

Multimodality treatment strategies have changed prognosis of peritoneal metastases

Corneliu Lungoci, Aurel Ion Mironiuc, Valentin Muntean, Traian Oniu, Hubert Leebmann, Max Mayr, Pompiliu Piso

Corneliu Lungoci, Aurel Ion Mironiuc, Valentin Muntean, Traian Oniu, Department of Surgery, "Iuliu Htieganu" University of Medicine and Pharmacy Cluj-Napoca, 400015 Cluj-Napoca, Cluj Province, Romania

Hubert Leebmann, Max Mayr, Pompiliu Piso, Clinic of Visceral and General Surgery, Krankenhaus Barmherzige Brueder, Academic Teaching Hospitals of the University Regensburg, 93049 Regensburg, Bavaria Province, Germany

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Correspondence to: Dr. Pompiliu Piso, Professor of Surgery, Dr. Honoris Causa, Clinic of Visceral and General Surgery, Krankenhaus Barmherzige Brueder, Academic Teaching Hospitals of the University Regensburg, 86 Profeninger Street, 93049 Regensburg, Bavaria Province, Germany. pompiliu.piso@barmherzige-regensburg.de
Telephone: +49-941-3692201
Fax: +49-941-3692206

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Abstract

For a long time, treatment of peritoneal metastases (PM) was mostly palliative and thus, this status was link with "terminal status/despair". The current multimodal treatment strategy, consisting of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), has been strenuously achieved over time, but seems to be the best treatment option for PM patients. As we reviewed the literature data, we could emphasize some milestones and also, controversies in the history of proposed multimodal treatment and thus, outline the philosophy of this approach, which seems to be an unusual one indeed. Initially marked by nihilism and fear, but benefiting from a remarkable joint effort of human and material resources (multi-center and -institutional research), over a period of 30 years, CRS and HIPEC found their place in the treatment of PM. The next 4 years were dedicated to the refinement of the multimodal treatment, by launching research pathways. In selected patients, with requires training, it demonstrated a significant survival results (similar to the Hepatic Metastases treatment), with acceptable risks and costs. The main debates regarding CRS and HIPEC treatment were based on the oncologists' perspective and the small number of randomized clinical trials. It is important to statement the PM patient has the right to be informed of the existence of CRS and HIPEC, as a real treatment resource, the decision being made by multidisciplinary teams.

Key words: Hyperthermic intraperitoneal chemotherapy; Peritonectomy procedures; Systemic chemotherapy; Peritoneal metastases; Survival

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Core tip: The multimodal treatment of peritoneal metastases (PM), involving cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, has been strenuously achieved over time, but seems to be the best treatment option, for selected cases. This paper addresses data about the multimodal treatment strategy, focused to patient's survival, the key indicator for assessing results, in the case of PM. Also, it were highlighted the treatment key aspects and the controversies, high in the 35 years of treatment implementing. By understanding the philosophy of multimodal treatment, physicians will be able to offer an alternative to the routine systemic chemotherapy.

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INTRODUCTION

Peritoneal metastases (PM) were described by Sampson *et al.*^[1] (1931) in an ovarian cancer patient. For a long time since then, treatment was mostly palliative and thus, PM was linked to "terminal status/despair". The current multimodal treatment consisting of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been strenuously achieved over time, but seems to be the best treatment option for selected PM cases.

As we reviewed the literature data, we could emphasize some milestones and also, controversies in the history of PM treatment and thus, outline the philosophy of proposed multimodal radical treatment, which seems to be an unusual one indeed. To understand this radical treatment, we start with the natural evolution of PM and "conventional" systemic chemotherapy approach, in fact the treatment of choice for stage IV cancer, regardless of the dissemination type and location. Four periods must be considered in the evolution of "dedicated" PM treatment: Before 1980; 1980-2000; 2000-2010 and 2010-present. The first time period, before 1980, was a period of palliative intraperitoneal treatment of ascites. In 1980-2000 were proposed the methods and define the foundation laying for a new multimodal approach of PM by intraperitoneal chemotherapy and CRS. The next periods, until 2010, were those of the progressive development of dedicated multimodal treatment strategy, concluding with the actual CRS-HIPEC. From 2010, the studies were focused about new research pathways. The PM treatment approach related survival was the main issue considered in this review.

NATURAL EVOLUTION OF PM

In the literature concerned with PM, the EVOCAPE I study^[2] is classical and it reflected the natural evolution of patients with non-gynecological PM. The mean survival (mS) was 6 mo, significantly correlated with the PM stage (Figure 1), according Gilly system^[3] (nodules/lumps < 5 mm: 9.8 mo; > 2 cm: 3.1 mo). PM of pancreatic origin had the lowest mS (2.9 mo), followed by PM of gastric origin (6.5 mo) and of colorectal origin (6.9 mo). The degree of differentiation had no influence on survival.

Several other "historical"^[4-6] studies confirmed the unfavorable prognosis of PM. Ascites is a negative prognostic factor: In pancreatic cancer, median survival (MS) was < 1 mo, with an important negative impact on the quality of life. Surgery was aimed at palliating gastrointestinal complications, as it was contraindicated in patients with gastric, pancreatic tumors or ascites^[4]. In colorectal cancer (marked by a favorable biological pattern), MS was significantly less for synchronous PM than that in metachronous (7 mo vs 28 mo, $P < 0.001$)^[6].

"CONVENTIONAL" SYSTEMIC CHEMOTHERAPY OF PM

Recent studies on colorectal cancer compared patients having only PM, as a distant metastatic location, with patients having other systemic dissemination. Franko *et al.*^[7] (2012) revealed a significantly lower ($P < 0.001$) global MS (12.7 mo vs 17.6 mo) and disease-free survival (5.8 mo vs 7.2 mo) for patients with PM vs other metastatic locations. Also, the poor global MS of PM metastasis patient was unchanged by various chemotherapy regimens (Figure 2).

Systemic chemotherapy carried MS significant benefit ($P = 0.026$) in colorectal PM patients only compared to those patients who did not receive chemotherapy (Figure 3): Increasing from 5 mo without chemotherapy (95%CI: 3-7 mo) to 11 mo with the fluorouracil-leucovorin protocol (95%CI: 6-9 mo), and to 12 mo with the oxaliplatin-irinotecan protocol (95%CI: 4-20 mo)^[8].

Despite the progressive development of systemic chemotherapy, in a population-based study, Lemmens *et al.*^[9] confirmed the poor MS in PM patients (1995-2001: 7 mo; 2002-2008: 8 mo), unlike that of patients with liver metastases, which underwent improvement (1995-2001: 8 mo; 2002-2008: 12 mo).

