Optimal patient selection for cytoreductive surgery and HIPEC

van Eden, W.J.

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CHAPTER 7

Peritoneal recurrences in patients with colorectal peritoneal metastases treated with cytoreductive surgery and HIPEC

Wijntje J. van Eden
Fortuné M.K. Elekonawo
Bas J. Starremans
Niels F.M. Kok
André J.A. Bremers
Johannes H.W. de Wilt
Arend G.J. Aalbers

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Abstract

Background: Colorectal peritoneal carcinomatosis (PC) is preferably treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal intraperitoneal chemotherapy (HIPEC). Peritoneal recurrence of disease after treatment can occur without distant metastases, with a variety of treatment options.

Objective: This study aimed to evaluate the management of isolated peritoneal recurrence after primary CRS-HIPEC.

Methods: In two tertiary referral centers, all patients who underwent CRS-HIPEC for colorectal PC between 2004 and 2015 and who developed isolated peritoneal recurrences were retrospectively evaluated. Location, treatment of peritoneal recurrences, and curative or palliative treatment intent were reported, and univariable and multivariable Cox regression analysis and survival analyses were performed.

Results: Of 414 patients treated with CRS-HIPEC for colorectal PC, 106 patients (26%) developed isolated peritoneal recurrence. Forty-three patients (41%) were treated with curative intent and 63 patients (59%) with palliative intent. Median overall survival (OS) in the patients treated with curative intent was 24.7 months (interquartile range (IQR) 12.1-61.7) compared to 7.6 months (IQR 2.5-15.9) in those treated with palliative intent ($P < 0.001$). In the patients treated with curative CRS ($n = 17$) and curative second CRS-HIPEC ($n = 15$) median overall survival was 51.7 months (IQR 14.4-NA) and 29.0 months (IQR 18.1-63.0), respectively ($P = 0.620$). The latter group had a significant higher region count (median 1 vs. 3; ($P < 0.001$). Postoperative complications and hospital stay did not significantly differ between first and second CRS-HIPEC.

Conclusion: After CRS-HIPEC for colorectal cancer, approximately one out of four patients will develop isolated peritoneal recurrences. A substantial amount of these patients can be safely treated with curative intent yielding long-term survival.

Introduction

Patients with colorectal peritoneal carcinomatosis (PC) are preferably treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). PC occurs in approximately 10% of all colorectal cancer patients and is associated with poor survival.[1, 2] Five-year overall survival (OS) rates are increasing up to 50% when selected patients have been treated with CRS-HIPEC, although locoregional and distant recurrences are common.[3-5]

Although nearly all patients who develop distant metastases in combination with peritoneal carcinomatosis are treated with systemic palliative treatment or best supportive care,[6] patients with isolated peritoneal disease can be candidates for curative treatment. Recurrence is strongly associated with lymph node status, extent of peritoneal disease and completeness of cytoreduction.[7, 8] Isolated peritoneal recurrences may have different drivers than the aforementioned factors. Golse et al. described no correlation between the extent of peritoneal disease and isolated peritoneal recurrences.[9]

Isolated peritoneal recurrence may still be treated with curative intent, either with complete cytoreduction or CRS-HIPEC, in carefully selected patients.[10, 11] Limited data are available in the literature but second CRS-HIPEC procedures are reported as a potential option to curatively treat patients. Brouquet et al. decribed a 5-year overall survival of 72.5% in patients with isolated peritoneal recurrences who underwent a second CRS-HIPEC. The objective of this study was to evaluate the management of isolated peritoneal recurrence and the effect on survival after previous CRS-HIPEC in patients with colorectal PC.

Methods

Patients

The current study was performed in two Dutch tertiary CRS-HIPEC centers - The Netherlands Cancer Institute (NCI) in Amsterdam and Radboud University Medical Centre (Radboudumc) in Nijmegen. The NCI started to perform CRS-HIPEC procedures in 1996, while the Radboudumc started in 2010. Data were retrieved from prospectively maintained databases. Patients with colorectal PC who had been treated with CRS-HIPEC between January 2004 and December 2015 and were diagnosed with isolated peritoneal recurrence of disease during follow up were eligible for inclusion in the study. However, patients were excluded if a R2b-resection was performed (remaining tumor nodules >2.5 mm after cytoreduction) or if distant metastases were present at time of peritoneal recurrence. Patients were usually followed for at least 10 years or until death. This study was performed in accordance with medical ethical institutional guidelines, and Institutional Review Board approval was not considered necessary because of the retrospective nature of the study.

