Cytoreductive surgery and intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis from colorectal origin

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SPECIAL ARTICLE

Cytoreductive surgery and intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis from colorectal origin

F. Losa · P. Barrios · R. Salazar · J. Torres-Melero · M. Benavides · T. Massuti · I. Ramos · E. Aranda

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Abstract Peritoneal carcinomatosis (PC) is a common form of tumour metastasis stemming from gastrointestinal and colorectal cancers. For a long time, PC has been considered a terminal clinical condition treated only with palliative systemic chemotherapy and associated with very limited results. During the last decade, the treatment of advanced colorectal disease has greatly improved with the emergence of new chemotherapy drugs and biological agents. However, the median survival rates still do not surpass 24 months, even though most of these studies correspond to groups of patients with metastatic disease to the liver and/or lung. The approach and development of cytoreductive radical surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC) are based on performing radical surgery of the entire visible tumour within the abdomen/peritoneum, followed immediately by HIPEC, which acts upon microscopic tumour that remains present after surgery and which is responsible for the persistence or relapse of peritoneal disease. Peritonectomy procedures are demanding surgical techniques that permit elimination of the tumour present in the peritoneal lining and any other organs and/or structures that are infiltrated. The synergistic effect of hyperthermia and chemotherapy has been well documented. Hyperthermia increases the cytotoxicity of some cytostatic agents and increases the penetration of certain drugs into the neoplastic cells. The prognosis for patients with PC who undergo combined treatment correlates with the volume of PC (tumour burden) measured as the Peritoneal Cancer Index (PCI) and the ability to perform a CRS, to completely eliminate the gross tumour. At least one phase III study and an important number of phase II studies have shown that CRS + HIPEC provides important survival benefits for patients with PC of colorectal origin. The combination of CRS + HIPEC is indicated for patients with good general health, a low PCI, absence of extra-abdominal metastasis and who can, technically, undergo CRS. The early identification of this group of patients, rapid referral to centres specialised in CRS + HIPEC, together with the correct application of this treatment, are key in achieving the best results.

Keywords Radical treatment of peritoneal carcinomatosis (PC) · Peritoneal carcinomatosis of colorectal origin · Radical cytoreductive surgery (CRS) · Hyperthermic intraperitoneal chemotherapy (HIPEC) · Peritoneal carcinomatosis surgical techniques · Sugarbaker's peritonectomy procedures

F. Losa (✉) · P. Barrios · I. Ramos
Consorci Sanitari Integral (H. Sant Joan Despí. Moisès Broggi. Barcelona), Barcelona, Spain
e-mail: ttd@ttdgroup.org

R. Salazar
Institut Català d'Oncologia (ICO-L'Hospitalet), Barcelona, Spain

J. Torres-Melero
Hospital Torrecárdenas (Almeria), Almeria, Spain

M. Benavides
Hospital Carlos Haya (Málaga), Málaga, Spain

T. Massuti
Hospital General de Alicante, Alicante, Spain

E. Aranda
Hospital Reina Sofía (Córdoba), Córdoba, Spain

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Introduction

Peritoneal carcinomatosis (PC) is a common form of tumour metastasis stemming from gastrointestinal and colorectal cancers. PC is characterised by the presence on the peritoneal surface of tumour implants, varying in size, number and distribution, with or without visceral infiltration [1].

In general, PC has been considered as an ominous manifestation of neoplastic diseases. Currently, for many groups, standard treatment remains systemic chemotherapy, with or without palliative surgery. However, its impact on patient survival and quality of life is limited [2, 3].

In 1985, Sugarbaker [4] first proposed a strategy of "regional therapeutic intensification" for treating malignant diseases of the peritoneal surface. In 1995, he then described a potentially radical combined-therapy approach, involving intense cytoreductive radical surgery (CRS) and intra-abdominal chemotherapy drugs, since PC was regarded as a locoregional tumour manifestation [5]. Chemotherapy can be delivered either by early postoperative intraperitoneal chemotherapy (EPIC) or by hyperthermic intraperitoneal chemotherapy (HIPEC) during surgery.

Initially, this treatment was applied in patients with peritoneal pseudomyxoma and peritoneal malignant mesothelioma and has now become the standard regimen based on the significant clinical benefits reported in association with these unusual diseases.

Since 2000, the use of CRS + HIPEC has been extended to other types of PC, such as carcinomatosis of colorectal origin. Indeed, it is now being used by an increasing number of cancer centres in Europe and North America [6]. The standardisation of the surgical techniques, initially described by Sugarbaker [7] as peritonectomy procedures to achieve CRS, and the systematisation of HIPEC, as reported by Elias [8] and other European groups, have made this combined therapeutic approach feasible, effective and safe, and promising results have been reproduced in several specialised centres.

The clinical results reported thus far show important improvements in patient survival and acceptable rates of morbidity and mortality. This may lead CRS + HIPEC to become the new standard treatment for PC of colorectal origin.

Incidence of PC of colorectal origin

The incidence of PC in colorectal cancer is frequent. It is estimated that at the time of diagnosis, the peritoneal surface may be involved in 8–15 % of colorectal cancer patients. Relapse in the peritoneum can occur in up to 50 % of patients who undergo ostensibly curative surgery, with or without chemotherapy [9–12]. Moreover, in about 25 % of the patients who experience a colorectal cancer relapse, the peritoneal cavity is the only site affected, even after a detailed hepatic and pulmonary search [13].

Mechanisms of development of PC

The peritoneum is a three-dimensional organ covering the structures contained in the abdominopelvic cavity. It is composed of a single layer of mesothelial cells on a basement membrane and five layers of connective tissue, with a total thickness of 90 microns. The connective tissue layers include interstitial cells, as well as a collagen matrix, hyaluronic acid and proteoglycans.

