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Murine models of intraperitoneal perfusion for disseminated colorectal cancer

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ABSTRACT

Background: Reproduction of the perfusion used in therapy (hyperthermic intraperitoneal chemotherapy) procedures preclinically represents a valuable asset for investigating new therapeutic agents that may improve patient outcomes. This article provides technical descriptions of our execution of closed and open "coliseum" abdominal perfusion techniques in a mouse model of peritoneal carcinomatosis of colorectal cancer.

Materials and Methods: BALB/c mice presenting with disseminated colorectal cancer (CT26-luciferin cells) underwent 30-min perfusions mimicking either the closed perfusion or the coliseum perfusion technique. Disease burden was monitored by bioluminescence signaling using an *in vivo* imaging system. Perfusion circuits consisted of single inflow lines with either a single or dual outflow line.

Results: Twelve mice presenting with disseminated disease underwent the closed perfusion technique. Surgical complications included perfusate leakage and organ constriction/suction into the outflow line(s). Nine mice underwent the coliseum perfusion technique with surgical debulking, using bipolar cauterization to remove tumors attached to the peritoneum. All mice survived the coliseum perfusion with limited intraoperative complications.

Conclusions: Fewer intraoperative complications were experienced with our coliseum perfusion technique than the closed perfusion. The methods described here can be used as a guideline for developing future perfusion murine models for investigating perfusion models useful for delivery of chemotherapy or other tumor-sensitization agents, including selective targeted agents, nanoparticles, and heat.

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Introduction

Peritoneal carcinomatosis (PC) is an advanced (stage IV) manifestation of cancers of pelvic and abdominal organs presenting as a widespread dissemination of tumor nodules over the surface of the peritoneum. The most common primary cancers associated with development of PC are gastric, colorectal, ovarian, pancreatic, and appendiceal.[1,2] The

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presence of peritoneal metastases portends a poor prognosis and is associated with significant morbidity and mortality. For example, in colorectal cancer (CRC), the 5-y survival rate for localized disease is nearly 90%, whereas metastatic disease survival plummets to below 14%; without treatment, CRC patients with PC have a mean survival time of only 6 mo.[3-5]

Historically, PC has been poorly amenable to conventional cancer treatments like surgery and chemotherapy. This poor response is in part due to the architecture and physiology of the peritoneal cavity. Structured like a fluid-filled "sac", it allows cancer cells to bathe and seed the large surface of the peritoneum and abdominal organs, leading to widespread disease dissemination and concealment of microscopic disease. The large surface area combined with CRC and appendiceal cancer subtypes that produce excessive mucus secretion upsurges the surgical challenges.[6] Cytoreductive surgery (CRS) and/or peritonectomy are most commonly performed to remove all macroscopic lesions in patients with PC.[7] Tumor nodules and micrometastases that escape CRS have the potential to reseed the peritoneal surface, leading to regrowth of tumors.[8] Traditionally, the issue of residual disease has been solved by administration of systemic chemotherapy; however, chemotherapeutic agents cannot reach significant concentrations inside the peritoneal cavity due to the presence of the peritoneum-plasma barrier.[9-11]

To bypass the peritoneum-plasma barrier, the incorporation of intraperitoneal (IP) chemotherapy for malignancies was investigated in the 1980s.[12,13] The justification for using IP chemotherapy include: 1) higher doses of chemotherapy (5-30 fold higher) can be used while reducing systemic toxicity due to peritoneal containment by the peritoneal plasma barrier, 2) the chemotherapy comes into direct contact with surface malignancies (PC tumors) that would otherwise receive minimal drug from an intravenous route due to abnormal vasculature.[14,15] IP delivery was then combined with CRS, a surgical approach to remove substantial tumor burden, to prolong survival.[16] The treatment of disseminated abdominal cancers was further transformed by the addition of hyperthermic intraperitoneal chemotherapy (HIPEC), following cytoreduction surgery in the 1990s.[16-18]

