



# Elevated Maximum Core Body Temperature During Hyperthermic Intraperitoneal Chemoperfusion (HIPEC) is Associated with Increased Postoperative Complications

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## ABSTRACT

**Background.** Hyperthermia enhances the cytotoxicity of chemotherapeutic agents used during cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC). However, this may result in an elevated core body temperature (CBT), with unintended effects on surgical morbidity. This study evaluates the relationship of maximum CBT during CRS/HIPEC on postoperative outcomes.

**Methods.** A retrospective review of patients undergoing CRS/HIPEC from January 2011 to July 2017 was performed. Outcomes were stratified according to maximum CBT reached during HIPEC. Primary study endpoints were 30-day morbidity and 30-day complication severity.

**Results.** Overall, 135 consecutive CRS/HIPEC cases were reviewed; 36 (27%) had a maximum CBT  $\geq 39.5$  °C during the 90-min HIPEC. CBT  $\geq 39.5$  °C was associated with an increase in 30-day postoperative complications (58% vs. 34%,  $p = 0.01$ ) and severe Clavien–Dindo grade III or higher complications (22% vs. 11%,  $p = 0.04$ ). On multivariate analysis, the adjusted odds ratio of having any complication was 3.77 (95% confidence interval [CI] 1.56–9.14) and a Clavien–Dindo grade III or higher complication was 3.46 (95% CI 1.10–10.95) when maximum CBT reached 39.5 °C. Flow rates  $\geq 2.35$  L/min were associated with lower average CBT ( $p = 0.05$ ) and improved peritoneal heating ( $p = 0.02$ ).

**Conclusion.** Maximum CBT  $\geq 39.5$  °C is associated with an increased risk of postoperative morbidity. Higher flow

rates are associated with improved intraperitoneal heating, lower CBT, and may contribute to optimizing the therapeutic benefit of HIPEC.

In the management of peritoneal surface malignancy, cytoreductive surgery (CRS) effectively reduces the tumor burden of macroscopic disease, while the subsequent delivery of heated intraperitoneal chemotherapy (HIPEC) targets residual microscopic deposits.<sup>1–7</sup> Hyperthermia functions as a chemosensitizing agent, with the magnitude of effect dependent on the chemotherapy agent utilized.<sup>8</sup> Compared with fever, which is an elevation of the physiologic set point of core body temperature (CBT), hyperthermia differs fundamentally and refers instead to a rise in CBT resulting from an external heat load or failure of heat dissipation.<sup>9</sup>

Mechanistically, HIPEC induces a regional hyperthermia within the abdominal cavity. Ultimately, this functions to increase the permeability of the peritoneal lining and improve the delivery of chemotherapy to cancer cells.<sup>8</sup> Rising temperatures induce vasodilation in healthy tissues, however this physiologic response is blunted in tumor, resulting in inefficient heat dissipation and a reduced pH, factors that synergistically increase cancer's sensitivity to hyperthermia.<sup>10–12</sup> Furthermore, hyperthermia has been linked to tumor-directed cytotoxic effects through induction of heat shock proteins, protein denaturation, and impairment of DNA repair mechanisms.<sup>10–12</sup>

The efficacy of regional hyperthermia during HIPEC is related to the target peritoneal temperature being achieved and subsequently maintained for the duration of chemoperfusion. In the setting of CRS/HIPEC, with the continuous infusion of heated perfusate directly into the abdomen, unwanted systemic hyperthermia may develop, as noted by a rise in CBT. Most data published on immunologic

changes in humans exposed to systemic heat demonstrate a threshold CBT of 39–39.5 °C, at which point alterations of immune system function may be identified.<sup>13–15</sup> Specifically, this degree of hyperthermia appears to induce a significant reduction in circulating CD4+ lymphocytes, reduce the ratio of CD4+ to CD8 + lymphocytes, and increase natural killer cell activity.<sup>13,15</sup> These changes in the cellular immune response are relatively nonspecific, but may be interpreted as part of a general response to the major physiologic stress of systemic hyperthermia.