The known functions of the peritoneum include the production of a lubricating substance that facilitates contact between the organs of the abdominal cavity and serving as an important organ of defence against intra-abdominal infections. Yet, another recently recognised function of the peritoneum is related to tumour development, acting as the first line of defence against tumour implantation and development. Any lesion or wound in the peritoneum can facilitate the implantation of malignant cells in the abdominal cavity and can intervene, together with other elements (e.g., the physiological mechanisms underlying tissue scarring and repair), in the course of tumour development, even in the case of low aggressive neoplasms [14, 15].

The abdominal cavity presents anatomical conditions that favour tumour implantation and development [6]. The peritoneum contains orifices that connect with the subperitoneal lymphatic system and which resemble minute organelles containing lymph vessels, lymphocytes, and macrophages (milky spots). The free tumour cells in the abdominal cavity tend to be deposited on lymphatic stomas and then proliferate in the submesothelial lymphatic space. They mostly distribute themselves on the inferior surface of the diaphragm, on the small intestine mesentery, on the greater omentum, on the epiploic appendices of the large intestine, and on the pelvic peritoneum. They are rarely detected on the hepatic capsule, on the surface of the spleen, or on the serosal surface of the stomach and small intestine, which explains why these organs only become affected during the final phase of peritoneal dissemination.

The most usual determinants of PC are tumour infiltration/perforation of the intestinal serosal surface, and/or manipulation or disruption of the tumour during surgery. Any of these situations can set into motion a sequence of steps leading to the development of PC; specifically: (1) spreading of the neoplastic cells from the primary tumour to the abdominal cavity; (2) adherence of free tumour cells to the injured peritoneal surface; (3) tumour invasion of the

subperitoneal space; and (4) tumour proliferation via vascular angiogenesis [6].

Treatment strategies for PC of colorectal origin

Systemic chemotherapy ± palliative surgery

Studies published on the natural history of PC of colorectal origin, such as the multicentre study EVOCAPE [3], that of Chu [1], and more recently that of Jayne [2], show a median survival of 5, 6 and up to 9 months, respectively.

For a long time PC was considered a terminal clinical condition, treated only with palliative systemic chemotherapy and associated with very limited results [16]. Up until the end of the 1990s, treatment consisted of 5-fluorouracil administered in various ways, with or without modulation. This achieved a poor but significant response rate of around 30 %, with a median survival of 9 to 12 months and a 3-year survival below 5 %, with almost no patients surviving beyond 5 years [17].

During the last decade, the treatment of advanced colorectal disease has greatly improved with the emergence of new drugs such as irinotecan/oxaliplatin, to which monoclonal antibodies against the vascular endothelial growth factor (VEGF) and the endothelial growth factor receptor (EGFR) should be added. Different combinations of chemotherapy drugs, in tandem with these new biological agents, currently comprise the main treatment strategy for advanced colorectal cancer. However, the median survival rates still do not surpass 24 months, and most of these studies correspond to groups of patients with metastatic disease of the liver and/or lung. Moreover, they are devoid of any information on those patients whose disease is confined exclusively to the peritoneal area [18–25], that reinforces the general opinion that cytostatic agents given systemically fail to reach peritoneal metastases in cytotoxically effective concentrations.

Palliative surgery is geared principally towards controlling symptoms and alleviating intestinal obstructions.

Radical combined treatment of PC: CRS + HIPEC

In 1989, Sugarbaker considered PC to be a neoplastic manifestation of a locoregional nature [10]. How long the peritoneum can serve as a barrier to tumour propagation is unknown, but it seems that the origin of the tumour, its histology and biology, as well as aspects related with the host, influence the aggressiveness of transperitoneal infiltrations.

The approach and development of CRS + HIPEC, also known as the Sugarbaker technique, is based on the current understanding of the physiology of the peritoneum. Numerous factors, all of which must be taken into account, include the technology permitting implantation, the rate of growth of tumours on the peritoneal surface, the benefits to tumour kinetics afforded by surgical cytoreduction, the pharmacokinetics of the chemotherapeutic agents given regionally (intraperitoneal), and the synergy between certain chemotherapeutic agents and hyperthermia. This therapeutic strategy is based on performing radical surgery of the entire visible tumour in the abdomen/peritoneum, followed immediately by HIPEC, which acts upon the remains of the microscopic tumour that are always present after surgery and which are responsible for the persistence or peritoneal relapse [10].

Cytoreduction radical surgery (CRS)

The prognosis for patients with PC who undergo combined treatment correlates with the volume of PC (tumour burden), measured as the peritoneal cancer index (PCI) and the ability to performed a CRS, to completely eliminate the gross tumour.

The volume of the peritoneal disease should be determined both pre- and post-surgery, as it establishes the indications for and the possibilities of CRS. The most widely used quantification system for peritoneal disease is the PCI, which describes 13 anatomical sites, dividing the abdominal cavity into 9 regions and the small intestine into another 4. Each region is scored from 0 to 3 points in relation to the size of the tumour lesion: 0 points, absence of gross lesion; 1 point, tumour $\leq$0.5 cm; 2 points, tumour 0.5 to 5 cm; and 3 points, tumour >5 cm or tumour confluence; the maximum possible score is therefore 39 points [26].

The PCI can also be used for making prognoses for patients with different types of PC [27–29] (Fig. 1).

Peritonectomy procedures are surgical techniques that permit elimination of the tumour present in the peritoneal lining and any other organs and/or structures that are infiltrated [30]. They were first described by Sugarbaker and consist of six surgical steps that must be done in sequence during the same surgical procedure, taking into account the distribution/extent of the PC and any associated visceral infiltration. Each procedure is defined according to the anatomic site and organ excised [14, 15] (Fig. 2).

