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The impact of the extent of surgery on late adverse effects following cytoreductive surgery and HIPEC

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ABSTRACT

Aim: To investigate the impact of the surgical extent on late adverse effects (LAE) following cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

Method: A prospective cohort study including patients undergoing CRS + HIPEC due to peritoneal metastases from gastrointestinal tumour origin. From 2006 through 2019, consecutive patients treated with CRS + HIPEC were followed at 3, 6 and 12 months, and LAEs were assessed using the symptom scales and items from the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30). Surgical extent was categorized into three groups (major, intermediate, minor) based on peritonectomy procedures and colorectal resections performed as part of CRS. EORTC data were analysed using a linear mixed effects regression model adjusted for age, gender, origin of tumour and comorbidity.

Results: In total, 257 patients who responded to at least one questionnaire during the follow-ups were included. Only diarrhoea symptoms were positively associated with surgical extent (mean differences: major vs. minor: 8.4 (−0.5; 17.2) (p = 0.06) and major vs. intermediate: 10.9 (3.8; 18.0) (p = 0.00)). Additionally, diarrhoea symptoms persisted throughout the study period and did not change over time (mean difference 12-3 months: −3.6 (−9.1; 1.7) (p-value = 0.18)). Overall, the levels of different symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, and appetite loss) significantly decreased from 3 to 12 months.

Conclusion: Patients undergoing extensive CRS suffer from persistent impaired gastrointestinal function in terms of diarrhoea compared patients undergoing to less extensive surgery. Attention should be directed at detecting such LAE and to guide patients accordingly.

1. Introduction

The introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has improved long-term survival for a selected group of patients with peritoneal metastases (PM) from gastrointestinal origin [1–4]. The principle of CRS is based on excision of all visible macroscopic tumour tissue (i.e. Peritonectomies) and resection of the visceral organs with tumour-involved peritoneum [5–7]. The extent of the CRS procedure varies according to the intraabdominal extent of the tumour spread [7]. After the CRS procedure, the intra-abdominal cavity is flushed with hyperthermic chemotherapy. The chemotherapeutic agent(s) and the flushing time differ according to HIPEC regimen [8,9].

With the increasing number of survivors following CRS + HIPEC, late adverse effects (LAEs) and the quality of the life beyond surgery becomes essential. A targeted questionnaire for patients with PM undergoing CRS + HIPEC has not yet been developed [10], and LAEs are often measured with questionnaires such as the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [11,12].

Reports regarding LAEs have been sparsely reported. In some recent systematic reviews, Leimkuhler et al. [13] and Balachandran et al. [12] reported that some symptoms (fatigue, dyspnoea, insomnia and diarrhoea) worsened within the first months, and except diarrhoea, all symptoms improved within 12 months. However, the direct association between the extent of CRS and LAEs following CRS + HIPEC has not been investigated.

Our primary aim was to describe the impact of the surgical extent of CRS on LAEs within the first 12 months after CRS + HIPEC.

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2. Method

2.1. Study design and setting

The study was carried out as a prospective cohort study at Department of Surgery at Aarhus University Hospital, Denmark. In the period from 2006 through January 2019 consecutive patients treated with CRS + HIPEC were included.

2.2. Participants

Patients were treated with CRS + HIPEC due to gastrointestinal malignancies (PM from colorectal cancer or appendiceal cancer including goblet cell, malignant peritoneal mesothelioma (MPM) or pseudomyxoma peritonei (PMP)). The treatment decision was planned at a multidisciplinary treatment (MDT) based on a contrast-enhanced (Positron Emission Tomography (PET)-) Computer Tomography (CT) of the thorax, abdomen and pelvis, and if deemed necessary, a diagnostic laparoscopy to evaluate the resectability.

The CRS + HIPEC procedure was initiated with a laparotomy with an initial re-evaluation of the tumour extent and eligibility criteria [14]. Any macroscopic tumour tissue was resected aiming to leave only tumour deposits <2.5 mm behind.

Peritonectomy procedures were performed as demonstrated and described by Sugarbaker [5]. Following CRS, while the abdomen was still open, the peritoneal cavity was flushed with heated Mytomycin C or Oxaliplatin, two-directional, depending on the histological diagnosis. All procedures were performed by 4 specialized consultant surgeons.

We considered all patients eligible for study analysis if they completed CRS + HIPEC and responded to at least one questionnaire within 12 months postoperatively.

2.3. Follow-up and assessment of late adverse effects

Patients were routinely followed in the outpatient clinic at 3, 6 and 12 months postoperatively aiming to detect recurrent disease. Each follow-up visit was preceded by a (PET-)CT of the thorax, abdomen and pelvis to identify potential recurrence, and the subsequent medical consultation took place either physical or by telephone including an invitation to fill out a questionnaire measuring LAEs. LAEs were assessed using the validated Danish version of the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) (version 3.0 or version 2.0), which is a generic 30-item questionnaire consisting of 1) an overall HRQoL-scale, 2) a range of functional-scales and 3) a number of symptom-scales. In case of recurrence, patients were generally not invited to a measurement of LAEs.

In current study we defined LAE as 'an unexpected medical problem that happens during treatment (i.e CRS + HIPEC)', hence we focused on symptoms scales from the EORTC QLQ-C30 and the overall HRQoL.

In the period from 2006 to 2016 information on LAEs were prospectively collected after each follow-up consultation in the outpatient clinic. From 2017 to 2018 information on LAEs were prospectively collected 1–2 days after each consultation using the EORTC QLQ-C30 v3.0 in Danish. From After February 2018 the EORTC QLQ-C30 v3.0 were sent to patients 1 week prior to the consultations to electronically fill out using the Danish questionnaire-platform AmbuFlex [15].