Following CRS, HIPEC is a technique where a warm chemotherapy solution (40°C-43°C) is perfused throughout the peritoneal cavity for 30-120 min, depending on the drug and drug dose.[17] Hyperthermia augments the activity of chemotherapy by affecting both drug pharmacokinetics and pharmacodynamics.[19] Most cytotoxic drugs used for HIPEC synergistically affect chemotherapy at target temperatures between 40°C and 45°C, and studies have shown that the penetration depth of the warm chemotherapy through tumors and tissues is 1.0-3.0 mm.[17,20-22]

HIPEC can be delivered by a few different perfusion methods but this article will focus on the two most common methods: the open abdomen ("coliseum") method or the closed abdomen method.[22] In the open abdominal perfusion method, the edges of the longitudinal abdominal incision are suspended with the use of a Thompson retractor, creating an open "bowl" to contain the chemotherapy solution.[22,23] Inflow lines are placed in the upper quadrant and outflow lines are placed in the lower quadrant and perfused at a rate of ~ 1 L/min[16] A plastic sheet is placed over the open cavity to prevent exposure of the surgical staff to chemotherapy by containing the liquid and aerosolized chemotherapy. A slit through the sheet allows the surgeon's hand to enter the peritoneum and manipulate its contents to distribute the chemotherapy. The advantages of the open technique are the ability to achieve homogenous temperature and even distribution of chemotherapy within the peritoneal cavity.[22] The disadvantages include the potential for exposing the operating room staff to chemotherapy as well as heat loss.[22,24]

In the closed abdominal perfusion method, the layers of the abdominal cavity are closed with a continuous running suture following CRS. Inflow and outflow lines are placed and heated chemotherapy is subsequently perfused varying from 400 mL/min to 1 L/min[24] The abdomen is vigorously compressed for the duration of perfusion to agitate the contents. The temperature of the perfusate is monitored on inflow and outflow to maintain the perfusate temperature.[25] The closed technique reduces the risk of operating room staff exposure to chemotherapy, increases chemotherapy perfusion through the peritoneal surfaces, and quickly reaches and maintains hyperthermic conditions.[22,26] However, the main caveats of using the closed technique encompass nonhomogenous distribution of chemotherapy and temperature within the cavity, thus leading to regions of undertreated and overtreated tissue.[26,27]

To quickly and more efficiently investigate efficacy of new adjuvants and methods for an HIPEC regimen, clearly defined animal models for reproducible studies are essential. Various animal models including mouse, rat, porcine, and rabbit have been utilized to evaluate the optimal HIPEC technique.[28] Specifically, several rodent models for developing disseminated abdominal cancer for PC treatments have been found to be translatable.[28-33] However, there is quite a bit of variation amongst the models, with most procedures using closed perfusion, which does not allow for direct manipulation of the abdominal organs during perfusion. In addition to perfusion of classical chemotherapy agents through the abdomen, researchers have been investigating the potential to deploy targeted therapies, such as nanoparticles- or radiation-inducing materials, directly to the tumor and spare the adjacent tissues from unnecessary therapy.[31,34,35] There has also been interest in using perfusates that can disrupt cells by changing the osmotic pressure or by utilizing agents that initiate the production of reactive oxygen species.[36-38] Only Graziosi *et al.*,[30] describes an open abdominal perfusion model in mice, and the other literature describes the use of closed technique. Although their model is excellent, it focused on dissemination of human gastric cancer in an immune-compromised mouse. A syngeneic mouse model is more preferred for evaluation with hyperthermia treatments though, so that the impact of heat on immune function can be included. For example, the use of MC38 CRC cells in C5Bl/6 mice or CT26 CRC cells in BALB/c mice.[38] Part of the challenges with utilizing a model of abdominal perfusion is the setup/instrumentation required for the perfusion circuit. This work outlines all the equipment needed and the approach taken to establish perfusion in both open and closed abdominal models of PC from CRC. The perfusion methods described here are meant to focus on the experimental setup of the perfusion model and can be adjusted accordingly to the users' needs. One of the goals of the work was to minimize the perfusion circuit volume, which is especially important when

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