

Peritoneal carcinomatosis of colorectal origin: Incidence, prognosis and treatment options

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Received: March 11, 2012 Revised: May 31, 2012

Accepted: June 8, 2012

Published online: October 21, 2012

Abstract

Peritoneal carcinomatosis (PC) is one manifestation of metastatic colorectal cancer (CRC). Tumor growth on intestinal surfaces and associated fluid accumulation eventually result in bowel obstruction and incapacitating levels of ascites, which profoundly affect the quality of life for affected patients. PC appears resistant to traditional 5-fluorouracil-based chemotherapy, and surgery was formerly reserved for palliative purposes only. In the absence of effective treatment, the historical prognosis for these patients was extremely poor, with an invariably fatal outcome. These poor outcomes likely explain why PC secondary to CRC has received little attention from oncologic researchers. Thus, data are lacking regarding incidence, clinical disease course, and accurate treatment evaluation for patients with PC. Recently, population-based studies have revealed that PC occurs relatively frequently among patients with

CRC. Risk factors for developing PC have been identified: right-sided tumor, advanced T-stage, advanced N-stage, poor differentiation grade, and younger age at diagnosis. During the past decade, both chemotherapeutic and surgical treatments have achieved promising results in these patients. A chance for long-term survival or even cure may now be offered to selected patients by combining radical surgical resection with intraperitoneal instillation of heated chemotherapy. This combined procedure has become known as hyperthermic intraperitoneal chemotherapy. This editorial outlines recent advancements in the medical and surgical treatment of PC and reviews the most recent information on incidence and prognosis of this disease. Given recent progress, treatment should now be considered in every patient presenting with PC.

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Key words: Colorectal cancer; Peritoneal carcinomatosis; Hyperthermic intraperitoneal chemotherapy; Chemotherapy; Prognosis

Peer reviewers: Dr. Marek Bebenek, MD, PhD, Department of Surgical Oncology, Regional Comprehensive Cancer Center, pl. Hirszfelda 12, 53-413 Wrocław, Poland; Jai Dev Wig, MS, FRCS, Former Professor and Head, Department of General Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Klaver YLB, Lemmens VEPP, Nienhuijs SW, Luyer MDP, de Hingh IHJT. Peritoneal carcinomatosis of colorectal origin: Incidence, prognosis and treatment options. *World J Gastroenterol* 2012; 18(39): 5489-5494 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v18/i39/5489.htm> DOI: <http://dx.doi.org/10.3748/wjg.v18.i39.5489>

INTRODUCTION

Peritoneal carcinomatosis (PC) secondary to colorectal

cancer (CRC) is characterized by the development of solid tumor deposits on the peritoneal surface^[1]. Cell shedding from the primary tumor is thought to be responsible for these peritoneal deposits, which may occur spontaneously or as a result of spillage during surgical procedures. Attachment of tumor cells to peritoneal mesothelial cells involves neoangiogenesis and is mediated by several growth factors^[2]. Tumor implantation and growth may lead to invasion of any organ or structure that is covered by peritoneum.

Common sites for peritoneal implants are the omentum, mesentery, bowel surface, pouch of Douglas, right paracolic gutter, and diaphragm^[3,4]. Patients initially present with nonspecific symptoms such as abdominal discomfort, nausea, weight loss, cachexia, and fatigue; however, these symptoms are often indistinguishable from more general features of malignant disease. The tumor growth on intestinal surfaces and associated fluid accumulation eventually result in signs of bowel obstruction^[5] and incapacitating volumes of ascites^[6,7]. Previously, providers were reluctant to treat these patients because of their extremely poor prognosis and invariably fatal outcomes^[8-10]. Therefore, PC resulting from CRC had received little attention from oncologic researchers. Hence, data was lacking regarding incidence, clinical disease course, and accurate treatment evaluation for patients with PC.

Since the 1980s, PC research has attracted renewed interest because of the observation that a subgroup of patients presents solely with peritoneal tumor implants without systemic metastases^[11,12]. This finding spurred the development of aggressive surgical treatment modalities which combined radical cytoreductive surgery with intraperitoneal chemotherapy^[13-17]. With this approach, prolonged overall survival and even disease cure have been reported^[18,18-26]. Here, we will discuss the recent advances in the characterization and treatment of these patients.

INCIDENCE OF PC

The extent of peritoneal disease is frequently underestimated by imaging modalities^[27], and the presence of peritoneal involvement often remains unknown until a laparotomy is performed. This uncertainty in preoperative diagnosis results from the low sensitivity and specificity of imaging techniques such as abdominopelvic ultrasound and computed tomography. The small size of tumor deposits (typically less than 1 cm) negatively affects sensitivity^[27-30]. Furthermore, peritoneal spread of tumor cells characteristically follows the anatomic outline of normal abdominal structures, making radiologic detection more challenging.