Non-responders were categorized into following causes; death, recurrence, not reached follow-up yet (time since surgery < follow-up date) and no reason.

Since the follow-up times could differ for the individual patient, we defined the HRQoL assessment to be at 3, 6 or 12 months if questionnaires were filled out at 3, 6 or 12 months ± 1.5 months, respectively.

2.4. Variables

All baseline variables were collected at the time of CRS + HIPEC.

We categorized the surgical extent into three groups.

1 Minor: No complete peritonectomy procedure of the upper peritoneal cavity and/or lower peritoneal cavity *AND* no colorectal resection
2 Intermediate: A complete peritonectomy procedure in upper and/or lower region *OR* colorectal resection with an anastomosis or with a stoma
3 Major: A complete peritonectomy in upper and/or lower region *AND* colorectal resection with an anastomosis or a stoma

2.5. Statistical methods

Baseline characteristics are presented for each surgical extent-group (minor, intermediate and major), and for the total population. Categorical variables are presented as numbers and percentages, and continuous variables as medians with ranges.

Data was analysed according to EORTC manual and the raw scores were aggregated into a linear score ranging from 0 to 100. A high score on the symptom scale indicates a high level of symptomatology/problems. A score was calculated if the patient had answered at least half of the items on the scale.

EORTC data were analyaed using a linear mixed effects regression model with surgical extent (minor, intermediate, and major) and time along with the interaction between them as categorical fixed effects. Patients were included as random effects. The analyses were adjusted for age, gender, origin of gastrointestinal tumour and comorbidity. Model validation was performed by comparing observed and expected within subject standard deviations and correlations and by inspecting QQ-plots.

EORTC symptomatology scales are presented as the average mean scores with standard deviations. Due to ceiling and floor effects in the HRQoL data, equality of mean scores between groups are presented as the difference of mean along with 95 % confidence intervals and associated p-values. The level of statistical significance was 5 %.

Finally, we performed two sub-analyses of potential confounders; 1) the impact of the type of colonic resection, and 2) the impact of the PCI score (registered from 2015) using a linear mixed effects regression model with type of colonic resections (previous or current) (right-sided colectomy including total colectomies and re-resections of anastomosis, left-sided, or no colonic resection) and time along with the interaction between them as categorical fixed effects in this period, and adjusted for gender, age, comorbidity and diagnosis of tumour origin. Second, we conducted the linear mixed effects regression model with surgical extent (minor, intermediate, and major) and time along with the interaction between them as categorical fixed effects, and adjusted for the PCI score (as a continuous variable), gender, age, comorbidity and diagnosis of tumour origin.

The Stata statistical software (STATA, IC 16.0, STATACorp LP, Texas, USA) was used in all calculations.

3. Results

From January 2006 through January 2019, 438 patients underwent CRS + HIPEC, among whom we included 257 patients (58.7 %) who responded to at least one EORTC QLQ C30 questionnaire (Fig. 1) within 12 months from surgery.

In total, response rates throughout the period were 76.3 % at 3 months (196 responders/257 included patients, n = 61 no reason), 56.1 % at 6 months (134 responders/239 included patients, n = 9 recurrence, n = 9 not reached follow-up, n = 105 no reason) and 44.9 % at 12 months (92 responders/205 included patients, n = 1 dead, n = 17 recurrence, n = 17 not reached follow-up and n = 113 no reason). Response rates for each surgical extent group are listed in Table 1.

Baseline variables are depicted in Table 1.

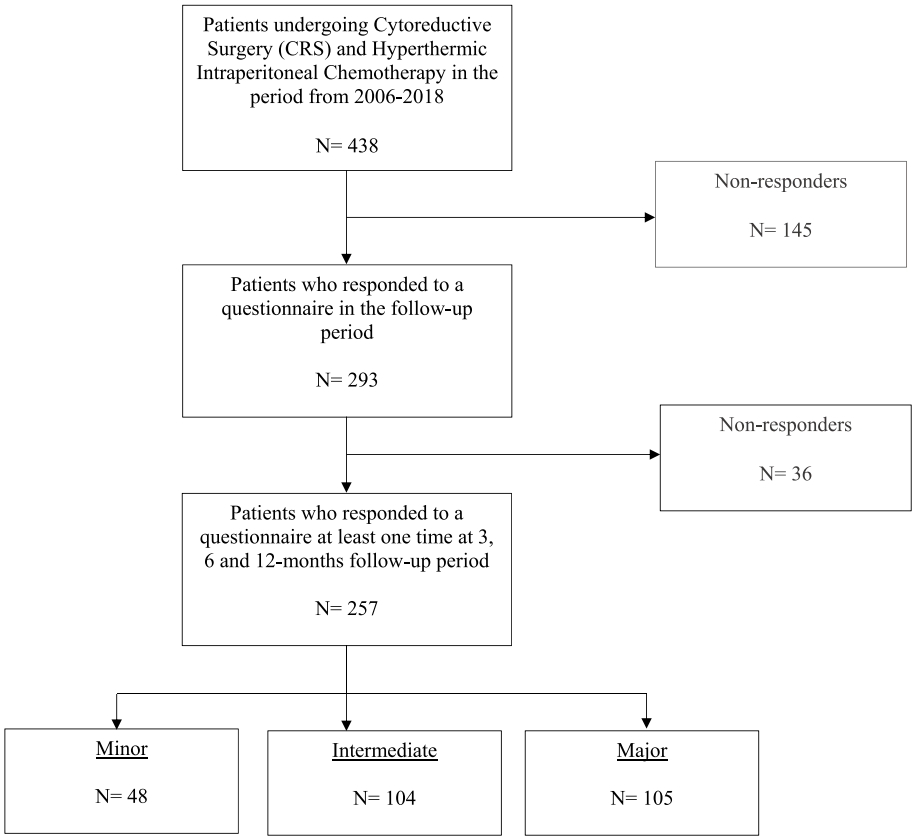

Fig. 1. Flowchart of patient inclusion.

