Journal of Visceral Surgery (2019) 156, 475—484

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy combined with liver resection for concurrent peritoneal and hepatic metastases of gastrointestinal and gynecological primary tumors

P. Horvath[a,*], S. Beckert[a], A. Königsrainer[a], S. Nadalin[a], I. Königsrainer[b]

[a] *Department of General, Visceral and Transplant Surgery, University of Tübingen, Comprehensive Cancer Center, Tübingen, Germany*
[b] *Department of General, Visceral and Thoracic Surgery, Academic Teaching Hospital Feldkirch, Carinagasse 47, 6807 Feldkirch, Austria*

Available online 16 July 2019

KEYWORDS
Peritoneal metastases;
Morbidity;
Liver metastases;
Curative treatment;
Ovarian cancer;
Colorectal cancer

Summary
Aim of the study: Cytoreductive surgery including liver resection and hyperthermic intraperitoneal chemotherapy provide survival benefit to selected patients but is associated with relevant morbidity and mortality rates. We aimed to report morbidity and mortality rates and parameters linked to increased morbidity.
Patients and methods: Retrospective analysis of 37 patients who underwent liver resection and cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy between 2006 and 2016. From a prospectively collected database the morbidity and mortality rates and survival data were analyzed.
Results: The mortality rate was 0% and grade III—IV morbidity was 42%. Re-operation rate was 27%. Patients with complications tended to have a higher peritoneal cancer index (16 vs. 13; $P = 0.23$). The performance of rectal resections was statistically significantly associated with morbidity ($P = 0.02$). Neither performance of other type of resections nor the hyperthermic intraperitoneal chemotherapy compound nor the completeness of cytoreduction score was associated with elevated morbidity. No complications related to liver resections were observed. Furthermore, origin of peritoneal metastases did not impact on occurrence of complications. Median overall survival for colorectal primaries was 22 months (range, 9—60 months) and 30 months (range, 12—58 months) for ovarian cancer.

* Corresponding author. Hoppe-Seyler-Strasse, 3, 72076 Tübingen, Germany.
E-mail addresses: philipp.horvath@med.uni-tuebingen.de (P. Horvath), stefan.beckert@med.uni-tuebingen.de (S. Beckert), alfred.koenigsrainer@med.uni-tuebingen.de (A. Königsrainer), silvio.nadalin@med.uni-tuebingen.de (S. Nadalin), chirurgie@lkhf.at (I. Königsrainer).

https://doi.org/10.1016/j.jviscsurg.2019.06.007

Conclusion: Simultaneous resection of hepatic and peritoneal metastases seems to provide a survival benefit for selected patients and is associated with acceptable morbidity and mortality rates. Knowledge of patients and operative factors linked to morbidity will help to provide a strict selection process and a safer surgical procedure.

Introduction

Colorectal cancer (CRC) remains a leading cause of death in developed countries. In the past metastasized CRC (i.e. liver and peritoneum) prompted the interdisciplinary decision to abandon further surgical efforts and patients underwent systemic chemotherapy with poor prognosis mostly due to progression of peritoneal tumor implants resulting in intestinal obstruction and ultimately death. In the last couple of years improvements in palliative chemotherapy and cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) were able to achieve a survival benefit even in patients with low-volume resectable liver metastasis of colorectal origin (CRLM) and peritoneal metastases (PM). The impact on survival of CRS and HIPEC in patients with CRC-PM as compared to systemic chemotherapy was demonstrated in a randomized trial [1]. Survival benefit was linked to a low peritoneal cancer index (PCI) and the completeness of cytoreduction (CC-) (i.e. 0 or 1). Approximately 25% of CRC patients suffer from synchronous CRLM and as this condition is equated with systemic disease these patients were not eligible for CRS and HIPEC in the event of simultaneous PM. Elias et al. [2] and Cavaliere et al. [3] reported clinical experience with combined surgical treatment of LM and PM in CRC patients. In contrast to the aforementioned studies [2,3], a meta-analysis from 2013 [4] showed better survival and lower morbidity and mortality rates primarily attributed to optimized patient selection and perioperative management. Selection criteria included response to systemic chemotherapy (RECIST criteria), a favorable histological subtype, low or intermediate PCI score, three or fewer LM and good performance status (ECOG ≤ 2). Apart from these criteria surgeons have to be aware of the pattern of morbidity due to this aggressive surgical approach and the prognostic impact of an elevated morbidity rate.

Unfortunately, virtually no data are available on simultaneous resection of hepatic and peritoneal metastases for non-colorectal cancers, making it difficult to propose a proper patient selection algorithm.

This study reviews our experience with this surgical approach regarding associated morbidity rates, prognostic impact of morbidity, outcome and patterns of recurrent disease.

Patients and methods

Patient selection criteria

From January 2006 to December 2016 a total of 37 patients underwent liver resection, CRS and HIPEC for LM and PM of various gastrointestinal and gynecological cancers and were considered for this retrospective analysis. Selection criteria were:

- response to systemic chemotherapy;
- low to intermediate PCI (15—20);
- achievable CC-0/1 status;
- three or fewer resectable LM;
- ECOG performance status ≤ 2.

Clinicopathological information was obtained from a prospectively collected database and electronic medical reports. The study was performed according to the guidelines of the local institutional board and the ethics committee (720/2017BO2). All patients gave informed consent prior to study inclusion.

