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Original Article

Cytoreductive Surgery and Intraperitoneal Chemotherapy for Colorectal Peritoneal Carcinomatosis: Prognosis and Treatment of Recurrences in a Cohort Study

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ABSTRACT

Background

Cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) treatment of colorectal peritoneal carcinomatosis (PC) is gaining acceptance, but controversy remains. The primary aims were to analyze the outcome and prognostic variables of colorectal PC patients treated with CRS and IPC, and to report on the outcome of additional surgical treatments of subsequent recurrences.

Methods

Patients referred for treatment of colorectal PC between 1996 and 2010 were included in a cohort. The following data was collected: clinicopathological parameters, survival, recurrences, perioperative chemotherapy and type of IPC (hyperthermic intraperitoneal chemotherapy, HIPEC; or sequential postoperative intraperitoneal chemotherapy, SPIC). Multivariable analyses were conducted on potential prognostic factors for overall survival (OS).

Results

In the 151-patient cohort, the median OS was 34months (range: 2-77) for CRS and HIPEC with five-year survival predicted at 40% (five-year disease-free survival 32%). For CRS and SPIC, the OS was 25months (range: 2-188) with five-year survival at 18%. Open-and-close patients survived 6months (range: 0-14) with no five-year survival (HIPEC vs. SPIC $p=0.047$, SPIC vs. open-and-close $p<0.001$). Adjuvant systemic chemotherapy was a noteworthy independent prognostic factor in the multivariable analysis. OS for patients undergoing additional surgical treatment of recurrences was 25months vs. 10months with best supportive care or palliative chemotherapy ($p=0.01$).

Conclusion

Substantial long-term survival is possible in patients with colorectal PC. HIPEC was associated with better OS than SPIC and adjuvant systemic chemotherapy may improve the outcome in patients. Good OS is achievable in selected patients undergoing additional surgical treatment of isolated liver or peritoneal recurrences after prior complete CRS.

Keywords: HIPEC, intraperitoneal chemotherapy, colorectal cancer, peritoneal carcinomatosis, cytoreductive surgery, recurrences

INTRODUCTION

There are several studies published comparing cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) with systemic chemotherapy for the treatment of colorectal peritoneal carcinomatosis (PC).[1-6] Concerning comparative studies, the method mainly investigated is intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) revealing significant improvement over systemic chemotherapy alone in one randomised and two case control trials.[1-3] Early postoperative intraperitoneal chemotherapy (EPIC) and sequential postoperative intraperitoneal chemotherapy (SPIC) have also been investigated against systemic chemotherapy.[4-6]

There are three multi-institutional observational IPC studies published: two French studies with 506 and 523 patients and one Italian study with 146 patients.[7-9] Additionally, two other observational studies are published with more than 100 patients.[10,11] These studies show the efficacy of CRS and HIPEC in treating colorectal PC and many medical and surgical oncologists will now routinely refer patients with colorectal PC for this treatment.[12-14] However, there still remains controversy concerning this treatment.[15,16] This is partly due to the small number of larger studies published and only one randomised trial evaluating both CRS and IPC together against systemic chemotherapy.[3] Furthermore, the development of newer biological chemotherapies has put the systemic treatment in a better position than it was at the time of the randomised control trial.[16,17]

Routines for additional surgical treatments of recurrences after prior complete CRS in colorectal PC patients are not established.[18] There are difficulties in conducting randomised trials in this setting due to the small number of patients and the patients' preference for invasive treatment when possible.[18] Four earlier studies have shown that there appears to be a survival benefit in performing a second CRS and IPC procedure if peritoneal recurrences reappear.[18-21] However, there are no previous reports, to our knowledge, on liver surgery performed due to liver recurrences after prior complete CRS.

The primary aims of this study were to analyze the outcome and prognostic variables of colorectal PC patients treated with CRS and IPC, and to report on treatment outcome of additional surgical treatments of recurrences after prior complete CRS.

