



Review Article

Peritoneal carcinomatosis treated with cytoreductive surgery and intraperitoneal chemotherapy

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ABSTRACT

Introduction: To evaluate the combined treatment with cytoreductive surgery and intraperitoneal chemotherapy for peritoneal carcinomatosis arising from colorectal cancer, pseudomyxoma peritonei and mesothelioma.

Methods: Data were obtained from 73 patients with peritoneal carcinomatosis arising from colorectal cancer (52.1%), pseudomyxoma peritonei (41.1%) or mesothelioma (6.8%) between 2002 and 2011. We reported the morbidity grade (II, III and IV), mortality and survival rates of the candidates after cytoreductive surgery and intraperitoneal chemotherapy.

Results: 41 (56.2%) women participated, and the median age was 50 years. Thirty-nine patients (53.4%) underwent complete cytoreductive surgery and intraperitoneal chemotherapy. Patients who underwent a complete cytoreduction received intraperitoneal chemotherapy with mitomycin C, from which only 16/39 (41%) had hyperthermic intraperitoneal chemotherapy (41–42°C). The overall morbidity rate was 23.3% and the grade III/IV complication rate was 12.3%. The overall mortality rate was 5.5%. The univariate analysis showed that cytoreductive surgery and intraperitoneal chemotherapy ($p = .029$), a blood transfusion ($p = .002$) and the operative time ($p = .001$) were significant for the occurrence of postoperative complications. Patients with peritoneal carcinomatosis from colorectal cancer who underwent complete cytoreductive surgery and intraperitoneal chemotherapy had overall survival rates of 81.3%, 12.5% and 12.5% at 1, 3 and 5 years, respectively. Patients with peritoneal carcinomatosis from pseudomyxoma peritonei who underwent complete cytoreductive surgery and intraperitoneal chemotherapy had overall survival rates of 84.2%, 77.7% and 77.7% at 1, 3 and 5 years, respectively.

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Conclusion: The combined treatment for peritoneal carcinomatosis may be performed safely with acceptable morbidity and mortality in a specialized unit setting. Although over half of patients underwent normothermic intraperitoneal chemotherapy, our results were comparable to results from others centers.

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Carcinomatose peritoneal tratada com cirurgia citoreductiva e quimioterapia intraperitoneal

R E S U M O

Palavras-chave:

Cirurgia citoreductora
Quimioterapia intraperitoneal
Carcinomatose peritoneal
Cancer colorretal
Pseudomixoma peritoneal

Introdução: O objetivo foi avaliar o tratamento combinado da cirurgia citoreductora e quimioterapia intraperitoneal em pacientes com carcinomatose peritoneal secundária ao câncer colorretal, pseudomixoma peritoneal e mesotelioma.

Métodos: Foram obtidos dados de 73 pacientes com carcinomatose peritoneal secundária ao cirurgia citoreductora (52,1%), pseudomixoma peritoneal (41,1%) ou mesotelioma (6,8%). Foram avaliados o grau de morbidade, a taxa de mortalidade e as taxas de sobrevida após a cirurgia citoreductora e quimioterapia intraperitoneal.

Resultados: 41 (56,2%) pacientes do sexo feminino participaram, com média de idade de 50 anos. 39 pacientes (53,4%) foram submetidos a cirurgia citoreductora completa e quimioterapia intraperitoneal. Todos esses receberam Mitomicina C, sendo 16/39 (41%) quimioterapia intraperitoneal hipertérmica (41–42°C). A morbidade global foi 23,3%, com taxa de mortalidade global de 5,5%. A análise univariada mostrou que câncer colorretal e quimioterapia intraperitoneal ($p = .029$), transfusão sanguínea ($p = .002$) e tempo operatório ($p = .001$) foram associados com complicações pós-operatórias. Pacientes com carcinomatose peritoneal secundária ao cirurgia citoreductora submetidos a cirurgia citoreductora completa e quimioterapia intraperitoneal tiveram sobrevida global de 81,3%; 12,5% e 12,5% em 1, 3 e 5 anos, respectivamente. Os pacientes com pseudomixoma peritoneal que foram submetidos a cirurgia citoreductora completa e quimioterapia intraperitoneal tiveram sobrevida global de 84,2%; 77,7% e 77,7% em 1, 3 e 5 anos, respectivamente.