Overall, little is known about the impact of CBT during HIPEC on oncologic or surgical outcomes. The primary aim of this study was to evaluate the effect of induced systemic hyperthermia, defined as a CBT  $\geq$  39.5 °C, on 30-day morbidity and 30-day complication severity following CRS/HIPEC. Additionally, we sought to investigate the potential for optimization of chemoperfusion by adjusting flow rates as a means to maximize regional hyperthermia while limiting systemic hyperthermia.

## METHODS

### *Data Sources*

This was a single-institution, retrospective cohort study. Baseline characteristics, intraoperative factors, chemoperfusion parameters, and postoperative complications were recorded prospectively. Complications were identified in accordance with definitions from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) and severity graded according to the Clavien–Dindo classification system.<sup>16,17</sup> The study was performed in compliance with the policies of our Institutional Review Board.

### *Patient Cohort*

Consecutive patients who underwent CRS/HIPEC at our institution from January 2011 to August 2017 were identified and their medical records reviewed. Cases were divided into two groups according to the maximum CBT recorded during HIPEC, i.e. those with a documented temperature  $\geq$  39.5 °C (CBT–High) and those with a maximum temperature  $<$  39.5 °C (CBT–Low).

### *Intraoperative Monitoring*

Standard intraoperative monitoring devices were utilized per American Society of Anesthesiologists guidelines. During the 90-min HIPEC, perfusion parameters (perfusion flow rate [L/min], inflow temperature [°C], outflow temperature [°C], and esophageal temperature

[°C]) were recorded at the start of chemoperfusion and every 15 min thereafter, for a total of seven time points. Inflow and outflow temperatures were monitored using temperature-sensing catheter probes. Esophageal temperature was measured by an esophageal temperature probe and used as a surrogate for CBT. Intraoperative management of physiologic aberrations related to CBT were made on a case-by-case basis with target outflow temperatures  $\geq$  40 °C and intraperitoneal temperatures of 40–42 °C.

### *Statistical Analysis*

Descriptive statistics were calculated for the entire cohort. The distribution of all covariates were compared between study groups using Chi square tests for categorical variables, and Student's *t* tests and Wilcoxon rank-sum tests for continuous variables. Statistical significance was assigned a threshold of  $p \leq 0.05$ . The primary study endpoints were 30-day morbidity and 30-day complication severity. Secondary endpoints included 90-day mortality and average flow rates during HIPEC. Separate logistic regression models were used to estimate the odds of any postoperative complication or severe Clavien–Dindo grade III or higher complication associated with the CBT–High group in reference to the CBT–Low group. Both models were adjusted for age, sex, intraoperative estimated blood loss (EBL), operation time, Peritoneal Cancer Index (PCI) score, and completeness of cytoreduction (CC) score. Adjusted odds ratio (aOR) with 95% confidence intervals (CI) were reported. All analyses were performed using STATA software version 15.1 (StataCorp LLC, College Station, TX, USA).

## RESULTS

### *Study Subjects*

A total of 135 consecutive patients undergoing CRS/HIPEC were included in this study. At the beginning of HIPEC after cytoreduction, mean CBT was 36.7 °C. During the 90-min chemoperfusion, all patients demonstrated some degree of systemic hyperthermia, with a maximum CBT range from 37.5 to 40.9 °C. The majority of patients (56%) had a documented maximum CBT between 38.5 and 39.5 °C. Ultimately, 36 patients (27%) had a documented maximum CBT  $\geq$  39.5 °C (CBT–High), while 99 patients (73.3%) had a documented maximum CBT  $<$  39.5 °C (CBT–Low). No patients developed malignant hyperthermia or hypothermia during HIPEC.

### Preoperative Characteristics

Median age was 56 years, and a minority of patients were male (34%). Medical comorbidities did not significantly differ between groups, except for body mass index (BMI) and hypertension (Table 1). The primary tumor histology leading to peritoneal dissemination was most commonly of appendiceal origin (67%), followed by colorectal origin (19%), but did not differ significantly between CBT groups ( $p = 0.63$ ). The extent of disease as measured by the PCI was 17.9 for the entire study population.

