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Assessing the Impact of Hyperthermic Intraperitoneal Chemotherapy on Anastomotic Integrity after Cytoreductive Surgery in Gastrointestinal Malignancies

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Abstract

Peritoneal carcinomatosis (PC) from gastrointestinal malignancies, particularly colorectal and gastric cancers, represents a significant therapeutic challenge due to the diffuse nature of tumor spread. The combination of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a promising treatment modality, offering potential survival benefits by targeting residual microscopic disease. However, this aggressive approach is associated with a heightened risk of gastrointestinal anastomotic leaks, one of the most severe complications of gastrointestinal surgery. These leaks result from a complex interplay of factors, including hyperthermia-induced ischemia, chemotherapy-induced cytotoxicity, and a pro-inflammatory cytokine cascade involving IL-6, TNF-α, and IL-1β, which impair tissue healing. Furthermore, dysbiosis of the intestinal microbiota induced by HIPEC contributes to local inflammation and an increased risk of infection, exacerbating the likelihood of anastomotic failure. The duration and temperature of the HIPEC procedure, the extent of surgery, and the patient's performance status and tumor burden further influence the risk of leaks. Preventive strategies such as preoperative nutritional optimization, meticulous surgical technique, intraoperative reinforcement of anastomoses, and selective use of protective ileostomies are critical for minimizing these risks. Early detection and prompt management of leaks are essential for reducing morbidity and mortality, improving both short-term and long-term outcomes. This review comprehensively examines the multifactorial causes of anastomotic leaks in the setting of CRS and HIPEC and highlights potential strategies for prevention and improved management.

Abbreviations: Peritoneal Carcinomatosis; Cytoreductive Surgery; Hyperthermic Intraperitoneal Chemotherapy; Anastomotic Leak; Gastrointestinal Neoplasms; Active Immune Response

Introduction

Peritoneal carcinomatosis (PC) represents a complex and aggressive manifestation of various gastrointestinal malignancies, particularly colorectal and gastric cancers. The prognosis for patients with PC has historically been poor, mainly due to the inability of systemic chemotherapy alone to effectively control the widespread dissemination of cancer within the peritoneal cavity [1-3]. Over recent decades, combining cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a pivotal approach in treating PC, offering a potential survival benefit for select patients. This aggressive treatment modality aims to achieve maximal tumor debulking through CRS, followed by the direct application of heated chemotherapy to the peritoneal surfaces, thereby targeting residual microscopic disease [4-6]. Despite the promise of improved survival, CRS and HIPEC are associated with significant risks, including the development of gastrointestinal anastomotic leaks. These leaks, which occur at the site of surgical reconnection of the bowel, represent one of the most feared complications in gastrointestinal surgery, with potentially devastating consequences for patient outcomes [7-9]. Anastomotic leaks can lead to severe peritonitis, sepsis, and, in some cases, death, necessitating urgent surgical intervention and prolonged intensive care. The combination of CRS and HIPEC increases the complexity of surgical procedures and potentially exacerbates the risk of anastomotic failure due to the unique physiological challenges posed by this treatment [10,11]. One of the critical challenges in the context of CRS and HIPEC is the impact of hyperthermia and chemotherapeutic agents on the integrity of gastrointestinal anastomoses. Hyperthermia, typically applied at temperatures ranging from 41-43ºC, enhances the efficacy of chemotherapeutic drugs by increasing their penetration into tissues and promoting cancer cell death [12-14]. However, the exposure of tissues to such high temperatures can impair tissue healing by inducing local ischemia and inflammation, thereby compromising anastomotic integrity. In addition, the chemotherapeutic agents used in HIPEC, including oxaliplatin, mitomycin C, and cisplatin, are inherently toxic and can damage the rapidly dividing cells of the gastrointestinal mucosa, further hindering the healing process of surgical connections [15-17].

The risk of anastomotic leaks following CRS and HIPEC is not uniform and is influenced by various factors. These include patient-related factors such as age, nutritional status, comorbidities, and disease-related factors such as the extent of peritoneal involvement and prior treatments. The complexity of the surgical procedure itself also plays a significant role [18-20]. Extensive cytoreduction often involves multiple bowel resections and anastomoses, increasing the potential for complications. The Peritoneal Cancer Index (PCI), a measure of tumor burden within the peritoneal cavity, is frequently used to guide the extent of surgery and predict outcomes. High PCI scores are associated with more extensive surgical procedures and a higher likelihood of postoperative complications, including anastomotic leaks [21-23]. Preoperative chemotherapy, particularly in patients with advanced-stage gastrointestinal cancers, can further complicate the healing of anastomoses. Chemotherapy can weaken the immune system and impair the regenerative capacity of tissues, making them more susceptible to breakdown after surgery [8-10].