"DEDICATED" INTRAPERITONEAL TREATMENT OF PM

Palliative treatment (< 1980)

The first attempts for a treatment approach of peritoneal malignancies began in 1950, with the sporadic use of intraperitoneal chemotherapy for malignant ascites. For this intraperitoneal treatment, hemisulphur mustard^[10],

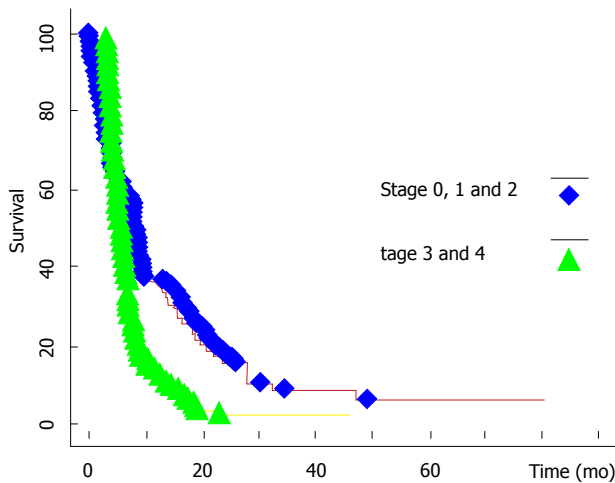


Figure 1 Kaplan-Meier survival curve of non-gynecological peritoneal carcinomatosis, stratified according to the Gilly staging system (Stage 0, 1 and 2 vs Stage 3 and 4)^[2] (with permission). Kaplan-Meier survival curve according to PM staging^[2]. Available from: URL: <http://click.info.copyright.com/?qs=e232cb87f594dcec17211f4d00b2929249713825e6b912c104538a1695c335dde91d3fd5f03fa97>. PM: Peritoneal metastases.

thiotepa^[11], nitrogen mustard^[12], quinacrine^[13] and bleomycin^[14] were used. Nitrogen mustard had a high digestive toxicity, so it was replaced by thiotepa (considered elective for ascites control in 1964), but even at that time it was foreseen that it would be replaced by 5-fluorouracil in digestive cancer palliation^[15]. Nevertheless, nitrogen mustard was the basis for developing further drugs: Cyclophosphamide, chlorambucil, uramustine, ifosfamide, melphalan, and bendamustine.

Multimodal treatment - methods and foundation-laying (1980-2000)

In 1978-1980, the first documented data became available, at first referring to the clearance of intraperitoneal cytostatic drugs^[16], then to circulating intraperitoneal cytostatic solutions, all thanks to the contributions of Speyer *et al.*^[17] and Spratt *et al.*^[18]. They were “the fathers” of regional intraperitoneal chemotherapy. Spratt augmented the cytostatic effect by hyperthermia using a specially designed device (Thermal Infusion Filtration System). Thus, the foundation was laid for a multimodal treatment of PM by normothermic and HIPEC.

The mechanism by which hyperthermia cytotoxic effects associating with and increasing the cytostatic drug effect is due to certain particularities of these drugs; studies regarding this aspect are exhaustive^[19-25].

The key merit in developing and implementing this multimodal treatment strategy belongs to Sugarbaker, who outlined and detailed the premises substantiating it. The starting model was that of PM in appendiceal cancer^[26]. The most important phase was the adjustment in the existing pathophysiological concept of PM, as a systemic disease and, consecutively, its treatment with systemic chemotherapy. In the new approach, the peritoneum was regarded as an organ (similar to the liver), the pathogeny of PM implying, first and foremost, peritoneal dissemination. Thus, it appears natural to use

a regional treatment in PM^[27-31]. Sugarbaker’s research was regarded mistrustfully, and 25 years had to pass before the “European contributions to the Sugarbaker protocol”^[32] appeared: One multicenter retrospective study^[33], two randomized prospective phase III studies^[34,35] and the use of oxaliplatin and irinotecan as new cytostatic drugs in the protocols for intraperitoneal chemotherapy^[36,37].

Sugarbaker also has the merit of being the first to have described and implemented the surgical procedures associated with regional chemotherapy, generically named “Peritonectomy”^[38]. So, the road lay open for the PM multimodal treatment by CRS and HIPEC.

He then brought in other special aspects regarding the surgical technique of Peritonectomy procedures: Required electrocautery, circumferential skin traction, dissection of subpyloric space and falciform ligament^[39-42]. He also described a method for staging PM and assessing the result of CRS, which were subsequently used in the majority of studies: The “Peritoneal Cancer Index” (PCI), based on the extension of peritoneal injury and the size of peritoneal deposits, respectively, the “Completeness of Cytoreduction Score” (CCRS), based on the size of the remaining peritoneal nodules/lumps^[43].

PM MULTIMODAL TREATMENT - CONFIRMATION, ASPECTS, PATIENT SELECTION, CONTROVERSIES (2000-2010)

“Confirmation”

Although the number of patients progressively and significantly increased and the so-called “long-term survivors” were identified, it took about 20 years before the “confirmations of a multimodal treatment option for PM” appeared. The initiator was Verwaal (2003)^[35], who carried out a randomized clinical trial for patients with colorectal PM. He showed that, during a mean follow-up of 21.6 mo, the MS of patients treated with CRS-HIPEC (22.3 mo) was significantly ($P < 0.032$) improved compared to patients treated with palliative surgery and systemic chemotherapy with fluorouracil-leucovorin (12.6 mo) (Figure 4A).

Verwaal’s research was confirmed by two other reference-worthy studies, which had the merit of comparing CRS-HIPEC with modern systemic chemotherapy treatment, in colorectal PM. Elias *et al.*^[44] (2009) compared systemic irinotecan-oxaliplatin chemotherapy with CRS-HIPEC. Global survival in the CRS-HIPEC group (2 years: 81%, 5 years: 51%) was significantly ($P < 0.05$) improved compared to the systemic chemotherapy (2 years: 65%, 5 years: 13%). Franko *et al.*^[45] (2010) analyzed systemic chemotherapy with irinotecan, oxaliplatin, bevacizumab, and cetuximab. MS in the CRS-HIPEC treatment group (34.7 mo) was significantly ($P < 0.01$) longer than systemic chemotherapy (16.8 mo) (Figure 4B). It was emphasized that the best results

