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Patients with colorectal peritoneal metastases and high peritoneal cancer index may benefit from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background: Peritoneal cancer index (PCI) >20 is often seen as a contraindication for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastases (PM) from colorectal cancer. The aim of this study was to compare the overall survival in colorectal PM patients with PCI >20 and PCI ≤20 treated with CRS and HIPEC to those having open-close/debulking procedure only.

Methods: All patients with colorectal PM and intention to treat with CRS and HIPEC in Uppsala Sweden 2004–2017 were included. Patients scheduled for CRS and HIPEC were divided into three groups, PCI >20, PCI ≤20, and those not operated with CRS and HIPEC stated as open-close including those treated with palliative debulking.

Results: Of 201 operations, 112 (56%) resulted in CRS and HIPEC with PCI ≤20, 45 (22%) in CRS and HIPEC with PCI >20 and 44 (22%) resulted in open-close/debulking. Median survival for CRS and HIPEC and PCI >20 was 20 months (95%CI 14–27 months) with 7% surviving longer than 5 years (n = 3). For CRS and HIPEC and PCI ≤20 the median survival was 33 months (95%CI 30–39 months) with 23% (n = 26) surviving >5years. The median survival for open-close was 9 months (95%CI 4–10 months), no one survived >5years.

Conclusion: Patients with PM from colorectal cancer and PCI >20 that were treated with CRS and HIPEC experience a one year longer and doubled overall survival compared with open-close/debulking patients. In addition to PCI, more factors should be taken into account when a decision about proceeding with CRS or not is taken.

Introduction

The treatment of peritoneal metastases (PM) from colorectal cancer (CRC) has improved markedly after the introduction of cytoreductive surgery (CRS) [1] and hyperthermic intraperitoneal chemotherapy (HIPEC) [2]. Patients with a disease previously considered palliative can now be offered a potential curative treatment. However it is still only a minority of patients with PM that are treated with CRS and HIPEC and the majority are offered palliative chemotherapy or best supportive care [3].

The knowledge on which patients should be operated on is still evolving. Patients with inoperable metastases in other organs than peritoneum [3], widespread disease on the small bowel [4] or physical poor performance [5] are generally not offered surgical treatment.

The biology of the tumour is of importance with signet ring cell differentiation [3], BRAF mutation [6] and gain in chromosomes 1p and 15q [7] all associated with a poor prognosis and should be part of the treatment decision if that information is available.

Not surprisingly, the prognosis is dependent on the success of surgery and the completeness of cytoreduction score (CCS) is the most widely used instrument to estimate the amount of macroscopic tumour left at the end of surgery [8]. Patients without macroscopic tumour at completion of surgery do have a better prognosis than those who have residual macroscopic tumour tissue

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after surgery [9].

The extent of the peritoneal involvement estimated by the peritoneal cancer index (PCI) is widely used for prediction of prognosis and also patient selection [10]. However, different limits are used for patient selection depending on treatment centres and tradition [5].

The aim of this study was to compare the survival in CRC PM patients with PCI >20 and PCI ≤20 treated with CRS and HIPEC to those having open-close/debulking procedure only.

Material and methods

This is a retrospective single center study including all patients with PM from CRC with the intention to be treated with CRS and HIPEC at the University hospital, Uppsala, Sweden.

Patients and follow-up

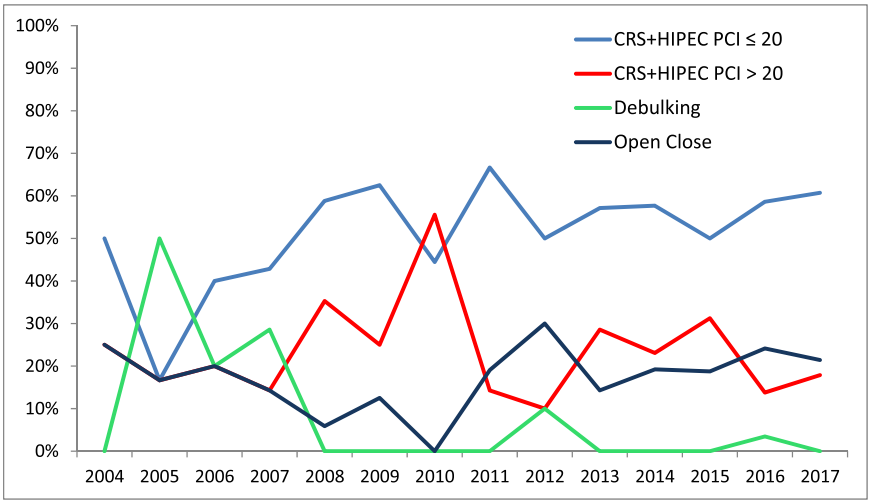
All patients with PM from CRC treated 2004–2017, with the intention to do CRS and HIPEC were included. Patients with previous CRS and HIPEC treatment, tumours other than CRC, PCI = 0, PCI missing and patients without follow-up information (mainly foreign citizens), were excluded. Clinical information and information on survival and recurrences was retrieved from the electronic hospital records, which was updated 2020-05-27.

