The role of cytoreductive surgery alone for the treatment of peritoneal carcinomatosis of colorectal origin. A retrospective

Original Paper

The Role of Cytoreductive Surgery alone for the Treatment of Peritoneal Carcinomatosis of Colorectal Origin. A Retrospective Analysis with regard to Multimodal Treatments

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ABBREVIATIONS:
Peritoneal Carcinomatosis (PC); Cytoreductive Surgery (CS); Colorectal Cancer (CRC)

ABSTRACT

Background/Aims: Patients with peritoneal carcinomatosis (PC) of colorectal origin have a poor prognosis (median survival of 6 months). Cytoreductive surgery (CS) with intra-peritoneal chemotherapy with or without hyperthermia (HIPEC or EPIC) allows encouraging survivals rates of 22-60 months to be obtained, with an acceptable mortality and morbidity. Nevertheless, the role of cytoreductive surgery alone is little explored in literature. The aim of this study was to better understand the role of CS alone in the treatment of PC of colorectal origin.

Methodology: The outcome of 27 patients with PC of colorectal origin who underwent surgery with curative intent without combined treatments from 1996 to 2006, has been retrospectively analyzed.

Results: the median overall survival rate was 15 months; there was a significant statistical difference between patients who had CCR0-1 surgery (N=22) and those who had CCR2 or no resection (N=5) (15.8 *vs.* 9.6 months respectively, p=0.02). The mortality and the morbidity rates were 7.3% and 29%.

Conclusions: This study suggests that CCR0-1 surgery alone as well as the extension of the disease are important variables influencing survival of patients with PC of colorectal origin. When a very aggressive procedure is needed to achieve a CCR0 resection, surgery should be considered rigorously because of the high risk of severe and potentially lethal complications even without chemohyperthermia. A prospective study should be realized to determine whether or not patients with PC could mostly benefit from combined treatments.

INTRODUCTION

Peritoneal carcinomatosis (PC) is the second cause of death for colorectal cancer (CRC) after liver metastasis (1). At initial diagnosis, peritoneal spread is present in 10-15% of patients (2,3) with CRC, and when palliative treatments are done, prognosis is very poor with a median survival of 5.2-7 months (4,5).

Since Sugarbaker has proposed that PC of colorectal origin could be assimilated to a locally advanced tumor, rather than to a generalized disease (6,7), several studies showed the benefit in survival for patients treated so aggressively (8-11), combining maximal cytoreductive surgery (CS) and intraperitoneal chemotherapy with or without hyperthermia (HIPEC or EPIC). All these studies agree about the need of CCR0-1 surgery as the most important prognostic factor. Nevertheless, the absolute demonstration of the effectiveness of combined treatments is still lacking in literature, and even though a prospective study is feasible, it is very hard to be accomplished because of objective difficulties in selecting a large number of eligible patients. To corroborate that, CS+HIPEC or EPIC has never been compared prospectively to CS alone in clinical trials. Moreover, most of these patients usually have one or more lines of chemotherapy that could influence the overall survival, making the interpretation of available data open to criticism. As a consequence, most surgeons still believe that patients with PC from CRC should be considered only for a palliative surgery and systemic chemotherapy (12,13). For these reasons, until 2006 combined aggressive approach was not systematically used in our institution, and patients with PC from colorectal origin, were considered for cytoreductive surgery without combined treatment. The aim of this study was to describe retrospectively the survival, the morbidity and the mortality of this group of

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patients, in order to better understand the role of CS alone.

METHODOLOGY

Twenty-seven patients with PC of colorectal origin have been selected from the database of the Digestive Surgery Unit, Department of Clinical Physiopathology of the University of Florence School of Medicine between 1996 and 2006. Inclusion criteria were absence of extra-abdominal disease, bowel occlusion or perforation, presence of abundant ascites with diffuse peritoneal spread, and ASA score ≥3. All patients had preoperatively: accurate clinical examination, laboratory tests, US, and thoraco-abdominal CT-Scan. Pet-Scan was selectively used.

In order to make the analysis of a such heterogeneous group of patients easier, PC has been classified as follows: localized peritoneal nodules resected en-bloc with primary tumor (localized PC); peritoneal nodules located close and/or distant from primary tumor, for which removal of the surgical resection has been extended to other involved organs (diffuse PC).

The aim of cytoreduction was to achieve a complete resection, and it has been classified as curative for CCR0-1 resections and palliative for CCR2 or no resections (14). No intra-peritoneal chemotherapy with or without hyperthermia was used in this group of patients.

