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Peritonectomy and hyperthermic antiblastic perfusion in the treatment of peritoneal carcinomatosis

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Aims: Some low-grade malignant tumours arising in the abdomen tend to remain loco-regionally confined to peritoneal surfaces, without systemic dissemination. In these cases complete surgical tumour cytoreduction followed by intra- or post-operative regional chemotherapy has curative potential. The aim of this study was to evaluate the outcome for patients treated in this way.

Methods: Peritonectomy was performed, involving the complete removal of all the visceral and parietal peritoneum involved by disease. After peritonectomy, hyperthermic antiblastic perfusion was carried out throughout the abdomino-pelvic cavity for 90 min, at a temperature of 41.5–42.5°C, with mitomycin C (3.3 mg/m^2/l) and cisplatin (25 mg/m^2/l) (for appendicular or colorectal primaries), or cisplatin alone (for ovarian primaries). Alternatively, the immediate post-operative regional chemotherapy was performed with 5-fluorouracil (13.5 mg/kg) and Lederfolin (125 mg/m^2) (for colonic or appendicular tumours) or cisplatin (25 mg/m^2) (for ovarian tumours), each day for 5 days.

Results: Thirty-five patients affected by extensive peritoneal carcinomatosis were submitted to peritonectomy, with no residual macroscopic disease in all cases except three. Twenty-six patients were able to undergo the combined treatment involving loco-regional chemotherapy. Complications were observed in 54% of the patients and led to death in four of them. At a mean follow-up of 17 months overall 2-year survival was 55.2%, with a median survival of 26 months.

Conclusions: After a learning curve of 18 months the feasibility of the integrated treatment increased to more than 90%, while mortality decreased dramatically. The curative potential of the combined therapeutic approach seems high in selected patients with peritoneal carcinomatosis not responding to systemic chemotherapy. Careful selection of patients can minimize the surgical risk, but the treatment should currently be reserved for clinical trials.

Key words: **peritoneal carcinomatosis; peritonectomy; hyperthermic antiblastic perfusion; intraperitoneal chemotherapy.**

Introduction

Peritoneal carcinomatosis can originate from transparietal spread of low-grade malignant tumours. In these cases, the peritoneal involvement is not a consequence of intrinsic biological aggressiveness, but due to the effects of gravity, intestinal peristaltic movements and peritoneal reabsorption. Sugarbaker has named this pathway neoplastic 'redistribution'.[1]

Traditional surgery has always had palliation as its only objective,[2] the peritoneal carcinomatosis being considered as a systemic disease. However, in 1968 Long *et al.*[3] reported long survival times in low-grade peritoneal carcinomatosis patients after repeated regional treatment. This suggested that the peritoneum could be the 'last margin' in selected cases and the intent of surgery should therefore be not simply to perform a debulking operation but to obtain complete tumour cytoreduction by peritonectomy.

After cytoreduction, intraoperative hyperthermic perfusion or immediate post-operative abdomino-pelvic antiblastic infusion provide direct contact between drugs and residual free neoplastic cells when they are exposed and vulnerable.

Peritonectomy has been proposed and codified in terms of rationale and surgical technique by Sugarbaker.[4] In his experience of 181 consecutive patients with peritoneal carcinomatosis, the association of peritonectomy and adjuvant chemotherapy resulted in an actuarial survival rate of 99% at 3 years in patients with grade I histology, no lymph node metastases and in whom complete cytoreduction had been achieved.[5]

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Based on this rationale, we employed the combination of peritonectomy and regional chemotherapy in patients with advanced peritoneal carcinomatosis from low-grade malignant tumours. The present paper reports our experience in 35 consecutive patients.

