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The Role of Hyperthermia in the Treatment of Peritoneal Surface Malignancies

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Abstract

Purpose of Review Hyperthermia is used to treat peritoneal surface malignancies (PSM), particularly during hyperthermic intraperitoneal chemotherapy (HIPEC). This manuscript provides a focused update of hyperthermia in the treatment of PSM.

Recent Findings The heterogeneous response to hyperthermia in PSM can be explained by tumor and treatment conditions. PSM tumors may resist hyperthermia via metabolic and immunologic adaptation. The thermodynamics of HIPEC are complex and require computational fluid dynamics (CFD). The clinical evidence supporting the benefit of hyperthermia is largely observational.

Summary Continued research will allow clinicians to characterize and predict the individual response of PSM to hyperthermia. The application of hyperthermia in current HIPEC protocols is mostly empirical. Thus, modeling heat transfer with CFD is a necessary task if we are to achieve consistent and reproducible hyperthermia. Although observational evidence suggests a survival benefit of hyperthermia, no clinical trial has tested the individual role of hyperthermia in PSM.

Keywords Hyperthermia · Hyperthermic intraperitoneal chemotherapy · Peritoneal surface malignancy · Peritoneal cancer · Cancer treatment · Thermodynamic model · Prognosis · Heat transfer · Survival

Introduction

Hyperthermic intraperitoneal chemotherapy (HIPEC) was first introduced in clinical practice by Spratt in 1980 [1]. Since then, the use of hyperthermia as a therapeutic component for peritoneal surface malignancies (PSM) has been adopted globally [2]. The combination of chemotherapy and hyperthermia has been proposed to eliminate microscopic disease, not addressed by cytoreductive surgery alone, thus improving the oncologic outcome of these patients [3]. In addition to the pharmacokinetic advantage inherent to the intracavitary delivery of cytotoxic drugs, which results in regional dose intensification, hyperthermia has the added advantage of direct cytotoxic effect on tumor cells [4••].

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The application of hyperthermia in HIPEC occurs through the intraabdominal perfusion of heated fluid. A machine, providing the flow and the heating mechanism, recirculates the fluid between the inflow and outflow catheters. The perfusion of fluid can occur via the open coliseum or closed techniques. In the open technique, the abdominal wall is retracted, a tent is developed to accommodate the fluid, and the chemotherapeutic agent is uniformly exposed to all anatomical structures by continuous manual stirring by the surgeon [5]. In the closed technique, the inflow and outflow catheters are placed in the abdominal cavity and the skin is sutured tightly to ensure an adequate seal prior to circulating the chemotherapeutic drug using a perfusion machine [6].

Despite its widespread acceptance, there is great variability in the protocols and techniques used for HIPEC [2]. In recent years, the results of randomized controlled trials have questioned the therapeutic benefit of HIPEC after complete surgical cytoreduction [7••, 8••]. However, it is still unclear whether these results are due to cancer-specific sensitivities, choice of chemotherapeutic agent, inadequate thermal exposure, or application of the protocol. The present review aims to provide a focused update of the current knowledge of hyperthermia in PSM, understand heat transfer and its clinical consequences during HIPEC, and review the most recent clinical studies.

The Cellular Response to Therapeutic Hyperthermia in Peritoneal Surface Malignancies

It is well known that elevated temperatures alone, by cause of protein denaturation and aggregation, can induce cell death. As described by Dewey, the survival of cell lines at temperatures above 43°C follows a straight line in an Arrhenius plot, indicating a dose-dependent relationship between temperature and time on survival. A biphasic plot was observed below this threshold, indicating the development of thermotolerance [9]. Based on these observations, equivalent thermal damage can be estimated as the thermal isoeffect dose, such as the cumulative equivalent minutes at 43°C [10]. Ultimately, cell death occurs early due to apoptosis or later due to necrosis, cell-cycle arrest, and loss of clonogenicity [11]. Because cancer cells are known to be more susceptible to thermal cytotoxicity than normal human cell lines [12], therapeutic hyperthermia can be exploited in patients with cancer.

The cellular response to non-lethal hyperthermia is largely governed by heat-shock proteins (HSP) [13]. Following heat exposure, heat-shock factor 1 is liberated from HSP70 and HSP90 (which are recruited to stressed proteins) and forms oligomers that bind more avidly to the heat shock element, increasing the expression of HSP [13, 14]. Elevated levels of HSP-70 and HSP-90 are demonstrated both in stomach cancer cells and in the serum of patients undergoing HIPEC for stomach cancer [15]. Among a vast array of functions, the HSP network works in the unfolding and refolding of stress-denatured proteins, regulation of the cell cycle, proliferation, and apoptosis [16]. In this manner, HSPs can prevent irreversible protein aggregation and cell death secondary to heat exposure and are widely regarded as targets for antitumor therapies [13, 17].