Selection of patients for CRS and HIPEC

National guidelines, made by the Swedish peritoneal surface group, have since 2015 been used for patient selection by the four hospitals offering CRS and HIPEC in Sweden. Both synchronous, metachronous and recurrent CRC PM are accepted for discussion at the local multidisciplinary HIPEC meetings. Histopathological results, CT thorax and abdomen not older than two months, colonoscopy within one year and tumour markers (CEA, CA 19-9, CA 72-4, CA125) are needed before the patient can be discussed at the meetings. In selected cases PET CT, MRI, and diagnostic laparoscopy are requested to further estimate the distribution of the disease.

Exclusion criteria are poor physical performance with Karnofsky performance status <70, inoperable distant metastasis in other organs than in the peritoneal cavity, small bowel engagement leaving less than 2 m healthy small bowel or duodenal and pancreatic involvement requiring Whipple procedure.

If the local HIPEC conferences consider that the patient is a candidate for CRS and HIPEC, several clinical settings justify that the patient is discussed at the national HIPEC videoconference, before a definitive treatment decision is made. Participants in this conference are all four Swedish hospitals in addition to colleagues at the Antoni van Leeuwenhoek clinic in Amsterdam. Examples of these clinical settings are: if the preoperative investigations suspect that patients have PCI >20; if PM recur within 12 months from last CRS and HIPEC; if the waiting times for CRS and HIPEC is more than 6 weeks; or if the patients asks for second opinion. If the patient is considered operable, neoadjuvant chemotherapy has not been obligatory in Sweden. Indeed there is a trend that fewer patients are receiving neoadjuvant chemotherapy before the CRS and HIPEC due to the perception that PM often responds poorly to chemotherapy missing the opportunity of radical CRS in patients with poor response. Neoadjuvant systemic chemotherapy is only used in selected cases in which a downstaging is needed because of tumor growth or extension into nearby vital structures.



	Number intended for CRS and HIPEC													
CRS and HIPEC PCI ≤20	2	1	2	3	10	10	4	14	5	4	15	8	17	17
CRS and HIPEC PCI > 20	1	1	1	1	6	4	5	3	1	2	6	5	4	5
Debulking		3	1	2					1				1	
Open Close	1	1	1	1	1	2		4	3	1	5	3	7	6
In total	4	6	5	7	17	16	9	21	10	7	26	16	29	28

CRS: Cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy;
PCI: Peritoneal cancer index

Fig. 1. The treatment outcome in patients scheduled for operation with CRS and HIPEC for peritoneal metastases from colorectal cancer at the University hospital of Uppsala, Sweden during the time period 2004–2017.

Surgical methods

During the study period, CRS was performed and HIPEC was administered as previously described by Sugarbaker [10]. Oxaliplatin 460 mg/m^2 was the main intraperitoneal chemotherapeutic agent used for 30 min at 42° together with 5 fluorouracil 400 mg/m^2 and calcium folinate 30 mg/m^2 used intravenously. The surgeon documented the PCI after careful initial abdominal exploration resulting in a score ranging from 0 to 39 as illustrated by Jacquet and Sugarbaker [11]. The score was documented on a PCI form by the surgeon directly after the operation and the total PCI was also documented in the operation records. When PCI documentation was missing, the patients were excluded from the CRS + HIPEC group, but not from the open-close or debulking group as the surgeon often had difficulties in determining the exact score due to limited access to the abdomen.

In case of PCI >20 a careful evaluation was made to see if CRS with CCS 0-1 was achievable. At least 2 m disease free small bowel including its mesentery was mandatory for continued CRS. In the judgement whether to proceed or not, the degree of invasiveness of PM into adjacent structures was also considered.

CRS and HIPEC resulting in CCS = 1 were included in the analysis but three patients with CCS = 2 operated in 2005–2006 with CRS + HIPEC were excluded from the analysis.

The term open-close was used when the intention was to perform CRS and HIPEC but the patient was considered to be inoperable after exploration and only biopsies were taken and the abdomen was closed again. The term debulking was used in the same situation but when the surgeon decided to excise some major tumour mass such as ovarian metastasis or omental cake without any radical operation performed. Patients treated with open-close or debulking are analysed together in this study and are herein

Table 1
Diagnostic and therapeutic data for patients with peritoneal metastasis from colorectal cancer, statistical comparison of: those treated with CRS and HIPEC + PCI ≤20 with CRS and HIPEC + PCI >20 and of all CRS and HIPEC with open-close/debulking.

