

Hyperthermic Intraperitoneal Chemotherapy

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Surgery for Peritoneal Carcinomatosis from Colorectal Origin : Techniques and Limitations

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Incidence and mechanisms

Colorectal cancer can give rise to peritoneal carcinomatosis (PC) by different mechanisms. Advanced (T3 or T4) tumors can cause PC by direct invasion of the peritoneum or shedding (exfoliating) of cells from the tumor's surface. When peritoneal washings from colon cancer patients are analysed with molecular techniques (RT-PCR), micrometastatic cells can be detected in up to 24% of patients (1). Loose cells are transported throughout the abdomen by the physiological peritoneal fluid flow. The diaphragm and greater omentum, where absorption of particulate matter occurs, are therefore frequent locations of PC.

Secondly, PC can be caused by inadvertent tumor spread during surgery from a primary colorectal cancer. The incidence of tumor seeding during curative resection of colorectal cancer varies from 3-28% (2).

Most patients with PC, however, are treated in the context of locally recurrent disease. In a small proportion of colorectal cancer patients, the peritoneal surface is the only site of recurrent disease. In a recent review, the incidence of (PC) in colorectal cancer patients was 13% (3). In that series, a total of 80 patients had localized disease in the absence of systemic metastases, representing 3 per cent (80 of 2756) of the study population. Calculations made in the Netherlands suggest that in that country, approximately 200 patients per year with colorectal cancer would be a candidate for debulking surgery for PC. Assuming a comparable incidence in Belgium, no more than 125 patients per year would require surgery.

Pathophysiology of peritoneal carcinomatosis

Despite the clinical importance of the condition, PC has received relatively little attention in the basic science literature. The rapidly evolving knowledge about the

metastatic process in human cancerogenesis can, however, be applied in part to the mechanisms giving rise to PC.

Since the original description of the 'seed and soil' hypothesis by Paget, the importance of a specific host environment has been recognised as a key factor in the development of tumor metastasis. The peritoneal cytokine, adhesion molecule and growth factor environment largely determines the growth of cancerous implants on the peritoneal mesothelium. This environment undergoes important changes following both open and laparoscopic surgical interventions (4). Surgical injury to the peritoneum triggers the mesothelial cells and peritoneal fibroblasts to an inflammatory response involving the release of a series of cytokines (IL-1, IL-6, TNF-alpha), growth factors (FGF, EGF, VEGF) and chemotactic factors (5). Mesothelial cells were also shown to produce several adhesion molecules, P-cadherin appearing to be the dominant one (6). Several of these factors are known to stimulate tumor growth. Indirect evidence for this mechanism is supplied by experiments aiming to avoid or interfere with the mesothelial inflammatory response. In an *in vitro* assay, Alkhamesi *et al.* demonstrated a significant decrease in peritoneal ICAM-1 expression and tumor cell adhesion by the administration of heparin (7). SHAHEEN *et al.* recently reported that administration of antibodies against the VEGF and EGF receptors significantly decreased tumor vascularity, tumor growth, and ascites formation in a mouse PC model (8).

The development of PC involves a number of well defined steps : shedding and transport of loose cancer cells, adhesion to the mesothelial layer, and invasion of the peritoneum and subperitoneal tissue. Adhesion of cancer cells to the mesothelial lining is mediated by a complex interaction of adhesion molecules. Although the precise mechanisms are not fully understood, several molecules have been reported to play a role in tumor-

mesothelium interaction including ICAM-1, CD44, and the integrin superfamily (9-11). Tumor adherence is rapidly followed by a destruction of the mesothelial layer characterized by tumor-induced apoptosis of mesothelial cells, mediated at least partly by a Fas-dependent mechanism (12). Once the peritoneal barrier has been invaded, further growth of peritoneal metastases occurs into the submesothelial connective tissue.