Preoperative diagnostics consisted of thorough clinical examination, blood tests, and a computed tomography (CT) scan. CT images were acquired with a 128-slice multidetector spiral CT. The reconstructed slice thickness was 5 mm without gaps between slices. Irresectability for CRS and HIPEC was defined as infiltration of the mesenteric axis, retroperitoneal plane, or the pancreatic head. Irresectability regarding LM was dictated by metastases located in both liver lobes that were not suitable for atypical resection and that needed extended liver resection. Eligibility for CRS and HIPEC and resection of concurrent liver metastasis was assessed by a surgical oncologist, a medical oncologist, a radiologist and a radio-oncologist, all of whom attended the interdisciplinary oncologic team meeting. Adverse events were classified according to the Clavien-Dindo complication score [5].

Cytoreductive surgery

After laparotomy through a mid-line incision and complete adhesiolysis, the PCI was determined following the criteria described by Jaquet and Sugarbaker [6]. Abdominal regions were categorized as the small bowel, consisting of Sugarbaker's abdominopelvic regions (SAPR) 9 to 12; the upper abdomen, consisting of SAPR 0 to 3; and the lower abdomen/pelvis consisting of SAPR 4 to 8. Tumor-involved structures were resected along with peritonectomy procedures described by Sugarbaker [7—9] aiming for complete cytoreduction (CC-0 and CC-1 [CC-0 indicated no visible disease; CC-1 indicated nodules smaller than 0.25 cm; CC-2 indicated nodules greater than 0.25 cm and smaller than 5 cm; CC-3 indicated nodules over 5 cm]).

Liver resection

All patients with low-volume LM or liver nodules of unknown dignity were scheduled for surgery. Routinely intraoperative ultrasonography was used. Depending on the site of LM, atypical or anatomical resections were performed. Minor liver resections were defined as removal of no more than

two liver segments. The Cavitro Ultrasonic Surgical Aspirator (CUSA) was routinely used for transection of liver parenchyma. No extended liver resections were performed. No intraoperative radiofrequency ablation or pedicle clamping were performed. Liver resections were performed prior to HIPEC. Drains were not routinely used at the resection site.

HIPEC

After complete cytoreduction and fashioning of intestinal anastomoses, HIPEC was administered for 30 to 90 minutes at 42 °C depending on the HIPEC compound using the closed-abdomen technique. The dosage for oxaliplatin was 300 mg/m^2, for mitomycin C 35 mg/m^2 and for cisplatin 75 mg/m^2 body surface area. After HIPEC completion the abdomen was washed out with 3 L of lactated Ringer solution, and the abdomen was reopened for removal of the perfusion catheters before fascial closure was performed.

Follow-up

Patients were followed in three-monthly intervals with clinical examination and radiological imaging including CT or positron emission tomography (PET)-CT scans. No blood tumor markers were evaluated during follow-up. Recurrence was defined as any new lesion detected by CT or PET-CT scans as compared to the findings of the first examination following CRS/HIPEC and liver resection.

Statistics

Categorical variables are represented as frequencies and proportions; continuous variables are represented either as mean and standard deviation (±SD) or as medians and interquartile range (IQR) depending on the distribution of the data. The normality of the distribution was evaluated using kurtosis, skewness, Q-Q plots and histograms.

The relationship between different base properties and the occurrence of complications was analyzed using Chi^2 tests or Fisher's accurate test. Independent sample *t*-tests were used to compare quantitative variables with normal distribution, while Mann-Whitney tests were used to evaluate skewed variables. Univariate logistic regression was also used to evaluate the association between each variable and the presence of complications. Next, we examined what demographic or clinical characteristics are associated with outcome complication through binary logistic regression analysis.

The disease-free relapse rates and all-cause mortality were calculated using the Kaplan-Meier method. The proportional hazard regression of Cox was used to evaluate the hazard ratio of the variables between different risk factors.

Statistical analysis was performed using IBM SPSS software (version 25.0 IBM SPSS Inc., Chicago, IL). All *P*-values were two-tailed and a probability value of $P < 0.05$ was considered statistically significant.

Results

From January 2006 to December 2016 a total of 37 patients underwent CRS and HIPEC and combined liver resection for PM and LM. There were 25 (68%) females and 12 (32%) males. Median age of all patients was 54 ± 9.5 (range, 39—76 years). Median age was 61 ± 9 (range, 49—72 years) in the males and 52 ± 9.5 (range, 39—76 years) in the females ($P = 0.09$). The majority of primary tumors were of colorectal ($n = 16$; 43%) or ovarian origin ($n = 12$; 32%). In five patients (14%) high-grade pseudomyxoma peritonei (PMP) (three of appendiceal and two of ovarian origin) was present. The remaining tumor etiologies are shown in Table 1. All patients had previous surgery and 78% of patients ($n = 29$) had previous systemic metastatic chemotherapy. All patients but two with ovarian cancer and all patients but three with CRC underwent chemotherapy. Patients with CRC received FOLFOX or FOLFIRI combined with EGFR or VEGF antibodies. Patients with ovarian cancer received carboplatin and taxol as systemic chemotherapy. None of our patients underwent previous CRS and HIPEC. The HIPEC compounds used were cisplatin (43%), oxaliplatin (combined with 5-FU intravenously) (30%) and mitomycin C (27%). In the course of CRS various multivisceral and gynecological resections, all listed in Table 1, were performed. Median PCI was 14 (range, 1—39). In 76% of the study patients macroscopic complete cytoreduction (CC-0) was achieved. In another nine (24%) patients CC-1 status was achieved. In total three (8%) patients underwent hemihepatectomy and the remaining 34 (92%) patients underwent atypical liver resection. Postoperative histopathological reports revealed metastatic involvement of the liver in 28 (76%) patients. In the remaining nine (24%) patients the resected liver specimen showed no metastases but instead fibrosis in four patients, cholangioma in two patients and hemangioma in the remaining three patients. Of the patients with positive histopathology 21 (75%) had one LM, three (11%) had two LM and four (14%) had three LM. Median LM size was 2 cm (range, 0.5—6.5 cm).

