Peritoneal Carcinomatosis from Colorectal Cancer

Review Article

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Abstract
Peritoneal carcinomatosis is the most frequent cause of death in patients treated for colorectal cancer. It presents with a rate of 25-35% and is traditionally followed by median survival of less than 6 months. In 1982, Paul Sugarbaker proposed combined cytoreductive surgery with intraperitoneal hyperthermic chemotherapy in the treatment of peritoneal carcinomatosis as a local relapse of the disease; he achieved a five-year survival rate of >30%. The spectrum of peritoneal carcinomatosis ranges from the presence of some tiny surface nodules, usually near the primary site of the tumour, to the full coverage of the peritoneal surface with invasive neoplastic massive tumours, with or without clinical evidence of systemic metastatic disease. In 10-15% of patients it appears synchronous with the primary tumour and in 20-50% as a late recurrence. The intrabdominal relapse of colorectal cancer can be successfully treated with radical oncologic cytoreductive peritonectomy and intraoperative intraperitoneal hyperthermic chemotherapy. The aim is the complete excision of the macroscopically visible neoplastic disease (peritonectomy and excision of all infected organs) as well as treatment of the remnant microscopic disease with intraoperative intraperitoneal hyperthermic chemotherapy. This combined approach can be performed with acceptable rates of surgical morbidity and mortality in high volume reference centres. A multivariate oncologic approach in combination with a meticulous patient selection, significantly improves the survival rate compared to the conventional palliative chemotherapy.

Key words:
Colorectal cancer, Peritoneal carcinomatosis, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy

Introduction
Generalized metastatic disease is the main cause of death in patients suffering from colorectal cancer. However, in contrast to other malignant diseases, the presence of distant metastatic tumour masses (e.g. Liver, Lungs) or peritoneal spread, does not preclude an attempt to treat a selected groups of patients, with an intention to cure.

Twenty-five to 35% of patients with colorectal cancer present with peritoneal carcinomatosis. The usual approach of aggressive surgical resection followed by systemic chemotherapy offers a median overall survival of no more than 6 months.

In 1982, P. Sugarbaker attempted to approach peritoneal carcinomatosis as a local relapse of colorectal cancer and developed a pioneer treatment method. This was based on a radical oncologic cytoreductive resection in combination with hyperthermic intraoperative intraperitoneal chemotherapy, in order to treat both macroscopic and remnant microscopic disease. As such, he achieved a 30% five-year survival rate for patients that, otherwise, would have been considered to be “end stage” [1].

Definition and Pathogenesis
The term “peritoneal carcinomatosis” was first used by Sampson in 1931 [2] to describe local recurrence of ovary cancer on the peritoneal surface. The pathogenesis was mostly attributed to the direct implantation of tumour cells and to a lesser extent to vascular or lymphatic invasion.

Nowadays, peritoneal metastasis from colorectal cancer is ascribed to the direct implantation of cancer cells that can be instigated by four different mechanisms:

- Immediate peritoneal spread from T4 colorectal cancer invasion of the peritoneal coat of the colon
- Local spread of cancer cells caused by colonic wall rupture due to an obstructive tumour
- Injury to the peritoneal coat of the colon, around the tumour, during surgical manipulations
- Dissemination of tumour cells through injured veins and lymphatic vessels, at surgical resection.
It becomes obvious that the risk of peritoneal metastatic dispersion rises significantly when the colorectal tumour is locally advanced.

Peritoneal carcinomatosis signifies the intraabdominal dispersion of colorectal cancer with or without evidence of systemic disease. Neoplastic growth of peritoneal nodules of different size, number and distribution can be noted. The recurrence can be isolated and in close proximity to the primary tumour site or generalized to cover a wide intraabdominal peritoneal surface [3].