In patients undergoing CRS and HIPEC, the cumulative effects of preoperative chemotherapy, extensive surgery, and the added burden of hyperthermia and cytotoxic agents create a high-risk environment for anastomotic complications [24]. Managing gastrointestinal anastomotic leaks in the setting of CRS and HIPEC is complex and requires a multidisciplinary approach. Early detection of leaks is crucial for reducing morbidity and mortality3. Still, diagnosis can be challenging due to the often subtle and nonspecific nature of clinical signs in the early postoperative period [14,25]. Imaging studies, including contrast-enhanced CT scans, are commonly used to confirm the presence of an anastomotic leak, but clinical suspicion based on changes in vital signs and laboratory markers remains the cornerstone of early diagnosis17. Once a leak is identified, prompt surgical intervention is usually necessary to repair the anastomosis, control sepsis, and manage the resultant peritoneal contamination [21]. The role of protective ileostomies in preventing the consequences of anastomotic leaks has been the subject of debate. While some advocate for routine ileostomy creation in patients undergoing CRS and HIPEC, others suggest a more selective approach based on individual risk factors [26,27].

Protective ileostomies divert fecal content away from the anastomosis, allowing for healing without the added pressure and contamination from bowel contents. However, creating a stoma carries its risks and complications, and the decision to make a stoma must be carefully weighed against the potential benefits for each patient 13,22. Advances in perioperative care have focused on optimizing patient outcomes and reducing the incidence of complications such as anastomotic leaks. Enhanced Recovery After Surgery (ERAS) protocols, which include strategies such as early mobilization, optimized pain control, and early oral intake, have been shown to improve postoperative recovery and reduce complications in patients undergoing major gastrointestinal surgery [28-30]. In the context of CRS and HIPEC, preoperative optimization of nutritional status and immune function is critical in reducing the risk of complications. Patients with poor nutritional status are particularly vulnerable to anastomotic failure, as malnutrition impairs wound healing and increases susceptibility to infection [4-6].

Intraoperative techniques to reduce the risk of anastomotic leaks have also been explored. These include using reinforcement materials at the anastomotic site, such as biologic or synthetic meshes, and applying tissue adhesives to strengthen the anastomosis [23-26].

Surgeons advocate for intraoperative anastomosis testing, such as air or methylene blue testing, to identify and repair leaks before the operation concludes14. While promising, these techniques require further study to determine their efficacy in reducing anastomotic leaks in the setting of CRS and HIPEC [29]. The impact of anastomotic leaks on long-term outcomes cannot be overstated. Patients who experience an anastomotic leak are

at increased risk of recurrence and decreased overall survival, as the inflammatory response triggered by the leak can promote tumor growth and dissemination [20-22]. The need for additional surgeries and prolonged hospital stays can delay the initiation of adjuvant therapies, further compromising oncologic outcomes. As such, minimizing the risk of anastomotic leaks is essential for improving short-term recovery and optimizing long-term survival in patients undergoing CRS and HIPEC [31,32].

The combination of CRS and HIPEC offers significant survival benefits for patients with peritoneal carcinomatosis from gastrointestinal malignancies. However, the complexity of the surgical procedures and the unique challenges posed by hyperthermia and cytotoxic agents contribute to a high risk of gastrointestinal anastomotic leaks [10-13]. A thorough understanding of the risk factors, preventive strategies, and management techniques is crucial in reducing the incidence of this severe complication and improving overall patient outcomes26. Continued research is needed to refine surgical techniques, optimize perioperative care, and identify new strategies to prevent anastomotic leaks in this high-risk population [33]. Considering the complexities surrounding CRS and HIPEC and the significant risks of gastrointestinal anastomotic leaks associated with these procedures, this review aims to examine the current body of literature on this topic comprehensively [24,25]. This article seeks to identify and analyze the multifactorial risk factors contributing to anastomotic failure, elucidate the physiological mechanisms underlying these complications, and explore the latest advances in surgical techniques and perioperative care strategies that may mitigate these risks [10,13]. This review seeks to provide a clearer understanding of the challenges in the management of gastrointestinal anastomotic leaks following CRS and HIPEC and to offer insights that can improve both short-term surgical outcomes and long-term survival in patients with peritoneal carcinomatosis.