METHODS

Study cohort and data collection

From 1996 to 2010, all patients registered in the Uppsala University hospital PC database with colorectal PC were included in the study cohort. No appendiceal cases were included. The eligibility requirements for treatment are as follows: histologically confirmed diagnosis of PC; no distant metastasis; adequate renal, hematopoietic and hepatic functions; and WHO performance status ≤ 2 . In colorectal PC, 1-3 liver metastases were accepted for synchronous hepatic and peritoneal resections. Age, gender, prior surgical score (PSS), peritoneal cancer index (PCI), completeness of cytoreduction (CC) score, and type of IPC treatment (HIPEC or SPIC) were collected from the PC database. Histopathology, laboratory data, 90-day morbidity, 90-day mortality, and systemic chemotherapy administered preoperatively were collected from the patient charts. The 90-day treatment-related morbidity was reported according to Common Terminology Criteria for Adverse Events v3.0 and only grades III to V adverse events were registered. The regional ethics committee approved the study.

Cytoreductive surgery and quantitative prognostic indicators

The cytoreductive surgery technique was applied according to the principles of Dr. Sugarbaker.[22] PSS, PCI, and CC scores were applied as described earlier.[23] The PSS is a measure of the surgical trauma prior to referral, such as the extent of the primary resection.

The PCI (ranges 0-39) is a measure of the distribution and size of tumour nodules on the peritoneum, which is calculated by summing lesion size scores (0-3) in 13 regions of the abdomen. Special attention was given the upper abdominal regions 1-3 to investigate whether extensive upper abdominal growth was a negative prognostic factor. The CC score is a measure of the result of the cytoreduction. CC 0 corresponds to no visible tumour tissue left in the abdomen. CC 1 means that there are tumour nodules <2.5mm remaining and for CC 2 it is >2.5mm, but <2.5cm. CC 3 means that there still exists bulky disease >2.5 cm.

Intraperitoneal chemotherapy

Two IPC treatments have been in use at the Uppsala Centre. SPIC was in use between 1996 and 2004 when HIPEC became the default treatment. However, due logistical and resource reasons, there was a certain overlap period where both treatments were offered.

For SPIC, a PORT-A-CATH (No. 21-2000-04, SIMS Deltec, Inc., St Paul, MN, USA) is placed subcutaneously above the periost of the lower ribs with the catheter tunnelled through the abdominal wall and directed towards the principal tumour site.[4] A SPIC treatment consisted of 5-fluorouracil 500-600mg/m² administered IP and leucovorin 60mg/m² administered IV once a day for six days. Eight cycles of SPIC were planned with 4-6 week intervals over a 6 month period as an adjuvant chemotherapy regimen.

HIPEC consisted of an intraoperative treatment conducted according to the coliseum method, as previously described.[24] The HIPEC treatment consisted of either a single drug treatment with mitomycin C 30mg/m² for 90 min (n=2), or double drug treatment with oxaliplatin 460mg/m² for 30 min IP combined with 5-FU 400mg/m² and calciumfolinate 60mg/m² IV (n=44); or triple drug treatment with oxaliplatin 360mg/m² and irinotecan 360mg/m² for 30 min IP combined with 5-FU 450-500mg/m² and calciumfolinate 60mg/m² IV (n=23). The intra-abdominal temperature measured with three thermal probes was targeted at 41-42°C with a flow rate of 1-2 L/min. Electrolyte-free glucose (50 mg/ml) was used for oxaliplatin perfusion and a low calcium peritoneal dialysis solution PD4 (Dianeal 13.6 mg/ml, Baxter, Deerfield, IL, USA) was used for mitomycin C. Before perfusion, the body temperature was lowered to 35°C with a cooling blanket (Allon 2001 Thermowrap, MTRE Advanced Technology Ltd. Yavne, Israel).

Cohort Follow-up

Information on recurrences was registered from patient charts as well as data on any invasive or surgical treatments performed on these recurrences. Postoperative chemotherapy was also registered during the follow-up period. Date and cause of death were retrieved from the Swedish death registry.

Analysis of recurrences

Patients with CC 0-1 result that recurred were divided into those with isolated liver recurrences, isolated peritoneal recurrences, and those with extra-abdominal recurrences present (see Table 1). Time to recurrence and survival was collected on each patient. In the liver and peritoneal groups, the patients going for additional surgical treatment were compared to those treated with best supportive care or systemic chemotherapy in terms of overall survival.