**Frequency of Peritoneal Carcinomatosis**

It is difficult to define the exact incidence of peritoneal carcinomatosis as a local recurrence. Most retrospective studies in large series of reoperation or autopsy studies have concluded that 10% to 15% of patients present synchronous peritoneal metastasis involving the primary tumour and 20% to 50% of patients develop metachronous metastasis. This places the frequency of peritoneal metastasis of colorectal cancer second only to liver metastasis [4].

However, during the past twenty years, with the widespread use of total mesorectal excision and neoadjuvant chemo-radiotherapy, the frequency of local recurrence of rectal cancer has diminished significantly [5].

Today, peritoneal carcinomatosis after radical resection of colon cancer varies from 4% to 12% [6] and for rectal cancer from 2% to 19% [7]. Recently, Jayne et al [8] retrospectively analyzed 3019 patients with colorectal cancer and reported that 214 patients (7%) had peritoneal carcinomatosis at the time of primary tumour resection, whereas 58% had no evidence of systemic metastatic disease; 135 (4.5%) presented late peritoneal carcinomatosis.

Gunderson et al [9] studied the areas of recurrence in 91 patients with Dukes stage B or C colon cancer that had undergone selective second look laparotomy at 6 to 12-month intervals from the primary surgical resection. The authors found that 48% of patients had a local recurrence and 21% had peritoneal carcinomatosis as the only clinical manifestation of recurrence.

Tong et al. [10] studied patients that underwent exploratory laparotomy due to suspicion of local recurrence after right colon cancer resection, and reported that 47% actually had a local recurrence and 44% generalized peritoneal carcinomatosis. Moreover, in 25% of these patients the peritoneum was the only site of metastasis, even after thorough clinical and imaging examination.

Brodskey et al [11] analyzed the follow-up of patients after radical excision and found that 25-35% had locoregional recurrence, only 15% of whom were suffering from isolated peritoneal spread.

In the autopsy of 45 patients that had died from colorectal cancer, Gilbert et al [12] noted that 18 had peritoneal carcinomatosis. Russell et al [13] studied 53 patients and found that 38% had local recurrence and 36% developed peritoneal carcinomatosis.

**Natural Course of Peritoneal Carcinomatosis**

Traditionally, peritoneal carcinomatosis from colorectal cancer was considered as a non-treatable condition with poor prognosis. Exploratory laparotomy or laparoscopy was performed to obtain a biopsy sample, along with extensive surgical excision or simple palliative enterostomy. Patients were then treated with systemic chemotherapy. Most of these patients died after a period of less than 9 months due to intestinal obstruction or cachexia [14].

Occasionally, patients with peritoneal carcinomatosis needed an emergency operation due to intestinal obstruction, bleeding, bowel perforation or ascites collection. However, in some cases, many surgeons were reluctant to intervene, due to the patient’s low rate of survival and poor overall outcome [15].

Peritoneal carcinomatosis is the most frequent cause of death for patients after curative resection of colorectal cancer. According to Sugarbaker [16], the continuous presence of cancer cells in the peritoneal cavity or pelvis is the main cause of death in 30% to 50% of these patients.

Few studies have analyzed the natural course of peritoneal carcinomatosis. Clinical data have emerged mostly from 3 studies. The first by Chu et al [3] prospectively studied 45 patients that were treated with 5-FU and Leucovorine, and displayed a mean survival of 6 months. A decade later, the multicentre prospective French study “EVOCAPE” by Sadeghi et al [14] of 118 patients with peritoneal carcinomatosis from colorectal cancer, reported a mean survival rate of 5.2 months. In 2002, Jayne et al [17] retrospectively studied 3019 patients with colorectal cancer, 13% of whom developed peritoneal carcinomatosis; in cases of synchronous disease, overall survival was less than 7 months.

It is clear that peritoneal carcinomatosis is the most frequent form of evolution of colorectal cancer. In a study by Esquivel et al [15] of 2756 colorectal cancer patients, 349 (13%) were diagnosed with peritoneal metastasis, of whom 214 displayed simultaneous and 135 late peritoneal dissemination. Among those with simultaneous disease, 125 (58%) patients were free of distant metastasis and 80 had