Conclusão: O tratamento combinado para carcinomatose peritoneal é seguro quando realizado em centros terciários com experiência no procedimento. Embora mais da metade dos pacientes tenham sido submetidos a quimioterapia intraperitoneal normotérmica após a cirurgia citoreductora completa, os resultados podem ser comparados a de outros centros que utilizam exclusivamente a quimioterapia hipertérmica.

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Introduction

Peritoneal carcinomatosis (PC) is now considered to be a locoregionally advanced form of presentation rather than a widespread system disease. Peritoneal metastasis may arise from several cancers, including colorectal adenocarcinoma (CACR), pseudomyxoma peritonei (PMP), mesothelioma (MST), ovarian adenocarcinoma and sarcoma.¹⁻⁴ In the Sugarbaker protocol, the main course of therapy is to treat the macroscopic disease with complete cytoreduction surgery (CRS) and treat the remaining microscopic malignant peritoneal disease with intraperitoneal chemotherapy (IPC). This combined treatment for some types of carcinomatosis brought new horizons for patients previously considered terminal with near and inevitable fatal outcomes.⁵ The results for patient survival with non-invasive cancers, such as PMP and MST, are better

than those for patients with invasive cancer such as colorectal cancer.⁶

The intraperitoneal chemotherapy is usually delivered as an intraperitoneal temperature of 41.0–42.5°C, the so-called HIPEC (hyperthermic intraperitoneal chemotherapy).⁷ However, the role of hyperthermia is not validated by any randomized clinical studies. In fact, during the Sugarbaker initial experience the normothermic chemotherapy was used. When the comparison of survival between patients with colorectal cancer who received normothermic chemotherapy versus those who received hyperthermic chemotherapy was done, the survival median survival was 33 months in both groups.⁸

The aim of this study was to evaluate the morbidity and mortality associated with the peritonectomy procedures and IPC (normothermic and hyperthermic) as well as survival in patients with PC treated at the University Hospital of the Federal University of Minas Gerais (UFMG), Brazil.

Patients and methods

Our study protocol was approved by the institutional review board at Federal University of Minas Gerais (Number: 155.494). We retrospectively evaluated all of the patients who were candidates for a laparotomy to treat PC with CRS and IPC at the Hospital of Minas Gerais Federal University during the period from 2002 to January 2012. Patients with invasive tumours, including colon and rectum cancers (CRC), and non-invasive tumours, including pseudomyxoma peritonei (PMP) and mesothelioma (MST), were included. To grade the complications, we used the classification proposed by Clavien et al.⁹ Before surgery, patients meeting the inclusion criteria signed a consent form after receiving oral and written information from a physician authorizing the future use of information regarding the procedure.

The peritoneal carcinomatosis index (PCI) was used to classify the extension of PC. The peritonectomy procedures were performed according to the Sugarbaker guidelines. All of the operations were performed by one of the authors with experience in cytoreductive surgery (RGS). The extent of peritoneal carcinomatosis was assessed during the surgical exploration according to the peritoneal cancer index (PCI), which assigns a score of 0 (no peritoneal carcinomatosis) to 3 (tumour nodules > 5 cm in diameter) to each of the 13 areas of the abdominal cavity based on invasion (final score, 0–39).⁵ The intention of the surgery was to remove all of the visible intraperitoneal tumours (completeness of cytoreduction CC-0) or, alternatively, to remove all of the tumours but leave small deposits of 2.5 mm or less (completeness of cytoreduction CC-1). Only patients with a complete CRS procedure (CC0/1) received IPC (either hyperthermic or normothermic). Intraperitoneal chemotherapy was delivered using the “coliseum” open abdomen technique.^{7,10} The patients who were administered this procedure were given peritoneal dialysis solution with mitomycin C at a dose of 15 mg/m² for men and 10 mg/m² for women over 90 min. When possible, the chemotherapy was delivered at a temperature of 41–42 °C. In other cases, the IPC was normothermic without circulation of the peritoneal solution. In the present study, we used only the complications classified as Group II, III, IV and V in the Clavien classification.⁹ The survival was measured from the date of procedure completion until the date of death or censoring.