Statistics

A univariate Cox proportional analysis for overall survival was used to assess the prognostic value of variables by calculation of hazard ratios on the whole cohort (except 1 patient where there was missing survival data). A multivariable Cox regression analysis was performed using all statistically significant variables from the univariate analysis. An all-

effects function was implemented using both forward and backward step-wise analysis. A second univariate and multivariable Cox proportional analysis was carried out in the same manner as the first one, but only including patients with CC 0. Missing data for the lymph node status was considered as an unknown group. For the platelet count, the missing data was replaced by the mean value for the patient cohort. Missing adjuvant treatment was left as an unknown treatment group (the result for this group was not included in the tables). Patients with missing data on recurrences were excluded from the recurrence analysis. Patients were considered censored if still alive at the last follow-up or if they died of other causes than cancer (post-operative deaths censored).

Kaplan-Meier curves for overall survival in various patient groups were plotted. Differences between the curves were calculated using the log-rank test. A comparison of morbidity between SPIC and HIPEC groups was done using Pearson χ^2 test. Statistical significance was set at $p < 0.1$ for all statistical analyses. Calculations were made with STATISTICA 10.1 software (StatSoft Inc, Tulsa, OK, USA).

RESULTS

Clinical data

The study cohort included 151 patients: 76 male and 75 female patients; mean age 55 years (range: 14-79 years). There were 126 treated with combination CRS and IPC (69 HIPEC and 57 SPIC), 23 were open and close, and two were treated with CRS without HIPEC or SPIC. Out of 126 patients treated with CRS and IPC, 47 received neoadjuvant treatment and 27 received post-operative adjuvant systemic chemotherapy. Site and time to recurrences are detailed in Table 1. There was missing data with regard to recurrences in eight patients. The grade III-IV 90-day morbidity occurred in 17 SPIC patients and in 28 HIPEC patients ($p=0.02$). The 90-day treatment-related mortality occurred in two SPIC patients and in three the HIPEC patients ($p=0.98$). Reoperation within 90 days for the whole cohort occurred in ten patients.

There was missing data for the lymph-node status in 27 patients, for the platelet count 38 patients, and for the post-operative adjuvant treatment variable 5 patients. The median follow-up was 49 months (range: 0.5-200).

Survival and prognostic factors

In Figure 1, the median overall survival (OS) was 34 months (range: 2-77) for CRS and HIPEC with a five-year survival predicted at 40%. For CRS and SPIC, the OS was 25 months (range: 2-188) with a five-year survival at 18%. Open-and-close patients survived 6 months (range: 0-14) with no five-year survival (HIPEC vs. SPIC $p=0.047$, SPIC vs. open-and-close $p < 0.001$). The median OS of HIPEC patients with CC 0 was 39 months and for SPIC patients with CC 0 it was 32 months ($p=0.3$). The disease-free survival (DFS) for HIPEC was 15 months and for SPIC 10 months ($p=0.048$) with a five-year DFS at 32% and 12%, respectively. Median OS for the entire cohort was 24 months and five-year OS at 20% (five-year DFS 15%).

PCI, CC score, type of IPC, white blood-cell count, and adjuvant systemic chemotherapy were independent prognostic factors in the multivariate analysis for OS (Table 2). In patients with CC 0 score, PCI and adjuvant chemotherapy were the only independent prognostic factors (Table 3). Extensive upper-abdominal growth was a negative prognostic factor in the univariate but not in the multivariable analyses.

Results of liver recurrence treatment

Sixteen patients developed isolated liver recurrences after the CRS and IPC. One patient was lost to follow up. Six patients received liver-specific interventions (3 hemihepatectomies, 1 segmental liver resection, 1 radio-frequency ablation, and 1 irradiation) and eight patients received palliative care: two patients received 1 line of chemotherapy, one patient received 2 lines of chemotherapy, two patients received no further chemotherapy, and in three patients there was insufficient data. One patient recurred recently and no decision concerning treatment was yet documented. Patients with liver-specific intervention had a 35 month (range: 12-48) median OS and the palliative treatment group had a median OS of 12 months (range: 4-26, $p=0.03$). In the intervention group, the median time to the liver recurrence was 12 months and in the non-intervention group it was 5 months.