Surgical procedure

Details of the procedure used for CRS-HIPEC have been previously described.[12] Cytoreduction preceded hyperthermia and intraperitoneal chemotherapy. Until March 2014, mitomycin C 35 mg/m^2 diluted in Dianeal was used, which was heated to 42-43^{o}C over a 90 min period. Thereafter, leucovorin and 5-fluorouracil (20 and 400 mg/m^2, respectively) were administered intravenously, and oxaliplatin 460 mg/m^2 diluted in Dianeal® (NCI) or 5%-dextrose (Radboudumc) heated to 42-43^{o}C was inserted in the abdominal cavity over a 30 min period while the abdomen was still open. In almost all patients who underwent a second CRS-HIPEC, the chemotherapeutic agent used was different from the agent used at the first CRS-HIPEC. However, two patients experienced neurotoxicity from previous received intravenous oxaliplatin, and mitomycin C was again preferred during the second CRS-HIPEC in these patients.

The extent of peritoneal disease was scored with the Dutch Region Count, which divided the abdomen into seven regions, and the Peritoneal Cancer Index (PCI).[13] Completeness of cytoreduction was scored based on the size of remaining tumor nodules. In an R1 resection, no visible macroscopic tumor nodules were seen; in an R2a resection remaining tumor nodules < 2.5 mm were left behind; and in the case of an R2b resection tumor nodules > 2.5 mm were left behind in the abdomen after cytoreduction.

Patients were postoperatively admitted to the intensive care unit, and each patient was pre- and postoperatively discussed in a multidisciplinary team meeting. Whether or not patients received perioperative or adjuvant chemotherapy was decided by the multidisciplinary team.

Follow-up and recurrences

During follow-up, details of recurrences were accurately recorded. The date of recurrence was reported, together with the modality which was used to diagnose peritoneal recurrence of disease, which was either radiological, surgical, or based on clinical symptoms or elevated tumor markers. The presence of histopathological evidence for peritoneal recurrence was recorded, along with the treatment and date of treatment of isolated peritoneal recurrences. Treatment could have had curative or palliative intent, which was discussed in a multidisciplinary team meeting. CRS-HIPEC, CRS and radiotherapy were considered to be curative treatment options, whereas palliative CRS, palliative radiotherapy, systemic chemotherapy, and supportive care were considered to be palliative treatment options. Based on the treatment intent, both a curative and a palliative treatment group were created. Hospital records were consulted to extract the intent of the treatment in patients with isolated peritoneal recurrences or in case of incomplete data.

Disease-free survival (DFS) was defined as time in months from date of curative treatment for isolated peritoneal recurrence to date of peritoneal re-recurrence. The date of last follow-up or

death were also recorded, and OS was defined as time in months between treatment for isolated peritoneal recurrence to the date of last follow-up or death.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY, USA). Categorical data were presented as numbers with percentages and Pearson's Chi square test, linear by linear, and Fisher's exact test were used as appropriate. Continuous data were presented as medians with their interquartile range (IQR) or minimum and maximum values, and the Kruskal-Wallis, Mann-Whitney-U and Wilcoxon signed-rank test were used as appropriate. With the Kaplan-Meier method, survival analyses were performed, and the log-rank test was used to test for statistical differences between groups. Furthermore, using Cox regression, univariable analyses were performed and variables with a P-value < 0.05 or clinically relevant variables were included in multivariable analysis. An interaction term was created for complication grade and treatment intent. Subgroup analyses were performed for the patients treated with curative intent. A P-value < 0.05 was used to reject the null hypothesis. For the Cox models, proportionally assumption was checked and fulfilled.

