preclinical foundations. Given the challenging results of HIPEC in CRC, there is a need for clinically relevant, reproducible, and high throughput models to study the immune and anticancer effects of HIPEC in a systematic way. Several groups have established mouse HIPEC models, which offer the advantage of antibody availability and the potential to use human cell lines.[98,99] Recent developments include the use of patient derived organoids and 'organs on a chip' in order to study the effects of hyperthermia combined with anticancer agents using patient derived tissue.[67,100,101]

### 5.4. Elucidation of the tumor microenvironment and the peritoneal ecosystem

It is increasingly evident that the behavior and treatment response of solid tumors is largely dictated by its biophysical, cellular, and molecular environment. This environment is radically different between primary tumors and their associated PM. Therefore, unraveling of the PM cascade and understanding the PM-associated tumor microenvironment (TME) are priorities for future research.[102] Furthermore, the immune contexture of PM and the peritoneal ecosystem, and how both are affected by extensive surgery, IP chemotherapy, and hyperthermia are barely studied and need to be characterized in detail.

### 5.5. High quality clinical trials

After a long period of skepticism, HIPEC has gathered significant momentum over the past years, with 121 centers offering the treatment in the US alone per November 2019.[103] In stark contrast, only a handful of RCTs has studied the efficacy of HIPEC. The obstacles faced by surgeon initiated trials are well known: perceived lack of equipoise, lack of training in clinical trial methodology, learning curve effects, and lack of funding.[104] Although the RCT remains the gold standard, possible alternative approaches that allow to facilitate gathering evidence on HIPEC include pragmatic trials, register based trials, patient preference trials, and adaptive (Bayesian) trial designs.[105]

## 6. Conclusions

There are compelling theoretical arguments in favor of the incorporation of heated IP chemotherapy in a multimodal strategy for the treatment of PM. Its current place is, however, uncertain due to the lack of drugs and platforms that are developed specifically for IP usage, and to the significant variability in the methods used to administer IP drugs. Successful further implementation of HIPEC will require a better basic understanding of how IP therapy affects the tumor TME and peritoneal ecosystem, the

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development of novel IP compounds and delivery systems, and the expansion of the clinical evidence base from randomized trials.

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