Methods

Peritonectomy

Total peritonectomy involves several surgical procedures, based on division of the peritoneum into different surgical areas. The dissection should remain extraperitoneal until most of the sub-diaphragmatic and parietocolic peritoneum is exposed. The peritoneum is then opened and the abdomen is carefully explored. Peritoneal washing is carried out and the fluid is analysed by both conventional cytology and immunocytology to detect the presence of neoplastic cells.[6,7] The results constitute a reference point, when the same analysis is repeated at the end of surgery and after regional chemotherapy. The surgical technique has been described in detail by Sugarbaker[4] and can be summarized as follows:

(1) Peritoneal stripping from the cephalic portion of the right hemiabdominal wall and right sub-diaphragm, together with peritonectomy of Morrison's pouch.
(2) Peritoneal stripping from the cephalic portion of the left hemiabdominal wall and left sub-diaphragm.
(3) Removal of the falciform and triangular ligaments of the liver and Glisson's capsule in its entirety, and cholecystectomy with peritoneal removal from the porta hepatis and lesser omentum.
(4) Omentectomy in continuity with the superficial layer of the transverse mesocolon and the anterior surface of the pancreas, followed by splenectomy.
(5) Peritoneal stripping from the right and left caudal portions of the abdominal wall, from the bladder and iliac fossa preserving the ureters; resection of the sigmoid colon and mesosigmoid from the origin of inferior mesenteric artery.
(6) Pelvic peritonectomy, dividing the subperitoneal rectum and vagina in women to remove *en bloc* all the neoplastic tissue in the peritoneal cul de sac; closure of the vagina and colorectal anastomosis, after mobilization of the entire left colon.
(7) The operation is completed by removing all traces of visceral disease, most frequently leading to right colectomy, the caecum and the right parietocolic peritoneum. Resection of the gastric antrum due to the presence of tumour deposits may also be necessary.

Hyperthermic antiblastic perfusion (HAP)

Prior to performing intestinal anastomoses, the peritonectomy procedure is completed by carrying out hyperthermic antiblastic perfusion throughout the abdomen by positioning two inflow catheters under the diaphragm and two large outflow drains in the pelvis. The extracorporeal circuit pump, equipped with heat exchanger and reservoir filter, pumps the heated perfusion isotonic fluid into the abdominal cavity, while the outflow from the abdomen through the drains into the reservoir occurs by gravity. Thermocouples are positioned at inflow and outflow sites, in the sub-diaphragmatic spaces, on the mesentery, in the pelvis and as close as possible to any residual neoplastic nodules which could not be removed, and the temperatures are monitored.

The perfusate is heated to 44–45°C in order to reach a temperature of 41.5–42.5°C throughout the abdomino-pelvic cavity, which according to our studies[8] corresponds to the optimal temperature to obtain effective synergism with the employed antineoplastic drugs, whilst limiting regional toxicity to acceptable levels. At this abdominal temperature, mitomycin C (3.3 mg/m^2/l) and cisplatin (25 mg/m^2/l) are introduced into the perfusion circuit for carcinomatosis originating from appendicular or colorectal tumours; cisplatin alone is utilized for primary ovarian tumours. Hyperthermic antiblastic perfusion is undertaken for 90 min, after which the abdomen is washed and immunocytology is again employed to search for neoplastic cells in the washing solution. Visceral anastomoses are then carried out and thoracic tubes are inserted in the right and left pleural cavities to evacuate fluid accumulating in the chest as a result of both electro-surgery on the sub-diaphragmatic peritoneum and the abdominal hyperthermic antiblastic perfusion. Finally, the abdomen is closed in routine fashion.

Post-operatively, initial management takes place in the Intensive Care Unit.

Early post-operative intraperitoneal chemotherapy (EPIC)

Early post-operative regional chemotherapy is carried out when intraoperative deterioration of the patient's general condition limits operative time and therefore HAP cannot be carried out. In this case, before closing the abdomen, two inflow catheters are placed in the left upper quadrant as close as possible to the ligament of Treitz and in the right sub-diaphragmatic space. Drains are positioned in the right parietocolic space and in the pelvis. One hour after the operation 1 l of 1.5% dextrose peritoneal dialysis solution at 37°C is infused through the inflow catheters as rapidly as possible. The outflow drains are closed during infusion and reopened after a short dwell time. This abdominal lavage is repeated every 6 h. The aim of this procedure is to prevent early adhesions and to cleanse the abdominal cavity.

Approximately 24 h post-operatively, chemotherapy is begun. The drains are closed and 1 l of 1.5% dextrose peritoneal dialysis solution is infused at body temperature, containing 5-fluorouracil (13.5 mg/kg) and Lederfolin (125 mg/m^2) for a primary colonic or appendicular tumour or cisplatin (25 mg/m^2) for a primary ovarian tumour. The drains remain closed for 23 h and are then reopened for 1 h until the next infusion is performed. The same procedure is repeated every 24 h for 5 days, using the same drug doses.