The expression of HSPs can also modulate the immune system. Akyol *et al.* demonstrated elevated levels of HSP10 in the serum of ovarian cancer patients, which inhibited the expression of CD3-zeta and prevented the activation of T cells [18]. When released into the circulation, HSPs can also be presented to dendritic cells (via CD91) and induce a Th1-like response against cancer [19]. Finally, Sedlacek *et al.* showed that HSP gp96 activates NK cells, inducing a phenotype of increased cytokine production [20].

The PSM comprise a histologically heterogeneous group of cancer cell lines with various origins, including gastric, colorectal, ovarian, uterine, mesothelial, and appendiceal [21]. As thermal sensitivity varies between cell lines [22–24], a single thermal isoeffect dose is unlikely to be effective for all. Indeed, it has been pointed out that the biological rationale of temperatures and heating periods in HIPEC is lacking [4••, 24], stressing the need for continued research.

In a recent study, Helderman *et al.* used human colorectal cancer cell lines and exposed them to increasing temperatures with and without chemotherapy [4••]. The *in vitro* studies showed a dose-dependent relationship between temperature and decreased cell viability at 48 hours, and decreased clonogenic activity at 10 days following 60 minutes of treatment, particularly with temperatures of at least 41°C. Likewise, Bespalov *et al* demonstrated that hyperthermia at 41°C improved the survival of female Wistar rats who were inoculated with ovarian cancer cells, increasing their life expectancy by 14 days [25].

Although hyperthermia can alone produce cell death, the most important purpose of hyperthermia in current HIPEC protocols is chemosensitization. *In vitro* studies show that the effect of platinum-based agents is temperature dependent, with increasing levels of apoptosis and a predominant arrest of all cell lines in the G1 and G2 phases [9]. Pharmacokinetic studies demonstrate that hyperthermia increases the concentration of chemotherapeutic agents in intraabdominal tissues and the rate of systemic absorption, with no significant changes in the maximum systemic concentrations [26, 27••].

Unfortunately, thermal enhancement is not uniform across chemotherapeutic agents or cells. For instance, Helderman *et al.* observed that while temperature-dependent

synergy occurred with platinum-based drugs (e.g., oxaliplatin, cisplatin, and carboplatin), colorectal cancer cells were equally susceptible to mitomycin or 5-FU, regardless of hyperthermia [4••]. In another study, de Bree *et al.* cultured ovarian cancer (SKOV-3, OVCAR-3) cells and exposed them to paclitaxel and docetaxel in conditions of normothermia (37°C) or hyperthermia (41.5°C) [24]. Exposure of SKOV-3 cells to hyperthermia only resulted in thermal enhancement at 24 hours, with no differences at 7 days. In contrast, OVCAR-3 cells had a higher proliferation rate at 24 hours, but evidence of thermal enhancement at 7 days. Interestingly, OVCAR-3 cells exposed to 2h of hyperthermia alone showed a trend toward increased proliferation at 7 days.

Atallah *et al.* exposed ovarian (IGROV-1) and colon cancer (Caco-2, HT-29) cells to oxaliplatin alone or in combination with 1h of hyperthermia at 42°C [22]. Hyperthermia effectively decreased the dose to achieve 50% growth inhibition across all cell lines by several orders of magnitude. Notably, while IGROV-1 cells arrested in G1 phase (via p53) or G2-M phases (upregulation of cyclins A and B), HT-29 cells arrested in mid-G1 (via ckd2 inhibition).

Several mechanisms of resistance to hyperthermia have been elucidated recently (Table 1). Kanamori *et al.* found

Table 1 Potential Mechanisms of Resistance to Therapeutic Hyperthermia in PSM Cell Lines

Author, year	Cell line	Type of cancer	Hyperthermia exposure	Mechanism(s) of resistance
Tu *et al.*, 2018 [15]	SGC7901	Gastric	41° C for 60 mins	Overexpression of HSP90 (stabilizes proteins for cell development, growth, and survival). Overexpression of HSP70 (interferes with apoptosis).
Tu *et al.*, 2018 [15]	AGS	Gastric	41° C for 60 mins	Overexpression of HSP90 (stabilizes proteins for cell development, growth, and survival). Overexpression of HSP70 (interferes with apoptosis).
Cesna *et al.*, 2019 [28]	OVCAR-3	Ovarian	43° C for 60 mins	Heme-oxygenase 1 prevents free heme from sensitizing cells to undergo apoptosis.
Sukovas *et al.*, 2019 [29]			40, 43° C for 60 mins	Stimulation of glutamine dehydrogenase (metabolic adaptation)
Kanamori *et al.*, 2021 [30•]	SKOV-3	Ovarian	46° C for 60 mins	Downregulation of glycolytic pathways and upregulation of mitochondrial pathways (metabolic adaptation)
Kong *et al.*, 2020 [31]			37, 39, 41, 43, 45° C for 60 mins	Overexpression of HSP27 ➔ reduced expression of Bax and Caspase-3 ➔ increased Bcl-2 ➔ reduced apoptosis.
Akyol *et al.*, 2006 [18]	Immune Function Study	Ovarian	No exposure	Expression of HSP10 inhibited CD3-zeta, preventing T-cell activation.
Kimura *et al.*, 2017 [32]	MKN45	Gastric	43° C for 180 mins	Expression of HSP110 and increased cell proliferation.
Hatakeyama *et al.*, 2016 [33]	SKOV3, HeyA8, ES2, and KLE	Ovarian	46° C for 60 mins	Upregulation of CTGF and modulation of glycolysis-related genes.
Lis *et al.*, 2011 [34]	SKOV3/CAOV3	Ovarian	42° C for 60-120 mins	Activation of CXCR4 (proliferation) through mesenchymal stem cell secretion of CXCL12.
Liu *et al.*, 2021 [35]	SH-10-TC, HGC-27	Gastric	42° C for 120 mins	CDK6 upregulation via hyperthermia-induced AKT inhibition, resulting in decreased apoptosis.

