Optimizing patient selection for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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1

General introduction and outline of the thesis

COLORECTAL PERITONEAL METASTASES

Colorectal cancer is reported as the second most−common cancer in the Netherlands and the third most−common cancer worldwide.[1,2] Up to 40% of patients with colorectal cancer develop peritoneal metastases (PM) during the course of the disease.[3-6] Colorectal PM has long been considered a terminal disease, with most patients dying within a few months after diagnosis.[3,7] The effect of modern systemic chemotherapy regimens and molecular targeting agents remains limited and only extends the median overall survival (OS) rate up to 24 months.[8-12] Long−term survivorship with these regimens alone has never been achieved.

Three decades ago, a paradigm shift occurred when colorectal PM was recognised as a locoregional spread of disease rather than an expression of diffuse metastatic disease. This hypothesis resulted in the development of a comprehensive locoregional treatment strategy combining aggressive cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC).[13-16] This extensive surgical treatment radically changed the survival outcomes in selected patients with limited and resectable colorectal PM, with reported median OS up to 63 months and 5-year survival rates of up to 54%.[17-20] During the 9th International Congress on Peritoneal Surface Malignancies in Amsterdam in 2014, CRS+HIPEC was established as standard care for selected patients with colorectal PM.

PRINCIPLES OF CRS+HIPEC

CRS+HIPEC procedures are performed worldwide with a variety of different techniques; as such, only the main concept and our standardised Dutch HIPEC protocol are summarised below.[20]

Cytoreductive surgery

The goal of cytoreductive surgery is to remove all macroscopic visible tumour deposits from the peritoneal surface in the abdominal cavity by performing both peritoneal and organ resections. CRS is only performed if the colorectal PM is deemed completely resectable during an exploratory laparotomy.

Hyperthermic intraperitoneal chemotherapy

After a complete cytoreduction has been achieved, the HIPEC procedure is performed to eliminate all remaining microscopic tumour cells in the abdominal cavity. At the UMCG, the open Coliseum technique is used for the administration of

a heated chemotherapeutic agent to the abdominal cavity.[21] In this open technique, the abdominal wall is pulled upward and a closed circuit is created using inflow and outflow drains attached to a perfusion device. Mitomycin C (35 mg/m^2) is used as the preferred chemotherapeutic agent in patients with colorectal PM, at a temperature of 41–42°C for 90 min. The addition of hyperthermia to the chemotherapeutic agent increases the local concentration and the penetration depth in the sites of tumour deposits.[22-24] Thereafter, the fluid is evacuated from the abdominal cavity and reconstruction surgery including bowel anastomoses with or without a stoma is performed.

IMPACT OF CRS+HIPEC

Treatment−related morbidity and mortality

CRS+HIPEC is a complex oncologic abdominal procedure associated with high postoperative morbidity rates and long hospital stays. A systematic review from 10 international high−volume referral centres reported major postoperative morbidity rates between 12 and 52% and mortality rates between 0.9 and 5.8%.[25] The 1−year mortality rate is 13%, and approximately 50% of patients will experience recurrence of the disease within the first year after CRS+HIPEC.[18,26-30] Severe complications after CRS+HIPEC have major consequences for our patients and our healthcare system, as they are associated with a diminished quality of life (QoL), a significant decrease in survival outcomes, and a serious increase in hospital costs of approximately 320%.[28,31-33]

Quality of life

Most studies report a significant decrease in various domains of QoL during the first six months after surgery.[34,35] Overall, at least 6–12 months recovery time is necessary to restore the QoL to preoperative levels.

PATIENT SELECTION FOR CRS+HIPEC

Patients who benefit the most in terms of survival and QoL with acceptable treatment−related morbidity and mortality should be selected for CRS+HIPEC. A complex interplay of patient, tumour, and treatment−related factors determines these postoperative outcomes. According to the available literature, survival outcomes after CRS+HIPEC are strongly determined by the extent of peritoneal disease, the completeness of macroscopic cytoreduction, and the presence of signet ring cell histology.[18,29,30,36-45]

Extent of peritoneal disease

The extent and distribution of colorectal PM is directly correlated to the complexity of the surgical procedure, the risk of developing major postoperative complications, and survival outcomes after CRS+HIPEC. The extent of peritoneal disease is scored by the peritoneal cancer index (PCI), which combines peritoneal lesions sizes with the exact distribution over 13 abdominopelvic regions (**Figure 1**). The PCI score ranges from 0 to 39 points; a higher score indicates a more extensive tumour burden. The optimal cut−off value of the PCI score remains a topic of debate, although most guidelines recommend performing CRS+HIPEC only in patients with colorectal PM with a PCI <20.[45] No extensive disease of the small bowel and its mesentery may be present, as complete resection will certainly lead to short bowel syndrome, which is a contra−indication to perform CRS+HIPEC. In addition, distant metastases are a contra−indication for CRS+HIPEC, with the exception of up to three resectable liver metastases.

Completeness of macroscopic cytoreduction

The completeness of cytoreduction score (CC−score) measures the amount of macroscopically visible disease after CRS. Completeness of cytoreduction is so essential that current guidelines recommend only performing HIPEC after a complete cytoreduction (CC−0, no visible residual disease) or nearly complete cytoreduction (CC−1, residual tumour lesions less than 2.5 mm) has been achieved.[45] The likelihood of achieving a complete cytoreduction depends on the extent and distribution of colorectal PM.

Signet ring cell histology

Colorectal tumours with histopathological confirmation of signet ring cells seem to metastasise more easily to the peritoneum, causing a greater peritoneal burden of disease.[46] There is a higher risk of the occurrence of a non−therapeutic laparotomy or the need to perform extensive resections with associated high postoperative morbidity rates in these patients. In addition, survival outcomes after CRS+HIPEC are poor, with no patients reported to be alive at 5−year follow−up.[42-44]

Other important patient−related factors

Moderate or severe comorbidity (i.e., American Society of Anaesthesiologists [ASA] score >3) and poor performance status (i.e., World Health Organization [WHO] score >2) are absolute contra−indications to perform CRS+HIPEC, because patients have to be able to withstand 8−12 h of surgery.[13,45] Obesity is reported as a risk factor for pulmonary complications but is not considered an absolute contra−indication.[47] Older age might be a relative contra−indication, although the exact cut−off age remains unclear.[48]

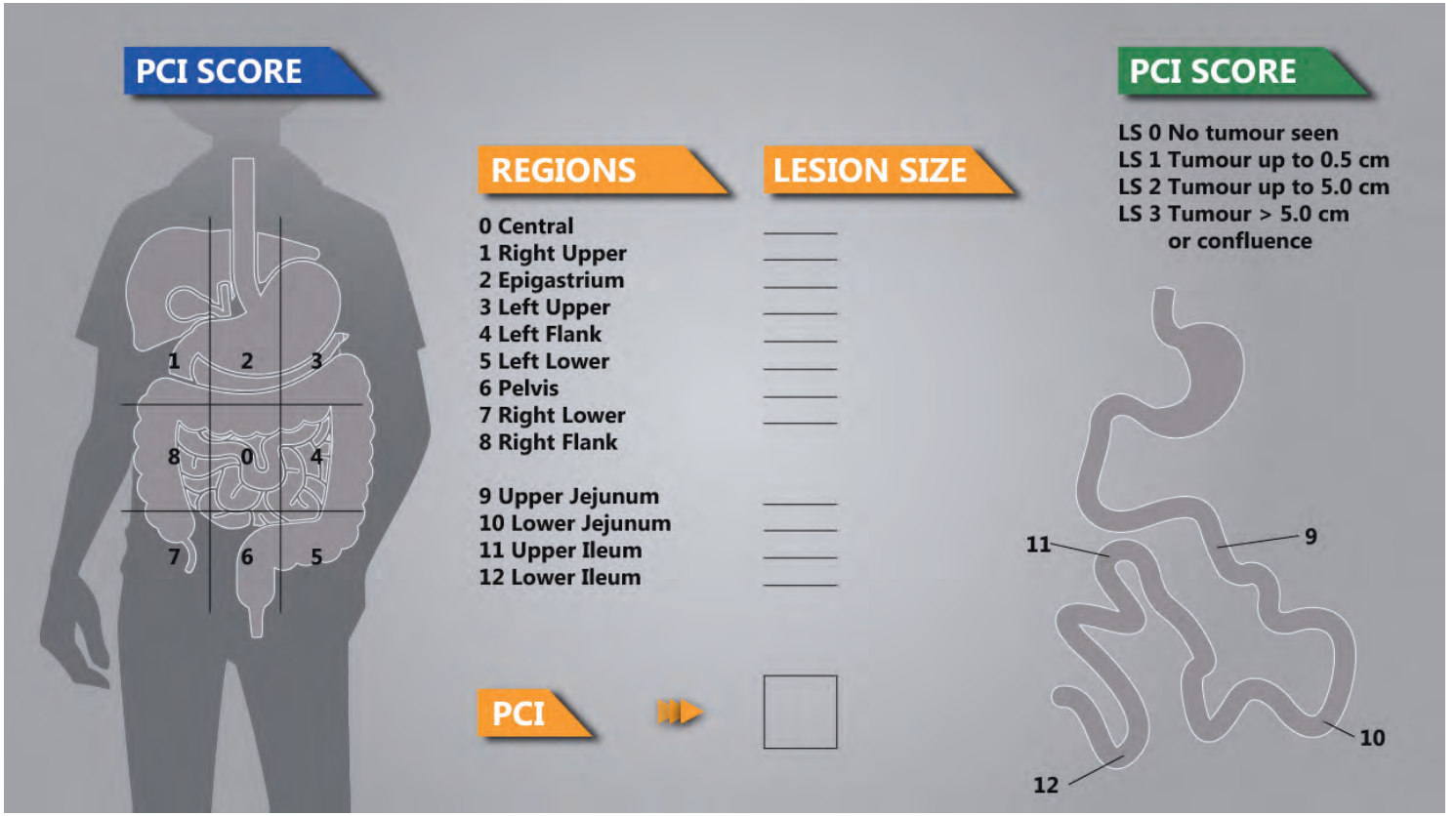

Figure 1 | The peritoneal cancer index (PCI) according to Sugarbaker.

CHALLENGES IN PATIENT SELECTION FOR CRS+HIPEC

There is no doubt that adequate patient selection is the main challenge in the field of CRS+HIPEC. Current preoperative imaging modalities fail to estimate the PCI to predict the possibility of achieving a complete cytoreduction.[49-52] Direct visualisation of the abdominal cavity is the most accurate method to assess the extent and distribution of colorectal PM, which causes patient selection to take place in the operating room rather than in an outpatient setting. Up to 50% of patients are excluded for CRS+HIPEC directly upon an exploratory laparotomy.[53-57] Identification of patients for whom CRS+HIPEC is not suitable at an earlier stage could spare these patients the morbidity of an unnecessary laparotomy. Additionally, a cancelled CRS+HIPEC procedure is time consuming and expensive from a healthcare perspective.

Preoperative patient selection is thus preferential, because it allows for a more patient−tailored approach, increased patient information, less morbidity, quick referral for systemic therapy in the case of extensive disease, and ultimately, better patient survival. Furthermore, prognostic factors that can be preoperatively assessed prevent unnecessary imaging, admission, and operations with associated costs. The search for prognostic factors that could further improve patient selection for CRS+HIPEC is constantly ongoing.

OUTLINE OF THIS THESIS

Patients with colorectal PM who benefit the most in terms of survival and QoL with acceptable treatment−related morbidity and mortality should be selected for CRS+HIPEC. Currently, the most powerful prognostic factors for survival after CRS+HIPEC are determined at the time of operative exploration rather than in a preoperative setting. The aim of this thesis is to identify new and promising preoperative factors in patients with colorectal PM to predict postoperative morbidity and survival outcomes after CRS+HIPEC. This thesis is subdivided into two parts.

PART I – Biological and clinical prognostic factors to further optimise patient selection for CRS+HIPEC

Tumour biology is very likely to play a key role in the survival outcomes after CRS+HIPEC for patients with colorectal PM, as the presence of signet ring cell histology is one of the most important independent predictors of poor survival after CRS+HIPEC. The onset of development of colorectal PM (i.e., synchronously or metachronously) might also be of relevance; the difference in either tumour biology

and behaviour or adequate initial treatment might influence survival outcomes after CRS+HIPEC. In **Chapter 2**, the impact of onset of colorectal PM on survival outcomes after CRS+HIPEC was retrospectively assessed from merged prospectively maintained institutional databases from two Dutch tertiary referral hospitals.

The PCI scoring system is used worldwide as a static single−time−point scoring system to assess the extent of peritoneal disease during an exploratory laparotomy for potential CRS+HIPEC and as such does not include disease progression over time. Since 2012, HIPEC surgeons from our academic centre have introduced diagnostic laparoscopy (DLS) as a part of the preoperative workup for CRS+HIPEC in patients with suspicion of colorectal PM to pathologically confirm the presence of peritoneal disease and to systematically assess the extent and resectability according to the PCI scoring system in an earlier stage. The aim of **Chapter 3** is to assess the impact of an increase in PCI between DLS and exploratory laparotomy (i.e., ΔPCI) on survival outcomes after CRS+HIPEC to create a more−dynamic prognostic factor.

Previous retrospective studies concluded that DLS is a safe, feasible, and accurate staging tool to assess tumour burden in patients with PM and could prevent non−therapeutic laparotomies. However, the limitations of these studies are the small number of patients, the variety of primary tumour types, and the highly selected way DLS is used. **Chapter 4** aims to determine the feasibility and safety of performing DLS routinely in a large cohort of patients with suspicion of colorectal PM to evaluate suitability for CRS+HIPEC. In addition, the perioperative reasons to exclude patients for CRS+HIPEC during DLS were investigated. The introduction of DLS in our preoperative workup for CRS+HIPEC provides the opportunity to compare a historical cohort of patients with colorectal PM who were scheduled for CRS+HIPEC before the introduction of DLS to those with colorectal PM who were scheduled for CRS+HIPEC after DLS was part of the preoperative workup. In **Chapter 5**, both cohorts are investigated to evaluate the implementation of DLS in the preoperative workup for CRS+HIPEC and to investigate the impact of DLS on preventing non−therapeutic laparotomies in this vulnerable patient population.

The extent of surgery (i.e., number of resected anatomical structures) during CRS+HIPEC is a well−known risk factor for treatment−related morbidity and mortality. Surgeons' abilities to correctly predict the extent of surgery in advance seems to be one of the key elements to estimate the individual risk for treatment−related morbidity. The large number of publications about the limitations of current imaging modalities in detecting PM and the occurrence of non−therapeutic laparotomies in

up to 50% of the patients suggest that surgeons experience difficulties in predicting the extent of surgery in advance. In **Chapter 6**, surgeons' abilities to correctly predict the extent of surgery in advance to CRS+HIPEC is described for the first time in a prospective, observational cohort study including 131 cases.

PART II – New Avenues for Research

Surgery−related muscle loss (SRML) occurs in at least one out of three cancer patients within one week after major surgery. However, this important phenomenon has hardly been investigated. The few reported studies demonstrate that clinically relevant SRML might be a major problem for our current healthcare system based on its impact on several short−term postoperative problems and its postoperative impact on QoL and fatigue up to six months after surgery. Prevention of clinically relevant SRML can be a promising strategy to improve morbidity and mortality and increase QoL after major surgery. **Chapter 7** extensively describes the design of the MUSCLE POWER study, an observational sing−centre prospective cohort study that investigates the presence, impact, and possible predictors for clinically relevant SRML in 178 cancer patients after major abdominal surgery using ultrasound measurements, squeeze and force measurements, and QoL questionnaires. Daily physical activity during the hospital stay will be monitored by a motility tracker, and protein intake will be monitored by a dietician. Crucial information regarding possible predictors for clinically relevant SRML can be used in future intervention studies to prevent postoperative muscle loss and subsequently improve postoperative outcome and QoL. The MUSCLE POWER study is open for inclusion and more than 50 patients have been enrolled over the past four months. Final results can be expected at the end of 2020.

Another promising line of research at the UMCG are the use of intraoperative imaging techniques to improve tumour detection during surgery. In patients with colorectal PM, complete cytoreduction during CRS+HIPEC is necessary to achieve long−term survival, and surgeons currently depend on visual and tactile inspection only to differentiate between benign and malignant lesions during surgery. In recent years, molecular fluorescence guided surgery (MFGS) has emerged as a promising real−time intraoperative imaging technique to improve tumour detection by using tumour−targeted fluorescence tracers. This technique can be applied intraoperatively to serve as a 'red−flag' imaging technique to assist in optimal tumour identification. Improved detection of tumour tissue could not only help attain a more complete cytoreduction but might also facilitate tailored surgery avoiding unnecessary resections of benign lesions and organs. **Chapter 8** provides

a chronological overview of MFGS development in patients with colorectal PM, including two completed phase I clinical trials using two different tumour–targeted fluorescence tracers during exploratory laparotomy. Bevacizumab-IRDye800CW, one of the promising tumour–targeted fluorescence tracers, will be used for a new phase I trial to detect tumour tissue from colorectal PM during DLS (i.e., the SELECT trial). If Bevacizumab-IRDye800CW is also feasible during DLS, it might provide a more accurate investigation of the extent of peritoneal disease at an earlier stage. Ultimately, these new strategies may reduce overtreatment, morbidity, and costs while maintaining the same or better effectiveness with a lower recurrence rate and improved QoL.

In **Chapter 9** the previous chapters are summarised and discussed in a broader perspective. A summary of the work undertaken is given in English and Dutch. Finally, this chapter provides directions for future research.

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PART I

BIOLOGICAL AND CLINICAL PROGNOSTIC FACTORS TO FURTHER OPTIMISE PATIENT SELECTION FOR CYTOREDUCTIVE SURGERY WITH HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

2

Impact of onset of colorectal peritoneal metastases on survival outcomes after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Purpose

Careful selection of patients with colorectal peritoneal metastases (PM) for cytoreductive surgery (CRS) with HIPEC is crucial. It remains unknown whether the time−of−onset of colorectal PM (synchronous versus metachronous) influences surgical morbidity and survival outcomes after CRS+HIPEC.

Methods

Patients with histologically proven colorectal PM who underwent CRS+HIPEC between February 2006 and December 2017 in two Dutch tertiary referral hospitals were retrospectively included from a prospectively maintained database. The onset of colorectal PM was classified as synchronous (PM diagnosed at the initial presentation with colorectal cancer) or metachronous (PM diagnosed after initial curative colorectal resection). Major postoperative complications (Clavien−Dindo grade ≥3), overall survival (OS), and disease−free survival (DFS) were compared between patients with synchronous and those with metachronous colorectal PM using Kaplan−Meier analyses, proportional hazard analyses, and a multivariate Cox regression analysis.

Results

The study enrolled 433 patients, of whom 231 (53%) had synchronous colorectal PM and 202 (47%) had metachronous colorectal PM. The major postoperative complication rate and median OS were similar between the patients with synchronous and those with metachronous colorectal PM (26.8 vs 29.7%; $p = 0.693$ and 34 vs 33 months, respectively; $p = 0.819$). The median DFS was significantly decreased for the patients with metachronous colorectal PM versus patients with synchronous colorectal PM (11 versus 15 months; adjusted hazard ratio, 1.63; 95% confidence interval, 1.18−2.26).

Conclusions

Metachronous onset of colorectal PM is associated with early recurrence after CRS+HIPEC compared with synchronous colorectal PM, without a difference in OS or major postoperative complications. Time−of−onset of colorectal PM should be taken into consideration to optimise patient selection for this major procedure.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide, with 1.4 million new cases and more than 700,000 deaths per year.[1] Approximately 30−40% of CRC patients experience peritoneal metastases (PM) at some point in time after initial diagnosis.[2-7] With the systemic therapy regimens, the median overall survival (OS) for patients with colorectal PM traditionally ranges from 12 to 24 months.[8-10]

Almost three decades ago, a curative−intent treatment option arose: cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC).[11,12] The main principle of this extensive procedure is removal macroscopic disease during CRS, followed by HIPEC for microscopic malignant tissue, resulting in an OS of up to 5 years for highly selected patients with colorectal PM.[11-13] However, CRS+HIPEC is accompanied by substantial early recurrence rates (up to 50% during the first year after treatment), morbidity (16−64%) and mortality (0−8%).[14-20] Therefore, careful patient selection is pivotal to prevention of early recurrence and therefore overtreatment, with the aim to increase survival and reduce morbidity and mortality.

At this writing, the most powerful prognostic factors for survival after CRS+HIPEC are extent of disease measured by the peritoneal cancer index (PCI), completeness of the performed cytoreduction, and signet ring cell histology.[21-27] These prognostic factors, on which surgeons rely heavily, are determined during or after the surgical procedure rather than in a preoperative setting. Therefore, more research on preoperative prognostic factors is of utmost importance to improvement of the decision−making process.

The development of PM metachronously or synchronously with the primary CRC diagnosis might be of relevance. The difference in either tumour biology and behaviour, or adequate initial treatment might influence OS and DFS. In an attempt to discover novel preoperative risk factors for worse outcomes, this study aimed to investigate the impact of the synchronous versus metachronous onset of colorectal PM on surgical morbidity and survival outcomes after CRS+HIPEC.

METHODS

Design, setting, and participants

In this multicentre observational study, data from all consecutive patients with histologically proven colorectal PM who underwent CRS+HIPEC between February 2006 and December 2017 were retrospectively extracted from a merged prospectively maintained institutional database of two Dutch tertiary referral hospitals.

No worldwide consensus exists concerning the definitions of synchronous and metachronous formation of PM. The most common definitions used in scientific literature were selected. Patients with synchronous colorectal PM had colorectal cancer diagnosed at the time of presentation, either on routine staging, on computed tomography (CT), or at laparotomy. Patients with metachronous colorectal PM were deemed to be clear of peritoneal disease at the initial "curative" colorectal resection, but subsequently became symptomatic during the follow−up period and had PM diagnosed on CT (**Figure 1**). The study was approved by the Institutional Ethics Committee of the University Medical Center Groningen (METc 201800395).

Preoperative evaluation and management

All the patients underwent a standardised preoperative workup to evaluate eligibility for CRS+HIPEC, with the aim of achieving complete cytoreduction with acceptable risk of treatment−related morbidity and mortality. This preoperative workup consisted of a clinical examination, preoperative laboratory testing, and thoracic, abdominal and pelvic CT with oral and intravenous contrast agents to quantify the peritoneal disease burden and rule out extra−abdominal metastases. If deemed necessary, a diagnostic laparoscopy (DLS) was performed to assess the location and extent of peritoneal disease using the PCI scoring system, as described by Sugarbaker et al.[28] Clinically suspect lesions during DLS were biopsied for pathological confirmation of colorectal PM.

