

Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemotherapy in Peritoneal Carcinomatosis

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Abstract

Background: Peritoneal carcinomatosis is an advanced form of cancer with poor prognosis that in the past was treated mainly palliatively. Today, the definitive approach to peritoneal surface malignancy involves peritonectomy, visceral resection and perioperative intra-abdominal hyperthermic chemotherapy. The anticipated results range from at least palliative to as far as intent to cure. Proper patient selection is mandatory.

Objectives: To determine whether cytoreductive surgery and intraperitoneal hyperthermic chemotherapy can extend survival, and with minor complications only, in patients with peritoneal carcinomatosis.

Methods: Twenty-two IPHP procedures were performed in 17 patients with peritoneal carcinomatosis in our institution between 1998 and 2007: 6 had pseudomyxoma peritonei, 5 had colorectal carcinoma, 3 had ovarian cancer and 3 had mesotheliomas. All patients underwent cytoreductive surgery, leaving only residual metastasis < 1 cm in size. Intraperitoneal chemotherapy was administered through four large catheters (2F) using a closed system of two pumps, a heat exchanger and two filters. After the patient's abdominal temperature reached 41°C, 30–60 mg mitomycin C was circulated intraperitoneally for 1 hour.

Results: The patients had a variety of anastomoses. None demonstrated anastomotic leak and none experienced major complications. Six patients had minor complications (pleural effusion, leukopenia, fever, prolonged paralytic ileus, sepsis), two of which may be attributed to chemotherapy toxicity (leukopenia). There was no perioperative mortality. Some patients have survived more than 5 years.

Conclusions: IPHP is a safe treatment modality for patients with peritoneal carcinomatosis. It has an acceptable complications rate and ensures a marked improvement in survival and in the quality of life in selected patients.

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Peritoneal carcinomatosis represents an advanced form of cancer associated with intraperitoneal seeding of tumor cells. Prognosis was historically poor, as was the patient's quality of life. Peritoneal carcinomatosis occurs commonly in colorectal carcinoma and is the second most frequent cause of death due to gastrointestinal carcinoma, after metastatic disease of the liver. Other tumors causing similar presentation of peritoneal spreading are pseudomyxoma peritonei with an ovarian or appendiceal origin. The third kind of malignancy in this category is peritoneal mesothelioma, a rare disease with a poor prognosis.

IPHP = intraperitoneal hyperthermic perfusion

Peritoneal carcinomatosis had long been considered a terminal condition, and surgery was offered only for palliation. If peritoneal seeding was found during elective surgery, treatment consisted solely of colectomy. The patient was then referred to systemic chemotherapy with expected survival ranging between 6 and 8 months and no 5 year survival [1]. Cytoreductive surgery attempts to macroscopically remove the visible tumor, including involved organs and peritonectomy, or at least to leave limited residual disease (lesions < 2.5 mm in size). This is done by stripping involved areas of the peritoneum, based on the fact that therapeutic concentration was only reached within 2 mm of the exposed surface [2,3]. Aggressive cytoreductive surgery combined with intraperitoneal hyperthermic chemotherapeutic drugs inserted directly into the abdomen was proposed in 1990 as a promising alternative to earlier conventional surgery in terms of prolonged survival and improved quality of life [4]. This combined treatment was reported to offer minimal morbidity and mortality. During the last three decades hyperthermia has been investigated as a treatment modality in cellular inactivation, tumor regression and tissue damage. The modern use of this modality is based on the occurrence of tumor remission in patients who experienced febrile episodes, despite the fact that hyperthermia alone has no benefit in the treatment of cancer. Perioperative intraperitoneal chemotherapy administered at the end of the operation is given to destroy residual microscopic disease, thereby preventing tumor cell implantation and recurrence.

We describe our 7 year experience with aggressive cytoreduction surgery combined with intraperitoneal hyperthermic chemotherapeutic drugs inserted directly into the abdomen in selected patients whose expected survival in the past would have been less than one year and whose quality of life would have been very poor.