that hyperthermia-resistant SKOV-3 cells responded to hyperthermia by downregulating glycolytic pathways (via ubiquitination of PKM 1/2) and sustaining ATP production by upregulating mitochondrial activity [30•]. In OVCAR-3 cells, metabolic adaptation to hyperthermia may occur via stimulation of glutamine dehydrogenase [29]. SKOV-3 cells can also resist hyperthermia-induced apoptosis via HSP27, which in turn promotes Bcl-2 expression and inhibits the expression of Bax and Caspase-3 [31]. *In vitro* studies suggest a variable expression of heme-oxygenase 1 among cell lines and that silencing heme-oxygenase 1 activity results in decreased cell viability of ovarian cancer cells (OVCAR-3), but not in gastric cancer cells (AGS) [28].

Hyperthermia can also exert indirect effects by modulating the immune response. For instance, 2 hours of mild preoperative hyperthermia (39°C) in patients undergoing colorectal surgery increased the levels of HSP60, 70, and 90, while ameliorating increases in TNF-α and procalcitonin [36]. Others have documented an increased antigen-specific cytokine response in T cells [37], and an enhanced IL-2 production by CD4 T-cell activation [38]. In contrast, Ahlers *et al.* showed that after 1 hour of whole-body radiant hyperthermia at 42°C, the populations of NK cells and γδ T cells increased, while the number of T cells decreased. In addition, the serum levels of IL-12 and INF-γ/IL-10 ratio decreased [39]. In patients undergoing HIPEC, Roth *et al.* found that longer durations of hyperthermia (60 and 90 minutes vs. 30 minutes) led to a secondary peak in CRP levels between postoperative days 5 and 8 [40].

Heat Transfer During HIPEC

In this section, we begin with the underlying physical principles necessary to comprehend and properly model HIPEC. Some of the limitations of the models used to describe the physical processes behind will be highlighted. From the physical point of view, an understanding of HIPEC requires connecting principles of heat transfer and fluid dynamics. Physical models of this process have been proposed in the literature [41–43], as well as experimental measurements of temperature distribution [44], the effect of high flow rates [45], and intraabdominal pressures during HIPEC [46].

The body temperature depends on the heat exchange during the surgery. The heat gained is heat transferred by the heated fluid and that due to the production from the metabolism. The first can be calculated with the input flow rate (assuming steady-state flow, no accumulation) and the inflow and outflow temperatures; the second one is primarily a function of the mass of the patient. The heat loss comes from mechanisms of energy transfer (radiation, convection, and conduction), as shown in Fig. 1A. Evaporative heat losses are negligible in the context of a closed HIPEC [43]. The heat loss by radiation, conduction, and convection is all roughly proportional to the surface area of the body, the skin, and the surrounding temperature. Because for radiation the rate of heat gain or loss is proportional to the fourth power of the absolute temperature of the skin (or clothing) minus the fourth power of the surrounding temperature, radiation is dominant in heat exchange when the temperature difference exceeds a few degrees (6°-10°) [47]. A complete quantitative analysis of the heat exchange is a formidable task since it is necessary to know various parameters, including air velocity, air humidity, barometric pressure, the contact area with the materials in the operating room, the thermal conductivity of these materials, etc., parameters generally not reported in the literature.

On the back of such concerns, one can focus on modeling the heat exchange in the abdominal cavity [42, 48••]. In a simplified way, a four-compartment model can be employed, with the four compartments being the organs, the peritoneal wall, the chemotherapeutic hot fluid, and the blood volume, as shown in Fig. 1D. The compartments exchange heat only through conduction and convection. A simplified model of the abdominal cavity was considered to simulate the inflow and outflow temperatures by Ladhari *et al*. [42] Recently, a more realistic model of the heat exchange in a rat was presented by Loke *et al.* [48••].