Median operative time was 431 minutes (range, 172—1076 minutes). Median length of hospital stay was nine days (range, 9—93 days). In total 21 patients suffered from any kind of postoperative complications. Grade III—IV morbidity according to the Clavien-Dindo classification was given in 42% of our patients. Patients with complications tended to have a higher PCI (16 vs. 12; $P = 0.32$). The performance of rectal resection was statistically significantly associated with morbidity ($P = 0.02$) (Table 2). Neither performance of other type of resections nor the HIPEC compound nor the CC-score was associated with elevated morbidity. Univariate analysis confirmed rectal resections as an independent predictor for elevated morbidity (Table 3). The occurrence of complications did not impact on recurrence-free survival (3-year recurrence-free survival: 65% vs. 54%; $P = 0.457$).

Re-operation rate was 27% ($n = 10$). Reasons for re-operation were intraabdominal bleeding at the diaphragm ($n = 1$), anastomotic insufficiency ($n = 4$), fascial dehiscence ($n = 2$), bile leakage ($n = 2$) and pancreatic fistula ($n = 1$). Furthermore, no 30- or 90-day mortality occurred.

In order to determine the impact of patient — and treatment-related variables on progression free — and overall survival, uni- and multi-variate analyses were performed. Univariate analysis (Table 4) revealed splenectomy to be significantly associated with decreased progression free survival ($P = 0.04$) which was not confirmed in multivariate analysis ($P = 0.25$). Multivariate analysis showed an increased risk of recurrence in patients receiving MMC (HR = 4.84) and cisplatin (HR = 3.82) as compared to oxaliplatin without reaching statistical significance ($P = 0.17$ and 0.25) (Table 5).

Analyses of association between predictor variables and overall survival showed that male gender is a statistically significant risk factor for death (HR = 4.05; $P = 0.03$). Patients receiving HIPEC with cisplatin tended to have a higher risk

Table 1 Clinicopathological variables.

Variables *n* (%)	PM + LM (*n* = 37)
Median age at CRS/HIPEC (range)	54 (39—76)
Sex	
Male	12 (32)
Female	25 (68)
Co-morbidities	
Total	10 (27)
Cardiovascular	9 (24)
Pulmonary	1 (3)
Tumor etiology	
Colorectal	16 (43)
Ovarian	12 (32)
PMP	5 (14)
Mesothelioma	1 (3)
Small bowel	1 (3)
Endometrium	1 (3)
Cervix	1 (3)
ASA score	
I	1 (3)
II	23 (62)
III	13 (35)
Previous treatment	
Surgery	37 (100)
Chemotherapy	29 (78)
HIPEC	0 (0)
Resections	
Stomach	2 (5)
Total	1 (3)
Subtotal	1 (3)
Colon	10 (27)
Right	4 (11)
Left	2 (5)
Sigmoid	1 (3)
Subtotal	3 (8)
Rectum	10 (27)
Appendectomy	2 (5)
Splenectomy	15 (41)
Cholecystectomy	11 (30)
Ovarectomy	4 (11)
Small intestine	12 (32)
Diaphragma	12 (32)
Pancreas tail	2 (5)
Omentum	21 (57)
Peritonectomy	32 (86)
HIPEC	
Yes	37 (100)
HIPEC compound	
Cisplatin	16 (43)
Mitomycin C	10 (27)
Oxaliplatin	11 (30)
Number of LM[a]	
1—2	24 (86)
>2	4 (14)
Median size of LM[b] *(range)*	2 (0.5—6.5)
Liver resection	
Major hepatectomy	3 (8)
Minor hepatectomy	34 (92)
Median PCI (range)	14 (1—39)
CC-Status	
CC-0	28 (76)
CC-1	9 (24)
Operative time in minutes (range)	431 (172—1076)
Length of hospital stay in days (range)	9 (9—93)
Morbidity	
Total	21 (57)
Re-operation rate	10 (27)
SSI	7 (19)
Deep	2 (5)
Superficial	5 (14)
Pneumonia	0 (0)
Pulmonary embolism	1 (3)
Fascial dehiscence	2 (5)
Intraabdominal bleeding	1 (3)
Anastomotic insufficiency	4 (11)
Leucopenia	5 (14)
Bile leckage	2 (5)
Pancreatic fistulas	2 (5)
Sepsis/SIRS	4 (11)
Mortality	
Total	0 (0)
30-day	0 (0)
90-day	0 (0)
Recurrent disease	
Total	11 (39)
Site of recurrence	3 (11)
Peritoneum	8 (29)
Liver	8 (1—20)
Median time to recurrence (months)	8 (1—20)

CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; PM: peritoneal metastasis; LM: liver metastasis; PMP: pseudomyxoma peritonei; ASA: American society of anesthesiologists; 5-FU: 5-Fluorouracil; ip: intraperitoneal; iv: intravenous; PCI: peritoneal cancer index; CC-score: completeness of cytoreduction score; SSI: surgical site infection; SIRS: systemic inflammatory response syndrome.

