# Cytoreductive surgery and intraoperative intraperitoneal hyperthermic chemotherapy in patients with peritoneal carcinomatosis of colorectal origin

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**The median survival in patients with peritoneal carcinomatosis from colorectal adenocarcinoma is, with conventional approaches, only about six months. Combined treatment consisting of maximum cytoreductive surgery plus intraoperative intraperitoneal hyperthermic chemotherapy has been shown, albeit in small non-comparative series, to increase disease-free survival and overall survival, compared with previous series. Further, a randomized trial has demonstrated better results (a median survival of 22.4 months) with cytoreduction plus intraperitoneal chemotherapy compared with conventional chemotherapy. Technical considerations, infrastructure requirements and possible complications imply specialized centres and staff. Surgery consists of peritonectomy of affected areas and fulguration of all macroscopic lesions. Intraperitoneal chemotherapy must reach all parts of the peritoneal cavity and the temperature of the hyperthermic procedure must be maintained between 42-44ºC. Three prognostic factors associated with this procedure are: pathologic tumour grade, peritoneal carcinomatosis index, and cytoreductive surgery grade.**

*Key words:* intraperitoneal chemotherapy, hyperthermia, colorectal cancer, peritoneal carcinomatosis.

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## INTRODUCTION

Stage IV colorectal cancer (CRC) is a rapidly fatal disease, with a five-year survival of 10% and a median survival of 14.4 months. In association with peritoneal carcinomatosis (PC) this time is reduced to just 6.7 months, compared with 18.1 months when no PC is present[1,2]. At the time of diagnosis, the peritoneal surface is involved in 10-15% of cases, and peritoneal involvement in recurrent disease is present in 40-70% of cases. Extended disease is limited to the peritoneal surface in just 5-8% of all colon cancers and 10-35% of patients who relapse after treatment[3-6].

Those patients who have peritoneal dissemination of CRC have a survival of less than six months with conventional therapeutic regimes (palliative excision of the tumour and systemic chemotherapy). Spratt et al were the first to report the use of intraperitoneal hyperthermic chemotherapy (IPHC) in 1980[7].

In 1982 Paul H. Sugarbaker suggested that involvement of the peritoneal serous membrane represents a locoregional stage of the disease, with the implanted tumour masses remaining limited to the peritoneal cavity for a long time. Sugarbaker's technique consisted of radical cytoreductive surgery with peritonectomy, followed by treatment of the microscopic residual disease with direct IPHC. Since then several groups have used and evolved this technique, with the consequent improvement in results. Five-year survival for patients with lung or liver metastasis of CRC who have undergone complete resection is 30-35%[8-10]. Likewise, patients with PC who are treated with complete macroscopic resection of the disease and IPHC nowadays have a five-year survival of 34%[11].

In this review we describe the underlying pathogenesis and rational basis for this therapeutic approach, as well as the options, results and complications as reflected in the medical literature.

## PATHOGENESIS AND RISK FACTORS

The pathogenic mechanism of implantation of CRC tumour cells in the peritoneum is still unknown,

although several causes have been postulated: a) intraperitoneal dissemination of free tumour emboli as a consequence of invasion or perforation of the serous membrane[12]; b) blood loss, sectioned lymph nodes or tissue fluid in the surgical field which may contain tumour cells in up to 90% of cases[13]; c) late dissemination in very advanced cases, as occurs with other primary tumours, and d) the presence of isolated cells in the peritoneal cavity, still in CRC stages I and II, prior to tumour excision[14].

Up to 10% of patients without macroscopic PC have peritoneal lavage positive for neoplastic cells[15]. Several risk factors have been implicated for this positivity: grade T primary CRC, the presence of liver metastasis, lymphatic invasion, more than 20 ml of ascites, ulcerated lesions with no clear borders and involvement of surrounding tissue[16]. In the revision by Sadeghi et al, PC was 25 times more common in T3 and T4 patients compared with T0 and T1 patients, and nine times more common in N1 compared with N0 patients[6].

The presence of PC in patients with primary T1 and T2 tumours, however, suggests the existence of haematogenous dissemination controlled by the interaction of organ-specific receptors between tumour cells and the sites of metastasis[14,17]. These contradictory findings show that the true pathogenesis of PC of CRC origin is not fully understood and that not all the risk factors are clinically important.