Results

Patients

Overall, 414 patients were treated with CRS-HIPEC for colorectal peritoneal carcinomatosis between January 2004 and December 2015; 106 of these patients (25.6%) were diagnosed with isolated peritoneal recurrence of disease after CRS-HIPEC, of whom 43 patients (40.6%) were treated with curative intent and 63 patients (59.4%) underwent treatment with palliative intent (Figure 1). Details on the baseline characteristics of all patients with isolated peritoneal recurrence are presented in Table 1.

Peritoneal recurrences

Details of the peritoneal recurrences are presented in Table 2. After diagnosis of isolated peritoneal recurrence, patients were treated after a median of 1.2 months (IQR 0.4-2.4). In the curative intent group, 42 patients (97.7%) were treated with CRS, whether combined with HIPEC or not (Figure 1). In 15 of 16 CRS-HIPEC procedures, and in 19 of 26 CRS procedures, an R1 resection was achieved. Two patients treated with an R1 resection died due to complications related to the procedure. One patient (2.3%) was curatively treated with radiotherapy.

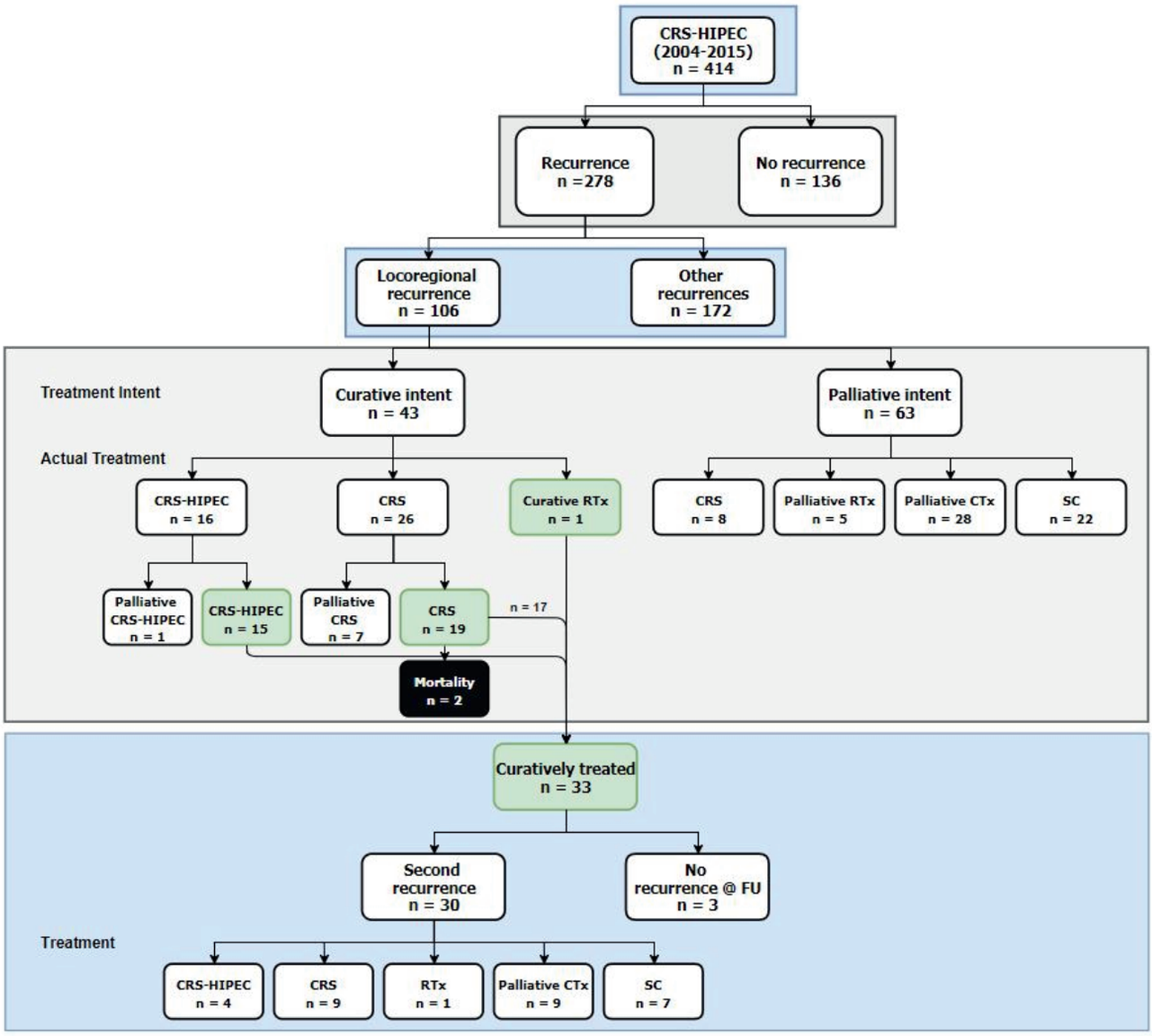


Figure 1. Patient selection and treatment characteristics. RTx, radiotherapy; CTx, systemic chemotherapy; SC, supportive care; FU, follow-up; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

During follow-up of the remaining 33 patients treated with curative intent, recurrence of disease was observed in 30 patients (90.9%), all of whom underwent treatment. Only three patients (9.1%) remained free of disease until the last date of follow-up. Details on the treatment strategies for the patients treated with palliative intent are also visualized in Figure 1.