Surgery was performed through a large midline incision. After lyses of adhesions, PC was recorded and histologically confirmed with frozen sections. Peritonectomy was performed according to Sugarbaker's recommendations (15) in the involved metastatic site. Multiple organ resections including colorectal resections combined with hystero-annexectomy, urinary resections or pelvectomies were systematically performed if completeness was attainable. Treatment-related complications were recorded and graded as follows: "minor complications" for mild and moderate events, "major complications" for severe and life-threatening or disabling events. In postoperative course, all patients were monitored in the intensive care unit for at least 48 hours, and systematically reviewed for clinical and biological examination four weeks after hospital discharge.

TABLE 1 Population Characteristics, Intraoperative and Postoperative Results

Number of patients	**27**
Sex W/M	16/11
Mean age ± sd	57.5±13.4
Patients with synchronous peritoneal carcinomatosis*	11(40.7%)
Mean interval between primitive tumor and PC [(months) range]	19.7(10-39)
Primary tumor location:	
Right Colon	9 (33.3%)
Left Colon	8 (29.6%)
Rectum	10 (37.1%)
Liver metastasis	9 (33.3%)
Patients with pre- or postoperative chemotherapy	18 (66.6%)
Intraoperative results	
Classification at initial procedure:	
Localized PC	12 (44.4%)
Diffuse PC	15 (55.6%)
Number of digestive resections or sutures	22 (81.4%)
Liver resections	6 (22.2%)
Combined peritonectomies	20 (74%)
Other combined resection	10 (37%)
Patients with CCR0-1	22 (81.4%)
Palliative	5 (18.6%)
Postoperative results	
Mortality**	2 (7.4%)
Number of patients with complications***	9 (33.3%)
Major complications:	
Digestive fistulas****	3
Peritonitis	2
Pneumonia	1
Septic ureperitoneum	1
Minor complications	
Wound infection	3
Postoperative ileus	1
Urinary tract infection	2
Number of reoperations	3 (11%)
Detail of reoperations:	
Jejunal perforation	1
Digestive anastomotic leakage	1
Ureteral anastomotic leakage	1
Hospitalization stay in days	16 (3-80)

*Diagnosed less than 3 months from the primary tumor diagnosis; **Two patients died on postoperative day 5 and 30 from cerebral stroke and pulmonary embolism; ***Six patients had two or more complications; ****one patient with digestive fistulas has been treated conservatively.

Statistical Analysis

The main endpoint was survival measured as time from initial procedure to death or point date. Other judgment criteria were morbidity and mortality rates. The survival was estimated by the Kaplan-Meier method and comparison of curves was made using the log-rank test. Univariate and multivariate analysis were performed using SPSS software (15.0 version). $P<0.05$ was considered significant.

RESULTS

From January 1996 to December 2006, among 546 patients with colorectal cancer, 27 (5%) patients with colorectal PC who underwent surgery with curative intent were selected for this study. There were 16 females and 11 males, mean age was 56.5 years (range 31-77). PC was synchronous in 11 (40.7%) and metachronous in 16 (59.3%) patients, with a mean interval between primary tumor excision and PC of 19.7 months (range 10-39). Six of 16 patients (37.5%) with metachronous PC recurred during chemotherapy treatment. An overall of 18 patients (66.6%) had postoperative chemotherapy. Twenty patients had digestive and or hepatic resections combined with peritonectomy. Overall mortality and morbidity rates were 7.4% (n=2) and 33% (n=9). Two patients died on postoperative day 5 and 30 from cerebral stroke and

pulmonary embolism. Six patients (22%) developed two or more complications (overall incidence of complications per patient = 1.45). In 8 cases complications were classified as minor and in 9 cases as major. Three patients were re-operated (11%), two of these for anastomotic leakage and jejunal perforation with septic shock, and one for septic uroperitoneum. In all cases re-operation was successful without any further complication. The population characteristics and the peroperative results are given in **Table 1**.

Overall median survival was 15 months. A significant statistical difference in survival rates was seen between the CCR0-1 group (n=22) and palliative group (n=5) (**Figure 1**, p=0.02). One- and 2-year survival rates of patients who underwent curative surgery were 63.6 and 13.6% respectively. Median survival calculated on the extension of the disease was 18.8 months for the localized PC group and 12 months for the diffuse PC group (**Figure 2**, p=0.019). There were no differences in survival rate between synchronous and metachronous PC.

In January 2008, four patients of the curative group were still alive at 24.2, 22, 17.3 and 17.5 months respectively, three of which are disease free. All the patients of the palliative group died during follow-up. Overall recurrence rate was 86.3%. Among the 18 patients who underwent surgery with curative intent died during follow-up, the timing of recurrence was available only for 10, with a median of 11.4 months.

