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Controlling perfusion temperature relates to better outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Felipe Lopez-Ramirez, Kseniia Uzhegova, Mary Caitlin King, Luis Felipe Falla-Zuniga, Andrei Nikiforchin, Ekaterina Baron, Carol Nieroda, Armando Sardi *, Vadim Gushchin

Mercy Medical Center, The Institute for Cancer Care, Department of Surgical Oncology, 227 St. Paul Place, Weinberg Building, 4th Floor, Baltimore, MD, 21202-2001, USA

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ABSTRACT

Background: Temperature variability during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) perfusion may affect cytotoxicity. We aimed to characterize an optimal thermal dose during perfusion and assess its impact on outcomes after CRS/HIPEC.

Methods: A retrospective cohort study was conducted (2004–2024) including CRS/HIPEC patients with complete cytoreduction (CC-0/1) and 90-minute perfusion. Using the minimum p-value approach to maximize overall survival (OS), an optimal combination of minimum perfusion temperature and time above such temperature was identified. Patients were classified as PASS if achieving these conditions, or FAIL otherwise. Subgroup multivariable Cox regression was performed.

Results: Optimal conditions were an outflow temperature of ≥40.5 °C for ≥70 % of perfusion time (PASS). Of 755 cases, 531 (70.3%) were PASS and 224 (29.7%) FAIL. Perfusion agents included mitomycin-C (n = 465, 63.1%), melphalan (n = 122, 16.5%), and platinum-based (n = 150, 20.4%). Groups were balanced by age, primary tumor site, peritoneal cancer index (PCI), cytoreduction degree, and major complications. FAIL had more males ($p < 0.01$), higher BMI ($p < 0.01$), and longer operative times ($p = 0.03$). Median follow-up was 80.4 months. PASS had significantly longer median OS (149.4 vs 80.3 months, $p < 0.01$) than FAIL. Subgroup multivariable regression showed a survival benefit of PASS conditions with mitomycin-C and melphalan, but not with platinum agents. PASS conditions were also associated with improved OS in CC-0 and PCI<25.

Conclusions: Maintaining outflow temperatures of ≥40.5°C for ≥70% of perfusion time was associated with improved survival. Thermal dose should be characterized and carefully controlled throughout the procedure. This benefit varied by chemotherapy agent and patient subgroup, warranting further investigation.

1. Introduction

Hyperthermia has demonstrated both intrinsic cytotoxicity and synergism with chemotherapy agents [1,2]. *In vitro* studies rigorously monitor hyperthermia and define thermal dose parameters that correlate with specific biological responses. This concept integrates the time-temperature relationship in hyperthermia into a single metric, enabling comparisons across different exposures [3,4]. Some regional cancer therapies, such as hyperthermic intraperitoneal chemotherapy (HIPEC), leverage this augmented cytotoxicity to selectively target malignant cells throughout the peritoneum [5]. However, despite the critical role of temperature, current HIPEC protocols lack a standardized definition of thermal dose, resulting in substantial variations in both temperature conditions and perfusion duration [6]. These inconsistencies may affect the degree of cytotoxicity, but their oncologic impact remains poorly understood. Applying the thermal dose concept to HIPEC, aiming to optimize cytotoxicity, may clarify the relationship between perfusion temperature and clinical outcomes in patients with peritoneal carcinomatosis [7].

Maintaining consistent thermal conditions during HIPEC is considerably more challenging than in controlled laboratory settings, owing to various technical and physiologic sources of variability. Despite similar perfusion parameters, significant differences in HIPEC temperature dynamics can be observed between patients. This variation may result from

* Corresponding author. Mercy Medical Center, The Institute for Cancer Care, Department of Surgical Oncology, 227 St. Paul Place, 4th Floor Weinberg, Baltimore, MD, 21202-2001, USA.
E-mail address: asardi@mdmercy.com (A. Sardi).

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individual patient factors, such as intraoperative heat loss and morphological characteristics that influence heat distribution. Additional variability stems from inconsistencies in temperature measurement points, sampling rates, and reporting practices [6]. The complexity of the time-temperature relationship, combined with this multifactorial variability, hampers efforts to define an optimal thermal dose using existing clinical records with long-term follow-up sufficient to assess oncologic outcomes.

Clinical studies often face challenges in stratifying patients based on biological variables to evaluate associations with outcomes and inform decision-making. Binarizing continuous variables can simplify interpretation and support threshold-based decisions. However, while some thresholds are grounded in biological rationale, others are set arbitrarily. In the context of HIPEC, defining an optimal thermal dose for patient stratification is particularly complex due to the dynamic interplay between time and temperature. One potential solution is to use data-driven approaches to identify the temperature conditions most strongly associated with improved outcomes. A well-established approach for this purpose is the *minimum p-value* method, often used in exploratory analyses of continuous biomarkers with unknown optimal cut-points [8]. Oncologic studies have applied this method to define prognostic thresholds, for example, for lymphocytic infiltration and gene expression in breast and colorectal cancer [9,10]. While the minimum p-value method raises concerns about generalizability and increased risk of type-I error due to multiple hypothesis testing, these can be mitigated with appropriate statistical corrections. When applied to a sufficiently large cohort that enables multiplicity correction, this method can yield valuable insights –such as identifying a potential threshold relating thermal dose and survival outcomes after HIPEC perfusion.