[a] Total number of patients with positive histopathology in the resected liver specimen is 25.

[b] Unit = cm.

for reduced overall survival without being statistically significant (HR = 1.32; *P* = 0.68) (Tables 6 and 7).

After a median follow-up of 23 (range, 5—92 months) months, 11 (39%) patients developed recurrent disease. There were eight hepatic and three peritoneal recurrences. Median time to recurrence was eight months (range, 1—20 months). Median overall survival for the entire patient cohort was 26 months (range, 5—92). Median overall survival for patients with PM and LM of colorectal origin was 22 months (range, 9—60 months) and for ovarian origin 30 months (range, 12—58 months).

Discussion

In the past the combination of PM and LM, irrespective of tumor etiology, ruled out any curative surgical approach and patients were primarily scheduled for palliative systemic chemotherapy. If CRC-PM or LM occurred alone, a surgical

Table 2 Descriptive characteristics of patients by the presence or absence of complications ($n = 37$).

	Complications ($n = 21$)	No complications ($n = 16$)	*P*-value
Gender n *(%)*			0.57[a]
Female	15 (71.4%)	10 (62.5%)	
Male	6 (28.6%)	6 (37.5%)	
Age mean (±SA)	52.38 (±10.19)	52.19 (±9.07)	0.95[c]
PCI mean (±SA)	16.05 (±8.01)	12.75 (±8.33)	0.23[c]
ASA n *(%)*			0.99[b]
1	1 (4.8%)	0 (0%)	
2	13 (61.9%)	10 (62.5%)	
3	7 (33.3%)	6 (37.5%)	
Co-morbidity: cardiovascular n *(%)*	5 (23.8%)	4 (25%)	0.99[b]
Co-morbidity: pulmonal n *(%)*	0 (0%)	1 (6.3%)	0.43[b]
Tumor etiology n *(%)*			0.76[b]
Colon	8 (38.1%)	4 (25%)	
Ovarian	5 (23.8%)	7 (43.8%)	
Pseudomyxoma peritonei (high-grade)	3 (14.3%)	2 (12.5%)	
Rectal	2 (9.5%)	2 (12.5%)	
Mesothelioma	1 (4.8%)	0 (0%)	
Small bowel	0 (0%)	1 (6.3%)	
Endometrial	1 (4.8%)	0 (0%)	
Cervical	1 (4.8%)	0 (0%)	
HIPEC compound n *(%)*			0.82[b]
MMC	5 (23.8%)	5 (31.3%)	
Cisplatin	9 (42.9%)	7 (43.8%)	
Oxaliplatin	7 (33.3%)	4 (25%)	
CC-score n *(%)*			0.72[b]
0	16 (76.2%)	11 (68.8%)	
1	5 (23.8%)	5 (31.3%)	
Resections			
Rectum *n* (%)	9 (42.9%)	1 (6.3%)	0.02[b]
Stomach *n* (%)	1 (4.8%)	2 (12.5%)	0.57[a]
Colon *n* (%)	2 (9.5%)	0 (0%)	0.50[a]
Hemihepatectomy *n* (%)	3 (14.3%)	0 (0%)	0.24[b]
Atypical liver resection *n* (%)	18 (85.7%)	16 (100%)	0.24[b]
Splenectomy *n* (%)	10 (47.6%)	5 (31.3%)	0.32[a]
Diaphragma *n* (%)	6 (28.6%)	5 (31.3%)	0.86[a]
Pancreatic tail *n* (%)	1 (4.8%)	1 (6.3%)	0.99[b]

ASA: American Society of Anesthesiologists; PCI: peritoneal cancer index; CC-score: completeness of cytoreduction; HIPEC: hyperthermic intraperitoneal chemotherapy; MMC: mitomycin C.
[a] Chi^2.
[b] Fisher Test.
[c] From (value) to (value).

Table 3 Univariate analysis of the association between specific variables and complications.

Variables	Univariate analysis		
	OR	95% CI	*P*-value
PCI	1.05	0.97—1.15	0.23
Rectal resection	11.25	1.25—101.6[a]	0.03
Splenectomy	2.0	0.51—7.80	0.32

[a] No multivariate analysis.

approach consisting of CRS and HIPEC for PM or metastasectomy of LM was available for a highly selected subset of patients, meaning those with a low PCI (<20) and resectable LM [4,10]. Elias and his co-workers stated the combined treatment of CRC-PM and LM was classified as feasible in selected patients presenting with three or fewer LM and a low PCI score. Such treatment generated a 3-year overall and disease-free survival of 41.5% and 23.6%, respectively [2]. The only significant prognostic factor was a number of less than three LM.

Table 4 Univariate survival analyses of association between predictor variables and progression free survival (Cox regression).