Patients and Methods

Since 1998 all patients presenting to our surgical services with peritoneal carcinomatosis were evaluated for this procedure. Those older than 80 years or with extraperitoneal metastatic disease were excluded. All patients were evaluated by an anesthesiologist to ensure that they could undergo major surgery and 13 who fulfilled the study criteria were scheduled for surgery. All had undergone a course of appropriate systemic chemotherapy preoperatively [Table 1].

Prior to surgery the study patients underwent a clinical examination, chest-abdominal-pelvic computed tomography and, later, positron emission tomography-CT, and laboratory tests for tumor markers (carcinoembryonic antigen, CA 19-9, CA 125). The diagnosis of pseudomyxoma peritonei, colorectal carcinoma or ovarian carcinoma was confirmed histologically from an open biopsy specimen.

The therapeutic protocol was described previously by Schneebaum et al. [4] and involves aggressive cytoreduction (< 2.5 mm) and IPHP with mitomycin-C chemotherapy at 41°C for 60 minutes.

Cytoreductive surgery

The surgical approach, which was latter developed by Sugarbaker and collaborators [5,6], is cytoreductive surgery or peritonectomy, which consists of the complete removal of the tumor. Surgery is followed by locoregional hyperthermic drug administration with the intent to eliminate microscopic and/or minimal residual tumor in the abdominal cavity after surgery.

The fully anesthetized patient is placed in a supine position. The abdomen is opened from the xiphoid to the pubis and exposure is achieved by means of a Bookwalter retractor. Cytoreduction involves the location and extension of the intra-peritoneal spread of the tumor as follows:

- Right colectomy with omentectomy and right parietal peritonectomy
- Pelvic peritonectomy with sigmoidectomy plus total abdominal hysterectomy and bilateral salpingo-oophorectomy
- Antrectomy, cholecystectomy, lesser omentectomy and duodenal-hepatic ligament dissection
- Right upper quadrant peritonectomy and Glisson capsule resection
- Left upper quadrant peritonectomy with splenectomy.

After full recovery from surgery and discharge from hospital, each patient receives adjuvant therapy according to the primary tumor.

Intraperitoneal hyperthermic perfusion

Following the cytoreduction phase, a chest tube (# 28) was placed in the Morison's pouch area (right subhepatic space) and another in the left subphrenic area and brought to the skin through a stab wound incision. Two AQRgyle Saratoga Model 28 sumps (Sherwood Medical Industries, St. Louis, MO, USA) were placed in the abdomen, one near the chest tube in Morrison's pouch and the other in the pouch of Douglas near the sump drain. Each was brought out in the same stab wound of the nearest drain. The drains were secured to the skin with a purse-string suture and the abdomen was closed. The two sump drains were then connected using a Y-connector to Bentley Baxter tubing (Baxter Bentley, Irvine, CA). The IPHP delivery system, a dual-filter system with a subsequent heat exchanger, is driven by two Sarns 7000 roller pumps (Sarns 3M, Ann Arbor, MI). The first pump passes the perfusate stream fluids to a cardiomy reservoir (Bentley Ber 3500, Baxter Bentley) with a 20 μ filter for air trapping. This filter also protects the second filter from large clots. The fluid then passes to the second filter (121163 μ filter, Gelman Scientific, Ann Arbor) which entraps cells, to a heat exchanger (Baxter

Bentley HE 100), and then through the chest tube to the patient. A continuous peritoneal temperature is obtained by using two intra-abdominal thermometers. After closure, the fascia, the skin and the four catheters are connected to an extracorporeal circuit. The polysaline perfusate (4–6 L) containing mitomycin-C (3.3 mg/m²/L) is instilled into the peritoneal cavity with a heart-lung pump at a mean flow of 600 ml/min for 60 minutes. The perfusate is rapidly drained at the end of perfusion.