### Intraoperative Variables

The extent of cytoreduction was similar in the two groups, as evidenced by the number of organ resections, anastomoses, and peritonectomy procedures (Table 2). Operative time was unchanged between groups (9.3 vs. 9.0 h,  $p = 0.92$ ), and provided further evidence of a

comparable case complexity. All patients underwent a 90-min chemoperfusion. A 30–40 mg mitomycin C HIPEC was most common (92%), with the drug delivered intraperitoneally over three divided doses. The remaining cases were managed with an 800 mg/m<sup>2</sup> carboplatin HIPEC (7%) or a 25 mg doxorubicin HIPEC (1%), again with drug delivery over three divided doses. No between-group differences were identified ( $p = 0.73$ ). A complete cytoreduction (CC), defined as a CC score of 0 or 1, was achieved in approximately 80% of cases in both groups ( $p = 0.31$ ).

### Chemoperfusion Parameters

The median average flow rate was 2.35 L/min. Flow rates  $\geq 2.35$  L/min were associated with a reduced CBT and improved intraperitoneal heating, as defined by increased peritoneal outflow temperatures and a reduced inflow/outflow temperature differential (Table 3). Patients with a documented maximum CBT  $\geq 39.5$  °C maintained

**TABLE 1** Baseline characteristics of the study population

| Characteristics                       | CBT-High ( $\geq 39.5$ ) [ $n = 36$ ] | CBT-Low ( $< 39.5$ ) [ $n = 99$ ] | $p$ value |
|---------------------------------------|---------------------------------------|-----------------------------------|-----------|
| Age, years [median (IQR)]             | 55.5 (49.5–60.5)                      | 57.0 (49.0–63.0)                  | 0.96      |
| Male sex                              | 11 (31)                               | 35 (35)                           | 0.60      |
| BMI, kg/m <sup>2</sup> [median (IQR)] | 25.3 (22.5–28.0)                      | 28.2 (23.9–33.4)                  | 0.03      |
| Primary tumor type                    |                                       |                                   | 0.63      |
| Appendix                              | 22 (61)                               | 69 (70)                           |           |
| Colorectal                            | 8 (22)                                | 17 (17)                           |           |
| Peritoneal mesothelioma               | 4 (11)                                | 8 (8)                             |           |
| Other primary                         | 2 (6)                                 | 5 (5)                             |           |
| Neoadjuvant chemotherapy              | 12 (33)                               | 35 (35)                           | 0.83      |
| Prior cytoreductive surgery           | 4 (12)                                | 7 (7)                             | 0.40      |
| Prior HIPEC                           | 1 (3)                                 | 3 (3)                             | 0.96      |
| PCI score                             |                                       |                                   | 0.33      |
| $< 10$                                | 7 (19)                                | 28 (28)                           |           |
| 10–20                                 | 9 (23)                                | 30 (30)                           |           |
| $> 20$                                | 20 (56)                               | 41 (41)                           |           |
| ASA class [median (IQR)]              | 3.0 (2.0–3.0)                         | 3.0 (2.0–3.0)                     | 0.76      |
| Hypertension                          | 9 (25)                                | 45 (46)                           | 0.03      |
| Diabetes                              | 1 (3)                                 | 11 (11)                           | 0.13      |
| Coronary artery disease               | 3 (8)                                 | 7 (7)                             | 0.82      |
| Chronic kidney disease                | 0 (0)                                 | 0 (0)                             | –         |
| Chronic obstructive pulmonary disease | 0 (0)                                 | 2 (2)                             | 0.39      |
| Ascites                               | 10 (28)                               | 19 (19)                           | 0.30      |
| Myocardial infarction                 | 0 (0)                                 | 3 (3.0)                           | 0.29      |
| Congestive heart failure              | 0 (0)                                 | 3 (3.0)                           | 0.29      |