## CLINICAL AND DIAGNOSTIC EVALUATION

Symptoms indicative of PC are ascites and obstruction of the small intestine[18]. Preoperative diagnosis of PC is very difficult, with lesions smaller than 2 cm on ultrasound examination or 5 mm on computed tomography (CT)[19]. A complete preoperative CT of the chest, abdomen and pelvis, with maximum oral and intravenous contrast enhancement, is useful for treatment planning, with a sensitivity of 70% for the diagnosis of lesions above 2 cm but only 28% for lesions smaller than 5 mm[20]. Other authors have failed to find CT useful to establish a treatment plan[21]. However, CT has proved beneficial for the quantification of the degree of disease in the peritoneal cavity in patients with mucinous adenocarcinoma, enabling selection of patients who would benefit from cytoreduction and IPHC[22].

## PROGNOSTIC FACTORS AND STAGING OF PERITONEAL CARCINOMATOSIS

Besides CT, three prognostic indicators of malignant peritoneal involvement are currently used to select patients who will benefit from cytoreduction and IPHC: a) anatomical and pathological study of the primary tumour, to determine the extent of invasion; b) the peritoneal cancer index (PCI); and c) the degree of cytoreduction achieved or desired.

### Anatomical and pathological study of the invasiveness of the primary tumour

Well- or moderately-differentiated noninvasive tumours may present extensive peritoneal disease which is completely resectable with peritonectomy, as well as having a low likelihood of lymph node involvement or distant haematogenous dissemination. The mucinous type of tumour appears to have a much worse prognosis than the intestinal type[23,24].

### Peritoneal cancer index

The PCI is a prognostic index calculated from the size of the peritoneal implants and their distribution in the peritoneal cavity. The index is used for planning the treatment of the implants. Two PCI systems have been developed. The first, by Gilly et al[25], is based on the size of the peritoneal nodes, and the second, by Gómez-Portilla et al[26], in addition to the size, also takes into account the tumour mass and the localization of the PC within the different anatomical regions of the abdomen.

Gilly's PCI depends mainly on the dimension of the peritoneal nodes:

1) Stage 0: no macroscopic disease.
2) Stage I: granular lesions each smaller than 5 mm limited to one part of the abdomen.
3) Stage II: granular lesions each smaller than 5 mm spread throughout the peritoneal cavity.
4) Stage IV: granular lesions with a maximum diameter between 5 mm and 2 cm.
5) Stage V: nodular lesions larger than 2 cm in greatest dimension ("cake lesions").

Using this scale, Shepherd et al found a median survival in Stage I cancer of 12.5 months compared with 2.7 months for patients with Stage IV cancer[27]. Treatment of these subgroups, which have a better prognosis, by cytoreduction and IPHC is the current challenge.

The PCI classification by Gómez-Portilla is much more precise, though at the same time more difficult to calculate. The size of the nodes (TN) is divided into four groups, using the size of the largest node but not their number (TN-0, no tumour in any region; TN-1, nodes smaller than 5 mm; TN-2, nodes from 0.5-5 cm; TN-3, nodes larger than 5 cm or the confluence or superposition of nodes which surpass this size). Furthermore, the abdomen is divided into 13 anatomical regions and the TN is applied to each of these regions, giving a final PCI of 0-39 (fig. 1). Using this classification, Sugarbaker found that patients with a PCI<11, and after combined treatment, had a median survival of 48 months and an actuarial 5-year survival of 50%[28]. Other authors have shown the usefulness of the PCI to predict the therapeutic benefit and survival in patients with sarcomatosis and peritoneal mesothelioma, respectively[29,30].

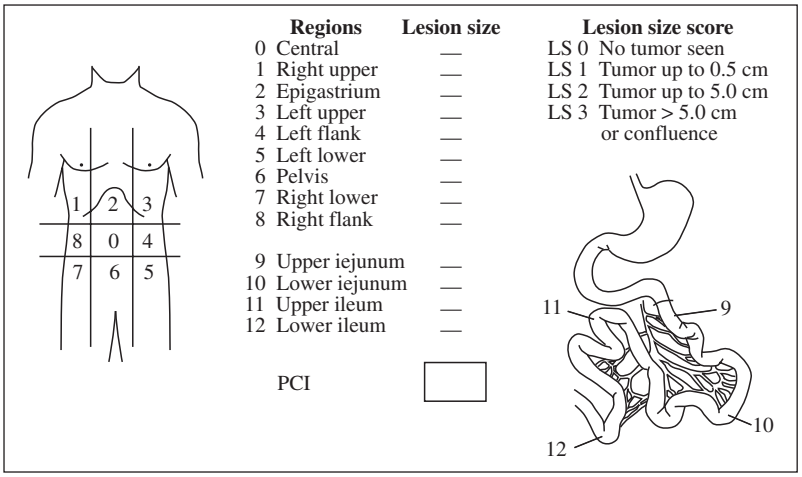


**Fig. 1. Peritoneal cancer index (PCI) calculated by the inter-relation of the tumour size in each of the anatomical regions.**