Temperature changes in a cross section of tissue vary according to the position and the sinusoidal heat flux created by the blood flow, as proposed by the Pennes equation. This equation is of common use in other models of therapeutic hyperthermia, such as the radiofrequency ablation of tumors [49]. To model the circulating hot fluid in the cavity, it is mandatory to use the Navier–Stokes equations, which describe a continuum of moving fluid and include other parameters such as pressure and velocity. Although exact solutions to the Navier–Stokes equations have only been obtained in particular cases, the problem can be numerically approximated using computational fluid dynamics (CFD). This area has recently seen significant advances, including the development of CFD software to simulate the dynamic flow, temperature, and drug distribution during HIPEC [48••, 50, 51]. Studies in rats have demonstrated that maximizing the distance between in- and outflows and adding multiple catheters leads to increased temperature homogeneity and stability [43, 48••, 52]. Moreover, a homogeneous distribution of temperature can be achieved when the abdomen is maximally distended and a high flow rate is maintained [44, 45, 48••].

The complexity of the CFD model required the use of various assumptions, such as a laminar flow and a temperature-independent fluid density [48••]. Because of the geometry of the flow region, the presence of obstacles, the manual shaking of the abdomen, and the gravitational effects, the use of a turbulence model is advised. Naturally, this entails considerable computation time. Finally, large vessels passing near