Survival after treatment of isolated peritoneal recurrences

During follow up, the median time until recurrence was 13.7 months (IQR 8.3-19.6) in all patients, and 11.0 months (IQR 6.3-15.2) in the patients treated with palliative intent compared 17.7 months (IQR 3.8-26.0) in those treated with curative intent ($P < 0.001$).

Table 1. Baseline characteristics

	Curative Treatment n = 43	%	Palliative Treatment n = 63	%	P-value
Patient characteristics					
Gender					0.076
Male	15	34.9%	33	52.4%	
Female	28	65.1%	30	47.6%	
Age	58.7 (24.1-76.8)	-	58.3 (24.4-77.6)	-	0.974
ASA Score					0.166
ASA 1	20	46.5%	37	58.7%	
ASA 2	20	46.5%	25	39.7%	
ASA 3	3	7.0%	1	1.6%	
Comorbidity					0.161
Absent	20	46.5%	38	60.3%	
Present	23	53.5%	25	39.7%	
Details of first CRS-HIPEC					
Intraperitoneal drug regimen					0.138
MMC	42	97.7%	56	88.9%	
Oxaliplatin	1	2.3%	7	11.1%	
Region count					0.808
0-2 regions	20	46.5%	25	39.7%	
3-5 regions	19	44.2%	32	50.8%	
6-7 regions	4	9.3%	6	9.5%	
Completeness of cytoreduction					0.233
R1	40	93.0%	53	84.1%	
R2a	3	7.0%	10	15.9%	
Classification of SAE					0.051
CTCAE 0-2	36	83.7%	42	66.7%	
CTCAE 3-4	7	16.3%	21	33.3%	
Systemic chemotherapy					0.195
No	10	23.3%	17	27.0%	
Neoadjuvant	5	11.6%	11	17.5%	
Adjuvant chemotherapy	26	60.5%	26	41.3%	
Perioperative	2	4.7%	9	14.3%	
Hospital stay (days)	14 (11-17)	-	15 (12-23)	-	0.123
Tumor characteristics					
pT-stage					0.063
≤ pT3	23	53.5%	24	38.1%	
pT4	17	39.5%	38	60.3%	
Unknown	3	7.0%	1	1.6%	
pN-stage					0.907
0	13	30.2%	16	25.4%	
1	16	37.2%	23	36.5%	
2	13	30.2%	20	31.7%	
Unknown	1	2.3%	4	6.3%	