### Grade of cytoreduction

The grade of cytoreduction (GCr) remains undetermined until the end of the surgical procedure. Consequently, it is of less interest when planning the treatment strategy. A GCr-0 indicates that no peritoneal disease remains; GCr-1, that a few granular lesions smaller than 2.5 mm remain; GCr-2, when the residual lesions are between 2.5 mm and 2.5 cm; and GCr-3, when the nodes are larger than 2.5 cm or there is a confluence of unresectable smaller nodes. GCr-0 and 1 are considered as complete cytoreductions, whereas GCr-2 and 3 are considered incomplete.

Verwaal et al, from the Dutch PC group, have recently described the Simplified Peritoneal Cancer (SPC) score. This score is calculated by multiplying the number of abdominal regions affected (divided into seven regions, i.e. pelvis and sigmoid colon, lower right quadrant, small intestine and mesenterium, epiploon and transverse colon, stomach and subhepatic area, right subphrenic area, and left subphrenic area) by the amount of tumour mass present in each region, stratified as 0 (no residual disease), 1 (less than 20 mm), 2 (20-50 mm) and 3 (more than 50 mm). Addition of the score for each region provides the overall SPC score, which ranges from 0-21 and which is also of prognostic value[31].

## SELECTION OF PATIENTS FOR TREATMENT

This type of combined treatment is aggressive for the patient and expensive for society. Treatment should therefore only be considered in patients with an otherwise good general state of health and who have, in theory, cancer limited to the peritoneum. Adequate patient selection is thus essential to achieve long-term survival benefits. For example, in patients with PCI>20, Sugarbaker et al reported a median survival less than 12 months, with no patient surviving beyond five years, and a P>20 is often associated with increased morbidity and mortality[28].

The ideal conditions are:

1) *Small peritoneal disease* (PCI<21 and the possibility of complete cytoreduction, i.e., GCr-0 or 1),

2) *Immediate treatment;* i.e., in one operation and after diagnosis of the PC status.

3) *Absence of distant systemic disease*, although for this point, the presence of limited distant disease resectable to a rigorous level of R0 is not contraindicative of cytoreduction[11]; Carmignani reported a significant benefit in survival after resection of distant metastasis and cytoreduction and IPHC for PC (20.6 months compared with 9 months)[32].

4) *Absence of symptoms of intestinal obstruction*, due to the associated consequences (e.g., malnutrition, risk of intestinal perforation, intraabdominal abscess, postoperative fistula) and because it is frequently associated with multifocal involvement of the lumen of the gastrointestinal tract, although in 10-30% of cases it may be due solely to the adherence syndrome[33].

## RATIONAL BASIS FOR CYTOREDUCTION AND IPHC

### Results with classic treatment (surgery and systemic chemotherapy)

The natural history of PC of CRC origin is associated with mean and median survival rates of 6-7 and 5-9 months, respectively, within a range that varies from one month to five years, depending on the PCI stage. Because it is considered an extended disease, it has been treated with systemic chemotherapy, with surgery limited to palliate the obstruction. Most patients have been treated with intravenous 5-fluorouracil (5-FU) and leucovorin, though no improvement in survival has been shown over the last 20 years. Despite the recent introduction of new cytostatic agents, such as

oxaliplatin or irinotecan, the results remain poor, with mean survival rates around 20 months and response rates of 25% in the best cases. The main problem is that the peritoneal metastases are not vascularized, and it is therefore very difficult for systemic chemotherapy to reach the cells of these metastases.

### Basis of cytoreductive surgical treatment: peritonectomy

Peritonectomy, both visceral and parietal, is absolutely necessary to achieve complete cytoreduction (GCr-0 or 1). Surgery is undertaken in the areas where the tumour is visible in order to eliminate all the macroscopic disease. Small nodes are eliminated by electroevaporization with an electrocautery device. Depending on the regional distribution, the volume and the depth of invasion of the PC, one or more of the following peritonectomy procedures may be necessary: a) greater omentectomy with splenectomy, b) peritonectomy of the upper left quadrant, c) peritonectomy of the upper right quadrant, d) lesser omentectomy with cholecystectomy, e) pelvic peritonectomy with resection of the sigmoid colon and rectum, and f) antrectomy. The greater omentum is the only area that is systematically completely excised. The procedure is technically very laborious and lengthy, but it nevertheless represents the first essential phase of combined therapy[34].