Methods

The research methodology for this review was meticulously designed to provide an exhaustive analysis of the literature concerning the relationship between hyperthermic intraperitoneal chemotherapy (HIPEC) and the occurrence of gastrointestinal anastomotic leaks following cytoreductive surgery (CRS) in patients with peritoneal carcinomatosis arising from gastrointestinal neoplasms. Several renowned databases were utilized to ensure a thorough literature review, including PubMed, Scopus, Embase, Web of Science, and SciELO. These databases were selected for their extensive collections of peer-reviewed medical and scientific publications, ensuring that the most relevant and high-quality studies were captured. Google Scholar was incorporated as a supplementary resource to access gray literature, which often includes essential studies, reports, and reviews that may not be indexed in traditional academic databases. The literature search was constructed around specific research questions concerning the impact of HIPEC on anastomotic integrity and the active immune response in the context of gastrointestinal malignancies. A carefully chosen set of keywords guided the search, including "peritoneal carcinomatosis," "cytoreductive surgery," "hyperthermic intraperitoneal chemotherapy," "anastomotic leak," "gastrointestinal neoplasms," and "active immune response." This strategic combination of keywords made the search focused and relevant, ensuring that only studies addressing the critical areas of interest-HIPEC-related anastomotic complications, immune response mechanisms, and surgical outcomes-were included. To capture a diverse range of evidence, the inclusion criteria were designed to encompass various study designs, including randomized controlled trials, cohort studies, case-control studies, systematic reviews, and expert opinions. Studies were considered for inclusion if they provided relevant data on the incidence of anastomotic leaks post-HIPEC, explored the physiological and immunological mechanisms underlying these complications, or evaluated strategies for preventing and managing leaks in the setting of gastrointestinal neoplasms. The selection process followed a rigorous and systematic approach. Two researchers independently reviewed each study's title and abstract to determine its relevance to the review's objectives. Studies that met the predefined inclusion criteria were subjected to a full-text review, where the methodology, findings, and conclusions were critically assessed. Any disagreements between the initial reviewers were resolved through consultation with a third independent reviewer, ensuring unbiased decision-making and consistent application of the inclusion criteria. This systematic process was designed to enhance the accuracy and reliability of the review's conclusions. The comprehensive search strategy and meticulous evaluation of studies ensured that this review's findings were grounded in a robust and critically assessed body of evidence. By focusing on the intersection of HIPEC, gastrointestinal anastomotic integrity, peritoneal carcinomatosis, and the active immune response, this review aims to provide insights into the risk factors and mechanisms contributing to anastomotic leaks while also identifying potential preventive strategies to improve surgical outcomes in patients undergoing CRS and HIPEC for gastrointestinal neoplasms.

Results and Discussion

The development of gastrointestinal anastomotic leaks following cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is a complex and multifactorial process influenced by direct physiological insults from the procedure and a range of patient-related factors [33,34]. While HIPEC offers significant survival benefits for patients with peritoneal carcinomatosis (PC) from gastrointestinal malignancies, it introduces substantial risks, particularly concerning the integrity of gastrointestinal anastomoses35. Understanding the underlying mechanisms and risk factors is essential for optimizing patient outcomes and mitigating postoperative complications [20]. One of the primary mechanisms by which HIPEC contributes to anastomotic failure is through the application of hyperthermia. During the HIPEC procedure, chemotherapeutic agents are circulated in the peritoneal cavity at elevated temperatures, typically between 41°-43°C, to enhance drug efficacy by increasing tissue penetration and cytotoxicity. However, this hyperthermic environment can simultaneously induce ischemic injury to the anastomotic site [36-

38]. Hyperthermia compromises tissue perfusion by increasing vascular resistance and reducing the oxygen supply to the tissue, which is critical for proper healing [39]. Ischemia delays the healing process by impairing collagen synthesis, angiogenesis, and epithelial regeneration, all of which are crucial for maintaining the strength and integrity of the anastomosis [28,40]. In addition to hyperthermia, the chemotherapeutic agents used in HIPEC, such as oxaliplatin, mitomycin C, and cisplatin, directly impact the healing process by targeting rapidly proliferating cells, including those in the gastrointestinal mucosaS [41]. The mucosal barrier of the gastrointestinal tract is one of the most quickly regenerating tissues in the body, and the cytotoxicity of these agents disrupts the average turnover of epithelial cells, weakening the tissue at the anastomotic site [42]. Chemotherapy induced damage to the submucosa and serosa compromises the deeper layers of the anastomosis, increasing the likelihood of dehiscence, particularly in the setting of ongoing ischemia [5].