All patients were followed up with examinations. CT of chest, abdomen and pelvis were performed at 6, 12, 18, 24, 36, 48 and 60 months after the surgery.

Patients with colorectal cancer received postoperative adjuvant chemotherapy for 3–6 months, mainly with 5-fluorouracil and folinic acid/leucovorin. Oxaliplatin regimen was not standard at Brazilian public health system in the period of the study and was not used in the majority of the cases.

Statistical analysis

The clinical data were recorded in a standard database form and evaluated by the same author. The continuous variables were expressed as medians and ranges. To study the relationship between variables, we used Student's t test for the

normal variables and the U Mann–Whitney test for non-normal variables. The categorical variables were compared using Chi-square and Fisher's exact tests when appropriate. The survival analysis was performed using the Kaplan–Meier method, and the comparison of curves was performed with the Long-rank test. A standard probability cut-off ($p < .05$) was chosen as the significance level.

Results

Seventy-three patients underwent laparotomy with the intention of treating CP with CRS and IPC. Forty-one (56.2%) patients were females, and 32 were males (43.8%). The median age was 50 years (range: 20–80). Only 2 patients had rectal cancer. Thirty-nine patients underwent a complete cytoreduction (53.4%), 18 (24.7%) underwent a palliative operation, and 16 (21.9%) underwent an open-and-close procedure.

The patients with a complete cytoreduction, 39/73 (53.4%), underwent IPC, and 16/39 (41%) of these patients were hyperthermic. In the other cases, the IPC was normothermic. All of these patients underwent 90 min of IPC (Table 1).

Colorectal cancer

Of the 38 cases of CRC, only 2 (5.3%) patients had PC due to rectal cancer. Eighteen were (47.4%) females, and their ages ranged between 24 and 71 years with a median of 47.5 years. Half of the patients were classified as having a mucinous histologic subtype, and 6 (15.8%) had ascites at the time of laparotomy. Sixteen patients (42.1%) were treated with complete CRS and IPC (CC-0/CC-1). Chemohyperthermia was possible in only 6 (15.8%) of the patients. Of the remaining 22 (57.9%) patients, 12 (31.6%) underwent some type of palliative procedure, and 10 (26.3%) underwent the open-and-close surgery. Twenty-five (65.8%) patients had lymph node metastases in the surgical specimen. The median PCI was 20 (ranging from 3 to 39). Ten patients (26.3%) had a PCI between 0 and 10, 12 (31.6%) between 11 and 20, and 16 (42.1%) had a PCI between 21 and 39. Among the 16 patients who underwent complete CRS, the PCI varied between 3 and 24 with a median of 10.5 ($p < .05$). The operative time, among all patients, ranged from 60 min to 670 min with a median of 277.5 min. Among the patients who underwent a complete cytoreduction, the operative time ranged between 150 and 670 min with a median of 480 min ($p < .05$). Eight (21.1%) patients received blood transfusions.

Pseudomyxoma peritonei

Among the 30 patients with PMP, 17 (56.7%) were female, and 13 (43.3%) were male. The median age was 53.5 years (ranging between 28 and 80 years). Fourteen patients (46.7%) were classified as having a disseminated peritoneal adenomucinosis (DPAM) subtype, 15 (50%) were classified as having a peritoneal mucinous carcinomatosis (PMCA), and one patient (3.3%) was classified as having mucinous carcinomatosis with intermediate or discordant features (PMCA-I/D). In all of the patients, the primary site of cancer was the appendix. Nineteen patients (63.3%) were treated with complete CRS (CC-0 or CC-1). In 8

Table 1 – Characteristics of 73 patients who underwent laparotomy with intention of treating PC with cytoreductive surgery and hyperthermic chemotherapy.