To better understand the quality of applied hyperthermia during HIPEC, we hypothesized that an effective thermal dose that enhances cytotoxicity exists and, therefore, its impact on the oncologic outcomes of patients with peritoneal carcinomatosis can be determined. Using data from our surgical oncology practice, we aimed to identify a data-driven threshold to characterize suboptimal hyperthermia and evaluate its impact on survival. Recognizing the methodological limitations and potential generalizability concerns, our primary objective is to describe oncologic outcomes across different thermal exposures rather than to establish a definitive clinical threshold.

2. Methods

A single-center, retrospective cohort study was conducted including patients with peritoneal carcinomatosis from different primaries who underwent cytoreductive surgery (CRS) and HIPEC with complete cytoreduction (CC-0/1) and 90-min closed-technique perfusion between 2004 and 2024. Patients with aborted procedures, incomplete cytoreduction (CC-2/3), or perfusion shorter than 90 min were excluded. Data from patients undergoing iterative CRS/HIPEC for recurrent disease were treated as independent cases, measuring outcomes from each procedure.

2.1. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC)

Surgical history was recorded using the prior surgical score (PSS) [11]. Peritoneal cancer index (PCI) was assessed at exploration [12], with PCI≥25 defined as high-tumor burden. Cytoreduction was performed as previously described [13]. After resection, completeness of cytoreduction score (CC-score) was determined with CC-0 defined as no visible tumor, CC-1 residual nodules <2.5 mm, CC-2 residual tumor from 2.5 mm to 2.5 cm, and CC-3 residual tumor >2.5 cm. HIPEC was performed using the closed technique with mitomycin-C (MMC) (40 mg), melphalan (50 mg/m^2), carboplatin (800 mg/m^2), or cisplatin + doxorubicin (50 mg/m^2 + 15 mg/m^2). ThermoChem-HT series (ThermaSolutions®) was used for perfusion, with the temperature bath heated to a target temperature of 41–43 °C and an inflow rate of 1000–1500 mL/min. Surgeons selected the intraperitoneal chemotherapy agents based on histologic features, previous systemic regimens, and suspected chemoresistance. Postoperative complications were graded for 90 days using the Clavien-Dindo classification, with grades III-IV considered major complications [14].

2.2. Temperature recordings

HIPEC perfusion data were retrospectively extracted from patient records, including temperature measurements captured every 5 min from the inflow catheter, the outflow catheter, and an esophageal probe (Fig. 1a). Patients with 3- or 10-minute sampling rates were also included, with data interpolated to 5-minute intervals. Records with other sampling rates were excluded. Outflow temperature was selected to evaluate perfusion quality as it best reflected the ongoing intraperitoneal thermal interaction with the inflowing heated chemotherapy, and showed the greatest variability across patients in a preliminary analysis.

2.3. Follow-up

Postoperative follow-up occurred at 2- and 4-weeks post-discharge, every 6 months for 5 years, and annually until year 10, or earlier if clinically indicated. Follow-up included a physical exam, tumor markers, and CT/PET-CT examination. Recurrence was defined as evidence of new disease on imaging, tumor marker elevation, and/or clinical presentation (e.g., intestinal obstruction).

2.4. Minimum p-value

Outflow temperatures were assessed to determine the optimal combination of minimum perfusion temperature and duration at that temperature to achieve the greatest survival advantage. Conditions were initially evaluated within the 39.0–42.5°C temperature range, and for 45–80% of perfusion time, using 0.5°C step and 5% step increments (72 combinations). To limit the number of hypotheses tested, only temperature-time combinations with sufficient representation in the resulting groups were selected, based on the overall cohort distribution (electronic supplementary: E2 – E3). From these, final cut-off conditions were evaluated in the 40.0–41.5°C temperature range for 65–80% of perfusion time (i.e., 16 combinations). Patients were categorized as either meeting (PASS) or not meeting (FAIL) the minimum conditions for each combination, and overall survival (OS) of the resulting groups was compared using the log-rank test. Effective conditions were identified as those yielding the highest chi-square statistic (i.e., minimum p-value), representing the largest OS difference. To account for the increased risk of type I error due to multiple hypothesis testing, a permutation bootstrapping procedure (1000 iterations) was performed to correct the p-value (electronic supplementary: E4) [8]. This approach evaluates the likelihood of finding significant associations by chance alone (i.e., random allocations of exposure (temperature conditions) and outcomes), and adjusts for potential false positives from the minimum p-value method. Statistical significance was determined based on a corrected p-value of <0.05.