### Dose modulated intraperitoneal (locoregional) hyperthermia chemotherapy

Weisberger was the first to describe the technique, in 1955, in patients with ovarian cancer[35]. The direct exposure of the tumour to cytostatic drugs has shown that intracavitary administration results in a concentration some 18-620 times greater than that obtained by administration in blood and with much less systemic toxicity[36-38]. However, these drugs only penetrate the tumour nodes to 1 mm, although the addition of hyperthermia has enabled the treatable tumour margin to be increased to 2.5 mm.

The greater intraperitoneal concentration of cytostatic agents, and thus their greater efficacy, is due to the low rate of systemic clearance resulting from the so-called "peritoneal-plasma barrier", presumably formed by subperitoneal connective tissue and capillary blood vessel walls, although its physical nature has not yet been shown. Both structures afford resistance to the transit of high molecular weight molecules, and together with the affinity for membrane lipids and hepatic clearance, they define the area under the curve (AUC), which is the relation between the intraperitoneal and the plasma levels of a drug; the most commonly used drugs, mitomycin C and 5-fluorouracil, have AUC values of 75-80 and 250-1,400, respectively[39] (table 1).

TABLE 1. **Values for the area under the curve (AUC) of peritoneal exposure of the different drugs used to treat peritoneal cancer**

| Cytostatic agent | Area under the curve (AUC) |
|---|---|
| Mitomycin C | 75-80 |
| 5-Fluorouracil | 250-1,400 |
| Carboplatin | 18 |
| Cisplatin | 12-20 |
| Oxaliplatin | 6-17 |
| Paclitaxel | 1,000 |
| Gemcitabine | 50 |
| Melphalan | 65 |
| Mitoxantrone | 1,400 |
| Irinotecan | 14 |
| Tumour necrosis factor | 4,854 |
| Doxorubicin | 500 |

The local administration of chemotherapy also helps to block the phenomenon of tumour trapping, which consists of: 1) embolization of free tumour cells within the peritoneal cavity, 2) trapping of fibrin in the tumour emboli, and 3) progression of the trapped tumour cells. This physiological fibrosis and adherence develops within 30 minutes of surgery and forms an authentic sanctuary for residual tumour cells. If intraperitoneal chemotherapy is delayed it then becomes ineffective[40].

The adherence syndrome associated with prior surgery generates an uneven and limited distribution of intraperitoneal chemotherapy. It is therefore necessary to spend time undertaking complete adhesiolysis of all visceral structures and the complete elimination of all areas of fibrosis. Another factor that hinders the regular, uniform distribution of chemotherapy in the cavity is gravity; the surgeon must therefore undertake manual uniform intraoperative distribution of the chemotherapy solution[40].

Data exist confirming the advantages of hyperthermia in association with intraperitoneal chemotherapy. Generally, heat has a more detrimental effect on tumour cells than on healthy cells (the more so the less vascularized the tumour), at the same time as it allows penetration of the chemotherapy into the tissues because the interstitial pressure of the tumour mass is reduced[41]. The exact biochemical mechanism of hyperthermia is unknown, but it is thought to induce denaturalisation of the protein membranes and increase vascular permeability. The inactivation of tumour cells begins at 40-41°C, with optimisation at 43°C (the temperature threshold applicable to human tumour cells is 44ºC, since at this temperature thermotolerance is induced and the small intestine would be damaged)[42]. Chemotherapy in association with hyperthermia cannot be tolerated without anaesthesia, and it should always be undertaken intraoperatively[43]. More specifically, the heat exerts a synergistic effect increasing the toxicity of some cytostatic agents, including

mitomycin C, platinum derivatives, tumour necrosis factor alpha, doxorubicin, irinotecan and vinblastin. In the case of mitomycin C, the destruction of hypoxic tumour cells has been shown to increase 40-fold in vitro at 43°C compared with ambient temperature. 5-FU, however, has no synergistic effect in the presence of heat, so that despite its very high AUC it is of no intraoperative use[44].

## THERAPEUTIC STANDARD: THE SUGARBAKER PROTOCOL

Since the appearance of his first reports in 1989, Paul H. Sugarbaker has been the true pioneer in the development of this therapeutic technique, both for treating PC of CRC origin and for PC originating from other types of tumour.