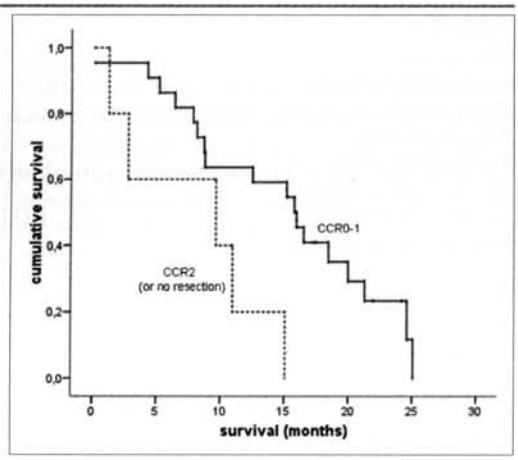

FIGURE 1
Comparative survival between patients with CCR0-1 *vs.* CCR2 or no resection (15.8 *vs.* 9.6 months; p=0.02).

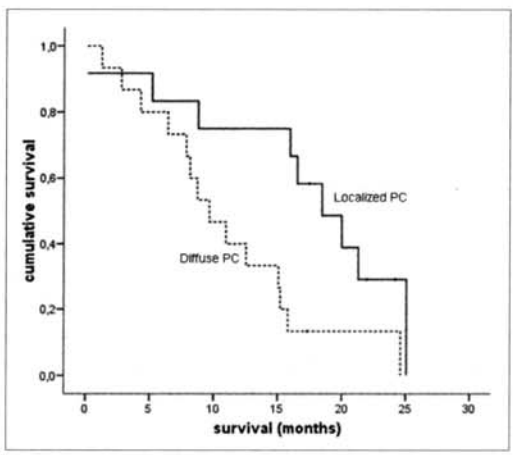

FIGURE 2
Comparative survival between patients with localized PC *vs.* diffuse PC (18.8 *vs.* 12 months; p=0.019).

DISCUSSION

The results of this study suggest that in selected patients with PC of colorectal origin, the cytoreductive surgery alone may allow an improvement in survival to be obtained, supporting the fact that CS plays an important role in the treatment of affected patients.

The poor prognosis of patients with metastatic CRC is correlated with lymphatic (16,17), hepatic (18) and peritoneal involvement (4,5). This last one represents the second cause of death for these patients (1), and is present in 10-15% of patients at initial diagnosis of CRC (2,3). Even if some adjuvant and neoadjuvant treatments have proved to be able to improve survival (19), the expected median survival rate for patients with PC of colorectal origin range between 5.2 and 7 months with palliative treatments (4,5). These data have allowed the development of new aggressive therapeutic strategies, combining maximal cytoreductive surgery with intraperitoneal chemotherapy with or without hyperthermia, and, in this regard, many studies pointed out that median survival rates resulted sensibly improved (7-11,14,20-22) **(Table 2)**. Sugarbaker first has suggested that, similarly to liver resection, the complete resection of PC may result in long term disease-free survival when CS is combined to intraperitoneal chemotherapy, with a survival rate of 36% at 3 years (7).

Other publications following this experience, confirmed these results. In 2003 Verwaal (8) published a randomized trial, comparing CS + HIPEC with systemic chemotherapy and palliative surgery, showing for the 54 patients enrolled into the experimental arm a median survival rate of 22.4 months *versus* 12.6 months of the standard arm. In this study the number of peritoneal regions involved (N≤5) and the success of CS (CCR0-1) were significant prognostic factors. In a multi-institutional experience (9), the data of 506 patients with PC of colorectal origin treated with CS + HIPEC were retrospectively analyzed. The Authors described an overall median survival of 19.2 months with a statistically significant difference between those having a CCR0-1 surgery (32.4 months) and those in which resection was not possible (8.4 months). Likewise Shen (22) showed an overall survival of 28 months in 38 patients treated with successful CS and HIPEC. In another study, da Silva and Sugarbaker (23) retrospectively analyzed by multivariate analysis the data of 70 patients with PC of colorectal origin having CCR0 surgery and HIPEC. Only PCI <20 *versus* PCI >20 (41 *vs.* 16 months) and lymph node status negative *versus* positive (186 *vs.* 29 months) were significant prognostic factors. Moreover, in 2007 Kianmanesh (10) reinforced this concept suggesting that even for patients with PC and associated liver metastasis the iterative CS combined