2.5. Statistical Analysis

Analysis was conducted using MATLAB (The MathWorks, 2024). Non-normally distributed continuous variables were presented as medians with interquartile range (IQR) and compared using the Mann-Whitney *U* test. Categorical variables were compared using the Pearson's chi-squared test. The Kaplan-Meier method was used for survival analysis. Progression free survival (PFS) was defined from CRS/HIPEC to recurrence or death, whichever occurred first. OS was measured from CRS/HIPEC to date of death or last contact. The log-rank test was used to

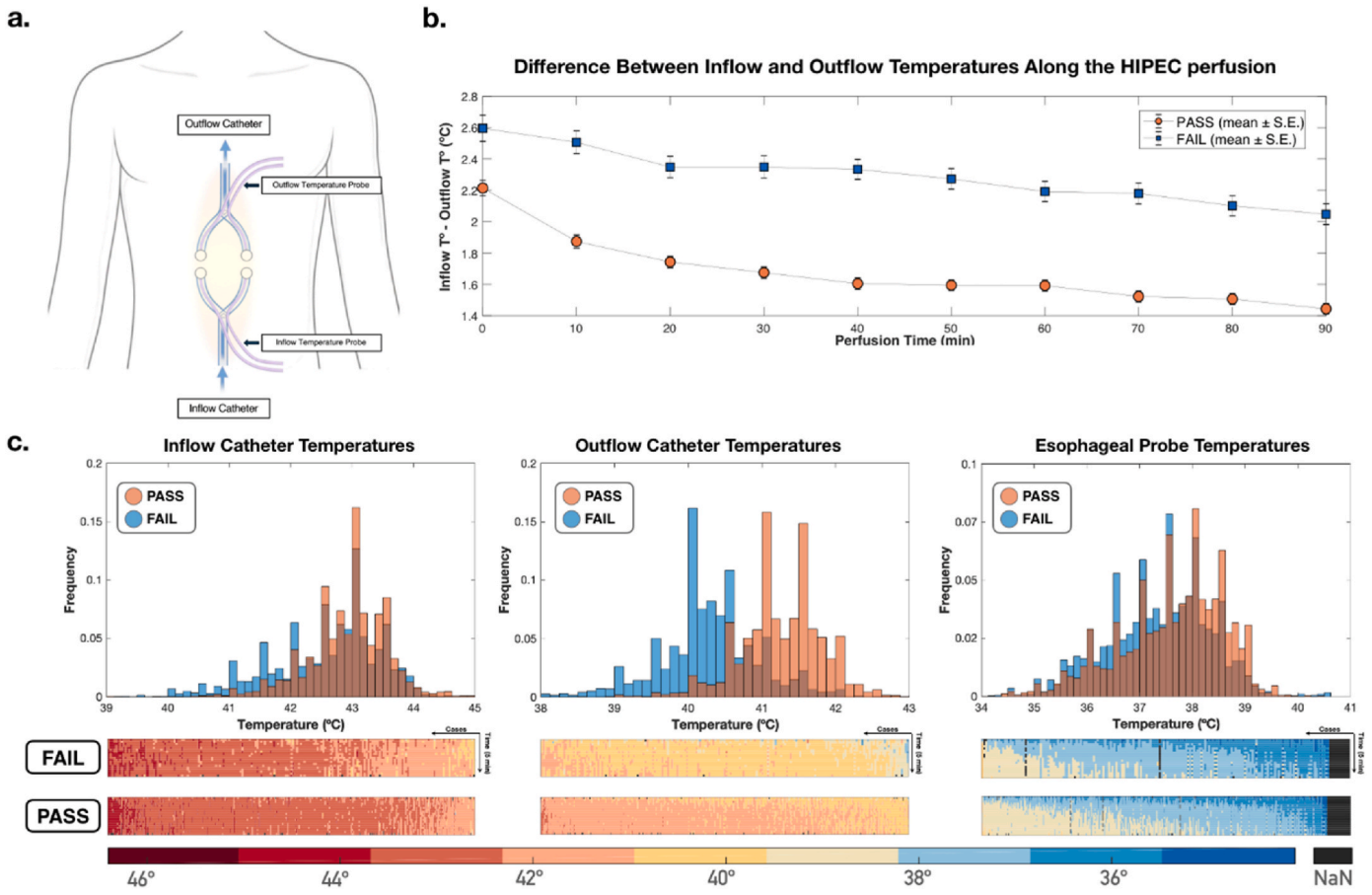

Fig. 1. a. Schematic diagram of intraperitoneal chemotherapy catheter placement illustrating the positioning of intraperitoneal temperature probe tips at the inflow and outflow catheter sites used for temperature recordings. **b.** Average difference between inflow and outflow catheter temperature at each 5-minute timepoint during perfusion in the **PASS** and **FAIL** cohorts. c. Histograms and heatmaps depicting inflow catheter, outflow catheter and esophageal temperature distributions in the **PASS** and **FAIL** cohorts. Heatmaps represent temperature values in 5-minute increments (rows) for different cases (columns). Patients achieving an outflow temperature of ≥40.5 °C for at least 70 % of the perfusion time were defined as the **PASS** cohort or **FAIL** if otherwise. **HIPEC:** hyperthermic intraperitoneal chemotherapy; **min:** minutes; **T°:** temperature: **S.E.:** standard error: **NaN:** not available.

compare survival outcomes between groups. Multivariable Cox proportional-hazards regression was performed to evaluate the effect of temperature conditions in different subgroups. Statistical significance was considered when p-value <0.05.

