

## Multimodal treatment of peritoneal malignancies – results of the implantation in a tertiary hospital

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**ABSTRACT: Introduction:** Peritoneal carcinomatosis is a condition that may be present in the natural history of colorectal cancer and some other tumors, such as pseudomyxoma peritonei. It has been associated with poor prognosis. The treatment for patients with this condition, up until recently, was systemic chemotherapy or palliative care to relieve the pain and suffering caused by peritoneal dissemination of certain cancers. Promising results, however, have been reported after the implementation of radical cytoreductive surgery followed by peroperative hyperthermic intraperitoneal chemotherapy. **Objective:** To evaluate the results of cytoreductive surgery and peroperative hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal carcinomatosis secondary to colorectal cancer and pseudomyxoma peritonei. **Results:** We retrospectively evaluated 24 patients from 2004 to 2011. Mean age was 51.31 years, and 54% were female. The primary diagnosis in 50.01% of the cases was pseudomyxoma peritonei, 41.66%, of colon cancer, and 8.33%, of mesothelioma. The overall complication rate was around 83%, two patients (8%) subsequently died between the 8<sup>th</sup> and 30<sup>th</sup> postoperative day. There was an association between the peritoneal carcinomatosis index (PCI) and operative time. The one-year survival rate in the group examined was 60% for colon cancer, and 78.5% for pseudomyxoma. Overall survival was 50% in three years. **Conclusion:** cytoreductive surgery combined with HIPEC is a treatment option for patients with peritoneal carcinomatosis of colorectal origin and pseudomyxoma. Despite the high rate of peroperative complications (83%), it was possible to achieve a superior survival rate in relation to conventional treatments reported in the literature.

**Keywords:** colorectal cancer; drug therapy; pseudomyxoma peritonei; surgery; peritoneum.

**RESUMO: Introdução:** A carcinomatose peritoneal é uma condição que pode estar presente na história natural do câncer colorretal e de algumas outras neoplasias, como o pseudomixoma peritoneal, sendo associada com um prognóstico desfavorável. O tratamento oferecido aos pacientes portadores dessa condição, até recentemente, era a quimioterapia sistêmica ou apenas os cuidados paliativos para aliviar a dor e o sofrimento causados pela disseminação peritoneal de determinadas neoplasias. Resultados promissores, no entanto, têm sido relatados após a implementação da cirurgia citorrredutora radical, seguida da quimioterapia hipertérmica intraperitoneal per-operatória. **Objetivo:** Avaliar os resultados da cirurgia citorrredutora e da quimioterapia intraperitoneal hipertérmica per-operatória (HIPEC) em pacientes portadores da carcinomatose peritoneal, secundária ao câncer colorretal e ao pseudomixoma peritoneal. **Resultados:** Foram avaliados, retrospectivamente, 24 pacientes de 2004 a 2011. A idade média foi de 51,31 anos, 54% eram do sexo feminino. O diagnóstico primário em 50,01% dos casos foi de pseudomixoma peritoneal, 41,66% de câncer de cólon e 8,33% de mesotelioma. A taxa de complicação global girou em torno de 83%, sendo que dois pacientes (8%) evoluíram para o óbito no pós-operatório, entre 8 e 30 dias. Houve associação entre o índice de carcinomatose peritoneal (PCI) e o tempo operatório. A sobrevida em um ano, no grupo analisado, foi de 60% para o câncer de cólon e de 78,5% para o pseudomixoma. A sobrevida global foi de 50% em 3 anos. **Conclusão:** A cirurgia citorrredutora combinada com a HIPEC é uma opção de tratamento para pacientes com carcinomatose peritoneal originária de câncer colorretal e de pseudomixoma. A despeito de uma alta taxa de complicação per-operatória (83%) foi possível alcançar uma sobrevida superior a do tratamento convencional relatado na literatura.

**Palavras-chave:** câncer colorretal; quimioterapia; pseudomixoma peritoneal; cirurgia; peritônio.

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## INTRODUCTION

Peritoneal carcinomatosis, which is usually considered as the end-stage of many malignant neoplastic diseases, has few treatment options, leading to suffering and fast aggravation of the general status. Conditions such as intestinal obstruction and cachexia appear, and they accelerate death in patients with this condition. Indeed, a compromised peritoneum leads to a reserved prognosis, with mean survival estimated in up to three months for more aggressive tumors, such as diffuse gastric cancer. This condition happens in 25% of colorectal tumors, being present in 8% of the cases at the moment of diagnosis, leading to a mean survival rate of 5.2 months<sup>1</sup>, if not treated, and 14 to 20 months, with systemic chemotherapy<sup>1</sup>. In 1982, Dr. Paul Sugarbaker described the cytoreductive surgery (CRS) followed by the peroperative hyperthermic intraperitoneal chemotherapy (HIPEC), and demonstrated an increased survival for different types of tumors with peritoneal compromise.