Data are expressed as  $n$  (%) unless otherwise specified

CBT core body temperature, IQR interquartile range, BMI body mass index, HIPEC hyperthermic intraperitoneal chemoperfusion, PCI Peritoneal Cancer Index, ASA American Society of Anesthesiologists

**TABLE 2** Intraoperative characteristics during CRS/HIPEC

| Characteristics                         | CBT-High ( $\geq 39.5$ ) [ $n = 36$ ] | CBT-Low ( $< 39.5$ ) [ $n = 99$ ] | <i>p</i> value |
|---|---------------------------------------|-----------------------------------|----------------|
| Operative time, h [median (IQR)]        | 9.3 (8.0–11.0)                        | 9.0 (8.0–11.5)                    | 0.92           |
| Estimated blood loss, L [median (IQR)]  | 0.3 (0.1–0.5)                         | 0.3 (0.2–0.5)                     | 0.74           |
| Crystalloid infusion, L [median (IQR)]  | 4.7 (4.0–7.0)                         | 5.0 (3.0–6.6)                     | 0.41           |
| Colloid infusion, L [median (IQR)]      | 0.0 (0.0–0.9)                         | 0.0 (0.0–0.5)                     | 0.10           |
| Urinary output, L [median (IQR)]        | 0.7 (0.4–1.0)                         | 0.6 (0.4–0.9)                     | 0.78           |
| Large bowel resection/anastomosis       | 7 (19)                                | 26 (26)                           | 0.42           |
| Small bowel resection/anastomosis       | 7 (19)                                | 24 (24)                           | 0.56           |
| Gastrectomy                             | 0 (0)                                 | 1 (1)                             | 0.55           |
| Splenectomy                             | 13 (36)                               | 28 (28)                           | 0.38           |
| Peritonectomy                           | 22 (61)                               | 46 (46)                           | 0.13           |
| Lesser omentectomy                      | 12 (33)                               | 17 (17)                           | 0.04           |
| Greater omentectomy                     | 33 (92)                               | 90 (91)                           | 0.89           |
| Cholecystectomy                         | 14 (39)                               | 23 (23)                           | 0.07           |
| Appendectomy                            | 12 (33)                               | 18 (18)                           | 0.06           |
| Hysterectomy                            | 4 (11)                                | 9 (9)                             | 0.73           |
| Salpingoophorectomy                     | 7 (19)                                | 22 (22)                           | 0.73           |
| CC score                                |                                       |                                   | 0.31           |
| 0/1                                     | 29 (80)                               | 80 (82)                           |                |
| 2/3                                     | 7 (20)                                | 18 (18)                           |                |
| Average flow rate, L/min [median (IQR)] | 2.1 (1.9–2.7)                         | 2.4 (1.9–3.0)                     | 0.10           |
| Intraoperative chemotherapy             |                                       |                                   | 0.73           |
| Mitomycin C                             | 34 (94)                               | 90 (91)                           |                |
| Carboplatin                             | 2 (6)                                 | 8 (8)                             |                |
| Doxorubicin                             | 0 (0)                                 | 1 (1)                             |                |

Data are expressed as *n* (%) unless otherwise specified

CRS cytoreductive surgery, HIPEC hyperthermic intraperitoneal chemoperfusion, CBT core body temperature, IQR interquartile range, CC completeness of cytoreduction

**TABLE 3** Perfusion parameters during HIPEC

| Characteristics                         | High flow ( $\geq 2.35$ L/min) [ $n = 65$ ] | Low flow ( $< 2.35$ L/min) [ $n = 70$ ] | <i>p</i> value |
|---|---|---|----------------|
| Average core body temperature           | 38.1 (37.8–38.4)                            | 38.3 (38.0–38.7)                        | 0.05           |
| Average inflow temperature              | 42.2 (41.8–43.0)                            | 42.5 (41.8–43.0)                        | 0.89           |
| Maximum inflow temperature              | 43.0 (42.0–43.4)                            | 43.1 (42.8–43.8)                        | 0.09           |
| Average outflow temperature             | 41.5 (41.0–42.2)                            | 41.1 (40.6–41.6)                        | 0.005          |
| Maximum outflow temperature             | 42.0 (41.6–43.0)                            | 41.7 (41.0–42.5)                        | 0.02           |
| Inflow/outflow temperature differential | 0.9 (0.3–1.5)                               | 1.3 (1.0–2.0)                           | 0.008          |