3.1. Symptom scales between groups of surgical extent of CRS

Symptom scales measured by the EORTC QLQ C30 are compared between groups of surgical extent (minor, intermediate and major) and demonstrated in Table 2.

In the period between 3 and 12 months, diarrhoea was the only symptom differing between the groups of surgical extent. Patients who underwent major surgical extent reported a significant higher level of diarrhoea symptoms (mean differences: major vs. intermediate: 10.9 (3.8; 18.0) (p = 0.00)) compared to patients undergoing intermediate CRS. The same association was demonstrated for patients undergoing minor surgery compared to major surgery (mean differences: major vs. minor: 8.4 (−0.5; 17.2) (p = 0.06)). As demonstrated in Table 2, these symptoms persisted throughout the period, and did not change over time (mean difference 12-3 months: −3.6 (−9.1; 1.7) (p-value = 0.18)).

3.2. Symptom scales over time

The development of symptom scales between 3 and 12 months postoperatively are demonstrated in Table 3. The level of some symptom scales decreased in the period from 3 to 12 months; fatigue (mean difference 12 to 3 months: −13.9 (−18.4; −9.5) (p = 0.0)), nausea and vomiting (mean difference 12 to 3 months: −6.2 (−10.1; −2.5) (p = 0.0)), pain (mean difference 12 to 3 months: −6.8 (−11.1; −2.5) (p = 0.0)), dyspnoea (mean difference 12 to 3 months: −9.8 (−14.5; −5.2) (p = 0.0)), appetite loss (mean difference 12 to 3 months: −8.4 (−13.2; −3.5) (p = 0.0)).

3.3. Overall HRQoL

We observed a significant improvement in overall HRQoL from 3 to 12 months, however we did not observe any difference between groups of surgical extent.

3.4. Subanalyses

3.4.1. Type of colorectal resection

Both patients who underwent right-sided colectomies (incl. total colectomies and re-resection of anastomosis) and left-sided colectomies reported a significant higher level of diarrhoea symptoms (right-sided resections vs. no resections: mean difference 10.3 (2.6; 18.) (p = 0.01) and left-sided resections vs. no resections: mean difference 10.8 (0.5; 21.0) (p = 0.04)) compared to patients who had never had resections of the colon or rectum. There was no difference in diarrhoea symptoms reported from patients with left colonic resections compared to right-sided colonic resections (0.5 (−8.3; 9.2) (p = 0.92)).

3.4.2. PCI score

The PCI score was registered from 2015 and forwards. Therefore, we conducted the linear mixed effects regression model with surgical extent (minor, intermediate, and major) and time along with the interaction between them as categorical fixed effects in this period, and adjusted for the PCI score (as a continuous variable), gender, age, comorbidity and diagnosis of tumour origin. The adjustment for PCI score did not affect previous presented results. Patients who underwent major surgical extent reported a significant higher level of diarrhoea symptoms (mean differences: major vs. intermediate: 10.5 (1.20; 19.9) (p = 0.02)) and (major vs. minor: 0.8 (−10.5; 12.2) (p = 0.88)) compared to patients undergoing intermediate CRS.

4. Discussion

In this prospective cohort study, we demonstrated that several symptoms such as fatigue, nausea and vomiting, pain, dyspnoea and appetite loss significantly improved in the period from 3 to 12 months after CRS + HIPEC. However, patients undergoing major CRS procedures (and HIPEC) reported a significant higher level of diarrhoea

Table 1
Baseline characteristics.