Natural history of PC

Limited data are available concerning the natural evolution of untreated or palliatively managed PC from non-gynecological origin. The French multicenter EVO-CAPE 1 study prospectively followed 370 PC patients, 118 of whom were from colorectal origin (13). Palliative chemotherapy was given to 46 (39%) of these patients. The median survival of colorectal cancer cases was 5.2 months, a figure resembling other reported outcomes (14).

Most of these patients already have or will ultimately develop systemic disease. Based on the clinical results of cytoreductive surgery, a small subgroup of patients exists with isolated PC and absent or late occurrence of distant disease. Undoubtedly, genetic profiling techniques will in the near future demonstrate a specific genotype that correlates with tumor behavior in this subgroup of patients.

Should patients with PC undergo surgery? Theoretical Considerations

Debulking surgery with or without the addition of intraperitoneal chemotherapy is an undertaking that, apart from the postoperative risk, entails considerable functional and quality of life consequences. Any survival benefit should therefore be carefully weighed against the individual patient's history, extent of disease, and expectations. Theoretically, the following considerations can be formulated :

1. Arguments in favor of a surgical approach

- a. In a subset of PC patients with pseudomyxoma peritonei, the natural history of the disease with slow accumulation of mucinous ascites rarely if ever gives rise to distant metastases and even repeated surgeries can result in a prolonged disease stabilization.
- b. It has been shown that complete (R0) resection is feasible in a proportion of patients. Achievement of a complete resection results in a clear survival advantage. Data from the Dutch randomized trial in colorectal cancer PC patients suggest that 18% of patients survive beyond 3 years after surgery.

- c. Symptomatic patients (ascites or subobstruction) are usually effectively palliated by surgery. More specifically, ascites does not recur following hyperthermic chemoperfusion.
- d. Systemic chemotherapy is relatively inefficient in patients with PC. From a pooling of 3825 trial patients with metastatic colorectal cancer patients treated with 5-FU based chemotherapy, the presence of PC proved to be an independent unfavorable prognostic factor (15).
- e. It is well known from cancer biology that systemic adjuvant chemotherapy will be much more efficient if the total mass of malignant cells is maximally reduced.

2. Arguments against a surgical approach

- a. In the only randomized trial in PC patients from colorectal origin, patients in the chemotherapy alone arm were treated with a regimen (5-fluorouracil) that is no longer comparable with modern second and third line agents that achieve a median survival up to 20 months in the palliative setting.
- b. Although the surgical literature is abundant with triumphant reports of a 'curative' approach of PC using surgery, in reality a long term cure is rarely achieved even in patients with low grade pseudomyxoma. It is better to define a good outcome as prolonged stable disease or clinical remission rather than 'cure'. Moreover, the use of the UICC R stage is often inappropriate or misleading, in that even an optimal cytoreduction with < 1 mm nodules remaining represents an R2 resection.
- c. Ascites and subobstruction have been shown to represent adverse prognostic variables in a number of retrospective series of debulking for PC.
- d. Finally, one should keep in mind the words of Cady : 'in the world of surgical oncology, Biology is King ; selection is Queen, and the technical details of surgical procedures are the Princes and Princesses of the realm'.

It is clear from the above that the decision to proceed to surgery should be the result of a multidisciplinary approach and be thoroughly discussed with the patient .

Rationale for intraperitoneal chemotherapy

The main rationale for intraperitoneal (ip) administration is based on the pharmacokinetic advantage conferred by the peritoneal-plasma barrier, allowing to administer much higher cytotoxic drug doses with less systemic absorption compared to intravenous (iv) administration. Numerous pharmacokinetic studies have shown a mean peritoneal/plasma area under the curve (AUC) ratio ranging from 6-1400 following ip drug

administration (16-19). Interestingly, this pharmacokinetic advantage remains unchanged following peritonectomy procedures (20). In addition, experimental work has confirmed a pharmacodynamic advantage of ip versus iv 5-FU administration, with significantly higher tumor drug concentrations following ip instillation (21). In general, however, tumor tissue penetration of cytotoxic drugs is restricted to 3-5 mm even when combined with hyperthermia and nodules larger than 5-10 mm are therefore unlikely to be completely sterilized by ip therapy (22).