Successful CRS and a low PCI value are the main prognostic indicators for survival [12]. To classify the degree of success in CRS, several systems have been proposed for determining the residual tumour size after surgery. Most of these classifications belong to the R system for classifying residual tumours and correspond to modifications of the *American Joint Committee on Cancer* [31]. The most used classification method is the *Completeness of Cytoreduction Score* (CC) [32]. In a PC of colorectal origin, CC-0 indicates the absence of a visible gross tumour; CC-1, residual tumour nodules $\leq$2.5 mm in

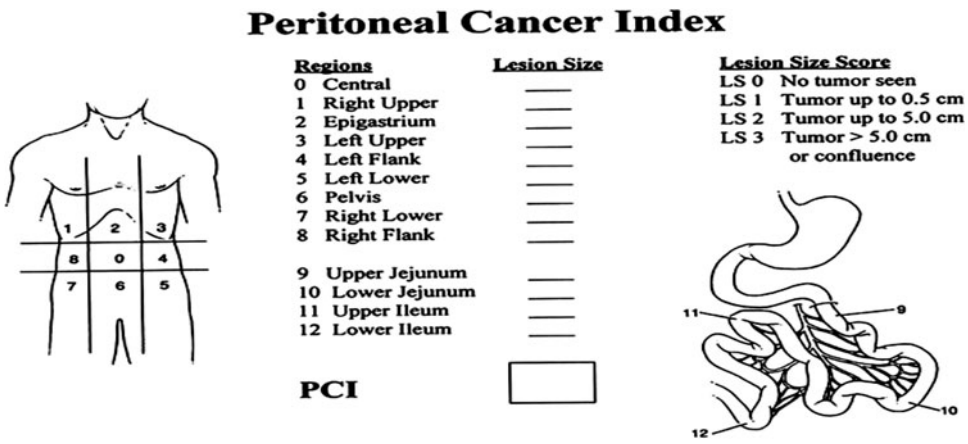

Fig. 1 Peritoneal Cancer Index (PCI). (Taken from Jacquet P and Sugarbaker PH. 1996 [26])

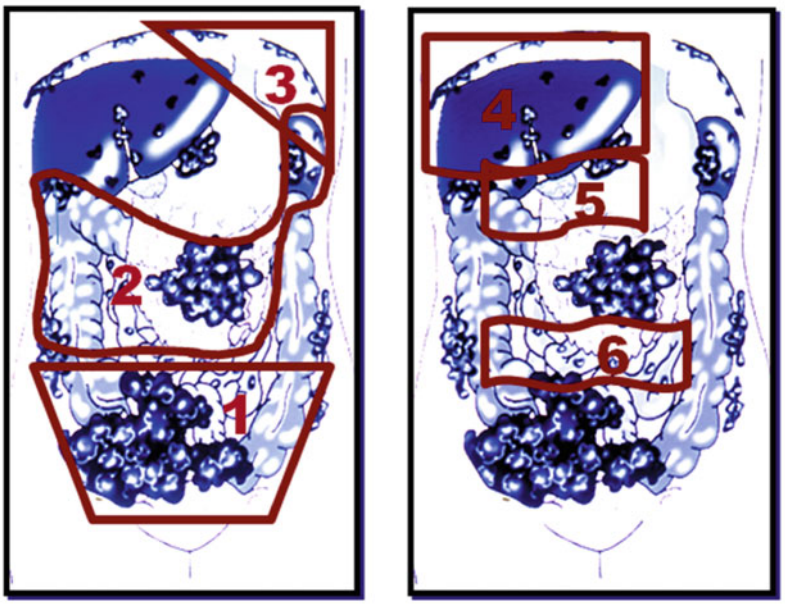

Fig. 2 Schematic chart of the surgical peritonectomy procedures (Taken from Barrios et al.[64]) *1* Pelvic peritonectomy ± rectosigmoid excision ± total hysterectomy, bilateral salpingo-oophorectomy ± low colorectal anastomosis. *2* Greater omentectomy ± splenectomy. *3* Peritonectomy of the left hemidiaphragm. *4* Peritonectomy of the right hemidiaphragm + excision of Glisson's capsule. *5* Minor omentectomy + cholecystectomy. *6* Associated visceral resections

diameter; CC-2, residual tumour nodules between 2.5 mm and 2.5 cm in diameter; and CC-3, residual tumour nodules >2.5 cm in diameter (Fig. 3).

The concept of CC in the combined treatment of PC is based on the ability of intraperitoneally administered chemotherapeutic agents to penetrate to the tumour tissue. Although both CC-0 and CC-1 are regarded as consistent with complete cytoreduction, in clinical practice CC-1 is only deemed an appropriate measure of HIPEC efficacy in PC-related colorectal cancer, while CC-0 is considered necessary before maximum survival indexes can be achieved [12]. In other types of PC, such as peritoneal pseudomyxoma, CC-0 and CC-1 scores show similar survival results [33, 34]. Only those patients who undergo CRS should receive HIPEC. HIPEC provides no clinical benefits to patients with incomplete cytoreductions (CC-2/CC-3), except in those cases when only palliative effects (control of ascites) are sought [35].

CRS in the treatment of PC is associated with morbidity rates of 27 to 56 %, which are no greater than those described for major abdominal surgery [36]. Moreover, the effectiveness of the former is dependent upon several factors: the patient's condition, the application of intraperitoneal chemotherapy and, especially, on the experience of the surgical team (learning curve [37–39]), thus emphasizing the importance of restricting this therapeutic