Variable	Surgical extent			Total	Non-responders
	Minor	Intermediate	Major		
	n = 48	n = 104	n = 105	n = 257	N = 145
Surgical extent					
Minor	48	0	0	48 (18.7)	22 (15.2)
Intermediate	0	104	0	104 (40.5)	42 (29.0)
Major	0	0	105	105 (40.8)	58 (40.0)
Missing	0	0	0	0 (0.0)	23 (15.)
Age, median (interquartile range)	60.5 (14)	60.5 (17)	61 (16)	61 (16)	61 (18)
Sex					
Female	30 (62.5)	57 (54.8)	69 (65.7)	156 (60.7)	78 (53.8)
Male	18 (37.5)	47 (45.2)	36 (34.3)	101 (39.3)	67 (46.2)
ASA score					
1	20 (41.7)	41 (39.4)	35 (33.6)	96 (37.5)	34 (23.5)
2	27 (56.2)	62 (59.6)	66 (63.5)	155 (60.5)	84 (57.9)
3	1 (2.1)	1 (1.0)	3 (2.9)	5 (2.0)	5 (3.4)
Missing	NA	NA	NA	NA	22 (15.2)
Tumour origin					
PMP	5 (10.4)	31 (29.8)	36 (34.3)	72 (28.0)	21 (14.5)
CRC	37 (77.1)	46 (44.2)	54 (51.4)	137 (53.3)	96 (66.2)
Appendix incl. goblet	4 (8.3)	19 (18.3)	12 (11.4)	35 (13.6)	14 (9.6)
Malignant mesothelioma	2 (4.2)	8 (7.7)	3 (2.9)	13 (5.1)	3 (2.1)
Other	NA	NA	NA	NA	2 (1.4)
Missing	NA	NA	NA	NA	9 (6.2)
Number of previous abdominal surgeries					
0	0 (0.0)	10 (9.6)	25 (23.8)	35 (13.6)	22 (15.1)
1	41 (85.4)	71 (68.3)	65 (61.9)	177 (68.9)	81 (55.8)
2	7 (14.6)	18 (17.3)	14 (13.3)	39 (15.2)	15 (10.3)
3	0 (0.0)	5 (4.8)	1 (1.0)	6 (2.3)	3 (2.0)
4	NA	NA	NA	NA	1 (1.0)
Missing	NA	NA	NA	NA	23 (15.8)
Extraperitoneal metastases at the time of CRS and HIPEC					
Yes	2 (4.2)	11 (10.6)	7 (6.7)	20 (7.8)	14 (9.6)
No	9 (18.7)	16 (15.4)	18 (17.1)	43 (16.7)	43 (29.7)
Missing	37 (77.1)	77 (74.0)	80 (76.2)	194 (75.5)	88 (60.7)
PCI, median (inter quartile range)	3.5 (4)	5.5 (6)	10 (9)	6 (8)	6.5 (9)
	*n = 30	*n = 62	*n = 49	*n = 141	*n = 104
Preoperative chemotherapy					
Yes	22 (45.8)	16 (15.4)	16 (15.2)	54 (21.0)	51 (35.2)
No	15 (31.3)	29 (27.9)	36 (34.3)	80 (31.1)	46 (31.7)
Missing	11 (22.9)	59 (56.8)	53 (50.5)	123 (47.9)	48 (33.1)
Peritonectomy					
Yes	0 (0.0)	45 (43.3)	105 (100)	150 (58.4)	74 (51.0)
No	48 (100)	59 (56.7)	0 (0.0)	107 (41.6)	48 (33.1)
Missing	NA	NA	NA	NA	23 (15.9)
Small bowel resection					
Yes	14 (29.2)	13 (12.5)	22 (21.0)	49 (19.1)	28 (19.3)
No	34 (70.8)	91 (87.5)	83 (79.0)	208 (80.9)	94 (64.8)
Missing	NA	NA	NA	NA	23 (15.9)
Colorectal resection					
None	48 (100)	45 (43.3)	1 (1.0)	94 (36.6)	38 (26.2)
Right hemicolectomy[a]	0 (0)	44 (42.3)	73 (69.5)	117 (45.5)	56 (38.6)
Other resection[b]	0 (0)	15 (14.4)	31 (29.5)	46 (17.9)	28 (19.3)
Missing	NA	NA	NA	NA	23 (15.9)
Colonic anastomosis					
Yes	1 (2.1) [c]	45 (43.3)	69 (65.7)	115 (44.8)	55 (37.9)
No	47 (97.9)	59 (56.7)	36 (34.3)	142 (55.2)	67 (46.2)
Missing	NA	NA	NA	NA	23 (15.9)
Completenes of cytoreduction					
CC-0	47 (97.9)	102 (98.1)	102 (97.1)	251 (97.7)	120 (82.8)
CC-1, CC-2	1 (2.1)	2 (1.9)	3 (2.9)	6 (2.3)	5 (3.5)
Missing	NA	NA	NA	NA	20 (13.8)
Referral to postoperative chemotherapy					
Yes, completed[e]	15 (31.3)	22 (21.2)	32 (30.5)	69 (26.8)	36 (24.8)
No[f]	22 (45.8)	23 (22.1)	20 (19.0)	65 (25.3)	61 (42.1)
Missing	11 (22.9)	59 (56.7)	53 (50.5)	123 (47.9)	48 (33.1)
Postoperative complication[d]					
Yes	15 (31.2)	33 (31.7)	47 (44.8)	95 (36.9)	58 (40.0)
No	33 (68.8)	58 (55.8)	50 (47.6)	141 (54.9)	55 (37.9)
Missing	0 (0.0)	13 (12.5)	8 (7.6)	21 (8.2)	32 (22.1)
Number of response, (response rate)					
3	31 (64.6)	85 (81.7)	80 (76.2)	196 (76.3)	NA
6	30 (62.5)	54 (51.9)	50 (47.6)	134 (52.1)	NA
12	19 (39.6)	39 (37.5)	34 (32.4)	92 (35.8)	NA

[a] Includes total colectomy (n = 17), subtotal colectomy (n = 13), re-resection of previous anastomosis (n = 9) and right colectomy (n = 78).
[b] Includes resection of the transverse colon (n = 1), left hemicolectomy (n = 7), sigmoid resection (Hartman) (n = 10), rectal resection (n = 25), the sigmoid and the rectum (n = 1) and an APE intersphinteric resection (n = 2).
[c] Ileotransversostomy (n = 1).
[d] Pus secretion from the rectum/vagina (n = 6), bowel fistula (n = 1), intraabdominal abscess (n = 17), urinary tract infection (n = 25), fascial rupture (n = 16), hernia (n = 3), pneumonia (n = 24), sepsis induced from the intravenous catheter (n = 1), wound infection (n = 3), pleural drainage (n = 28), anastomotic leakage (n = 15).
[e] Yes, but the chemotherapy was ended due to intolerable side effects (n = 19).
[f] Patient's choice (n = 4).

compared to patients in whom the extent of CRS was categorized as intermediate surgery. The same association was clearly demonstrated between patients undergoing major vs. minor surgery. These symptoms persisted throughout 12 months.