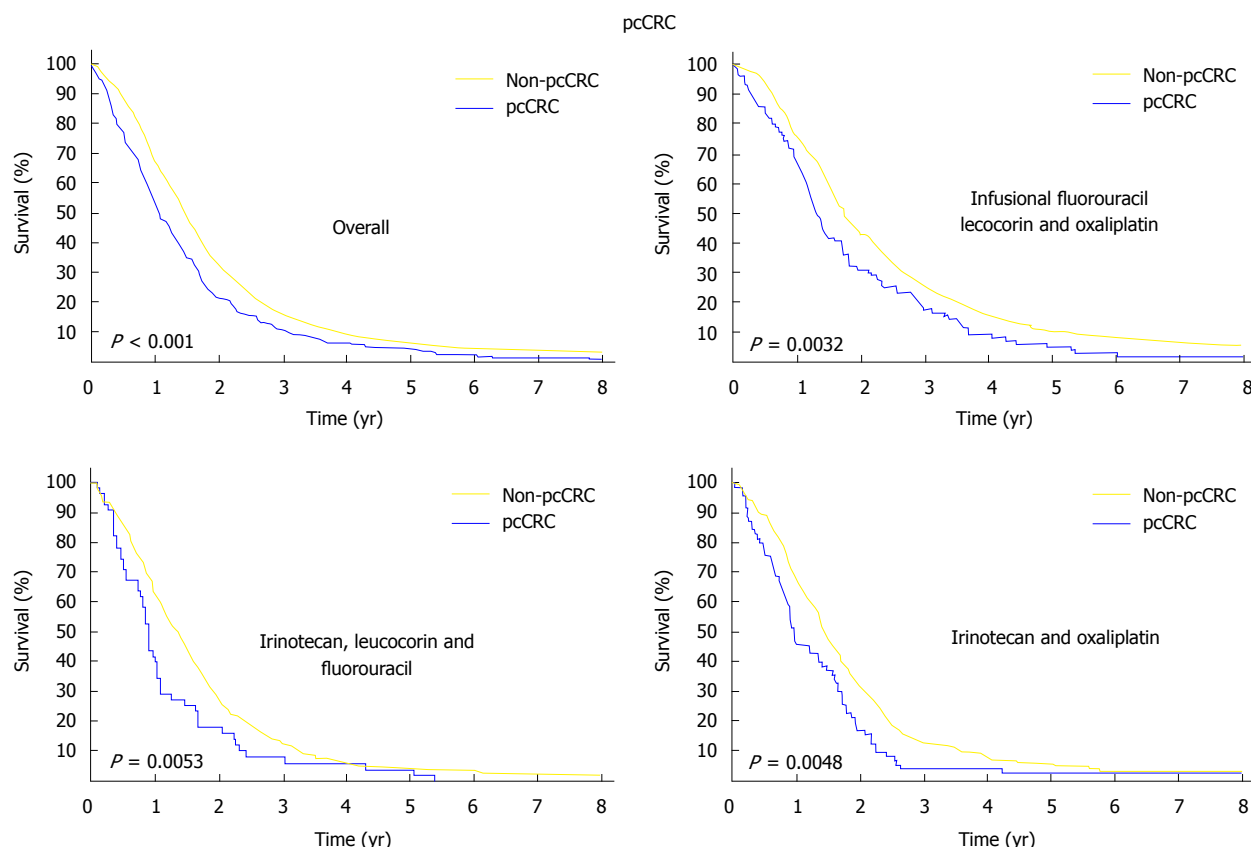


Figure 2 Kaplan-Meier survival curve of metastatic colorectal cancer stratified according to the metastatic locations (peritoneal carcinomatosis vs non peritoneal carcinomatosis) and chemotherapy protocols (fluorouracil, leucovorin and oxaliplatin; fluorouracil, leucovorin and irinotecan; irinotecan and oxaliplatin)^[7] (with permission). Kaplan-Meier survival curve of Metastatic Colorectal Cancer stratified by peritoneal metastatic status and chemotherapy protocols^[7]. Available from: URL: <http://click.info.copyright.com/?qs=da4305023350a474912bb7bdbc04210a63a294c209e715b6497fdff613ea3697d486bdb9bffe0470>. pcCRC: Peritoneal carcinomatosis from colorectal cancer.

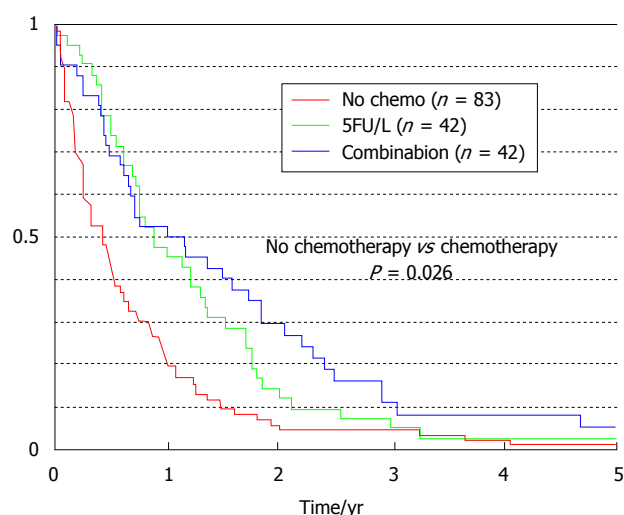


Figure 3 Kaplan-meier survival curve of colorectal peritoneal carcinomatosis stratified by chemotherapy protocols^[8] (with permission). Kaplan-Meier survival curve of Colorectal PM stratified by chemotherapy protocols^[8]. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (Available from: URL: <http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. PM: Peritoneal metastases. 5FU: 5-fluorouracil.

systemic chemotherapy.

For gastric PM, studies also showed a benefit in terms of survival. The prospective randomized clinical trial GYMSSA^[46] compared survival in patients treated with CRS-HIPEC and systemic chemotherapy vs systemic chemotherapy treatment alone. Within the limitation of a small number of patients, it showed a longer MS (11.3 mo vs 4.3 mo) for CRS-HIPEC treatment trial arm.

Likewise, Yang *et al.*^[47] showed in a phase III randomized clinical trial the importance of connecting CRS with HIPEC, in the treatment of PM of gastric cancer origin. The CRS-HIPEC association vs CRS alone significantly ($P = 0.046$) increased MS: 11 mo (95%CI: 10-11.9 mo) vs 6.5 mo (95%CI: 4.8-8.2 mo) (Figure 5).

A meta-analysis of randomized clinical trials performed by Yan *et al.*^[48] showed that in advanced gastric cancer, HIPEC associated with surgery led to a significant increase in survival, compared with patients benefiting from surgery alone.

In addition to randomized clinical trials (the gold standard in the treatment implementation), there are a series of multi-center studies showing survival results for patients treated with CRS-HIPEC.

Thus, several multi-center studies, focused on pseudomyxoma peritonei, colorectal and ovarian cancers, were conducted in France (Figure 6). For the treatment of