Morbidity and mortality

Morbidity and mortality post-cytoreduction and IPHP are classified into four categories: no complications (grade 1), minor complications (grade 2), major complications (grade 3), and in-hospital mortality (grade 4). A minor complication was defined as a postoperative fistula (that resolved spontaneously), a biliary fistula, a prolonged ileus, and pleural effusion. A major complication meant the necessity of reoperation, admission to the intensive care unit, or interventional radiology. Toxicity was evaluated according to World Health Organization criteria.

Results

The 17 patients with peritoneal carcinomatosis included in the study comprised 9 females and 8 males, with an average age of 58.2 years (range 32–80). Six patients had pseudomyxoma peritonei with appendicular origin, five had peritoneal carcinomatosis of colorectal origin, three had carcinomatosis of ovary and three had mesotheliomas. Ten patients had been treated in the past with chemotherapy and 12 patients had undergone surgery for various types of carcinoma [Table 1].

All patients underwent complete resection of the lesions. Two procedures were performed in two patients and four procedures in one patient. Seven patients experienced grade 2 (minor) complications: one had pleural effusion, two had leukopenia and one had sepsis, one had prolonged paralytic ileus and two patients had fever. Two of the complications may be attributed to chemotherapy toxicity (leukopenia). No patient experienced major complications and there were no deaths during the immediate postoperative period. Patients with pseudomyxoma had a favorable survival: three patients survived 119, 70 and 54 months and three patients are alive 29, 26 and 3 months after surgery respectively. Patients with metastatic colon carcinoma survived 96, 73 and 26 months, and one patient is alive 8 months after surgery. Of the three patients with ovarian cancer who underwent surgery, one died 17 months later and the remaining two are alive 13 and 2 months after surgery. One patient with mesothelioma who was operated died 6 months after surgery and 2 patients are alive 20 and 8 months after surgery [Table 1].

Discussion

In the past, peritoneal carcinomatosis by definition had essentially been a terminal illness. It has its origins in three major malignancies: pseudomyxoma peritonei, colorectal carcinoma, and peritoneal mesothelioma. Affected individuals had a poor prognosis when the treatment relied on systemic chemotherapy or cytoreduction alone [7]. For selected patients with this disease, however, currently available combined cytoreductive surgery with