Variables	HR	95% CI	*P*-value
Sex: female	1.67	0.47—6.01	0.43
PCI			
0—10	Ref		
11—20	1.25	0.36—4.31	0.73
21—30	1.17	0.31—4.35	0.82
Co-morbidity: cardiovascular	0.79	0.22—2.82	0.71
Tumor etiology			
Gynecological	Ref		
Gastrointestinal	0.69	0.24—2.01	0.5
Others (pseudomyxoma/mesothelioma)	Na		
HIPEC compound			
MMC	7.00	0.82—60.6	0.08
Cisplatin	6.05	0.76—48.4	0.09
Oxaliplatin	Ref		0.20
CC-score			
CC-0	Ref		
CC-1	1.27	0.40—4.08	0.68
Resections			
Stomach	1.80	0.40—8.06	0.44
Colon	1.51	0.20—11.64	0.69
Hemihepatectomy	0.97	0.13—7.45	0.98
Atypical liver resection	1.03	0.13—7.89	0.98
Rectal resection	1.04	0.33—3.33	0.94
Splenectomy	3.20	1.07—9.59	0.04
Diaphragma	0.59	0.17—2.13	0.42
Pancreatic tail	2.83	0.35—22.79	0.33

Table 5 Multivariate analyses of association between predictor variables and progression free survival (Cox regression).

Variables	HR	95% CI	*P*-value
HIPEC			
MMC group	4.84	0.50—46.93	0.17
Cisplatin group	3.82	0.40—36.48	0.25
Oxaliplatin group	Ref		0.40
Splenectomy	2.53	0.61—6.60	0.25

A couple of other patient- and treatment-related parameters should be evaluated before scheduling patients suffering from CRC-PM and LM for this aggressive surgical approach. An unfavorable histology (i.e. signet-ring cells), a poor performance status or major co-morbidities should be regarded as contraindications [11—14]. A strict patient selection process and the awareness of risk factors of postoperative morbidity should be highlighted.

In the current study we were able to work out variables associated with elevated postoperative morbidity and to deliver further evidence that patients with PM and concurrent LM should not primarily be excluded from curative surgical therapy.

A large number of publications focused on the occurrence, severity and predisposing parameters of CRS- and HIPEC-associated morbidity in recent and past literature [15—20]. However, the major problem is comparability of results, because indications, HIPEC-protocols, surgical technique and documentation of adverse events are not uniform. A systematic review published in 2009 including 24 centers reported a major morbidity rate ranging from 12% to 52% and a mortality rate ranging from 0.9% to 5.8% [21], which is in line with our results with a total grade III/IV morbidity rate of 42% and no 30- and 90-day mortality. Studies demonstrated a decline in major morbidity rate over time [1,19] as well as an increase in macroscopic and microscopic complete cytoreductions [22]. A better understanding of patient and operative parameters linked to morbidity and mortality will allow for a strict patient selection and decision making. A review published in 2016 summed up operative and patient factors contributing to morbidity and mortality [23]. Patient factors which showed a strong association with morbidity after CRS and HIPEC were age, hypoalbuminemia and performance status. In our study we did not find an association between age, gender or ASA score (Table 2). This may be mainly attributed to the low sample size but literature suggest that especially patient aged above 70 years will not only have higher rates of major morbidity but also a statistically significantly higher risk of 30- and 90-day mortality [24]. Hypoalbuminemia was associated with 58% morbidity and mortality rates on review of the NSQIP database [25].

In our study the presence of cardiovascular or pulmonal co-morbidities were not linked to increased morbidity but Baratti et al. found that Eastern Cooperative Oncology

Table 6 Univariate survival analyses of association between predictor variables and overall survival (Cox regression).

Variables	HR	95% CI	*P*-value
Sex: male	2.24	1.00—5.01	0.05
PCI value			
0—10	Ref		
11—20	1.06	0.45—2.50	0.90
21—30	0.69	0.26—1.79	0.45
Co-morbidity: cardiovascular	1.32	0.58—3.01	0.52
Tumor etiology			
Gynecological	Ref		
Gastrointestinal	1.22	0.56—2.62	0.62
Others (pseudomyxoma/mesothelioma)	0.09	0.01—0.71	0.22
HIPEC			
MMC	0.45		0.16
Cisplatin	0.65	0.15—1.35	0.36
Oxaliplatin	Ref	0.25—1.66	0.36
CC-Score			
0	Ref		
1	0.82	0.34—1.96	0.65
Resections			
Hemihepatectomy	1.82	0.54—6.19	0.34
Atypical liver resection	0.55	0.16—1.87	0.33
Stomach	1.67	0.49—5.69	0.41
Colon	1.28	0.30—5.47	0.74
Rectal resection	1.26	0.55—2.87	0.59
Splenectomy	0.96	0.45—2.04	0.92
Diaphragma	1.15	0.53—2.49	0.73
Pancreatic tail	2.99	0.69—13.07	0.15

Table 7 Multivariate analyses of association between predictor variables and overall survival (cox regression).

Variables	HR	95% CI	*P*-value
Sex: male	4.05	1.17—13.95	0.03
HIPEC			
MMC	0.46	0.15—1.47	0.19
Cisplatin	1.32	0.35—4.96	0.68
Oxaliplatin	Ref		
Pancreatic tail resection	2.56	0.48—13.52	0.27

Group (ECOG) performance status > 0 was an independent predictor of grade III—V morbidity [26].

Operative factors which are strongly linked to postoperative morbidity have been reviewed extensively. One of the most consistent independent predictor of morbidity is the extent of disease, measured by the PCI [26—30]. In our study we also made the observation that an elevated PCI is linked to an increased postoperative morbidity. Patients with complications had a mean PCI of 16 compared to a PCI of 12 in patients without complications ($P = 0.32$). A higher PCI is linked to a more aggressive surgical procedure thus triggering postoperative complications. Saxena et al. analyzed 145 patients receiving CRS and HIPEC for PMP and showed that a PCI > 21 and ASA score > 3 were linked to grade IV/V morbidity [31]. A retrospective-cohort, multicentric study from 23 French centers showed that the PCI and the performing center were statistically significantly linked to increased postoperative morbidity. In this study centers were classified as experienced (>7 years of practice) and as inexperienced (<7 years of practice). This data once again highlight the importance of center experience to provide low-morbidity CRS and HIPEC [32].