This technique is currently considered as the standard treatment for pseudomyxoma peritonei (PMP), as well as a treatment option for colorectal carcinomatosis, since it provides increased survival, from 30 to 50% in 5 years. As for the carcinomatosis originating from ovarian tumors, gastric cancer and other intra-abdominal neoplasms, there is not a well established benefit, being source for clinical studies.

In these cases, prognosis, as well as the response to CRS and HIPEC, depend mainly on the selection of patients, besides other factors, such as the histology of the primary neoplasm, the degree of differentiation, the success of cytoreduction and response to the adjuvant systemic chemotherapy (CT). The therapeutic decision addressed by the histological type and primary location of the neoplasm provides the necessary tools to individualize care and select patients with higher chances of having better results with the cytoreductive surgery, with or without HIPEC.

This study aims to evaluate the results obtained from patients with neoplasms that compromise the peritoneum who were treated with CRS and HIPEC, all of whom were referred to treatment after all the possibilities of a conventional treatment had been ruled out. The study was approved by the Ethics Committee of Hospital Felício Rocho (CEP-HFR), protocol number 393/11.

## MATERIALS AND METHODS

The study was conducted at Hospital Felício Rocho from 2004 to 2011. Twenty four patients were included, all of whom were submitted to complete CRS, with or without hyperthermic intraperitoneal chemotherapy.

These patients' data were registered in a specific protocol for follow-up purposes. Data were collected during admission for surgical treatment, subsequent admissions and postoperative outpatient clinic follow-up. Gender, age group, peritoneal carcinomatosis index (PCI), length of surgery, obtained surgical results, histopathological pattern, morbidity, time of admission to intensive care and hospital, and survival rate of treated patients were analyzed.

The patients were submitted to preoperative staging in order to analyze the extension of the disease in the abdomen, as well as to rule out distant disease. The presence of resectable liver metastases was not considered as an isolated criterion to contraindicate the procedure.

A computed tomography or a nuclear magnetic resonance (NMR) of abdomen and pelvis was performed to evaluate the extension of the abdominal disease. A thoracic tomography was also used to study the distant disease, and in case of dubious lesions, the positron emission tomography was performed (PET-CT).

### **Surgical procedure**

At first, a balanced general anesthesia was administered and all hemodynamic parameters were carefully monitored.

The procedure was performed with a broad median laparotomy for unrestricted access to the abdominal cavity, thus enabling the complete evaluation and detection of possible contraindications to CRS. Afterwards, PCI was analyzed. When necessary, primary tumor resection was performed according to the oncologic criteria (lymph node excision and proper surgical margins). The peritoneum was resected in compromised sites, with high power electrocautery of the remaining tumor granulation, with the objective to extinguish all macroscopic disease. The liver capsule was also resected, when necessary, after the injection of subcapsular air, in order to facilitate dissection and after chemotherapy. Lesions smaller than 3 mm in loops or on visceral surfaces, which are difficult to resect, were cauterized with argon scalpel.

According to CRS criteria, cytoreduction is considered as complete (CRC-0) when there is no macroscopic implant left. In case implants <2.5 mm remain, cytoreduction is considered as CRC-1. When the remaining implants are between 2.5 mm and 2.5 cm: CRC-2; and when they are >2.5 cm, CRC-3.

In the analyzed cases, cytoreduction was complete, and no detectable macroscopic lesion remained (CRC-0).

### Peritoneal chemotherapy

In all cases, the “coliseum technique” was used (open technique)<sup>1</sup>. Mitomycin was applied for most of the cases<sup>1</sup>, with perfusion time of 90 minutes, being part of the dose at the beginning and the other part on the second half of the time, with the objective to reach a more stable level of chemotherapy during perfusion, and at the same time, maintaining adequate diuresis and temperature between 41 and 43°C. Drains were left, and the patients were systematically referred to the Intensive Care Unit (ICU). Abdominal drainage was progressively removed when the drainage was reduced to less than 100 mL in 24 hours. The thorax was drained every time the diaphragm was opened, and then the drainage was removed after the patient was taken out of mechanic ventilation due to the risk of pneumothorax for pleural lesion caused by the chemotherapy. Anastomoses and/or the confection of ostomy were performed as soon as possible, regardless of performing intracavitary CT. When the vagina had to be opened, it was sutured before CT in order to avoid burns caused by extravasation of chemotherapeutics in the perineum.