Next, the eligibility for CRS+HIPEC according to the preoperative workup was determined for each patient at a multidisciplinary oncology team meeting. In the Netherlands, candidates for CRS+HIPEC are generally those with colorectal PM amenable to complete cytoreduction, a PCI below 20, no extra−abdominal metastases, and a performance status that allows for major surgery. The presence of up to three resectable liver metastases is not an absolute contraindication for CRS+HIPEC.[17]

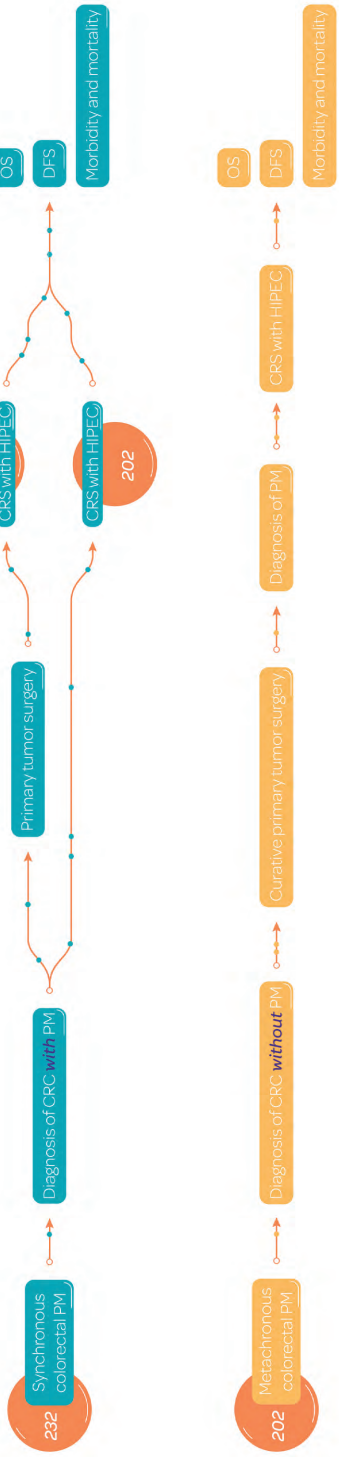

Figure 1 | Definitions of synchronous and metachronous colorectal peritoneal metastases.
Synchronous colorectal peritoneal metastases: peritoneal metastases diagnosed at the time of initial presentation with colorectal cancer.
Metachronous colorectal peritoneal metastases: peritoneal metastases diagnosed after initial curative colorectal resection.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

For the patients in this study, CRS was performed only if the colorectal PM was deemed to be completely resectable after exploratory laparotomy, whereas HIPEC was performed only in case of a (near) complete cytoreduction. The two institutions performed CRS+HIPEC under the same standardised Dutch HIPEC protocol, as previously described.[17] Restrictions were imposed on the extent of surgery as far as it was compatible with sufficient postoperative function. At the end of surgery, the completeness of cytoreduction (CC) score was determined, with CC−0 indicating that no residual tumour was visible or palpable in the peritoneal cavity, CC−1 indicating residual tumour deposits smaller than 2.5 mm, CC−2 indicating residual tumour deposits between 2.5 mm and 2.5 cm, and CC−3 indicating residual tumour deposits above 2.5 cm or a confluence of nodules. [28]

The HIPEC procedure was then performed by circulating a heated solvent infused with chemotherapeutic medication throughout the abdomen using the open Coliseum technique.[29] In most cases, mitomycin (35mg/m^2) was administered in the open abdominal cavity, with a temperature of 41−42ºC for 90 minutes. After this, the fluid was evacuated from the abdomen, and the continuity of the gastrointestinal tract was restored. After surgery, patients were admitted to the intensive care unit for at least one postoperative day until both cardiac and pulmonary functions were stable.

Follow−up

All the patients were followed by a standardised follow−up protocol. Physical examination and carcinoembryonic antigen (CEA) measurements were performed on a 3− to 6− month basis for a minimum of 4 years. If recurrence of the disease (e.g., clinical symptoms or increase in CEA levels) was suspected, a CT of the thorax and abdomen was performed, with tissue biopsies in selected cases.

Data collection

Data on patient characteristics, tumour characteristics, operative characteristics, postoperative morbidity and mortality, recurrence, and overall survival were collected prospectively. Data on postoperative complications were collected up to 60 days after CRS+HIPEC and registered according to the Clavien−Dindo classification system.[30] Data regarding the use of perioperative chemotherapy were divided into three categories. Chemotherapy before CRS+HIPEC was recorded as “neoadjuvant chemotherapy”. Chemotherapy after CRS+HIPEC was recorded as “adjuvant chemotherapy”, and when chemotherapy was used in the past (e.g., before or after

a primary colorectal tumour resection), it was recorded as “prior chemotherapy”. Data were collected and stored in compliance with the Declaration of Helsinki.

Primary and secondary outcomes

The primary outcome was overall survival (OS), defined as the time between CRS+HIPEC and death, or date of the last follow−up visit in censored cases. The secondary outcomes were disease−free survival (DFS) and major postoperative complications. In this study, DFS was defined as the time between CRS+HIPEC and the date of the first recurrence or last follow−up visit in censored cases. Major postoperative complications were classified as grade 3 (severe adverse events requiring interventional procedures) and grade 4 (life−threatening adverse events requiring a return to the operating theatre or intensive care support). Procedure−related mortality was defined as patient death within 30 days of surgery or during the hospital stay (grade 5).

Statistical analyses

All statistical analyses were conducted using SPSS® Statistics version 24.0 (IBM Corporation, Armonk, NY, USA). All *p* values equal to or lower than 0.05 were considered statistically significant. Quantitative values were reported as mean ± standard deviation (SD) or median (interquartile range [IQR]), and categorical variables as numbers and percentages. Categorical variables were compared between patients with synchronous and those with metachronous colorectal PM using the Chi−square test or Fisher’s exact test. Continuous variables were compared between both groups by using the student *t*−test or Mann−Whitney *U* test. OS and DFS were compared between the two groups using Student’s *t* test or the Mann−Whitney *U* test. Both OS and DFS were compared between the two groups using the log−rank test.

Subsequently, a multivariable Cox regression analysis was performed to determine the impact of metachronous versus synchronous colorectal PM on survival outcomes after adjustment for potential confounders. The potential confounders included were either those with a *p* value lower than 0.20 in the univariate survival analysis or those known from the literature. Results were reported as hazard ratio (HR) with 95% confidence interval (CI).

RESULTS

Baseline characteristics

The study analysed 433 patients with colorectal PM who underwent CRS+HIPEC. For 231 patients (53%) synchronous colorectal PM was diagnosed, whereas for 202 patients (47%) metachronous colorectal PM after initial curative colorectal resection was diagnosed. Of the patients with synchronous colorectal PM, 202 (87.4%) underwent CRS+HIPEC directly, whereas 29 (12.6%) underwent primary surgery and were referred to one of the tertiary referral hospitals in which CRS+HIPEC was performed in a second stage (**Figure 1**).

Table 1 presents the patient characteristics, tumour characteristics, and surgical characteristics of the entire cohort, as well as a comparison of these characteristics between patients with synchronous and those with metachronous colorectal PM. At baseline, the patients with synchronous colorectal PM differed significantly from the patients with metachronous colorectal PM. The patients with metachronous colorectal PM less frequently presented with signet ring cell histology (1.5 vs 11.7%, $p < 0.001$), less frequently had an N2 status (25.2 vs 45.0%, $p < 0.001$), and were less frequently treated with neoadjuvant (14.9 vs 30.3%, $p < 0.001$) or adjuvant chemotherapy (21.8 vs 53.3%, $p < 0.001$) or neoadjuvant biological therapy (4.5 vs 11.7%, $p = 0.012$). Other baseline characteristics were similar between the two groups.

Surgical morbidity and mortality

Table 2 presents the mortality and overall postoperative morbidity rates divided by type and severity of the postoperative complication. The number of major postoperative complications was similar between patients with synchronous and those with metachronous colorectal PM (26.8 vs 29.7%, $p = 0.693$). The perioperative mortality for the entire cohort was 1.6% and showed no significant difference between the two groups ($p = 0.575$). The causes of treatment−related death were cardiac events ($n = 2$), major postoperative bleeding ($n = 2$), anastomotic leakage ($n = 1$) and intra−abdominal abscesses ($n = 2$).

Survival outcomes

In the univariate analysis, the median OS was similar between the patients with synchronous colorectal PM and those with metachronous colorectal PM (34 vs 33 months, $p = 0.819$) (**Figure 2**). During the follow−up period, recurrence was diagnosed in 270 patients (62.4%). In the univariate analysis, the median DFS was

significantly shorter for the patients with metachronous colorectal PM (11 months; 95% CI 10−12 months) than for the patients with synchronous colorectal PM (15 months; 95% CI 11−19 months)($p < 0.001$ (**Figure 3, Table 3**).

In multivariate analysis, adjusted for tumour location, signet cell histology, PCI score, resection status, prior chemotherapy, and adjuvant chemotherapy after CRS+HIPEC, metachronous colorectal PM was associated with a worse DFS than synchronous colorectal PM (adjusted HR 1.63; 95% CI 1.18−2.26; $p < 0.01$)(**Table 3**). The location of recurrent disease was available for 242 patients and included colorectal PM only ($n = 113$, 46.7%), colorectal PM and distant metastases ($n = 70$, 28.9%), and distant metastases only ($n = 59$, 24.4%).

Organ−specific localisations of the distant metastases were most likely the liver ($n = 62$, 48.0%), the lung ($n = 43$, 33.3%), or both organs simultaneously (n = 20, 15.5%). The localisation of recurrent disease did not differ significantly between the two groups ($p = 0.482$).

Table 1 | Comparison of baseline characteristics between patients with synchronous versus metachronous colorectal peritoneal metastases who underwent CRS+HIPEC.

	Total n = 433	**Synchronous colorectal PM** n = 231	**Metachronous colorectal PM** n = 202	*P value*
Age, y ± SD	64 ± 10.8	62 ± 11	63 ± 11	0.126
Female sex, n (%)	224 *(51.7)*	115 *(49.8)*	109 *(54.0)*	0.753
BMI, kg/m² ± SD	25.7 ± 4.6	25.8 ± 5.9	25.1 ± 4.7	0.366
ASA, n (%)				0.688
1	41 *(9.5)*	23 *(10.0)*	18 *(8.9)*	
2	343 *(79.2)*	181 *(78.4)*	162 *(80.2)*	
3	48 *(11.1)*	27 *(11.7)*	21 *((10.4)*	
4	1 *(0.2)*	0 *(0.0)*	1 *(0.5)*	
Comorbidity, n (%)				
NIDDM	48 *(11.1)*	26 *(11.3)*	22 *(10.9)*	0.819
IDMM	5 *(1.2)*	2 *(0.9)*	3 *(1.5)*	
Cardiovascular comorbidity	54 *(12.5)*	28 *(12.1)*	26 *(12.9)*	0.338
Hypertension	86 *(19.9)*	40 *(17.3)*	46 *(22.8)*	0.206
Lung comorbidity	13 *(3.0)*	6 *(2.6)*	7 *(3.5)*	0.893
Renal comorbidity	8 *(1.8)*	3 *(1.3)*	5 *(2.5)*	0.611
Primary tumour, n (%)				0.115
Right colon	149 *(34.4)*	92 *(40.0)*	57 *(28.2)*	
Transverse colon	34 *(7.9)*	17 *(7.4)*	17 *(8.4)*	
Left colon	40 *(9.2)*	17 *(7.4)*	23 *(11.4)*	
Sigmoid	143 *(33.0)*	66 *(28.7)*	77 *(38.1)*	
Rectum	66 *(15.2)*	38 *(16.5)*	28 *(13.9)*	
Signet cell histology, n (%)	30 *(6.9)*	27 *(11.7)*	3 *(1.5)*	**<0.001**
T stage, n (%)				0.599
≤3	184 *(42.5)*	93 *(40.3)*	91 *(45.0)*	
4	*216 (49.9)*	120 *(51.9)*	96 *(47.5)*	
N status, n (%)				**<0.001**
0	119 *(27.5)*	43 *(18.6)*	76 *(37.6)*	
1	126 *(29.1)*	66 *(28.6)*	60 *(29.7)*	
2	155 *(35.8)*	104 *(45.0)*	51 *(25.2)*	
Prior chemotherapy, n (%)	147 *(33.9)*	30 *(13.0)*	117 *(57.9)*	**<0.001**
Prior biological therapy, n (%)	10 *(2.3)*	4 *(1.7)*	6 *(3.0)*	0.392

Table 1 | Continued

	Total n = 433	Synchronous colorectal PM n = 231	Metachronous colorectal PM n = 202	*P value*
Synchronous liver metastases, n (%)	40 *(9.2)*	23 *(10.0)*	17 *(8.4)*	0.581
Neoadjuvant chemotherapy, n (%)				**<0.001**
Yes	100 *(23.1)*	70 *(30.3)*	30 *(14.9)*	
Neoadjuvant biological therapy, n (%)				**0.012**
Yes	36 *(8.3)*	27 *(11.7)*	9 *(4.5)*	
Adjuvant chemotherapy, n (%)				**<0.001**
Yes	161 *(37.2)*	120 *(53.3)*	41 *(21.8)*	
Adjuvant biological therapy, n (%)				0.510
Yes	13 *(3.0)*	9 *(4.0)*	4 *(2.0)*	
PCI at HIPEC (IQR)	8 (4–12)	8.0 (5–12)	7 (3–12)	0.06
HIPEC regimen				0.720
MMC	383 *(88.5)*	204 *(88.3)*	179 *(88.6)*	
Oxaliplatin/5FU/LV	39 *(9.0)*	22 *(9.5)*	17 *(8.4)*	
Cisplatin	1 *(0.2)*	0 *(0.0)*	1 *(0.5)*	
Other regiment	10 *(2.3)*	5 *(2.5)*	5 *(2.5)*	
Number of resections (IQR)	4 (3–6)	4 (3–6)	4 (2–6)	0.139
Operation time, min (IQR)	383 (312–461)	378 (307–462)	390 (315–460)	0.27
Stoma post HIPEC	232 *(53.6)*	125 *(54.1)*	107 *(53.0)*	0.812
Resection status				0.590
CC-0 or CC-1	431 *(99.5)*	230 *(99.4)*	201 *(99.4)*	
≥CC-2	2 *(0.5)*	1 *(0.5)*	1 *(0.5)*	
Length of hospital stay, days (IQR)	13 (8–20)	13 (9–21)	13 (8–20)	0.770
OS, months (95% CI)	34 (30–38)	34 (28–40)	33 (28–38)	0.819
DFS, months (95% CI)	13 (11–15)	15 (11–19)	11 (10–12)	**<0.001**

Table 2 | Comparison of major postoperative complications between patients with synchronous versus metachronous peritoneal metastases who underwent CRS+HIPEC.

	Synchronous colorectal PM n = 231	**Metachronous colorectal PM n = 202**	*P value*
SAE score, n (%)			0.693
1–2	70 *(30.3)*	56 *(27.7)*	
≥3	62 *(26.8)*	60 *(29.7)*	
Reoperation, n (%)	35 *(15.2)*	30 *(14.9)*	0.931
Hospital mortality, n (%)	3 *(1.3)*	4 *(2.0)*	0.575
Grade ≥3 complications, n (%)			
Anastomotic leakage	15 *(6.5)*	16 *(7.9)*	0.589
Postoperative bleeding	3 *(1.3)*	2 *(1.0)*	0.714
Intra-abdominal abscess	28 *(12.1)*	32 *(15.8)*	0.379
Wound infection	5 *(2.2)*	3 *(1.5)*	0.468
Urinary tract infection	1 *(0.4)*	2 *(1.0)*	0.361
Pneumonia	3 *(1.3)*	4 *(2.0)*	0.549
Other infection	3 *(1.3)*	8 *(4.0)*	0.735
Ileus	6 *(2.6)*	4 *(2.0)*	0.630
Gastroparesis	5 *(2.2)*	6 *(3.0)*	0.650
Electrolyte disorder	0 *(0.0)*	1 *(0.5)*	0.636
Anaemia	0 *(0.0)*	0 *(0.0)*	1.00
Fistula formation	2 *(0.9)*	2 *(1.0)*	0.660
Wound dehiscence	10 *(4.3)*	7 *(3.5)*	0.650
Urinoma	4 *(1.7)*	1 *(0.5)*	0.286
Pulmonary embolism	1 *(0.4)*	0 *(0.0)*	0.338
Cardiac disease	5 *(2.1)*	3 *(1.5)*	0.368

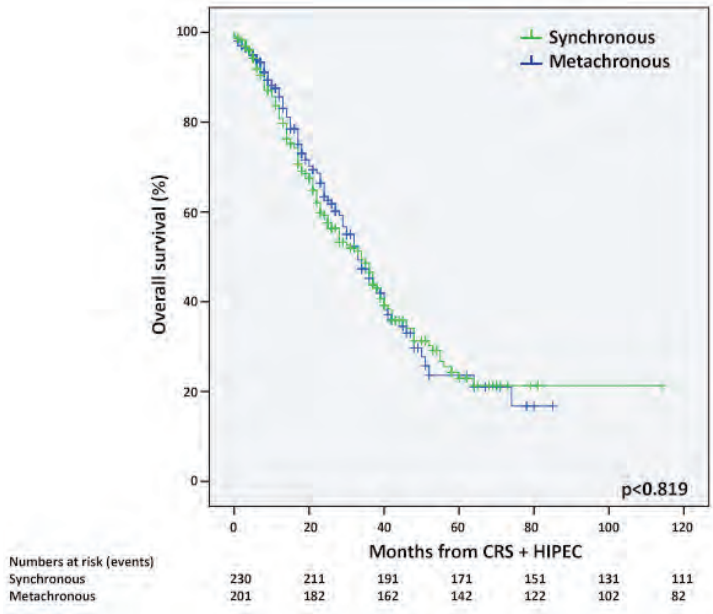

Figure 2 | Overall survival of patients with synchronous versus metachronous colorectal peritoneal metastases who underwent CRS+HIPEC.

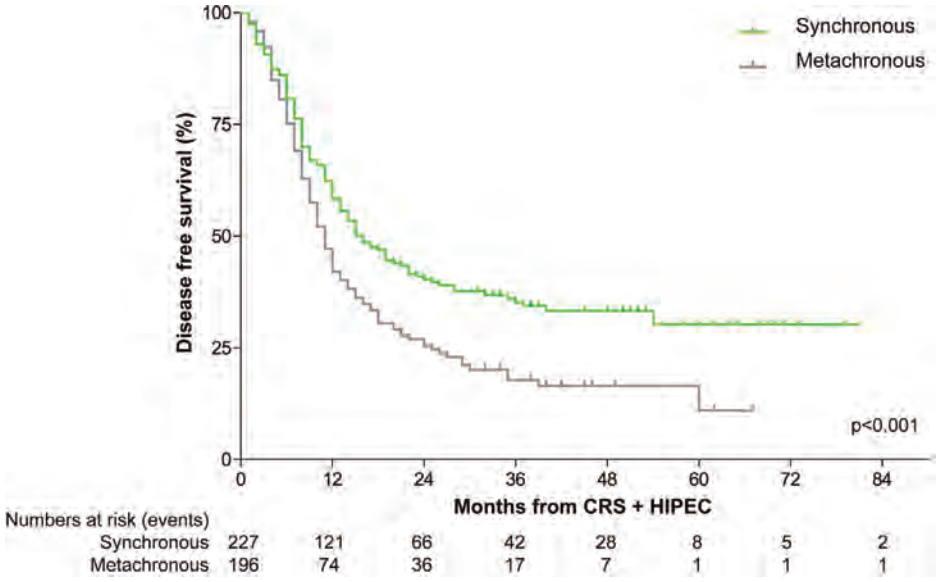

Figure 3 | Disease-free survival of patients with synchronous versus metachronous colorectal peritoneal metastases who underwent CRS+HIPEC.

The OS and DFS for all 433 patients according to the PCI score are shown in **Figure 4A** and **B**. The PCI scores were categorised into five different subgroups. A lower PCI score at the time of exploratory laparotomy was associated with a better OS and DFS ($p < 0.001$).

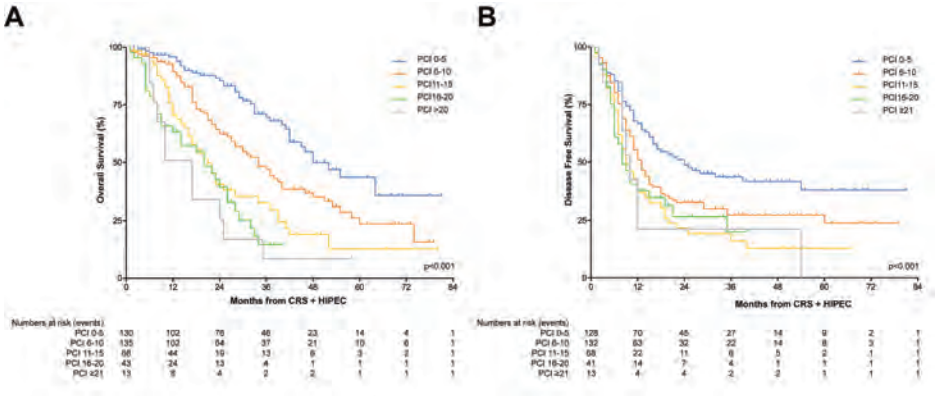

Figure 4 | Kaplan–Meier survival curves for all 433 patients according to peritoneal cancer index (PCI) score.

A. Overall survival (OS). B. Disease–free survival (DFS)

Table 3 | Univariable and multivariable comparison of disease−free survival between patients with synchronous versus metachronous colorectal peritoneal metastases after CRS+HIPEC.

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	*P value*	**HR**	**95% CI**	*P value*
Onset of colorectal PM						
Synchronous	1.00	-	-	1.00	-	-
Metachronous	1.51	1.19–1.93	**0.001**	1.63	1.18–2.26	**<0.01**
Age	0.99	0.98–1.00	0.20			
Sex						
Female	1.00	-	-			
Male	1.01	0.79–1.28	0.95			
Primary tumour						
Rectum	1.00	-	-	1.00	-	-
Right colon	0.95	0.65–1.93	0.79	1.00	0.66–1.52	0.99
Transverse colon	0.76	0.44–1.32	0.34	0.75	0.41–1.38	0.35
Left colon	1.05	0.63–1.73	0.86	1.5	0.66–2.00	0.63
Sigmoid	0.91	0.62–1.33	0.62	0.81	0.53–1.23	0.32
Signet ring cell histology						
No	1.00	-	-	1.00	-	-
Yes	1.23	0.79–1.90	0.36	1.18	0.70–1.99	0.53
PCI score during CRS+HIPEC						
0–5	1.00	-	-	1.00	-	-
6–10	1.47	1.07–2.04	**0.02**	1.33	0.96–1.88	0.09
11–15	2.06	1.42–2.99	**<0.001**	2.05	1.38–3.07	**<0.001**
16–20	1.99	1.27–3.11	**<0.01**	1.94	1.22–3.09	**<0.01**
>20	2.00	0.99–4.02	0.05	2.28	1.10–4.71	**0.03**
CC−score						
CC−0 or CC−1	1.00	-	-			
CC ≥2	3.84	0.54–27.58	0.18			
Prior chemotherapy						
No	1.00	-	-	1.00	-	-
Yes	1.41	1.10–1.81	**<0.01**	1.07	0.78–1.47	0.67
Neoadjuvant chemotherapy (CRS+HIPEC)						
No	1.00	-	-			
Yes	0.99	0.74–1.32	0.93			
Adjuvant chemotherapy (CRS+HIPEC)						
No	1.00	-	-	1.00	-	-
Yes	0.63	0.54–0.81	**<0.001**	0.72	0.54–0.97	**0.03**
Neoadjuvant biological therapy (CRS+HIPEC)						
No	1.00	-	-			
Yes	1.20	0.76–1.89	0.44			

Additional analyses of patients with metachronous colorectal PM

The patients with metachronous colorectal PM had a significantly shorter DFS than the patients with synchronous colorectal after CRS+HIPEC, without a difference in OS. Further analyses were deemed necessary to find an explanation for this difference, and to identify which specific metachronous colorectal PM patient is at risk for a decreased DFS after CRS+HIPEC.

The group of patients with metachronous colorectal PM in our cohort appeared to be very heterogeneous. We performed a subanalysis, comparing metachronous cancer patients with early (<1 year) and late (≥1 year) recurrences after CRS+HIPEC (**Supplementary Table 1**). The mean OS was significantly shorter for the early recurrence group (19 months; 95% CI 16−21 months) than for the patients who had a late recurrence (30 months; 95% CI 26−35 months; $p < 0.001$). At baseline, the patients who had metachronous colorectal PM with early recurrence differed significantly from the patients with late recurrence. The patients with an early recurrence had a shorter period between primary surgery and onset of metachronous colorectal PM ($p = 0.017$), a higher PCI score ($p < 0.001$), a longer surgery (422 vs 352 minutes; $p < 0.001$), and more blood loss (800 vs 600 ml; $p = 0.008$) during CRS+HIPEC, which was accompanied by more major postoperative complications (31.2 vs 24.4%; $p = 0.005$) and a longer hospital stay (14 vs 11 days; $p = 0.002$) (**Supplementary Table 1**). We adjusted for these potential cofounders in the multivariate regression analyses.