Results of peritoneal recurrence treatment

Twenty patients had an isolated peritoneal recurrence and one patient had a combination of peritoneal and liver recurrence ($n=21$). One patient was lost to follow up. Eight second CRS and IPC procedures (4 SPIC and 4 HIPEC) were performed and 1 local abdominal wall recurrence resection was performed. The remaining 11 patients received palliative care: two patients received 1 line of chemotherapy, one patient received 2 lines of chemotherapy, three patients received no further chemotherapy and in five patients there was insufficient data. The median time to the peritoneal recurrence was 12 months in the surgery group and 7 months in the non-surgery group. The median survival of the surgery group was 23 months (range: 9-98) and in the palliative treatment group it was 6 months (range 1-26; $p=0.007$). Aggressive intervention vs. palliative care (systemic chemotherapy or best supportive care) for both peritoneal and liver recurrences is displayed in Figure 2. Median OS in detail as follows: intervention vs. systemic chemotherapy (25 vs. 15 months, $p=0.02$), intervention vs. best supportive care (25 vs. 2 months, $p=0.03$), and intervention vs. unknown palliative group (25 vs. 8 months, $p=0.01$).

Result of extra abdominal recurrences

Patients with extra-abdominal recurrences were not subjected to further surgical intervention. There were 29 patients with extra-abdominal systemic recurrences (see Table 1). The median OS from the time of the recurrence in each group is detailed in Table 1. The overall median OS was 12 months (range 3-28).

DISCUSSION

HIPEC or SPIC

Our Centre has employed two different IPC regimens for treating colorectal PC, HIPEC and SPIC. A previous small comparison study from our Centre using only colonic cancer and CC 0 patients has demonstrated that HIPEC is associated with better survival than SPIC.[25] This current study appears to confirm this conclusion. There seemed to be one exception in the outcome of CC 0 patients where HIPEC was not statistically significantly better. However, the earlier above mentioned study adjusted for this variable (as well as for PCI) and still demonstrated superior results with HIPEC.[25]

Between 1996 and 2004 only SPIC was offered; and thereafter, the default treatment was HIPEC with some exceptions during an early overlap period. As such, the most important confounding factor is the learning curve, which cannot be easily accounted for. The earlier case-matched comparison study between HIPEC and SPIC addressed this issue more succinctly. It referred to the study of the learning curve of colorectal PC treated with CRS and IPC which found no difference in overall survival when comparing only R1 resections.[26] It is improbable, then, that the learning curve alone could account for the survival benefit. In light of current data and in the absence of a randomised trial, HIPEC appears to be associated

with better outcome than SPIC in colorectal PC.

Prognostics

In the multivariate analysis, PCI, CC score, types of IPC, the white blood-cell count, and the adjuvant chemotherapy were independent prognostic factors for OS. PCI and CC score are well known factors from earlier HIPEC studies and increased preoperative platelet and neutrophil counts have also been shown to be independent prognostic factors, but in liver metastasis resections.[27] Interestingly, a recent study on C-reactive protein in colorectal PC treated by CRS and IPC also found a negative survival association with increased inflammation.[28] As such, the inflammation status of colorectal PC may be an important prognostic factor to consider in patient selection and further studies are needed to elucidate this issue. Adjuvant systemic chemotherapy as an independent prognostic factor in both multivariate analyses is an important finding. One earlier multi-institutional study with 523 patients also showed a benefit from adjuvant systemic chemotherapy.[7] In line with this observation most centres doing CRS and IPC for colorectal PC add adjuvant chemotherapy. However, prior to establishing this as a clinical routine, we would like to get proof of the utility of such treatment from a prospective clinical trial.

Recurrences

In our study, patients with isolated liver and peritoneal recurrences undergoing surgery or invasive treatment had a considerably longer survival than those receiving palliative treatment (best supportive care or systemic chemotherapy). Earlier studies have shown that early recurrences after CRS and HIPEC are a negative prognostic factor.[18] Time to recurrence was longer in the aggressively treated groups and this alone is cause for selection bias as a major confounding factor rendering the comparison moot. As such, the palliative treatment group should be viewed as a reference group rather than a comparison group. However, the median OS of 23 and 35 months for peritoneal and liver relapses following local intervention is impressive. Four studies on treatment of peritoneal recurrences after prior CRS and HIPEC have been published with median OS between 10 and 39 months.[18-21] No publications exist on liver surgery after prior CRS and IPC. Thus, for patients in good performance status and with the ability to combat adverse events, further aggressive surgical treatment of peritoneal or liver recurrences even after a prior CRS and IPC procedure may be associated with long OS.