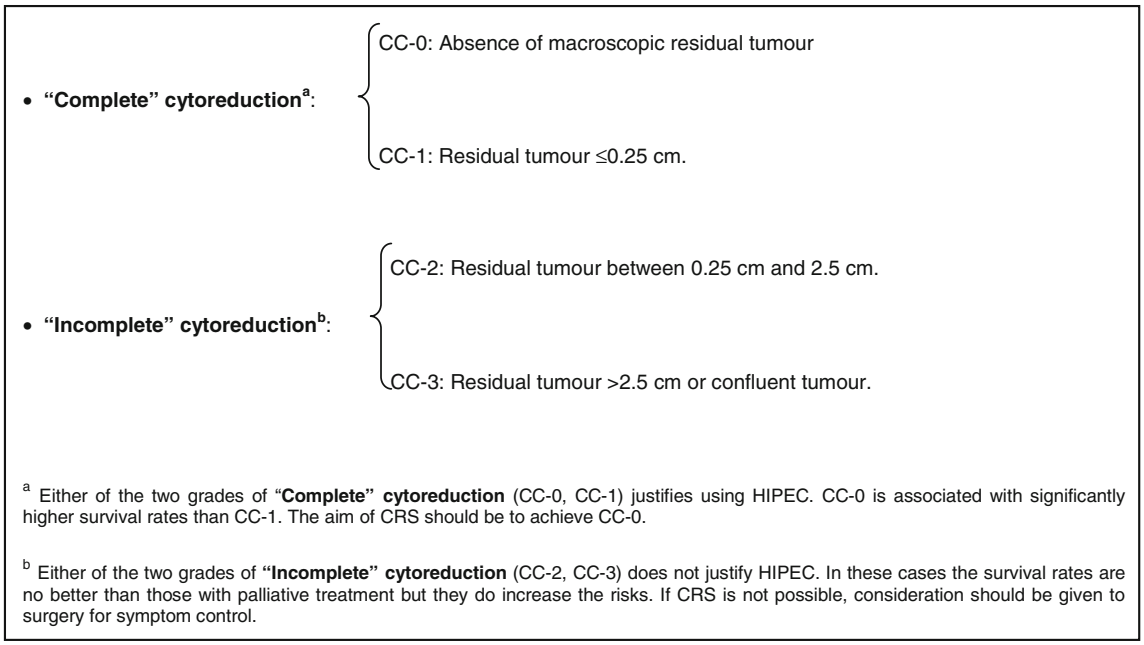

Fig. 3 Completion of surgical cytoreduction in peritoneal carcinomatosis of colorectal origin. (Completeness of Cytoreduction Score. CC)

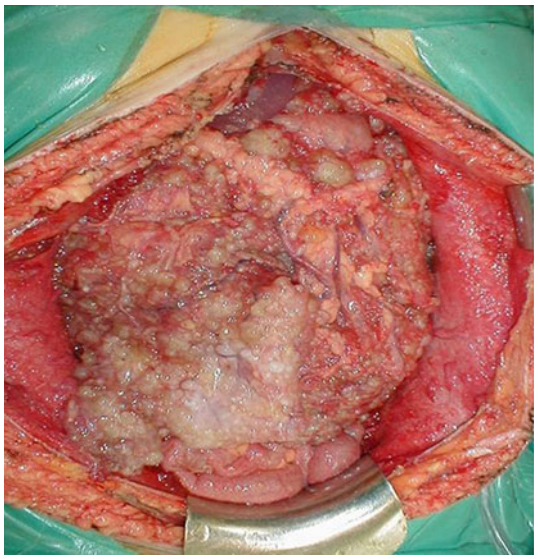

Fig. 4 CP mucinous colorectal tumour (Taken from Barrios et al. [64])

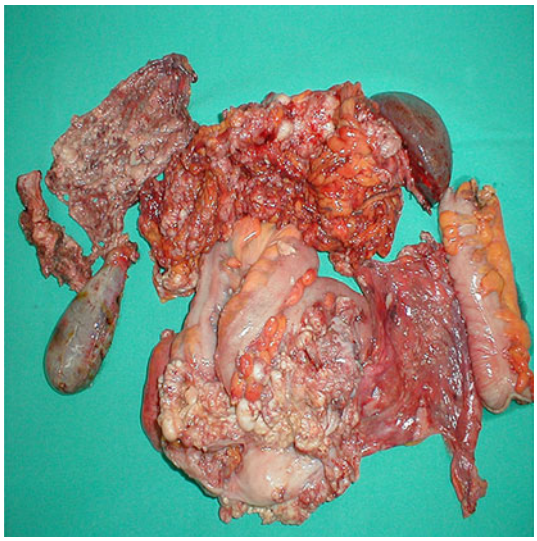

Fig. 5 Specimen from a peritonectomy. CRS (Taken from Barrios et al. [64])

mode to specialised centres that regularly treat such patients [40–42]. The most commonly encountered complications are abdominal abscesses, intestinal perforations, fistulas, prolonged ileus, bile duct leaks, pancreatitis, pneumonia, deep vein thrombosis, and pulmonary thromboembolism [43–46]. Multivariate analysis has shown that such adverse events are related to the PCI, the duration of the surgery, the number of anastomoses made, and the blood volume replaced [47]. (Figs. 4, 5).

Intraperitoneal chemotherapy

Chemotherapy administered intraperitoneally, particularly in relation to the dose used, permits more intensive treatment of certain tumours located in the abdominal cavity.

Intraperitoneal chemotherapy, depending on the agent used, achieves peak peritoneal concentrations 200 to 1,000 times greater than those achieved in plasma [48]. These high differences in peritoneal cavity concentrations have

been shown for an important number of cytostatic agents, including doxorubicin, melphalan, mitomycin C, cisplatin, gemcitabine, mitoxantrone, oxaliplatin, etoposide, irinotecan, paclitaxel, docetaxel, 5-fluorouracil, carboplatin, etc., achieving peritoneum/plasma gradients of 20 to 400:1 [49–51]. This increase in the regional concentration of the drug intensifies the direct anti-tumour effect, with minimal systemic repercussions.

The molecular weight of the drug, its water solubility and capillary permeability determine its passage to the systemic circulation. Other factors to consider when weighing the use of intraperitoneal administered chemotherapy are the systemic circulation elimination time and the capacity to pass to the portal system.

Belonging to the group of non-specific cell-cycle chemotherapeutic agents is one of the chief conditions for the intraperitoneal use of such drugs, and this is particularly true for HIPEC [52, 53].

Various studies have established a maximum of 2–3 mm depth penetration of chemotherapeutic agents into tumour tissue. This tissue penetration capacity explains why the optimum established limit for tumour residue after radical surgery is $\leq$2.5 mm [54]. Excision of the peritoneum following peritonectomy procedures does not influence the pharmacokinetic properties of intraperitoneal chemotherapeutic agents [55, 56].