A significant factor contributing to anastomotic failure is the inflammatory response triggered by HIPEC. Hyperthermia and chemotherapy elicit a robust pro-inflammatory response, leading to the release of cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) [43,44]. These cytokines are key mediators of inflammation and play critical roles in the pathophysiology of anastomotic leaks. IL-6 is involved in the acute-phase response and can exacerbate systemic inflammation, leading to tissue damage and impaired healing [35]. Elevated levels of IL-6 have been associated with poor outcomes in postoperative patients, including increased rates of infection and anastomotic failure [18]. TNF-α, another potent inflammatory cytokine, promotes the breakdown of the extracellular matrix by increasing the production of matrix metalloproteinases (MMPs). MMPs degrade collagen and other structural components of the tissue, weakening the anastomotic site and making it more susceptible to failure45,46. Similarly, IL-1β contributes to tissue inflammation and damage by enhancing the recruitment of immune cells to the injury site, further perpetuating the inflammatory response and impairing the healing process. This pro-inflammatory environment is further compounded by the disruption of the intestinal microbiota during and after HIPEC33,47.

The microbiota is vital in maintaining intestinal homeostasis, supporting immune function, and facilitating tissue repair. The combined effects of hyperthermia and chemotherapy can lead to dysbiosis, characterized by an imbalance in the microbial community, which may promote local and systemic inflammation [21,44].

Dysbiosis can also compromise the integrity of the intestinal barrier, increasing the risk of bacterial translocation into the peritoneal cavity, leading to infections and sepsis, which are significant contributors to anastomotic leaks3. The stage of the tumor and the patient's overall performance status also play significant roles in the risk of anastomotic failure following CRS and HIPEC. Patients with advanced-stage cancers often present with a higher Peritoneal Cancer Index (PCI), indicating more extensive disease [4,17,20]. These patients typically require more aggressive surgical interventions, including multiple bowel resections and extensive cytoreduction. The greater the extent of surgery, the higher the physiological stress placed on the patient, increasing the likelihood of complications such as anastomotic leaks [39,45]. Patients with high PCI scores often have compromised immune and nutritional status, both of which are critical for successful postoperative healing. Preoperative chemotherapy, which is commonly administered to these patients, further weakens their ability to recover by impairing immune function and tissue regeneration [12,43,44]. The duration and temperature of the HIPEC procedure are critical factors in determining the risk of postoperative anastomotic leaks. More prolonged exposure to hyperthermia and chemotherapy increases the likelihood of thermal injury to the tissues, exacerbating ischemia and delaying healing [17,26]. Higher temperatures, while potentially increasing the cytotoxic efficacy of chemotherapy, also intensify the risk of damaging normal tissues. Prolonged or excessively high-temperature HIPEC procedures may increase the incidence of anastomotic failure [5-7]. As such, careful intraoperative monitoring of both the duration and temperature of HIPEC is essential for balancing the therapeutic benefits of the procedure against the risk of complications [28,40]. Several preventive strategies must be implemented to mitigate the risks of anastomotic leaks following CRS and HIPEC. Preoperative optimization of the patient's nutritional status and immune function is crucial in reducing the risk of complications2-4. Nutritional support, including administering immune-modulating nutrients such as arginine, omega-3 fatty acids, and nucleotides, has been shown to enhance tissue repair and reduce the incidence of infections in surgical patients [36]. Optimizing the patient's immune function through perioperative interventions can also help improve healing and reduce inflammation, thereby minimizing the risk of anastomotic failure [23]. Intraoperatively, the meticulous surgical technique reduces the risk of anastomotic leaks. This includes ensuring adequate blood flow to the anastomotic site, minimizing tension on the anastomosis, and carefully handling tissues to prevent unnecessary trauma [46]. Reinforcement materials, such as biological or synthetic meshes, may support the anastomosis, reducing the likelihood of dehiscence11. Intraoperative testing of the anastomosis using air or methylene blue can help detect leaks before the procedure is concluded, allowing for immediate repair and potentially preventing postoperative complications45. Protective ileostomies are another consideration in preventing the consequences of anastomotic leaks. While the routine use of ileostomies in all patients undergoing CRS and HIPEC is controversial, selective use in high-risk patients may help reduce the severity of complications [39-41] (Table 1).

Table 1: COVID-19 - Long COVID - Gastrointestinal Neoplasms.