Table 1. Characteristics of the study patients

No. of patients	No. of procedures	Age/ Gender	Primary site	Previous chemotherapy	Previous surgery	Surgery date	Morbidity	Laparotomy+ peritonectomy +	Months survival since first surgery	Outcome
1	1	58/F	Appendix, pseudomyxoma	None	Appendectomy, TAH+BSO, omentectomy Dec 2004	May 2005	Pleural effusion		26	A
2	2	42/M	Appendix, pseudomyxoma	Thalidomide, 5fu	Appendectomy 2001	Feb 2001	Leukopenia	Rt. hemicolectomy	54	D/D
	3					Oct 2002	Not available to follow-up	Cytoreduction		
3	4	57/M	Appendix, pseudomyxoma	Yes 5fu (i.p.)*	Appendectomy, Rt. colectomy July 1997, Debulking + intraperitoneal chemotherapy Sept 2001	Oct 2004	Fever	Cytoreduction	70	D/D
4	5	80/M	Appendix, pseudomyxoma, ascites			April 2007	Not available to follow-up	Omentectomy	3	A
5	6	45/F	Appendix, pseudomyxoma	Yes	TAH+BSO 1999	Feb 2005	Not available to follow-up	Cytoreduction	29	A
6	7	65/M	Appendix, pseudomyxoma	No	Rt. colectomy 1996	Aug 1997	Not available to follow-up	Splenectomy, metastasectomy	119	D/D
	8					May 1999	Not available to follow-up	Cytoreduction		
	9					Jan 2001	Fever	Small bowel resection, cytoreduction		
	10					July 2003	Prolonged paralytic ileus	Cytoreduction, gastrostomy		
7	11	40/F	Mesothelioma	Yes	Laparoscopic biopsy, bladder perforation		Not available to follow-up	Rt. colectomy	20	A
8	12	48/M	Mesothelioma	Yes Cisplatin, n2vp16	No	Feb 2001	Sepsis	Omentectomy, splenectomy	6	D/D
9	13	67/F	Mesothelioma	Alinta, cysplatin	Open biopsy June 2005	Nov 2006	Not available to follow-up	Rt. colectomy	8	A
10	14	63/F	Adenocarcinoma of colon, ascites	No	No	July 1999	Leukopenia	Extended Rt. colectomy, TAH+BSO	96	D/D
11	15	32/M	Adenocarcinoma of colon		Subtotal colectomy Feb 1999	June 2001	Not available to follow-up	Small bowel resection, wedge resection of mesenterium	73	D/D
	16	32/M				Oct 2002	Fever	Debulking		
12	17	63/M	Adenocarcinoma of colon		Sigmoidectomy June 2004	May 2005	Not available to follow-up	Metastasectomy, debulking	26	D/D
13	18	71/M	Adenocarcinoma of colon			Dec 2006	Not available to follow-up	Lt. colectomy, peritoneal metastasectomy	8	A
14	19	59/F	Adenocarcinoma of colon	Yes	Hepatectomy, splenectomy, TAH+BSO 1997	Dec 1998	Not available to follow-up	Low anterior resection, excision of tumor from abdominal wall and diaphragm. Radio-immune guided surgery	41	D\D
15	20	69/F	Adenocarcinoma of ovary	Yes Taxol, cisplatin	Appendectomy, omentectomy, TAH+BSO May 1997	June 1998	Not available to follow-up	Debulking	17	D/D
16	21	62/F	Adenocarcinoma of ovary	Carboplatin, gemzar, taxoter	TAH+BSO 1998	May 2007	Not available to follow-up	Subtotal colectomy, subtotal gastrectomy, splenectomy	2	A
17	22	68/F	Adenocarcinoma of ovary	Carboxil, oxaliplatin, 5fu	Cholecystectomy	June 2006	Not available to follow-up	TAH+BSO, total abdominal colectomy	13	A

TAH+BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy, D/D = dead of disease, A = alive.

intraperitoneal hyperthermic chemotherapy does not only enable far better palliative results but even eradication of the disease [8]. By carefully observing the stringent entry criteria when we chose candidates for this aggressive combined procedure, we were left with a relatively small study cohort but it emerged that our excellent short-term results more than justified these precautions.

The main characteristic of pseudomyxoma peritonei dissemination within the peritoneal cavity was defined by Sugarbaker and colleagues [5,6] as a completely redistributive phenomenon with a major anatomic location of the tumor, such as the pelvis, gutters and the perihepatic area. The classification of pseudomyxoma peritonei is disseminated peritoneal adenomucinosis, peritoneal mucinous carcinomatosis and an intermediate group: their 10 year survival rates are reportedly 68%, 3% and 21%, respectively. The first is a metastatically inefficient tumor compared to the aggressive peritoneal mucinous carcinomatosis that invades peritoneal and visceral organs with the presence of serous ascites.

Treatment options for patients with stage IV colorectal cancer have improved significantly in the past years. In selected patients systemic treatment alone is no longer appropriate for those with limited peritoneal dissemination from a primary or recurrent colon cancer. The surgical management of peritoneal surface malignancies of colorectal origin with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy has been clearly defined and has resulted in an improved median survival.

Peritoneal mesothelioma is a rare disease with a poor prognosis. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy was proven acceptable in terms of morbidity and mortality in patients with peritoneal mesothelioma, suggesting a positive impact on outcome in selected patients.

An international registration of a large population (n=506) of patients with one of these three types of peritoneal carcinomatosis and peritoneal spreading who underwent a combination of cytoreduction and intraperitoneal chemotherapy showed dramatic improvement in survival rates [9]. The overall median times of prolonged living for 19.2 months and for 3 and 5 years were 39% and 19%, respectively. The reported morbidity and mortality rates were 22.9% and 3.7%, respectively. The morbidity rate correlated with carcinomatosis, which acts as an independent negative prognostic indicator [10].