Table 2
Mean difference between groups of surgical extent (minor, intermediate, and major) measured by the European Organization for Research and Treatment of Cancer QLQ-C30 in the period from 3 to 12 months after CRS + HIPEC. The analyses were adjusted for age, gender, origin of gastrointestinal tumour (PMP, CRC, appendix incl. goblet, MPM) and comorbidity measured by the ASA score.

EORTC QLQ C-30 subscales	Adjusted *Adjusted for age, gender, ASA score and disease	
	Mean difference with 95 % confidence interval	P-value
Overall HRQoL		
Surgical extent		
Intermediate vs. minor	−0.5 (−7.4; 6.4)	0.88
Major vs. minor	−1.0 (−8.0; 6.0)	0.78
Major vs. intermediate	−0.5 (−6.1; 5.2)	0.87
Fatigue		
Surgical extent		
Intermediate vs. minor	3.6 (−4.8; 12.1)	0.39
Major vs. minor	2.6 (−6.0; 11.1)	0.55
Major vs. intermediate	−1.1 (−7.9; 5.8)	0.76
Nausea and vomiting		
Surgical extent		
Intermediate vs. minor	0.4 (−4.9; 5.8)	0.87
Major vs. minor	1.9 (−3.6; 7.3)	0.50
Major vs. intermediate	1.4 (−3.0; 5.8)	0.52
Pain		
Surgical extent		
Intermediate vs. minor	3.9 (−3.8; 11.6)	0.32
Major vs. minor	−2.5 (−10.4; 5.3)	0.53
Major vs. intermediate	−6.4 (−12.7; −0.1)	0.05
Dyspnoea		
Surgical extent		
Intermediate vs. minor	0.5 (−6.4; 7.4)	0.88
Major vs. minor	2.6 (−4.4; 9.6)	0.46
Major vs. intermediate	2.1 (−3.5; 7.8)	0.46
Insomnia		
Surgical extent		
Intermediate vs. minor	−8.6 (−18.4; 1.1)	0.08
Major vs. minor	−7.3 (−17.2; 2.6)	0.15
Major vs. intermediate	1.3 (−6.7; 9.3)	0.74
Appetite loss		
Surgical extent		
Intermediate vs. minor	3.6 (−3.2; 10.4)	0.30
Major vs. minor	0.5 (−6.4; 7.5)	0.88
Major vs. intermediate	−3.1 (−8.6; 2.5)	0.28
Constipation		
Surgical extent		
Intermediate vs. minor	−1.4 (−7.5; 4.7)	0.65
Major vs. minor	−3.1 (−9.2; 3.1)	0.33
Major vs. intermediate	−1.7 (−6.6; 3.3)	0.51
Diarrhoea		
Surgical extent		
Intermediate vs. minor	−2.16 (−11.2; 6.1)	0.56
Major vs. minor	8.4 (−0.5; 17.2)	0.06
Major vs. intermediate	10.9 (3.8; 18.0)	0.00
Financial difficulties		
Surgical extent		
Intermediate vs. minor	4.7 (−2.0; 11.5)	0.17
Major vs. minor	3.2 (−3.7; 10.1)	0.36
Major vs. intermediate	−1.5 (−7.0; 4.0)	0.59

Our results in current study are in accordance with the existing literature describing an impaired gastrointestinal function as LAEs following CRS + HIPEC [12,13,16].

It is well-known that resections of the colon and/or rectum in CRC patients are associated with gastrointestinal dysfunction [17–20]. First, Emmertsen et al. demonstrated that rectal cancer patients suffer from long-term bowel dysfunction, and the "Low Anterior Resection Syndrome" (LARS) is well described with proposed treatment algorithms [18]. In our population, very few patients underwent rectal resections, yet the LARS is unlikely to be the primary cause to the diarrhoea symptoms in the major extent group. Recently, some studies have shown that bowel dysfunction, mainly in terms of constipation, urge to defecation and diarrhoea, also affects patients undergoing surgery for colon cancer [17,19,21] and is a problem in patients treated with major abdominal surgery [22–24]. The pathophysiology is multifactorial and incompletely understood, still. Several causes have been suggested among others bile acid malabsorption (BAM) diarrhoea, interruption of the ileal brake and absence of the ileocecal junction leading to bacterial overgrowth in the small intestine [17,19], and decreased water absorption due to a shortened colon [19]. The BAM diarrhoea is primarily due to disturbance in the enterohepatic circulation of bile acids due to resection of ileum decreasing the absorptive capacity. There has been demonstrated a positive association between the length of the resected ileum and the severity of BAM diarrhoea [25–27]. A large part of the patients in our 'major extent'-group underwent right colectomy including a resection of the ileum. In current study, information regarding small bowel resections were dichotomous (yes/no), and the length of the resected small bowel was not quantified. However, in our sub-analysis we did not demonstrate any significant difference in diarrhoea symptoms between right- and left-sided resections, which indicates that other factors may drive the causes to diarrhoea.

Some patients have had resection of the primary tumour previously, and undergo CRS + HIPEC due to metachronous PM or recurrent PMP. In such case, PM patients have often received chemotherapy both before and after surgery and underwent repeated resections with risk of adhesions and relative intestinal stenosis, which all predisposes to impaired gastrointestinal function. Furthermore, some hypotheses have been raised regarding the hyperthermia's potential to induce impairments in bowel function by increasing bowel cramps and impairing gut integrity [28–30]. However, our results indicate that extensive surgery has an impact, yet this study cannot draw conclusions regarding the extent of hyperthermia's effect on the bowel function.