	CRS and HIPEC PCI ≤20	CRS and HIPEC PCI >20	p$^{\alpha}$	Open-close/debulking*	p$^{\beta}$
Number of patients	112	45		44	
Male	53 (47%)	17 (38%)	.277	24 (55%)	.134
Female	59 (53%)	28 (62%)		20 (45%)	
Age, median (range)	63 (23–79)	58 (13–72)	.026	59 (26–80)	.837
Karnofsky = 100	82 (73%)	33 (73%)	.883	20 (45%)	.002
Karnofsky = 90	21 (19%)	9 (20%)		16 (36%)	
Karnofsky = 80	6 (5%)	2 (4%)		4 (9%)	
Karnofsky ≤ 70	1 (1%)	0		4 (9%)	
Karnofsky na	2	1		0	
Colon	101 (90%)	40 (89%)	.809	37 (84%)	.292
Rectum	11 (10%)	5 (11%)		7 (16%)	
Histopathology of PM					
Non mucinous adenocarcinoma	59 (53%)	13 (29%)	.015	23 (52%)	.713
Mucinous adenocarcinoma	37 (33%)	19 (42%)		13 (30%)	
Signet ringcells cancer	16 (14%)	13 (29%)		8 (18%)	
CEA ≤ 6 μg/L	61 (55%)	16 (36%)	.032	13 (36%)	.132
CEA >6 μg/L	49 (45%)	28 (64%)		23 (64%)	
Missing	2	1		8	
Neoadjuvant chemo Yes	57 (51%)	24 (53%)	.782	19 (43%)	.324
Neoadjuvant chemo No	55 (49%)	21 (47%)		25 (55%)	
Adjuvant chemo Yes	52 (47%)	25 (57%)	.263		na
Adjuvant chemo No	59 (53%)	19 (43%)			
Missing	1	1			
PCI, median (range)	11 (2–15)	27 (21–37)	na	30 (11–39)	
CC score 0	107 (95%)	34 (72%)	<.001	0	na
CC score 1	5 (4%)	11 (23%)		0	
Complications 30 day postop					
Clavien dindo <3	86 (77%)	26 (58%)	.017	40 (91%)	.008
Clavien dindo 3a	14 (13%)	8 (18%)	.389	1 (2%)	.031
Clavien dindo 3b	8 (7%)	4 (9%)	.710	1 (2%)	.201
Clavien dindo 4	4 (4%)	6 (13%)	.024	0	na
Clavien dindo 5 = death	0	1 (2%)	na	2 (5%)	.059
90 day mortality	1 (1%)	2 (4%)	.142	13 (30%)	<.001

CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy; Chemo: Chemotherapy; PM: Peritoneal metastasis; PCI: Peritoneal cancer index; CC: Completeness of cytoreduction; na: Not available.
α; comparison between CRS and HIPEC PCI ≤20 and CRS and HIPEC PCI >20; β; comparison between CRS + HIPEC and Open-close/debulking; * 8 patients were treated with palliative debulking.

referred to as open-close/debulking.

Ethical approval

The study was approved by the ethics committee of Uppsala County (Dnr 2013/203).

Statistical analyses

Overall survival was measured from the date of surgery to the date of death from all causes using median time in years and 95% confidence interval (95%CI). Similarly, recurrence free survival was calculated from date of surgery to first mentioning of recurrence in the medical records. Kaplan Meier curves were used for presentation of survival time and Log rank test for statistical comparisons between patients with PCI >20 and PCI ≤20 treated with CRS and HIPEC and those having an open-close/debulking procedure to the groups receiving CRS and HIPEC. Cox proportional hazard models was used for uni- and multivariate regression analyses of factors likely to be associated with survival or recurrence. Survival analysis was conducted in R [12] using survival, survminer and ggplot2 packages [13]. Chi-Square test was used to analyse differences between groups regarding categorical data and Mann-Whitney *U* test was used for comparison of continuous variables. P < .05 was considered statistically significant.