The PCI score had a significant impact on OS and DFS for all 433 patients. We performed additional analyses to identify a possible cut−off point for the PCI score of the patients with metachronous colorectal PM for performing CRS+HIPEC regarding OS and DFS. The PCI scores of the 202 patients with metachronous colorectal PM were divided into the following five different subgroups: PCI of 0−5 , PCI of 6−10, PCI of 11−15, PCI of 16−20, and PCI higher than 20. The median OS in the different subgroups was respectively 46 months (95% CI 39−53 months), 34 months (95% CI 22−46 months), 20 months (95% CI 15−25 months), 22 months (95% CI 9−35 months), and 10 months (95% CI 6−14 months). The DFS in the different subgroups was respectively 17 months (95% CI 10−24 months), 11 months (95% CI 9−14 months), 9 months (95% CI 7−12 months), 8 months (95% CI 4−12 months), and 9 months (95% CI 7−11 months).

DISCUSSION

This prospective observational study that included 433 patients with colorectal PM, showed that the patients with metachronous PM had a worse median DFS than the patients with synchronous PM after CRS+HIPEC, whereas OS and surgical morbidity were similar between the two groups.

Currently, most available prognostic factors for survival after CRS+HIPEC are determined in the operating theatre. However, these factors cannot be used preoperatively during multidisciplinary HIPEC meetings when clinicians are assessing which patient will benefit from this major procedure. The impact of the time when the colorectal PM developed might be of relevance in predicting outcomes. Synchronous onset of PM might be considered as a proof of aggressive presentation. However, our finding that patients with synchronous PM have an increased DFS contradicts this theory. On the other hand, metachronous PM could be seen as a proof of the recurrent character of the disease, especially when there is little time between the first tumour and the finding of colorectal PM. However, substantial knowledge and scientific evidence of the impact on survival is lacking. Currently only three studies have reported the impact that the onset of colorectal PM has on OS.[19,31,32] The data of these three studies (319 patients) were combined in a meta−analysis, in which the pooled HR demonstrated that onset of colorectal PM has no effect on OS (HR 1.21; 95% CI 0.87−1.68]; p = 0.25), comparable with our results.[22] None of these studies reported on DFS.

In our cohort, the patients with synchronous colorectal PM more frequently received neoadjuvant and adjuvant chemotherapy around the CRS+HIPEC procedure than the patients with metachronous colorectal PM. It could be argued that this led to the difference in DFS after CRS+HIPEC between the two groups. First, an explanation for the difference in frequencies could be that most metachronous patients experience PM shortly after primary resection and adjuvant chemotherapy (data not shown). Development of PM shortly after the use of chemotherapy can cause the HIPEC surgeon to decide to perform CRS+HIPEC without using neoadjuvant chemotherapy, because the patient is already experiencing progression of peritoneal disease shortly after the use of chemotherapy. We looked at the impact of perioperative chemotherapy on DFS in our multivariate analyses. Only the use of adjuvant chemotherapy was associated with an increase in DFS, but the onset of colorectal PM (synchronous or metachronous) remained an independent risk factor for a decreased DFS. Despite the widespread use of perioperative systemic chemotherapy, no randomised studies have investigated its impact on survival

outcomes after CRS+HIPEC, leading to controversy regarding its efficacy, timing, and risks. Consequently, no worldwide consensus exists on the use and timing of perioperative chemotherapy, which varies considerably between HIPEC centers.[33] We hope that the CAIRO 6 trial, a multicentre, open−label, phases 2 and 3 randomised controlled trial (RCT), will provide some answers about the oncological efficacy of perioperative systemic therapy and CRS+HIPEC versus upfront CRS+HIPEC (control arm) for isolated resectable colorectal PM (NCT02758951).

The clinical relevance of the finding that the metachronous colorectal PM had earlier recurrences than the synchronous colorectal PM patients, without a difference in OS, raises many questions. Most metachronous colorectal PM patients undergo their primary colorectal tumour resection and experience their first recurrence several months later (e.g., colorectal PM >6 months later). Subsequently, after undergoing CRS+HIPEC, the patients in this cohort had their second recurrence' after a median of 11 months, while most were still recovering from this major surgical procedure.[34-40] Although OS between synchronous versus metachronous colorectal PM was still comparable, we suspect that the quality of life (QoL) in the months after the second recurrence for the patients with metachronous colorectal PM after CRS+HIPEC might be poor and can therefore not be compared with their synchronous counterparts who are still without a recurrence at this stage.[34,41] Qualitative data about the true impact of CRS+HIPEC on different life domains of QoL are still lacking. At this writing, we are performing semi−structured interviews with patients before and 3 months after CRS+HIPEC to identify its true impact on different life domains because we suspect it will contribute to the discussion about QoL after CRS+HIPEC.

The group of patients with metachronous colorectal PM in our cohort appeared to be very heterogeneous. Evaluating the data of our multivariate regression analysis, it seems that these patients had a tumour with variable pathogenesis (**Supplementary Table 1**). The Mean OS was significantly shorter for the early recurrence group (19 months; 95% CI 16−21 months) than for the patients who had a late recurrence (30 months; 95% CI 26−35 months; $p < 0.001$). This result is comparable with that of previous studies, which showed early recurrence after CRS+HIPEC to be associated with a decrease in OS.[1,19,21,26,42-45] These findings illustrate the difficulty of predicting early recurrence after CRS+HIPEC.

New avenues for research

In our total cohort, the average DFS was only 13 months after CRS+HIPEC, despite achievement of complete macroscopic CRS in 431 patients (99.5%). This indicates

that the outcomes of CRS+HIPEC might be further improved only if we focus on microscopic (invisible) disease. Local recurrence or colorectal PM will be caused in particular by insufficient treatment of microscopic disease and aggressive tumour biology, rather than by macroscopic visible peritoneal disease. For example, several studies have identified four molecular subtypes among patients with colorectal tumours, called the consensus molecular subtypes (CMS1 to CMS4).[46-49] In particular, CMS4 represents highly aggressive tumours, which have been associated with worse DFS and OS. Tumour biology could be an additional selection criterion for CRS+HIPEC in the future.

High recurrence rates after CRS+HIPEC also could be caused by misinterpretation of the completeness of cytoreduction by the HIPEC surgeons. Surgeons still rely on visual and tactile inspection for intraoperative differentiation between tumour and benign tissue to reach a complete cytoreduction. A clear need exists for an intraoperative imaging technique to improve tumour detection. In recent years, optical molecular imaging using tumour−targeted fluorescence tracers has emerged as a promising real−time imaging technique to improve tumour detection.[50-52] The first phase I clinical trials have been performed.[53,54] Although no conclusions can be drawn to date with regard to the impact on clinical decision−making, it appears that molecular fluorescence−guided surgery has the potential to help identify tumour tissue during DLS and to attain a more complete cytoreduction during CRS+HIPEC.

Strengths and limitations

The current study included a relatively large sample. Follow−up evaluation between the patients with synchronous and those with metachronous colorectal PM did not differ and could therefore not explain the difference in DFS. Although data were prospectively maintained, some were missing, which may have had an impact on the results of this study. The patients included in this study underwent surgery in two highly experienced and high−volume HIPEC−centres. Thus, our results might not be generalisable to other medical centres.

We should take into account that the patients with synchronous colorectal PM more frequently had signet cell histology than those with metachronous colorectal PM. Moreover, they more frequently had an N2 status and were more frequently treated with neoadjuvant and adjuvant chemotherapy. However, we adjusted for these potential cofounders in the multivariate regression analysis, and the development of metachronous colorectal PM remained a significant independent risk factor for reduced DFS.

CONCLUSIONS

Patients with metachronous colorectal PM have a worse DFS after CRS+HIPEC than patients with synchronous colorectal PM, whereas OS and surgical morbidity are similar between the two groups. Therefore, we recommend extra carefulness in the selection of patients with metachronous colorectal PM who have a PCI above 10 for CRS+HIPEC, because of the markedly worse OS and DFS in this specific group of patients. Therefore, next to other risk factors for a worse outcome, time−to−onset of colorectal PM development should be taken into consideration to optimise patient selection for this major procedure.

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SUPPLEMENTARY DATA

Supplementary Table 1 | Baseline characteristics according to early and late recurrence after CRS+HIPEC in patients with metachronous colorectal peritoneal metastases.

	Early recurrence n = 112	**Late recurrence n = 86**	*P value*
Age, y ± SD	65 ± 10	65 ± 11	0.271
Female sex, n (%)	62 *(55.4)*	46 *(53.5)*	0.826
ASA, n (%)			0.712
1	10 *(8.9)*	8 *(9.3)*	
2	92 *(82.1)*	67 *(77.9)*	
3	9 *(8.0)*	11 *(12.8)*	
4	1 *(0.9)*	0 *(0.0)*	
Smoking, n (%)	21 *(18.8)*	23 *(26.7)*	0.704
Synchronous liver metastases, n (%)	11 *(9.8)*	6 *(7.0)*	0.139
Interval primary surgery to PM, months ±SD	17 ± 15	18 ± 29	**0.017**
Neoadjuvant chemotherapy, n (%)	14 *(12.5)*	14 *(16.3)*	0.104
Adjuvant chemotherapy, n (%)	19 *(17.0)*	22 *(25.6)*	0.129
T4 primary tumour, n (%)	47 *(42.0)*	48 *(55.8)*	0.059
Perforated primary tumour, n (%)	3 *(2.7)*	6 *(7.0)*	0.156
PCI at HIPEC, n (%)			
0-5	28 *(25.0)*	40 *(46.1)*	**<0.001**
6-10	36 *(32.1)*	28 *(32.6)*	
11-15	22 *(19.6)*	7 *(8.1)*	**<0.001**
16-20	11 *(11.6)*	4 *(4.7)*	
>21	4 *(3.6)*	2 *(2.3)*	
Unknown	9 (8.0)	5 *(5.8)*	
Operation time, min ± SD	422 ± 106	352 ± 125	
Blood loss, ml ± SD	800 ± 1038	600 ± 1139	**0.008**
Stoma post−HIPEC, n (%)	62 *(55.4)*	43 *(50.0)*	0.741
Resection status, n (%)			0.950
CC−0 or CC−1	112 *(100)*	86 *(100)*	
≥CC−2	0 *(0.0)*	0 *(0.0)*	
Length of hospital stay, days ± SD	14 ± 15	11 ± 16	**0.002**
SAE score, n (%)			**0.005**
1−2	37 *(33.1)*	19 *(22.1)*	
≥3	35 *(31.2)*	21 *(24.4)*	
Re−operation, n (%)	18 *(16.1)*	11 *(12.8)*	0.092
OS, months (95% CI)	19 (16−21)	30 (26−35)	**<0.001**

3

Safety and visibility of laparoscopic evaluation in patients with suspicion of colorectal peritoneal metastases

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ABSTRACT

Background

The aim of the present study was to determine the feasibility and safety of performing diagnostic laparoscopy (DLS) routinely in patients with suspicion of colorectal peritoneal metastases (PM) to evaluate suitability for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC).

Methods

Data for consecutive patients who underwent DLS between 2012 and 2018 were extracted retrospectively from an institutional database. The primary outcome was the degree of visibility of the abdominal cavity during DLS. Good laparoscopic evaluation of the abdominal cavity was defined as visibility of at least the regions of the diaphragm, pelvis and small bowel. Secondary outcomes were reasons for perioperative exclusion for CRS+HIPEC, major postoperative complications (Clavien–Dindo grade III or above) and difference in overall survival (OS) between patients deemed suitable or non-suitable for CRS+HIPEC. Kaplan–Meier analyses were performed.

Results

Some 184 patients were analysed. Good laparoscopic evaluation was possible in 138 patients (75.0%), and 24 (13%) had conversion to an open procedure. Ninety-three patients (50.5%) were excluded for CRS+HIPEC, most commonly because of absence of colorectal PM (34 patients, 37%) or extensive disease (peritoneal cancer index 20 or above)(33 patients, 35%). Major complications occurred in five patients (2.7%), with no postoperative deaths. Median OS was significantly decreased in patients who were excluded due to extensive disease (14 months; 95% CI 10–18 months) compared with patients suitable for CRS+HIPEC (35 months; 95% Cl 30–40 months; $p < 0.001$).

Conclusion

Routinely performing DLS in patients with suspicion of colorectal PM to evaluate suitability for CRS+HIPEC is feasible and safe, avoiding the morbidity of an unnecessary laparotomy in patients with extensive disease.

INTRODUCTION

Patients with resectable peritoneal metastases (PM) from colorectal cancer can be treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC).[1-4] This abdominal procedure begins with surgical removal of all visible tumour tissue followed by perfusion of the peritoneal cavity with heated chemotherapy to eliminate remaining microscopic disease.[5] The most powerful prognostic factors for survival after CRS+HIPEC are the extent of peritoneal disease (measured with the peritoneal cancer index [PCI]) and completeness of the performed cytoreduction (measured with the completeness of cytoreduction score [CC]).[2,6-8] CRS+HIPEC can be performed with curative intent only in patients with colorectal PM with a PCI of less than 20 in whom a (nearly) complete cytoreduction can be achieved (for example CC−0, no visible residual disease, or CC−1, residual tumour deposits smaller than 2.5 mm).[3,7,9-11]

Current preoperative imaging modalities fail to estimate the PCI in order to predict the possibility of achieving a complete cytoreduction.[12-14] Direct visualization of the abdominal cavity and its contents, such as the small bowel, seems to be the only reliable method to assess PCI and tumour resectability. Up to 50% of patients with colorectal PM are excluded for CRS+HIPEC directly on exploratory laparotomy.[15-17] Identification at an earlier stage in patients for whom CRS+HIPEC is not suitable could spare them the morbidity of an unnecessary laparotomy.

Direct visualisation can also be achieved with diagnostic laparoscopy (DLS), to evaluate the presence and resectability of colorectal PM. Some argue that adhesions from the cancer or previous abdominal surgery impede optimal visualisation during DLS, which could result in an underestimation of the PCI and an increased rate of intraoperative and postoperative complications. In contrast, seven retrospective studies concluded that DLS is a safe, feasible, and accurate staging tool for assessing tumour burden in patients with PM.[15-21] Therefore, several institutions worldwide perform DLS routinely in patients with PM to investigate their presence and resectability. However, current publications on this subject have involved small series of patients with PM from a variety of primary tumour types and, most importantly, DLS was used in a mostly selective way and not incorporated into a standard preoperative workup for CRS+HIPEC.

The aim of the present study was to determine the feasibility and safety of performing DLS routinely in all patients with suspicion of colorectal PM to evaluate suitability for CRS+HIPEC, and to investigate reasons for perioperative exclusion for CRS+HIPEC.

METHODS

Design, setting, and patients

Data for all consecutive patients with suspicion of colorectal PM, based on recent imaging or a surgical procedure, who had DLS to examine the presence and extent of peritoneal disease between January 2012 and August 2018 were extracted retrospectively from a prospectively maintained institutional database. The study was approved by the Institutional Ethics Committee of the University Medical Center Groningen (METc 201800395).

Preoperative evaluation and staging

All patients had a standard preoperative assessment to confirm the presence of colorectal PM and to evaluate eligibility for CRS+HIPEC. All were staged by thoracic, abdominal, and pelvic computed tomography (CT). Patients with suspicion of colorectal PM who might be a candidate for CRS+HIPEC routinely underwent DLS to confirm the diagnosis of colorectal PM and to evaluate resectability of the metastases.

A multidisciplinary team consisting of a radiologist, gastroenterologist, medical oncologist, and oncological surgeons then determined eligibility for CRS+HIPEC according to the preoperative assessment. Contraindications to CRS+HIPEC included: moderate or severe co−morbidity (American Society of Anaesthesiologists [ASA] score above 3); extra−abdominal metastases; massive disease involvement of the small bowel or its mesentery; extensive peritoneal disease (PCI 20 or above); unresectable primary tumour; invasive growth into the retroperitoneal space; and Eastern Cooperative Oncology Group performance status (ECOG) greater than 2. Patients with no colorectal PM during DLS were also excluded from CRS+HIPEC.

Laparoscopic evaluation

Under general anaesthesia, a pneumoperitoneum was established by using an optical trocar. The site of first port placement during DLS was based on imaging and clinical findings of the patient. The 30º laparoscope was introduced through an umbilical port. One or two additional operative trocars were positioned on the left and right side of the optical trocar under direct vision. Adhesiolysis was performed minimally. All visible areas of the peritoneal cavity were reviewed systematically. In all patients the laparoscopic PCI and possibility of performing a complete cytoreduction were determined and recorded in the operation report. Cytology samples and biopsies were taken as indicated. When the tumour size was

unacceptably large or there was unresectable disease at DLS, palliative surgery was performed at the surgeon's discretion. The main reasons for perioperative exclusion in patients deemed unsuitable for CRS+HIPEC were noted in the medical record.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

Each CRS+HIPEC procedure was started with an exploratory laparotomy. CRS was performed only when the colorectal PM were deemed to be completely resectable, whereas HIPEC was performed only when there was complete or nearly complete cytoreduction. CRS+HIPEC was performed according to the standardised Dutch HIPEC protocol.[22] The CC score was classified at the end of the cytoreduction: CC−0, no residual tumour visible or palpable in the peritoneal cavity; CC−1, residual tumour deposits small than 2.5 mm; CC−2, residual tumour between 2.5 mm and 2.5 cm; and CC−3, residual tumour larger than 2.5 cm or a confluence of nodules.[23] After cytoreduction, HIPEC was performed in patients with CC−0 (complete) or CC−1 (nearly complete) cytoreduction according to the open Coliseum technique with mitomycin C (35 kg/m^2) for 90 minutes at 40−41 ºC.

Follow−up

Physical examination and carcinoembryonic antigen (CEA) measurements were performed on a 3−monthly basis for at least 4 years. When disease recurrence was suspected (for example, clinical symptoms or increase in CEA level), CT of thorax and abdomen was performed, with tissue biopsies in selected patients.

Data collection

Data on patient characteristics, tumour characteristics, operative details, postoperative morbidity and mortality, and overall survival (OS) were collected prospectively. Data on perioperative reasons for exclusion for CRS+HIPEC were obtained retrospectively by reviewing the digital medical records.

Primary and secondary outcomes

The primary outcome was the degree of visibility of the abdominal cavity during DLS: grade I, visibility of two or fewer abdominopelvic regions; grade II, visibility of three to eight abdominopelvic regions; grade III, visibility of at least the diaphragm, pelvis and small bowel regions; or grade IV, visibility of all 13 abdominopelvic regions. Grade III or IV was deemed necessary for adequate judgement of the extent of disease, and therefore defined as a good laparoscopic evaluation of the abdominal cavity. Secondary outcomes were the proportion of patients excluded for CRS+HIPEC, perioperative reasons for exclusion for CRS+HIPEC, major postoperative

complications, and OS in suitable and unsuitable patients. Major postoperative complications were defined as grade III or above according to the Clavien–Dindo classification system.[24] OS was defined as the time between DLS and death, or date of last follow–up in censored cases.

Statistical analyses

All statistical analyses were conducted using SPSS Statistics version 24.0 (IBM Corporation, Armonk, NY, USA). Continuous values with a normal distribution are given as mean ± standard deviation (SD) and those without a normal distribution as median (interquartile range [IQR]). Categorical variables are reported as numbers with percentages. Patient and tumour characteristics were compared and analysed using the χ^2 test. The Kruskal–Wallis *H* test was used for continuous variables. Kaplan–Meier survival analyses were performed to describe OS for the different groups of patients. All test were performed two–sided and $p < 0.050$ was considered statistically significant.

RESULTS

Baseline characteristics

Data for all 184 patients with suspicion of colorectal PM who had undergone DLS between January 2012 and August 2018 were analysed. During DLS, 91 patients (49.5%) were deemed suitable for CRS+HIPEC, and 93 patients (50.5%) were rejected for the procedure. The group of 93 patients deemed unsuitable for CRS+HIPEC was very heterogeneous, and for further analyses was subdivided into the following categories: no indication for CRS+HIPEC because of absence of colorectal PM (29 patients); signs of extensive disease (54 patients); and other reasons for perioperative exclusion (10 patients).

Table 1 provides an overview of patient and tumour characteristics for the entire cohort, and a comparison of these characteristics between patients suitable for CRS+HIPEC and patients who were unsuitable. Patients who were unsuitable for CRS+HIPEC owing to signs of extensive disease presented more frequently with signet ring cell histology compared with those who were suitable for CRS+HIPEC (20.4 vs 8.8%, respectively; $p < 0.001$). Patients with no indication for CRS+HIPEC were less likely to have an N2 status than those who were suitable for CRS+HIPEC (11 vs 40%, respectively; $p = 0.034$). The median age of patients who were unsuitable for CRS+HIPEC for other reasons was greater than that of patients who were suitable for CRS+HIPEC (74 vs 65 years, respectively; $p = 0.021$). Other baseline characteristics were similar between the four groups of patients.

Table 1 | Baseline characteristics according to suitability for CRS+HIPEC.

	Total n = 184	Suitable for CRS+HIPEC n = 91	No CRS+HIPEC indication n = 29	Unsuitable for CRS+HIPEC due to extensive disease n = 54	Unsuitable for CRS+HIPEC due to other reasons n = 10	*P value* †
Age, years, median [IQR]	65 [58–70]	65 [54–69]	64 [56–71]	67 [60–70]	74 [63–76]	**0.021‡**
Gender, female, n (%)	83 *(45.1)*	45 *(49.5)*	12 *(41.4)*	20 *(37.0)*	6 *(60.0)*	0.368
BMI, kg/m², median [IQR]	26.3 [24.1–29.0]	26.5 [24.3–30.4]	27.2 [25.4–28.3]	26.2 [23.5–28.6]	25.9 [23.6–31.3]	0.811‡
ASA, n (%)						0.079
1	22 *(12.0)*	10 *(11.0)*	4 *(13.8)*	7 *(13.0)*	1 *(10.0)*	
2	139 *(75.5)*	72 *(79.1)*	22 *(75.9)*	41 *(75.9)*	4 *(40.0)*	
3	23 *(12.5)*	9 *(9.9)*	3 *(10.3)*	6 *(11.1)*	5 *(50.0)*	
Co−morbidity, n (%)						
Diabetes	19 *(10.3)*	8 *(8.8)*	2 *(6.9)*	9 *(16.7)*	0 *(0.0)*	0.238
Cardiovascular disease	28 *(15.2)*	12 *(13.2)*	4 *(13.7)*	9 *(16.7)*	3 *(30.0)*	0.336
Pulmonary disease	19 *(10.3)*	9 *(9.9)*	5 *(17.2)*	4 *(7.4)*	1 *(10.0)*	0.536
Previous surgery for colorectal cancer, n (%)	142 *(77.2)*	84 *(92.3)*	23 *(79.3)*	27 *(50.0)*	8 *(80.0)*	
Primary tumour, n (%)						0.557
Appendix	9 *(4.9)*	7 *(7.7)*	1 *(3.4)*	1 *(1.9)*	0 *(0.0)*	
Right colon	68 *(37.0)*	27 *(29.7)*	10 *(34.5)*	27 *(50.0)*	4 *(40.0)*	
Transverse colon	10 *(5.4)*	6 *(6.6)*	0 *(0.0)*	3 *(5.6)*	1 *(10.0)*	
Left colon	16 *(8.7)*	14 *(15.4)*	1 *(3.4)*	0 *(0.0)*	1 *(10.0)*	
Sigmoid	53 *(28.8)*	26 *(28.6)*	10 *(34.5)*	14 *(25.9)*	3 *(30.0)*	
Rectum	23 *(12.5)*	11 *(12.1)*	5 *(17.2)*	7 *(13.0)*	0 *(0.0)*	
Rectosigmoid	5 *(2.7)*	0 *(0.0)*	2 *(6.9)*	2 *(3.7)*	1 *(10.0)*	
Signet cell histology, n (%)	19 *(10.3)*	8 *(8.8)*	0 *(0.0)*	11 *(20.4)*	0 *(0.0)*	**<0.001**
T category of primary tumour, n (%)						0.400
≤ 3	70 *(45.5)*	38 *(45.8)*	12 *(44.4)*	14 *(40.0)*	6 *(66.7)*	
4	84 *(54.5)*	45 *(54.2)*	15 *(55.6)*	21 *(60.0)*	3 *(33.3)*	

Table 1 | Continued.