There exists no specific tool for measuring LAEs following CRS + HIPEC. Yet, all LAEs were measured by the EORTC QLQ-C30, which is the most commonly used following CRS + HIPEC [12]. In the EORTC QLQ-C30, the diarrhoea symptom is based on a single question which may not cover all content [31]. The gastrointestinal function could be detailed targeted with for example the Wexner Score [32], Stool consistency defined by the Bristol Stool Chart [33] and St. Marks Faecal Incontinence score [34]. Regarding the gastrointestinal function, the EORTC QLQ-C30 may not be reliable and responsive to measure any impairment or change, and it is unknown whether it under- or overestimates the proportion of patients with impaired gastrointestinal function.

Even though current study demonstrates significant increased

Table 3
Raw scores from each follow-up time (3, 6 and 12 months) and mean difference (from 3 to 12 months) of symptom scales measured by the European Organization for Research and Treatment of Cancer QLQ-C30. The mixed analysis was adjusted for age, gender, origin of gastrointestinal tumour (PMP, CRC, appendix incl. goblet, MPM) and comorbidity measured by the ASA score.

EORTC QLQ C-30 subscales	Time (months)			Mixed analysis Adjusted for gender, age, comorbidity and diagnosis	
	Unadjusted raw scores				
	3 months	**6 months**	**12 months**	Mean difference 12 - 3 months	P-value
	Minor (n = 31) Intermediate (n = 85) Major (n = 80)	Minor (n = 30) Intermediate (n = 54) Major (n = 50)	Minor (n = 19) Intermediate (n = 39) Major (n = 34)		
Overall HRQoL					
Surgical extent					
Minor	72.6 (64.0; 81.1)	73.3 (65.5; 81.2)	71.8 (61.7; 81.8) (n = 18)	10.1 (6.6; 13.7)	0.00
Intermediate	71.7 (67.3; 76.1) (n = 84)	72.1 (65.9; 78.2)	80.6 (73.8; 87.4)		
Major	66.1 (61.5; 70.8) (n = 78)	74.0 (68.4; 79.6)	77.7 (71.9; 83.5)		
Fatigue				−13.7 (−18.0; −9.5)	0.00
Surgical extent					
Minor	35.1 (24.5; 45.7)	31.1 (22.2; 40.1)	31.0 (20.6; 41.3)		
Intermediate	38.4 (32.7; 44.1)	35.6 (27.8; 43.4)	26.8 (19.4; 34.1)		
Major	42.9 (37.4; 48.4)	34.0 (26.7; 41.3)	28.8 (21.4; 36.1)		
Nausea and vomiting				−6.2 (−10.1; −2.5)	0.00
Surgical extent					
Minor	13.4 (4.6; 22.3)	5.6 (0.8; 10.3)	4.4 (−0.1; 8.9)		
Intermediate	10.0 (6.2; 13.8)	8.3 (3.4; 13.3)	4.7 (0.8; 8.6)		
Major	11.0 (6.8; 15.0)	8.8 (3.6; 14.1)	6.4 (0.6; 12.1)		
Pain				−6.8 (−11.1; −2.5)	0.00
Surgical extent					
Minor	19.9 (11.2; 28.6)	20.0 (10.0; 30.0)	19.3 (8.5; 30.1)		
Intermediate	23.7 (17.8; 29.7)	22.2 (14.9; 29.5)	12.4 (6.4; 18.4)		
Major	21.1 (15.8; 26.4) (n = 79)	18.0 (11.9; 24.1) (n = 49)	13.7 (8.5; 19.0)		
Dyspnoea				−9.8 (−14.5; −5.21)	0.00
Surgical extent					
Minor	14.0 (5.8; 22.2)	13.3 (4.3; 22.3)	8.8 (1.5; 16.0)		
Intermediate	16.9 (11.6; 22.1)	13.6 (8.1; 19.0)	7.9 (0.5; 15.3) (n = 38)		
Major	20.3 (15.0; 25.5) (n = 79)	16.3 (10.1; 22.5) (n = 49)	6.9 (2.1; 11.6)		
Insomnia				−0.1 (−6.1; 5.8)	0.96
Surgical extent					
Minor	31.2 (20.3; 42.1)	29.9 (16.6; 43.2) (n = 29)	29.8 (13.0; 46.7)		
Intermediate	21.6 (15.6; 27.5)	24.7 (15.8; 33.6)	23.9 (14.7; 33.2)		
Major	30.8 (23.7; 38.0) (n = 79)	27.2 (18.5; 35.9) (n = 49)	25.5 (16.0; 35.0)		
Appetite loss				−8.4 (−13.2; −3.5)	0.00
Surgical extent					
Minor	14.0 (2.3; 25.7)	7.8 (1.5; 14.1)	5.3 (−2.8; 13.3)		
Intermediate	15.3 (10.3; 20.3)	13.0 (6.3; 19.7)	9.4 (2.9; 15.9)		
Major	14.3 (9.2; 19.5) (n = 79)	9.5 (4.4; 14.7) (n = 49)	4.9 (−0.2; 10.0)		
Constipation				−3.9 (−7.8; 0.0)	0.05
Surgical extent					
Minor	14.0 (4.6; 23.3)	9.2 (2.5; 15.9) (n = 29)	7.0 (0.3; 13.7)		
Intermediate	10.6 (5.9; 15.3)	7.4 (1.4; 13.4)	4.4 (−0.2; 8.9) (n = 38)		
Major	6.8 (3.1; 10.5) (n = 78)	8.2 (3.2; 13.2) (n = 49)	5.9 (0.5; 11.2)		
Diarrhoea				−3.6 (−9.1; 1.7)	0.18
Surgical extent					
Minor	19.4 (9.5; 29.2)	16.7 (8.2; 25.2)	15.8 (6.0; 25.6)		
Intermediate	16.1 (10.9; 21.2)	16.0 (8.8; 23.3)	14.0 (5.7; 22.3) (n = 38)		
Major	27.0 (19.7; 34.3) (n = 78)	26.5 (17.6; 35.5) (n = 49)	26.5 (15.5; 37.5)		
Financial difficulties				2.1 (−1.9; 6.0)	0.31
Surgical extent					
Minor	2.2 (−0.9; 5.2)	6.7 (−0.2; 13.5)	9.3 (1.6; 16.9) (n = 18)		
Intermediate	9.9 (5.5; 14.4)	10.5 (4.2; 16.8)	10.5 (3.3; 17.8)		
Major	9.8 (5.0; 14.7) (n = 78)	8.8 (1.9; 15.8) (n = 49)	14.7 (4.3; 25.1)		