were achieved by associating CRS-HIPEC treatment with

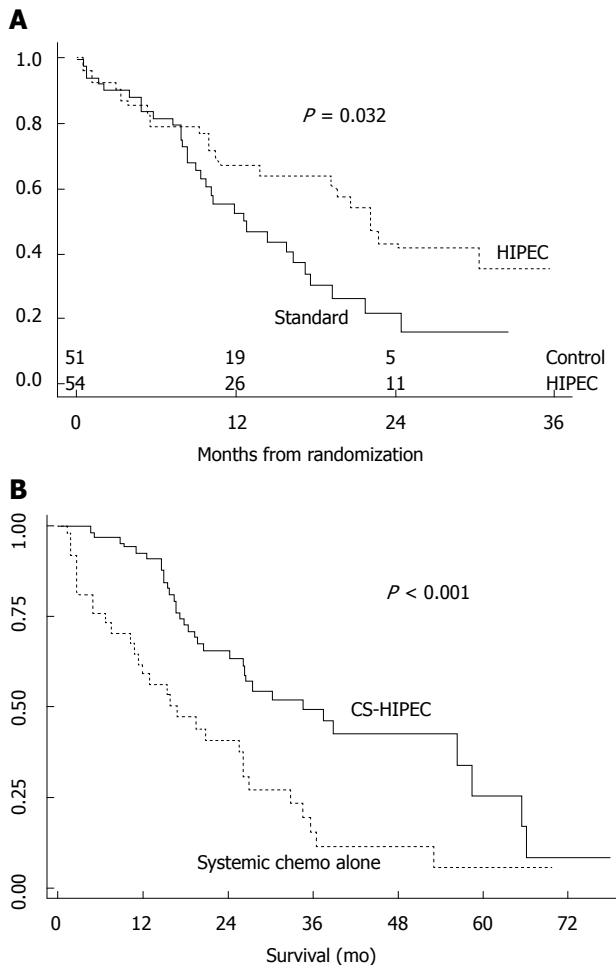


Figure 4 Kaplan-Meier survival curve comparing hyperthermic intraperitoneal chemotherapy to standard treatment, for colorectal peritoneal carcinomatosis^[35] (with permission) (A) and comparing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy treatment to systemic chemotherapy alone, for colorectal peritoneal carcinomatosis^[45] (with permission) (B). A: Kaplan-Meier survival curve comparing HIPEC to standard treatment, for Colorectal PM^[35]. Available from: URL: <http://click.info.copyright.com/?qs=2b7046b10dd0c5471bbb8bac0096e00e895f442c0326423c4ec2ccdd7b4701b99fd4bd5b32f0283>; B: Kaplan-Meier survival curves comparing CRS-HIPEC treatment to systemic chemotherapy alone, for Colorectal PM^[45]. Available from: URL: <http://click.info.copyright.com/?qs=2b7046b10dd0c5471bbb8bac0096e00e895f442c0326423c52a23497a2d7e22ca0949c16bf1f>. CRS-HIPEC: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; PM: Peritoneal metastases.

pseudomyxoma peritonei, CRS-HIPEC was designated the “gold standard” due to the yielded results (at 5 years: 73% global survival, 56% disease-free survival)^[49]. Favorable results were shown for colorectal cancer (at 5 years: 27% global survival, 10% disease-free survival)^[50], and also for ovarian cancer (global survival: Advanced forms 35.4 mo, recurrent forms 45.7 mo)^[51].

The results were also confirmed by a long-term data analysis in the Netherlands, after the implementation of the CRS-HIPEC treatment: MS was 33 mo (95%CI: 28-38 mo) in colorectal cancer and 130 mo (95%CI: 98-162 mo) in pseudomyxoma peritonei (Figure 6)^[52].

The experience of a reference center for PM treatment (St. George's Hospital, Sydney) sustains the higher results obtained by the use of CRS-HIPEC treatment in

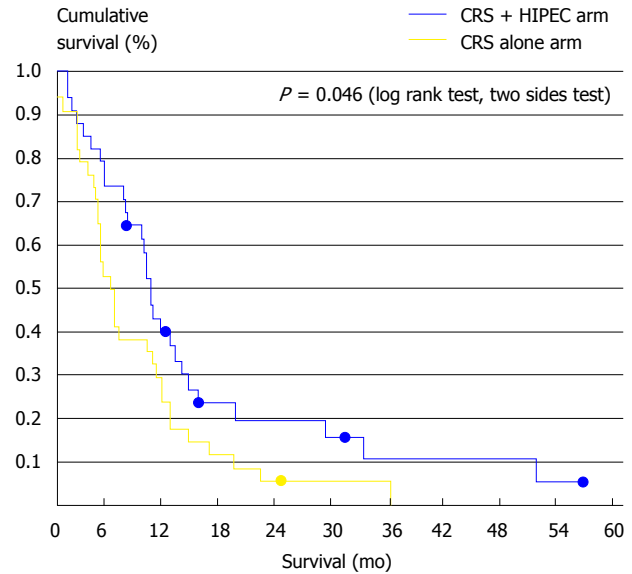


Figure 5 Kaplan-Meier survival curves comparing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy treatment to cytoreductive surgery alone, for gastric peritoneal carcinomatosis^[47] (with permission). Kaplan-Meier survival curves comparing CRS-HIPEC treatment to CRS alone, for Gastric PM^[47]. This is an open access article distributed under the terms of the Creative Commons Attribution Noncommercial License, which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited. CRS-HIPEC: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; PM: Peritoneal metastases.

pseudomyxoma peritonei (MS 104 mo; 5-year survival 75%) and colorectal cancer (MS 33 mo; 3-year survival 46%)^[53].

A series of systematic reviews were conducted under the leadership of Sugarbaker, demonstrating a better survival for CRS-HIPEC treatment compared to conventional systemic chemotherapy. PMs of different origins were analyzed: Colorectal^[54], gastric^[48], ovarian^[55] cancers, and malignant peritoneal mesothelioma^[56]. Other systematic review studies also reported higher results for CRS-HIPEC in colorectal^[57] and gastric^[58] cancers.

All these studies (numerous and enrolling an increased number of patients) shows joint international efforts to identify the role of CRS-HIPEC in multimodal PM treatment. They have allowed the development of an important medical database which, by confirming the higher results in terms of survival and disease-free survival, upholds this treatment strategy. This is also confirmed by the evidence-based medicine approach studies^[59].

The MS, as a result of CRS-HIPEC treatment, related to the tumor entities and study type, were presented in Table 1.

As a recognition of the foundation-laying treatment of PM with CRS-HIPEC, this was included in the treatment guidelines in France^[60], Germany^[61], United Kingdom (<http://www.nice.org.uk/guidance/IPG331/PublicInfo>), the Netherlands^[52,62]. There are a number of ongoing symposia focused on Peritoneal Surface Malignancies, under the patronage of the European Society of Surgical