Rationale for hyperthermia

A detailed discussion of the molecular and cytological effects of hyperthermia is beyond the scope of this paper. Interested readers are referred to an excellent recently published review (23). Briefly, the rationale for the addition of hyperthermia is based on 1. the selective antitumoral effects of hyperthermia ; 2. synergism with both radiation and chemotherapeutic drugs ; and 3. modulation or reversal of drug resistance.

Combined cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) : general aspects

The cytoreduction procedures for PC involve a stepwise resection of involved organs and peritoneal surfaces aiming to reach a macroscopically complete debulking or, when this is unfeasible, resection of all nodules greater than 5 mm in diameter. Technical details of the procedure have been adequately provided by Sugarbaker and involve the use of high power ball tip coagulation in order to facilitate peritonectomy from the diaphragmatic surfaces (24-27).

Considerable variation exists in the description of different technical aspects of the hyperthermic perfusion. Generally, following cytoreduction one or more Tenkhoff-type inflow drains and three multiperforated outflow drains are placed together with temperature probes ; chemotherapy is added to the perfusate (usually peritoneal dialysis solution) once a temperature of 41-44° Celsius is reached inside the abdomen. Perfusion can be performed following temporary closure of the abdomen or with an open abdomen (coliseum) technique, covering the abdomen with a plastic sheet and evacuating drug vapor to protect the OR personnel. Proponents of the latter technique claim better drug distribution by continuous manipulation of the abdominal organs. Closed perfusion, on the other hand, has the advantage of increasing intraabdominal pressure which could lead to increased convection-driven drug penetration of macromolecular drugs such as TNF. Consensus is lacking as regards the optimal target temperature. Intraabdominal temperatures ranging from 41-44°C

have been described ; both toxicity considerations and data from in vitro experiments warrant a mild to moderate hyperthermia not exceeding 43°C in most cases. Moreover, important variations are present in the published series concerning the duration of perfusion, type and administration of drug, carrier solution, and perfusate flow.

Mitomycin C remains the best studied cytotoxic drug in association with HIPEC ; it is very active against colon cancer cell lines and moderately toxic. Platinum compounds such as oxaliplatin are also frequently used due to their demonstrated activity in systemic second line treatment of colorectal cancer, but have a more pronounced toxicity.

Procedure steps during HIPEC

Cytoreduction for PC is largely similar to any major abdominal surgery, but some technical aspects are specific to the procedure and will be highlighted in more detail. Personally, I try to perform the operation in a standard order :

1. Verification of resectability
2. Mobilization of bowel package
3. Omentectomy +/- spleen, pancreatic tail
4. Peritonectomy LUQ, RUQ
5. Cytoreduction liver hilus ; lesser omentum
6. Peritonectomy pelvis +/- posterior exenteration or (U)LAR
7. Abdominal wall peritonectomy

Since the complete procedure usually takes at least 8 hours, careful measures should be taken to prevent hypothermia and vascular or nerve injury caused by faulty positioning. Also, surgery should be swift but as bloodless as possible with liberal use of ultrasonic shears, argon coagulation, CUSA, and vascular staplers.

1. Verification of resectability

The procedure is abandoned when :

- Systemic metastasis is present in the liver (most PC patients will have peritoneal implants on the Glisson capsule)
- The remaining length of small bowel and/or colon is insufficient to preserve digestion.

Dilatation or invasion of the ureters or iliac vessels is usually not a contraindication for surgery.

2. Mobilization of the bowel package

The colon and small bowel are completely mobilized to ascertain the remaining healthy bowel length.