Data are expressed as median (interquartile range)

HIPEC hyperthermic intraperitoneal chemotherapy

lower average flow rates (2.1 vs. 2.4 L/min,  $p = 0.10$ ) compared with patients whose CBT remained  $< 39.5$  °C.

### Postoperative Outcomes

Patients who reached a maximum CBT  $\geq 39.5$  °C during HIPEC experienced more 30-day postoperative

complications and severe Clavien–Dindo grade III or higher complications (Table 4). On univariate analysis, a CBT  $\geq 39.5$  °C suggested a potentially significant association with both 30-day morbidity (OR 3.00, 95% CI 1.37–6.61) and 30-day complication severity (OR 2.29, 95% CI 0.84–6.25). Multivariate analysis was used to account for both clinically relevant and statistically

**TABLE 4** Postoperative outcomes of the study population

| Characteristics                                       | CBT-High ( $\geq 39.5$ )<br>[ <i>n</i> = 36] | CBT-Low ( $< 39.5$ )<br>[ <i>n</i> = 99] | <i>p</i> value |
|---|--|--|----------------|
| Hospital length of stay, days [median (IQR)]          | 9 (8–11)                                     | 8 (7–10)                                 | 0.38           |
| 30-day postoperative complication                     | 21 (58)                                      | 34 (34)                                  | 0.01           |
| Superficial SSI                                       | 0 (0)  | 2 (2)                                    | 0.39           |
| Deep SSI  | 0 (0)  | 1 (1)                                    | 0.55           |
| Wound dehiscence                                      | 1 (3)  | 0 (0)                                    | 0.10           |
| Perianastomotic abscess/leak                          | 4 (11)                                       | 8 (8)                                    | 0.58           |
| Ileus   | 6 (17)                                       | 8 (8)                                    | 0.15           |
| Pleural effusion                                      | 5 (14)                                       | 9 (9)                                    | 0.17           |
| Pneumonia   | 1 (3)  | 2 (2)                                    | 0.79           |
| Reintubation  | 0 (0)  | 3 (3)                                    | 0.29           |
| MI  | 0 (0)  | 0 (0)                                    | 0.00           |
| Urinary tract infection                               | 2 (6)  | 3 (3)                                    | 0.49           |
| Acute renal failure                                   | 1 (3)  | 1 (1)                                    | 0.45           |
| Deep venous thrombosis                                | 1 (3)  | 2 (2)                                    | 0.79           |
| TIA/CVA   | 0 (0)  | 2 (2)                                    | 0.39           |
| 30-day Clavien–Dindo grade III or higher complication | 8 (22)                                       | 11 (11)                                  | 0.04           |
| 30-day reoperation                                    | 2 (6)  | 4 (4)                                    | 0.68           |
| 90-day mortality                                      | 0 (0)  | 1 (1)                                    | 0.55           |

Data are expressed as *n* (%) unless otherwise specified

CBT core body temperature, IQR interquartile range, SSI surgical site infection, MI myocardial infarction, TIA transient ischemic attack, CVA cerebrovascular accident

significant covariates. Controlling for age, sex, intraoperative EBL, operation time, PCI score, and CC score, a maximum CBT  $\geq 39.5$  °C demonstrated a statistically significant association with both 30-day morbidity (aOR 3.77, 95% CI 1.56–9.14) and Clavien–Dindo complication severity (aOR 3.46, 95% CI 1.10–10.95) [Table 5]. The 90-day mortality rate for the entire cohort was 0.8%. Mortality rates did not vary by maximum CBT (0% vs. 1%, *p* = 0.55).