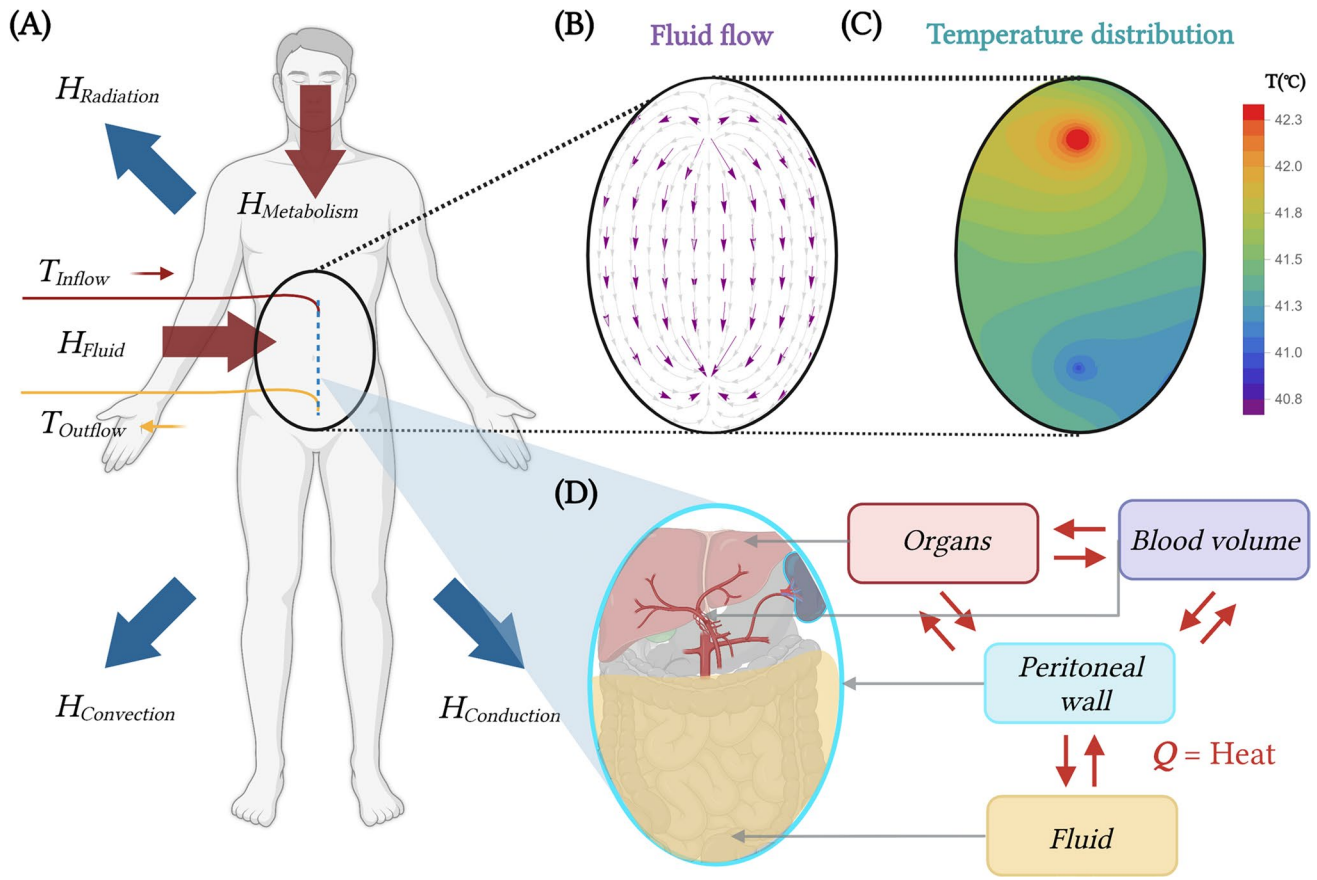

Fig. 1. Schematic Representation of the Thermodynamic Model for Closed HIPEC. (**A**) The human silhouette shows an inflow catheter with a temperature T_{Inflow} and an outflow catheter with a temperature $T_{Outflow}$, as well as the heat exchange with the fluid and the environment. $H_{Radiation}$, $H_{Convection}$, and $H_{Conduction}$ are the heat current of radiation, convection, and conduction, respectively. All three are proportional to $\left(T_S^n - T_A^n\right)$ with $n=1$ for conduction and convection and $n=4$ for radiation, where T_S and T_A are the skin (superficial) temperature and ambient temperature, respectively. H_{Fluid} and $H_{Metabolic}$ are the heat current transferred by the fluid and that due to the metabolism, respectively. In the abdominal cavity, the fluid flow (**B**) and temperature distribution (**C**) are pictured for illustrative purposes only; the directions and numbers are not suitable for interpretation. (**D**) A compartment model of the abdominal cavity. The arrows indicate where heat is exchanged by convection and conduction. Image created with Biorender®.

or through the intraabdominal cavity can conduct heat loss causing heterogeneities in temperature distribution [53–55]. These vessels can act as heat exchangers between the blood and the intraabdominal cavity during HIPEC and should also be included in future models of hyperthermia in HIPEC.

Because the tissues are poor conductors of heat, tissues outside of the abdominal and pelvic cavities (e.g., the brain, the extremities) gain heat primarily via the blood vessels [56]. Thus, the rate of heat transfer in the body is dictated by the blood flow, which could help predict overheating. Poiseuille's law shows that blood flow increases as blood viscosity decreases, assuming a constant blood pressure during surgery. Experimentally, it has been observed that blood viscosity increases as hematocrit increased and as temperature decreased [57–59]. Consequently, blood temperature and hematocrit determine the resistance to blood flow and limit the rate of heat transfer out of the abdominal cavity.

Finally, the thermal conductivity of the tissues needs to be considered. For instance, the fatty tissue has a low thermal conductivity and likely interferes with heat transfer in obese people, acting as an insulating barrier [60]. Moreover, both blood flow and temperature affect the thermal conductivity in living tissues [47, 61]. As thermal conductivity increases linearly with temperature [61], future research would benefit to consider such changes in future models.

Clinical Measurements During Hyperthermia in Humans

The physiological response to intraabdominal hyperthermia has several components. Intraoperatively, the hemodynamic response is characterized by increased cardiac index, heart rate, and central venous pressure, along with a decreased

stroke volume variation [62, 63]. Owing to vasodilatation and a decreased blood viscosity, a reduction in systemic vascular resistance has also been observed [64•]. Within studied parameters, changes in the intraabdominal pressure (8-12 vs. 18-22 mmHg) seem to only affect the central venous pressure [63]. As reported by Reis *et al.,* high intraabdominal pressures (but not temperature) caused an increase in peak inspiratory pressure [63]. Moreover, patients may experience metabolic changes associated with the degree of hyperthermia. In a study by Ceelen *et al.,* a linear relationship was found between the area under the curve of temperature and the changes in glucose, sodium, and lactate levels, with near significant changes for bicarbonate levels [65]. Finally, because HIPEC occurs several hours after the beginning of anesthesia, the thermodynamic state at the beginning of perfusion assumes that heat redistribution from core to the periphery has stabilized [66].

According to Rettenmaier *et al.,* the temperature of the intraabdominal fluid demonstrates an initial gain of ~1°C during the first 15 minutes of HIPEC and remains constant thereafter [44]. As such, while inflow temperatures in their study were maintained at 42.5°C, outflow temperatures increased from 41 to 42°C. Accordingly, all percutaneously placed intraabdominal temperature probes (upper, midline, and suprapubic quadrants) showed a ~1°C temperature increase from their respective baseline prior to stabilizing, in line with the inflow/outflow temperature gradient.

Despite a relatively constant fluid temperature, other measures of hyperthermia are highly variable in clinical conditions. Hendrix *et al.* studied a total of 135 subjects undergoing CRS/HIPEC [67•]. Their 90-minute HIPEC protocol included a starting mean core-body temperature (CBT) of 36.7°C, mean perfusion flow of 2.35 L/min, and target outflow and intraperitoneal temperatures of ≥40°C and 40-42°C, respectively. Overall, the sample achieved maximum temperatures between 37.5 and 40.1°C. About half of the patients (56%) achieved temperatures of 38.5-39.5°C, while only 27% were above 39.5°C. Goldenshluger *et al.* reported a study of 115 patients undergoing CRS/HIPEC via the closed-abdomen technique, using a volume of 3-5 L of solution and an inflow temperature of 44°C to achieve a mean inflow/outflow of 41.7°C for 60-90 minutes. The authors reported a mean bladder temperature of 38.1°C ±0.9°C and mean CBT of 37.5°C ±0.7°C, with no patients exceeding 40°C [68].