2.6. Ethics

Institutional Review Board approved consent was obtained for all patients.

3. Results

Overall, 988 patients undergoing 1067 CRS/HIPECs for peritoneal carcinomatosis were identified. From these, 100 (9.3%) cases had incomplete (CC-2/3) cytoreduction, 41 (3.8%) underwent open-technique HIPEC, 29 (2.7%) had perfusions under 90 minutes, 111 (10.4 %) had missing or under-sampled temperature recordings, and 14 (1.3%) had uncommon primary tumors (e.g., breast, prostate, unknown primaries) and were excluded. The remaining 717 patients undergoing 755 CRS/HIPEC procedures were included.

3.1. Optimal temperature conditions and temperature profiles

From the minimum p-value method, optimal conditions with the greatest impact on OS were a minimum outflow temperature of 40.5°C for at least 70% of the perfusion time (raw p-value = 0.0028; corrected p-value = 0.030, electronic supplementary: E1 – E4). Of 755 cases, 531 (70.3%) achieved these conditions (PASS), while 224 (29.7%) did not (FAIL). Average outflow temperatures were 41.2 ± 0.4°C for PASS and 40.2 ± 0.4 °C for FAIL ($p < 0.01$), with significantly different distributions throughout the perfusion (Fig. 1a, $p < 0.01$). The FAIL cohort exhibited a lower average temperature (average difference of 1.0 ± 0.1°C) compared to the PASS cohort at all time points (Fig. 1c). The average difference between inflow and outflow temperatures was significantly lower in the PASS vs FAIL groups at the beginning of the HIPEC perfusion (2.2 vs 2.6°C, $p < 0.01$). This trend persisted throughout the perfusion, with a significantly lower inflow-outflow temperature difference in the PASS group at the end of the perfusion (1.4 vs 2.1°C, $p < 0.01$), reflecting a stronger tendency toward steady state in this group (Fig. 1b).

3.2. Cohort description

Patient demographics are described in Table 1. Overall, 411 (77.4%) PASS and 149 (66.5 %) FAIL patients were female ($p < 0.01$). Median age at surgery was 58 (IQR: 48–66) years in PASS vs 56 (IQR: 48–65) years in FAIL ($p = 0.55$). Median body mass index (BMI) was 26.4 (IQR: 23.4–31.0) kg/m^2 in PASS vs 27.8 (IQR: 25.0–31.8) kg/m^2 in FAIL ($p < 0.01$). Primary tumor sites in PASS vs FAIL included 286 (53.9%) vs 101 (45.1%) appendix, 79 (14.9%) vs 34 (15.2%) colorectal, 127 (23.9%) vs 62 (27.7 %) ovarian, and 39 (7.3%) vs 27 (12.1%) other tumors, respectively ($p = 0.12$). Median PCI was 21 (IQR: 8–31) in PASS vs 22

Table 1
Clinicopathological perioperative characteristics by temperature group.

Variable		FAIL (N = 224)	PASS (N = 531)	p-value
Female (N, %)		149 (66.5%)	411 (77.4%)	**<0.01**
Age at Surgery, years (Median [IQR])		56 [48–65]	58 [48–66]	0.55
BMI (Median [IQR])		27.8 [25.0–31.8]	26.4 [23.4–31.0]	**<0.01**
BMI ≥30 (N, %)		79 (35.3%)	162 (30.5%)	0.21
PSS ≥2 (N, %)		82 (36.6%)	190 (35.8%)	0.98
Primary Tumor	Appendix - Low Grade (N, %)	59 (26.3%)	164 (30.9%)	0.12
	Appendix – High Grade (N, %)	42 (18.8%)	122 (23.0%)	
	Colorectal (N, %)	34 (15.2%)	79 (14.9%)	
	Ovarian (N, %)	62 (27.7%)	127 (23.9%)	
	Other[a] (N, %)	27 (12.1%)	39 (7.3%)	
Cytoreduction	CC-0 (N, %)	176 (78.6%)	404 (76.1%)	0.52
	CC-1 (N, %)	48 (21.4%)	127 (23.9%)	
PCI (Median [IQR])		22 [11–31]	21 [8–31]	0.86
PCI ≥ 25 (N, %)		92 (41.1%)	227 (42.7%)	0.73
Iterative Procedure (N, %)		18 (8.0%)	30 (5.6%)	0.29
Chemotherapy Agent	Mitomycin-C (N, %)	120 (53.6%)	345 (65.0%)	**<0.01**
	Melphalan (N, %)	57 (25.4%)	65 (12.2%)	
	Carboplatin (N, %)	32 (14.3%)	67 (12.6%)	
	Cisplatin + Doxorubicin (N, %)	9 (4.0%)	42 (7.9%)	
Perfusate Volume, L (Median [IQR])		3.5 [3.0–3.6]	3.5 [3.0–3.6]	0.62
Length of Surgery, minutes (Median [IQR])		529 [439–622]	494 [400–611]	**0.03**
Length of Hospital Stay, days (Median [IQR])		9 [8–12]	9 [8–12]	0.64
90-day Major Postoperative Complications[b] (N, %)		44 (19.6%)	123 (23.2%)	0.33
90-day Mortality (N, %)		8 (3.6%)	7 (1.3%)	0.08