The maximum benefits of intraperitoneal chemotherapy are achieved when it is used immediately after the surgery and before the onset of tumour cell trapping by fibrin and before compartmentation of the abdominal cavity caused by the surgery begins to occur.

The modes of administration for intraperitoneal chemotherapy vary according to the time and delivery route of the drug(s) and the presence (or absence) of heat (hyperthermia).

Early postoperative intraperitoneal chemotherapy (EPIC)

Intraperitoneal chemotherapy given between 0 and 5 days after surgery is known as Early Postoperative Intraperitoneal Chemotherapy (EPIC). EPIC consists of repeated peritoneal lavages with peritoneal dialysis solution beginning after tumour excision. It serves to draw out and eliminate the fibrin and microscopic cells from the abdominal cavity. The latter is homogenously bathed with the chemotherapeutic solution, which is maintained for 24 h, being withdrawn or replaced on a daily basis via catheters at those anatomical sites established for the programmed administration of the chemotherapy [57]. Various cycles are administered with this mode of intraperitoneal chemotherapy, increasing the likelihood that any remaining tumour cells are exposed to the cytostatic agent, though unfortunately this procedure also induces more adverse effects [58].

Hyperthermic intraperitoneal chemotherapy (HIPEC)

Heat has a direct effect on the growth of neoplastic cells. The cell membrane and cytoskeleton, as well as macromolecule synthesis and the mechanisms of DNA repair, are affected by a hyperthermic state [49]. Additionally, temperatures above 43 °C have a direct cytostatic effect on neoplastic cells [40].

Heat can play a role in intraperitoneal chemotherapy by boosting the therapeutic effects of certain chemotherapeutic agents, resulting in a direct toxic shock to the tumour cells that is proportional to the thickness of the tumour volume [59].

The synergistic effect of hyperthermia and chemotherapy has been well documented. Hyperthermia increases the cytotoxicity of some cytostatic agents and increases the penetration of certain drugs, like mitomycin C and cisplatin, into neoplastic cells [60–63].

HIPEC can be applied by either of two methods: the open and the closed technique. The technique described by Sugarbaker, called the open or coliseum technique, consists in performing HIPEC with the abdomen open. After completing the CRS, the surgeon administers a solution of chemotherapeutic agents at temperatures above 41 °C (preferably 42–43 °C), distributing it homogenously throughout the entire abdominal cavity using an exposure time based on the type of chemotherapy used. After finishing this abdominal bath of chemotherapeutic agents, the gastrointestinal anastomosis are completed, and the abdomen is closed [64].

The other mode of administering HIPEC, the closed technique, involves applying a hot solution of chemotherapeutic agents once all the surgical processes have been completed (including the gastrointestinal anastomosis) and the abdomen has been closed. The aim of this mode of HIPEC is to increase the penetration of the chemotherapy into the tumour by utilizing the greater abdominal pressure that results from solution-rich volumes that are higher than those used with the open technique [64].

No study has yet shown that one mode of HIPEC administration is superior to the other in terms of greater clinical benefits, and they can be used with equal confidence. In theory, the open (coliseum) technique may be more advantageous by allowing for a more uniform distribution of the cytostatic agents within the peritoneal cavity, albeit at the expense of greater exposure risks for the operating room personnel. Both techniques involve the introduction into the peritoneal cavity of large volumes of chemotherapeutic agents at 42°–43 °C, with a high circulation flow rate and an optimal duration of 30 to 90 min, depending on the type of PC and the drug used [6].

The choice of drugs for intraperitoneal chemotherapy depends on the origin of the PC and decisions are typically

based on the available data regarding its systemic administration, its pharmacodynamic and pharmacokinetic properties, its potentiation by heat, and the potential synergy between the different chemotherapeutic agents [65–67].

CRS in patients with PC is contraindicated if there exists extensive or diffuse involvement of the small intestine, which would hamper maintenance of an adequate intestinal length, in cases of tumours involving of the hepatobiliary hilum, in tumour retraction of the mesentery, and/or in patients presenting massive retroperitoneal lymph node involvement.

Only those patients who undergo CRS can receive HIPEC. No method of intraperitoneal chemotherapy provides benefits, in terms of survival, for those patients undergoing incomplete surgical cytoreduction: CC-2/CC-3. In such cases, HIPEC is usually restricted to controlling symptoms like refractory ascites [35].

It is not yet possible to analyse the morbidity and mortality rates associated with HIPEC independently of CRS, as both procedures are carried out jointly during the same surgery. The side effects associated with intraperitoneal chemotherapy are haematological toxicity due to myelosuppression and renal failure, most often as a result of the use of cisplatin [9]. The published mortality rates in CRS + HIPEC range from 0 to 11 % (mean 4–6 %) [42]. The most common causes of death due to the application of combined therapy are intestinal perforation, myelosuppression, respiratory failure, infection with *Staphylococcus*, and pulmonary embolism [40]. (Figs. 6, 7).

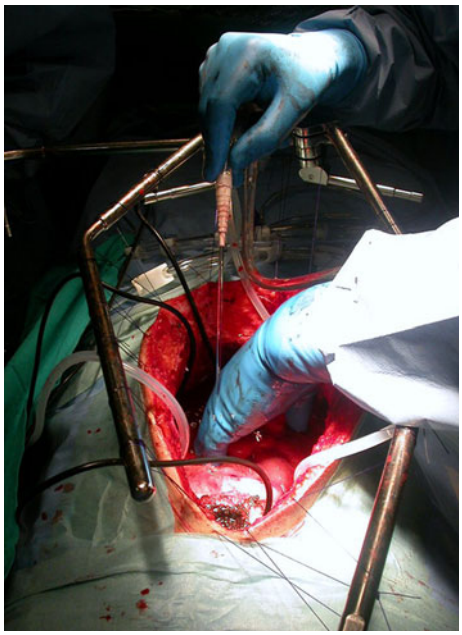

Fig. 6 HIPEC. Frontal view of the coliseum technique: abdomen support mechanism, perfusion cannulas and intra-abdominal temperature catheters. Intraoperative management of peritoneal chemotherapy. Open (coliseum) type (Taken from Barrios et al. [64])