TABLE 2 Literature Review concerning Survival, Mortality and Morbidity

Author	Year Patients	No. (months)	Median survival (%)	1 year (%)	2 year (%)	Mortality (%)	Morbidity (%)
Elias[27]	2001	64	-		60	9.3	54.6
Verwaal[8]	2003	54 (HIPEC)	22	67	44	-	-
		51 (NO HIPEC)	13	56	22		
Elias[24]	2004	16 (EPIC)	-	60	-	18	50
		19 (NO EPIC)	-	60	-	-	37
Mahteme[28]	2004	18 (EPIC)	32	-	60	-	-
		18 (NO EPIC)	14	-	10		
Multi-institutional[9]	2004	Overall 506	19	72	-	4	22.9
		271 (CCR0)	32	87	-		
Da Silva[22]	2006	70	33	88	-	-	-
Glehen[13]	2004	Overall 53	13	55	32	-	-
		23 (CCR0)	33	85	54		
Elias[29]	2006	30	60	-	73	-	-
Verwaal[25]	2005	Overall 117	22	75	-	6	-
		59 (CCR0)	43	94	-		
Shen P[21]	2004	Overall 77	16	56	-	-	-
		37 (CCR0)	28	77	-	-	-
Cavaliere F[30]	2000	14	-	-	64	-	-
Pilati P[31]	2003	46	18	-	31	-	-
Kecmanovic[32]	2005	18	15	-	-	-	-
Yan TD[33]	2006	Overall 30	29	72	64	-	-
		21 (CCR0)	-	85	71	-	31
		30 (CCR0)	63	-	-		

with HIPEC allow to improve the survival of affected patients, with a median survival of 35.3 *versus* 36 months respectively for patients with PC alone and those with PC and liver metastasis.

All these studies support the efficacy of combined aggressive approach, but have the bias to be retrospective or prospective without comparison between CS + HIPEC or EPIC with CS alone. In fact, literature concerning the outcome of CS alone for the treatment of PC of colorectal origin is still lacking. It seems that surgeons overcome a step, promptly shifting from systemic chemotherapy and palliative surgery to the combination of systemic chemotherapy, cytoreductive surgery and intraperitoneal chemotherapy with or without hyperthermia. The results of this multimodal treatment seem to be so encouraging that surgeons oncologist are agree in performing CS + HIPEC or EPIC as first line of treatment, even without the evidence of a prospective randomized study (24), thus reproducing the history of the surgery for liver metastasis from CRC.

Reviewing the literature, we founded only one randomized trial, published by a referral center (25), in which 16 patients treated with CS + EPIC were compared to 19 treated with CS alone. The study was unexpectedly stopped after 35 patients included in 4 year, because patients were disagree to not be included in the EPIC group in view of the fact that they were referred for it. In this regard, the randomized trial was considered unethical by patients. Surprisingly the overall survival rates were 60% at 2 years in both groups, underlining the importance of CS as single prognostic factor.

For these reasons we believe that, even with the bias of a retrospective study, our analysis of patients with PC of colorectal origin treated with CS alone may add new insight to the debate. Looking into the database of our department, we found 27 patients with PC of colorectal origin that underwent surgery alone with curative intent between 1996 and 2006. The median overall survival rate was 15 months, with a significant statistical difference between the group who had CCR0-1 surgery and the group in which CS was not possible at laparotomy. The one- and two-year overall survival rates were significantly better for patients who underwent CCR0-1 surgery. Also, we found a significant statistical difference in survival rates between patients with localized and diffuse PC, confirming that the extension of the disease should be considered as a prognostic variable. We did not find a difference in survival rate between synchronous and metachronous PC, thus legitimating the role of CS even for recurrent disease.

The second main point of our analysis was to evaluate mortality and morbidity. It is common opinion that combined procedures make higher risk of complications because of HIPEC-related morbidity and mortality. These are hematological, renal, respiratory and abdominal, due to the systemic effect of drugs and to the burn-like effects of hyperthermia. With regard to the literature we found morbidity and mortality rates ranging between 23-50% and 2.5-18% respectively (8-10,25,26) when CS is performed in combination with HIPEC or EPIC.

In our experience overall mortality and morbidity rates were 7.4% and 33%, while 18.5% patients had

major complications. It is notable that in our series two or more complications occurred only in patients who underwent an extended surgery including the resection of primary tumor combined with peritonectomy and other organ resections (hysteroannexectomy, urinary resections). These results suggest that mortality and morbidity are mainly surgery-related but, it is indubitable that HIPEC or EPIC adds morbidity and mortality. In fact, a minor leucocytopenia could be life threatening during postoperative course because of earlier nadir (10-12 days).

In conclusion, we believe that CS plays an important role in improving survival of patients with PC of colorectal origin. Nevertheless, if an aggressive procedure is needed to achieve a CCR0 resection, surgery should be considered rigorously because of the high risk of severe and potentially lethal complications even without chemohyperthermia. The right balance between the extension of the disease and the aggressiveness of surgery seems to be the most demanding challenge for surgeons. In this regard, we encourage studies with the aim to carry out a clinical score able to classify patients in surgical risk categories. A prospective study should be realized to determine whether or not patients with PC could mostly benefit from combined treatments.

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