In cases of colorectal tumors, in which PCI was higher than 22, surgical resection was contraindicated, except when this index was not well established in literature. In that case, resection was performed even with PCI higher than 30. For those who underwent surgery for more than 12 hours, HIPC was performed afterwards, 2 or 3 days after peritonectomy. In one of these cases, CT was not performed due to the patient’s unstable condition.

The obtained results were compared to data from literature, considering as sources the following online data bases: Medline, Embase, PubMed, Cochrane Database of Systematic Reviews and Database of Abstracts and Reviews.

Kaplan-Meier test was used to analyze the global survival (GS) stratified by the base disease.

## RESULTS

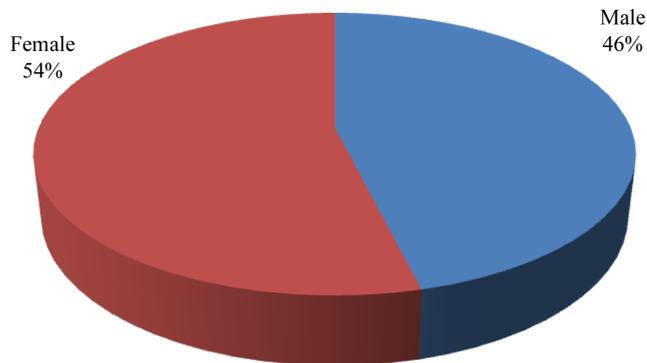
### Characteristics of the patients

The characteristics of 24 patients were related to the treatment and its surgical and postoperative analyzed results from 2004 and 2011, retrospectively. Variables such as the histopathological origin of the lesion, PCI, time of surgery, resected organs, presence of anastomoses, used chemotherapeutic, time of intensive care and hospitalization, postoperative complications and presence of recurrence were factors analyzed in the results.

Out of the 24 patients, 54% were females, and 40% underwent cytoreduction due to stage IV colorectal neoplasm. Mean age was 51.31 years (Table 1, Graph 1).

### Surgical procedure

PCI was 18.81, in average, ranging from 3 to 39, and mean operating time was 8h and 33 min (Table 2).



Graph 1. Gender of patients.

Table 1. Description of the patients’ age.

	Descriptive statistics				
	Mean	Median	Standard deviation	Minimum	Maximum
Age	51.31	51.00	13.01	14	80

At the end of the surgery, all the 24 patients were CRC-0.

There was statistical significance between PCI and operating time ( $p=0.03$ ).

The global complication rate was 83%, and the most common ones were: evisceration (33%), abdominal sepsis (25%), pancreatic fistula (17%) and atrial fibrillation (17%). The mean of complications was 18.8% (Table 3).

### Chemotherapy

HIPEC was performed in 21 patients (84%). Out of these, mitomycin was used in 20 cases (95.2%), and 90-minute perfusion was performed in 85.7% of the time. In one patient, it was 75 minutes, and 60 minutes for another one.

For one patient, HIPEC was performed with oxaliplatin and irinotecan for 30 minutes, 1 h after peroperative systemic CT with fluorouracil (5-FU) and leucovorin, as standardized by Elias et al.<sup>2</sup>.

### Recurrence and survival

There was no statistical significance between the presence of complications and the base disease ( $p>0.05$ ), nor between complications and PCI ( $p>0.05$ ).

Time of intensive care stay was not statistically correlated with PCI.

As to survival, however, PCI seems to establish the inverse relation. That is, for the same base disease, in each case, survival was higher and lower than the PCI.

The association between survival and diagnosis was demonstrated based on the Kruskal-Wallis test, through the Kaplan-Meier curve (Graphs 2 and 3).

**Table 2.** Kolmogorov-Smirnov test.

	PCI	Time of surgery (h)
n	24.00	24
Mean	18.81	8.33
Standard deviation	12.66	4.02
Kolmogorov-Smirnov	0.70	0.56
p-value	0.70	0.91

PCI: peritoneal carcinomatosis index.

## DISCUSSION

Carcinomatosis can occur simultaneously with the primary tumor or with the recurrence after surgical resection. In the first case, the dissemination of malignant cells is spontaneous, after the tumor invades the serous membrane or perforates affected organs. In the second case, carcinomatosis can happen even in the absence of angiolymphatic invasion or hematogenous metastasis.