Results

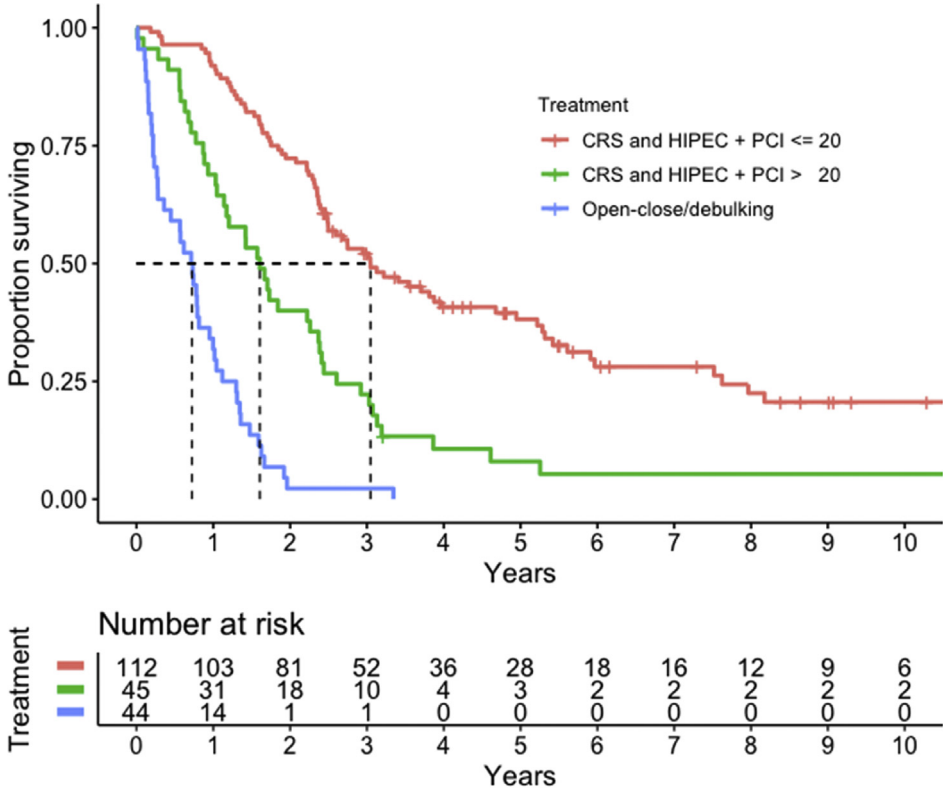
Of the 201 patients with PM from CRC intended for CRS and HIPEC, 157 (78%) were treated with CRS and HIPEC but 44 (22%) were not eligible for CRS and HIPEC but underwent open-close (n = 36) or debulking (n = 8). Out of the 157 receiving CRS and HIPEC, 45 (29%) had PCI >20 and 112 (71%) had a PCI ≤20.

Patients with PCI >20 constituted around 20% of all index operations and debulking was rarely done in case of CRC PM during the more recent years (Fig. 1).

The median age of all patients was 61 years (range 13–80) and female-male gender ratio was roughly equal (Table 1).

The open-close/debulking group had worse Karnofsky performance status, fewer postoperative complications according to Clavien Dindo and a higher 90 day mortality than the total CRS and HIPEC group (Table 1).

Comparisons between those treated with CRS and HIPEC with PCI ≤20 and CRS and HIPEC with PCI >20 revealed younger



Comparisons Log Rank	P
CRS and HIPEC + PCI ≤20 vs CRS and HIPEC + PCI >20	<.001
CRS and HIPEC + PCI ≤20 vs Open-close/debulking	<.001
CRS and HIPEC + PCI >20 vs Open-close/debulking	<.001

CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy; PCI: Peritoneal cancer index ; CCS: Completeness of cytoreduction score

Fig. 2. Overall survival in patients treated for peritoneal metastases from colorectal cancer, plotted with Kaplan Meier method up to 10 years. Comparison of those treated with CRS and HIPEC with PCI >20, CRS and HIPEC with PCI ≤20 and open-close/debulking. The dotted line points to the median survival for each group.

patients, higher CCS, CEA and more complications in those treated with CRS and HIPEC with PCI >20 (Table 1). Moreover the histopathology of the PM were more likely to be mucinous adenocarcinoma or signet ring cell carcinoma in those with CRS and HIPEC and PCI >20 compared with more non mucinous adenocarcinoma in CRS and HIPEC and PCI <20 group (Table 1).

The median PCI was 14 (range 2–37) for the 157 patients in the CRS and HIPEC group, for patients undergoing open-close/debulking, the PCI was available for 36 patients with a median score of 30 (range 11–39).

It was more likely that CRS and HIPEC resulted in CCS >0 if PCI >20 ($p < .001$, Table 1).

The failure sites for those treated with CRS and HIPEC resulting in CCS = 1 (n = 16) were described as mucinous or fibrin film on bowel (n = 5), diffuse small tumours or white strings on bowel (n = 4), fibrotic pelvis (n = 1), fibrotic tissue right ureter (n = 1), retroperitoneal disease (n = 1), small inoperable tumours in liver hilum (n = 1) and no description in three cases.

For the open-close/debulking group the failure sites were given as small bowel engagement in majority of the cases (n = 39; 89%). For nine of these patients other reasons such as high PCI, liver metastasis, pancreatic involvement, retroperitoneal disease and engaged mesentery were also stated as a failure sites. The remaining five patients had open-close/debulking due to advanced liver metastasis, retroperitoneal disease, poor physical performance and pancreatic involvement.