	Total n = 184	Suitable for CRS+HIPEC n = 91	No CRS+HIPEC indication n = 29	Unsuitable for CRS+HIPEC due to extensive disease n = 54	Unsuitable for CRS+HIPEC due to other reasons n = 10	*P value* †
N category of primary tumour, n (%)						**<0.001**
0	48 *(31.8)*	24 *(28.9)*	14 *(51.9)*	7 *(21.9)*	3 *(33.3)*	**0.006**
1	46 *(30.5)*	26 *(31.3)*	10 *(37.0)*	9 *(28.1)*	1 *(11.1)*	0.157
2	57 *(37.7)*	33 *(39.8)*	3 *(11.1)*	16 *(50.0)*	5 *(55.6)*	**0.034**
Preoperative imaging, n (%)						
CT	171 *(94.5)*	79 *(88.8)*	29 *(100)*	54 *(100)*	9 *(90.0)*	**0.035**
MRI	33 (17.9)	13 *(14.3)*	7 *(24.1)*	11 *(20.4)*	2 *(20.0)*	0.501
PET	72 (39.1)	35 *(38.5)*	15 *(51.7)*	19 *(35.2)*	3 *(30.0)*	**0.030**
Onset of suspicion of colorectal PM, n (%)						0.143
Synchronous	99 *(54.1)*	41 *(45.6)*	15 *(51.7)*	38 *(70.4)*	5 *(50.0)*	
Metachronous	84 *(45.9)*	49 *(54.4)*	14 *(48.3)*	16 *(29.6)*	5 *(50.0)*	
Suspicion of colorectal PM based on, n (%)						0.796
Preoperative imaging	128 *(69.6)*	53 *(58.2)*	24 *(82.8)*	43 *(79.6)*	8 *(80.0)*	
Recent surgical procedure	25 *(13.6)*	17 *(18.7)*	2 *(6.9)*	5 *(9.3)*	1 *(10.0)*	
Perforated tumour	2 *(1.1)*	1 *(1.1)*	1 *(3.4)*	0 *(0.0)*	0 *(0.0)*	
Preoperative imaging + surgical procedure	26 *(14.3)*	17 *(18.7)*	2 *(6.9)*	6 *(11.1)*	1 *(10.0)*	
Preoperative imaging + perforated tumour	1 *(0.55)*	1 *(1.1)*	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*	
Liver metastases, n (%)	21 *(11.4)*	10 *(11.0)*	1 *(3.4)*	9 *(16.7)*	1 *(10.0)*	0.344
Lung metastases, n (%)	5 *(2.7)*	1 *(1.1)*	0 *(0.0)*	4 *(7.4)*	0 *(0.0)*	0.090

† $\chi 2$ test, except ‡ Kruskal–Wallis *H* test.

Perioperative reasons for exclusion for CRS+HIPEC

Table 2 presents an overview of the reasons for perioperative exclusion of the 93 patients (50.5%) deemed unsuitable for CRS+HIPEC. The reasons can be divided into five categories: absence of colorectal PM; signs of extensive disease; patient characteristics; severe complications after DLS; and tumour biology. In the majority of the patients (65%) only one reason resulted in exclusion for CRS+HIPEC, whereas for fewer patients two (28%) or three reasons (8%) reasons led to the exclusion. The most common perioperative reasons for exclusion for CRS+HIPEC were: absence of colorectal PM in 34 patients (37%) and extensive peritoneal disease (PCI 20 or above) in 33 patients (35%). Other signs of extensive disease (widespread colorectal PM in the small bowel, unresectable primary tumour, liver or lung metastases, or an indication for neoadjuvant chemotherapy) were present in 35 patients (38%). Patient characteristics were less frequently the perioperative reason for exclusion for CRS+HIPEC: age in three patients (3%), poor patient condition in three patients (3%), and presence of severe co−morbidity in five patients (5%).

Table 2 | Reasons for perioperative exclusion for CRS+HIPEC during diagnostic laparoscopy.

Criteria	No. of patients (n = 93)
No. of reasons reported, n (%)	
1	60 *(65)*
2	26 *(28)*
3	7 *(8)*
No signs of colorectal PM, n (%)	34 *(37)*
Signs of extensive disease, n (%)	
PCI >20	33 *(35)*
Probably PCI too high during open procedure*	6 *(6)*
Widespread colorectal PM in bowel/mesentery	7 *(8)*
Rapid progression of disease	7 *(8)*
Indication for neoadjuvant therapy	5 *(5)*
Liver metastases	4 *(4)*
Lung metastases	5 *(5)*
Unresectable primary tumour	1 *(1)*
Patient characteristics, n (%)	
Patient preference	7 *(8)*
Co−morbidity	5 *(5)*
Patient condition	3 *(3)*
Patient age	3 *(3)*
Severe complications after DLS, n (%)	3 *(3)*
Tumour biology (signet cell histology), n (%)	2 *(2)*

* Peritoneal cancer index (PCI) during diagnostic laparoscopy (DLS) below 20, but estimated as above 20 during exploratory laparotomy.

Visibility of abdominal cavity during diagnostic laparoscopy

Grade III or IV visibility of the abdominal cavity was possible in 138 of the 184 patients (75.0%) (**Table 3**). In 24 patients (13.0%) DLS was converted to an open procedure because of an inadequate laparoscopic overview. Grade of visibility of the abdominal cavity during DLS was not significantly different between patients who were suitable and those who were unsuitable for CRS+HIPEC due to absence of colorectal PM or extensive disease (p = 0.807). In the small group of patients who were unsuitable for CRS+HIPEC for other reasons, the grade of visibility of the abdominal cavity was poor overall (7 of 10 patients, 70%; p = 0.008).

Surgical morbidity and mortality

Table 3 presents postoperative morbidity rates after DLS, by type and severity according to the Clavien−Dindo classification system.[24] Major postoperative complications occurred in five patients (2.7%), who were all deemed not suitable for CRS+HIPEC. Three patients (1.6%) with symptoms of preoperative obstruction received direct palliative surgery during DLS without any subsequent clinical improvement. In one morbidly obese patient, a widespread haematoma of the abdominal wall was infected after DLS and required surgical evacuation at three different time points. In the fifth patient, myocardial infarction was diagnosed immediately after DLS. Following percutaneous coronary intervention, the patient recovered successfully within 7 days.

Treatment strategies after diagnostic laparoscopy

The different treatments that patients received after DLS are presented in **Tables 4** and **5** according to suitability for CRS+HIPEC. Only 75 of the 91 patients (82%) deemed suitable for CRS+HIPEC eventually underwent the full procedure. The remaining 16 patients (18%) had an open−close procedure after exploratory laparotomy (non−therapeutic laparotomy), due to a high PCI (9 patients), excessive involvement of the small bowel (2 patients), unresectable primary tumour (4 patients) or liver metastases (1 patient). In retrospect, good or excellent laparoscopic evaluation of the abdominal cavity during DLS had been possible in 12 of these 16 patients. In the remaining four patients it was not possible to investigate all abdominopelvic regions but it was estimated that the PCI would probably be below 20.

In patients deemed unsuitable for CRS+HIPEC, treatment strategy depended on the perioperative reason(s) for exclusion (**Table 5**). Fourteen of the 29 patients (48%) who had a primary tumour *in situ* with no colorectal PM had surgery with curative intent. Most patients with no primary tumour *in situ* did not receive any additional

treatment (7 patients, 24%). During a median follow−up of 16 months (95% CI 14−28 months), four of these 29 patients (14%) developed additional colorectal PM, diagnosed in only two patients (7%) within 6 months after DLS.

In the 54 patients unsuitable for CRS+HIPEC with signs of extensive disease, palliative treatment strategies consisted of comfort care (24%), palliative chemotherapy (37%), radiotherapy (4%) or a combination of treatments (17%).The majority of patients who were unsuitable for CRS+HIPEC for other reasons received only comfort care (40%).

Table 3 | Morbidity and visibility of diagnostic laparoscopy according to suitability for CRS+HIPEC.

	Total n = 184	**Suitable for CRS+HIPEC n = 91**	**No CRS+HIPEC indication n = 29**	**Unsuitable for CRS+HIPEC due to extensive disease n = 54**	**Unsuitable for CRS+HIPEC due to other reasons n = 10**	*P value* †
Interval from primary surgery to DLS, months, median [IQR]	11 [2–23]	12 [2–23]	6 [6–33]	6 [1–20]	11 [2–25]	0.397‡
Interval from suspicion of PM to DLS, months, median [IQR]	1 [0–2]	1 [0–2]	1 [0–2]	1 [0–2]	1 [0–3]	0.158‡
Grade of visibility, n (%)						**0.008**
I (very poor)	25 *(13.6)*	13 *(14.3)*	5 *(17.2)*	4 *(7.7)*	3 *(30.0)*	0.220
II (poor)	17 *(9.2)*	6 *(6.6)*	4 *(13.8)*	3 *(5.8)*	4 *(40.0)*	**0.003**
III (good)	23 *(12.5)*	11 *(12.1)*	2 *(6.9)*	9 *(17.3)*	1 *(10.0)*	0.623
IV (excellent)	115 *(62.5)*	59 *(64.8)*	18 *(62.1)*	36 *(69.2)*	2 *(20.0)*	**0.040**
Conversion rate, n (%)	24 *(13.0)*	15 *(16.5)*	3 *(10.3)*	5 *(9.3)*	1 *(10.0)*	0.398
PCI at DLS, n (%)						**<0.001**
0–5	84 *(51.2)*	43 *(55.1)*	28 *(100)*	10 *(19.6)*	3 *(60.0)*	**<0.001**
6–10	23 *(14.2)*	19 *(24.4)*	0 *(0.0)*	3 *(5.9)*	1 *(20.0)*	**0.006**
11–15	11 *(6.0)*	9 *(11.5)*	0 *(0.0)*	1 *(2.0)*	1 *(20.0)*	0.100
16–20	14 *(8.6)*	7 *(9.0)*	0 *(0.0)*	7 *(13.7)*	0 *(0.0)*	0.144
21–25	13 *(8.0)*	0 *(0.0)*	0 *(0.0)*	13 *(25.5)*	0 *(0.0)*	**<0.001**
>25	17 *(10.5)*	0 *(0.0)*	0 *(0.0)*	17 *(33.3)*	0 *(0.0)*	**<0.001**
Length of hospital stay, days, median [IQR]	2 [1–4]	2 [2–3]	3 [1–5]	2 [1–4]	2 [1–14]	0.839‡

Table 3 | Continued.

	Total n = 184	Suitable for CRS+HIPEC n = 91	No CRS+HIPEC indication n = 29	Unsuitable for CRS+HIPEC due to extensive disease n = 54	Unsuitable for CRS+HIPEC due to other reasons n = 10	*P value* †
Clavien–Dindo complication rate, n (%)	17 *(9.2)*	4 *(4.4)*	4 *(13.8)*	6 *(11.1)*	3 *(30.0)*	**0.027**
I	3 *(1.6)*	0 *(0.0)*	1 *(3.4)*	2 *(3.7)*	0 *(0.0)*	0.293
II	7 *(3.8)*	4 *(4.4)*	0 *(0.0)*	2 *(3.7)*	1 *(10.0)*	0.516
III	7 *(3.8)*	0 *(0.0)*	3 *(10.3)*	2 *(3.7)*	2 *(20.0)*	**0.030**
Complication, n (%)						**0.040**
Ileus	4 *(2.2)*	0 *(0.0)*	0 *(0.0)*	3 *(5.6)*	1 *(10.0)*	**0.038**
Wound infection	3 *(1.6)*	1 *(1.1)*	1 *(3.4)*	0 *(0.0)*	1 *(10.0)*	0.211
Gastroparesis	1 *(0.5)*	0 *(0.0)*	0 *(0.0)*	1 *(1.9)*	0 *(0.0)*	0.490
Bowel perforation	1 *(0.5)*	0 *(0.0)*	1 *(3.4)*	0 *(0.0)*	0 *(0.0)*	0.146
Intra-abdominal abscess	1 *(0.5)*	1 *(1.1)*	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*	0.795
Urinary tract infection	1 *(0.5)*	1 *(1.1)*	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*	0.795
Pneumonia	1 *(0.5)*	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*	1 *(10.0)*	**0.001**
Myocardial infarction	1 *(0.5)*	0 *(0.0)*	1 *(3.4)*	0 *(0.0)*	0 *(0.0)*	0.146
Decompensated liver cirrhosis	1 *(0.5)*	0 *(0.0)*	0 *(0.0)*	1 *(1.9)*	0 *(0.0)*	0.490
Electrolyte disorder	1 *(0.5)*	0 *(0.0)*	0 *(0.0)*	1 *(1.9)*	0 *(0.0)*	0.490
Bacteremia (cause unknown)	1 *(0.5)*	1 *(1.1)*	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*	0.795
Enterocutaneous fistula	1 *(0.5)*	0 *(0.0)*	1 *(3.4)*	0 *(0.0)*	0 *(0.0)*	0.146

† $\chi 2$ test, except ‡ Kruskal–Wallis *H* test.

Table 4 | Treatment received after diagnostic laparoscopy in patients deemed suitable for CRS+HIPEC.

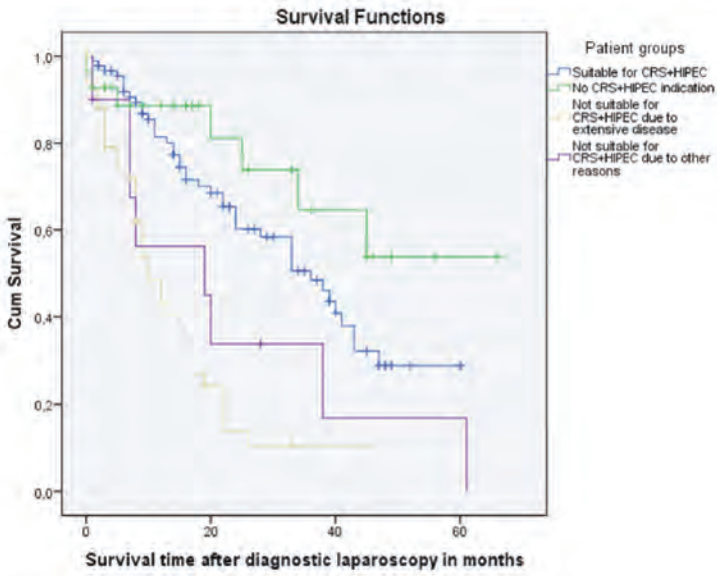
	No. of patients (n = 91)
Type of HIPEC, n (%)	
Open CRS+HIPEC	75 *(82)*
Open−close procedure	16 *(18)*
Reason for open−close procedure, n (%)	
PCI too high	9 *(56)*
Small bowel involvement	2 *(13)*
Unresectable primary tumour	4 *(25)*
Liver metastases	1 *(6)*
No. of anatomical resections, median [IQR]	4 [2-7]
PCI during CRS+HIPEC, n (%)	
0-5	16 *(20)*
6-10	22 *(28)*
11-15	19 *(24)*
16-20	12 *(15)*
21-25	7 *(9)*
>25	4 *(5)*
No. of anastomoses, n (%)	
0	36 *(40)*
1	39 *(43)*
≥ 2	16 *(18)*
Stoma after HIPEC, n (%)	40 *(44)*
Stoma type, n (%)	
Double−barrel ileostomy	2 *(5)*
Ileostomy	7 *(18)*
Double−barrel colonostomy	3 *(8)*
Colonostomy	28 *(70)*
Blood loss, mL, median [IQR]	600 [200−1188]
Duration of surgery, min, median [IQR]	471 [370−523]
CC score, n (%)	
0	74 *(81)*
1	3 *(3)*
≥ 2	14 *(15)*
Length of hospital stay, days, median [IQR]	19 [13−27]
Clavien−Dindo complication rate, n (%)	
No complications	29 *(32)*
I-II	31 *(34)*
≥ III	31 *(34)*
Reoperation, n (%)	16 *(18)*
Adjuvant chemotherapy, n (%)	26 *(29)*

Table 5 | Treatments received after diagnostic laparoscopy in patients who were deemed unsuitable for CRS+HIPEC.

	No. of patients (n = 93)
No indication for CRS+HIPEC (n = 29)	
No/palliative treatment, n (%)	7 *(24)*
Systemic chemotherapy, n (%)	3 *(10)*
Combined treatments, n (%)	5 *(17)*
Curative surgery, n (%)	14 *(48)*
Not suitable for CRS+HIPEC due to extensive disease (n = 54)	
No/palliative treatment, n (%)	13 *(24)*
Systemic chemotherapy, n (%)	20 *(37)*
Radiotherapy, n (%)	2 *(4)*
Combined treatments, n (%)	9 *(17)*
Unknown, n (%)	10 *(19)*
Not suitable for CRS+HIPEC for other reasons (n = 10)	
No/palliative treatment, n (%)	4 *(40)*
Palliative surgery, n (%)	2 *(20)*
Systemic chemotherapy, n (%)	1 *(10)*
Combined treatments, n (%)	1 *(10)*
Unknown, n (%)	2 *(20)*

Survival outcomes

Figure 1 shows the median OS after DLS between patients who were suitable for CRS+HIPEC and those who were not suitable owing to the absence of colorectal PM, signs of extensive disease, or other reasons for perioperative exclusion. Median OS for patients deemed suitable for CRS+HIPEC was 36 months (95% CI 27−45 months), and that the three subgroups of patients deemed unsuitable was 49 months (95% CI 40−60 months), 14 months (95% Cl 10−18 months) and 24 months (95% Cl 9−38 months) respectively ($p < 0.001$).



Number at risk

Suitable for CRS+HIPEC	91	46	16	2
No CRS+HIPEC indication	29	12	6	1
Extensive disease	54	7	1	0
Other reasons	10	4	1	1

Figure 1 | Kaplan–Meier survival curves according to suitability and different reasons for perioperative exclusion for CRS+HIPEC.

DISCUSSION

In this observational study of 184 consecutive patients with suspected colorectal PM, routinely performed laparoscopic evaluation of the abdominal cavity was possible in the majority of the patients, with a low risk of major postoperative morbidity. The study demonstrates that patients with extensive disease can be spared an unnecessary laparotomy.

The extent of peritoneal disease (PCI) and the possibility of achieving a complete cytoreduction are the most powerful prognostic factors for survival after CRS+HIPEC, and as current preoperative imaging modalities fail to predict PCI and complete cytoreduction, direct visualisation of the abdominal cavity appears to be the only reliable way to assess both prognostic factors. To spare patients the morbidity of a laparotomy, the presence and resectability of colorectal PM could be evaluated by DLS as part of a two–step approach. In this study, good or excellent laparoscopic evaluation of the abdominal cavity was possible in 75% of patients with suspected

colorectal PM, despite the fact that 83.7% of these patients had a history of previous abdominal surgery. Major postoperative complications occurred in only five patients (2.7%), with no postoperative deaths.

Comparison of the main results of the present study with those from the seven previously published retrospective studies on the value of DLS in the preoperative workup for CRS+HIPEC is challenging.[15-21] There are striking differences in patient populations, tumour types, definitions of a good laparoscopic evaluation of the abdominal cavity, and the indications for performing DLS or CRS+HIPEC. None of the other studies focused solely on patients with suspicion of PM of colorectal origin; three to nine primary tumour types were included per study. The number of patients with suspected colorectal PM in these studies ranged from 11 to 74. In most studies, it was not possible to subtract the data from patients with colorectal PM from the entire cohort. Only three studies made use of DLS as part of a two−step approach for CRS+HIPEC. [15,17,19] In these three studies, complete laparoscopic evaluation according to the PCI scoring system was possible in 73−86% of the patients with PM. DLS resulted in 28−57% of the patients being excluded for CRS+HIPEC. These results are in line with those of the present study. All studies used different definitions of a good laparoscopic evaluation of the abdominal cavity, and three studies gave no definition at all. Only von Breitenbuch and colleagues used a definition similar to that is used in the present study, resulting in a good laparoscopic evaluation in 88% of patients with no history of previous abdominal surgery and in 70% of those with such a history.[20] Postoperative complication rates from the seven retrospective studies ranged between 0 and 2%.[15-21] These studies included only patients without palliative surgery during DLS, and for this specific group the results of the present study are comparable.

Another important finding of the present study was the unexpectedly high rate (50.5%) of patients who were potential candidates for CRS+HIPEC according to preoperative imaging, but were eventually deemed not suitable for CRS+HIPEC during DLS. On the one hand this reflects the low validity of imaging for colorectal PM to predict the presence and extent of peritoneal disease, and on the other hand it supports the added value of DLS before CRS+HIPEC; almost half of the patients with suspicion of colorectal PM were spared unnecessary laparotomy by performing a DLS. Findings in the present study were comparable to those of the other three studies that used DLS in a standardised way.[15,17,19]

A good laparoscopic evaluation of the abdominal cavity in patients with suspicion of colorectal PM not only allows the exclusion of residual disease and prediction of the

likelihood of complete cytoreduction, thereby avoiding an unnecessary laparotomy, but also confers several other advantages. First, DLS allows tissue samples from suspicion lesions to be obtained for analysis or cytological examination. Cytological analysis is gaining in importance, as positive peritoneal cytology seems to be independently associated with a poor median OS compared with negative cytology.[24] Biopsies from suspicious lesions can confirm the presence or absence of peritoneal disease. For example, in the present study, biopsy prevented an unnecessary laparotomy in 34 patients without colorectal PM (37%). Furthermore, biopsies can provide additional information for future systemic therapy or identify a previously unknown primary tumour. Patients who are deemed unsuitable for CRS+HIPEC because of extensive disease can undergo additional systemic or palliative chemotherapy at an earlier stage than patients who are still recovering from a non−therapeutic laparotomy. In patients who seem suitable for CRS+HIPEC, DLS can provide more detailed information on the burden and location of disease before CRS+HIPEC. This can result in a better informed consent at the outpatient clinic, and may reduce patient anxiety regarding the exact extent of the procedure. Finally, it is also possible during DLS to identify patients who are not fit enough for major surgery.

The present study has some limitations owing to its retrospective design and the fact that all patients came from a single centre. It is possible that the positive results regarding the visibility of the abdominal cavity during DLS were due to extensive experience of the HIPEC surgeons in performing DLS in patients with a history of previous abdominal surgery, and may therefore not be extrapolated to all centres. No patient deemed unsuitable for CRS+HIPEC during DLS underwent an exploratory laparotomy to confirm this assumption. The authors suspect that DLS would understage rather than overstage the extent of peritoneal disease in patients with signs of extensive disease. Therefore, the assumption that a patient is deemed unsuitable for CRS+HIPEC due to extensive disease would probably not change during exploratory laparotomy. However, small peritoneal lesions might be missed during DLS, leading to a false−negative conclusion. In the present study, the likelihood of this appeared to be low, as only two of 29 patients (7%) developed colorectal PM within 6 months after a negative DLS.

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This study was registered before conducting the research in the authors' institutional research register (UTOPIA, number 201800395). The preregistration adheres to the disclosure requirements of the institutional research registry.

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4

Preventing non−therapeutic laparotomies during cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Purpose

To evaluate the introduction of diagnostic laparoscopy (DLS) in patients with colorectal peritoneal metastases (PM) to prevent non−therapeutic laparotomies during cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC).

Methods

Patients with histologically proven colorectal PM who underwent a laparotomy for potential CRS+HIPEC from January 2006 to January 2019 were retrospectively identified from a prospectively maintained database. In 2012, DLS was introduced in the preoperative workup for CRS+HIPEC in our academic centre. The rates of non−therapeutic laparotomies, major postoperative complications (Clavien−Dindo ≥III), and survival outcomes were investigated for patients who underwent a laparotomy before the introduction of DLS (cohort A) and patients who underwent a laparotomy after the introduction of DLS (cohort B). Reasons to refrain from DLS in cohort B were retrospectively explored from medical records.