diarrhoea symptoms in the group of patients undergoing major CRS procedures it may not be equivalent to impaired QoL. As demonstrated in Tables 2 and 3, Overall HRQoL improved significantly from 3 to 12 months, but did not differ between the groups of surgical extent. However, The EORTC Quality of Life Group has published reference values [35] for the background population and reference scores for diarrhoea symptoms for all cancer patients with recurrent/metastatic disease were 10.7 (SD 22.4) and for colorectal cancer patients with recurrent/metastatic disease 15.4 (SD 25.6). In comparison, patients in the major surgical extent group reported diarrhoea symptoms with a mean score of 26.5 (15.5; 37.5) 12 months after surgery.

Finally, using the EORTC QLQ-C30 introduce some statistical challenges, yet the EORTC Quality of Life Group has defined valid thresholds for clinical importance for the absolute mean scores [36]. A clinical importance is defined as any aspect of a health problem that makes it relevant for the clinical encounter, and refers to limitations in daily living, perceived need for treatment or care, and disease- or treatment-related worry [37]. The clinical threshold for diarrhoea is 17. As demonstrated in Table 2, nearly all absolute mean scores for the minor and intermediate group were <17 (except the mean score at 3 months for the minor group (mean score 19.4)), whereas the mean score for the major group was >25 at all time points. This threshold for the clinical importance supports the findings of our statistical results. Most patients undergoing CRS + HIPEC are followed by surgical oncologists,

who do not necessarily be aware of diagnosing and treating gastrointestinal symptoms. Several studies describe LAEs in this population of patients undergoing CRS + HIPEC, yet interventions aiming to treat these are lacking.

To our knowledge this is the largest, prospective cohort study describing such data following CRS + HIPEC. All QoL data were collected prospectively, thus avoiding potential recall bias. Further, patients are included from a single national treatment centre, thus the study population is to be considered as representative for the CRS + HIPEC patients.

However, there are also limitations of present study. First, some variables of interest for the outcome were not available, i.e. a quantification of the resections of small intestines. Furthermore, the PCI score registration was restricted to a short time period. The PCI score may act as confounding by indication, as it is associated with the exposure (surgical extent) of interest in the population without being an intermediate step in the causal pathway between the exposure and the disease. It must be noted, however, that the PCI score in itself does not necessarily determine the extent of the surgery. Further, we performed a subanalysis adjusting for the PCI (restricted to the period of the variable), and still, patients undergoing major surgery reported a higher score of diarrhoea symptoms compared to patients undergoing minor and intermediate surgery. Second, in current study no baseline measurements were measured, which potentially compromises the actual development over time, thus limits the interpretation of the effect of CRS + HIPEC. Third, even though response rates are low, they are similar to other studies [12,13,38,39]. All non-responders may introduce survivor bias, which is a type of selection bias preventing direct comparison of average estimates between groups because the outcome is unknown for lost subjects. Potentially, non-responders were more frequent within the major extent group, and the implications of the presence of survivor bias would underestimate the true incidence. However, the magnitude of non-responders is unknown, and as demonstrated in Table 1 baseline characteristics did not differ from the total population. Due to the number of non-responders and the potential effect on the certainty of the estimates, we terminated the follow-up at 12 months. Fourth, the surgical extent is not an international recognized definition, thus the categorization of the surgical extent into minor, intermediate and major was not validated. However, from a surgical point of view it makes sense to categorize the extent of surgery according to extensive peritonectomy procedures and colorectal resections. Finally, the statistical analyses produce a large numbers of significance tests. It is evident, that performing multiple testing long enough, will produce something which is 'significant'. We must beware of attaching too much importance to a lone significant result among a mass of non-significant ones. However, our results were supported by the threshold for the clinical importance.

We demonstrated a convincing difference in diarrhoea symptoms according to the extent of the CRS procedures. Patients undergoing major CRS suffer from persistent impaired gastrointestinal function in terms of diarrhoea following CRS + HIPEC. Attention should be directed at detecting these adverse effects and guidance of these patients.

CRediT authorship contribution statement

Sissel Ravn: Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review. **Jonas Møller Grønfeldt:** Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript preparation, Manuscript editing, Manuscript review. **Henriette Vind Thaysen:** Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript editing, Manuscript review. **Lene Hjerrild Iversen:** Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript editing, Manuscript review.

Declaration of Competing interest

All authors have nothing to declare.

References

[1] Verwaal VJ, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21(20):3737–43.