Underestimation of PC due to poor preoperative imaging diagnostics, combined with the aforementioned lack of interest, likely explains the virtual absence of data on PC incidence. Most available data were retrieved from single hospital-based studies that reported inci-

dence of PC encountered during laparotomy. In the largest study, which included 2756 patients with CRC, 214 (8%) patients were diagnosed with synchronous PC and 135 (5%) with metachronous disease^[10]. Two older studies, also single hospital-based, reported that 10% to 15% of patients with colon cancer presented with PC^[9,31]. Recently, two population-based studies reported the incidence of synchronous PC in The Netherlands (4.8%) and in Sweden (4.3%)^[32,33]. Risk factors for developing PC include right-sided tumor, advanced T-stage, advanced N-stage, poor differentiation grade, and younger age at diagnosis.

In clinical studies, metachronous PC is reported in 4% to 12% of patients following curative resection for colon cancer and in 2% to 19% of patients following curative resection for rectal cancer^[34]. In patients undergoing repeat procedures for CRC following primary curative resection, 21% to 44% of patients are diagnosed with peritoneal tumor deposits^[35,36]. In autopsy studies, PC is found in up to 40% of patients who die from colorectal carcinoma^[37,38]. On a population level, 4.2% of Swedish patients with CRC developed metachronous PC following initial treatment^[33]. Risk factors for developing metachronous PC are similar to those for synchronous PC, but also include initial emergency procedures and non-radical initial tumor resection^[33].

TREATMENT

Systemic treatment

Few studies have been published describing the effectiveness of systemic chemotherapy in patients with PC. Due to an inability to accurately measure tumor load and treatment response, patients with peritoneal tumors usually do not meet the inclusion criteria for randomized trials^[39]. The few studies describing chemotherapeutic treatment response focus on systemic 5-fluorouracil (5-FU) and leucovorin using retrospective analysis. The results invariably show a disappointing response to systemic treatment and a poor prognosis compared to other metastatic sites. A French prospective multicenter study of 118 patients with PC of colorectal origin showed a median survival of only 5.2 mo^[40]. In a large series of CRC patients, which included 392 patients with peritoneal involvement, Jayne *et al.*^[10] showed a median survival of 7 mo. Chu *et al.*^[9] reported a median survival of 6 mo in a series of 45 patients who were treated primarily with 5-FU and leucovorin. A sub-analysis by Köhne *et al.*^[41] of patients with PC treated with 5-FU-based therapy showed a median survival of 7.7 mo. Slightly better results were reported by Bloemendaal *et al.*^[8], who described 50 patients with PC but without hematogenous metastases who were treated with systemic chemotherapy and palliative surgery. Their overall median survival was 12.6 mo, with a 2-year survival rate of approximately 18%^[8,24]. However, selection bias probably explains these findings, because these patients were initially referred for hyperthermic intraperitoneal chemoperfusion (HIPEC)-

treatment but eventually randomized to the study control group. It is conceivable that these patients were healthier and their PC disease was more limited compared to the average PC patient.

A few studies have aimed to describe the effect of newer chemotherapeutic combinations, such as oxaliplatin plus irinotecan^[8,42,43]. Results are conflicting and require careful interpretation. Many of these studies were performed to compare systemic treatment with surgical treatment. Selection bias may play a role in these studies because only patients in good condition with limited disease and without systemic metastases were eligible. Nevertheless, the median survival of 23 mo, as described by Elias *et al.*^[18] and obtained with modern systemic chemotherapy, is remarkable and dispels the notion that PC is chemotherapy-resistant. A similar conclusion may be drawn from the only population-based study to investigate this topic thus far. From 1995 to 2008, the administration of chemotherapy to patients with PC gradually increased, from 16% to 46% ($P = 0.001$), with the treatment rate rising to 64% for younger patients^[41]. However, a survival benefit was only apparent after 2005 when modern chemotherapy schedules were introduced^[44].

Introduction of targeted therapies, including monoclonal antibodies specifically targeted to epidermal growth factor receptor and vascular endothelial growth factor, has resulted in a significantly increased survival among patients with metastasized CRC^[41,45,46]. Although these agents are now routinely included in the treatment of patients with stage IV disease, only one small retrospective study has evaluated the effect of adding targeted therapies in patients with PC; a survival of 22.4 mo was observed when biologicals were added to first line of treatment in this patient group^[47].