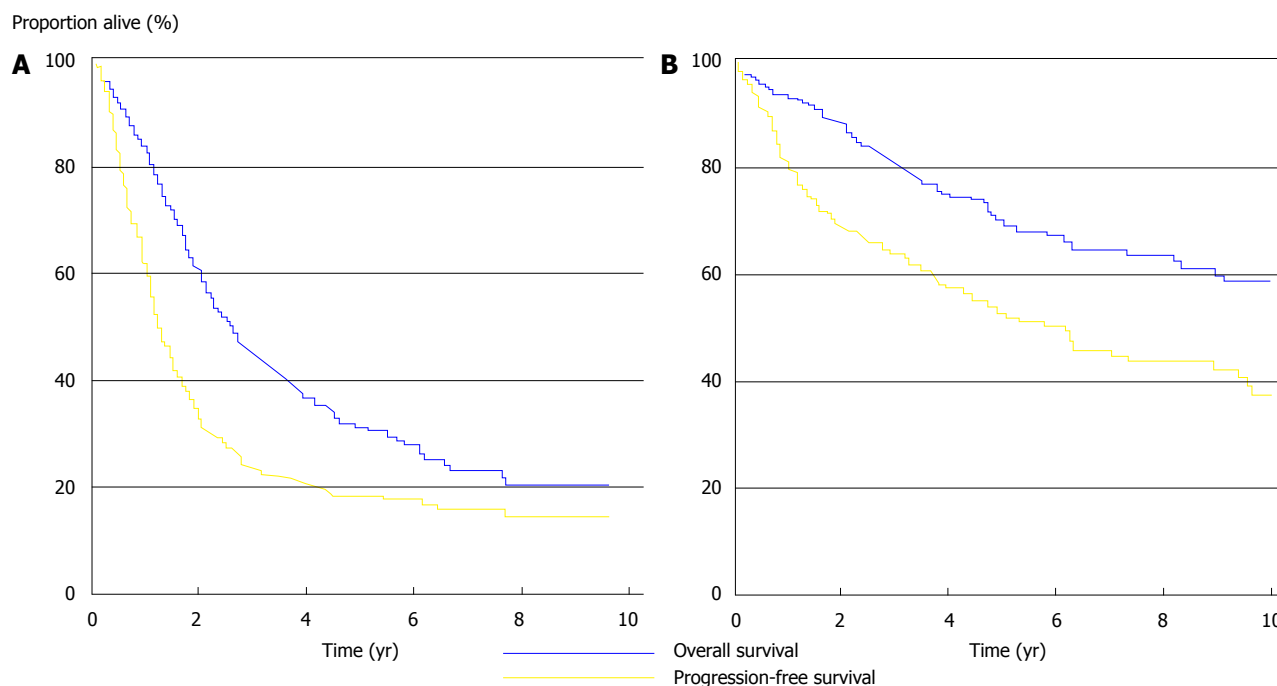


Figure 6 Overall survival compared with disease-free survival for pseudomyxoma peritonei (A) and colorectal peritoneal carcinomatosis (B), treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, from the Netherlands^[52] (with permission). Overall and disease-free survival of Pseudomyxoma Peritonei (A) and Colorectal PM (B), treated with CRS-HIPEC, from the Netherlands^[52]. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CRS-HIPEC: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; PM: Peritoneal metastases.

Table 1 Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy median survival, related to the tumor entities and study type

Primitive tumor origin	Study type	Median survival (mo)
Colorectal	Randomized clinical trials	22.3 ^[35]
	Single center experience	33 ^[33] , 34.7 ^[45]
	Systematic reviews	13-29 ^[34]
	Multi-institutional studies	33 ^[52]
Gastric	Randomized clinical trials	11.3 ^[46] , 11 ^[47]
	Multi-institutional studies	104 ^[53]
Pseudomyxoma peritonei	Single center experience	130 ^[52]
Ovarian	Multi-institutional studies	35.4-45.7 ^[51]
	Systematic reviews	22-54 ^[55]
	Systematic reviews	34-92 ^[56]
Malignant peritoneal mesothelioma	Systematic reviews	34-92 ^[56]

Oncology, as well as a world congress.

The view of those who consider that multimodal PM treatment is "more of an experimental kind, based on common-sense evidence rather than on solid data"^[63,64] is already obsolete. Even so, the confirmation of CRS-HIPEC, as an effective treatment approach by medical studies, such as randomized clinical trials, is not mandatory^[65]. And more than that, the life of patients could be endangered by denying them a treatment resource, since the validation process may take as long as 40 years^[66].

Aspects

Unfortunately, there is no single perfect treatment

option, valid in any setting, so the problems raised were concerned with treatment risk (morbidity, mortality, medical team risk), costs and with the indication of CRS-HIPEC, in terms of prognostic factors.

In the beginning, morbidity and mortality were the key factors initiating distrust among patients and physicians^[67]. The causes of morbidity and mortality may well be suspected to belong to either CRS (surgery proper), or HIPEC (thermal effects of circulating fluid and toxic cytostatic drug effects). In a systematic-review study, morbidity was 21.5% and mortality 4.8%^[68], but literature reports data within a large range: Morbidity 12%-67% and mortality 0%-9%. The main complications include digestive fistulae, postoperative bleeding, pleural-pulmonary complications, bone marrow suppression, hemodynamic instability and renal failure. Protective ileostomy, chest drain and postoperative thoracic imaging are routinely used.

However, it was shown that morbidity and mortality were not significantly increased, compared to extensive organ resection surgery (e.g., Whipple's operation)^[69]. Treatment complications were significantly correlated with the number of Peritonectomy procedures, left diaphragmatic Peritonectomy, duration of surgery and the number of large bowel anastomoses^[70]. The global incidence for the 1st to 4th degree of gastrointestinal toxicities (according to the Common Terminology Criteria for Adverse Events) was 17%, and for symptomatic surgical site infections incidence reached 35.85% (with a global morbidity of 45%)^[71].

The learning curve must be respected by any medi-

cal procedure, even more so when it implies new skills for the surgeon. The “breaking points” of the learning curve in achieving complete CRS, of a morbidity less than 3th degree and an absence of treatment-related mortality are evaluated to be 141, 158 and 144 cases, respectively (the Milan experience), or 126, 134 and 60 cases, respectively (the Bentivoglio experience)^[72].

As the Dutch model of CRS multimodal treatment implementation was analyzed, it was proven that, unlike in the initial stage (experience gathering), in the stage of treatment becoming standard, the percentage of radical surgeries increased significantly (66% vs 86%, $P < 0.001$) and major morbidity (3th-5th degree) decreased significantly (64% vs 32%, $P < 0.001$)^[73].

If there existed accreditation centers and HIPEC registers, coursing through the learning curve could be faster^[74]. Suggestions were made for training in CRS-HIPEC to begin during the residency programmer^[75].

As for the risks the medical team are exposed to during HIPEC, it was shown in several pharmacological studies that, in relation to the HIPEC method (closed/open), with required training, these risks may be reduced to a minimum^[76-78].

The costs implied by CRS-HIPEC treatment are definitely high, but financial calculations show that it is a better solution in terms of treatment results^[53,79-81]. This is why in Germany, HIPEC is adopted, considered a surgical procedure and coded as such^[61].

Patient selection

One of today's challenges in treating PM is patient selection. This is why literature studies are focused on factors/variables correlating with survival.

The randomized clinical trial performed by Verwaal *et al.*^[35] showed that in colorectal cancer, the variables with the highest impact are extension of PM and the radical feature of CRS ($P < 0.0001$) (Figure 7). The GYMSSA randomized clinical trial^[46] also showed that essential conditions for a significant increase in survival in gastric cancer are complete CRS and a PCI ≤ 15 .

A single-center experience, the most comprehensive in terms of the number of patients (1000 patients), shows that the prognostic factors significantly correlated with survival ($P < 0.001$) are: The performance index, the location of the primary tumor, the CCRS, and the center experience^[82]. Another single-center experience (109 patients) correlated survival to the following factors: Histology of non-adenocarcinoma ($P = 0.001$), appendiceal location ($P = 0.001$), absence of liver metastases ($P = 0.01$), and complete resection of all gross disease ($P < 0.001$)^[83].

A multi-center French study shows that in colorectal cancer, CCRS is the most important prognostic factor for MS: 32.4 mo for complete vs 8.4 mo for incomplete CCRS ($P < 0.001$) (Figure 8)^[33]. The multi-center SITILO study^[84] also reveals in colorectal cancer the following independent prognostic variables correlated with survival: PCI, CCRS, and presence of hepatic metastases.