In our study tumor etiology did not impact on occurrence of postoperative complications, which is in line with other studies. Mizumoto et al. [22] and Kusamura et al. [18] included 250 and 205 patients and found no association between origin of PM and morbidity rates. Unlike the latter, Chua et al. retrospectively analyzed 243 patients with a total grade III and IV morbidity rate of 43% and a re-operation rate of 16% and found out that patients suffering from CRC-PM had statistically significantly lower grade III—V morbidity rates ($P = 0.04$). The authors concluded that these results might be linked to a better selection process for patients with CRC-PM [33].

The independent contribution of HIPEC to morbidity seems to be quite low, as suggested by the few existing data. Yang et al. compared patients with CRS only and CRS plus HIPEC in patients with PM originating from gastric cancer and found no significant difference in the occurrence of serious adverse events (11.7% vs. 14.7%; $P = 0.839$) [34]. These results suggest that morbidity is mainly due to the extensive surgical procedures. In our study the performance of rectal resections was statistically significantly linked to morbidity (Table 2). Other types of operative procedures did not

reach statistical significance. Results on impact of special surgical procedures contributing to postoperative morbidity are heterogeneous but the performance of bowel resections, diaphragm stripping and distal pancreatectomy seem to be strong associated with morbidity [23]. Colon resection and left upper quadrant peritonectomy was linked to grade IV—V morbidity at univariate analysis in the study from Saxena et al. [31]. Chua et al. also found left upper quadrant peritonectomy and small bowel resections to be linked to increased morbidity [33]. Peritonectomy procedures in the left upper quadrant and stripping of the diaphragm are often linked to removal of the spleen and the pancreatic tail in order to achieve a CC-0 score. In our study splenectomy was not linked to increased morbidity and we experienced one pancreatic fistula after pancreatic tail resection. Resections involving the pancreas should be carefully considered because this procedure is linked to a higher complication rate per se, mainly due to occurrence of pancreatic fistulas. Downs-Canner et al. showed that the total rate of POPF (postoperative pancreatic fistulas) did not differ in patients with pancreatic resections compared to patients in whom pancreatic resections were performed at the time of CRS and HIPEC, although the rate of serious POPF (grade B and C), requiring non-surgical or surgical interventions, was significantly higher in the CRS and HIPEC group [35].

The performance of intestinal resections (small and large bowel) is necessary in the vast majority of patients to achieve CC-0/1 scores. Especially low or ultralow rectal resections are at risk and the anastomotic leak rate ranges between 3 and 15% [36]. Animal studies showed that after HIPEC with cisplatin and MMC there is a lower density in the formation of collagen in the sutured anastomoses [37,38]. The decision in favor of ostomy should be reserved for ultra low rectal resections because data suggest are very high reversal-related morbidity of 67% after CRS and HIPEC [39]. In our study we did not encounter anastomotic leak or fistulas concerning the small bowel and anastomotic leaks after rectal and colon resections occurred in 11% of patients, which is in line with the current literature. In patients with ovarian cancer the performance of visceral resections and the amount of performed anastomoses did not impact on occurrence of complications (data not shown; $P = 0.479$).

Recent literature suggests that the addition of even minor hepatic resections to cytoreduction and HIPEC leads to an elevation of morbidity rates [40—43]. An analysis from Mouw TJ et al. [40], Morales Soriano R et al. [43] and Cloyd JM et al. [41] found statistically significantly increased morbidity rates after synchronous liver resection. In our study even major liver resections were not linked to increased morbidity but due to the low sample size these data must be interpreted with caution. Authors of the aforementioned studies advocated a staged approach in terms of a delayed liver resection procedure. Data on the morbidity rates of this algorithm are not available in current literature and have to be assessed in the future. Moreover preoperative PET-CT scan, for further evaluation of hepatic lesions, might be a future perspective in order to prevent unnecessary liver resections.

Cloyd JM et al. [41] also documented a higher risk for re-operation (13%) in the patients after liver resection but medical reasons for re-operation were not specified. The re-operation rate in our study was 27%, which is in line with other reports [42,44].

Complications linked to individual HIPEC compounds have also been extensively reviewed in literature. In our study the usage of either MMC or platin-compounds was not linked to increased morbidity and the exposure of the liver resection margins to intraperitoneal heated chemotherapeutic agents did not trigger bile leakage or bleeding.

In a former publication of our group we found a statistically significantly increase in grade III neutropenia in PMP patients receiving MMC-based HIPEC [45]. In the current study five patients suffered from leucopenia after HIPEC with MMC but no medical treatment was necessary. The patient requiring re-operation for intraabdominal bleeding in our study did not receive platin-based HIPEC. The efficacy and toxicity of MMC versus platin-compounds is mixed throughout literature and mainly determined by the underlying histology. Prada-Villaverde et al. showed different efficacy of MMC and oxaliplatin for CRC-PM depending on the peritoneal surface disease severity score (PSDSS) [46]. Data suggest that the higher PSDSS is the more patients will benefit from oxaliplatin-based HIPEC. In our study, noting that different tumor etiologies were included, multivariate analysis showed an increased risk of recurrence in patients receiving MMC (HR = 4.84) and cisplatin (HR = 3.82) as compared to oxaliplatin without reaching statistical significance ($P = 0.17$ and 0.25) (Table 5).