Cytoreductive surgery and intraperitoneal chemotherapy

The observation that some patients present with PC in the absence of systemic metastases has led to the hypothesis that PC results from locoregional spread rather than systemic metastasis. This belief has encouraged surgical oncologists to examine possibilities for locoregional therapies. In the 1980s and 1990s, physicians and researchers developed new treatment strategies consisting of aggressive cytoreductive surgery plus intraperitoneal chemotherapy, often combined with hyperthermia.

Surgical procedures invariably start with a careful and systematic abdominal exploration and registration of the extent of peritoneal disease. The abdomen is divided in 13 regions and for each region, the number and size of tumor deposits are assessed and recorded. The sum of these scores represents the peritoneal cancer index (PCI), which ranges from 0 to 39. For PC resulting from CRC, a PCI score of 15 or more is generally accepted as exclusion criterion for HIPEC. In The Netherlands, the simplified PCI (sPCI) is commonly used to describe the PC involvement of 9 regions of the abdomen^[24]. The PCI and sPCI are well-known predictive outcome indices for

patients undergoing cytoreductive surgery and perioperative chemotherapy^[48,49].

During cytoreductive surgery, surgeons attempt to remove all visible tumor deposits from the peritoneal surface. To achieve a radical resection, resection of grossly involved organs may be required. Additionally, peritonectomy may be performed^[15]. Resection completeness is recorded using the completeness of cytoreduction score (CCR). A CCR-0 score indicates that no macroscopic peritoneal tumor remains following cytoreduction. A CCR-1 score occurs when tumor nodules less than 2.5 mm persist following cytoreduction. Residual disease measuring 2.5 mm to 2.5 cm is scored as CCR-2. A CCR-3 score indicates the presence of tumor nodules greater than 2.5 cm, or a confluence of unresectable tumor nodules at any site within the abdomen or pelvis^[50]. Alternatively, the R1-R2a-R2b scoring system classifies R1 as no macroscopic residual tumor, R2a as macroscopic residual disease less than 2.5 mm, and R2b as tumor deposits greater than 2.5 mm^[24]. Treatment outcomes are poorer in the presence of residual tumor following optimal cytoreduction, particularly for residual tumor diameters exceeding 2.5 mm. It is hypothesized that 2.5 mm is the maximum penetration depth of chemotherapeutic agents^[48].

After macroscopically complete cytoreduction, intraperitoneal chemotherapy is administered to eradicate microscopic disease. This chemotherapy can be administered immediately following surgery in the operating room, usually in combination with HIPEC or on postoperative days 1 to 5 (early postoperative intraperitoneal chemotherapy). HIPEC perfusion may be performed with a closed abdomen, or with an open “coliseum technique”. Chemotherapeutic agents and doses vary widely between centers worldwide, with mitomycin C and oxaliplatin being the most frequently used agents.

Only one completed phase III randomized trial investigating the outcome of surgical intraperitoneal treatment has been published to date. Verwaal *et al.*^[24,25,51] reported a significant increase in median overall survival among patients treated with cytoreductive surgery and HIPEC, as compared to patients receiving standard palliative care using systemic 5-FU and leucovorin. The promising outcomes observed in this study have convinced many surgeons to accept this technique as standard of care for selected patients with PC, and HIPEC treatment is now offered in specialized centers all over the world. However, this study was heavily criticized for not including a control group of patients receiving cytoreductive surgery only. Therefore, it remains unclear whether cytoreductive surgery and HIPEC are both required to improve survival, or if the observed benefit was due to a single component^[52]. Ideally, these questions should be addressed in randomized trials. However, this type of study has proven difficult to implement, as demonstrated by a phase III trial in France that failed to enroll enough patients due to patient dissatisfaction

with randomization^[53]. Recently, investigations of cytoreductive surgery and HIPEC in PC animal models have provided a sound scientific rationale for the application of intraperitoneal chemotherapy in conjunction with cytoreductive surgery^[54-56], although the additional value of hyperthermia is questionable^[54].

The best available clinical evidence now comes from multi-institutional registries^[18-23]. These data require careful interpretation, as surgeon experience, technique and perioperative care differs widely between institutions^[57]. However, reported median survival rates of up to 63 mo following cytoreductive surgery and HIPEC with limited postoperative morbidity and mortality^[58,59] suggest that treatment should be considered in all patients with PC secondary to CRC.

In conclusion, PC of colorectal origin was formerly considered untreatable, with an extremely poor prognosis. Recent treatment advances using modern systemic chemotherapy or cytoreductive surgery combined with HIPEC have improved patient outcomes. In our opinion, treatment should be considered for every patient presenting with PC due to CRC. However, further understanding of PC pathogenesis, optimal diagnostics and treatment requires ongoing experimental and clinical research.

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