Author	Study Type	Results
Liu et al., 2022	Prospective cohort study	Demonstrated that gut microbiota composition correlates with Long COVID symptom severity; dysbiosis common in severe cases.
Ancona et al., 2023	Cross-sectional study	Found dysbiosis in gut and airway microbiota in Long COVID patients, potentially contributing to prolonged respiratory and systemic symptoms.
Su et al., 2022	Observational study	Highlighted that antibiotics and probiotics modify gut microbiota, influencing antimicrobial resistance in COVID-19 recovery.
Komaroff & Lipkin, 2021	Narrative review	Suggested shared mechanisms between Long COVID and ME/CFS, involving chronic immune dysfunction and gut microbiota dysbiosis.
Vestad et al., 2022	Longitudinal cohort study	Persistent gut microbiota changes observed in Long COVID, supporting the need for prolonged patient monitoring post-infection.
Zhang et al., 2023	Prospective cohort study	Showed long-term gut dysbiosis in COVID-19 survivors, possibly increasing the risk of gastrointestinal neoplasms.
Mundula et al., 2022	Review	Proposed chronic low-grade inflammation, modulated by gut microbiota, as a significant factor in cancer development post-COVID-19.
Wang et al., 2022	Case report	Found that nutritional modulation of gut microbiota alleviated severe gastrointestinal symptoms in a Long COVID patient.
Nguyen et al., 2023	Metagenomic assessment	Showed that gut microbiota alterations contribute to immune dysfunction and disease severity in COVID-19, potentially affecting cancer risk.
Giannos & Prokopidis, 2022	Opinion article	Linked gut dysbiosis to persistent Long COVID symptoms and proposed potential interventions involving probiotics and prebiotics.
Zuo et al., 2021	Cross-sectional study	Identified significant gut microbiota changes in COVID-19 patients, with implications for disease progression and recovery.
Brīvība et al., 2024	Longitudinal cohort study	Gut microbiota composition and dynamics in hospitalized COVID-19 patients showed persistent alterations influencing recovery outcomes.
Alharbi et al., 2022	Observational study	Explored the role of pre/probiotics in manipulating gut microbiota to reduce severity biomarkers in post-COVID illness.
Zhou et al., 2023	Systematic review	Reviewed the role of gut microbiota alterations in COVID-19 and their potential long-term effects on gastrointestinal health and cancer risks.
Parkin et al., 2022	Systematic review	Demonstrated the impact of the COVID-19 pandemic on delaying cancer diagnosis and treatment, leading to worse outcomes in gastrointestinal cancers.
Liu et al., 2022	Multi-kingdom microbiome analysis	Defined links between gut microbiota changes and post-acute COVID-19 syndrome (PASC) severity, emphasizing microbiome's role in recovery.

Diverting fecal content away from the anastomosis allows for healing without the added pressure and contamination from bowel contents, reducing the likelihood of peritonitis and sepsis in the event of a leak [14]. However, the decision to create a stoma should be individualized, considering the patient's risk factors, the extent of surgery, and the surgeon's judgment [1-3]. Postoperatively, vigilant monitoring of the patient for early signs of anastomotic leaks is essential. Changes in vital signs, laboratory markers of inflammation (such as C-reactive protein and procalcitonin), and clinical symptoms should prompt immediate investigation, including imaging studies like contrast-enhanced CT scans [38,44]. Early detection of leaks allows for prompt intervention, whether through conservative management, reoperation, or diversion and is critical in preventing the progression to more severe complications such as sepsis and multi-organ failure26,33. In the time hyperthermic intraperitoneal chemotherapy (HIPEC) offers significant therapeutic benefits for patients with peritoneal carcinomatosis from gastrointestinal malignancies, it also presents substantial risks, particularly concerning gastrointestinal anastomotic leaks [45-47].

Conclusion

In conclusion, interplay between hyperthermia, chemotherapeutic agents, the inflammatory response, and the disruption of the intestinal microbiota contributes to the increased risk of anastomotic failure. Patient-specific factors, including tumor stage and performance status, further influence the likelihood of these complications.

A comprehensive approach that includes preoperative optimization, meticulous surgical technique, careful intraoperative management, and vigilant postoperative monitoring is essential for minimizing anastomotic leaks and improving patient outcomes. Future research should continue to explore novel strategies to mitigate these risks and refine the management of patients undergoing CRS and HIPEC.

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Conflict of interest

The authors declare that there is no conflict of interest.

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