One 30 day mortality was seen in patients treated with CRS and HIPEC (1%) and it occurred in the group with PCI >20, the death was due to suicide. Two open-close/debulking patients died within 30 days (5%), one caused by aspiration due to paralytic obstruction and the other cause was unknown as the patient had been transferred to the referral hospital.

The 90 day mortality was 2% in CRS and HIPEC, with two of them seen in PCI >20 and one in PCI ≤20. The 90 day mortality was 30% in the open-close/debulking group which was statistically significantly higher than in the CRS and HIPEC group ($P < .001$, Table 1).

The median survival for open-close/debulking was 9 months (95%CI 4–10 months) and 30 months (95%CI 29–33 months) for all CRS and HIPEC. The median survival for CRS and HIPEC with PCI >20 (n = 45) was 20 months (95%CI 14–27 months) with 7% (n = 3) surviving more than 5 years. The median survival for CRS and HIPEC with PCI ≤20 (n = 112) was 33 months (95%CI 30–39 months) with 23% (n = 26) surviving >5 years. The survival differences between the three groups; CRS and HIPEC PCI >20, CRS and HIPEC PCI ≤20 and open-close/debulking are further demonstrated by the Kaplan-Meier graph in Fig. 2.

Univariate Cox regression analysis of common prognostic variables revealed that low Karnofsky performance status, high serum CEA, high PCI and CCS = 1 were associated with death, with CEA and PCI independently associated with increased risk of death in multivariate analysis (Table 2). Repeating these analyses including only CRS and HIPEC cases revealed similar results but also that mucinous histology was associated with lower risk for death compared with non-mucinous adenocarcinoma patients (HR 0.57;

Table 2
Risk of death in patients intended for treatment with CRS and HIPEC for peritoneal metastasis from colorectal cancer. Uni- and multivariate Cox regression analysis using common prognostic variables with the hazard ratio (HR) revealing risk of death with 95% confidence interval (CI).

	Univariate HR (95%CI)	P	Multivariate HR (95%CI)	p
Male	refs			
Female	0.83 (0.61–1.10)	.228		
Age <70	refs			
Age ≥70	0.95 (0.62–1.5)	.817		
Karnofsky = 100	refs		refs	
Karnofsky ≤ 90	1.60 (1.2–2.20)	.003	1.30 (0.95–1.90)	.090
Colon	refs			
Rectum	1.20 (0.72–1.90)	.524		
Non mucinous adenocarcinoma	refs			
Mucinous adenocarcinoma	0.77 (0.54–1.10)	.132		
Signet ring cell carcinoma	1.10 (0.72–1.70)	.664		
CEA ≤6 μg/L	refs		refs	
CEA >6 μg/L	1.70 (1.20–2.40)	<.001	1.50 (1.11–2.10)	.010
CA19-9 ≤15 μg/L	refs			
CA19-9 >15 μg/L	1.30 (0.98–2.40)	.071		
No neoadjuvant chemotherapy	refs			
Neoadjuvant chemotherapy	0.90 (0.66–1.20)	.515		
No adjuvant chemotherapy*	refs			
Adjuvant chemotharapy	1.0 (0.73–1.50)	.816		
PCI ≤20; CRS and HIPEC	refs		refs	
PCI >20; CRS and HIPEC	2.50 (1.70–3.60)	<.001	2.5 (1.64–3.70)	<.001
Open-close/debulking	8.60 (5.60–13.1)	<.001	7.70 (4.91–12.1)	<.001
CC score 0*	refs		refs	
CC score1	1.80 (1.00–3.20)	.040	1.30 (0.72–2.3)	.391

CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; PCI: Peritoneal cancer index; CC: Completeness of cytoreduction; refs: Reference value; * CRS and HIPEC only.