Systemic metatases prior to CRS-HIPEC					**0.009**
Absent	32	74.4%	59	93.7%	
Present	11	25.6%	4	6.3%	
Peritoneal carcinomatosis					0.272
Synchronous	22	51.2%	39	61.9%	
Metachronous	21	48.8%	24	38.1%	
Location primary tumor					0.273
Appendix	4	9.3%	6	9.5%	
Colon	32	74.4%	53	84.1%	
Rectum	7	16.3%	4	6.3%	
Differentiation primary tumor					**0.046**
Good/Moderate	27	62.8%	31	49.2%	
Poor	9	20.9%	26	41.3%	
Unknown	7	16.3%	6	9.5%	
Histology primary tumor					0.090
Adenocarcinoma	22	51.2%	29	46.0%	
Mucinous adenocarcinoma	19	44.2%	22	34.9%	
Signet ring cell carcinoma	2	4.7%	12	19.0%	

Legend. Baseline characteristics. Data are expressed as numbers with percentages and medians with minimum and maximum values (age) or interquartile range (hospital stay).
Abbreviations. ASA, American Society of Anaesthesiologists; MMC, Mitomycin C; SAE, Serious Adverse Event; CTCAE, Common Toxology Criteria of Adverse Events; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

Table 2. Characteristics of isolated peritoneal recurrences

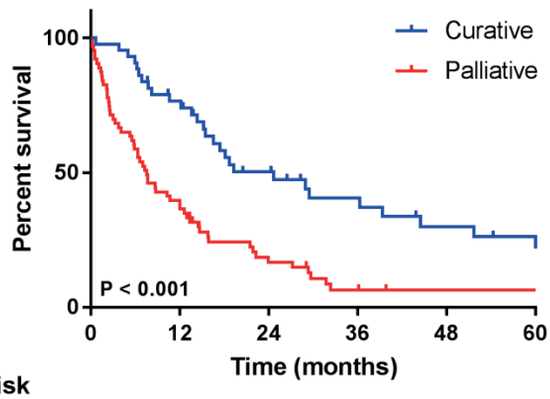
	Curative Treatment n = 43	**%**	**Palliative Treatment n = 63**	**%**	**P-value**
Time until recurrence*	17.7 (13.8-26.0)	-	11.0 (6.3-15.2)	-	**< 0.001**
Diagnostic method					**< 0.001**
Radiological	32	74.4%	30	47.6%	
Surgical	7	16.3%	5	7.9%	
Clinical (symptoms)	4	9.3%	28	44.4%	
Recurrence histologically confirmed†					**< 0.001**
No	5	11.6%	32	50.8%	
Yes	38	88.4%	31	49.2%	
Extent of peritoneal recurrence∞					**0.021**
Solitary	14	32.6%	8	12.7%	
Multifocal	29	67.4%	51	81.0%	
Unknown	0	0.0%	4	6.3%	

Legend. Characteristics of peritoneal recurrences after initial CRS-HIPEC. Data are expressed as numbers with percentages, and medians with interquartile ranges.
Symbols. * Time from first CRS-HIPEC to time of peritoneal recurrence. † At time of diagnosis of isolated peritoneal recurrence. ∞ At imaging or surgical inspection.

Median OS after treatment of isolated peritoneal recurrence was favorable in patients treated with curative intent compared with those treated with palliative intent - 24.7 months (IQR 12.1-61.7) versus 7.6 months (IQR 2.5-15.9), respectively (P < 0.001) (Figure 2).

Patients treated with curative intent had 1-, 2-, and 3-year survival rates after treatment of 74, 50, and 37%, respectively, while survival rates for patients treated with palliative intent were 36, 16, and 6% after 1-, 2-, and 3-years, respectively.

In multivariable Cox regression analysis, complication grade 3-4 after first CRS-HIPEC (Hazard Ratio (HR) 7.02, 95% CI 2.51-19.62) compared with complication grade 0-2 (P < 0.001), and treatment of peritoneal recurrence with palliative intent (HR 2.74, 95% CI 1.49-5.05) compared with treatment with curative intent (P = 0.001), were associated with a poorer OS (Table 3). There was a significant interaction between complication grade and treatment intent in multivariable analysis that was inserted in the model (HR 0.20, 95%CI 0.06-0.61; P = 0.005) (Table 3).



Numbers at risk						
Curative patients	43	31	18	12	8	6
Palliative patients	63	24	9	3	1	1

Figure 2. Overall survival since treatment of first peritoneal recurrence with curative or palliative intent.