Drainage fluid is examined for neoplastic cells using conventional cytology and immunocytology.

Patients and results

Between April 1995 and December 1998, 35 patients with peritoneal carcinomatosis (27 female, eight male) were

Table 1. Breakdown of patients related to previous surgical treatments

Primary tumour	No. patients	Previous surgery	Surgical procedures	*n*
Ovarian	18	14	Hystero-oophorectomy	14
			Removal of recurrence	9
			De-bulking with residual disease	6
			Laparoscopy or explorative laparotomy	7
Colorectal	11	10	Colonic resection	13
			Other visceral resection	5
			Posterior pelvic exenteration	3
			De-bulking with residual disease	4
			Intestinal by-pass or stoma	5
			Laparoscopy or exploratory laparotomy	5
Mesothelial	4	4	Removal of primary tumour	3
			Removal of recurrence	2
			De-bulking with residual disease	1
			Explorative laparotomy	3
Appendicular	2	2	Appendicectomy	2
			Hystero-oophorectomy	1
			De-bulking with residual disease	1

Table 2. Breakdown of patients related to previous chemotherapy

Primary tumour	No. patients	Previous chemo (no. patients)	Drugs	patients
Ovarian	18	17	CDDP; EPI; EDX; TAX	5
			CDDP; EPI; EDX	2
			CDDP; ADM; EDX	2
			CBDCA; EDX	1
			CDDP; ADM; EDX; CBDCA; EPI; TAX	2
			CBDCA; EPI; TAX	2
			CDDP; LND; TAX; IFO; MESNA	2
			CDDP; EPI; LND	1
Colorectal	11	6	FUFA	3
			5-FU; MMC	1
			5-FU; CDDP	1
			5-FU; CPT11	1
Mesothelial	4	2	NVT; MTX; INF-beta; EDX	1
			CDDP; ADM	1
Appendicular	2	1	FUFA; INF-alpha; MMC	1

CDDP: cisplatin; EPI: epirubicin; EDX: edatrexate; TAX: taxol; AOM; doxorubicin; CBDCA: carboplatin; LND: lonidamine; IFO: ifosfamide; 5-FU: 5-fluorocil; FA: folinic acid; MMC: mitomycin-C; CPT11; irinotecan; NVT: mitoxantrone.

submitted to peritonectomy. Their median age was 50 years (range 17 to 71 years). The primary tumour was an ovarian cystadenocarcinoma in 18 cases, a mucinous colonic adenocarcinoma in 10, malignant mesothelioma in four and an appendicular adenocarcinoma in two. Most of the patients had previously undergone several surgical procedures and had recurrences or disease progression after two or more regimens of intravenous chemotherapy (Tables 1 and 2).

The carcinomatosis was extensive in all cases, with a Sugarbaker peritoneal cancer index (PCI)[9] of 16. Pre-operatively, five patients had symptoms of intestinal obstruction and one had previously undergone an ileo-transversostomy elsewhere for this reason. Seven patients had ascites. Pre-operatively all the patients were staged by spiral abdominopelvic CT scan, and when indicated with peritoneography, to exclude the presence of untreatable mesenteric disease. CT peritoneography was performed after infusion of 21 of isotonic solution and contrast medium into the abdominal cavity, and was highly effective in detecting small implants on the serosal surfaces. It allows detection of disease on the mesentery which, if extensive, represents a contraindication to peritonectomy.

Total peritonectomy was performed in 20 patients, while subtotal peritonectomy was carried out in 15 because of less widespread carcinomatosis (or developing complications).

At the end of the learning curve, the average duration of the surgical procedure was 10 h (range 6 to 15 h), excluding the HAP time. Intraoperative complications occurred in six patients, and in three forced peritonectomy to be abandoned before the cytoreduction was completed (Table 3).