### Cytoreduction: technical aspects of peritonectomy[34]

Laparotomy should initially be xiphoid-pubic. Depending on the extension of the disease, from 1-6 surgical peritonectomy procedures may be necessary, aiming for GCr 0 or 1. Each step usually lasts 2-3 hours. Almost all the series have shown that incomplete cytoreduction (GCr 2 or 3) is accompanied by poor results and the current tendency is not to undertake the technique in these cases. Only those peritoneal areas with visible involvement are resected or destroyed by electrofulguration. The whole small intestine and the mesenterium should be freed for careful inspection[34]. When the implants are in the small intestine, it is necessary to repair the seromuscular layer, which is denuded by electroevaporation. When multiple transmural resections, or resection of several segments are required the risk of recurrence and formation of fistulas is greater. It is therefore advisable to undertake an ileostomy or other type of stoma to minimize the risk of disruption of the anastomosis or enterorrhaphy. Likewise, if involvement is so much that it may, in the medium term, cause a short bowel syndrome, cytoreduction is contraindicated. The treatment of the colon is similar. The open hollow viscera are closed temporally with staples to be treated with IPHC; the anastomoses are undertaken at the end of the intraoperative treatment, thereby acting against the trapping phenomenon in these suture lines.

### Intraperitoneal hyperthermic chemotherapy

The efficacy of IPHC requires bathing the surfaces of all the viscera and intraabdominal walls and maintaining a homogenous temperature, as near as possible to 43ºC. This latter condition requires the presence of a closed circuit to continuously warm and circulate the perfusion liquid. After resection of the whole tumour mass, a Tenckhoff catheter and at least three abdominal aspiration drainages are inserted via the abdominal wall. A thermal sensor is placed at the tip of each drainage tube to provide continuous temperature readings, which should be kept from 42-44ºC, at no time falling below 42°C.

Since the beginning, Sugarbaker has used the open technique, also referred to as the coliseum technique. This procedure allows the surgeon to displace the organs and thereby treat all the surfaces, as well as keeping the correct temperature throughout the 90 minutes the perfusion lasts (fig. 2). The drug most commonly used is mitomycin C, although recent pharmacokinetic studies have shown the benefit of oxaliplatin and irinotecan for CRC. Other groups have developed technical variants for the intraoperative intraperitoneal infusion of chemotherapy[45]. After the intraoperative perfusion is completed, the abdomen is aspirated and emptied, anastomosis is undertaken and drainages placed.

Mitomycin C ____ mg to 2 liters of 1.5 % dextrose peritoneal dialysis solution. Dose of mitomycin C for males 12.5 mg/m$^2$; dose of mitomycin C for females 10 mg/m$^2$.

Use 33 % dose reduction for heavy prior chemotherapy; marginal renal function, age greated than 60, extensive intraoperative trauma to small bowel surfaces or prior radiotherapy.

Send 1 liter of 1.5 % dextrose peritoneal dialysis solution to test the perfusion circuit.

Send 1 liter of 1.5 % dextrose peritoneal dialysis solution for immediat postoperative lavage.

**Fig. 2. Standardized Sugarbaker protocol for the administration of intraperitoneal hyperthermic chemotherapy with mitomycin C.**

### Early postoperative intraperitoneal chemotherapy

Unlike many groups which do not concede much importance to early postoperative intraperitoneal chemotherapy (EPIC), Sugarbaker's protocol includes it. Using the same infusion catheter and drainage tubes, intraperitoneal infusion of 5-FU is done on postoperative days 1-5 (fig. 3).

## TREATMENT COMPLICATIONS

Complications are mainly derived from the aggressiveness of the surgery and the toxicity of the cytostatic agents. The rates of disease vary from 27-55%, with mortality at 0-11%. Moreover, up to 35% of patients require reoperation as a consequence of complications, mostly related with digestive fistulas due to anastomotic dehiscence. Disease is mainly associated with surgical complications, with the tumour load being the

Add to ____ ml 1.5 % dextrose peritoneal dialysis solution (a)
____ mg 5-fluoruracil (650 mg/m$^2$ X ____ m$^2$)
(maximum dose 1,500 mg) and (b) 50 meq. sodium bicarbonate.

Intraperitoneal fluid volume: 1 liter for patients ≤ 2.0 m$^2$,
1.5 liters for > 20 m$^2$.

Instill for 5 consecutive days on ____ through ____ .

Drain all fluid from the abdominal cavity prior to instillation,
then clamp abdominal drains.

Run into abdominal cavity through Tenckhoff catheter
as rapidly as possible the chemoterapy solution.
Dwell for 23 h and drain for 1 h prior to next instillation.

Continue to drain the abdominal cavity after final dwell
until Tenckhoff catheter is removed.

Use 33 % dose reduction for heavy prior chemotherapy,
age greater than 60, extensive intraoperative trauma to small
bowel surface or prior radiotherapy.