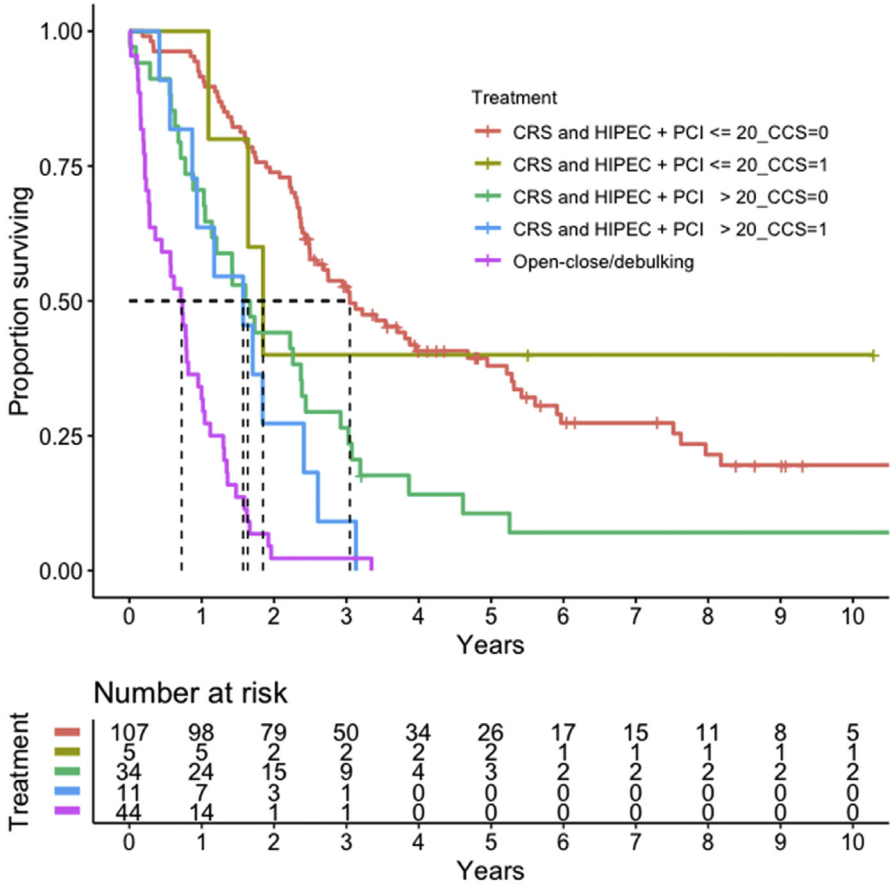
95%CI 0.37–0.88).

Further categorisation according to PCI and CCS revealed that the overall survival did not differ between PCI >20 and CCS = 0, median 20 months (95%CI 13–29 months) compared with PCI >20 and CCS = 1, median 19 months (95%CI 11–22 months) (Fig. 3). For PCI ≤20 and CCS = 0 median survival was 33 months (95%CI 30–39 months) compared with PCI ≤20 and CCS = 1 median 22 months (95%CI 13–67 months). Open-close/debulking patients had significantly worse survival than all CRS and HIPEC groups (Fig. 3). However no long term survivors were seen in CRS and HIPEC with PCI >20 and CCS = 1 (Fig. 3).

In the CRS and HIPEC group with PCI >20, a slightly longer survival was seen for PCI >30 (n = 14) median survival 24 months (95%CI 13–30 months) compared with PCI ≤30 (n = 31) experiencing a median survival of 17 months (95%CI 11–22 months). The PCI >30 were more likely to have mucinous histology of PM (n = 9; 64%) compared with PCI ≤30 (n = 10; 32%, p = .044).

Information on recurrences were available for 141 CRS and HIPEC patients with 121 (86%) developing recurrence with median time to recurrence of 9 (range 1–62) months. The recurrence location was known for 103 patients with 71 (69%) developing recurrence within the peritoneum of whom 44 (62%) also had other distant metastasis. The median time from recurrence to death analysed for 102 deceased patients was 16 (range 0–76) months.

Patients treated with CRS and HIPEC having PCI ≤20 had significantly lower risk for recurrence compared with CRS and HIPEC with PCI >20 (P .001, Fig. 4). Cox regression analysis revealed that high serum CEA and high PCI were independently associated



Cox proportional hazard model			
	HR	95%CI	P*
CRS and HIPEC + PCI ≤20 _ CCS = 0	referens		
CRS and HIPEC + PCI ≤20 _ CCS = 1	0.89	0.28 - 2.80	.847
CRS and HIPEC + PCI >20 _ CCS = 0	2.24	1.47 - 3.40	<.001
CRS and HIPEC + PCI >20 _ CCS = 1	3.53	1.85 - 6.80	<.001
Open-close/debulking	8.66	5.66 - 13.30	<.001

CRS: Cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; PCI: Peritoneal cancer index ; CCS: completeness of cytoreduction score; HR: Hazard ratio; 95%CI: 95% confidence interval; * compared with reference

Fig. 3. Overall survival in patients treated for peritoneal metastases from colorectal cancer, plotted with Kaplan Meier method up to 10 years. Comparison of those treated with CRS and HIPEC with PCI >20, CRS and HIPEC with PCI ≤20 and open-close/debulking, with the CRS and HIPEC groups categorized according to completeness of cytoreduction score (CCS). The dotted line points to the median survival for each group. The table shows comparisons between the different groups with Cox proportional Hazard using CRS and HIPEC with PCI ≤20 and CCS = 0 as a reference.

with increased risk of recurrence in multivariate analysis (Table 3).

Discussion

This study reveals that patients with PM from CRC, treated with CRS and HIPEC and having PCI >20, do have significantly better survival than patients with inoperable disease treated with open-close or debulking. The median survival difference was one year which is a substantial gain in a group with short expected survival.