The consensus conference on PM treatment in

colon cancer statutes that the indication of CRS-HIPEC treatment should be based on complete CRS^[85].

All those prognostic factors are in dynamics, the trend being towards broadening the indication range, except for the radical feature of CRS: It is absolutely necessary that this should be complete, or at least optimal. Traditionally, the treatment approach in PM was reserved for colon or appendicular cancer, pseudomyxoma peritonei and peritoneal malignant mesothelioma, but now the range of indications includes rectal, gastric and ovarian cancers. The importance of PCI is not an absolute one, it must be correlated with primary tumor location (colonic PM origin vs gastric), histological grading (well and moderate differentiated vs poorly differentiated and undifferentiated), and the anatomical sites involved (Treitz ligament, porta hepatis and suprahepatic veins, coelic axis and mesenteric vessels). The presence of other systemic dissemination (abdominal or extra-abdominal) was a contraindication for the treatment approach in PM, but this is no longer (Figure 9) the case provided that complete CRS can be obtained^[86-89].

Except for the patient status (evaluated by the performance index), the main CRS-HIPEC treatment contraindication is small bowel involvement^[90], which is regarded as an independent prognostic factor^[91-93].

A series of studies have confirmed the prognostic value of tumor grading in colorectal cancer. The “signet-ring cell” vs other types of differentiation has a significantly poorer MS (14.1 mo vs 35.1 mo; $P < 0.01$) and an increased relapse rate (68.8% vs 43.7%; $P = 0.05$)^[94]. CRS-HIPEC treatment carries no survival benefit in colorectal PM with signet-ring cell histology, unless complete CRS is obtained^[95]. Also, for the aggressive type of pseudomyxoma peritonei, systemic chemotherapy is indicated instead of CRS-HIPEC treatment^[96].

In some studies, the prognostic factors were grouped into scores. The Peritoneal Surface Disease Severity Score may be used to stratify patients in clinical trials^[97]. Different scores used in PM of colorectal origin are: The Peritoneal Surface Disease Severity Score, the Prognostic Score, and the Colorectal Peritoneal Score. The Colorectal Peritoneal Score (value ≥ 6) identifies patients with an unfavorable prognosis in terms of survival, and it does so better than PCI (value > 20) or the other two scoring systems^[98].

Controversies

At the same time, there are also reserved attitudes regarding the CRS-HIPEC approach of PM. This is mainly the position of oncologists, who are refractory to this treatment option, using the argument of the risk/benefit ratio. The theoretical premise they use is based on the lack of difference (pathophysiology, evolution, and treatment) between PM and other systemic dissemination. The treatment is not adapted, so different protocols of systemic chemotherapy (from the classic de Gramont chemotherapy to oxaliplatin, irinotecan and biological molecular agents) are given in different clinical

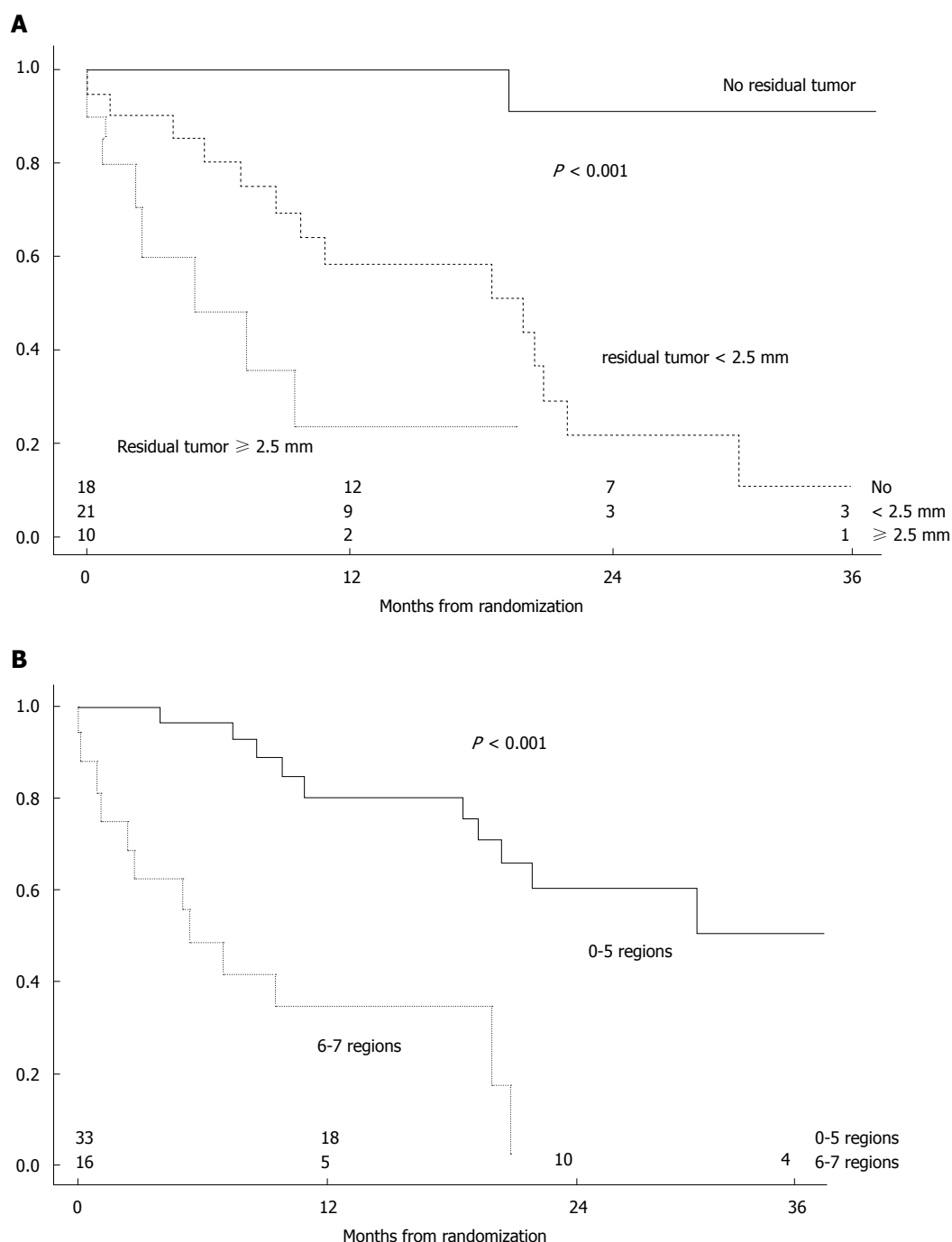


Figure 7 Kaplan-Meier survival curve of colorectal peritoneal carcinomatosis treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, stratified according to the size of residual tumors (A) and the number of regions with residual tumors (B)^[35] (with permission). Kaplan-Meier survival curve of CRS-HIPEC treatment, for Colorectal PM, stratified by the number of regions affected (A) and the number of regions with residual tumors (B)^[35]: <http://click.info.copyright.com/?qs=2b7046b10dd0c5471b8bb8bac0096e00e895f442c0326423c4ec2ccdd7b4701b99fd4bd5b32f0283>. CRS-HIPEC: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; PM: Peritoneal metastases.

trials, without considering the variances between the specific dissemination biology^[99-101]. The indispensable condition that oncologists require for inclusion in a clinical trial is the presence of measurable lesions. In the case of PM, this condition is almost impossible to meet. Imaging modalities have a low sensitivity in detecting the peritoneal dissemination, and this is true for computer tomography as well as for magnetic resonance imaging. The only parameters based on which the results of CRS-

HIPEC treatment may be assessed are disease-free survival and global survival.