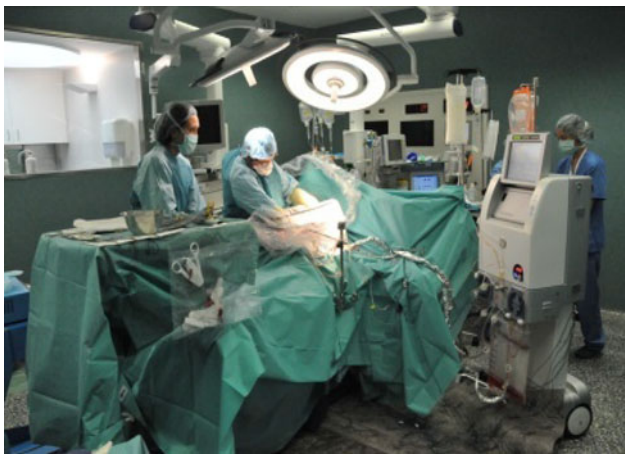

Fig. 7 General view of the application of HIPEC. Environment protection measures, external perfusion circuit and digital heating pump. Open (coliseum) type. (Taken from Barrios et al. [64])

Levels of evidence and patient selection criteria for radical combined therapy of PC of colorectal origin: CRS + HIPEC

To date, two randomised controlled trials have been published, though only one of them was completed as planned [68, 69]. Verwaal has published the only randomised study to date of CRS + HIPEC + systemic chemotherapy vs. palliative surgery + systemic chemotherapy in patients with PC of colorectal origin (this study included a small percentage of patients with appendiceal cancer). CRS was achieved in 41 % of the cases, with overall survival (OS) and progression-free survival (PFS) rates almost double in the group that received CRS + HIPEC (OS 22.4 m vs. 12.6 m; PFS 12.6 m vs. 7.7 m), both reached statistical significance [68]. Notable among the prognostic factors studied were the extent of the surgery (CC-0) and the number of regions affected by the peritoneal tumour [68]. Verwaal [70] has now reported the survival rates of these patients at 8 years of follow-up, with the survival rates remaining the same.

Elias undertook a retrospective analysis of 523 patients treated with CRS + HIPEC or EPIC from 25 centres in France, and additionally identified the independent prognostic factors of achieving CC-0 and a low PCI. Other significant variables were lymph node involvement and having received adjuvant systemic chemotherapy [71]. Glehen [72] also reached the same conclusions after studying 506 patients. It therefore seems likely that the survival rate of PC-related cancers of colorectal origin depends mainly upon the extent of the PC and on the

completion of surgical cytoreduction. In fact, nearly all of the studies agree about the important prognostic repercussions that may be expected with those surgeries that achieve a CC-0.

Franko [73], however, in a recent retrospective study of patients with colorectal PC (as a sole metastatic manifestation), found a median survival rates of 34.7 months in those who had undergone CRS + HIPEC and 16.8 months in those who had been treated with systemic chemotherapy plus biological agents.

In conclusion, the PCI and the achievement of CRS, together with the age, the patient's general health, and such clinical factors as intestinal occlusion and ascites, have defined the main criteria for selecting candidates suitable for combined therapy [74–76]. Other factors related to prognosis in patients with colorectal PC include the tumour histology with signet ring cells and the degree of tumour differentiation [76], the history of prior surgery, which could favour tumour spread resulting from violation/rupture of the protective peritoneal barrier, the disease-free interval between diagnosis/treatment of the primary tumour and the presentation of the PC, lymph node and liver metastases, and the lines of chemotherapy given before the radical combined treatment regimen was begun.

Most groups consider very important to limit the application of this treatment to patients with a PCI <20, even though CC-0 is the only significant independent factor affecting their rate of survival [47, 64]. The contraindications accepted by most groups for use of radical combined therapy are: (1) patients who are not medically able to support CRS; (2) who have a technically unresectable liver metastasis [77] or extra-abdominal tumour disease; (3) who present voluminous retroperitoneal involvement; (4) preoperative clinical/radiological criteria that dismisses CRS from a technical standpoint (as evaluated by a specialised surgical team); and (5) age >70 years (an age limit that is currently under discussion) [78] (Fig. 8). The presence of prior highly aggressive abdominal surgery, failure to respond to a previous administration of chemotherapeutic agents, and/or poorly differentiated histological findings are other negative factors that must be weighed when interpreting clinical results in these patients.

Although current evidence regarding CRS + HIPEC for treating a PC of colorectal origin remains diverse (IB-III), with most of the numerous case series being retrospective or suffering from methodological limitations [11], survival time varies from 22 to 60 months and the 5-year survival rates range from 11 to 48.5 % (at experienced centres they are 32 to 51 %) with 34 % of the patients being disease-free for this same period [64, 79]. All of the studies report better survival rates in patients who undergo CRS + HIPEC versus those who receive systemic chemotherapy (with or without biological agents) [73]. Likewise, in those patient subgroups with limited PC who undergo CRS + HIPEC, the median 5-year survival rate is 51 %, compared to 13 % in those treated with chemotherapy alone [80]. These results can be considered comparable to those achieved with the radical treatments of liver metastases, provided that the evidence-gathering process was more or less the same, with adjustments made according to clinical practice versus data obtained with prospective studies [81]. For this reason, several countries now consider this therapeutic modality to be the best treatment for PC secondary to colorectal cancer in select patients [10, 67, 82, 83]. (Figs. 9, 10, 11).