Treatment with curative intent

In the 33 patients successfully treated with curative intent, time to second recurrence was 10.3 months (IQR 5.7-15.7). Median OS in these patients was 36.3 months (IQR 15.2-63.0) compared with 7.7 months (IQR 5.9-18.7) in patients who did not respond to intentionally curative treatment (P = 0.005).

Median OS in the 17 patients who underwent curative CRS was 51.7 months (IQR 14.4-NA), and 29.0 months (IQR 18.1-63.0) in the 15 patients who underwent curative CRS-HIPEC (P = 0.620) (Supplementary Figure 1). In patients with recurrences limited to one or two regions, CRS only was the preferred treatment; these patients had a median region count of 1 (IQR 1-1) during surgery.

Patients with multifocal peritoneal recurrences were significantly more often treated with CRS-HIPEC, and these patients had a median region count of 3 (IQR 1-5; $P < 0.001$).

Comparing the first and second CRS-HIPEC procedures, low- and high-grade postoperative complications did not significantly differ. Median hospital stay was 15 days (IQR 11-20) for the first CRS-HIPEC and 14 days (11-28) for the second CRS-HIPEC.

Discussion

A substantial survival benefit was observed in patients who had isolated, recurrent peritoneal metastases who were treated with curative intent. Approximately 25% of all patients treated with CRS-HIPEC in our cohort recurred intraperitoneally only; in 41% of these patients, a curative treatment option was considered. Although most of these patients face recurrence again, their average survival is prolonged.

Repeated CRS-HIPEC was feasible in some patients with isolated peritoneal recurrences in this study, which is concordant with several other studies[9-11, 14-16] and appears to be similar in our study. Complication rates and length of hospital stay for the first and second CRS-HIPEC procedure in this cohort were not statistically significantly different, as opposed to the study of Golse et al. in which a higher complication rate for secondary CRS-HIPEC procedures was reported.[9] The only systematic review about repeat CRS (by Williams et al.) concluded that repeat CRS gives possible survival benefit in carefully selected patients.[17] Braam et al. evaluated the treatment options of all recurrences after CRS-HIPEC,[18] and showed that patients with locoregional and/or systemic recurrences who were treated with curative intent showed significantly better survival than those who received palliative treatment, i.e., 43 months versus 12 months, respectively.[18] The same conclusion could be drawn based on the current study, which is focused on a cohort with isolated peritoneal recurrence.

Ideally, patients eligible for locoregional treatment would be appropriately selected preoperatively to limit the burden of surgery to patients in which complete cytoreduction is feasible. Patients who were scheduled for surgery with curative intent, but in whom complete CRS was not feasible, clearly did not benefit from therapy and were exposed to surgical complications. In patients with primary colorectal PC, it is hard to preoperatively estimate the extent of disease and to select patients appropriately using computed tomography (CT) imaging only.[19] Laparoscopy is often used to get better insight into the peritoneal tumor burden. In recurrent peritoneal metastases, laparoscopy is difficult due to previous CRS-HIPEC, and it may be hard to distinguish scar tissue and limited peritoneal metastases on CT imaging. Magnetic resonance imaging (MRI), whether combined with diffusion weighted imaging (DWI) or not, may aid radiological diagnosis. Recently published