Results

One hundred and seventy−two patients were included (cohort A, 48 patients [27.9%]; cohort B, 124 patients [72.1%]). A significant drop in the rate of non−therapeutic laparotomies occurred in cohort B compared to cohort A (21.0 vs 35.4%, $p = 0.044$, respectively), despite only 85 patients (68.5%) from cohort B undergoing DLS in our academic centre. The most important reason to refrain from DLS was a recently performed DLS or laparotomy in the referring hospital (48.7%). Major postoperative complications, in−hospital mortality, and survival outcomes were similar for both cohorts.

Conclusions

Performing DLS during the preoperative workup for CRS+HIPEC prevents non−therapeutic laparotomies in patients with colorectal PM. We recommend performing this laparoscopic screening in an experienced HIPEC centre.

INTRODUCTION

Worldwide, carefully selected patients with limited and resectable colorectal peritoneal metastases (PM) are treated with cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) with the aim of achieving long–term survival.[1-5] Patients with low tumour burden, as expressed by the peritoneal cancer index (PCI), and in whom a complete cytoreduction of all macroscopic visible colorectal PM can be achieved (CC–0) benefit the most from this extensive surgical procedure in terms of survival.[5-9] Therefore, CRS+HIPEC for patients with colorectal PM is restricted to those with a PCI ≤20, in whom a complete macroscopic cytoreduction can be reached.[8-11]

Today, surgical oncologists are still discovering the real extent and potential resectability of colorectal PM at the time of operative exploration, as current imaging modalities underestimate both important prognostic factors.[12-14] Unfortunately, 20–40% of these patients are excluded for CRS+HIPEC directly after exploratory laparotomy, resulting in an open–close procedure (i.e., non–therapeutic laparotomy).[15,16] For patients, this is a very undesirable postoperative outcome, as it is not only associated with a significant risk of postoperative complications and a diminished quality of life (QoL) in the short term but also delays enrolment into other therapies. From a healthcare perspective, an aborted CRS+HIPEC procedure is expensive and lead to a longer wait list.

Suggestions have been made to use diagnostic laparoscopy (DLS) in the preoperative workup for CRS+HIPEC to prevent non–therapeutic laparotomies during cytoreductive surgery in patients with colorectal PM.[17,18] Several studies show that DLS is an accurate and safe staging tool in patients with peritoneal disease.[16,18-23] However, the limitations of these studies are the variety of primary tumours that are included and the highly selected way a DLS is used. Since 2012, HIPEC surgeons from our academic centre have introduced DLS as part of the preoperative workup for CRS+HIPEC to prevent unnecessary laparotomies. This provides the opportunity to compare a historical cohort of patients with colorectal PM who were scheduled for CRS+HIPEC before the introduction of DLS to those with colorectal PM who were scheduled for CRS+HIPEC after DLS was part of the preoperative workup. Our aim was to evaluate the implementation of DLS in the preoperative workup for CRS+HIPEC and the impact on preventing non–therapeutic laparotomies in this vulnerable population.

METHODS

Design, setting, and participants

All consecutive patients with histologically proven colorectal PM who underwent an exploratory laparotomy for potential CRS+HIPEC from January 2006 to January 2019 were retrospectively identified from a prospectively maintained institutional database. Patients were divided into two different cohorts according to their operation date to evaluate the implementation and impact of performing DLS during the preoperative workup for CRS+HIPEC to prevent non−therapeutic laparotomies. Study cohort A consisted of a historical group of patients with colorectal PM who underwent an exploratory laparotomy for potential CRS+HIPEC before the introduction of DLS in the preoperative workup for CRS+HIPEC (January 2006 to December 2011), and study cohort B consisted of patients with colorectal PM who underwent an exploratory laparotomy for potential CRS+HIPEC after the introduction of DLS in the preoperative workup for CRS+HIPEC (January 2012 to January 2019). The Ethics Committee of the University Medical Center Groningen approved this study (METc 201800395).

Primary and secondary outcomes

The primary outcome was the rate of non−therapeutic laparotomies during cytoreductive surgery for cohorts A and B. Secondary outcomes were major postoperative complications, in−hospital mortality, disease−free survival (DFS), and overall survival (OS). Furthermore, to evaluate the implementation of DLS in the preoperative workup, we calculated the number of patients who did not undergo DLS in our academic centre after the introduction of DLS in the preoperative workup for CRS+HIPEC (i.e., cohort B). Reasons for refraining from DLS were retrospectively explored from digital medical records.

Major postoperative complications are defined as grade 3 or higher according to the Clavien−Dindo classification system and registered up to 90 days after surgery.[24] These types of complications require endoscopic, radiologic, or surgical interventions or admission to the intensive care unit. Postoperative mortality is defined as death within 30 days after surgery. OS is defined as the time between the initial exploratory laparotomy and death or date of last follow−up in censored cases. DFS was defined as the time between CRS+HIPEC and the date of first recurrence or last follow−up in censored cases.

Preoperative evaluation and staging

All referred patients with colorectal PM underwent a standardised preoperative evaluation to investigate the extent and resectability of the peritoneal disease and rule out other distant metastases. All patients were staged with a computed tomography (CT) of thorax, abdomen, and pelvis. Since 2012, laparoscopic evaluation in our academic centre has been part of the preoperative workup for CRS+HIPEC to further assess the extent of colorectal PM and the possibility of performing a complete cytoreduction. Patients with an absolute contra−indication for CRS+HIPEC on imaging (i.e., extra−abdominal metastases or more than three liver metastases) were directly referred to a medical oncologist and did not undergo DLS. These patients are not represented in this manuscript as they were not scheduled for CRS+HIPEC.

Every laparoscopic evaluation was performed under general anaesthesia and a pneumoperitoneum was established by using an optical trocar. In all cases, a 30° laparoscope was used and introduced through an umbilical port. One or two additional trocars were placed under direct vision according to the surgeon's discretion. All thirteen abdominopelvic regions of the peritoneal cavity were systematically reviewed and adhesiolysis was only performed when deemed necessary. The laparoscopic PCI was calculated and the possibility to perform a complete cytoreduction during an exploratory laparotomy was estimated. The visibility of each abdominopelvic region, the laparoscopic PCI, and the possibility to achieve a complete cytoreduction were all recorded in the operation report. Cytology samples and biopsies were only taken as indicated. During several expert sessions with our four HIPEC surgeons we created a 4−point scale for the degree of visibility of the abdominal cavity during DLS (i.e., grade I; visibility of two or less abdominopelvic regions, grade II; visibility of three to eight abdominopelvic regions, grade III; visibility of at least diaphragm regions, pelvis region and small bowel regions , and grade IV; visibility of all thirteen abdominopelvic regions).

Hereafter, during a weekly multidisciplinary meeting, eligibility for CRS+HIPEC was determined by an experienced team consisting of medical oncologists, gastroenterologists, radiologists, and oncologic surgeons. In general, patients with colorectal PM were considered eligible for CRS+HIPEC when they met the following criteria: (I) PCI ≤ 20; (II) resectable primary tumour; (III) absence of extra−abdominal metastases; (IV) absence of massive peritoneal disease involvement of the small bowel or its mesentery; (V) Eastern Cooperative Oncology Group (ECOG) performance status ≤3; and (VI) American Society of Anaesthesiologists (ASA) <3. Up to three resectable liver metastases were not considered a contra−indication for CRS+HIPEC.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

CRS+HIPEC was performed according to the Dutch protocol.[3] In summary, CRS was performed only in patients with completely resectable colorectal PM, and HIPEC was performed only after reaching a complete or nearly complete cytoreduction.

Each procedure started with an exploratory laparotomy to calculate the PCI score and judge resectability of the colorectal PM. The procedure was terminated in cases where the patient was deemed not suitable for CRS+HIPEC, and palliative surgery was performed only according to the surgeon's discretion (i.e., non−therapeutic laparotomy). Patients with resectable colorectal PM underwent CRS with the aim of removing all visible tumour tissue. The resection status after CRS was judged with the completeness of cytoreduction score (CC−score).[25] CC−0 indicates no visible or palpable residual tumour tissue in the peritoneal cavity; CC−1 indicates residual tumour deposits <2.5 mm; CC−2 indicates residual tumour deposits between 2.5 mm and 2.5 cm; and CC−3 indicates residual tumour deposits >2.5 cm or confluence of unresectable tumour deposits at any site within the abdomen or pelvis.

HIPEC was performed in the case of a complete (CC−0) or nearly complete (CC−1) cytoreduction, whereby the abdominal cavity was perfused with mitomycin C (35 mg/m^2) according to the open Coliseum technique, with a temperature of 40−41 °C for 90 min.[26] After HIPEC, reconstruction surgery including bowel anastomoses, and if deemed necessary a colostomy, was performed. All patients were admitted to the intensive care unit for at least one postoperative day until cardiac and pulmonary functions were normal.

Follow up

Clinical follow−up occurred within one month after surgery and thereafter on a quarterly basis for a minimum of 5 years. In the case of suspected recurrence based on clinical symptoms or an increase in carcinoembryonic antigen (CEA) level, a CT of the thorax and abdomen was performed.

Data collection

Relevant data were prospectively collected in an institutional database and consisted of patient characteristics, tumour characteristics, extent of peritoneal disease, previous treatments, operative characteristics, postoperative mortality and morbidity, and short− and long−term survival outcomes.

Reasons to refrain from DLS after the introduction in 2012 were retrospectively explored from digital medical records.

Statistical analyses

All statistical analyses were conducted using SPSS® Statistics version 24.0 (IBM Corporation, Armonk, NY, USA). Categorical variables are reported as number (n) and percentages (%) and were analysed using the χ^2 test or Fisher's exact test. Continuous variables are reported as median (interquartile range [IQR]) or mean ± standard deviation (SD) and were analysed using a Student's *t* test or the Mann–Whitney *U* test. Kaplan–Meier survival analyses were performed to describe DFS and OS for study cohorts A and B. All tests were performed two−sided, and a *p* value below 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

One hundred seventy−two patients with histologically proven colorectal PM underwent an exploratory laparotomy for potential CRS+HIPEC in our academic centre between January 2006 and January 2019. Forty−eight patients (27.9%) underwent an exploratory laparotomy before the introduction of DLS in the preoperative workup for CRS+HIPEC (i.e., cohort A), whereas 124 patients (72.1%) underwent an exploratory laparotomy after the introduction of DLS in the preoperative workup for CRS+HIPEC (i.e., cohort B). **Table 1** shows a comparison of patient characteristics and tumour characteristics between cohorts A and B. Patients from cohort B were on average older (62 vs 55 years, $p < 0.002$) and had a higher body mass index (BMI) (26.6 vs 23.4 kg/m^2, $p < 0.001$). Furthermore, they were less frequently diagnosed with an N2 (41.1 vs 45.8%, $p = 0.024$) or M1 status (50.0 vs 77.1%, $p = 0.004$), and were less frequently treated with adjuvant chemotherapy (25.0 vs 41.7%, $p = 0.001$). On the other hand, patients from cohort B were more frequently diagnosed with metachronous onset of colorectal PM (54.0 vs 33.3%, $p = 0.015$). Other baseline characteristics were similar between the cohorts.

Table 1 | Baseline characteristics from all patients with colorectal PM who underwent an exploratory laparotomy for potential CRS+HIPEC stratified by the operation date (cohort A, between 2006 and 2011; and cohort B, between 2012 and 2019).

	Cohort A n = 48	**Cohort B n = 124**	*P value*
Patient characteristics			
Age, years, mean ± SD	55.0 ± 9.7	62 ± 9.9	**0.002**
Gender, female, n (%)	22 *(45.8)*	60 *(48.4)*	0.764
BMI, kg/m², mean ± SD	23.4 ± 4.7	26.6 ± 4.7	**<0.001**
ASA, n (%)			0.871
1	6 *(12.5)*	19 *(15.3)*	
2	37 *(77.1)*	91 *(73.4)*	
3	5 *(10.4)*	14 *(11.3)*	
4	0 *(0.0)*	0 *(0.0)*	
Comorbidity, n (%)			
Diabetes mellitus	4 *(8.3)*	11 *(8.9)*	0.379
Hypertension	7 *(14.6)*	26 *(21.0)*	0.256
Cardiac comorbidity	7 *(14.6)*	12 *(9.7)*	0.878
Lung comorbidity	7 *(14.6)*	13 *(10.5)*	0.206
Tumour characteristics			
Primary tumour location, n (%)			0.455
Right colon	23 *(47.9)*	41 *(33.1)*	
Transverse colon	2 *(4.2)*	10 *(8.1)*	
Left colon	4 *(8.3)*	15 *(12.1)*	
Sigmoid	13 *(27.1)*	40 *(32.3)*	
Rectum	6 *(12.5)*	18 *(14.5)*	
Signet cell histology, n (%)	4 *(8.3)*	12 *(9.7)*	0.759
T stage primary tumour, n (%)			0.087
≤3	18 *(37.5)*	56 *(45.2)*	
4	25 *(52.1)*	66 *(53.2)*	
N status primary tumour, n (%)			**0.024**
0	7 *(14.6)*	35 *(28.2)*	
1	14 *(29.2)*	36 *(29.0)*	
2	22 *(45.8)*	51 *(41.1)*	
M status primary tumour, n (%)			
0	9 *(18.8)*	57 *(46.0)*	**0.004**
1	37 *(77.1)*	62 *(50.0)*	
Onset of colorectal PM, n (%)			
Synchronous	32 *(66.7)*	57 *(46.0)*	**0.015**
Metachronous	16 *(33.3)*	67 *(54.0)*	
Synchronous liver metastases, n (%)	4 *(8.3)*	12 *(9.7)*	0.785
Prior CRC treatments			
Prior CRC surgery, n (%)	42 *(87.5)*	112 *(90.3)*	0.588
Prior chemotherapy, n (%)	14 *(29.2)*	48 *(38.7)*	0.360
Neoadjuvant chemotherapy, n (%)	4 *(8.4)*	24 *(19.4)*	0.568
Adjuvant chemotherapy, n (%)	20 *(41.7)*	31 *(25.0)*	**0.001**

Table 2 | Treatment characteristics from all patients with colorectal PM who underwent an exploratory laparotomy for potential CRS+HIPEC stratified by the operation date (cohort A, between 2006 and 2011; and cohort B, between 2012 and 2019).

	Cohort A n = 48	Cohort B n = 124	*P value*
DLS routinely performed, yes, n (%)	0 *(0.0)*	85 *(68.5)*	**<0.001**
HIPEC type, n (%)			**0.044**
Open CRS+HIPEC	31 *(64.6)*	98 *(79.0)*	
Open−close procedure	17 *(35.4)*	26 *(21.0)*	
Main reason open−close procedure, n (%)			0.496
PCI>20	8 *(47.1)*[¥]	13 *(50.0)*	
Too much small bowel involvement[≈]	4 *(23.5)*	4 *(15.4)*	
Irresectable primary tumour[Δ]	2 *(11.8)*	7 *(26.9)*	
Irresectable liver metastases	3 *(17.6)*	2 *(7.7)*	
PCI at HIPEC, n (%)			0.121
0−5	4 *(36.4)*	34 *(28.8)*	
6−10	2 *(18.2)*	26 *(22.0)*	
11−15	0 *(0.0)*	20 *(16.9)*	
16−20	0 *(0.0)*	16 *(15.0)*	
21−25	3 *(27.3)*	13 *(11.0)*	
>25	2 *(18.2)*	9 *(7.6)*	
Total anatomic resections, median [IQR]	4 [1−6]	4 [2−7]	0.410
Anastomoses, n (%)			0.161
0	31 *(64.6)*	57 *(46.0)*	
1	12 *(25.0)*	44 *(35.5)*	
≥2	5 *(10.5)*	23 *(18.5)*	
Stoma post−HIPEC, n (%)	21 *(43.8)*	63 *(50.8)*	0.406
Operation time, min, median [IQR]	493 [364−614]	471 [352−538]	0.217
Blood loss, mL, median [IQR]	700 [475−1325]	750 [500−1500]	0.790
Resection status, n (%)			0.126
CC−0 or CC−1	31 *(64.6)*	98 *(79.0)*	
≥ CC−2	17 *(35.4)*	26 *(21.0)*	
Length of hospital stay, days, median [IQR]	15 [10−21]	16 [12−24]	0.239
Reoperation, n (%)	4 *(8.3)*	15 *(12.1)*	0.480
In hospital mortality, n (%)	1 *(2.1)*	2 *(1.6)*	0.833
Complication rate, Clavien−Dindo, n (%)			0.424
Grade I	4 *(8.3)*	10 *(8.1)*	
Grade II	14 *(29.2)*	40 *(32.3)*	
Grade III	7 *(14.6)*	23 *(18.5)*	
Grade IV	7 *(14.6)*	6 *(4.8)*	

[¥] During study period A (2006-2011) the PCI classification system was not used systematically in the Netherlands. In five patients with an open−close procedure from cohort A we concluded that the PCI would most likely have been above 20 based on the information from the operation report (i.e., extensive disease involvement of all nine abdominal regions).

[≈] Massive peritoneal disease involvement of the small bowel or its mesentery, whereby removal very likely will lead to short bowel syndrome.

[Δ] Tumour intertwined with vital structures making safe removal impossible.

Non-therapeutic laparotomies

Table 2 presents the surgical characteristics of the exploratory laparotomy and postoperative morbidity rates for cohorts A and B.

None of the patients from cohort A underwent DLS during the preoperative workup for CRS+HIPEC, as it was not common clinical practice between 2006 and 2011. An unexpectedly low number of 85 patients (68.5%) underwent DLS in our academic centre after the introduction of DLS in the preoperative workup for CRS+HIPEC The number of non−therapeutic laparotomies for the entire cohort was 43 (25.0%). A non−therapeutic laparotomy occurred less frequently in cohort B when compared to historical cohort A (21.0 vs 35.4%, $p = 0.044$). Causes for the occurrence of a non−therapeutic laparotomy did not differ between both cohorts ($p = 0.496$).

As the number of patients who underwent DLS in cohort B was unexpectedly low, additional analyses were performed to identify the direct effect of DLS on the prevention of non−therapeutic laparotomies. In this specific case, patients were no longer divided by their operation date (i.e., cohort A or B) but by whether they underwent DLS ($n = 89$) or not ($n = 83$). Non−therapeutic laparotomies occurred less frequently in patients who underwent DLS compared to patients who did not undergo DLS (18.0 vs 32.5%, respectively, $p = 0.028$).

Reasons to refrain from DLS

An overview of the reasons to refrain from DLS for patients in cohort B after the introduction of the preoperative workup for CRS+HIPEC is presented in **Table 3a**. Refraining from DLS in our academic centre was most frequently caused by the fact that the patient recently underwent a laparotomy (30.8%) or DLS (17.9%) in the referring hospital or a laparotomy in our own academic centre (17.9%). For these patients, in the decision−making process additional DLS in our academic centre after recent abdominal surgery was not considered useful. Furthermore, DLS was not performed in seven patients (17.9%) who showed a clear response to neoadjuvant chemotherapy on CT imaging. In six patients (15.4%), reasons to refrain from DLS could not be identified from the digital medical records.

Interestingly, in patients who did not undergo DLS after its introduction in the preoperative workup for CRS+HIPEC, a non-therapeutic laparotomy occurred in 11 patients (28.2%). The specific reason for refraining from DLS was not predictive of an occurrence of a non−therapeutic laparotomy ($p = 0.437$) [data not shown]. There seemed to be a trend toward an increase in non−therapeutic laparotomies

in patients from cohort B who did not undergo DLS compared to patients from the same cohort who underwent DLS in the preoperative workup (28.2 vs 17.6%, respectively), but this trend did not reach significance (p = 0.107).

Laparoscopic evaluation

Table 3b presents the surgical characteristics of the DLS and postoperative morbidity rates of the 85 patients (68.5%) from cohort B who underwent DLS prior to exploratory laparotomy. Good laparoscopic evaluation of the abdominal cavity (i.e., grade ≥III) was possible in 64 patients (74.1%). The conversion rate during DLS amounted to 21.2%, and no reoperations occurred. The postoperative complication rate was low (3.5%) and consisted only of Clavien–Dindo grade II complications (i.e., urinary tract infection and bacteraemia). In patients who underwent DLS in the preoperative workup for CRS+HIPEC, only 15 non−therapeutic laparotomies (17.6%) occurred.

Surgical morbidity and mortality

Table 2 presents the surgical characteristics of the exploratory laparotomy and the postoperative morbidity rates for cohorts A and B. One hundred and twenty−nine patients (75.0%) underwent CRS+HIPEC during an exploratory laparotomy. Treatment characteristics, consisting of the number of anatomic resections, PCI score, operating time, blood loss, and resection status, were similar for both cohorts.

Major postoperative complications after exploratory laparotomy occurred in 14 patients (29.2%) from cohort A and in 29 patients (23.4%) from cohort B (p = 0.424). Relaparotomy was necessary in 4 (8.3%) and 15 patients (12.1%), respectively (p = 0.480). Overall in−hospital mortality was 1.7% and did not differ between the cohorts (p = 0.833).

Table 3a | Reasons for not performing a DLS routinely in patients with colorectal PM from cohort B (n = 39).

Reasons for not performing DLS routinely, n (%)	
Recent laparotomy in other hospital (<4 weeks)	12 *(30.8)*
Recent DLS in other hospital (<4 weeks)	7 *(17.9)*
Recent laparotomy in our academic centre (<4 weeks)	7 *(17.9)*
Clear response on neoadjuvant therapy on imaging	7 *(17.9)*
Unknown	6 *(15.4)*
Impact on open–close procedures	
HIPEC type, n (%)	
Open CRS+HIPEC	28 *(71.8)*
Open–close procedure	11 *(28.2)*
Main reason open–close procedure, n (%)	
PCI>20	5 *(45.5)*
Too much small bowel involvement[≋]	2 *(18.2)*
Irresectable primary tumour	3 *(27.3)*
Irresectable liver metastases	1 *(9.1)*

[≋] Massive peritoneal disease involvement of the small bowel or its mesentery, whereby removal very likely will lead to short bowel syndrome.

Table 3b | Visibility and postoperative morbidity of the DLS in patients with colorectal PM from cohort B (n = 85).

Time intervals	
Interval colorectal PM to DLS, months, median [IQR]	1 [0–2]
Interval colorectal PM to HIPEC, months, median [IQR]	2 [2–4]
Visibility during DLS	
Grade of visibility, n (%)*	
I (very poor)	11 *(12.9)*
II (poor)	8 *(9.4)*
III (good)	11 *(12.9)*
IV (excellent)	53 *(62.4)*
Conversion rate, n (%)	18 *(21.2)*
PCI at DLS, n (%)	
0–5	22 *(25.9)*
6–10	19 *(22.4)*
11–15	17 *(20.0)*
16–20	10 *(11.8)*
21–25	5 *(5.9)*
>25	4 *(4.7)*
Recovery after DLS	
Length of hospital stay, days, median [IQR]	2 [2–3]
Reoperation, n (%)	0 *(0.0)*
Complication rate, Clavien–Dindo, n (%)	
Grade I	0 *(0.0)*
Grade II	3 *(3.5)*
Grade III	0 *(0.0)*
Grade IV	0 *(0.0)*
Complication type, n (%)	
Urinary tract infection	2 *(2.4)*
Bacteraemia with unknown cause	1 *(1.2)*
Impact on open–close procedures	
HIPEC type, n (%)	
Open CRS+HIPEC	70 *(82.4)*
Open–close procedure	15 *(17.6)*

* *Grade I* visibility of two or less abdominopelvic regions, *grade II* visibility of three to eight abdominopelvic regions, *grade III* visibility of at least diaphragm regions, pelvis region, and small bowel regions, *grade IV* visibility of all thirteen abdominopelvic regions.

Survival outcomes

The mean OS for the entire group of patients was 30.1 months (95% CI 26.0–34.2 months). The mean OS was similar for cohorts A and B (25.9 months [95% CI 19.5–32.3] vs 29.5 months [95% CI 25.9–33.1 months], respectively, $p = 0.132$).