BMI: body mass index; **CC:** completeness of cytoreduction score**; IQR:** interquartile range; **L:** liters; **PCI:** peritoneal cancer index; **PSS:** prior surgical score. Numbers in bold indicate statistical significance ($p < 0.05$).
PASS: Outflow temperature ≥40.5°C for 70% or more of the perfusion time, **FAIL** if not.
[a] Other tumors included: gastric, small bowel, peritoneal mesothelioma, endometrial carcinoma, and uterine sarcoma.
[b] Grade III-IV postoperative complications according to the Clavien-Dindo classification.

(IQR: 11–31) in FAIL ($p = 0.86$). CC-0 was achieved in 404 (76.1%) PASS vs 176 (78.6%) FAIL ($p = 0.52$). Median length of surgery was 494 (IQR: 400–611) minutes in PASS vs 529 (IQR: 439–622) minutes in FAIL ($p = 0.03$). Median length of hospital stay was 9 (IQR: 8–12) days in PASS vs 9 (IQR: 8–12) days in FAIL ($p = 0.64$). Grade III-IV 90-day postoperative complications occurred in 123 (23.2%) PASS vs 44 (19.6%) FAIL ($p = 0.33$), with 90-day mortality in 7 (1.3%) PASS vs 8 (3.6%) FAIL patients ($p = 0.08$).

3.3. HIPEC agents

HIPEC perfusion agent was MMC in 465 (63.1%), melphalan in 122 (16.5%), and platinum-based in 150 (20.4%) cases. PASS conditions were achieved in 345 (74.2%) MMC, 65 (53.3%) melphalan, and 109 (72.7%) platinum-based cases ($p < 0.01$).

3.4. Survival outcomes

Median follow-up was 80.4 (confidence interval [CI] 95%: 72.3–88.4) months. Median PFS was 69.2 (CI95%: 44.3–111.3) months with a 5-year PFS of 51.6 % for PASS vs 31.7 (CI95%: 24.4–45.4) months and 39.2 % for FAIL ($p < 0.01$). Median OS was 149.4 (CI95 %: 111.3–not reached [NR]) months with a 5-year survival of 66.1% for PASS vs 80.3 (CI95%: 51.4–100.0) months with a 5-year survival of 54.7% for FAIL ($p < 0.01$) (Fig. 2). Median OS for cases perfused with MMC was 199 vs 115 months in PASS vs FAIL ($p = 0.05$) (Fig. 3a). For cases perfused with melphalan, median OS was 58.2 vs 37.9 months in PASS vs FAIL ($p = 0.027$) (Fig. 3b). For cases perfused with platinum agents, median OS was 69.3 vs 80.3 months in PASS vs FAIL ($p = 0.96$) (Fig. 3c).

3.5. Multivariable regression and subgroup analysis

Cox-regression analysis for OS is shown in Table 2. After adjusting for sex, age at surgery, primary tumor, degree of cytoreduction, HIPEC agent, PCI, and BMI, the overall hazard ratio (HR) for PASS conditions was 0.72 (CI95%: 0.56–0.92, $p = 0.01$). Subgroup multivariable regression showed a survival benefit of PASS conditions in females (HR: 0.71, $p = 0.02$), patients <65 years old (HR: 0.69, $p = 0.01$), PCI <25 (HR: 0.66, $p = 0.02$), BMI <30 (HR: 0.67, $p = 0.01$), and CC-0 (HR: 0.61, $p < 0.01$). Patients with PASS conditions perfused with MMC (HR: 0.65, CI95 %: 0.46–0.93) or melphalan (HR: 0.59, CI95%: 0.35–0.99) showed an adjusted survival benefit, which was not seen with platinum-based perfusion agents.

4. Discussion

We analyzed the impact of applied thermal dose during 90-minute closed-technique HIPEC on oncologic outcomes in a large cohort of patients with peritoneal carcinomatosis from various primary tumors. Based on the hypothesis that sustained hyperthermia enhances cytotoxicity, we employed a data-driven approach to identify a clinically relevant time-temperature threshold. In our cohort, maintaining an outflow temperature above 40.5°C for at least 70% of the perfusion time was significantly associated with improved survival outcomes, highlighting the importance of precise temperature control during CRS/HIPEC. Despite uniform adherence to a standard perfusion protocol and consistent inflow temperature settings, outflow temperature recordings showed substantial interpatient variability, resulting in 29.7% of patients experiencing suboptimal hyperthermia (FAIL). These patients had significantly shorter survival than those who achieved the target conditions (PASS), even after adjusting for potential confounders including sex, age at surgery, primary tumor site, PCI, BMI, completeness of cytoreduction, and HIPEC agent. Subgroup analyses showed a survival benefit associated with PASS conditions in female patients, patients under 65 years, those with PCI <25, BMI <30, and CC-0 cytoreduction, as well as MMC or melphalan regimens.