A major obstacle to predicting the development of hyperthermia is the heterogeneity of HIPEC protocols in current practice. In a recent systematic review, Yurttas *et al.* demonstrated that exposure times among the 171 reports analyzed varied between 20 and 120 minutes, with perfusate volumes between 2 and 6, closely related to the technique used (open vs. closed) [69••]. Regarding hyperthermia, studies mostly reported inflow temperatures of 42°C, while intraabdominal temperatures ranged anywhere from 38.5°C to 44°C. In the study of Hendrix *et al.*, patients experiencing core-body hyperthermia of at least 39.5°C had a lower BMI (25.3 vs. 28.2 Kg/m^2, p=0.03) and suffered less frequently from hypertension (25 vs. 46%, p=0.03). Recently, we performed an analysis of 214 patients undergoing CRS/HIPEC to determine the predictors of bladder hyperthermia according to several prespecified definitions [70•]. Overall, the incidences of mild (T≥38°C) and moderate-to-severe (T≥39°C) hyperthermia were 53.27% and 6.54%, respectively. After multivariate analysis, independent predictors for hyperthermia included age (OR=0.968, 95% CI 0.945-0.992, p=0.01), BMI (0.953, 95% CI 0.913-0.995), female gender (OR=0.208, 95% CI 0.108-0.403), type of chemotherapy (cisplatin vs mitomycin, OR=0.235, 95%CI 0.104-0.503, p=0.036), and duration of chemotherapy (OR= 1.094, 95%CI 1.018-1.177).

The Clinical Role of Hyperthermia in PSM

In the treatment of PSM, hyperthermia has been largely judged by the overall impact of HIPEC on survival outcomes. Because PSM is a group of diseases, differences in the median overall survival (OS) in patients undergoing CRS/HIPEC are best understood by the primary histology of the tumor. In a large cohort study by Kyang *et al.*, median OS was reported to be 30, 35, 60, 63, and 248 months for ovarian, colorectal, mesothelioma, high-grade appendiceal, and low-grade appendiceal carcinomas, respectively [71].

Considerable evidence supports the benefit of CRS/HIPEC over systemic therapy in selected surgical candidates [72–75]. In a landmark study, Verwaal *et al.* randomized 105 colon cancer patients to either CRS/HIPEC or systemic chemotherapy and found that CRS/HIPEC significantly improved OS (HR= 0.55, 95% CI 032-0.95; p=0.032), prolonging the median OS by 10 months [76••]. Robust observational data support CRS/HIPEC for PSM of appendiceal etiology [77•]. For malignant peritoneal mesothelioma, a pooled analysis of 1047 patients (20 studies) reported OS of up to 92 months [74]. Finally, better OS rates (HR=0.61, 95% CI 0.41-0.76; p<0.01) have been shown in patients with PSM secondary to ovarian cancer that receive HIPEC in addition to CRS with or without systemic therapy, particularly in studies with larger sample sizes, longer durations of hyperthermia, and CRS/HIPEC followed by chemotherapy [75].

Just recently, experimental studies started to address the independent effect of HIPEC in patients undergoing CRS. Table 2 describes the HIPEC protocols, and the measures of hyperthermia published in comparative trials. In the COLOPEC trial, 202 patients with perforated colon cancer were randomized to receive CRS and adjuvant chemotherapy with

Table 2 Protocols and Measures of Hyperthermia in Comparative Phase III Trials of HIPEC in PSM