Research in context

A review from 2011 of CRS and HIPEC results in patients with colorectal PC showed a median OS for all patients in the range 18-63 months.[17] The conclusion from this review was that CRS and HIPEC is only clearly beneficial for pseudomyxoma peritonei and mesothelioma and that for colorectal cancer the treatment should be continued preferably in the setting of randomised control trials. Furthermore, new advances in systemic chemotherapy have put this treatment option in a new position, making cause for a reserved attitude towards CRS and IPC.[17] Clearly, some apprehension still exists concerning this treatment option for colorectal PC.

Liver resection for colorectal liver metastases has never been investigated in a randomised control trial, but no one disputes its legitimacy as a treatment alternative today. At some point the massing evidence produced by surgical treatments of liver resections reached a point where it was considered to be beyond what could be achieved with systemic chemotherapy. The question is if this point has now also been reached for colorectal PC. This study is the third largest study after the two French multi-centre studies demonstrating the

efficacy of CRS and IPC (particularly HIPEC) having median OS and five-year survival rates beyond any systemic treatment regimen published to date. Further randomised trials between systemic chemotherapy and CRS with IPC may be difficult to conduct at this stage, which has also been demonstrated by an earlier failed randomised trial between systemic chemotherapy and CRS with EPIC.[5] It appears more important to develop a standardised patient selection protocol. The number of “open and close” cases needs to be decreased as their survival is particularly dismal (median OS 6.5 months) and a full laparotomic exploration may actually put them in a worse position than having gone directly to palliative systemic chemotherapy.

Conclusion

This cohort study shows that impressive OS and DFS is possible to achieve in patients with colorectal PC following CRS and IPC, that HIPEC is associated with better outcome than SPIC, and that adjuvant chemotherapy might be beneficial. Randomised trials for colorectal PC may not be feasible, but rather the development of a patient selection protocol. Furthermore previous CRS and IPC should not automatically exclude patients from further surgical treatment following isolated disease recurrences, as good OS is still possible in this population.

CONFLICT OF INTERESTS

No conflicts to declare.

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Table 1 - Recurrences after CRS and IPC treatment for colorectal PC

Recurrence	Number (%)	Disease-free Interval in months (range)	Median Survival in months
Surgery grossly not complete	41 (27.2%)	0	6.7
No recurrences	37 (24.5%)	N/A	Not reached
Isolated peritoneal	20 (13.2%)	10.7 (2.8-38)	12.5
Isolated liver	16 (10.6%)	7.5 (0.5-24)	14.6
Isolated lung	10 (6.6%)	5.4 (0.5-22)	6.7
Both peritoneal and systemic	14 (9.3%)	6.7 (3-36)	14.1
Multiple systemic sites	3 (2.0%)	4.9 (1-12)	Not reached
Isolated brain	1 (0.7%)	2.0 (N/A)	11.6
Isolated testicle	1 (0.7%)	33.0 (N/A)	Not reached
Missing data	8 (5.3%)	N/A	N/A
Total	151		

Abbreviations: CRS – cytoreductive surgery, IPC – intraperitoneal chemotherapy, PC – peritoneal carcinomatosis, N/A – not available

Figure 1 – Overall Survival of Whole Cohort (N=150^a)

^a There was missing overall survival data in one patient

^b HIPEC vs. SPIC $p=0.047$, SPIC vs. open and close $p<0.001$

Abbreviations: HIPEC – Hyperthermic intraperitoneal chemotherapy, SPIC- sequential postoperative intraperitoneal chemotherapy

Table 2 - Prognostic analysis for overall survival in the whole cohort (n=150^a)