Table 3. Cox regression for OS

	Univariable OS			Multivariable OS	
	Median (IQR)	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender					
Male	12.0 (3.7-24.7)	1.31 (0.85-2.00)	0.218	-	-
Female	14.4 (5.8-44.5)	1		-	-
Age					
< 50 years	12.0 (7.0-29.3)	0.99 (0.61-1.61)	0.971	-	-
≥ 50 years	13.6 (3.7-29.5)	1		-	-
ASA					
ASA 1	13.4 (5.8-29.5)	1	0.668	-	-
ASA 2	13.6 (5.6-31.7)	1.04 (0.67-1.61)	0.878	-	-
ASA 3	5.9 (0.5-6.4)	1.72 (0.53-5.56)	0.369	-	-
Comorbidity					
Absent	12.0 (5.0-29.3)	1		-	-
Present	14.5 (5.6-31.7)	0.87 (0.57-1.33)	0.521	-	-
Systemic metastases prior to CRS-HIPEC					
Absent	12.0 (5.0-24.7)	1		1	
Present	31.7 (13.6-44.5)	0.45 (0.22-0.89)	**0.023**	0.63 (0.27-1.47)	0.287
Systemic chemotherapy*					
No	10.6 (6.2-21.9)	1	0.177	-	-
Neoadjuvant	5.8 (2.2-16.6)	1.51 (0.77-2.98)	0.230	-	-
Adjuvant	17.4 (6.3-39.4)	0.76 (0.45-1.28)	0.300	-	-
Perioperative	12.2 (3.0-27.2)	0.87 (0.40-1.89)	0.721	-	-
Chemotherapy IP used*					
Mitomycin C	13.6 (5.8-29.5)	1		-	-
Oxaliplatin	6.6 (1.3-12.9)	1.66 (0.76-3.61)	0.204	-	-
Region Count*					
0-2 regions	15.5 (5.8-51.7)	1	0.210	1	0.449
3-5 regions	12.2 (5.8-24.7)	1.48 (0.93-2.36)	0.098	1.37 (0.82-2.28)	0.253
6-7 regions	10.6 (3.7-24.0)	1.60 (0.73-3.51)	0.242	1.04 (0.34-3.16)	0.951
Completeness of cytoreduction*					
R1	13.4 (5.6-31.7)	1		1	
R2a	10.6 (5.8-15.9)	1.68 (0.92-3.05)	0.091	1.09 (0.53-2.26)	814
Complication grade*					
CTCAE 0-2	16.6 (5.8-39.4)	1		1	
CTCAE 3-4	7.6 (3.8-12.0)	2.76 (1.58-4.20)	**< 0.001**	7.02 (2.51-19.62)	**<0.001**
pT-stage					
≤ pT3	15.8 (6.6-29.7)	1		-	-
pT4	10.3 (3.7-29.5)	1.14 (0.74-1.77)	0.547	-	-
pN-stage					
pN0	15.5 (6.6-36.3)	1	0.429	1	0.333
pN1	8.7 (3.0-29.3)	1.37 (0.80-2.34)	0.256	1.40 (0.80-2.49)	0.245
pN2	13.6 (4.1-27.2)	1.39 (0.80-2.44)	0.246	1.53 (0.85-2.77)	0.159
Peritoneal carcinomatosis					

Synchronous	10.6	(3.7-29.0)	1		-	-
Metachronous	13.4	(7.7-29.7)	0.78 (0.51-1.21)	0.272	-	-
Location primary tumor						
Appendix	8.2	(6.9-22.3)	0.89 (0.43-1.86)	0.763	-	-
Colon	12.2	(5.0-29.3)	1	0.811	-	-
Rectum	19.3	(6.2-29.7)	0.81 (0.40-1.62)	0.548	-	-
PA type primary tumor						
AC	13.4	(3.3-39.4)	1	0.354	-	-
MC	15.8	(7.7-29.0)	0.98 (0.62-1.55)	0.936	-	-
SRCC	7.0	(3.0-12.6)	1.56 (0.81-3.00)	0.182	-	-
Differentiation						
Good/Moderate	15.8	(6.3-29.7)	1		-	-
Poor	7.7	(2.5-29.3)	1.34 (0.84-2.14)	0.224	-	-
Treatment intent of recurrence						
Curative	24.7	(12.2-61.7)	1		1	
Palliative	7.6	(2.5-15.9)	2.68 (1.68-4.28)	**< 0.001**	2.74 (1.49-5.05)	**0.001**
Extent recurrence						
Solitary	31.7	(12.0-71.2)	1		1	
Multifocal	10.7	(3.7-22.3)	2.46 (1.36-4.44)	**0.003**	1.53 (0.81-2.90)	0.195
Time until recurrence						
< 1 year	8.7	(2.6-21.8)	1.38 (0.90-2.11)	0.139	-	-
≥ 1 year	15.8	(6.3-32.4)	1		-	-
Complication grade * Treatment intent		NA	2.20 (1.30-3.71)	**0.003**	0.20 (0.06-0.61)	**0.005**