Author, Year	Sample Size	Primary Tumor Histology	HIPEC Technique	Perfusion Parameters	Measures of Temperature	Intraoperative Management of Hyperthermia	Main Results
Verwaal *et al.*, 2003 [76••]	105	Colorectal	Open	Type of fluid: Isotonic. Volume: 3 L. Flow: 1-2 L/min. Duration: 90 min. Chemotherapy: Mitomycin C.	Inflow T: 41-42°C Outflow T: Intraabdominal T: ≥40°C CBT: Not reported Other sites of temperature: Not reported	Inflow temperature adjusted if CBT >39°C. Other management strategies were not reported.	HIPEC reduced the risk of death (HR=0.55, 95% CI 0.32-0.95; p = .032) at a median follow-up of 21.6 months.
Klaver *et al.*, 2019 (COLOPEC) [8••]	202	Colorectal	Open and closed. Single, multiperforated inflow and outflow catheters.	Type of Fluid: Isotonic Dialysis. Volume: ≥2L. Flow: 1-2 L/min. Duration: 30 min. Chemotherapy: Oxaliplatin	Inflow T: 42-43°C Outflow T: Not reported Intraabdominal T: Not reported CBT: Not reported Other sites of temperature: Not reported	Not reported.	No difference in RFS (80.9% vs. 76.2%, p=0.28) at 18 months.
Goere *et al.*, 2020 (PROPHYLOCHIP-PRODIGE 15) [78]	150	Colorectal Cancer	Open	Type of fluid: Dextrose 5% Volume: 2L/m^2 Flow: Not reported Duration:30 min Chemotherapy: Oxaliplatin	Inflow T: 45°C Outflow T: 42-42.5°C Intraabdominal T: 43°C CBT: Not reported Other sites of temperature: Not reported	Not reported	3-year RFS was 53% in the surveillance group vs. 44% in second look + HIPEC (HR=0·97, 95% CI 0·61–1·56; p=0·82).
Quenet *et al.*, 2021 (PRODIGE 7) [7••]	265	Colorectal Cancer	Open and closed.	Type of fluid: Dextrose Volume: 2L/m^2. Flow: Not reported Duration: 30 min. Chemotherapy: Oxaliplatin	Inflow T: 43°C Outflow T: Not reported Intraabdominal T: Not reported CBT: Not reported Other sites of temperature: Not reported	Not reported.	No difference in median OS (41.7 vs. 41.2 months, p=0.99, HR=1.00, 95% CI 0.63-1.58) or RFS (13.1 vs. 11.1 months, p=0.43, HR= 0.91, 95% CI 0.71-1.15).
Antonio *et al.*, 2021 (CARCINOHIPEC)	71	Ovarian Cancer	Open	Type of fluid: Dialysis Volume: 3L. Flow: 0.5-0.7 L/min Duration: ≥60 min. Chemotherapy: Cisplatin	Inflow T: Not reported. Outflow T: Not reported. Intraabdominal T: Goal of 42-43°C CBT: Goal to maintain an esophageal temperature of 37°C. Other sites of temperature: Not reported	Physical measures and intravenous fluids.	RFS was improved by HIPEC, HR=0.12, 95% CI 0.02-0.89; p=0.038 in multivariate analysis. OS at 5 years: 45% (HIPEC) vs. 25% (Control).

Table 2 (continued)

Author, Year	Sample Size	Primary Tumor Histology	HIPEC Technique	Perfusion Parameters	Measures of Temperature	Intraoperative Management of Hyperthermia	Main Results
Zivanovic *et al.*, 2021 [79]	98	Ovarian Cancer	Closed	Type of fluid: Normal Saline. Volume: 3L. Flow: Not reported Duration: 90 min. Chemotherapy: Carboplatin.	Inflow T: 41-43°C. Outflow T: Not reported. Intraabdominal T: Not reported CBT: Not reported Other sites of temperature: Not reported	Not reported.	RFS for HIPEC was similar (HR=1.49, 95% CI 0.96-2.32; p=0.076) OS for HIPEC was similar (HR=1.33, 95% CI 0.69-2.56; p=0.39)
van Driel *et al.*, 2018 [80•]	245	Ovarian Cancer	Open	Type of fluid: Not specified. Volume: Variable (ensure adequate exposure). Flow: 1 L/min (adjusted if intraabdominal T <40°C. Duration: 90 min. Chemotherapy: Cisplatin.	Inflow T: 41-42°C. Outflow T: 40°C. Intraabdominal T: 40°C CBT: Not reported Other sites of temperature: Not reported.	Not reported.	RFS for HIPEC was better (HR=0.66, 95% CI 0.5-0.97; p=0.003). OS for HIPEC was better (HR=0.67, 95% CI 0.48-0.94; p=0.02).

CBT: Core-body Temperature. CI: Confidence Interval. HIPEC: Hyperthermic Intraperitoneal Chemotherapy. HR: Hazard Ratio. OS: Overall survival. RFS: Recurrence-free survival.

or without the administration of HIPEC [8••]. The primary outcome was defined as the peritoneal metastasis-free survival at 18 months after surgery. No significant differences were noted between the two groups (69 vs. 69.3%, p=0.99). Because the protocol allowed for HIPEC to occur at the time of surgery or at 5-8 weeks, many patients in the experimental group had evidence of peritoneal metastasis prior to receiving adjuvant HIPEC. Addressing these limitations, the PRODIGE-7 trial randomized 265 patients to either CRS alone or CRS/HIPEC [7••]. Again, the authors did not identify differences in the OS between the two groups (HR= 1·00, 95% CI 0·63–1·58; p=0.99), prompting them to not recommend the use of HIPEC in this population. However, critics of this trial contend that the duration of HIPEC (30 minutes of oxaliplatin) administered may have contributed to the lack of improvement in survival. This criticism is further strengthened by the fact that when patients were stratified by PCI (peritoneal carcinomatosis index); the cohort of patients with a PCI of 11-15 did have an improvement in overall survival in comparison with patients who did not receive hyperthermic intraperitoneal chemotherapy (41.6 months vs 32. 7 months, p=0.021).