In a prospective randomized study conducted in 2000, Sadeghi et al. [7] demonstrated that patients with peritoneal carcinomatosis from non-gynecological malignancies had an average survival rate of 3.1 months. In 2004, Verwaal and co-workers [11,12] conducted a prospective randomized study of patients with peritoneal carcinomatosis due to colorectal carcinoma who underwent cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy and reported a significant improvement in their survival rate. Specifically, the median survival rate was 21.8 months, with 3 and 5 year survival rates of 28% and 19%, respectively. Extensive cytoreduction of macroscopic disease enhanced the action of the locally perfused chemotherapy by decreasing the depth of the tumor mass and exposing greater contact surface with the chemotherapy, doing so with low systemic toxicity. Their high but acceptable rate of complications emphasized the necessity for

careful patient selection. They noted that age older than 65 years and cardiorespiratory or renal failure seemed to be significantly negative prognostic factors, and we chose our study patients according to their recommendations for patient selection.

Our experience with the combined procedure was highly gratifying for patients with pseudomyxoma and metastatic colon cancer. Five patients had prolonged survival of 4.5 years or more (45%) and five patients are still alive, with the longest follow-up of 29 months. The small number of patients with ovary adenocarcinoma and mesothelioma does not allow us to draw any conclusion about the survival of such patients although it seems to be unfavorable.

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References

1. Jackson SL, Fleming RA, Loggie BW, Geisinger KR. Gelatinous ascites: a cytohistologic study of pseudomyxoma peritonei in 67 patients. *Mod Pathol* 2001;14:664-71.
2. Deraco M, Casali P, Kusamura S. Peritoneal mesothelioma treated by induction chemotherapy, cytoreductive surgery, and intraperitoneal hyperthermic perfusion. *J Surg Oncol* 2003;83:147-53.
3. Deraco M, Nonaka D, Baratti D, Kusamura S. Prognostic analysis of clinicopathologic factors in 49 patients with diffuse malignant peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion. *Ann Surg Oncol* 2006;13:229-37.
4. Schneebaum S, Arnold MW, Martin EW Jr. Intraperitoneal hyperthermic perfusion with mitomycin C for colorectal cancer with peritoneal metastases. *Ann Surg Oncol* 1996;3:44-50.
5. Sugarbaker PH, Graves T, DeBruijn EA. Early postoperative intraperitoneal chemotherapy as an adjuvant therapy to surgery for peritoneal carcinomatosis from gastrointestinal cancer: pharmacological studies. *Cancer* 1990;50:5790-4.
6. Sugarbaker PH, Zhu BW, Shmookler B. Peritoneal carcinomatosis from appendiceal cancer: results in 69 patients treated by cytoreductive surgery and intraperitoneal chemotherapy. *Dis Colon Rectum* 1993;36:323-9.
7. Sadeghi B, Arvieux C, Gilly F. Peritoneal carcinomatosis from non-gynecologic malignancies. Results of the EVOCAPE 1 Multicentric Prospective Study. *American Cancer Society*, 2000.
8. Sutton SW, Yancey LW, Chase VA, Hunley EK, Loggie BW. Intraoperative modality of treatment for peritoneal carcinomatosis: use of hyperthermic intraperitoneal chemoperfusion. *Perfusion* 2002;17:441-6.
9. McQuellon RP, Loggie BW, Fleming RA, Russell GB, Rambo TD. Quality of life after intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. *Eur J Surg Oncol* 2001;27:65-73.
10. Loggie BW, Fleming RA, Geisinger KR. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of gastrointestinal origin. *Am Surg* 2000;66:561-8.
11. Verwaal VJ. Cytoreduction and HIPEC for peritoneal carcinomatosis from colorectal origin: the Amsterdam experience. *Acta Chir Belg* 2006;106:283-4.
12. Verwaal VJ, Van Tinteren H, Van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. *Br J Surg* 2004;91:739-46.

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