Legend. Univariable and multivariable Cox regression analyses for overall survival in all patients (n=106) after treatment of isolated peritoneal recurrence.
Symbols. *, Factors related to first CRS-HIPEC.
Abbreviations. OS, overall survival; IQR, interquartile range; HR, Hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; IP, intraperitoneal; CTCAE, Common Toxology Criteria of Adverse Events; AC, adenocarcinoma; MC, mucinous adenocarcinoma; SRCC, signet ring cell carcinoma; CRS, cytoreductive sugery; HIPEC, hyperthermic intraperitoneal chemotherapy.

studies from Dohan et al. and Michielsen et al. support the possible additional value of MRI in patients with PC.[20, 21]

Predictive factors associated with a poor prognosis in patients with primary colorectal PC who underwent CRS-HIPEC include the extent of peritoneal disease, completeness of cytoreduction, postoperative complications, and lymph node status of the primary tumor, which has been previously described.[7, 8] Only the presence of postoperative complications after the first CRS-HIPEC was identified as a factor in multivariable analysis when isolated peritoneal recurrences were treated. These complications probably influenced the decision whether patients received curative or palliative treatment. Patients with high-grade complications were more often treated with palliative intent. The lack of other associations in this cohort could imply that isolated peritoneal recurrences behave independently of the primary CRS-HIPEC characteristics, i.e. positive lymph nodes of the primary tumor. The exact mechanism of PC remains unclear; however, it is known that most tumor

cells in the peritoneal cavity die, but a fraction survive and attach to the mesothelium.[22] The tumor microenvironment and cancer-associated fibroblasts (CAFs) present in the stroma play an important role in these attached cells, which contributes to tumor growth, invasion, and progression.[22, 23] It could be that due to the biology of the tumor, these patients respond differently to intraperitoneal mitomycin C or oxaliplatin, which was also one of the main reasons to preferably change the chemotherapeutic agent during the second CRS-HIPEC. Patients with PC, even those with relatively limited disease, clearly represent a heterogeneous group.

The retrospective design of this study causing selection bias is the most important limitation that precludes firm inferences. These patients have been selected, among others, to undergo primary CRS-HIPEC. Subsequently, they recurred intraperitoneally and some were selected for treatment with curative intent. However, it is clear that surgery or radiotherapy led to prolonged survival in some patients.

Conclusion

Locoregional treatment of isolated peritoneal recurrences after CRS-HIPEC is feasible in approximately half of the patients and should be considered if distant metastases are absent at the time of diagnosis. When curative treatment is obtained, long-term survival can be achieved.

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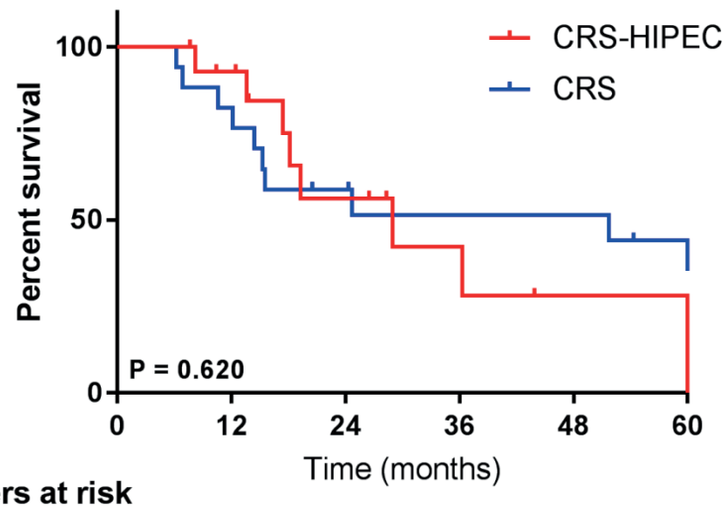
Supplementary data



Numbers at risk

CRS-HIPEC	15	12	6	3	1	1
CRS	17	14	9	7	7	5

Supplementary Figure 1. Overall survival for patients with isolated peritoneal recurrence treated with curative intent with CRS-HIPEC or cytoreductive surgery