Conflicting results have been reported in ovarian cancer. In the CARCINOHIPEC trial, Antonio *et al.* randomized 79 women with PSM secondary to ovarian cancer to CRS alone or with cisplatin HIPEC [81]. Multivariate analysis suggested that the risk of recurrence was reduced in patients receiving HIPEC (HR= 0.12, 95% CI 0.02-0.89; p=0.038). In contrast, Zivanovic *et al.* could not demonstrate a superior treatment strategy between CRS with or without carboplatin HIPEC [79]. In a recently published RCT by van Driel *et al*., the addition of HIPEC to cytoreductive surgery in patients with stage III ovarian cancer showed an improvement in both recurrence free (14.2 months vs 10.7 months) and overall survival (45.7 months vs 33.9 months) compared to cytoreductive surgery alone at a median follow-up of 4.7 years [80•].

To date, no experimental study has addressed the independent effect of temperature in the prognosis of patients with PSM. As a secondary outcome, our group analyzed a sample of 214 patients undergoing CRS/HIPEC [70•]. Our results showed that OS and recurrence-free survival curves were consistent with the primary tumor histology. Interestingly, we found that the lack of mild hyperthermia (≥38°C) at the end of perfusion was independently associated with worse recurrence-free and overall survival. Moreover, a trend toward improved survival was noticed for patients who achieved bladder hyperthermia for at least 30 minutes during perfusion [70•].

Concerning safety, the evidence from clinical trials is conflicted by the presence of chemotherapy and the implications of major abdominal surgery. For instance, staged HIPEC alone had a lower complication rate and a shorter

length of stay than simultaneous HIPEC in the COLOPEC trial [8••]. Moreover, the PRODIGE-7 trial demonstrated that the length of stay and the interval between surgery and food intake were longer in those undergoing CRS/HIPEC versus CRS alone. Although the incidence of grade 3 or higher adverse events was higher in the CRS/HIPEC group, individual differences were only significant for hematological events such as neutropenia and thrombocytopenia. Neither Antonio *et al.* or Zivanovic *et al.* observed differences in the short-term postoperative outcome of women undergoing CRS/HIPEC for ovarian cancer [79, 81]. Finally, Koole *et al*. did not find significant differences in the quality of life between patients randomized to CRS alone or CRS/HIPEC [82].

Few observational studies have addressed the independent effect of hyperthermia in postoperative complications. Hendrix *et al.* found that elevated core-body temperatures (defined as ≥39.5°C) were associated with a higher risk of 30-day postoperative complications (OR=3.77, 95% CI 1.56-9.14) [67•]. For Goldenshluger *et al.,* each Celsius degree increase in CBT raised the odds of postoperative complications by more than two-fold (OR 2.68, 95% CI 1.2–6.01, p = 0.02) [68]. In contrast, our study showed that bladder hyperthermia was not an independent risk factor of 30-day complications [70•]. In a propensity score-matched study, Gremonprez *et al*. analyzed the postoperative outcome of 90 colorectal cancer patients undergoing CRS with either normothermic (n=45) or hyperthermic (n=45) intraperitoneal chemotherapy [83]. Overall, the differences in major postoperative morbidity at 30 days between the HIPEC and normothermic groups did not reach statistical significance (35.6% vs. 26.7%, p=0.362).

Conclusion

Patients with PSM receive therapeutic hyperthermia in the context of HIPEC. Although hyperthermia induces and enhances cellular death [9, 22, 26], cancer cells can resist it through HSP upregulation [13], metabolic adaptation [30•], and modulation of the immune system [39]. Because the response to hyperthermia (at the temperatures administered in HIPEC) is variable, clinical practice will benefit from molecular markers that predict the individual response to therapy.

Unlike a well-circumscribed tumor, the residual disease of PSM is invisible when the patient has undergone an optimal cytoreduction. As a result, applying thermal dosimetry principles to HIPEC is problematic. While the intraabdominal fluid temperature is relatively constant, heat uptake is variable and depends on patient variables and the perfusion protocol. Thus, we need better indicators of adequate heat transfer to the tissues, such as the core-body or bladder temperatures. To understand the role of hyperthermia in PSM, we need a better ability to model hyperthermia during HIPEC, so that clinical trials can adequately test specific temperature, goals, and outcomes.

Despite the existing gaps in knowledge, the growing body of literature is encouraging. HIPEC is being increasingly evaluated for PSM secondary to stomach [84, 85], pancreatic [86], and hepatobiliary [87] malignancies. As the use of computational fluid dynamics and thermodynamic models improves our understanding of hyperthermia [42, 43, 48••], the inclusion of real-world data will allow such developments to individualize therapy and increase its margin of safety. New clinical trials are underway, including those testing the individual effect of hyperthermia in HIPEC [88–90].

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. This article cites an already published retrospective study by Dr. Guerra-Londono on human subjects, which was performed with the permission of the corresponding institutional review board that waived the requirement of informed consent.

Conflict of Interest The authors declare no conflicts of interest.

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