For additional analyses of overall and disease−free survival after CRS+HIPEC, patients with a non−therapeutic laparotomy were excluded ($n = 43$). The mean OS for patients after CRS+HIPEC was 36.4 months (95% CI 31.6–41.2 months). The mean OS was similar for cohorts A and B (34 months [95% CI 25.9–42.1 months] vs 34 months [95% CI 30.2–37.8 months], respectively, $p = 0.523$). The mean DFS for the entire cohort of patients was 20.7 months (95% CI 16.1–25.2 months). The mean DFS was similar between cohorts A and B (20.9 months [95% CI 13.2–28.7 months] vs 18.5 months [95% CI 14.7–22.4 months], respectively, $p = 0.706$).

DISCUSSION

In this observational study, consisting of 172 consecutive patients with colorectal PM, we demonstrated that non−therapeutic laparotomies during cytoreductive surgery occurred less frequently after the introduction of DLS as part of the preoperative workup for CRS+HIPEC.

Proper selection of patients with colorectal PM for CRS+HIPEC is a known challenge, as possible survival gain is difficult to weigh against treatment−related morbidity and mortality. From this perspective, for patients and clinicians, the most disappointing outcome after this major procedure is a non−therapeutic laparotomy, as it is associated with an increased risk of postoperative morbidity and a diminished QoL without providing any improvement in survival. These days, up to 40% of patients with PM are still confronted with a non−therapeutic laparotomy during cytoreductive surgery.[15,16] Previous research showed that DLS is an accurate and safe staging tool in patients with PM and might prevent non−therapeutic laparotomies in patients with extensive disease. [16,18-23] In this study, we showed that the rate of non−therapeutic laparotomies significantly dropped from 35.4 to 21.0% after the introduction of DLS in our preoperative workup, despite the fact that only 68.5% of the patients underwent DLS in our academic centre after this introduction. In the group of patients who underwent DLS, a trend towards an ever−lower rate of non−therapeutic laparotomies was found (17.6%). Additional analyses showed that recent abdominal surgery in two out of three patients was the main reason to refrain from DLS in our academic centre, resulting in an unexpectedly higher rate

of non−therapeutic laparotomies (28.2%) in these patients. An explanation for this phenomenon might be the fact that surgeons from the referral centres in most cases were confronted unexpectedly with colorectal PM during a primary tumour resection. At that moment, the focus would be on referring the patient to a highly experienced HIPEC centre as quickly as possible, and therefore less attention might be paid to the true extent of the peritoneal disease.

In our current study some significant differences in baseline characteristics were found between patients who underwent an exploratory laparotomy for potential CRS+HIPEC before and after the introduction of DLS in the preoperative workup for CRS+HIPEC (i.e., cohort A and B, respectively). Patients from cohort B were on average older and had a higher BMI, which can be explained by the increase of the global average life expectancy and the increase in rates of obesity during the past 20 years. Age and BMI are both not considered a contraindication for CRS+HIPEC in our academic centre. Patients from cohort B were also less frequently treated with adjuvant chemotherapy. Due to a lack of scientific evidence there is no worldwide consensus about the use and timing of perioperative chemotherapy. Over the years, we have become more careful in applying adjuvant chemotherapy to patients after CRS+HIPEC, because of the increase in morbidity and temporally decrease in QoL that are both associated with chemotherapy. It is very unlikely that these differences in age, BMI, and the use of adjuvant chemotherapy could explain the rate drop of non−therapeutic laparotomies in cohort B. Furthermore, patients from cohort B were also more frequently diagnosed with metachronous onset of colorectal PM. The most likely explanation for this phenomenon seems the shift towards an increased awareness about CRS+HIPEC among surgeons from regional hospitals. In the past, especially patients with metachronous colorectal PM were frequently referred to a medical oncologist for palliative treatment options instead of an experienced HIPEC centre. These days, patients are referred to our academic centre in a low−threshold way, resulting in the treatment of more patients with metachronous onset of colorectal PM. To the best of our knowledge, there are no scientific publications about the impact of onset of colorectal PM on the rate of non−therapeutic laparotomies during CRS+HIPEC.

Overall, six other studies have reported data about the impact of DLS on preventing non−therapeutic laparotomies in patients with PM during cytoreductive surgery.[16,19-23] It should be noted that none of these studies focused only on patients with colorectal PM; a variation of three up to eleven primary tumour types were included per study. The overall rate of non−therapeutic laparotomies during cytoreductive surgery in

patients who underwent DLS ranged from 12.5 to 37.0%. In most studies, DLS was used in only highly selected patients.[19,21,22] When DLS was routinely performed in all patients with PM, low rates of non−therapeutic laparotomies during cytoreductive surgery were reported (ranging from 15.2 to 17.0%).[20,23] In only three studies was it possible to compare rates of non−therapeutic laparotomies between patients who underwent DLS and patients who did not undergo DLS prior to cytoreductive surgery.[16,19,22] These studies all reported a significant drop in the rate of non−therapeutic laparotomies in patients who underwent DLS when compared to patients who did not undergo DLS prior to cytoreductive surgery. However, it remains challenging to compare the results from our present study with the current literature because of differences in patient populations, tumour types, and indications to perform DLS.

In the Netherlands, HIPEC procedures are performed only in highly experienced tertiary referral centres by a dedicated team of surgeons. As mentioned before, most surgeons from referral centres have less experience in reporting the extent of colorectal PM according to the PCI score and therefore might under stage the extent of disease and overestimate the possibility to achieve a complete cytoreduction. With this obtained knowledge, we are paying more attention to early detection and referring of patients with colorectal PM to our academic centre. Patients will undergo laparoscopic evaluation by one of our HIPEC surgeons to investigate the extent and resectability of the colorectal PM, independently of prior abdominal surgery performed at the referral centre. With these adjustments, we suspect that the rate of non−therapeutic laparotomies in patients with colorectal PM will drop even further in our academic centre in the following years.

In the near future, it is possible that DLS will play a smaller role in patient selection because detection rates of PM from current preoperative imaging modalities are improving.[27,28] In a recent study consisting of 49 patients with colorectal PM, MRI PCI was strongly correlated with the surgical PCI.[28] Two radiologists with extensive experience in detecting colorectal PM could identify all patients with resectable disease based on a PCI below 21. Larger series are still necessary to provide more evidence of the accuracy of detection and staging of colorectal PM. DLS in the preoperative workup for CRS+HIPEC will not be easily curbed, as other advantages remain, such as taking biopsies to confirm the presence or absence of peritoneal disease and provide additional information for future systemic therapies.

This study has certain strengths and limitations. To the best of our knowledge, this is the first study that specifically describes the impact of DLS to prevent non−

therapeutic laparotomies in a large cohort of patients with colorectal PM. Another strength of the current study is the presence of an adequate comparison group; a historical cohort of all consecutive patients who underwent an exploratory laparotomy for potential CRS+HIPEC before DLS was introduced in our academic centre. Gathered knowledge from this study provided crucial information about our daily practice to further improve the implementation of DLS in the preoperative workup for CRS+HIPEC. On the other hand, our study has some limitations due to the retrospective design and the single−centre approach. Selection bias might have occurred, although most data were obtained from a prospectively maintained institutional database and reasons to refrain from DLS in a subset of patients were further investigated. Although our HIPEC surgeons are extensively trained to perform CRS+HIPEC procedures and already had extensive experience in gastrointestinal surgery, study results may also have been influenced by their learning curves in the beginning of this study period. Learning curves from our academic centre and other Dutch hospitals have already been published elsewhere.[29]

CONCLUSIONS

Non−therapeutic laparotomies during cytoreductive surgery (i.e., open−close procedures) are prevented in patients with colorectal PM when DLS is performed during the preoperative workup for this major abdominal procedure. We recommend that only HIPEC surgeons perform this laparoscopic evaluation to ensure adequate staging of the extent of colorectal PM and the possibility of achieving a complete cytoreduction.

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5

ΔPCI: a new dynamic prognostic parameter for survival after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background

The peritoneal cancer index (PCI) calculated during exploratory laparotomy is a strong prognostic factor for overall survival (OS) in patients with colorectal peritoneal metastases (PM) who undergo cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC). Progression of the PCI between diagnostic laparoscopy (DLS) and potential CRS+HIPEC (ΔPCI) might be a more dynamic prognostic factor for OS after CRS+HIPEC.

Methods

Between 2012 and 2018, all colorectal PM patients who underwent an exploratory laparotomy for potential CRS+HIPEC after DLS were retrospectively identified from a prospectively maintained database. Patients were divided into stable disease (ΔPCI 0–3), mild progression (ΔPCI 4–9), or severe progression (ΔPCI ≥10). Kaplan–Meier analysis and a multivariate Cox regression were performed.

Results

Eighty−four patients (ΔPCI 0–3, *n* = 35; ΔPCI 4–9, *n* = 34; and ΔPCI ≥10, *n* = 15) were analysed. Median OS after CRS+HIPEC was significantly decreased in patients with a ΔPCI of 4–9 (35.1 months [95% CI 25.5−44.6 months]) or ΔPCI ≥10 (24.1 months [95% CI 11.7−36.5 months]) compared to patients with a ΔPCI of 0–3 (47.9 months [95% CI 40.0−55.7 months], p = 0.004). In multivariate regression analysis, ΔPCI remained an independent risk factor for OS: ΔPCI 4–9 HR 3.1 (95% CI 1.4−7.2, p = 0.007) and ΔPCI ≥10 HR 4.4 (95% CI 1.5−13.1, p = 0.007).

Conclusions

A high ΔPCI is an independent dynamic prognostic factor for OS and might reflect a more aggressive tumour biology in patients with colorectal PM. HIPEC surgeons should be aware of a high−ΔPCI−associated diminished prognosis and should reconsider CRS+HIPEC when confronted with a ΔPCI ≥10.

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer worldwide.[1] Up to 40% of patients with colorectal cancer develop peritoneal metastases (PM) during the course of the disease, whereby the median overall survival (OS) with systemic therapy regimens ranges from 12 to 24 months.[2-4]

These days, carefully selected patients with resectable and limited colorectal PM can be treated with curative intent by cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC).[5-8] During cytoreductive surgery, all macroscopically visible tumour tissue in the abdominal cavity will be removed, followed by perfusion with heated chemotherapy to eliminate remaining microscopic disease.[9-11] In highly selected patients with colorectal PM, the survival gain due to CRS+HIPEC can be up to five years.[7,12,13] However, CRS+HIPEC is associated with substantial morbidity and mortality and a decline in quality of life (QoL) in the first year after treatment.[15-18] Thus, one of the major challenges is to adequately select patients who will benefit most from this treatment with acceptable treatment–related morbidity and mortality in terms of OS and QoL.

Understandably, oncologists and surgeons are very interested in prognostic indicators that can be used in the selection process. According to the available literature, the extent of peritoneal disease, completeness of the performed cytoreduction, and signet ring cell histology especially have a great influence on the survival outcomes after CRS+HIPEC.[6,19-24] The resectability of the peritoneal disease and thus the possibility to achieve a complete cytoreduction, is determined by various factors, such as the extent of the peritoneal disease, disease involvement of the small bowel, the deep mesenteric root, or the hepatic hilus. The extent of peritoneal disease is scored by the peritoneal cancer index (PCI), which combines peritoneal lesions sizes with the exact distribution over 13 abdominopelvic regions. The PCI score ranges from 0 to 39 points; a higher score indicates a more extensive tumour burden. Most HIPEC teams perform CRS+HIPEC only in patients with colorectal PM with a PCI <20 with the possibility to perform a (nearly) complete cytoreduction.

Pre–operative assessment of the PCI score remains challenging, as current radiological imaging techniques have limited sensitivity and resolution in detecting PM.[25-27] As such, several institutions worldwide perform a diagnostic laparoscopy (DLS) in addition to investigating the presence and resectability of colorectal

PM.[28-30] At this moment, the PCI scoring system is predominantly used as a static single−time−point scoring system during an exploratory laparotomy for potential CRS+HIPEC, and as such does not include disease progression over time. Recently, the Sydney CRS+HIPEC research group created a more dynamic prognostic factor in 182 HIPEC patients with metachronous colorectal PM by combining tumour volume (i.e., laparotomy−PCI) with the time period over which the extent of disease developed (i.e., time between primary tumour resection and CRS+HIPEC).[31] Patients with a high volume−time−index had a significantly decreased median OS compared to patients with a low volume−time−index (23 vs 44 months, p = 0.002). Although PCI has been repeatedly identified as one of the most important independent prognostic factors for survival, the score lacks information about the time frame over which peritoneal disease develops.

Laparoscopic evaluation is part of our standardised preoperative workup for CRS+HIPEC to assess the extent and resectability of colorectal PM, and therefore the opportunity arose to investigate the impact of an increase in PCI in a short−time frame on survival outcomes after CRS+HIPEC. We hypothesised that an increase in PCI score within a relatively short timeframe might reflect a more aggressive tumour biology with a worse prognosis even when the PCI score is still below 20 and might differentiate patients with a less favourable outcome despite CRS+HIPEC. Thus, the aim of the current study is to identify the impact of an increase in PCI from DLS to CRS+HIPEC on OS in patients with colorectal PM.

METHODS

Design, setting, and participants

Between 2012 and 2018, all consecutive patients with histologically proven colorectal PM who had undergone DLS and an exploratory laparotomy for potential CRS+HIPEC were retrospectively identified from a prospectively maintained institutional database. The study protocol was approved by the Medical Ethical Committee of the University Medical Center Groningen (protocol number 201800395).

From all included patients, the difference in PCI score between DLS and exploratory laparotomy for potential CRS+HIPEC (i.e., ΔPCI) was calculated. Patients were divided into three groups according to the ΔPCI score: ΔPCI 0–3, ΔPCI 4–9, and ΔPCI ≥10. This group classification was determined by our research group in advance with the analyses to distinguish between clinically stable disease (ΔPCI 0–3), mild progression of disease (ΔPCI 4–9), or severe progression of disease (ΔPCI ≥10).

Primary and secondary outcomes

The primary outcome was OS after exploratory laparotomy for potential CRS+HIPEC, calculated from the operation date until the date of death or last follow−up in censored cases. Secondary outcomes were disease−free survival (DFS), postoperative complications (according to the Clavien–Dindo classification system[32]), and the rate of non−therapeutic laparotomies during exploratory laparotomy (i.e., open–close procedures). DFS was calculated from the date of CRS+HIPEC to the date of first recurrence or last follow−up in censored cases.

Preoperative evaluation and staging for CRS+HIPEC

All referred patients with colorectal PM for evaluation of potential candidates for CRS+HIPEC underwent a standardised preoperative screening. This screening consisted of reviewing previous operation and pathology reports; a clinical examination; carcinoembryonic antigen (CEA) measurement; CT of the chest, abdomen, and pelvis; and colonoscopy if not already performed within the previous 6 months.

DLS was also included in this standardised evaluation. During DLS, a 12 mm trocar with the use of a 30° camera and at least one 5 mm trocar were placed in the midline for visualisation of the abdominal cavity. The operating table was placed sequentially into Trendelenburg, anti−Trendelenburg, and right and left tilt positions to systematically assess the abdominal cavity. The extent of colorectal PM was calculated according to the standard PCI score; lesion sizes (from 0 to 3 points) and distribution of peritoneal deposits were measured in nine abdominopelvic regions and four small bowel segments. If deemed necessary, minor adhesiolysis was performed to reduce the risk of bowel injury. DLS evaluations were performed or supervised by one of the five experienced HIPEC surgeons. Clinically suspected lesions were biopsied for pathological confirmation of colorectal PM.

During several expert sessions with our four HIPEC surgeons we created a 4−point scale for the degree of visibility of the abdominal cavity during DLS (i.e., grade I; visibility of two or less abdominopelvic regions, grade II; visibility of three to eight abdominopelvic regions, grade III; visibility of at least diaphragm regions, pelvis region and small bowel regions , and grade IV; visibility of all 13 abdominopelvic regions). A score of three or higher was deemed required for adequate judgement of the extent of disease. Conversion from DLS to an exploratory laparotomy in case of poor visibility only occurred in patients without previous pathological confirmation of colorectal PM or in case of severe obstruction symptoms in order to create a stoma.

A multidisciplinary team comprising surgeon oncologists, medical oncologists, radiologists, and pathologists reviewed the preoperative screening and judged if the patient was a suitable candidate for CRS+HIPEC, aiming to achieve complete cytoreduction with acceptable treatment−related morbidity and mortality. Patients who were deemed unsuitable for CRS+HIPEC during this multidisciplinary oncology team meeting were excluded from the current study. Absolute contra−indications for CRS+HIPEC were moderate or severe co−morbidity (American Society of Anaesthesiologists [ASA] score above III), extraperitoneal disease, extensive disease with involvement of the small bowel, or a PCI score ≥20 during DLS. The presence of hepatic metastases was not a contraindication as long as there were only up to three resectable lesions.[17]

Patients with a good or excellent visibility during DLS with a borderline DLS−PCI (i.e., DLS−PCI 15−20) were offered rapid CRS+HIPEC within two weeks to prevent further spreading of the disease. Patients with poor visibility during DLS with a borderline DLS−PCI were referred for palliative treatment options, as the PCI during laparotomy would have been above our national PCI cut−off value of 20. Patients with poor visibility during DLS without a borderline DLS−PCI were given the benefit of doubt and were scheduled for CRS+HIPEC.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

Our institute performed all CRS+HIPEC procedures according to the standardised Dutch HIPEC protocol.[17] In summary, CRS was performed only when the colorectal PM were deemed to be completely resectable and HIPEC was performed only after a (nearly) complete cytoreduction.

Each CRS+HIPEC procedure was initiated with an exploratory laparotomy to recalculate the PCI score in an open setting. The laparotomy PCI was calculated in a similar fashion as described before. In patients who were deemed not eligible for CRS+HIPEC during exploratory laparotomy because of extensive or not resectable disease, the procedure was terminated without further treatment (i.e., open−close procedure). If the patient was deemed eligible for CRS+HIPEC, all macroscopically visible disease was resected. After completion of the cytoreduction, the completeness of cytoreduction score was determined.[33] CC−0 indicated that no residual tumour was visible or palpable in the peritoneal cavity; CC−1 indicated residual tumour deposits smaller than 2.5 mm; CC−2 indicated residual tumour between 2.5 mm and 2.5 cm; and CC−3 indicated residual tumour larger than 2.5 cm or a confluence of nodules.

The HIPEC procedure was then performed by using the open Coliseum technique.[34] In this open technique, the abdominal wall is pulled upward and a closed circuit is created using inflow and outflow drains attached to a pump and a heating unit is set up. Mitomycin C (35 mg/m^2) was circulated in the abdominal cavity with a temperature of 41–42ºC for 90 min. Afterwards, reconstruction surgery including bowel anastomoses with or without a colostomy was performed. All patients were admitted to the intensive care unit for at least one postoperative day.

Follow–up

Clinical follow–up of each patient occurred within one month after surgery and thereafter on a 3–6 month basis for a minimum of five years. Follow–up included clinical examination and CEA measurements. A CT scan of the thorax and abdomen was performed in cases of suspected recurrence of the disease by the presence of clinical symptoms or an increase in CEA levels.

Data collection

Data on patient and tumour characteristics, operative characteristics, postoperative outcome, survival, and recurrence were collected prospectively. Postoperative complications were collected up to 60 days after surgery and registered according to the Clavien–Dindo classification system.[32]

Statistical analyses

All statistical analyses were performed with SPSS® Statistics version 24.0 (IBM Corporation, Armonk, NY, USA.). All tests of statistical significance were two–sided. $P < 0.05$ was considered statistically significant. Quantitative variables are presented as mean (± SD) or median (interquartile range, IQR) and qualitative variables are presented as count (percentage). Patient and tumour characteristics were compared using a Chi square or Fisher's exact test. OS between the ΔPCI groups was assessed and calculated according to the Kaplan–Meier method and Log-rank Test. Subsequently, a multivariable Cox regression analysis was performed to examine the association of ΔPCI with the risk of death after adjustment for potential confounders. Potential confounders were identified from the current literature or identified in the univariate survival analysis ($p < 0.20$). Results from the univariate and multivariate analyses were presented as hazard ratio (HR) with 95% confidence interval (CI).

RESULTS

One hundred and sixty−four patients with colorectal PM underwent an exploratory laparotomy for potential CRS+HIPEC during the inclusion period (**Figure 1**). Sixty−two patients (37.8%) were excluded from the analysis because no DLS was performed during the preoperative workup, and 18 patients (11.0%) were excluded because one or two PCI scores from the surgical procedures were missing. Eighty−four patients (51.2%) were included for further analyses. ΔPCI was calculated for all included patients. Patients were divided into three subgroups according to ΔPCI: ΔPCI 0–3 (n = 35), ΔPCI 4–9 (n = 34), and ΔPCI ≥10 (n = 15).

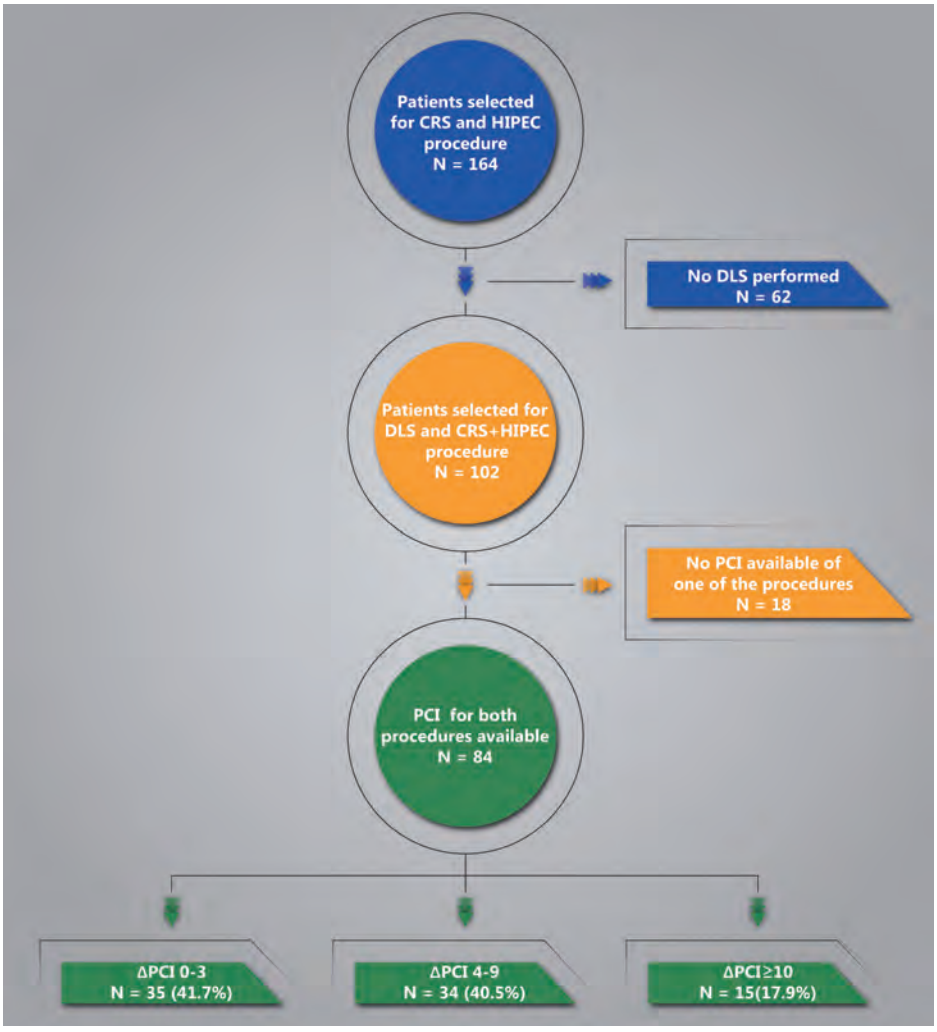

Figure 1 | Flow chart of the patient selection process.

Table 1 | Baseline characteristics from all 84 patients divided into the three different ΔPCI groups.