CRS and HIPEC was initially used mainly for peritoneal surface malignancies from appendiceal neoplasms including pseudomyxoma peritonei or mesoteliomas. In recent decades it has been increasingly used for PM from CRC as randomized studies have shown survival benefits of CRS plus locoregional chemotherapy versus systemic chemotherapy only [14,15].

In patients with widespread peritoneal metastatic disease surgery can be demanding for the patient with risk of complications and prolonged hospital stay. In patients that already have limited survival time, it is of importance to only perform major surgery if it really improves the quality of life and prolongs survival [16].

PCI is the most widely used instrument to estimate the tumour burden of the peritoneal disease, PCI has a strong association to prognosis and is often used for patient selection. The PCI has low interobserver variation and is higher when estimated in the end of the CRS procedure compared with the beginning [17]. However, PCI can be difficult to estimate correctly in the preoperative radiological workup with CT scans underestimating the tumour burden due to difficulties in identifying small PM [18]. Even during the CRS it can be difficult to separate PM from benign fibrotic lesions resulting in overestimation of true malignant PM [19,20].

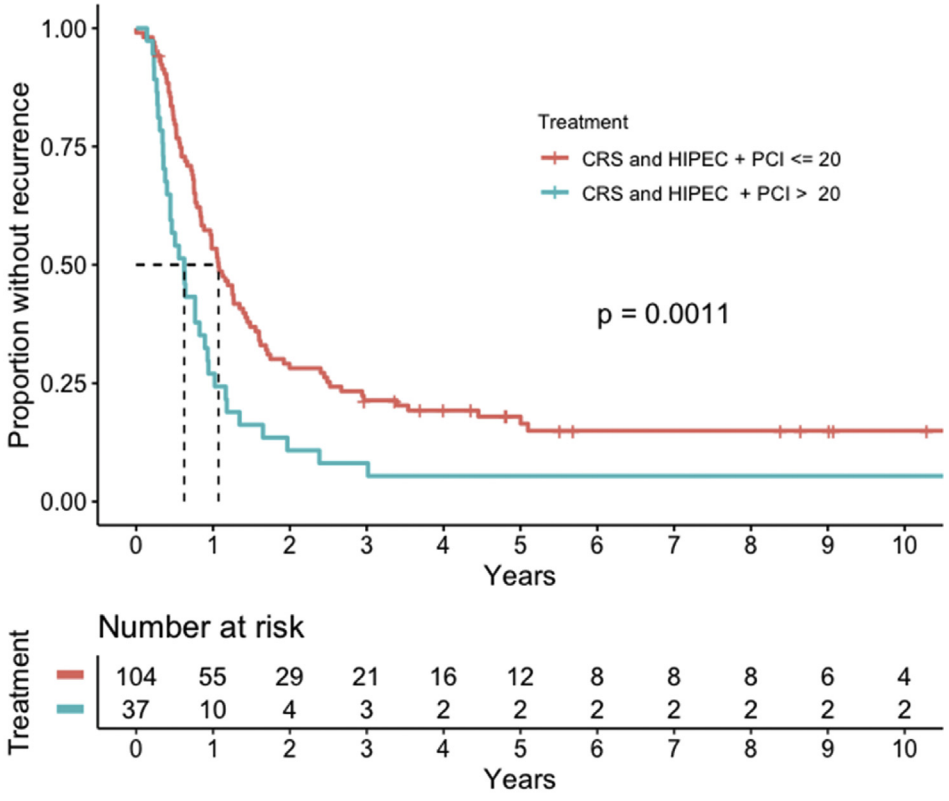
Patients with PCI >20 was early on shown to have much worse prognosis when compared with patients with lower PCI scores [21,22] and a French group has recently argued against operating patients with PCI higher than 17 due to poor survival [23]. However, ongoing randomized trials such as the CAIRO06 trial does not have high PCI as an exclusion criteria [24].

At the University hospital, Uppsala, high PCI score has not been seen as an absolute contraindication to CRS and HIPEC as in some cases large volume of disease can be surgically radically removed even if PCI is above 20. This is in line with previous observation published in 2014 revealing a curative potential of CRS and HIPEC in patients with PM from CRC and high PCI [25].

An interesting finding in the present study is the statistically non-significant longer survival for PCI >30 compared with PCI ≤30, probably depending on mucinous cancers with high tumour load generating high PCI score but seemingly operable disease.

Small bowel engagement was the most common cause for open-close/debulking operations as patients with less than 2 m of small bowel left will have a poor quality of life together with short survival. An attempt to use the PCI score only for the small bowel for prognostic estimates have recently been made revealing the importance of the small bowel involvement [4].