3. Cytoreduction left Upper Quadrant

The omentum is removed alone or en bloc with the colon or spleen. When possible, the spleen should be preserved since splenectomy increases postoperative morbidity. Some patients will need resection of the pancreatic tail.

Peritonectomy is performed over the left diaphragm. This is straightforward over the muscular part, where normal electrocoagulation is sufficient. Over the tendinous part, removal of all tumor often requires resection of a part of the diaphragm with primary closure. In this case, care should be taken to avoid spilling of tissue in the pleural cavity. Routine chest drainage should be performed following partial diaphragm resection.

4. Cytoreduction right diaphragm

The liver should be thoroughly mobilized both laterally, inferiorly and superiorly with skeletonizing the inferior vena cava. A peritonectomy can then be performed along the lateral, posterior, and inferior aspect of the right upper abdomen. Care should be taken not to damage the right adrenal gland whilst performing the peritonectomy over its surface.

5. Cytoreduction of the liver hilus and lesser omentum

Usually, in these locations complete cytoreduction is not possible. Cholecystectomy is performed along with peritonectomy over the hepatogastric ligament. Often, however, tumor extends along the insertion of the round ligament and along the liver fissures deep into the liver tissue rendering complete (R0) removal impossible. The same applies for the layer of PC covering Glisson's capsule, usually treated with high power argon fulguration.

The stomach is usually only involved along the antrum. Cytoreduction around the stomach involves ligation of the right and left gastroepiploic artery and right gastric artery. When approaching the lesser omentum, care should be taken not to damage the left gastric artery. Although Sugarbaker has described a technique to combine cytoreduction with total gastrectomy when the stomach is extensively involved, I prefer not to perform gastrectomy since this dramatically worsens the patient's quality of life and almost certainly will not alter the prognosis.

6. Cytoreduction fo the pelvis

Along with the omentum and diaphragm, the pelvic peritoneum is preferentially affected in PC patients and most patients will require at least a posterior exenteration.

In approximately 50% of patients a low or very low colorectal anastomosis is possible, always with a deviat-

ing ileostomy. Peritonectomy over the bladder and pelvis minor is usually straightforward, but care should be taken not to devascularize the bladder. With unilateral ureteral involvement, reimplantation on the contralateral ureter is easy and safe, even without use of a double J stent.

Toxicity and complications of cytoreduction with HIPEC procedures

Mortality ranges from 3-8% in the various papers, with a morbidity rate ranging from 20%-50% (28, 29). It is likely, that the postoperative complication rate mainly depends upon the extent of the procedure. Although minor side effects such as prolonged paralytic ileus are a concern, systemic or local toxicity of the chemotherapy itself is usually limited although severe abdominal pain or bone marrow depression can occur. Depending on the applied temperature, some degree of small bowel edema is usually noted. When oxaliplatin is used for HIPEC, severe hyperglycemia and acidosis can develop because this agent can only be administered in a 5% dextrose solution. Early administration of insulin by infusion pump and regular blood glucose assay are therefore essential.

In a review of 200 patients by Stephens et al, the postoperative complication rate was associated with the extent of surgery and not to variables related to the administration of chemohyperthermia (30). A similar conclusion was proposed by GLEHEN *et al.*, who found duration of surgery and carcinomatosis stage to be the most common predictors of morbidity in an analysis of 217 HIPEC procedures (31). Others have, however, noted increased morbidity and mortality with rising intraabdominal target temperature (32).

One of the main causes of postoperative serious morbidity following HIPEC is the occurrence of an anastomotic leak. The incidence of a digestive fistula was 15% in the randomized trial by Verwaal and 8.3% in the meta-analysis by Glehen. Most patients will have at least 1 bowel anastomosis performed, and the effects of chemohyperthermia on anastomotic healing are therefore important to note. Intestinal anastomoses are usually constructed after the perfusion in order to facilitate uniform distribution of heat and drug. In animal studies, anastomotic healing is impaired following intraperitoneal mitomycin C, but not following 5-fluorouracil at normal temperature (33, 34). Local hyperthermia in itself has no adverse effects on rat anastomotic healing (35). When combined with preoperative irradiation, however, hyperthermia increases anastomotic complications in a rat model (36).