The formation of tumor emboli at the peroperative period can be responsible for the implantation in the peritoneum<sup>2,3</sup>. The beginning of every treatment is based on the fact that carcinomatosis can be considered as a local dissemination of the disease to the peritoneum, instead of a systemic disease, as it was first considered.

Since 1980, new methods to treat patients with tumor dissemination to the peritoneum appeared in literature. These patients are difficult to treat, both therapeutically and emotionally, once they are in a context of therapeutic failure, with progressive loss in quality of life<sup>4</sup>.

The peritoneal dissemination of some tumors should be treated as the locoregional progress of the disease<sup>1,4,5</sup>. Thus, a therapeutic alternative was developed based on the surgical resection of the macroscopic peritoneal disease, followed by HIPEC to treat the remaining microscopic disease.

With this therapeutic approach, the significant increase of 5 years in survival rates was reported, in 30 to 50% of the selected group of patients, who were previously considered as end-stage<sup>6</sup>.

**Table 3.** Descriptive statistics: types and rates of complications.

Complications	Rates (%)
Evisceration	33
Abdominal sepsis	25
Pancreatic fistula	17
Atrial fibrillation	17
Anastomotic fistula	12
Bleeding	0.4
SIRS	100
Global rate	83

SIRS: systemic inflammatory response syndrome.

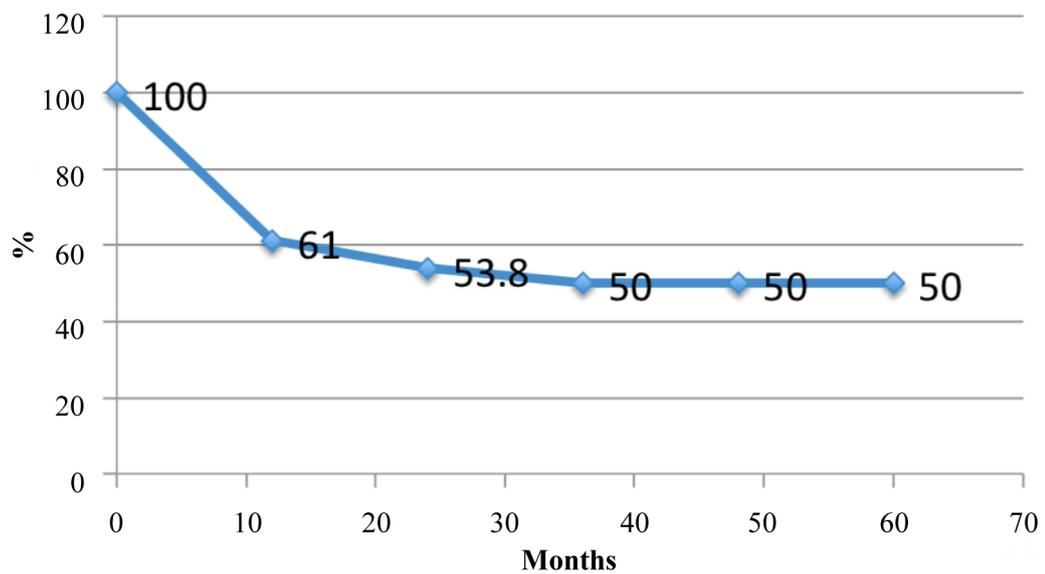
However, it is worth to mention that CRS is associated with high morbidity rate, so the selective indication and choice of the patients are necessary.

In our series, the morbidity and the mortality have been in accordance with the rates described in literature. Most of the cases led to cytoreduction had been diagnosed for 10 months, in average.