During the study period, the amount of cases with PM from CRC has been steadily increasing but the proportion of cases operated on with CRS and HIPEC have been constant as well the proportion of open-close operations. This shows that the awareness of CRS and HIPEC as a treatment option for PM at the hospitals who do refer patients has been increasing.



CRS: Cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; PCI: Peritoneal cancer index

Fig. 4. Time to recurrences in patients treated for peritoneal metastases from colorectal cancer, plotted with Kaplan Meier method up to 10 years. Comparison of those treated with CRS and HIPEC with PCI >20 with CRS and HIPEC with PCI ≤20. The dotted line points to the median survival for each group.

Table 3
Risk of recurrence in patients treated with CRS and HIPEC for peritoneal metastasis from colorectal cancer. Uni- and multivariate Cox regression analysis using common prognostic variables with the hazard ratio (HR) revealing risk of death with 95% confidence interval (CI).

	Univariate HR (95%CI)	P	Multivariate HR (95%CI)	p
Male	refs			
Female	0.85 (0.59–1.20)	.362		
Age <70	refs			
Age ≥70	0.96 (0.57–1.6)	.878		
Karnofsky = 100	refs			
Karnofsky ≤90	1.10 (0.75–1.70)	.580		
Colon	refs			
Rectum	1.20 (0.66–2.10)	.569		
Non mucinous adenocarcinoma	refs			
Mucinous adenocarcinoma	0.85 (0.57–1.30)	.413		
Signet ring cell carcinoma	1.07 (0.65–1.80)	.798		
CEA ≤6 μg/L	refs		refs	
CEA >6 μg/L	1.89 (1.31–2.70)	<.001	1.86 (1.29–2.70)	<.001
CA19-9 ≤15 μg/L	refs			
CA19-9 >15 μg/L	1.30 (0.90–1.90)	.157		
No neoadjuvant chemotherapy	refs			
Neoadjuvant chemotharapy	0.95 (0.66–1.40)	.762		
No adjuvant chemotherapy	refs			
Adjuvant chemotherapy	0.98 (0.68–1.40)	.904		
PCI ≤20	refs		refs	
PCI >20	1.90 (1.30–2.90)	<.001	1.84 (1.24–2.70)	.003
CC score 0	refs			
CC score 1	1.10 (0.57–2.10)	.792		

CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; PCI: Peritoneal cancer index; CC: Completeness of cytoreduction; refs: Reference value.

To be operated with CRS and HIPEC and having PCI >20 comes to some costs as they had significantly more complications scoring three or higher according to the Clavien Dindo classification compared with PCI ≤20 although not with higher postoperative mortality. The increased risk of complications in those with PCI >20 has to be weighed against the benefits of gaining one more survival year than open-close/debulking and having 7% chance of surviving more than 5 years compared with 0% in open-close/debulking. Previous studies on the survival of open-close patients with CRC PM have shown median survival of 9.8 months with around 75% of the patient able to receive palliative chemotherapy which gave a 11.2 months median survival compared with 2.7 months for those who were not able to receive palliative chemotherapy [26]. This poor survival for open-close/debulking patients is in line with other smaller studies showing median survival of 6.3 months [27] and 12.7 months [28].

Open-close/debulking patients are not fully comparable to those patients that have been operated on with CRS and HIPEC and PCI >20 as these patients do have more tumour burden on the small bowel that can cause small bowel obstruction with subsequent inability to have chemotherapy, enteral nutrition and risk of peritonitis resulting in shorter survival. In this study low Karnofsky performance status was associated with open-close/debulking probably explaining its association with death in univariate Cox regression analysis and not in the multivariate analysis.

Recurrences were common and were mainly observed in the peritoneal cavity although liver and lung metastasis also were common. As most patients developing recurrence eventually die, no major differences were seen in Cox multivariate analyses between risk of recurrence and death. High PCI and CEA were the only significant risk factors in both analyses.

To obtain complete cytoreduction is of greatest importance to be able to gain long term survival especially in those with high PCI score as shown by the present study. It is therefore our perception that CRS and HIPEC resulting in radical operation on selected patients with high PCI can result in prolonged survival, which for individual patients and relatives can be of major importance.

The indications and selection of patients with PM from CRC for CRS and HIPEC and high tumour burden is constantly evolving. The selection process is multifactorial but will in the end focus on how to prolong survival and improve quality of life. The treatment options have to be discussed openly with the patients preoperatively informing about the risks and giving realistic hope.

In conclusion, patients with PM from CRC and PCI >20 who were treated with CRS and HIPEC gain about 1 year in survival and have double overall survival compared with patients where the operation resulted in open-close/debulking. More factors than PCI should be taken into account when a decision about proceeding with the operation or not is taken.

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The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report or in the decision to submit for publication.

Declaration of competing interest

The authors declare no conflicts of interest.

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