Characteristic(n)	Univariate Hazard Ratio	Univariate <i>p</i> -value	Multivariate <i>p</i> -value	
<i>General</i>				
Female gender (75)	0.65 (0.43-0.98)	0.04	0.41	
Age	0.99 (0.98-1.00)	0.19		
Synch vs. metach (102 vs. 48)	0.86 (0.56-1.32)	0.50		
<i>Histology</i>				
LN-positive vs. negative (95 vs. 29)	1.49 (0.83-2.68)	0.67	0.09	
Mucinous (89)	1.00 (0.66-1.51)	0.98		
Signet-cell (18)	1.01 (0.54-1.91)	0.97		
Tumour grade				
Low (45)	0.84 (0.44-1.63)	0.99		
Intermediate (87)	0.71 (0.39-1.32)	0.25		
High (18)	Reference			
Rectal vs. colon cancer (15 vs. 135)	1.12 (0.59-2.10)	0.73		
<i>Laboratory results</i>				
Haemoglobin < 120g/L (56)	1.17 (0.76-1.78)	0.47		0.15
White blood cell count > 9x10 ⁹ /L (32)	1.71 (1.07-2.75)	0.01		
Platelet count < 350x10 ⁹ /L (38)	1.72 (1.06-2.78)	0.03		
<i>Prognostic scores</i>				
PCI (as continuous variable)	1.05 (1.03-1.08)	<0.001	0.004	
PCI I:1-10 (49)	Reference			
PCI II: 11-20 (45)	1.32 (0.76-2.31)	0.19		
PCI III: 21-39 (56)	3.24 (1.95-5.39)	<0.001	0.30	
PSS 0 (19)	1.20 (0.54-2.66)	0.18		
PSS 1 (29)	0.70 (0.36-1.40)	0.06		
PSS 2 (60)	1.34 (0.81-2.23)	0.19		
PSS 3 (42)	Reference			
CC 1-3 vs. CC 0 (97 vs. 53)	5.51 (3.57-8.51)	<0.001	0.006	
<i>Tumour distribution according to PCI region 1-3.</i>				
No tumour present (63)	0.30 (0.12-0.75)	0.04	0.39	
Tumour in one region (20)	0.44 (0.19-1.03)	0.31		
Tumour present multiple regions (67)	2.49 (1.59-3.91)	0.02		
<i>Chemotherapy</i>				
Neoadjuvant chemotherapy (47)	1.14 (0.65-2.02)	0.64	0.003	
Adjuvant chemotherapy ^b (27)	0.27 (0.12-0.58)	<0.001		
HIPEC vs. SPIC (69 vs. 57)	0.60 (0.36-0.99)	<0.001		

^a Missing data for overall survival in one patient^b n=145 (missing data in 5 patients)

Abbreviations: Synch – synchronous, Metach – metachronous, PCI – peritoneal cancer index, PSS – prior surgical score, CC – completeness of cytoreduction, HIPEC – hyperthermic intraperitoneal chemotherapy, SPIC – sequential postoperative intraperitoneal chemotherapy

Table 3 - Prognostic analysis for overall survival in patients with a CC 0 result (n=98). Same variables were analysed as in Table 2, but only statistically significant data is detailed here.

Characteristic	Univariate Hazard Ratio	Univariate <i>p</i> -value	Multivariate <i>p</i> -value
<i>Prognostic scores</i>			
PCI (as continuous variable)	1.03 (1.00-1.07)	0.08	0.001
PCI I (1-10)	Reference		
PCI II (11-20)	1.19 (0.59-2.41)	0.57	
PCI III (21-39)	2.08 (0.95-4.53)	0.08	
<i>Chemotherapy</i>			
Adjuvant chemotherapy ^a	0.42 (0.18-1.00)	0.005	0.001
HIPEC vs. SPIC	0.71 (0.37-1.34)	0.07	0.36

^a n=93 (missing data in 5 patients)

Abbreviations: PCI – peritoneal cancer index, HIPEC – hyperthermic intraperitoneal chemotherapy, SPIC – sequential postoperative intraperitoneal chemotherapy

Figure 2 – Third-line surgical treatment of liver and peritoneal recurrences

^a For specifics within the palliative care group see the result section.

^b Third-line surgery or local intervention for both peritoneal and liver recurrences ($p=0.01$)