Table 3. Adjuvant treatment in patients with intraoperative complications

Complication	Patients	Adjuvant treatment	Outcome
Cardiac failure	3	2 i.v. chemo	2 persistence of disease 1 hospital death
Bleeding	2	1 i.v. chemo	1 alive with disease 1 hospital death
Respiratory failure	1	HAP	1 alive, no evidence of disease

Hyperthermic antiblastic perfusion was performed in 21 carcinomatosis patients (11 from ovarian cystoadeno-carcinoma, five from colorectal adenocarcinoma, two from malignant mesothelioma and two from adenocarcinoma of the appendix), while immediate post-operative intra-abdominal chemotherapy was administered in five patients (four from colonic adenocarcinoma and one from ovarian cysto-adenocarcinoma). When loco-regional chemotherapy could not be given, systemic chemotherapy was administered.

Major post-operative complications occurred in 13 patients, requiring reoperation in six and leading to death in two (Table 4). The duration of the surgical procedure was directly correlated with the clinical outcome ($P = 0.03$) (Fig. 1).

Malignant cells were present in the peritoneal washing in 70% of patients at the time of peritonectomy and remained positive soon after the loco-regional chemotherapy in 36%, but no correlation with survival was recorded. The delayed analysis of drainage fluid was positive in only two patients, who both had early recurrence.

Table 4. Post-operative complications and treatment

Complication	%	Conservative treatment	Surgical treatment	Death
Small bowel fistula	11.4	2	2	1
Anastomotic leak	5.7	1	1	
Abscess	5.7	2		
ARDS	2.8	1		1
Bleeding	2.8		1	
Intestinal necrosis	2.8		1	
Vescico-vaginal fistula	2.8		1	
Ileus	2.8	1		

The median age of patients with complications was 52.

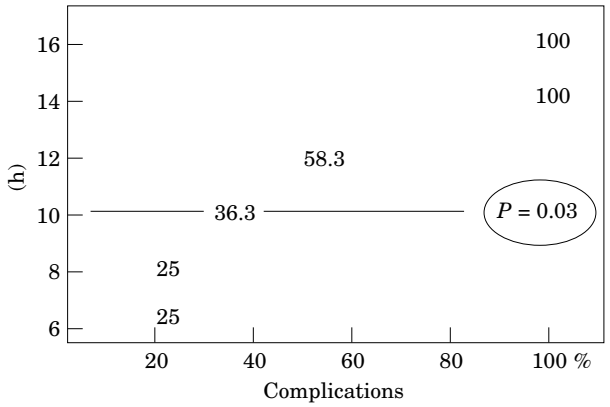

Fig. 1. Operative time and complication rate. The operative time does not include the HAP time.

Table 5. Survival related to primary tumour

	2 years survival (%)	Median survival (months)	Longest disease-free survival (months)
Ovarian	46.1	23	34
Colorectal	54.7	not reached	24*
Append. + Mesoth.	100	not reached	33*
Total	55.2	26	

* Curve is open.

After discharge, all patients were frequently reviewed and none were lost to follow-up. At a median follow-up of 17 months the overall 2-year survival was 55.2% with a median survival of 26 months. Survival breakdown is summarized in Table 5.

Discussion

Peritoneal carcinomatosis frequently presents as extensive regional disease, without haematogenous metastases.[10] This is the rule for low-grade malignant tumours that 'redistribute', giving rise to a syndrome which is clinically very similar to pseudomyxoma peritonei.[11] Characteristically, such tumours invade the peritoneum, migrating through the milky spots,[12] but rarely implanting on the surfaces of the small intestine due to active peristaltic movements that cause displacement of the neoplastic emboli towards less mobile areas such as the ileo-caecal and rectosigmoid junctions and the gastric antrum. Other sites of neoplastic deposits are the peritoneal 'cul de sac' in the pelvis, the parietocolic grooves and Morrison's pouch, where the migrating neoplastic cells accumulate by gravity.[1] Aggressive, mucin-producing tumours show a similar pattern of spread, but areas of serosal infiltration exist where the neoplastic cells, migrating with the peritoneal liquid to the reabsorption sites, establish contact with the peritoneum. In summary, three factors are characteristically involved in the abdominal spread of low-grade or mucinous cancer: peristalsis, gravity and reabsorption.[1,11–14] These, together with the biological aggressiveness of the tumour, lead to a wide range of 'random redistribution'.