**Fig. 3. Standardized Sugarbaker protocol for the administration of intraperitoneal hyperthermic chemotherapy with 5-fluoruracil.**

deciding factor and which determines the duration of surgery, the number of peritonectomies or resections to be done and the number of suture lines. Mortality is related with advanced age and with an intraabdominal temperature kept above 41.5°C[46].

Peripancreatitis is related with intraoperative disruptions, probably inadvertent, of the pancreatic capsule during peritonectomy. Digestive fistulas appear due to extensive lysis of fibrous and, occasionally, tumour adherences present between the loops of the small intestine and to the number of segmental resections and anastomoses required for reconstruction, as well as from the additional deleterious effect of the hyperthermia. Ostomy and deferred reconstruction are recommended. Another frequent complication is postoperative bleeding, which often requires transfusion. Haematological toxicity (WHO grade III or IV) is probably usually due to increased absorption of the cytostatic agent via the peritoneal-plasma barrier[47].

Respiratory complications are also common. Chen et al reported 86% morbidity related with the pleuro-pulmonary system. Bibasal atelectasis (76%) and pleural effusion (64%) were the most common complications, associated with mitomycin C toxicity, surgery and abdominal hyperpressure derived from the volume of liquid introduced into the peritoneal cavity. These complications mostly resolved with positive pressure ventilation or simple thoracocentesis, without the requirement for reoperation. Other less frequent complications included noncardiogenic pulmonary oedema (24%), pneumonia (5%) and pneumothorax (5%)[48].

Acute renal failure is probably due to transitory intraoperative hypoperfusion associated with increased absorption of nephrotoxic cytostatic agents, especially mitomycin C and cisplatin. The incidence of acute renal failure is 2-3%.

## RESULTS

The paramount aim is complete cytoreduction of all visible peritoneal implants (GCr 0 or 1). Marcus et al reported results of overall survival at two years in 58 patients with PC who underwent cytoreduction and standard adjuvant systemic chemotherapy. Patients who underwent complete resection had a better survival than patients who had residual macroscopic disease, but with a generally high rate of peritoneal relapse at five years[49].

The first attempts to treat microscopic peritoneal disease after cytoreduction were based on EPIC, with infusion of mitomycin C on the first postoperative day and 5-FU on days 2-5. In 2001, the Institut Gustave-Roussy published a series of 64 patients with PC of CRC origin treated by complete cytoreduction, 19 with distant metastasis (mostly hepatic) which were also resected. Their rates of disease-free survival at two and five years were 54.7% and 18.4% (overall survival rates of 60.1% and 27.4%) respectively. Negative prognostic factors were the presence of nonperitoneal metastasis and a PCI>16[50]. In 1996, Sugarbaker et al reported their series of 64 patients treated with an identical protocol. Complete cytoreduction was only possible in 36 cases, with a five-year survival of 37% compared with 0% for the group that had surgery with results of GCr2 or 3[24]. Considering that the American series did not include patients with liver metastasis, the results are superimposable. Similar results were reported by Culliford et al for a series of 64 selected patients with PC of appendix or colorectal origin who received treatment with floxuridine and leucovorin in a deferred intraperitoneal regimen; with a median survival of 34 months, 54% of the 19 patients with complete cytoreduction lived five years, compared with just 16% of the others[51]. As demonstrated by Elias, cytostatic agents only act on the free surfaces of the denuded peritoneum, with the inevitable recurrence in trapping areas; his results are those of an isolated series and do not validate the delayed intraperitoneal method. Surgery alone in such selected patients would probably have achieved similar results (table 2).

No randomised study has been undertaken to compare EPIC with traditional systemic chemotherapy. The French group studied a group of patients with radical surgical cytoreduction and postoperative chemotherapy, randomised to EPIC or no EPIC, but were able to include just 35 of the 90 patients, with similar two-year survival results in both groups (60%), a zero mortality in the control group versus 18.7% in those who received EPIC and a greater prevalence of liver metastasis in the experimental group. There was thus a therapeutic advantage, though not reported probably due to the small sample size, in favour of the patients treated with EPIC[52].