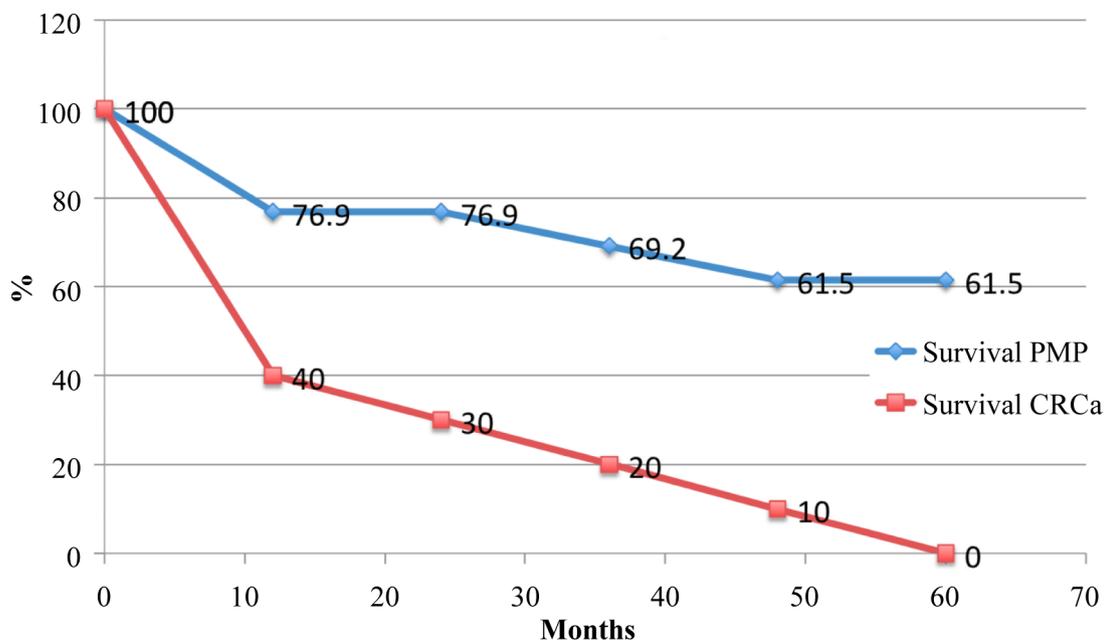
PCI, unfavorable compromised locations, presence of liver metastases and complete cytoreduction

can be understood as independent prognostic factors correlated with survival<sup>1,4,7,8</sup>.

Some studies have shown that PCI>13 (in cases of colorectal cancer) and incomplete cytoreduction have a reserved prognosis. Our experience corroborates with the result of these studies, especially concerning the global survival rate. IN these cases, HIPEC also has minimum benefits as to the increased survival, thus being contraindicated.



Graph 2. Global survival in months.



PMP: pseudomyxoma peritonei; CRCa: colorectal carcinoma.

Graph 3. Global survival for base disease (in months)

**Table 4.** Descriptive statistics of peritoneal carcinomatosis index per type of complication.

	Complications						Total	
	No complications		Severe complications		Other complications		n	%
	n	%	n	%	n	%		
CRC	3	60.0	0	0.0	9	50.0	12	46.2
Others	0	0.0	0	0.0	2	11.1	2	7.7
PMP	2	40.0	3	100.0	7	38.9	12	46.2
General	5	100.0	3	100.0	18	100.0	26	100.0

CRC: colorectal cancer; PMP: pseudomyxoma peritonei.

At the end of one year, global survival in our study was 61.1% (Table 4). Despite the heterogeneous volume of cases throughout the analyzed years, we obtained a curve similar to that of major studies that have already been published.

As we do not have the 5-year follow-up of all the 24 patients, we discriminated the number of cases according to the follow-up years for the analysis of survival.

In this curve, we were also able to reproduce what has already been published in literature, with mean survival of 50% in 5 years.

Systemic CT with 5-FU+leucorovin associated with HIPEC with oxaliplatin and irinotecan was used in one patient, who had not responded well to the conventional adjuvant CT scheme. However, she had already presented good response to irinotecan, which was a decisive factor to indicate cytoreduction, thus motivating the adoption of this new scheme<sup>2,3</sup>.

However, it is worth to mention that this sample is small, and the nature of the analysis is purely empirical, in order to create hypotheses, so no definitive conclusion can be made.

The presented results suggest that the selective choice of patients that may really benefit from this treatment is essential. In our service, we follow the criteria adopted at the Peritoneal Surface Oncology Group, in 2006<sup>6</sup>.

## CONCLUSION

Peritoneal carcinomatosis has been characterized as an end-stage disease of limited survival and little response to palliative treatment with systemic CT for a long time<sup>1,4,9</sup>.

We can compare the situation of peritoneal carcinomatosis to that of the isolated liver metastases, in which high survival rates can be obtained with surgical resection of the macroscopic disease and subsequent treatment with systemic CT for the microscopic residual disease. The combination CRS+HIPEC to treat for colorectal peritoneal carcinomatosis leads to a survival rate of 5 years, similar to that published for the resection of liver metastases of the same origin<sup>9</sup>.

The standardization of treatment protocols, as well as multicentric studies, have been proposed to better understand this therapy and to optimize clinical results<sup>8</sup>.

CRS+HIPEC are currently doable procedures that tend to increase survival. They represent the potential cure for selected patients who do not dispose of alternatives<sup>1,4,9</sup>.

The results of this study corroborate with the present status, and validate the applicability of this treatment strategy in our service.

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