Furthermore, concerning the oncologists' perspective, there is at least one more important argument supporting the dedicated multimodal treatment of PM: The studies matching hepatic metastases vs PM. These have shown that the pathway of dissemination are different and the treatment results are comparable (Figure 10), if treatment is potentially radical^[102-104].

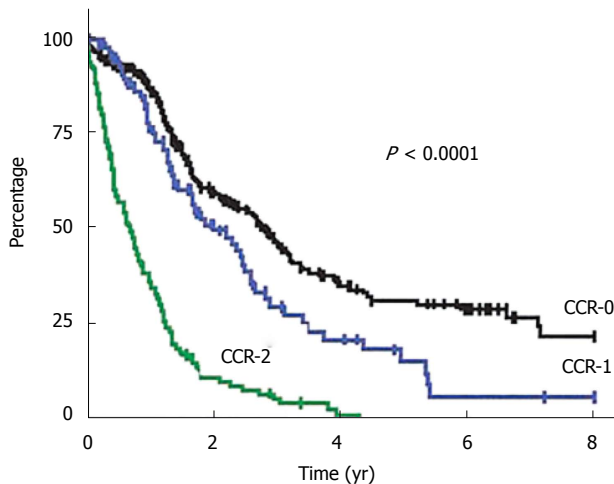


Figure 8 Kaplan-Meier survival curve of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy treatment, for colorectal peritoneal carcinomatosis, stratified by completeness of cytoreduction score^[33] (with permission). Kaplan-Meier survival curve of CRS-HIPEC treatment, for Colorectal PM, stratified by CCRS^[33]. Available from: URL: <http://click.info.copyright.com/?qs=2b7046b10dd0c5471bbb8bac0096e00e895f442c0326423b795894c1892230b84270e7e00c4e014>. CCRS: Completeness of cytoreduction score; CRS-HIPEC: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; PM: Peritoneal metastases.

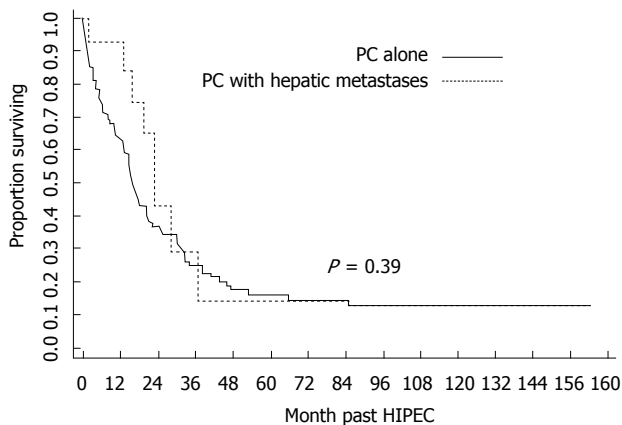


Figure 9 Kaplan-Meier survival curve of colorectal peritoneal carcinomatosis stratified according to hepatic involvement (peritoneal carcinomatosis alone vs peritoneal carcinomatosis with hepatic metastases)^[86] (with permission). Kaplan-Meier survival curve of Colorectal PM alone and PM with Hepatic Metastases^[86]. Available from: URL: <http://click.info.copyright.com/?qs=2b7046b10dd0c5471bbb8bac0096e00e895f442c032642364879a25688a50cc82757e6f8509f6e1>. PM: Peritoneal metastases.

Nowadays, in colorectal cancer, by analogy with Hepatic Metastases, multimodal CRS-HIPEC treatment has been adopted and is the indicated approach for CP, in most institutions in the United States^[31].

PM MULTIMODAL TREATMENT - RESEARCH PATHWAYS (2010-2014)

Currently, there is reason to talk about a higher level, where the problem of timing for CRS-HIPEC is raised. There are studies showing that PM prophylaxis is a valid approach.

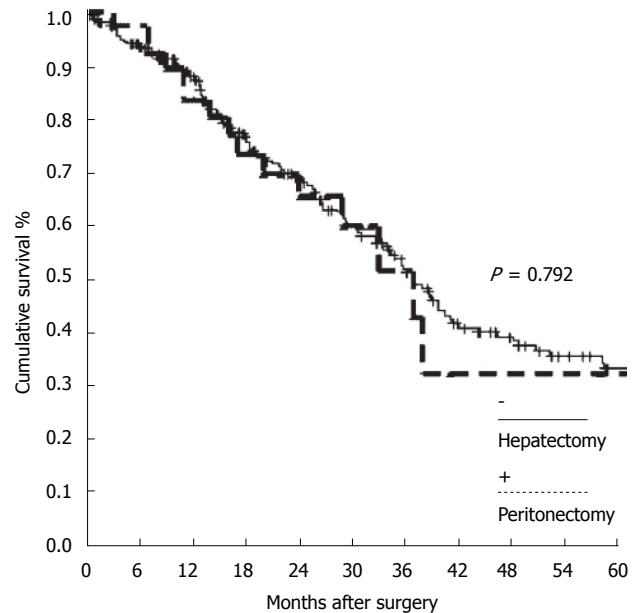


Figure 10 Kaplan-Meier survival curve for colorectal peritoneal metastases and colorectal hepatic metastases, who achieved optimal treatment^[102] (with permission). Kaplan-Meier survival curve for Colorectal PM and Colorectal Hepatic Metastases, with optimal treatment^[102]. Available from: URL: <http://click.info.copyright.com/?qs=751ae7c8f8e03ecb0a4741c79a3b341599b5318899e258b3d458148f31158885e37d98de5cb03229>. PM: Peritoneal metastases.

“Proactive management” defines a treatment concept, targeting patients with a high risk to develop PM, and prescribes surgery with HIPEC. In colorectal cancer, this has brought about a significant results ($P < 0.03$), related to control group (only surgery), in terms of PM developed and local recurrence (4% vs 28%, over a 48-mo follow-up period). Patients had also significant longer MS (59.2 mo vs 52 mo; $P < 0.04$) and disease-free survival ($P < 0.05$)^[105].

There was a hypothesis of second-look surgery at 1 year in patients at high risk for PM, after the first radical surgery for colorectal cancer. PM might be identified and treated at an earlier stage in about 55% of patients^[106]. Such researches were also led for gastric cancer, with promising preliminary results^[107,108].

In the same context of colorectal PM prophylaxis, the HIPEC laparoscopic approach was described and indicated after a mean interval of 6 wk (3-9 wk). This approach showed its feasibility^[109].