Nevertheless, EPIC, with the simple infusion of cytostatic agents into the peritoneal cavity via a catheter

TABLE 2. **Results of series of radical cytoreductive surgery and early postoperative intraperitoneal chemotherapy (Elias and Sugarbaker) and deferred (Culliford)**

| Authors | Number cases | Complete vs. no cytoreduction | Median follow-up | 2 year survival | 5 year survival | Morbidity | Mortality | Notes |
|---|---|---|---|---|---|---|---|---|
| Elias et al (2001) | 64 | 64 / 64 (100%) | 12 months | 60.1/54.7% | 27.4/18.4 % | 54.6% | 9.3% | Liver metastasis in 19 cases (29.6%) |
| Sugarbaker et al (2000) | 64 | 36 / 28 (56.2%) | 12 months | 42% | 20%* | 23.2% | 0% | * Overall survival whole group 5 year overall survival: 37% GCr 0/1; 0% GCr 2/3 |
| Culliford et al (2001) | 64 | 64 / 64 (100%) | | | 28%* | | | * Overall survival whole group Deferred intraperitoneal chemotherapy with fluxoridine and leucovorin |

placed at the time of surgery, is associated with an inadequate and irregular distribution of the drugs throughout the peritoneal serous membrane, which might be responsible for the high relapse rates. This, then, opens the door to treatment with intraoperative intraperitoneal chemotherapy with mitomycin C and adjuvant hyperthermia to enhance its effect (IPHC). For CRC the use of specific new chemotherapeutic agents such as oxaliplatin or irinotecan, with AUC of 14 and 17 respectively (less than mitomycin C), may hold promise for the future. Although the procedure has not yet been standardized –there are multiple variations in the open or closed exposure techniques, drugs used, drug doses, perfusion time and intraabdominal temperature during hyperthermia– the results of series of IPHC are promising and reflect an overall survival of patients with PC of CRC origin of 20% at five years, which with better patient selection could reach 40% in the coming years[38,53,54].

Shen et al have reported the largest series of patients with PC of colorectal origin treated with IPHC (mitomycin C) and cytoreduction, with 77 cases. When GCr 0 or 1 was achieved (in just 48% of the patients), the five-year survival was 34%, with a median survival of 28 months for a 10% mortality[55]. Pilati et al reported their experience with 34 patients with PC of CRC origin treated by complete cytoreduction and IPHC with mitomycin C and cisplatin; the respective rates of overall and disease-free survival at two years were 31% and 10%[56]. Witkamp et al was able to perform complete cytoreduction in 26 of 29 cases treated with intraperitoneal mitomycin C and systemic 5-FU; with a mean follow-up of 38 months, the overall survival rates at two and three years were 45% and 23%, respectively[57]. Beaujard et al used IPHC with mitomycin C combined with surgery in 83 patients with digestive tumours; of these, 27 had CRC with cytoreduction being possible in 21, with a mean survival of 12 months and overall three-year survival of 25%[58]. The most spectacular results, however, have only recently been reported, by Elias et al. In a group of 24 patients who underwent complete resection of the whole peritoneal disease and IPHC with oxaliplatin, the rate of disease-free survival at three years reached 50.8%. Moreover, for the first time the presence of nonperitoneal metastasis had no statistical impact on survival (provided it was completely resected), and only patients with a PCI<24 had a worse survival[59]. Other series reporting fewer numbers of patients are shown in table 3[60-62].

Verwaal et al published the first phase III randomised trial of IPHC with mitomycin C and cytoreduction in comparison with standard treatment in 105 patients with PC or colorectal origin, randomised to a control group who underwent palliative surgery and systemic chemotherapy with 5-FU and leucovorin, and another group who received combined radical therapy. After a mean follow-up of 21.6 months, survival was 43% for the IPHC group (median of 22.4 months) and just 16% for the control group (12.6 months), with a p=0.032, despite the fact that complete cytoreduction (GCr 0 or 1) was only possible in 79% of the patients (39 cases, of which 21 had microscopic GCr 1 disease); the actuarial survival curve at five years suggested values around 20%, which support those seen after phase II trials[63].

Once the therapeutic benefit of these regimens had been confirmed in patients with PC of CRC origin, studies were undertaken to determine whether it was possible to reduce the rate of local recurrence or increase the survival of high risk patients with resected CRC. Scheithauer et al randomised 236 high risk pa-

TABLE 3. **Results of the series of radical cytoreductive surgery and intraoperative intraperitoneal hyperthermic chemotherapy (IPHC) for treatment of peritoneal carcinomatosis of colorectal origin (series of at least 14 patients)**