While precisely controlled temperature conditions can be reliably maintained *in vitro* [15–19], replicating these ideal conditions in the operating room poses significant technical challenges. During HIPEC perfusion, hyperthermia must compensate for substantial heat loss after prolonged operative times and patient-specific factors impacting thermodynamics. This challenge was reflected in our cohort, where despite minimal variations in inflow temperatures, outflow temperatures differed significantly between the PASS and FAIL groups. The FAIL group also consistently demonstrated a greater inflow-outflow temperature gradient throughout the perfusion (Fig. 1a and b). One potential explanation for this discrepancy is failing to reach steady-state thermodynamics before initiating chemoperfusion, possibly related to the longer operative times seen in the FAIL cohort. Patient-specific characteristics may also affect the heat exchange, as suggested by the lower BMI and higher proportion of females in the PASS group. Fine-tuning perfusion parameters to individual characteristics might help optimize the thermal dose delivery. Preclinical and computational studies have demonstrated that dynamic inflow adjustments, such as increasing abdominal pressure, modifying inflow rates, and altering catheter designs, can improve thermal stability [20–25]. Translating these strategies into clinical practice could promote uniform perfusion temperatures

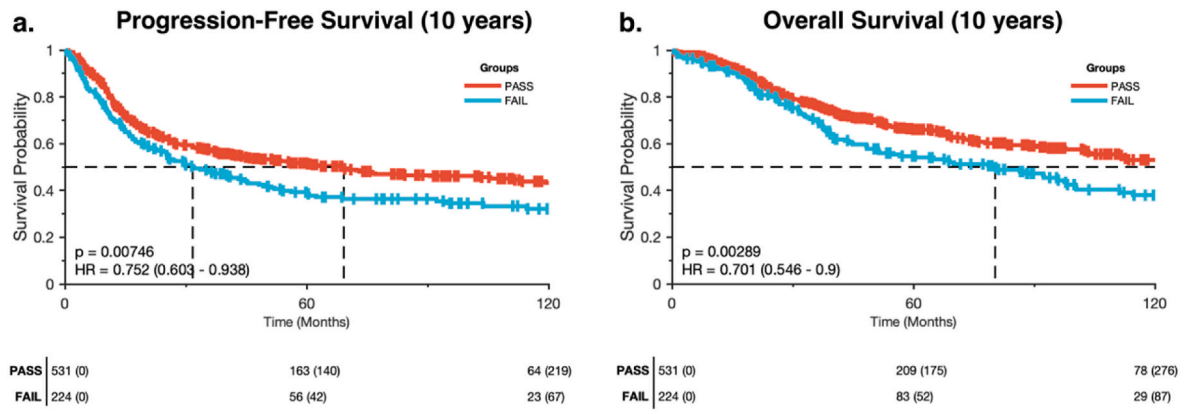

Fig. 2. Kaplan-Meier **a.** progression-free and **b.** overall survival analysis comparing the **PASS** versus **FAIL** cohorts. Median survival times are represented as dashed lines. Censoring points are represented as vertical lines on the curves and numbers in parentheses in the risk tables. Log-rank tests were used to compare survival outcomes. **HR:** hazard ratio (95% confidence interval).

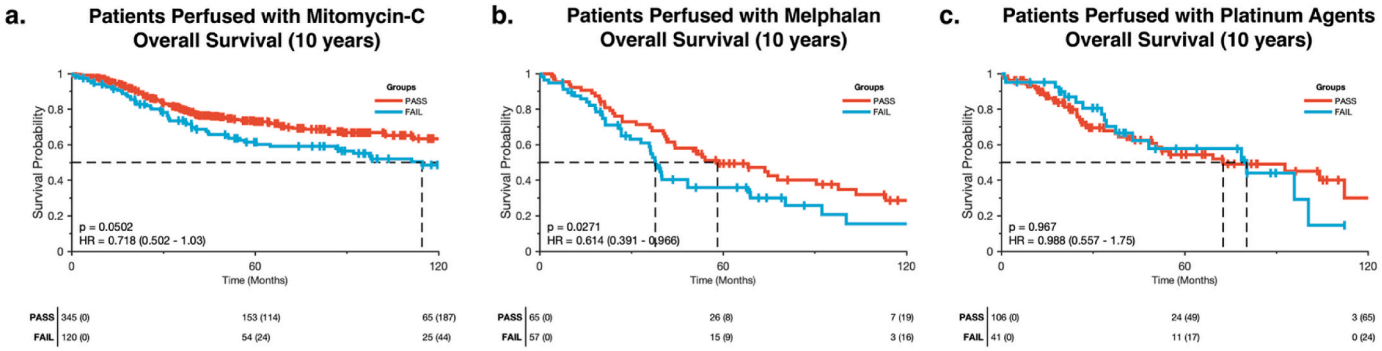

Fig. 3. Kaplan-Meier survival analysis comparing overall survival for the **PASS** versus **FAIL** cohorts by HIPEC chemotherapy agents for **a.** mitomycin-C. **b.** melphalan and **c.** platinum-based (i.e., carboplatin or cisplatin + doxorubicin). Median survival times are represented as dashed lines. Censoring points are represented as vertical lines on the curves and numbers in parentheses in the risk tables. Log-rank tests were used to compare survival outcomes. **HIPEC:** hyperthermic intraperitoneal chemotherapy; **HR:** hazard ratio (95% confidence interval).

and facilitate achieving optimal therapeutic levels that balance efficacy and patient safety.

