Editorial

Transforming hyperthermic intraperitoneal chemotherapy: using computer simulation to improve HIPEC treatments

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Hyperthermic intraperitoneal chemotherapy (HIPEC) is a well-established treatment for patients with peritoneal surface malignancies (1). HIPEC targets microscopic tumor deposits that cannot be removed by cytoreductive surgery (2). Since the location of the tumor deposits is often invisible, drug and heat delivery during HIPEC must be homogeneous despite the irregular geometry of the peritoneal cavity (3). Unfortunately, many authors have highlighted the wide variability and lack of consistent scientific rationale for many HIPEC parameters in routine practice (4,5). These knowledge gaps on HIPEC fluid and temperature dynamics limit our ability to improve clinical outcomes. Currently, expert consensus recommendations constitute the main method to standardize care for patients undergoing HIPEC (6).

To bridge these gaps, recent studies have incorporated computer simulation (3,7,8). Simulation studies in HIPEC use computational fluid dynamics (CFD) to reproduce certain *in vivo* conditions. Moreover, they can incorporate different types of flow, measure variables at pre-specified areas, and simulate heat transfer. This approach is appealing as it provides a sound scientific rationale for the HIPEC regimen, allowing researchers to refine hypotheses used in preclinical and clinical studies. While still being developed, CFD models in HIPEC have been reported to have an acceptable correlation with clinical data (8).

In the August issue of the *Journal of Gastrointestinal Oncology*, Cooney *et al.* reported the results of a simulated HIPEC model to evaluate the fluid flow dynamics at specific intra-abdominal at-risk locations (7). Their model included the main intrabdominal organs, two flow rates (800 and 1,120 mL/min), and two fluid directions. Moreover, it resembled several conditions of a clinical case, such as the number and locations of catheters and the duration of treatment. Assuming them as rigid, the authors highlighted how organs can impede homogeneous fluid and temperature distribution in certain locations. Specifically, this was described in probe 2, inferior to small bowel mesentery, where forward flow was blocked by the transverse colon mesentery. Furthermore, the results showed improved dynamics with a reversed flow configuration (lower pelvis to upper abdomen direction) and higher flow rates. Interestingly, the authors reported that even in the best combination tested, certain locations did not reach the target temperature by 30 minutes. Finally, the authors concluded that the outflow temperature may not accurately represent the actual temperature at many intraabdominal locations.

The results from Cooney *et al.* add to a growing body of literature on computer simulation of HIPEC treatments. Previously, Loke *et al.* developed and validated CFD models of HIPEC treatments (3). Their model was first

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developed using rat computed tomography images to create an anatomical model of the abdominal cavity. Both heat transfer and chemotherapy models were made and compared to published experimental data. Their findings suggested the superiority of a four-inflow approach to achieve temperature homogeneity. These CFD models have also studied the effect of several treatment parameters (e.g., catheter configuration, changes in temperature, etc.) in temperatures and flows during HIPEC. In another simulation study, Loke *et al.* created a three-dimensional CFD model using human data and produced a realistic representation of the abdominal cavity (8). Subsequently, a life-size, anatomically correct 3D phantom was used to validate the thermal model of an open HIPEC setup (9).

Significant differences can be appreciated between the CFD models created and validated by Loke *et al.* and those by Cooney *et al.* These include anatomical accuracy, the higher number of catheter setups, chemotherapy modules, and different software. Notably, we can also appreciate similitudes between them. For instance, changing flow direction can improve temperature heterogeneity in regions where forward flow is insufficient. In clinical practice, however, flow reversal is only used to relieve an obstruction. Moreover, modifying the catheter setup and flow direction in the middle of treatment can risk brief flow interruptions and result in decreased fluid temperatures. Furthermore, catheter positioning must minimize the risk of thermal or mechanical tissue injury. Simulation studies also agree on a period of temperature stabilization. We consider time an essential variable in ensuring an optimal HIPEC treatment, as it determines an adequate thermal dose. These findings agree with the results of the PRODIGE-7 trial, where a 30-minute course of HIPEC did not alter survival in patients with metastatic colorectal cancer (10). Finally, another common characteristic of both approaches is their comparison to published clinical or preclinical data. This is encouraging, as it generates some validity in the findings. Still, considerable validation is required using more experiments and *a priori* definitions of accuracy.

Although disease-specific, the recurrence rate for any peritoneal malignancy is expectedly high. In appendiceal cancer, Kong *et al.* observed a recurrence rate of 25% with a median time to recurrence of about 20 months (11). In a mixed cancer sample, Wong *et al.* reported 1-, 3-, and 5-year progression-free survival rates of 64.4%, 24.8%, and 16.1%, respectively (12). Previously, we observed that failure to reach bladder hyperthermia during HIPEC was associated with worse progression-free and overall survival (13). Thus, it remains paramount to understand the role of HIPEC if we are to improve the survival of these patients. As of today, the certainty of evidence behind the survival advantage of HIPEC continues to be rated low (6).

Evaluating the performance of HIPEC treatments is a very complex endeavor. We commend Cooney *et al.* for their efforts to advance the knowledge of HIPEC. CFD simulations are complex tasks requiring multidisciplinary collaboration, advanced knowledge of bioengineering and physics, and significant computational power. As such, we consider them a step forward to improve HIPEC treatments worldwide.

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