Even at moderate temperatures, HIPEC during 90 minutes invariably causes edema of the small bowel wall. In order to avoid anastomotic leaks, it is therefore probably

safer to construct small bowel anastomoses before the perfusion starts. A recent retrospective analysis confirms that this is indeed a safe option (37). In this series of 203 patients, bowel complications were not increased when primary unprotected anastomoses were performed before chemoperfusion with the closed technique.

Clinical results of HIPEC for PC of colorectal or appendiceal origin

The use of hyperthermic intraperitoneal chemoperfusion has been reported in numerous small case series, one prospective randomized trial comparing cytoreduction + HIPEC + adjuvant chemotherapy versus palliative chemotherapy alone, and one recent multicenter meta-analysis of non randomized data.

Most of the 13 reported non randomized phase II series concern small patient numbers and report 3 year survival rates ranging from 20-60% (38-51).

These results warranted a randomized trial, ultimately reported by Verwaal et al in 2003 (52). They randomized 105 patients with PC of colorectal origin to either systemic 5-FU based chemotherapy and palliative surgery or cytoreduction / HIPEC followed by systemic chemotherapy. Perfusion was performed during 90 minutes at a temperature >40°C using mitomycin C. Median survival was significantly better in the HIPEC group (22.3 months vs 12.6 months ; p = 0.032).

Survival was significantly worse if more than 5 abdominal regions were affected or when resection was macroscopically incomplete (R0).

Recently, a multicenter retrospective series of 506 patients with PC of colorectal cancer (appendiceal cancers were excluded) treated with cytoreduction followed by early postoperative chemotherapy, HIPEC, or both was reported by GLEHEN *et al.* (53). Overall, median survival was 19.2 months, very similar to the result reported by Verwaal with the use of HIPEC. Survival was significantly better when complete cytoreduction could be achieved (32.4 months versus 8.4 months, p > 0.001). Lymph node and liver involvement, neoadjuvant chemotherapy, and poor histological grade adversely affected survival. Interestingly, survival results were not different with either early postoperative chemotherapy or HIPEC alone, but improved with the combined use of both modalities.

Unresolved issues and future perspectives

One of the key issues concerning the use of debulking with HIPEC is the contribution of the hyperthermic perfusion itself versus the role of maximal cytoreduction. Given the fact that most clinical trials have shown a clear relationship between both the preoperative tumor burden and the extent of cytoreduction on one hand and survival

on the other hand, one may hypothesize that the improved survival shown in various trials depends mainly on the cytoreduction itself. To address this issue, a randomized trial comparing debulking with versus without HIPEC using cisplatin and early postoperative intraperitoneal chemotherapy was recently initiated by the National Cancer Institute (protocol NCI 03-C-0085). Future clinical studies will address the role of HIPEC in other cancer types involving peritoneal surface spread, with ovarian cancer and peritoneal mesothelioma representing theoretically ideal candidates.

Recommendations and conclusion

Extensive surgery followed by HIPEC can offer a survival advantage in selected patients with PC from colorectal origin. The efficacy of the procedure mainly depends on the completeness of cytoreduction, and it is not yet clear what the relative contribution of the hyperthermic chemoperfusion in itself represents. Since survival mainly depends on the extent of both the initial disease and the completeness of cytoreduction, early referral to an expert center is mandatory rather than taking this step after multiple forms of chemotherapy have failed.

Future randomized trials will address this issue and redefine the role of HIPEC in the era of modern biologicals.

When the different genotype of PC only patients compared with systemic disease is confirmed, better selection of patients will be achieved with the use of genomic profiling on biopsy material.

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