	Total n = 84	ΔPCI 0–3 n = 35	ΔPCI 4–9 n = 34	ΔPCI ≥10 n = 15	*P value*
Patient characteristics					
Age, years, median [IQR]	63 [54–68]	60 [53–67]	65 [58–69]	66 [51–70]	0.292
Gender, female, n (%)	43 *(51.2)*	19 *(54.3)*	15 *(44.1)*	9 *(60.0)*	0.527
BMI, kg/m², median [IQR]	26.2 [24.2–30.6]	26.7 [23.6–31.2]	25.8 [24.3–28.1]	25.9 [22.9–31.9]	0.455
ASA, n (%)					0.860
1	9 *(10.7)*	4 *(11.4)*	4 *(11.8)*	1 *(6.7)*	
2	67 *(79.8)*	29 *(82.9)*	26 *(76.5)*	12 *(80.0)*	
3	8 *(9.5)*	2 *(5.7)*	4 *(11.8)*	2 *(13.3)*	
Comorbidity, n (%)					
Diabetes	7 *(8.3)*	2 *(5.7)*	3 *(8.8)*	3 *(20.0)*	0.516
Cardiovascular disease	25 *(29.8)*	9 *(25.7)*	11 *(32.4)*	5 *(33.3)*	0.727
Pulmonary disease	9 *(10.7)*	6 *(17.1)*	2 *(5.9)*	1 *(6.7)*	0.266
Prior CRC surgery, n (%)	75 *(89.3)*	32 *(91.4)*	30 *(88.2)*	13 *(86.7)*	0.307
Tumour characteristics					
Primary tumour, n (%)					0.084
Right colon	26 *(31.0)*	11 *(31.4)*	9 *(26.5)*	6 *(40.0)*	
Transverse colon	7 *(8.3)*	1 *(2.9)*	6 *(17.6)*	0 *(0.0)*	
Left colon	11 *(13.1)*	6 *(17.1)*	4 *(11.8)*	1 *(6.7)*	
Sigmoid	26 *(31.0)*	9 *(25.7)*	9 *(26.5)*	8 *(53.3)*	
Rectum	14 *(16.7)*	8 *(22.9)*	6 *(17.6)*	0 *(0.0)*	
Signet cell histology, n (%)	8 *(9.5)*	3 *(9.1)*	4 *(12.5)*	1 *(6.7)*	0.851
T stage of primary tumour, n (%)					0.687
≤3	39 *(48.1)*	19 *(55.9)*	15 *(44.1)*	5 *(35.7)*	
4	42 *(51.9)*	15 *(44.1)*	18 *(52.9)*	9 *(60.0)*	

Table 1 | Continued

	Total n = 84	ΔPCI 0–3 n = 35	ΔPCI 4–9 n = 34	ΔPCI ≥10 n = 15	*P value*
N stage of primary tumour, n (%)					0.321
0	21 *(26.3)*	10 *(29.4)*	8 *(25.0)*	3 *(21.4)*	
1	30 *(37.5)*	12 *(35.3)*	9 *(28.1)*	9 *(64.3)*	
2	29 *(36.3)*	12 *(35.3)*	15 *(46.9)*	2 *(14.3)*	
Onset of colorectal PM, n (%)					0.926
Synchronous	34 *(40.5)*	15 *(42.9)*	13 *(38.2)*	6 *(40.0)*	
Metachronous	50 *(59.5)*	20 *(57.1)*	21 *(61.8)*	9 *(60.0)*	
Synchronous liver metastases, n (%)	15 *(17.9)*	5 *(14.3)*	7 *(20.6)*	3 *(20.0)*	0.769
Perioperative chemotherapy					
Neoadjuvant chemotherapy, n (%)	10 *(11.9)*	5 *(14.3)*	4 *(11.8)*	1 *(6.7)*	0.747
Adjuvant chemotherapy, n (%)	20 *(23.8)*	6 *(18.2)*	10 *(30.3)*	4 *(30.8)*	0.466

Patient and tumour characteristics

Table 1 shows that there were no significant differences at baseline in patient and tumour characteristics between the different ΔPCI groups.

Table 2 presents the treatment characteristics of the DLS and the exploratory laparotomy for the different ΔPCI groups. There were no significant differences in the treatment characteristics for the DLS between the ΔPCI groups. In the entire cohort, good laparoscopic evaluation of the abdominal cavity (i.e., visibility grade ≥III) was possible in 62 patients (73.8%), resulting in conversion to an open procedure in 20 patients (23.8%). Postoperative complications occurred in three patients (3.6%) and consisted of a prolonged gastroparesis postoperatively (grade II), fever without a specific focus (grade II), and a small bowel perforation (grade III).

The median time between DLS and exploratory laparotomy was 1 month (IQR 1–2) and was comparable between the ΔPCI groups (p = 0.938). The median PCI significantly increased from 4 at DLS to 10 at exploratory laparotomy (p < 0.0001). Seventy−one patients (84.5%) underwent CRS+HIPEC during the exploratory laparotomy and 13 patients (15.5%) had a non−therapeutic laparotomy, because of a PCI >20 (nine patients), too much small bowel involvement (one patient), more than three liver metastases (one patient), or an irresectable primary tumour (two patients). The PCI score during the exploratory laparotomy was as expected higher in the ΔPCI 4–9 and ΔPCI ≥10 groups compared to the ΔPCI 0–3 group (p < 0.0001). In addition, non−therapeutic laparotomies occurred more frequently in patients with a ΔPCI 4–9 (20.6%) or ΔPCI ≥10 (33.3%) compared to patients with a ΔPCI 0–3 (2.9%) (p = 0.014).

Overall and disease−free survival

The median OS after exploratory laparotomy for the entire cohort was 36.2 months (95% CI 30.1−42.2 months). **Figure 2** shows that the median OS after exploratory laparotomy was significantly decreased in patients with a ΔPCI of 4–9 (30.6 months [95% CI 21.9−39.2 months]) or ΔPCI ≥10 (21 months [95% CI 10.3−31.7 months]) compared to patients with a ΔPCI of 0–3 (46.8 months [95% CI 38.9−54.7 months], p < 0.0001). **Figure 3** shows the same significant trend within the group of 71 patients who underwent CRS+HIPEC. Median OS after CRS+HIPEC was significantly decreased in patients with a ΔPCI of 4–9 (35.1 months [95% CI 25.5−44.6 months]) or ΔPCI ≥10 (24.1 months [95% CI 11.7−36.5 months]) compared to patients with a ΔPCI of 0–3 (47.9 months [95% CI 40.0−55.7 months], p = 0.004).

Additional analyses were performed within the subgroup of 43 patients (51.2%) in whom an excellent laparoscopic view on all 13 abdominopelvic regions could be achieved to rule out the possibility of an increase in PCI over time caused by inadequate assessment of the DLS-PCI. The median OS after exploratory laparotomy was also in this subgroup of patients significantly decreased in patients with a ΔPCI of 4–9 (19.0 months [95% CI 7.7−30.3 months]) or ΔPCI ≥10 (22.6 months [95% CI 6.4−38.8 months]) compared to patients with a ΔPCI of 0–3 (54.1 months [95% CI 45.3−63.0 months], p = 0.004). For the subgroup of 36 patients who successfully underwent CRS+HIPEC, median OS was also significantly decreased in patients with a ΔPCI of 4–9 (31.5 months [95% CI 22.0−41.1 months]) or ΔPCI ≥10 (23.2 months [95% CI 5.8−40.5 months]) compared to patients with a ΔPCI of 0–3 (54.1 months [95% CI 45.3−63.0 months], p = 0.014).

Table 2 | Treatment characteristics of the diagnostic laparoscopy and exploratory laparotomy for potential cytoreductive surgery with HIPEC from all 84 patients divided into the three different ΔPCI groups.

	Total n = 84	ΔPCI 0–3 n = 35	ΔPCI 4–9 n = 34	ΔPCI ≥10 n = 15	*P value*
Diagnostic laparoscopy					
Grade of visibility, n (%)[¥]					0.826
I (very poor)	3 *(3.6)*	2 *(5.7)*	1 *(2.9)*	0 *(0.0)*	
II (poor)	19 *(22.6)*	10 *(28.6)*	6 *(17.6)*	3 *(20.0)*	
III (good)	*19* (22.6)	6 *(17.1)*	9 *(26.5)*	4 *(26.7)*	
IV (excellent)	43 *(51.2)*	17 *(48.6)*	18 *(52.9)*	8 *(53.3)*	
Conversion rate, n (%)	20 *(23.8)*	8 *(22.9)*	9 *(26.5)*	3 *(20.0)*	0.874
PCI at DLS, n (%)					0.387
0–5	51 *(60.7)*	25 *(71.4)*	18 *(52.9)*	8 *(53.3)*	
6–10	16 *(19.0)*	7 *(20.0)*	6 *(17.6)*	3 *(20.0)*	
11–15	10 *(11.9)*	2 *(5.7)*	5 *(14.7)*	3 *(20.0)*	
16–20	7 *(8.3)*	1 *(2.9)*	5 *(14.7)*	1 *(6.7)*	
Complication rate, Clavien–Dindo, n (%)					0.481
Grade I	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*	
Grade II	2 *(2.4)*	1 *(2.9)*	0 *(0.0)*	1 *(6.7)*	
Grade III	1 *(1.2)*	1 *(2.9)*	0 *(0.0)*	0 *(0.0)*	
Grade IV	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*	0 *(0.0)*	
Length of hospital stay, days, median [IQR]	1 [1-2]	1 [1-2]	1 [1-2]	1 [1-3]	0.904
Time between DLS and CRS+HIPEC, months, median [IQR]	1 [0-2]	1 [0-2]	1 [0-1]	1 [0-2]	0.938
CRS+HIPEC					
HIPEC type, n (%)					**0.014**
Open CRS+HIPEC	71 *(84.5)*	34 *(97.1)*	27 *(79.4)*	10 *(66.7)*	
Open–close procedure	13 *(15.5)*	1 *(2.9)*	7 *(20.6)*	5 *(33.3)*	
PCI at HIPEC, n (%)					**<0.0001**
0–5	22 *(26.2)*	22 *(62.9)*	0 *(0.0)*	0 *(0.0)*	
6–10	22 *(26.2)*	8 *(22.9)*	14 *(41.2)*	0 *(0.0)*	
11–15	18 *(21.4)*	4 *(11.4)*	9 *(26.5)*	5 *(33.3)*	
16–20	13 *(15.5)*	1 *(2.9)*	7 *(20.6)*	5 *(33.3)*	
>20	9 *(10.7)*	0 *(0.0)*	4 *(11.8)*	5 *(33.3)*	

Table 2 | Continued

	Total n = 84	ΔPCI 0–3 n = 35	ΔPCI 4–9 n = 34	ΔPCI ≥10 n = 15	*P value*
Total anatomic resections, median [IQR]	4 [2-6]	4 [2-5]	5 [3-7]	7 [1-8]	0.246
Anastomoses, n (%)					0.059
0	35 *(41.7)*	19 *(54.3)*	11 *(32.4)*	5 *(33.3)*	
1	34 *(40.5)*	13 *(37.1)*	13 *(38.2)*	8 *(53.3)*	
≥2	15 *(17.9)*	3 *(8.6)*	10 *(29.4)*	2 *(13.3)*	
Stoma post–HIPEC, n (%)	42 *(50.0)*	16 *(45.7)*	15 *(44.1)*	11 *(73.3)*	0.136
Operation time, min, median [IQR]	471 [358-522]	451 [378-492]	490 [347-544]	505 [271-571]	0.508
Blood loss, mL, median [IQR]	775 [500-1500]	600 [400-1500]	850 [347-544]	1000 [575-1500]	0.317
Resection status, n (%)					**0.021**
CC–0 or CC–1	71 *(84.5)*	34 *(97.1)*	27 *(79.4)*	10 *(66.7)*	
≥CC–2	13 *(15.5)*	1 *(2.9)*	7 *(20.6)*	5 *(33.3)*	
Length of hospital stay, days, median [IQR]	18 [12-27]	16 [13-27]	18 [12-28]	19 [12-30]	0.965
Reoperation, n (%)	15 *(17.9)*	8 *(22.9)*	5 *(14.7)*	2 *(13.3)*	0.596
Complication rate, Clavien–Dindo, n (%)					0.134
Grade I	5 *(6.0)*	0 *(0.0)*	2 *(5.9)*	3 *(20.0)*	
Grade II	23 *(27.4)*	13 *(37.1)*	5 *(14.7)*	5 *(33.3)*	
Grade III	20 *(23.8)*	9 *(25.7)*	9 *(26.5)*	2 *(13.3)*	
Grade IV	6 *(7.1)*	2 *(5.7)*	2 *(5.9)*	2 *(13.3)*	
Grade V	2 *(2.4)*	1 *(2.9)*	1 *(2.9)*	0 *(0.0)*	

¥ *Grade I:* visibility of two or less abdominopelvic regions; *Grade II:* visibility of three to eight abdominopelvic regions; *Grade III:* visibility of at least diaphragm regions, pelvis region and small bowel regions; *Grade IV:* visibility of all 13 abdominopelvic regions.

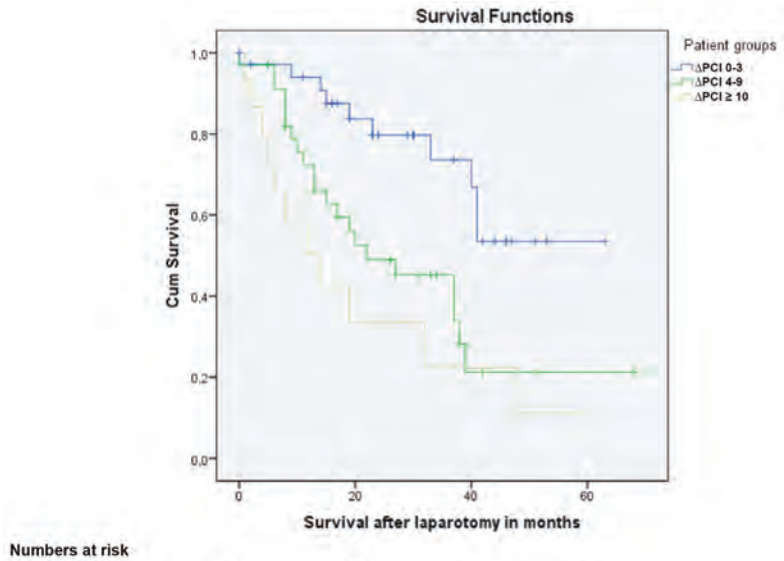

Figure 2 | Kaplan–Meier survival curves for all 84 patients who underwent an exploratory laparotomy for potential CRS+HIPEC divided into the three different ΔPCI groups.

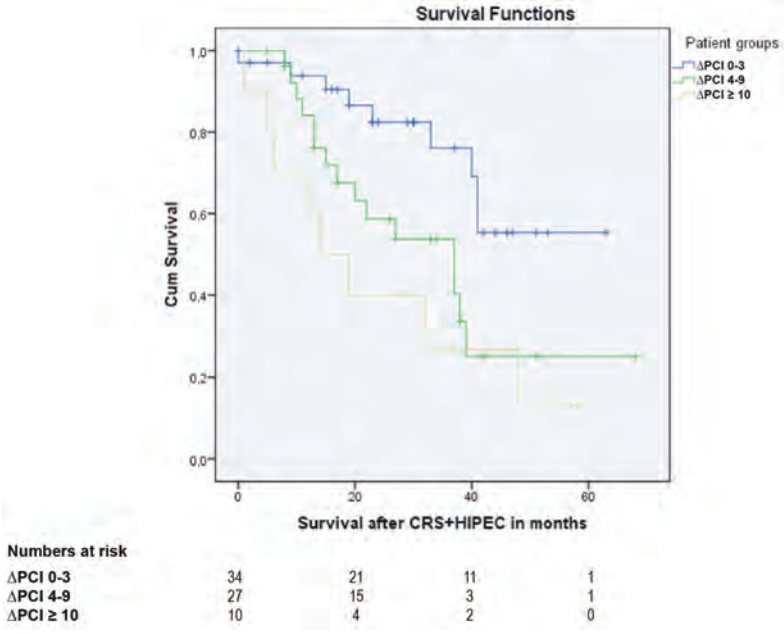

Figure 3 | Kaplan–Meier survival curves for all 71 patients who underwent CRS+HIPEC dived into the three different ΔPCI groups.

Table 3 | Univariate and multivariate analysis to examine the association of ΔPCI with the risk of death.

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	*P value*	**HR**	**95% CI**	*P value*
Patient characteristics						
Age	1.020	0.989–1.052	0.208			
Gender						
Female	1.00	-	-			
Male	0.973	0.530–1.785	0.929			
Tumour characteristics						
Primary tumour						
Rectum	1.00	-	-	1.00	-	-
Right colon	0.520	0.147–1.836	0.310	1.467	0.772–2.787	0.242
Transverse colon	0.690	0.261–1.825	0.455	0.443	0.165–1.188	0.106
Left colon	1.065	0.499–2.271	0.870	0.937	0.431–2.033	0.868
Sigmoid	1.160	0.440–3.060	0.764	1.245	0.631–2.456	0.528
Signet cell histology						
No	1.00	-	-	1.00	-	-
Yes	0.337	0.046–2.462	0.284	1.525	0.666–3.492	0.318
Onset of colorectal PM						
Synchronous	1.00	-	-			
Metachronous	1.293	0.685–2.437	0.428			

Table 3 | Continued

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P value*	HR	95% CI	*P value*
Perioperative chemotherapy						
Neoadjuvant chemotherapy						
No	1.00	-	-			
Yes	0.954	0.374–2.435	0.921			
Adjuvant chemotherapy						
No	1.00	-	-			
Yes	1.305	0.677–2.517	0.427			
Operative characteristics						
PCI at HIPEC	1.074	1.034–1.112	**<0.001**	1.021	0.964–1.082	0.481
CC-score						
CC-0 or CC-1	1.00	-	-	1.00	-	-
CC ≥2	4.809	2.127–10.876	**<0.001**	0.420	0.252–0.700	**0.001**
ΔPCI score						
0–3	1.00	-	-	1.00	-	-
4–9	2.839	1.322–6.097	**0.007**	3.122	1.357–7.178	**0.007**
≥10	4.900	2.061–11.648	**<0.001**	4.447	1.515–13.054	**0.007**

A multivariable Cox regression analysis was performed to examine the direct association of ΔPCI with the risk of death after adjustment for potential confounders. In univariate analysis, the PCI during laparotomy ($p < 0.001$), the CC−score ($p < 0.001$), and a ΔPCI of 4–9 ($p = 0.007$) or ΔPCI ≥10 ($p < 0.001$) were significant prognostic factors (**Table 3**). Other potential important prognostic factors identified from the current literature were the primary tumour site and the presence of signet cell histology. In a multivariate regression analysis, correcting for all previous mentioned potential confounders, ΔPCI remained an independent risk factor for OS: ΔPCI 4–9 HR 3.1 (95% CI 1.4−7.2, $p = 0.007$) and ΔPCI ≥10 HR 4.4 (95% CI 1.5−13.1, $p = 0.007$).

The median DFS for all patients who underwent CRS+HIPEC was 22.4 months (95% CI 16.5−28.4 months). There was no significant difference in median DFS between the three ΔPCI groups (29.5, 18.2, and 11.1 months for ΔPCI 0–3, ΔPCI 4–9, and ΔPCI ≥10, respectively, $p = 0.139$).

Postoperative complications

Table 2 also provides an overview of the postoperative morbidity after exploratory laparotomy, divided by ΔPCI group and severity of the complication according to the Clavien–Dindo classification system. Major postoperative complications (i.e., Clavien-Dindo grade ≥III) occurred in 28 patients (33.3%) and did not differ between the three ΔPCI groups ($p = 0.134$). Two patients (2.4%) died within the first 30 days after CRS+HIPEC. An asystole occurred in one patient 10 days after surgery without successful resuscitation (ΔPCI 0–3 group), and multi-organ failure occurred in one patient after multiple laparotomies because of intra-abdominal abscesses (ΔPCI 4–9 group).

DISCUSSION

In this observational study, consisting of 84 patients with histologically proven colorectal PM, we demonstrated that ΔPCI might be a novel, more dynamic prognostic factor for OS after CRS+HIPEC. We found that a higher ΔPCI was clearly associated with a decreased OS. As such, we postulate that ΔPCI reflects a more aggressive tumour biology and disease progression in patients with colorectal PM and might serve as an adjunct tool for intraoperative clinical decision making beyond static PCI scoring at the time of exploratory laparotomy for potential CRS+HIPEC.

Worldwide, authors agree that one of the key independent prognostic factors for survival after CRS+HIPEC in patients with colorectal PM is the PCI score during

exploratory laparotomy.[19,22,35-38] This concept of tumour burden expressed by the PCI score does not take the dynamic aspect of the biological behaviour of the tumour into account, whether it is slow or fast growing. In our clinic, patients with a PCI score <20 during DLS were deemed eligible for CRS+HIPEC according to common practice. Unfortunately, in our series, cases had been seen where the HIPEC surgeons were confronted with a rapid increase in PCI score of more than 5 points in a few weeks' time, but with a PCI still below 20. Consequently, according to the current guidelines, CRS+HIPEC was executed. Intuitively, this increased tumour burden over a short time period should have been taken into account as a negative prognostic indicator. To the best of our knowledge, there are no previous data on this topic to confirm the clinical observation. As such, we have translated this into the development of a new prognostic parameter, ΔPCI, which is able to stratify three groups of rate progression. We have shown that a rapid increase in ΔPCI is an independent risk factor for OS in patients with colorectal PM and should be considered as an additional clinical decision−making tool prior to execution of CRS+HIPEC.

Other possible explanations, rather than purely tumour biology, were also investigated for the increase in PCI within the short−time frame between DLS and laparotomy. An underestimation of the DLS−PCI will automatically lead to a higher ΔPCI due to better access and staging of disease during laparotomy. In our subgroup of 43 patients (51.2%) with excellent laparoscopic view on all abdominopelvic regions the same significant trend was observed between the ΔPCI and the survival outcomes after laparotomy. In addition, in 12 out of 15 patients (80.0%) with a ΔPCI ≥10 a good laparoscopic evaluation was possible during DLS. Progression of disease during the waiting period between DLS and CRS+HIPEC might also be found more frequently in this study population as systemic treatment regimens are not considered standard therapy in the Netherlands. Despite the widespread use of perioperative systemic chemotherapy, a recent systematic review showed that there is not enough evidence to draw conclusions on the benefit of perioperative systemic therapy for patients with isolated resectable colorectal PM who are candidates for CRS+HIPEC.[39] The CAIRO 6 trial, a multicentre, open−label, Phase II−III RCT, will provide some answers as to the oncological efficacy of perioperative systemic therapy and CRS+HIPEC vs upfront CRS+HIPEC (control arm) for isolated resectable colorectal PM (NCT02758951).

Patients with colorectal PM should undergo DLS routinely prior to exploratory laparotomy for potential CRS+HIPEC to allow calculation of a ΔPCI score. These days, several HIPEC centres worldwide already use DLS routinely, as previously conducted

studies showed that DLS is a safe, accurate, and feasible staging tool in patients with PM from various tumours and might prevent non−therapeutic laparotomies in patients with extensive disease.[28-30,40-43] However, incidental complications such as small bowel perforation or abrasions have been described in the past. For patients who are eligible for CRS+HIPEC, such complications can be of great impact or even fatal, leading to a high chance of excluding a potential curative treatment. Therefore, DLS should be performed without extensive adhesiolysis and with great caution to minimise this risk. Conversion to an open−procedure in case of poor visibility during DLS is only indicated for very specific indications such as the need to create a stoma because of severe obstruction symptoms. In other cases of poor visibility, patients can be given the benefit of doubt after good clinical counselling and be scheduled for CRS+HIPEC with an increased risk of the occurrence of an open−close procedure.