Finally, the therapeutic approach of patients with PC should be undertaken using a multidisciplinary perspective, integrated and coordinated by different specialists,

Inclusion criteria:

- Age ≤70 years. Older patients with localised PC and good general health can be considered on an individual basis
- Performance status (*Eastern Cooperative Oncology Group*): < 2
- PCI < 20 in colorectal PC (≤10 in gastric PC and undetermined in peritoneal pseudomyxoma)

Exclusion criteria:

- Presence of extra-abdominal tumour disease
- Presence of technically unresectable liver metastasis
- Presence of bile duct obstruction tumour and/or infiltration of the hepatic hilum
- Presence of ureteral obstruction and/or bladder tumour retraction (confirmed by cystoscopy)
- Presence of intestinal obstruction (except in single site cases)
- Presence of extensive involvement of the small intestine and/or mesenteric tumour retraction
- Presence of other active malignant tumour disease
- Infection or other clinical situation preventing the patient from receiving the proposed treatment (cardiorespiratory, renal, hepatic failure, etc)
- Impossibility of adequate patient follow-up
- Not signing the specific informed consent for this type of treatment

Fig. 8 Inclusion and exclusion criteria for radical combined therapy of peritoneal carcinomatosis: CRS + HIPEC

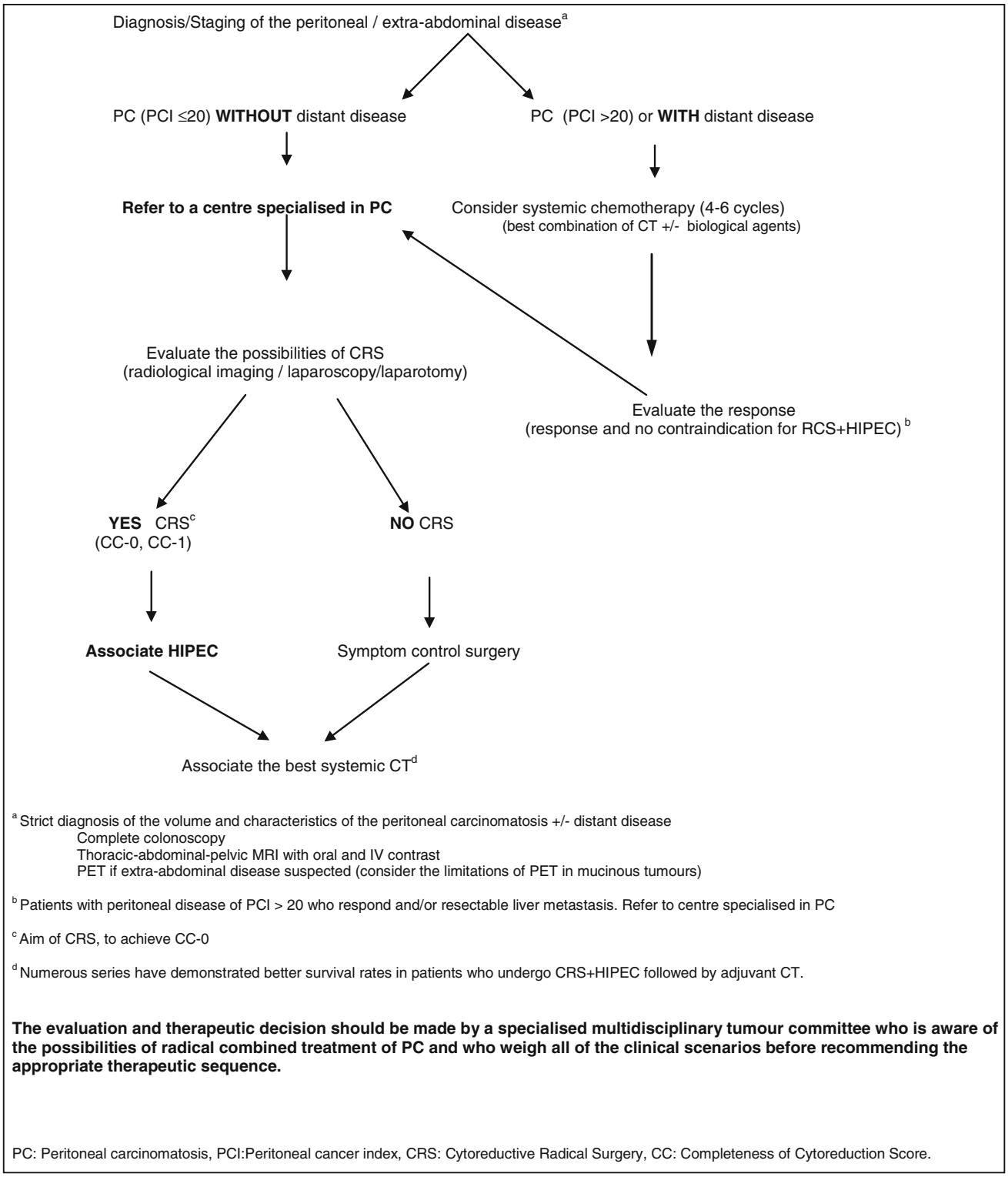

Fig. 9 Indications for radical combined treatment: CRS + HIPEC in a peritoneal carcinomatosis of colorectal origin. (Modified from Esquivel [86])

including specialised surgeons, medical oncologists, pathologists, radiologists, and anaesthetists, who can establish the clinical benefits provided by combined treatments, the technical possibilities of CRS, and who can assess the general health of the patients and the risks from treatment, as well as the ideal treatment sequence

- Younger patients.
- Low PCI scores.
- Completion of CRS: CC-0.
- Well-differentiated tumour histology.
- Absence of ascites.
- No occlusive symptoms.
- No weight loss >10%.
- Prior absence of multiple chemotherapeutic treatments.
- Good response to induction CT.
- Patients not treated surgically or with prior non-aggressive surgery

Fig. 10 Factors associated with a good response to radical combined therapy: CRS + HIPEC in colorectal PC

(including here the role of chemotherapy induction and adjuvant chemotherapy). The administration of systemic adjuvant or neoadjuvant chemotherapy with CRS + HIPEC is currently a common clinical practice in most groups, even though no comparative data are available. Accordingly, in the absence of greater evidence or an agreed-upon definition, decisions about treatment with systemic chemotherapy should be made by a multidisciplinary committee with the participation of oncologists and expert surgeons [71, 72, 80].