| Authors | Number cases | Complete vs. no cytoreduction | Mean follow-up | Overall survival (years) | Overall 3-year survival | Morbidity | Mortality | Mean survival | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Shen et al (2004) | 77 | 37 / 40 (48%) | 15 months | 56% (1 año) | 25% | 30% | 10% | 16 months | If complete disease resection, 5-year survival of 34% with median survival of 28 months |
| Verwaal et al (2003) | 49 | 39 / 10 (79.6%) | 21.6 months | 44% | 38% | 44.80% | 8.10% | 22.4 months | Randomized phase III trial of IPCH with mitomycin C vs. standard systemic chemotherapy (experimental arm) |
| Pilati et al (2003) | 46 | 34 / 12 (76.9%) | 14.5 months | 31% | (-) | 35% | 0% | 18 months | Intraoperative intraperitoneal chemotherapy with mitomycin C and cisplatin only if cytoreduction complete |
| Witkamp et al (2001) | 29 | 26 / 3 (89.6%) | 38 months | 45% | 23% | 11% | 3% | Not reached | Systemic postoperative chemotherapy with 5-FU |
| Beaujard et al (2000) | 27 | 21 / 6 (77.7%) | (-) | 35% | 25% | 9.60% | 3.60% | 12 months | Within a group of 83 patients with digestive tract tumours<br>Overall mortality and morbidity of the series |
| Elias et al (2004) | 30 | 24 / 6 (80%) | 27.4 months | 74.80% | 65.45 | 30% | 6.60% | Not reached | Systemic postoperative chemotherapy with oxaliplatin or irinotecan<br>IPHC with oxaliplatin |
| Loggie et al (2000) | 38 | 18 / 20 (47.3%) | 27 months | 39% | 24% | 35% | 8% | 14.6 months | Within a group of 83 patients with digestive tract tumours |
| Cavaliere et al (2000) | 14 | 14 / 14 (100%) | 30 months | 63.50% | (-) | 35% | 8.50% | Not reached | Early postoperative chemotherapy combined with 5-FU |
| Nishimura et al (1996) | 14 | 14 / 14 (100%) | 12 months | 50% | 25% | 26% | 6% | Not reached | (-) |

tients with stage III or stage II CRC (T4N0) and treated with systemic chemotherapy based on 5-FU to two arms, with and without intraperitoneal chemotherapy. At 48 months, 57% of the control group and 77% of the intraperitoneal chemotherapy group were free of disease (p=0.001), but with no differences regarding recurrence during the follow-up (5% vs. 2% in favour of the control group). However, the intraperitoneal chemotherapy arm of the stage III subgroup had a better rate of overall survival and disease-free survival[64]. Vaillant et al randomised 267 patients with stage II and III CRC to surgery with or without intraperitoneal chemotherapy with 5-FU, with no significant differences in peritoneal relapse or survival between the two groups. Sugarbaker et al randomised 66 high risk patients who underwent surgery for CRC to systemic chemotherapy with 5-FU or intraperitoneal chemotherapy with the same drug, but saw no difference in five-year survival or disease-free survival[65].

Despite the radicalism and aggressiveness of combined therapy, recurrence of the disease occurs in up to 80% of cases, either in the abdomen or at a distance. Some authors have reported the use of a second cytoreduction procedure after progression, with an overall survival of 64% at three years in those patients in whom it was again possible to achieve a GCr 0 or 1[26]. Verwaal et al proposed as selection criteria for third line therapy a complete prior cytoreduction and an interval of time to recurrence greater than 12 months[66]. A retrospective review has recently been published, collecting more than 506 patients with PC of colorectal origin from different centres during a period of 15 years and a mean follow-up of 53 months, with a median overall survival of 19.4 months, which rose to 32.4 months in those cases in which cytoreduction was complete compared with just 8.4 months in cases in which this was not possible. The mean rates of survival for the patients with GCr 0 or 1 were 87%, 47% and 31% at one, three and five years, respectively. Multivariate analysis showed that positive prognostic factors for survival were complete cytoreduction, treatment with a programmed second procedure, limited extension of the PC, age below 65 years and the use of adjuvant systemic chemotherapy. Negative prognostic factors were lymph node involvement, the presence of liver metastasis, the use of neoadjuvant systemic chemotherapy and a low histological differentiation grade[67].

**SUMMARY**

Peritoneal carcinomatosis of colorectal cancer origin is a terminal disease for which intravenous chemotherapy has always been the standard treatment. The only randomised trial reported (phase III) confirmed the efficacy of maximum cytoreductive surgery associated with IPHC to achieve a statistically significant prolonged survival compared with patients treated with systemic chemotherapy. Further similar randomised trials are unlikely to be undertaken because of ethical considerations. Future lines of research will be based on improving and refining the different techniques of IPHC, as well as an increasingly careful patient selection process (using imaging techniques and molecular biology studies, and establishing protocols based on prognostic factors for survival) to achieve the best survival with the minimum rates of disease and mortality[68]. Likewise, prospective studies must be designed to define the possible existence of subgroups of high risk patients with CRC (initially without PC but with a risk of developing it after curative surgery) who can be treated preventively with IPHC or EPIC.

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