Hyperthermia not only exerts direct cytotoxicity, but can also synergistically potentiate certain perfusion agents [17–19,26]. Studies have demonstrated various mechanisms by which different agents exhibit increased cytotoxicity under hyperthermic conditions [19,27,28]. In our study, a survival benefit was associated with increased thermal dose in patients treated with MMC or melphalan, but not with platinum-based regimens. Notably, in the MMC subgroup, while the unadjusted analysis showed a borderline difference in OS, the adjusted analysis demonstrated a significant association (HR: 0.65, 95% CI: 0.46–0.93), suggesting a potential for thermal enhancement with this agent. Other studies have also reported varying degrees of hyperthermia-induced chemotherapy potentiation. For example, Fujimura et al. demonstrated improved survival outcomes in advanced gastric cancer using a combined perfusion regimen of cisplatin and MMC at 41–42 °C [29]. These discrepancies raise important questions about whether the benefit stems from direct thermal cytotoxicity, specific chemotherapy enhancement, or tumor biology. Schaaf et al. reported a 40°C threshold that significantly potentiated cisplatin and doxorubicin *in vitro*, with their clinical data further validating its relevance through observed survival benefits [30]. In contrast, our study did not show a survival advantage in the platinum-treated cohort, potentially due to the predominance of carboplatin use, which may exhibit different thermal sensitivity than cisplatin. Additionally, the potential for agent degradation at elevated temperatures warrants consideration. Sugarbaker et al. previously raised concerns about a temperature-dependent accelerated melphalan degradation [31]. In response, our protocol employed lower target temperatures during melphalan perfusion, resulting in fewer of these patients achieving PASS conditions. Despite this, the significant survival benefit observed among melphalan-treated patients who met PASS conditions suggests that a higher thermal dose may still offer therapeutic advantage. These findings emphasize the importance of tailoring perfusion settings to both patient characteristics and the thermal properties of chemotherapy agents. Further studies are needed to better understand this complex interaction and optimize protocols accordingly.

Completeness of cytoreduction is a well-established prognostic factor in CRS/HIPEC. Interestingly, in this study, CC-score also modified the effect of thermal dose on survival outcomes. While “complete” cytoreduction typically includes residual disease <2.5 mm (CC-0/1), based on evidence that intraperitoneal chemotherapy can penetrate up to 3 mm into tissue [32], only patients with a CC-0 cytoreduction experienced an adjusted survival benefit from PASS conditions (Table 2). Preclinical organoid models support these findings, demonstrating that increasing tumor thickness significantly reduces hyperthermia-induced cytotoxicity and showing marked cell viability differences between 30-minute and 2-hour exposures [33]. These observations highlight the importance of complete macroscopic tumor removal, and delivering an adequate thermal dose to maximize the therapeutic effect on microscopic residual disease. Our results further support this need for sustained thermal exposure, as maintaining the target temperature for at least 70% of the perfusion maximized the observed survival benefit. Including this temporal component reduces the patchiness of

Table 2
Cox Proportional-Hazards regression for overall survival for PASS/FAIL temperature conditions by subgroups.

Subgroup		FAIL	PASS	Univariable		Multivariable[a]	
				HR [CI95%]	p-value	HR [CI95%]	p-value
Sex	Female	149	411	0.66 [0.50–0.87]	**<0.01**	0.71 [0.54–0.95]	**0.02**
	Male	75	120	0.73 [0.46–1.16]	0.18	0.77 [0.46–1.29]	0.32
Age at surgery	<65	161	376	0.71 [0.53–0.95]	**0.02**	0.69 [0.51–0.93]	**0.01**
	≥65	63	155	0.67 [0.45–1.01]	0.06	0.77 [0.50–1.20]	0.25
Primary Tumor	Appendix Low-Grade	59	164	0.75 [0.39–1.43]	0.38	0.74 [0.38–1.43]	0.37
	Appendix High-Grade	42	122	0.98 [0.60–1.61]	0.94	1.14 [0.63–2.06]	0.66
	Colorectal	34	79	0.51 [0.31–0.85]	**0.01**	0.50 [0.28–0.88]	**0.02**
	Ovarian	62	127	0.84 [0.54–1.32]	0.45	0.79 [0.50–1.27]	0.34
	Other[b]	27	39	0.38 [0.18–0.83]	**0.01**	0.32 [0.13–0.76]	**0.01**
Cytoreduction	CC-0	176	404	0.65 [0.49–0.86]	**<0.01**	0.61 [0.46–0.82]	**<0.01**
	CC-1	48	127	0.85 [0.53–1.36]	0.50	0.90 [0.54–1.50]	0.68
Agent	Mitomycin-C	120	345	0.72 [0.51–0.99]	**0.05**	0.65 [0.46–0.93]	**0.02**
	Melphalan	57	65	0.61 [0.39–0.95]	**0.03**	0.59 [0.35–0.99]	**0.05**
	Carboplatin	32	67	1.02 [0.56–1.86]	0.94	1.02 [0.54–1.93]	0.94
	Cisplatin + Doxorubicin	15	54	1.46 [0.40–5.35]	0.57	0.64 [0.09–4.66]	0.66
PCI	<25	132	304	0.59 [0.43–0.82]	**<0.01**	0.66 [0.47–0.94]	**0.02**
	≥25	92	227	0.81 [0.57–1.14]	0.22	0.77 [0.53–1.11]	0.16
BMI	<30	143	367	0.62 [0.46–0.82]	**<0.01**	0.67 [0.50–0.90]	**0.01**
	≥30	79	162	0.92 [0.60–1.41]	0.69	0.81 [0.52–1.27]	0.36
Overall		224	531	0.70 [0.55–0.89]	**<0.01**	0.72 [0.56–0.92]	**0.01**