Conclusions and future directions

CRS + HIPEC is increasingly being used for the treatment of PC of colorectal origin, as results of several phase II trials suggested improved results in eradicating the macro- and microscopic disease of the peritoneal cavity [6, 86].

At least one phase III study and an important number of phase II studies with this comprehensive approach suggested improved survival of patients with PC of colorectal origin[13, 68] and a positive influence on the quality of life of patients treated for PC [87, 88]. It could therefore become the standard treatment for many of such patients [6, 33, 86, 89, 90].

Expert panels on PC have reached a consensus, establishing that systemic therapy alone may not be the most appropriate treatment for patients with limited PC of colorectal origin. In addition, this consensus holds that patients who have completely resectable PC by CRS could be considered for HIPEC using drugs such as oxaliplatin (associated with IV 5-fluorouracil and folinic acid-bidirectional chemotherapy) or mitomycin C for 30 and

HIPEC: only with complete CRS: CC-0, CC-1 (HIPEC protocols).

Elias protocol[80,84]

Bidirectional chemotherapy (systemic and intraperitoneal):

1st Intravenous administration of folinic acid 20 mg/m^2, followed by 400 mg/m^2 of 5-FU in perfusion for 30 minutes, infused 1 hour before the administration of the HIPEC.

2nd HIPEC: open technique (coliseum):

Drugs used : Oxaliplatin: 460 mg/m^2.
Solution: glycosated at 5%.
Perfusion volume: 2 L/m^2.
Administration flow: 500-600 ml/min.
Stable peritoneal temperature desired: 43 °C.
Real time of the HIPEC: 30 minutes

Sugarbaker protocol (colorectal and appendiceal cancer)[85]

Bidirectional chemotherapy:

1st Intravenous administration of 400 mg/m^2 of 5-FU and 20 mg folinic acid in rapid infusion for 6-8 min.

2nd HIPEC: open technique (coliseum):

Drugs used: mitomycin C 15 mg/m^2 + doxorubicin 15 mg/m^2.
Solution used: dialysis at 1.5% dextrose.
Perfusion volume: 1.5 L/m^2.
Mean peritoneal temperature: 41.5 °C (41-43°C)
Hyperthermia time: 90 min.

3º EPIC:

5-fluorouracil 600 mg/m^2 (men) and 400 mg/m^2 (women), administered via intraperitoneal catheter over 15 min. Maintain the infusion in the peritoneal cavity for 23h and then withdraw for 1h.
Perform the process each day for the first 4 postoperative days.
Not indicated in those patients who have received at least one complete cycle of FOLFOX before the CRS or who present postoperative complications.

Fig. 11 Radical combined therapy of PC of colorectal origin: CRS + HIPEC [80, 84, 85]

90 min, respectively, either with the open or closed method, with or without chemotherapy and induction, and followed by the best available systemic chemotherapy [86, 89–91].

A multicentre, randomised, open-label study currently in phase III (PRODIGE 7), with parallel groups and two treatment arms comparing CRS + HIPEC + system chemotherapy pre- or post-surgery versus CRS + systemic chemotherapy pre- or post-surgery, is seeking to elucidate the true role of HIPEC in the context of radical combined therapy. Once this study is completed, we should have considerably more evidence regarding the efficacy of this treatment modality [84].

Various topics have been discussed relating to the future of this treatment strategy, one of which is the standardisation of the technical surgical procedures and the availability of the equipment at more centres, as the surgical techniques needed for CRS can be time-consuming and highly complex, requiring the experience of a specialised surgical team and specific technological recourses [40].

The combination of CRS + HIPEC is not indicated for all patients with colorectal PC. Patients with good general health, a low PCI, and an absence of extra-abdominal metastasis and who can, technically, undergo CRS, are those who most benefit from this treatment. The early identification of this group of patients, rapid referral to specialised centres in CRS + HIPEC, together with the correct application of this treatment, are key in achieving the best results [33].

The complexity and aggressiveness, as well as the morbidity, mortality, and costs associated with the combined treatment of PC has led various international health care agencies to recommend its application in specialised centres of proven experience and capacity. Those centres should guarantee, among other aspects, a rigorous selection of patients and the provision to patients of adequately detailed and objective information about the potential benefits and risks of the procedure. These efforts have been complicated, however, by the demand by certain sectors of the scientific community for additional data. Oncological societies and scientific groups should therefore participate in formulating these protocols and encourage the development of multicentre studies, given that this treatment modality is becoming increasingly popular and the 5-year survival figures are now reaching 50 % in cases that, until very recently, had been considered terminal [42, 92, 93].

The clinicians and specialists who manage patients with colorectal cancer should be aware of the therapeutic possibilities and the results afforded by CRS + HIPEC in those patients who present or develop PC, as well as the basic general criteria for the indication of this treatment, in order to select potential candidates before referring them to a specialised centre. The physicians involved in the different care levels need agile referral circuits to these centres and systems should be established for the exchange of information among all of the professionals involved. The patients should be followed up at the centre nearest their home and his/her treatment should be based on health care protocols that contemplate continued care.

Spain currently has various centres specialised in the combined treatment of PC that together comprise the Grupo Español de Cirugía Oncológica Peritoneal (GECOP) (http://www.seoq.org/grupos), which has a registry and a national database of peritoneal carcinomatosis. Finally, it is important to promote and encourage clinical trials to redefine the role of radical combined therapy and the effects of better patient selection, even using genome studies on biopsy material to establish treatment profiles based on new response-predicting biomarkers. The future of this therapeutic modality runs parallel to the development of new clinical trials, greater multidisciplinary interaction, translational research (determining new biological markers and the use of intraperitoneal biological agents), and a consistent policy for the accreditation of centres in order to guarantee the effective application of this complex treatment.

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Conflict of interest None.

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