## DISCUSSION

Regional therapy for the management of primary peritoneal disease or peritoneal metastasis was first described in the 1980s and remains a key component of present-day management.<sup>18–23</sup> Herein, we report on the potential postoperative morbidity of systemic hyperthermia that develops to varying degrees during HIPEC. Patients whose CBT reached a threshold value of 39.5 °C were found to be at increased risk of developing a postoperative complication, and, if a complication did arise, it was more likely to be severe (Clavien–Dindo grade III or higher). Elevated CBT  $\geq 39.5$  °C did not correlate with improved intraperitoneal heating. The extent of cyto-reduction did not

appear to influence CBT during CRS/HIPEC, and, despite the varying degree of CBT elevation, all patients completed the intended 90-min chemoperfusion. Although there was no statistically significant difference in the average flow rate between the CBT-High and CBT-Low groups (2.1 vs. 2.4 L/min, *p* = 0.10), chemoperfusion flow rates  $\geq 2.35$  L/min were shown to improve intraperitoneal heating and reduce average CBT during HIPEC.

When utilizing hyperthermia as a therapeutic adjunct, such as with HIPEC, the two key components are time and temperature. It has been shown that a critical threshold of 40 °C must be reached for potentiation of intraperitoneal cytotoxic chemotherapy.<sup>24</sup> Accordingly, intraperitoneal target temperatures during HIPEC typically range from 40 to 43 °C.<sup>21–23</sup> To accomplish this, inflow temperatures may be increased to 45 °C over the course of the 90-min perfusion, particularly in the setting of a low flow rate. Given the peritoneum's high potential for heat transfer, systemic hyperthermia may develop, as manifested by a rising CBT.

Little is known about the morbidity of systemic hyperthermia that develops during HIPEC, however our data suggest an association between maximum CBT  $\geq 39.5$  °C and 30-day postoperative complications. A recent study by Goldenshluger et al. investigated the effect of both CBT

**TABLE 5** Univariate and multivariate logistic regression analyses of predictors associated with any 30-day complication or a severe Clavien–Dindo grade III or higher complication

| Variable  | Univariate |           | Multivariate |            |
|---|------------|-----------|--------------|------------|
|   | OR         | 95% CI    | aOR          | 95% CI     |
| <i>30-day complication</i>                      |            |           |              |            |
| CBT $\geq$ 39.5                                 | 3.00       | 1.37–6.61 | 3.77         | 1.56–9.14  |
| Age   | 1.01       | 0.97–1.05 | 1.01         | 0.97–1.05  |
| Male sex  | 0.75       | 0.36–1.56 | 0.74         | 0.32–1.67  |
| Intraoperative EBL                              | 1.01       | 1.00–1.04 | 1.00         | 1.00–1.01  |
| Operation time                                  | 1.21       | 1.04–1.42 | 1.10         | 0.91–1.34  |
| PCI score                                       |            |           |              |            |
| < 10  | Ref        | Ref       | Ref          | Ref        |
| 10–20   | 2.38       | 0.90–6.24 | 2.04         | 0.71–5.91  |
| > 20  | 1.99       | 0.81–4.84 | 1.06         | 0.34–3.29  |
| CC score 0/1                                    | 1.43       | 0.59–3.50 | 1.03         | 0.33–3.18  |
| <i>30-day Clavien–Dindo grade III or higher</i> |            |           |              |            |
| CBT $\geq$ 39.5                                 | 2.29       | 0.84–6.25 | 3.46         | 1.10–10.95 |
| Age   | 1.01       | 0.96–1.07 | 1.01         | 0.95–1.06  |
| Male sex  | 1.92       | 0.72–5.13 | 2.40         | 0.78–7.44  |
| Intraoperative EBL                              | 1.01       | 1.00–1.04 | 1.00         | 1.00–1.01  |
| Operation time                                  | 1.27       | 1.03–1.56 | 1.26         | 0.98–1.63  |
| PCI score                                       |            |           |              |            |
| < 10  | Ref        | Ref       | Ref          | Ref        |
| 10–20   | 1.94       | 0.45–8.42 | 1.57         | 0.32–7.64  |
| > 20  | 2.09       | 0.53–8.18 | 0.58         | 0.11–3.03  |
| CC score 0/1                                    | 0.62       | 0.20–1.91 | 0.35         | 0.08–1.46  |