Conversely, the less differentiated aggressive tumours that are not producing mucin, when overcoming the intestinal wall release emboli that are distributed in a disorderly fashion, but always starting close to the primary tumour, since the adhesion molecules cause neoplastic cells to implant on the first structure encountered, regardless of any other mechanism.[1]

In our series, all patients showed widespread and often symptomatic carcinomatosis, with a Sugarbaker peritoneal cancer index of 16, but small bowel implants were rare, while resectable liver metastases were observed in only two patients, both with colorectal primaries.

On the basis of these considerations, a two-stage treatment with curative intent becomes feasible: complete cytoreductive surgery, where the peritoneum represents the 'last margin', and loco-regional hyperthermic chemotherapy intraoperatively or immediately post-operative.

Complete cytoreduction is mandatory because intra-abdominal chemotherapy is unlikely to be curative if neoplastic aggregates are larger than a few millimetres.[9] No statistical difference in survival using intra- or post-operative intra-abdominal chemotherapy was recorded in our series nor is it described in the literature. In both procedures the timing is critically important: drugs must come into direct contact with the neoplastic cells at a time when they are most vulnerable, before inflammation mediators are released and fibrin adhesions form.[15,16]

In the early part of our experience, we did not perform several HAPs because of the longer operative time due to the technical learning curve, delaying the loco-regional chemotherapy to the first operative day, but EPIC administration was often jeopardized by the post-operative general conditions of the patients. After this early experience, significant decreases in operative time and in intraoperative blood loss allowed us to switch to HAP and in the following 18 months we achieved a combined treatment feasibility of more than 90%.

Some major problems influenced the surgical performance, for the most part in the early part of our experience. Firstly, peritoneal stripping from both the

tendinous and the posterior aspects of the diaphragm, due to difficult access and the muscular contractions stimulated by electrosurgery, sometimes led to penetration of the pleural cavity. As a result neoplastic cells were found in one patient on routine immunocytological examination of drained pleural fluid.

Subsequently, the frequency of diaphragmatic penetration was reduced with deeper anaesthesia, and finally avoided completely by employing an ultrasound knife (Ultracision-Ethicon Endosurgery, Cincinnati, OH, USA) to dissect the diaphragmatic peritoneum. This technique is somewhat slower, but appears to be safe and reliable, avoiding diaphragmatic penetration without significant bleeding.

Another initial problem was excessive blood loss, which could have interfered with the completeness of cytoreduction. It is mandatory, due to the long operative time, to proceed carefully, controlling any bleeding step by step. Particular attention must be paid to bleeding caused by the stripping of Glisson's capsule both in the presence of a few neoplastic implants on the liver surface or of bulky disease not penetrating the liver parenchyma. In the former situation, the procedure of choice is a smooth dissection; in the latter the only possibility is electrosurgical destruction, layer by layer, of the neoplastic mass.

The complication rate remains high, approximately 50%, but it has to be pointed out that almost all the patients included in this series had been previously treated by surgery and several regimens of systemic chemotherapy.

We did not find any correlation between loco-regional chemotherapy and complication rate, neither overall, nor considering anastomotic dehiscences alone; on univariate analysis, the duration of the surgical procedure seemed to be directly correlated to the clinical outcome.

The mortality rate progressively decreased to the present level of 11%, with no new event recorded from December 1996.

A search for neoplastic cells in the peritoneal washing seems mandatory. We employed both conventional cytological examination and immunocytochemistry with a panel of monoclonal antibodies, specific for the malignancy being examined.[6,17] The combination of the two assays provided a sensitivity of 98%.[7] Positivity after intraoperative hyperthermic antiblastic abdominal perfusion or immediate post-operative intra-abdominal chemotherapy indicates a need for further chemotherapy and/or second look cytoreductive surgery.

With regard to the oncological outcome, a 55% 2-year survival is an unexpected result in patients with such extensive disease. Moreover, all the ovarian carcinomatoses were stage III or IV (FIGO), 94% of them progressive after at least two i.v. chemotherapy regimens, and 36% of the colorectal carcinomatoses had resectable hepatic metastasis or distant metastatic lymph nodes.