BMI: body mass index; **CC:** completeness of cytoreduction; **CI95 %:** 95 % confidence interval; **HR:** hazard ratio; **PCI:** peritoneal cancer index.
Numbers in bold indicate statistical significance ($p < 0.05$).
[a] Adjusted by sex, age, PCI, cytoreduction, BMI, primary tumor and chemotherapy agent.
[b] Other tumors included gastric, small bowel, peritoneal mesothelioma, endometrial carcinoma and uterine sarcoma.

temperature peaks and valleys, improving consistency in the applied hyperthermia. Together, these findings reinforce that incorporating both target temperature and duration of exposure into the definition of HIPEC thermal dose is essential for maximizing cytotoxicity and improving oncologic outcomes.

This study has several limitations inherent to its retrospective, single-center design. To ensure consistency in procedural conditions and reduce potential confounding, approximately 20% of the initial patient pool was excluded due to factors such as use of the open technique, shorter perfusion, or incomplete cytoreduction. While necessary, these exclusions may limit generalizability and introduce the risk of selection bias. Additionally, the loss of approximately 10% of patients due to missing or under sampled temperature data represents a meaningful statistical limitation and raises the possibility of attrition bias. Regarding treatment effects, although a higher thermal dose was associated with improved survival, the identified threshold may reflect overfitting to center-specific practices and patient characteristics, warranting external validation. This concern is especially relevant given the use of the minimum p-value method. Although statistical corrections were applied to mitigate the increased type-I error risk (electronic supplementary: E1 – E4), the magnitude of the observed effects might still be overestimated. Therefore, the focus should be placed on the presence of a clinically meaningful threshold rather than its effect size. Additionally, the thermodynamic evaluation was limited by the relatively low temperature sampling rate (5 min) and absence of multiple intra-abdominal temperature probes. Moreover, outflow temperatures alone fail to capture the full intra-abdominal heat exchange. Continuous temperature monitoring using probes placed at key abdominal sites could provide a more comprehensive understanding of HIPEC thermodynamics and help refine the definition of 'optimal' conditions.

5. Conclusion

This study supports the existence of a critical thermal dose that optimizes the oncologic efficacy of CRS/HIPEC in patients with peritoneal carcinomatosis from various primary tumors. In our cohort, patients achieving PASS temperature conditions (≥40.5°C for ≥70% of perfusion time) had significantly longer overall and progression-free survival, without increased morbidity. The magnitude of this benefit varied across subgroups and warrants further exploration. These findings highlight the importance of tighter temperature control during HIPEC and the need to standardize the applied thermal dose to potentially enhance the cytotoxic effects of hyperthermia.

Author contributions (CRediT)

- **Conceptualization:** Felipe Lopez-Ramirez, Mary Caitlin King, Armando Sardi, Vadim Gushchin
- **Methodology:** Felipe Lopez-Ramirez, Mary Caitlin King, Armando Sardi, Vadim Gushchin
- **Data Curation:** Felipe Lopez-Ramirez, Kseniia Uzhegova, Mary Caitlin King, Luis Felipe Falla-Zuniga, Andrei Nikiforchin, Ekaterina Baron
- **Validation:** Felipe Lopez-Ramirez, Mary Caitlin King, Kseniia Uzhegova
- **Formal Analysis:** Felipe Lopez-Ramirez, Kseniia Uzhegova
- **Statistical Analysis:** Felipe Lopez-Ramirez
- **Writing – Original Draft:** Felipe Lopez-Ramirez, Kseniia Uzhegova
- **Writing – Review & Editing:** Felipe Lopez-Ramirez, Kseniia Uzhegova, Mary Caitlin King, Luis Felipe Falla-Zuniga, Andrei Nikiforchin, Ekaterina Baron, Vadim Gushchin, Carol Nieroda
- **Supervision:** Vadim Gushchin, Mary Caitlin King

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.110536.

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