	CRC	PMP	MST	Total
Patients	38 (52%)	30 (41.1%)	5 (6.9%)	73 (100%)
Age (years)				
Median (range)	47.5 (24–71)	53.5 (28–80)	42 (20–71)	50 (20–80)
Sex				
Male	20 (52.6%)	13 (43.3%)	1 (20%)	32 (43.8%)
Female	18 (47.4%)	17 (56.7%)	4 (80%)	41 (56.2%)
Completeness of cytoreduction				
Complete (CC-0 and CC-1)	16 (42.1%)	19 (63.3%)	4 (80%)	39 (53.4%)
Palliative procedure	12 (31.6%)	6 (20%)	–	18 (24.7%)
Open-and-close	10 (26.3%)	5 (16.7%)	1 (20%)	16 (21.9%)
Intraperitoneal chemotherapy				
Yes	16 (42.1%)	19 (63.3%)	4 (80%)	39 (53.4%)
No	22 (57.9%)	11 (36.7%)	1 (20%)	34 (46.6%)
Hyperthermia				
Hyperthermic (41–43°C)	6 (15.8%)	8 (26.7%)	2 (40%)	16 (21.9%)
Normothermic	23 (26.3%)	11 (36.7%)	2 (40%)	23 (31.5%)
NA	22 (57.9%)	11 (36.7%)	–	34 (46.6%)
Operative time (Min)				
Median (range)	277.5 (60–670)	415 (60–840)	360 (60–480)	360 (60–840)
PCI				
0–10	10 (26.3%)	4 (13.3%)	–	14 (19.2%)
11–20	12 (31.6%)	3 (10%)	2 (40%)	17 (23.3%)
21–39	16 (42.1%)	21 (70%)	3 (60%)	40 (54.8%)
Data missed	–	2 (6.7%)	–	2 (2.7%)
Hemotransfusion				
Yes	8 (21.1%)	12 (40%)	1 (20%)	21 (28.8%)
No	30 (78.9%)	18 (60%)	4 (80%)	52 (71.2%)

CRC, colon and rectal cancer; PMP, pseudomyxoma peritonei; MST, mesothelioma; NA, not applied; Min, minutes; PCI, peritoneal carcinomatosis index.

(26.7%) of the patients, chemohyperthermia was possible. Of the remaining 11 (36.7%), 6 (20%) underwent some type of palliative procedure, and 5 (16.7%) underwent the open-and-close procedure. The PCI ranged from 5 to 39 with a median of 39. Four (13.3%) patients had a PCI between 0 and 10, 3 (10%) had a PCI between 11 and 20, and 21 (70%) has a PCI between 21 and 39. The PCI data could not be obtained from two patients (6.7%). In the patients undergoing CRS, the PCI ranged from 5 to 39 with a median of 28. The operative time in this group of patients ranged from 60 min to 840 min with a median of 415 min. Twelve (40%) patients received blood transfusions.

Mesothelioma

We only evaluated 5 patients with mesothelioma, of which 4 (80%) were female. The age ranged between 20 and 71 with a median of 42 years. Four (80%) were treated with complete CRS and IPC (CC-0 or CC-1). In two of the patients (40%), chemohyperthermia was possible. The male patient (20 years-old) underwent the open-and-close surgery. The PCI ranged from 15 to 39 with a median of 28. Two patients (40%) had a PCI between 11 and 20, and 3 (60%) had a PCI between 21 and 39. The operative time ranged from 60 min to 480 min with a median of 360 min.

Morbimortality

The overall rate of type II, III and IV complications was 23.3%, and the most common complication was an anastomotic leak, which occurred in 4 cases (5.48%). Other complications were divided according to the severity classes.

Of the variables studied, treatment with complete CRS and IPC was related to complications compared with patients undergoing a palliative procedure or open-and-close surgery ($p = .029$). The operative time ($p = .001$) and blood transfusions ($p = .002$) were also associated with complications.

Four patients died postoperatively, with an overall mortality rate of 5.5%. Among these patients, two developed pneumonia, respiratory failure and death after prolonged hospitalization in the intensive care unit. The other two patients died in the first days after surgery, with an increased inflammatory response to surgical trauma and multiple organ failure.

In patients who underwent a complete cytoreduction and IPC, the rate of postoperative mortality was 7.7% (3/39). If we consider only the severe complications (grades III and IV) in this group, the rate of complications was 17.9%. There were no grade II, III or IV complications in the open-and-close group.