At a median follow-up of 17 months, the disease-free survival curve with a median not yet reached is very encouraging in patients with advanced colorectal carcinomatosis.

Despite the short series, and in agreement with the Sugarbaker results, integrate treatment seems mandatory in peritoneal carcinomatosis from primary appendicular tumour where the 2-year disease-free survival is absolute.

Although no conclusions can be drawn, only 28% of the patients that could not be treated by loco-regional chemotherapy and who were submitted to systemic chemotherapy are alive at a median follow-up of 17 months *vs* 79% of the patients who completed the combined treatment ($P = \text{NS}$).

In conclusion, the curative potential of this combined therapeutic approach is high in patients with peritoneal carcinomatosis not responding to systemic chemotherapy. Peritonectomy is supported by a convincing rationale and the intra-abdominal antineoplastic drug administration, intra- or immediately post-operatively, has been demonstrated to optimize the loco-regional control of disease in an adjuvant setting.

The procedure is still burdened by relatively high morbidity and mortality rates, even though the technical learning curve has led to shorter surgical times and no mortality has been recorded in the last 2 years. Strict patient selection criteria can reduce the surgical risk and improve the post-operative outcome. At present, however, such combined treatment should be confined to clinical trials.

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COMMENTARY

Commentary regarding: F. Cavaliere *et al.*—Peritonectomy and hyperthermic antiblastic perfusion in the treatment of peritoneal carcinomatosis.

It is a great pleasure for me to review the initial work of this highly respected group of cancer surgeons with the treatment of peritoneal surface malignancy. They accepted for treatment 35 patients, and 32 had a complete resection to no visible evidence of cancer. Twenty-six had heated peritoneal perfusion in the operating room, while nine had five consecutive days of intraperitoneal chemotherapy in the early post-operative period. None of these patients had both heated intraoperative and early post-operative intraperitoneal chemotherapy as is routinely used at the Washington Cancer Institute. Of special mention is a treatment-related mortality of 11% and a morbidity of 54%.

In order to place this study in perspective one must first review the patient selection utilized at Regina Elena National Cancer Institute. Thirty-three of their 35 patients had aggressive and metastatically efficient cancer (18 ovarian, 11 colorectal and four peritoneal mesothelioma). Not only would these invasive cancers be difficult or impossible to adequately cytoreduce, but most will develop systemic disease that will confound any prolongation of survival caused by loco-regional control. Thirty of these 35 aggressive cancers were recurrent and all were extensive. Information regarding the peritoneal cancer index (PCI) was not provided but I suspect from reviewing their table that all patients had a PCI of greater than 20.[1] A quote from a recent manuscript may be appropriate,

> 'For a curative approach to peritoneal carcinomatosis or sarcomatosis, the malignancy should be minimally invasive so that the peritonectomy procedures can provide a margin of excision. If the cancer is of moderate to high grade by histology, minimal invasion comes by definitive treatment early in the course of the disease. . . . Desperate attempts to palliate patients with large volume peritoneal carcinomatosis or sarcomatosis by intraperitoneal drug delivery are associated with high complication rates, no benefit to the patient, and high cost of health care dollars.'[2]

I agree with these authors regarding the cause of the 54% morbidity. It results from the demanding, even heroic, surgery that the management of peritoneal surface malignancy requires. No evidence to suggest that hyperthermic perfusion added to the complication rate is presented here or in other publications.

There is one lesson in cytoreduction I learned the hard way, and this group is also learning from experience. When the patient and the surgical oncologist are pushed to the limit, a diverting ostomy may be 'the better part of surgical valour'. The judicious use of the time-honoured diverting and decompressing ileostomy may have reduced the morbidity to less than half by eliminating fistula, anastomotic leak, intestinal necrosis and prolonged ileus. Closure with a second look at 6–9 months is routine in about one-third of our patients.

I disagree with these authors regarding the need for further clinical trials. These management strategies work, but the learning curve of 18 months and 35 patients is insufficient to claim expertise. To provide the greatest benefit at minimal cost to patients and providers, referral centres that commit themselves over many years to a high level of competency are mandatory. Knowledgeable patient selection and a high level of surgical oncology skill will take many years of practice.

I congratulate this group on their early efforts in this important new component of gastrointestinal and gynaecological malignancy.

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