The main issue is selecting high-risk patients for developing PM. The debated risk factors are: Invasion of or beyond the serosa (pT3, pT4), perforated tumors, positive peritoneal cytology (augmented by immunohistochemistry), occurrence of Krukenberg tumors and mucinous type of tumor^[110]. Following a systematic review, three situations were identified to be associated with an increased frequency of metachronous PM development: Synchronous PM, ovarian metastases, and perforated tumor^[111].

Despite all human and material efforts dedicated to CRS-HIPEC treatment, there are patients in whom evolving disease occurs. The right question is whether

Table 2 Key aspects and peritoneal metastases model in the evolution of multimodal treatment

Period	PM treatment	Key aspects	PM model
All the period	"Conventional" systemic chemotherapy	Significant lower survival for PM <i>vs</i> other type of metastases	Colo-rectal
1950-1980	"Dedicated" intraperitoneal treatment - Palliative treatment	The basis for developing further cytostatic drugs	Malignant ascites
1980-2000	"Dedicated" intraperitoneal treatment - Multimodal radical treatment	Regional intraperitoneal normothermic and hyperthermic chemotherapy Peritonectomy procedures Define PCI and CCRS	Appendicular
2000-2010	Multimodal radical treatment - confirmation, aspects, patient selection, controversies	Significant higher survival <i>vs</i> palliative surgery and diverse systemic chemotherapy regimes Acceptable morbidity and mortality, no significant risk for medical team Respect de learning curve High costs Define the prognostic factors Position of oncologists Comparison with hepatic metastases	Colo-rectal Appendicular Pseudomyxoma peritonei Malignant peritoneal mesothelioma Gastric Ovarian PM with hepatic metastases
2010-2014	Multimodal treatment - research pathways	PM prophylaxis Laparoscopic HIPEC Integration of chemotherapy with surgery Extension of CRS	High-risk patients for developing PM Recurrent PM

PM: Peritoneal metastases; CCRS: Completeness of cytoreduction score; CRS-HIPEC: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; PCI: Peritoneal cancer index.

iterative treatment of PM might be a solution. There are at least three problems: Estimate the morbidity/mortality associated with the iterative treatment; documentation the prognostic factors; estimation the treatment results in terms of survival. The only few related studies define no clear attitude, supported by statistically significant data. Morbidity/mortality does not seem to differ significantly^[112-114], only one single study reporting increased values^[115].

HIPEC remains an important tool in the treatment of recurrent PM. Age ($P = 0.049$), time lapse between surgeries ($P = 0.08$), association of HIPEC ($P = 0.005$), and small bowel resections ($P < 0.001$) are statistically correlated with survival in PM appendiceal origin and malignant peritoneal mesothelioma^[113]. The iterative approach of colorectal PM results in a MS of 22.6 mo, with the following survival percentages: 1 year - 94%; 2 years - 48%; 3 years - 12%^[114].

The iterative approach treatment of the patient with PM and Hepatic Metastases has also promising results^[116].

An important research pathway is the way by which chemotherapy might be integrated into various treatment approaches: Perioperative neoadjuvant; HIPEC; bidirectional intraoperative; early postoperative intraperitoneal. The multidisciplinary approach of PM is based on treatment with complete CRS. Unfortunately, this cannot be achieved in approximately 70% of patients^[31].

The place of systemic chemotherapy in PM mul-

timodal treatment is difficult to assess. There are definite reports regarding the results of perioperative neoadjuvant chemotherapy, demonstrated by histological response in colon cancer^[117] and by increased survival in appendix cancer^[118]. Likewise, in gastric cancer, survival benefits have been shown for perioperative neoadjuvant and early postoperative intraperitoneal chemotherapy^[119].

The complexity of multimodal treatment approach is also certified by the wide range of cytostatic drugs and the occurrence of new principles. It is possible that Mitomycin C, in colorectal PM, in the context of complete CRS, may yield superior survival results compared to oxaliplatin^[120]. For gastric PM, catumaxomab seems to confirm positive results^[119], but in colorectal PM, bevacizumab leads to a double mortality rate after CRS-HIPEC treatment^[121].

Furthermore, as far as the array of CRS treatment is concerned, along with visceral resection and Peritonectomy procedures, surgery on the urinary tract was assessed. Partial cystectomy and ureter segmental resection were the most used. There was no further increase in the recorded morbidity or mortality and survival was comparable to that of patients with CRS-HIPEC without urinary tract surgery^[122,123]. The same statute was dedicated to the hepatobiliary procedures^[124].

At present, there are over 50 clinical trials underway, aimed at assessing multimodal radical PM treatment (<http://clinicaltrialsfeeds.org/clinical-trials/results/?term=HIPEC>). Out of these, some were reported in the literature: GASTRICHIP (D2 gastric resection and HIPEC

for locally advanced gastric cancer)^[125], COMBATAC (multimodal treatment of PM of appendiceal and colorectal origin)^[126], NCT01095523 (second-look and CRS-HIPEC treatment for colorectal cancer at risk for PM)^[127].

Key aspects and PM model in the evolution of multimodal treatment strategies

We summarized the key aspects of the evolution of multimodal treatment strategies in Table 2.

CONCLUSION

Initially marked by nihilism and fear, but benefiting from a remarkable joint effort of human and material resources (multi-center and -institutional research), over a period of 30 years, CRS-HIPEC found its place in the multimodal treatment of PM. The next 4 years were dedicated to the refinement of multimodal treatment, by launching research pathways. In selected patients, with requires training, it demonstrated a significant survival results (similar to the Hepatic Metastases treatment), with acceptable risks and costs. Also, CRS-HIPEC opens a lot of new opportunities with reference to the patients' selection and adopted methodology of this multimodal treatment.

The main debates regarding CRS-HIPEC were based on the oncologists' perspective and the small number of randomized clinical trials. It is hard to find a common view on different challenges, raised by CRS-HIPEC in the treatment of PM. Probably, Dr. Bernard Fisher met the same mistrust as he revolutionized breast cancer treatment and the same could be said about the surgical approach to metastatic melanoma. Indeed, there is a discrepancy between the great number of multi-center, -institutional studies and the small number of randomized clinical trials.

We may say that there are a series of determining factors, for the long-term assessment of multimodal PM treatment and the bias in medical studies type. Treatment complexity, results from the interaction between different therapeutic principles (surgery, chemotherapy, and hyperthermia), are an essential factor. Also, the peritoneal cavity is a complex anatomical space, and the pathogenesis of PM is indeed multifactorial conditioning (loco-regional and systemic dissemination). Not least, the multidisciplinary approach of PM implies the teamwork of specialists with different training, treatment concepts and results assessment, making it difficult to find a common view.

It is important to statement the patients with colorectal, appendicular, gastric, and ovarian peritoneal carcinomatosis, as well as patients with pseudomyxoma peritonei and peritoneal malignant mesothelioma must be informed about CRS-HIPEC as a valid treatment resource. The eligibility criteria for patients' selection will be assessed by multidisciplinary teams, in high level, dedicated treatment centers, according to the performance index, PCI, histological grading, the perspective to obtaining a complete CRS, and the availability of sustaining chemotherapy protocols.

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