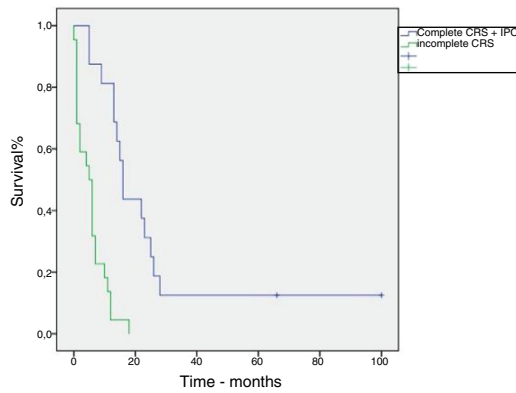


Fig. 1 – Kaplan–Meier curve. Overall survival of patients with peritoneal carcinomatosis secondary to colorectal cancer treated with cytoreductive surgery and intraperitoneal chemotherapy.

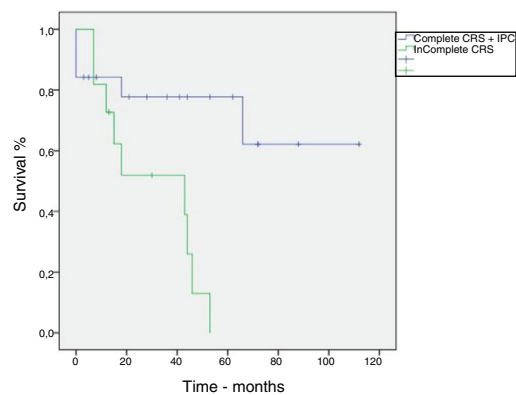


Fig. 2 – Kaplan–Meier curve. Overall survival of patients with peritoneal carcinomatosis secondary to pseudomyxoma peritonei treated with cytoreductive surgery and intraperitoneal chemotherapy.

Survival

The overall survival of patients with CRC undergoing treatment with complete CRS and IPC was 81.3%, 12.5% and 12.5% at 1, 3 and 5 years, respectively, with a median survival of 16 months. Among the patients who did not undergo the combined treatment, the survival was 45% at 1 year and 0% at 3 years ($p < .05$). The median survival was 5 months (Fig. 1).

The overall survival of patients with PMP undergoing treatment with complete CRS and IPC was 84.2%, 77.7% and 77.7% at 1, 3 and 5 years, respectively. A median survival was not reached. Among the patients who did not undergo the combined treatment, the survival rates were 72.7%, 39% and 0% at 1, 3 and 5 years, respectively ($p < .05$), with a median survival of 43 months (Fig. 2).

Among the 5 patients with MST, 4 were alive at follow-up times of 14, 40, 53 and 56 months. Among these four surviving patients, one underwent the open-and-close procedure and had a PCI of 39. One patient died after a postoperative laparotomy for bowel obstruction and had recurrent disease after 9

months of follow-up. She was classified as CC0-CC-1 after the cytoreductive surgery and underwent chemohyperthermia.

Discussion

In the present study, we observed good survival curves in patients with PC secondary to PMP and CRC submitted to CRS and IPC, regardless of the addition of hyperthermia. The rate of morbidity was also low in the present series. Our results are consistent with previous reports in the literature.^{4,10-18}

The majority of published studies have used the chemohyperthermic regimen. In this study, patients with a complete cytoreduction (39/73) underwent IPC, but only 16/39 (41%) of these patients had chemohyperthermic therapy. In the other cases, the IPC was normothermic due to unavailability of the hyperthermia and perfusion apparatus. Despite the inability to compare our IPC results (some were under normothermic and some were under hyperthermic conditions), our study achieved similar results in terms of survival and complications when we compared our results to others studies in the literature. Doubts about the necessity of hyperthermia have not been resolved. In a randomized study, rats treated with IPC had longer survival rates than those treated only with chemotherapy with or without hyperthermia.¹⁹ However, no randomized controlled trial in humans comparing normothermic versus chemohyperthermic IPC currently exists. In addition, it is interesting to note that in the Sugarbaker series of complete cytoreductive surgery in CRC patients, the difference in survival between patients who received normothermic chemotherapy versus those who received hyperthermic chemotherapy was not statistically significant. In fact, the survival median survival was the same (33 months) in both groups.⁸ Therefore, the role of the hyperthermia in this treatment regimen is still controversial.