OR odds ratio, CI confidence interval, aOR adjusted odds ratio, CBT core body temperature, EBL estimated blood loss, PCI Peritoneal Cancer Index, CC completeness of cytoreduction

and intra-abdominal pressure in HIPEC.<sup>25</sup> To the best of our knowledge, this was the first published study to evaluate the impact of rising CBT during HIPEC on postoperative outcomes. CBT was measured continuously and a calculated mean CBT was used for subsequent regression analyses. While our data support their ultimate conclusion that elevated CBT is associated with an increased risk of postoperative complications, there are fundamental differences to address. In our study, the mean CBT for the entire cohort was 38.2 °C, significantly higher than the mean CBT of 37.5 °C in the study by Goldensluger et al. Furthermore, there was no report on maximum CBT reached during HIPEC, which we found to be the most predictive measure of 30-day morbidity. Most importantly, we believe that reporting results in reference to maximum CBT, as opposed to mean CBT, provides the opportunity to guide real-time intraoperative decision making and intervention. A clearly defined maximum CBT threshold has the value of being an easily understood and objective metric that can be assessed at any time during HIPEC. If CBT approaches that critical value of 39.5 °C, then passive and/or active cooling measures can be implemented.

Higher flow rates have been shown to improve heating during HIPEC by facilitating more rapid achievement of peritoneal target temperature and maintaining inflow/outflow temperature gradients.<sup>26</sup> We observed similar findings in this study. Flow rates  $\geq$  2.35 L/min were associated with better peritoneal heating, as shown by increased outflow temperatures and a reduced inflow/outflow temperature differential, while generating less systemic hyperthermia. Mechanistically, it is possible higher chemoperfusion flow rates act to mitigate the effects of the body's heat sink, thus minimizing systemic hyperthermia while maximizing locoregional hyperthermia. Achieving higher flow rates during HIPEC represents a potentially effective measure to decrease the risk of postoperative complications observed with an elevated maximum CBT, while optimizing the oncologic efficacy of hyperthermia within the peritoneal cavity.

#### Limitations

This study has the limitations inherent in a single-institution, retrospective review of observational data. During the study period, there was no defined CBT

protocol. Rather, the objective was achievement and maintenance of regional peritoneal hyperthermia by increasing perfusion flow rates and inflow temperatures as needed. While CBT was monitored, there were no titratable endpoints to follow. Accordingly, all intraoperative management decisions related to an elevated CBT were made at the discretion of the attending surgeon and anesthesiologist based on a given patient's hemodynamic status and overall clinical condition. The small sample size of the study limited the number of variables that could be controlled for and the overall power of the regression model, thus we cannot exclude the possibility of other relevant covariates. Lastly, it is important to note that our conclusions regarding CBT and flow rates are limited to short-term outcomes and cannot be extrapolated to long-term outcomes.

## CONCLUSION

While locoregional hyperthermia is the goal during HIPEC, the oncologic impact of systemic hyperthermia is yet to be determined. Our findings suggest that reaching a maximum CBT  $\geq 39.5$  °C at any time during chemoperfusion is associated with an increased risk of both 30-day morbidity and grade III/IV complications. Accordingly, we recommend target outflow temperatures of at least 40 °C with an intraperitoneal target temperature between 40 and 42 °C. This approach should provide therapeutic intraperitoneal hyperthermia without excessive elevations in CBT, particularly if target temperatures are achieved through a combination of inflow temperature adjustment and increased flow rates.

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