Patients with CRC-PM and LM had a median overall survival of 22 months and the median PCI of these patients was 15, with eight patients having a PCI of > 15 suggesting that the vast majority of patients in our study had an intermediate-volume PCI rather than a more favorable PCI below 12. Kianmanesh et al. [47] and Chua et al. [48] reported a PCI cut-off of 12 to 13 for patients who would benefit the most from this aggressive surgical approach.

Data on the simultaneous treatment of PM and LM of other tumor etiologies are scarce. The second largest patient subpopulation in our study suffered from ovarian cancer with PM and LM. Recent and past literature contains no reports on surgery, survival or treatment-related morbidity of patients with metastasized ovarian cancer undergoing this surgical approach. As seems to be true for PM of colorectal origin, there appears to be a PCI cut-off between 12 and 15 for ovarian cancer [49—51]. In our study only four patients had a PCI > 11, and in all patients a CC-0/1 status was achieved. Grade III/IV morbidity rates was 23%, which is in line with another study including 91 patients with primary and recurrent ovarian cancer with a grade III/IV morbidity rate of 25% [36]. Contrary to our study, no liver resections were performed routinely and HIPEC was performed using paclitaxel. In the latter, morbidity was linked to a PCI > 12 and to intestinal resections [36]. These data suggest that these patients should not be excluded form an aggressive surgical approach.

Conclusion

Highly selected patients, meaning those with low-volume PM and no more than 3 resectable LM of gastrointestinal and gynecological primary tumors, should be critically evaluated regarding the described surgical approach. Patient and operative parameters are associated with serious adverse events and knowledge of these factors will allow a better management and the performance of a safer procedure. A staged approach, meaning performance of delayed hepatic resections, might be an appealing approach in order to further minimize postoperative morbidity.

Acknowledgments

None.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Verwaal VJ, van Ruth S, de Bree E, 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;21:3737—43.
[2] Elias D, Benrizi E, Pocard M, Ducreux M, Boige P, Lasser P. Treatment of synchronous peritoneal carcinomatosis and liver metastases from colorectal cancer. Eur J Surg Oncol 2006;32:632—6.
[3] Cavaliere F, De Simone M, Virzi M, et al. Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. Italian multicenter study S.I.T.I.L.O. Eur J Surg Oncol 2011;37:148—54.
[4] de Cuba EMV, Kwakman R, Knol DL, Bonjer HJ, Meijer GA, Te Velde EA. Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases: systematic review of all literature and meta-analysis of observational studies. Cancer Treat Rev 2013;39:321—7.
[5] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205—13.
[6] Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res 1996;82:359—74.
[7] Sugarbaker PH. Peritonectomy procedures. Surg Oncol Clin N Am 2003;12:703—27.
[8] Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995;221:29—42.
[9] Sugarbaker PH. Surgical management of peritoneal carcinosis: diagnosis, prevention and treatment. Langenbecks Arch Chir 1988;373:189—96.
[10] Simkens GA, Rovers KP, Nienhuijs SW, de Hingh IH. Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer. Cancer Manag Res 2017;30:259—66.
[11] Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. Ann Surg Oncol 2005;12:900—9.
[12] Esquivel J, Elias D, Baratti D, Kusamura S, Deraco M. Consensus statement on the loco regional treatment of colorectal cancer with peritoneal dissemination. J Surg Oncol 2008;98:263—7.
[13] Varban O, Levine EA, Stewart JH, McCoy TP, Shen P. Outcomes associated with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy in colorectal cancer patients with peritoneal surface disease and hepatic metastases. Cancer 2009;115:3427—36.
[14] Carpizo DR, D'Angelica LM. Liver resection for metastatic colorectal cancer in the presence of extrahepatic disease. Lancet Oncol 2009;10:801—9.
[15] Cavaliere F, Valle M, De Simone M, et al. 120 peritoneal carcinomatoses from colorectal cancer treated with peritonectomy and intra-abdominal chemohyperthermia: a S.I.T.I.L.O. Multicentric study. In Vivo 2006;20(6):747—50.
[16] Gusani NJ, Cho SW, Colovos C, et al. Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. Ann Surg Oncol 2008;15(3):754—63.
[17] Smeenk RM, Verwaal VJ, Zoetmulder FA. Learning curve of combined modality treatment in peritoneal surface disease. Br J Surg 2007;94(11):1408—14.
[18] Kusamura S, Younan R, Baratti D, et al. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. Cancer 2006;106(5):1144—53.
[19] Glehen O, Osinsky D, Cotte E, et al. Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. Ann Surg Oncol 2003;10(8):863—9.
[20] Sugarbaker PH, Alderman R, Edwards G, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol 2006;13(5):635—44.
[21] Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatotis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. Ann Surg 2009;249:900—7.
[22] Mizumoto A, Canbay E, Hirano M, et al. Morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy at a single institution in Japan. Gastroenterol Res Pract 2012;2012:836425.
[23] Newton AD, Bartlett EK, Karakousis GC. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a review of factors contributing to morbidity and mortality. J Gastrointest Oncol 2016;7(1):99—111.
[24] Votanopoulos KI, Newman NA, Russell G, et al. Outcomes of Cytoreductive Surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients older than 70 years: survival benefit at considerable morbidity and mortality. Ann Surg Oncol 2013;20(11):3497—503.
[25] Bartlett EK, Meise C, Roses RE, Fraker DL, Kelz RR, Karakousis GC. Morbidity and mortality of cytoreduction with intraperitoneal chemotherapy: outcomes from the ACS NSQIP database. Ann Surg Oncol 2014;21(5):1494—500.
[26] Baratti D, Kusamura S, Mingrone E, Balestra MR, Laterza B, Deraco M. Identification of a subgroup of patients at highest risk for complications after surgical cytoreduction and hyperthermic intraperitoneal chemotherapy. Ann Surg 2012;256(2):334—41.
[27] Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer 2010;116(24):5608—18.
[28] Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 2012;30(20):2449—56.
[29] Bakrin N, Bereder JM, Decullier E, et al. Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. Eur J Surg Oncol 2013;39(12):1435—43.
[30] Macrì A, Arcoraci V, Belgrano V, et al. Short-term outcome of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: preliminary analysis of a multicentre study. Anticancer Res 2014;34(10):5689—93.
[31] Saxena A, Yan TD, Chua TC, Morris DL. Critical assessment of risk factors for complications after cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. Ann Surg Oncol 2010;17(5):1291—301.
[32] Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal

chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28(1):63—8.
[33] Chua TC, Saxena A, Schellekens JF, et al. Morbidity and mortality outcomes of cytoreductive surgery and perioperative intraperitoneal chemotherapy at a single tertiary institution: towards a new perspective of this treatment. Ann Surg 2010;251(1):101—6.
[34] Yang XJ, Huang CQ, Suo T, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol 2011;18:1575—81.
[35] Downs-Canner S, Ding Y, Magge DR, et al. A comparative analysis of postoperative pancreatic fistulas after surgery with and without hyperthermic intraperitoneal chemoperfusion. Ann Surg Oncol 2015;22:1651—7.
[36] Cascales Campos P, Gil J, Parrilla P. Morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with primary and recurrent advanced ovarian cancer. Eur J Surg Oncol 2014;40(8):970—5.
[37] Elias D, Honoré C, Ciuchendéa R, et al. Peritoneal pseudomyxoma: results of a systematic policy of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Br J Surg 2008;95:1164—71.
[38] Fumagalli U, Trabucchi E, Soligo M, et al. Effects of intraperitoneal chemotherapy on anastomotic healing in rats. J Surg Res 1991;50:82—7.
[39] de Cuba EM, Verwaal VJ, de Hingh IH, et al. Morbidity associated with colostomy reversal after cytoreductive surgery and HIPEC. Ann Surg Oncol 2014;21(3):883—90.
[40] Mouw TJ, Lu J, Woody-Fowler M, et al. Morbidity and mortality of synchronous hepatectomy with cytoreductive surgery/hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). J Gastrointest Oncol 2018;9:828—32.
[41] Cloyd JM, Abdel-Misih S, Hays J, Dillhoff ME, Pawlik TM, Schmidt C. Impact of synchronous liver resection on the perioperative outcomes of patients undergoing CRS-HIPEC. J Gastrointest Surg 2018;22:1576—84.
[42] Navez J, Remue C, Leonard D, et al. Surgical treatment of colorectal cancer with peritoneal and liver metastases using combined liver and cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: report from a single-centre experience. Ann Surg Oncol 2016;23:666—73.
[43] Morales Soriano R, Morón Canis JM, Molina Romero X, et al. Influence of simultaneous liver and peritoneal resection on postoperative morbi-mortality and survival in patients with colon cancer treated with surgical cytoreduction and intraperitoneal hyperthermic chemotherapy. Cir Esp 2017;95:214—21.
[44] Glockzin G, Renner P, Popp FC, et al. Hepatobiliary procedures in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2011;18:1052—9.
[45] Horvath P, Beckert S, Struller F, Königsrainer A, Königsrainer I. Incidence of leukopenia after intraperitoneal vs combined intravenous/intraperitoneal chemotherapy in pseudomyxoma peritonei. World J Gastrointest Pharmacol Ther 2016;7(3):434—9.
[46] Prada-Villaverde A, Esquivel J, Lowy AM, et al. The American Society of Peritoneal Surface Malignancies evaluation of HIPEC with mitomycin C versus oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. J Surg Oncol 2014;110:779—85.
[47] Kianmanesh R, Scaringi S, Sabate JM, et al. Iterative cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis of colorectal origin with or without liver metastases. Ann Surg 2007;245:597—603.
[48] Chua TC, Yan TD, Zhao J, Morris DL. Peritoneal carcinomatosis and liver metastases from colorectal cancer treated with cytoreductive surgery, perioperative intraperitoneal chemotherapy and liver resection. Eur J Surg Oncol 2009;35:1299—305.
[49] Zanon C, Clara R, Chiappino I, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for recurrent peritoneal carcinomatosis of ovarian cancer. World J Surg 2004;28:1040—5.
[50] Cotte E, Glehen O, Mohamed F, et al. Cytoreductive surgery and intraperitoneal chemo-hyperthermia for chemo-resistant and recurrent advanced epithelial ovarian cancer: prospective study of 81 patients. World J Surg 2007;31:1813—20.
[51] Di Giorgio A, Naticchioni E, Biacchi D, et al. Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer. Cancer 2008;13:315—25.