[2] Verwaal VJ, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15(9):2426–32.

[3] Iversen LH, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: the Danish experience. Colorectal Dis 2013;15(7):e365–72.

[4] Narasimhan V, et al. Prognostic factors influencing survival in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for isolated colorectal peritoneal metastases: a systematic review and meta-analysis. Colorectal Dis; 2020.

[5] Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995;221(1):29–42.

[6] Sugarbaker PH. Colorectal cancer metastases: a surgical perspective. Surg Oncol Clin 2013;22(2):289–98.

[7] Sugarbaker PH. Management of peritoneal metastases - basic concepts. J BUON 2015;20(Suppl 1):S2–11.

[8] van Stein RM, et al. Hyperthermic intraperitoneal chemotherapy for ovarian and colorectal cancer: a review. JAMA Oncol 2021;7(8):1231–8.

[9] Pletcher E, Gleeson E, Labow D. Peritoneal cancers and hyperthermic intraperitoneal chemotherapy. Surg Clin 2020;100(3):589–613.

[10] Piso P, et al. Quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies. J Surg Oncol 2009;100(4):317–20.

[11] Groenvold M, et al. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J Clin Epidemiol 1997;50(4):441–50.

[12] Balachandran R, et al. Organ-specific adverse effects after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol; 2022.

[13] Leimkühler M, et al. Systematic review of factors affecting quality of life after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2020;27(10):3973–83.

[14] Danish Colorectal Cancer Group. HIPEC behandling af peritoneal karcinose til patienter med kolorektalkræft (national guideline). 2019 [cited 2020 August]; Available from: https://dccg.dk/wp-content/uploads/2020/01/Peritoneal-karcinose-og-HIPEC_AdmGodk_100120.pdf.

[15] Schougaard LMV, et al. AmbuFlex: tele-patient-reported outcomes (telePRO) as the basis for follow-up in chronic and malignant diseases. Qual Life Res 2016;25(3):525–34.

[16] Bayat Z, et al. Impairments in bowel function, social function and quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol; 2019.

[17] Yde J, et al. Chronic diarrhoea following surgery for colon cancer-frequency, causes and treatment options. Int J Colorectal Dis 2018;33(6):683–94.

[18] Emmertsen KJ, Laurberg S. Bowel dysfunction after treatment for rectal cancer. Acta Oncol 2008;47(6):994–1003.

[19] Larsen HM, et al. Long-term bowel dysfunction after right-sided hemicolectomy for cancer. Acta Oncol 2020;59(10):1240–5.

[20] Elfeki H, et al. Bowel dysfunction after sigmoid resection for cancer and its impact on quality of life. Br J Surg 2019;106(6):805.

[21] Hope C, et al. Systematic review: the effect of right hemicolectomy for cancer on postoperative bowel function. Support Care Cancer 2020;28(10):4549–59.

[22] Andreyev HJ, et al. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut 2012;61(2):179–92.

[23] Douma KF, et al. Quality of life and consequences for daily life of familial adenomatous polyposis (FAP) family members. Colorectal Dis 2011;13(6):669–77.

[24] Wolf ND, et al. Quality of life after restorative proctocolectomy and ileal pouch-anal anastomosis in patients with familial adenomatous polyposis: a matter of adjustment. Colorectal Dis 2011;13(11):e358–65.

[25] Aldini R, et al. Bile acid malabsorption and bile acid diarrhea in intestinal resection. Dig Dis Sci 1982;27(6):495–502.

[26] Camilleri M, Vijayvargiya P. The role of bile acids in chronic diarrhea. Am J Gastroenterol 2020;115(10):1596–603.

[27] Skouras T, et al. Brief report: length of ileal resection correlates with severity of bile acid malabsorption in Crohn's disease. Int J Colorectal Dis 2019;34(1):185–8.

[28] Ye J, et al. A precise temperature control during hyperthermic intraperitoneal chemotherapy promises an early return of bowel function. Cancer Biol Ther 2020;21(8):726–32.

[29] Koch F, et al. Heat stress directly impairs gut integrity and recruits distinct immune cell populations into the bovine intestine. Proc Natl Acad Sci U S A 2019;116(21):10333–8.

[30] Lian P, et al. Beyond heat stress: intestinal integrity disruption and mechanism-based intervention strategies. Nutrients 2020;12(3).
[31] Aaronson NK, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365–76.
[32] Jorge JM, Wexner SD. Etiology and management of fecal incontinence. Dis Colon Rectum 1993;36(1):77–97.
[33] O'Donnell LJ, Virjee J, Heaton KW. Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. BMJ 1990;300(6722):439–40.
[34] Vaizey CJ, et al. Prospective comparison of faecal incontinence grading systems. Gut 1999;44(1):77–80.
[35] Scott Nw FP, Aaronson NK, Bottomley A, Graeff A, Groenvod M, Gundy C, et al. Sprangers AG M on behalf of the EROTC quality of life group, EORTC QLQ-C30 reference values. 2008.
[36] Cocks K, et al. Evidence-based guidelines for determination of sample size and interpretation of the European organisation for the research and treatment of cancer quality of life questionnaire core 30. J Clin Oncol 2011;29(1):89–96.
[37] Giesinger JM, et al. Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. J Clin Epidemiol 2020;118:1–8.
[38] Tsilimparis N, et al. Quality of life in patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: is it worth the risk? Ann Surg Oncol 2013;20(1):226–32.
[39] Hill AR, et al. Survival and quality of life following cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colonic origin. Ann Surg Oncol 2011;18(13):3673–9.