The median PCI of patients who were candidates for CRS and IPC at our institution was 25, demonstrating that our study included cases with advanced carcinomatosis. Elias et al. showed that a PCI greater than 24 is an important prognostic factor for relapse in patients with CRC. In this study, only one of six patients showed no recurrence with this degree of carcinomatosis.²⁰ da Silva et al. evaluated 70 patients with CRC who underwent complete cytoreduction at the Washington Cancer Institute and found that the PCI was an important prognostic factor. The median survival of patients with a PCI less than 20 was 41 months versus 16 months for patients with a PCI greater than 20.⁸ In the present study, the survival of patients with CRC undergoing treatment with complete CRS and IPC was 81.3%, 12.5% and 12.5% at 1, 3 and 5 years, respectively. The survival of patients with PMP undergoing combined treatment was 84.2%, 77.7% and 77.7% at 1, 3 and 5 years, respectively. The median survival was not reached. In this series, most patients with CRC who were subjected to the combined treatment regimen had no access to modern chemotherapy, undergoing treatment regimens based on 5-fluorouracil. Modern drugs are unavailable in the Brazilian public health system, which was the source of the patients in this study. This might have affected the survival curve of patients with CRC in this series because it was lower than that of other published series.

The good survival rates found in this study occurred at the expense of considerable complication rates (23.3%). The combined procedure is complex, extensive and is associated with high complication rates. In addition, the learning curve is long.²¹ This study resulted morbidity rates that are consistent with previous reports in the literature.²²

Four patients died postoperatively, resulting in an overall mortality rate of 5.5%. The interpretation of these data is limited due to the small sample size. In the initial experience of Shen et al. with 77 patients, the mortality rate was 8%.²³ However, when considering centers with hundreds of cases, the mortality rate is reduced. Sugarbaker et al. reported a 1.5% postoperative mortality rate.² This finding certainly reflects the experience of the surgeon and the centers in the procedure.

In this study, we identified prognostic factors that may predict postoperative complications. Of the variables studied, the cytoreduction completeness, the operative time and blood transfusions were associated with complications. Saxena et al. stated that the risk factors for complications include a PCI > 12, transfusion of red blood cells greater than 4 bags, greater than three surgical procedures, peritonectomy of the upper left quadrant and greater than one anastomosis.²⁴ Even so, we believe that the completeness of cytoreduction was the main risk factor related to complications. We did not performed multivariate analysis because the variables found in the univariate analysis reflect the same thing, more prolonged cases. We can infer that a greater number of procedures lead to a longer operative time and an increased need for blood transfusions.

The efficacy of the combined treatment of CRS and IPC for CP to CRC, PMP and MST is well established in the literature.²⁵ A Brazilian study published with a series of 46 cases of cytoreduction and IPC. Fifteen of these cases were due to ovarian adenocarcinoma, and only 13 were due to CRC. In this study, Akaishi et al. concluded that the combined treatment improves the survival of patients with PC caused by certain types of cancer at the expense of acceptable morbidity and mortality rates.²⁶

There are limitations to any retrospective study, including the present study. Despite using data collected prospectively since 2002, this is indeed a retrospective study. Many patients referred to our institution have undergone previous operations at other institutions as well as different chemotherapy regimens (neoadjuvant or adjuvant). Because this series spans an extended period of time, some data were not known. Even so, we managed to collect sufficient data from 73 patient candidates for treatment with CRS and IPC.

In summary, the combined treatment of CRS and IPC in our institution was able to achieve significant improvements in survival rates at the expense of morbidity, which is comparable to findings described in the literature. Although the survival outcomes for CRC patients and complete cytoreduction rates were lower than the rates of the largest referral centers, we believe that refinement in patient selection and increasing the experience of the group can improve these results. The data related to PMP are positively comparable to those in the literature, despite the use of normothermic IPC in the majority of the cases.

Conclusion

The combined treatment for PC may be performed safely with acceptable morbidity and mortality in a specialized unit setting. Correct diagnosis and high suspicion before definitive cytoreduction may facilitate the feasibility and improve the outcome of this therapy to achieve long-term survival. Optimal cytoreduction achieves the best outcomes. Although over half of patients underwent normothermic intraperitoneal chemotherapy, our results were comparable to results from others centers.

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