Differences in ΔPCI seem to be a reflection of subtypes of disease. We postulate that future research for colorectal PM should focus on molecular characteristics of tumour lesions that distinguish somnolent from a more aggressive tumour phenotype in patients with colorectal PM. At this moment, several studies have identified four molecular subtypes in colorectal tumours (consensus molecular subtypes, CMS1 to CMS4).[44-47] Guinney et al. showed that 60% of primary colorectal tumours and 75% of colorectal PM belong to the CMS4 subtype.[48] CMS4, also known as the mesenchymal subtype, represents a particular class of highly aggressive tumours that seems to be associated with worse DFS and OS and a poorer response to anticancer therapy.[48-51] For example, patients with stage III colorectal CMS4 tumours did not benefit from systemic adjuvant oxaliplatin treatment as compared to the other subtypes. Strikingly, oxaliplatin is a commonly used chemotherapeutic agent in HIPEC procedures, so identification of the molecular subtype of colorectal PM can have therapeutic consequences.[51] In the future, we will attempt to identify the molecular subtypes associated with the degree of change of ΔPCI and as such the underlying mechanisms for each subgroup.

This retrospective study has potential limitations. The patient cohort was taken from a single institution over a long period of seven years. We can hypothesise that over time patients are diagnosed with colorectal PM at an earlier stage with less disease progression. However, this seems unlikely, as accurate diagnostic staging tools for colorectal PM are still lacking and peritoneal tumour deposits are still difficult to detect with currently available imaging techniques. Also there is no worldwide consensus about the true PCI cut−off value in patients with colorectal PM in which CRS+HIPEC should be contra−indicated. Patients from this cohort were all treated

according to our national Dutch HIPEC protocol, where CRS+HIPEC is only performed in patients with a PCI ≤20. Thus, results from our current study might not be fully generalisable to other highly experienced HIPEC centres worldwide. Although we reported one of the largest series of patients with colorectal PM who underwent DLS with an attempt at undergoing CRS+HIPEC, the number of patients is still insufficient to perform various sub−analysis in the different ΔPCI groups.

CONCLUSIONS

ΔPCI seems to be a new, more dynamic prognostic factor for OS after CRS+HIPEC in patients with colorectal PM. This prognostic factor appears to reflect on a more aggressive tumour biology and disease progression. When confronted intraoperatively with a high ΔPCI of ≥10, HIPEC surgeons should be aware of a more aggressive tumour type and therefore diminished prognosis and reconsider the execution of the CRS+HIPEC procedure.

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6

Surgeons' ability to estimate the extent of surgery prior to cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Purpose

The extent of surgery (ES) during cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) is a well−known risk factor for major postoperative morbidity. Interestingly, the reliability of surgeons to predict the ES prior to CRS+HIPEC is unknown.

Methods

In this prospective, observational cohort study, five surgeons predicted the ES prior to surgery in all consecutive patients with peritoneal metastases (PM) who were scheduled for CRS+HIPEC between March 2018 and May 2019. After the preoperative workup for CRS+HIPEC was completed, all surgeons independently predicted for each individual patient the resection or preservation of 22 different anatomical structures and the presence of a stoma post−HIPEC according to a standardised ES form. The actual ES during CRS+HIPEC was extracted from the surgical procedure report and compared with the predicted ES. Overall and individual positive and negative predictive values (i.e., PPV and NPV) for each anatomical structure were calculated.

Results

One hundred and thirty−one ES forms were collected from 32 patients who successfully underwent CRS+HIPEC. The number of resections was predicted correctly 24 times (18.3%), overestimated 57 times (43.5%), and underestimated 50 times (38.2%). Overall PPVs for the different anatomical structures ranged between 33.3 and 87.8%. Overall NPVs ranged between 54.9 and 100%, and an NPV greater than 90% was observed for 12 anatomical structures.

Conclusions

Experienced surgeons seem to be able to predict better the anatomical structures that remain *in situ* after CRS+HIPEC, rather than predict the resections that were necessary to achieve a complete cytoreduction.

INTRODUCTION

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) is used in highly selected patients with peritoneal metastases (PM) from gastrointestinal, gynaecological, or primary peritoneal cancers.[1–4] This treatment strategy combines the surgical removal of all macroscopically visible disease with perfusion of the abdominal cavity with heated chemotherapy to eradicate residual microscopic disease. Cumulative scientific evidence shows an important improvement in survival outcomes compared to systemic chemotherapy alone.[5–7]

CRS+HIPEC is accompanied by a high treatment–related mortality rate of 0–8% and grade 3–4 morbidity rate of 18–52% in experienced centres.[8–14] In addition, CRS+HIPEC negatively impacts the quality of life (QoL) up to one year after surgery.[15,16] For clinicians and patients, it remains a challenge to weigh the potential survival benefit from CRS+HIPEC against the risk of substantial treatment–related morbidity, mortality, and potentially diminished QoL.

The extent of surgery (ES) has been identified as an independent risk factor for treatment–related morbidity and mortality.[17–20] The ES during CRS obviously depends on the extent of involved organs because of metastases or close relation with metastases, which makes it surgically mandatory to remove the affected anatomical structures. The extent of peritoneal disease widely varies between patients. To predict postoperative outcomes prior to surgery, it is pivotal for every surgeon to appreciate the ES before deciding in a patient–shared decision to proceed with CRS+HIPEC.

However, the correlation between the predicted ES by experienced surgeons in advance with the actual ES during CRS is unknown. As such, the aim of the present study is to determine the correlation between the predicted ES with the actual ES during CRS.

METHODS

Design, setting, and participants

In this prospective, observational cohort study, five surgeons from one Dutch tertiary referral centre (University Medical Center Groningen) predicted the ES prior to surgery in all consecutive patients with histologically proven PM of any origin who were scheduled for CRS+HIPEC. Surgeons with extensive experience in gastrointestinal surgery and CRS+HIPEC procedures were asked to participate in

this study. The learning curve from these surgeons has been studied before and was published by the Dutch Peritoneal Oncology Group (DPOG) elsewere.[21] Data on patient and tumour characteristics, operative and postoperative characteristics were collected prospectively and stored in our institutional database in compliance with the Declaration of Helsinki.[22] The Institutional Ethics Committee of the University Medical Center Groningen approved the study protocol (METc201800157). Written informed consent was obtained from all patients.

Every surgeon predicted the ES before each CRS+HIPEC procedure based on the information from our standardised preoperative workup for CRS+HIPEC and after our weekly multidisciplinary oncology meeting, which are described later. Each surgeon predicted the ES for every patient undergoing CRS+HIPEC irrespective of being the operating surgeon of the case. The surgeons anonymously filled in the 'Extent of Surgery' form to ensure a standardised way of estimating the ES (**Appendix 1**). In summary, this ES form included 22 anatomical structures that might be resected during CRS+HIPEC and a separate question about the presence of a stoma post–HIPEC. The surgeons were instructed to predict the resection or preservation of each anatomical structure and to predict the presence or absence of a stoma post–HIPEC. In cases in which an open–close procedure (i.e., non–therapeutic laparotomy) was expected by the surgeon, he indicated this on the ES form and did not make any predictions regarding the anatomical structures or the presence of a stoma.

After surgery, the ES forms were compared to the actual ES during CRS+HIPEC retrieved from the surgical procedure report. For every anatomical structure, four scenarios could occur: (I) the surgeon predicted correctly that an anatomical structure would be resected during CRS+HIPEC; (II) the surgeon predicted correctly that an anatomical structure would remain *in situ* after CRS+HIPEC; (III) the surgeon predicted incorrectly that an anatomical structure would be resected during CRS+HIPEC; or (IV) the surgeon predicted incorrectly that an anatomical structure would remain *in situ* after CRS+HIPEC. Because our study aimed to correlate the predicted ES to the actual ES, only fully completed ES forms from patients who underwent complete CRS+HIPEC were included in the final analyses.

Primary and secondary outcomes

The primary outcome was the overall ability of the surgeons to predict the ES prior to CRS+HIPEC. The primary outcome was divided into overall positive and negative predictive values per anatomical structure (PPV and NPV, respectively). A high PPV suggests that the surgeon is well able to predict if the anatomical structure will be

resected, whereas a high NPV indicates that the surgeon is well able to predict if the anatomical structure will remain *in situ*. Secondary outcomes included overall and individual PPVs and NPVs for the presence of a stoma post–HIPEC, individual PPVs and NPVs per anatomical structure, overall sensitivity and specificity per anatomical structure, and the occurrence of major postoperative complications. Major postoperative complications were defined as grade ≥III according to the Clavien–Dindo classification system.[23]

Appendix 1 | Extent of Surgery (ES) Form

Date: _____

Surgeon ID: ☐1 ☐2 ☐3 ☐4 ☐5 *(personal surgeon ID)*

Patient ID: _____

I expect that the following anatomical structures will be resected during the CRS+HIPEC procedure:

☐ Stomach	☐ Right diaphragm
☐ Duodenum	☐ Left diaphragm
☐ Jejunum	☐ Right peritoneum
☐ Ileum	☐ Left peritoneum
☐ Ileocecal	☐ Lymph nodes
☐ Right colon	☐ Spleen
☐ Transverse colon	☐ Pancreas
☐ Left colon	☐ Gallbladder
☐ Sigmoid	☐ Bladder
☐ Rectum	☐ Urether
☐ Appendix	☐ Uterus

Total number of resected anatomical structures:

_____

Stoma post HIPEC?

☐ Yes ☐ No

Preoperative evaluation and staging for CRS+HIPEC

All referred patients with PM underwent a standardised preoperative workup for CRS+HIPEC consisting of a clinical examination, laboratory testing, and a thoracic, abdominal, and pelvic computed tomography (CT) to quantify the extent and resectability of peritoneal disease and to rule out other distant metastases. If deemed necessary, additional magnetic resonance imaging (MRI) was performed to further investigate the extent of PM. In patients with colorectal PM, diagnostic laparoscopy (DLS) was routinely performed by one of our HIPEC surgeons to pathologically confirm the presence of PM and to systematically assess the extent and resectability of peritoneal disease according to the peritoneal cancer index (i.e., DLS PCI).[24]

Afterwards, during a weekly multidisciplinary oncology meeting, results from all patients were discussed and eligibility for CRS+HIPEC was determined. In general, patients who were candidates for CRS+HIPEC had limited and resectable PM with no evidence of extra−abdominal disease and were deemed fit for extensive abdominal surgery. Up to three resectable liver metastases were not considered as absolute contra−indication. Extensive small bowel resection resulting in a short bowel syndrome was an absolute contra−indication. No definite PCI limitations were used in patients with PM from pseudomyxoma peritonei (PMP), low−grade appendiceal mucinous neoplasm (LAMN), or mesothelioma. The absolute PCI cut off point to perform CRS+HIPEC in patients with colorectal PM was 20.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

Every CRS+HIPEC procedure was performed by two HIPEC surgeons according to our standardised Dutch HIPEC protocol.[25] CRS was performed only in patients whereby both surgeons judged the PM as completely resectable. In addition, HIPEC was performed only after a complete cytoreduction was achieved.

Each procedure started with an exploratory laparotomy to assess the extent of peritoneal disease in an open setting (i.e., laparotomy PCI). In cases of extensive or not−resectable PM, the procedure was prematurely terminated (i.e., open–close procedure). When the patient was deemed eligible for CRS+HIPEC, all macroscopically visible disease was removed by performing peritonectomies and organ resections. The completeness of cytoreduction score (CC−score) was determined at the end of the cytoreduction.[24] The cytoreduction was considered complete if a CC−score of 0 or 1 was established (i.e., no residual tumour or residual tumours deposits smaller than 2.5mm, respectively).

When complete cytoreduction was achieved, HIPEC was performed for 90 min at a temperature of 41–42 °C by using the open Coliseum technique. Mitomycin C (35mg/m^2) was used in patients with colorectal PM, LAMN, PMP, and small bowel carcinoma. A combination of cisplatin (50 mg/m^2) with doxorubicin (15 mg/m^2) was used in patients with mesothelioma.

Hereafter, the fluid was evacuated from the abdominal cavity and reconstruction surgery including bowel anastomoses with or without a stoma was performed. Patients were admitted to the intensive care unit for strict monitoring for at least one day. Patients were transferred to the nursing ward when cardiac and pulmonary functions were stable.

Data collection

Relevant data on patient characteristics, tumour characteristics, operative characteristics and postoperative morbidity, and mortality were extracted from a merged prospectively maintained institutional database. Postoperative complications within 90 days after surgery were registered according to the Clavien–Dindo classification system.[23] Operative details including the anatomical resections, the presence of a stoma post–HIPEC, the operation time, and total blood loss were retrospectively extracted from the surgical procedure reports.

All fully completed ES forms from patients who underwent complete CRS+HIPEC were registered per surgeon and compared to the actual ES. For every anatomical structure, the four previously described possible scenarios were identified and registered.

Statistical analyses

Categorical variables are reported as number (n) and percentages (%) and continuous variables are reported as median (interquartile range [IQR]). The PPV, NPV, sensitivity, and specificity for each anatomical structure and the presence of a stoma post–HIPEC were calculated in total and per surgeon. In addition, the prevalence of all resections during CRS+HIPEC was determined according to all ES forms. For example, when only one patient underwent a stomach resection during CRS+HIPEC, the total prevalence to correctly predict a stomach resection in this study cohort was five, as five surgeons filled in an ES form.

Thereafter, three categories were created to further classify the surgeon's ability to correctly predict the resection or preservation of each anatomical structure. The

three categories consisted of (I) good PPV/NPV (i.e., >80%), (II) moderate PPV/NPV (i.e., 50–80%), and (III) poor PPV/NPV (i.e., <50%). The prevalence of each anatomical resection was taken into account when these categories were interpreted. All statistical analyses were conducted using SPSS® Statistics version 24.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Thirty−eight consecutive patients underwent an exploratory laparotomy for potential CRS+HIPEC in our academic centre between March 2018 and May 2019. One−hundred fifty−six ES forms were completed during this study period. Because of the aim of the study, not all completed ES forms could be used for final analyses. **Figure 1** provides a structured flow chart explaining this selection process. In six patients (15.8%), it was not possible to correlate the corresponding 24 ES forms (15.4%) to the actual ES, as an open–close procedure occurred. Interestingly, in only 2 out of these 24 ES forms (8.3%) was an open–close procedure correctly predicted in advance. In addition, 1 out of the remaining 132 ES forms was also excluded for analyses, as the surgeon incorrectly predicted an open–close procedure and therefore did not make any predictions about the resection of the different anatomical structures. In summary, the data presented in this manuscript are based on 131 ES forms from 32 patients who successfully underwent CRS+HIPEC.

Patient and tumour characteristics

Table 1 provides an overview of the baseline characteristics. The majority of the patients had already undergone abdominal surgery in the past (90.6%) and were diagnosed with a metachronous onset of PM (56.3%) The most commonly treated tumour types were colorectal (77.4%) and appendiceal (12.9%) cancer. In all patients, radiological examinations were performed during the preoperative evaluation for CRS+HIPEC to assess the extent of disease and included CT for 32 patients (100%), MRI for 10 patients (31.3%), and PET-CT for 12 patients (37.5%). Median time between CT and CRS+HIPEC was 4 weeks (IQR 1−6 weeks) and median time between MRI and CRS+HIPEC was 3 weeks (IQR 1−6 weeks). Furthermore, half of the patients underwent DLS in our centre to pathologically confirm the presence of PM and to systematically assess the extent and resectability of peritoneal disease according to the PCI. DLS was refrained in the other half of the patients, because a DLS or exploratory laparotomy was recently performed to confirm the presence of PM and to investigate the extent of peritoneal disease.

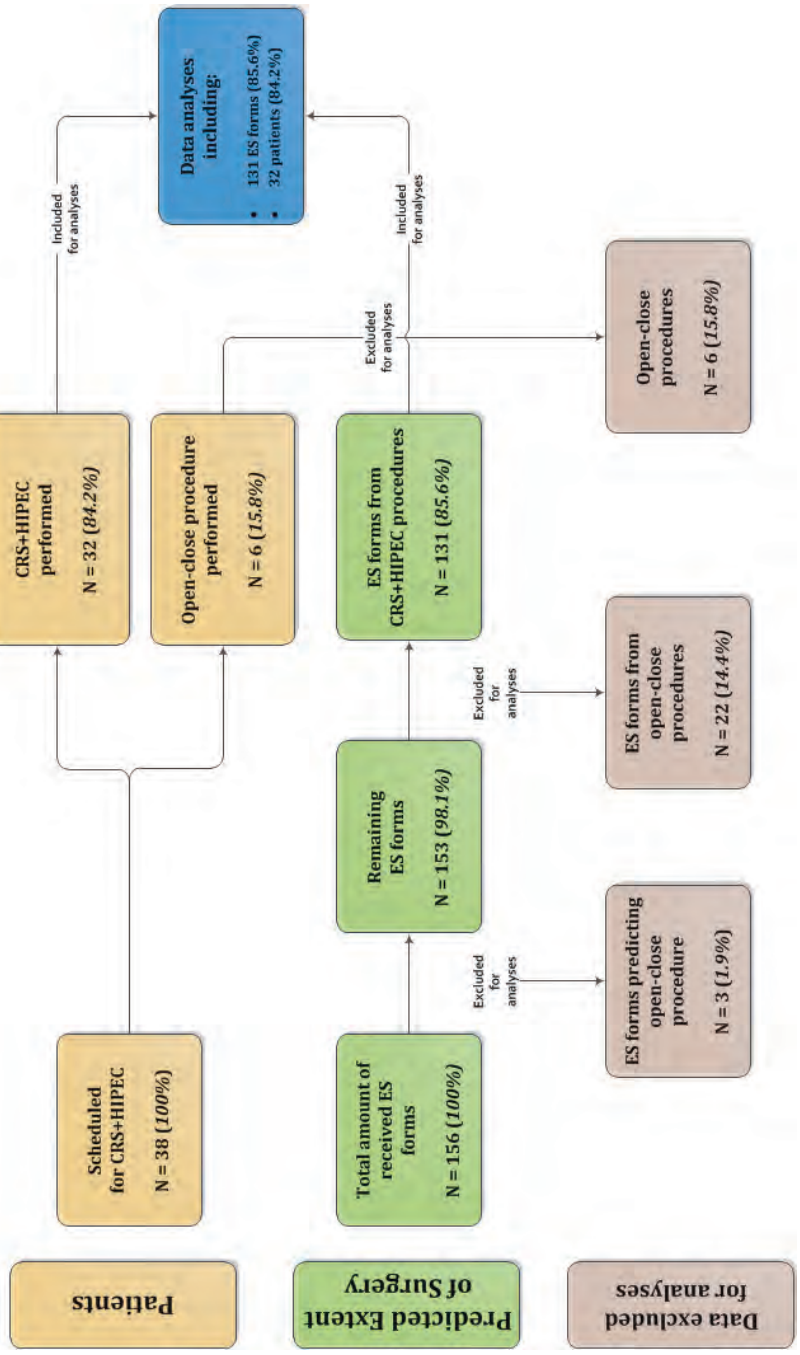

Figure 1 | Overview of selection process of collected extent of surgery (ES) forms for final analyses.

Intraoperative outcomes

The intra−operative outcomes including the anatomical resections are listed in **Table 2**. The median PCI was 5 (IQR 3−11), the median operation time was 468 min (IQR 368−599), and the median amount of intraoperative blood loss was 800 mL (IQR 350−2100). In all patients, a complete cytoreduction (i.e., CC−0 or CC−1) was achieved. During CRS, a median of four anatomical structures were resected, and the most common resections were omentum (96.9%), small bowel (68.8%), rectum (56.3%), sigmoid (50.0%), and ovaries (28.1%). A stoma was created in 19 patients (59.4%).

Table 1 | Baseline characteristics from all 32 patients who successfully underwent CRS+HIPEC.

Patient characteristics	
Age, years, median [IQR]	59 [53-71]
Gender, male, n (%)	13 *(40.6)*
BMI, kg/m², median [IQR]	24.9 [21.7-28.1]
ASA, n (%)	
1	2 *(6.3)*
2	29 *(90.6)*
3	1 *(3.1)*
Prior CRC surgery, n (%)	29 *(90.6)*
Prior chemotherapy, n (%)	10 *(31.3)*
Tumour characteristics	
Primary tumour, n (%)	
Appendix	5 *(15.6)*
Right colon	7 *(21.9)*
Transverse colon	1 *(3.1)*
Left colon	3 *(9.4)*
Sigmoid	8 *(25.0)*
Rectum	6 *(18.8)*
Small bowel	1 *(3.1)*
Signet cell histology, n (%)	5 *(15.6)*
T stage of primary tumour, n (%)	
≤3	9 *(34.6)*
4	17 *(65.4)*
N stage of primary tumour, n (%)	
0	6 *(24.0)*
1	9 *(36.0)*
2	10 *(40.0)*
M stage of primary tumour, n (%)	
0	15 *(55.6)*
1	12 *(44.4)*
Onset of PM, n (%)	
Synchronous	14 *(43.8)*
Metachronous	18 *(56.3)*
Synchronous liver metastases, n (%)	2 *(6.3)*
Primary tumour *in situ*, n (%)	6 *(18.8)*
Presence of a stoma pre-HIPEC, n (%)	6 *(18.8)*
Preoperative evaluation for CRS+HIPEC	
HIPEC indication, n (%)	
Colorectal PM	24 *(77.4)*
PMP	2 *(6.5)*
LAMN	4 *(12.9)*
Mesothelioma	1 *(3.2)*
Small bowel carcinoma	1 *(3.2)*
Preoperative imaging, n (%)	
CT scan	32 *(100)*
MRI scan	10 *(31.3)*
PET scan	12 *(37.5)*
DLS routinely performed, yes, n (%)	16 *(50.0)*

Table 2 | Treatment characteristics from all 32 patients who successfully underwent CRS+HIPEC.

CRS+HIPEC procedure	
PCI at HIPEC, median [IQR]	5 [3–11]
Total anatomic resections, median [IQR]	4 [4–6]
Stomach, n (%)	1 *(3.1)*
Jejunum, n (%)	5 *(15.6)*
Ileum, n (%)	9 *(28.1)*
Ileocecal, n (%)	8 *(25.0)*
Appendix, n (%)	4 *(12.5)*
Right colon, n (%)	5 *(15.6)*
Transverse colon, n (%)	1 *(3.1)*
Left colon, n (%)	7 *(21.9)*
Sigmoid, n (%)	16 *(50.0)*
Rectum, n (%)	18 *(56.3)*
Omentum, n (%)	31 *(96.9)*
Right diaphragm, n (%)	5 *(15.6)*
Left diaphragm, n (%)	3 *(9.4)*
Right peritoneum, n (%)	6 *(18.8)*
Left peritoneum, n (%)	5 *(15.6)*
Lymph nodes, n (%)	5 *(15.6)*
Spleen, n (%)	2 *(6.3)*
Gallbladder, n (%)	6 *(18.8)*
Bladder, n (%)	2 *(6.3)*
Urether, n (%)	4 *(12.5)*
Uterus, n (%)	5 *(15.6)*
Ovaries, n (%)	9 *(28.1)*
Anastomoses, n (%)	
0	11 *(34.4)*
1	12 *(37.5)*
≥ 2	9 *(28.1)*
Stoma post–HIPEC, n (%)	19 *(59.4)*
Operation time, min, median [IQR]	468 [368–599]
Blood loss, mL, median [IQR]	800 [350–2100]
Resection status, n (%)	
CC–0	30 *(93.8)*
CC–1	2 *(6.3)*
Postoperative recovery	
Length of hospital stay, days, median [IQR]	17 [13–24]
Reoperation, n (%)	7 *(21.9)*
In-hospital mortality, n (%)	1 *(3.1)*
Complication rate, Clavien–Dindo, n (%)	
Grade I–II	10 *(31.2)*
Grade III–IV	12 *(37.5)*
Complication type grade ≥ III, n (%)	
Anastomotic leakage	2 *(6.3)*
Postoperative bleeding	1 *(3.1)*
Intra–abdominal abscess	5 *(15.6)*
Wound infection	5 *(15.6)*
Wound dehiscence	3 *(9.4)*
Fistula formation	2 *(6.3)*
Urinoma	1 *(3.1)*
Electrolyte disorder	1 *(3.1)*

Overall ability to predict the extent of surgery

The number of resections necessary to achieve a complete cytoreduction were predicted correctly 24 times (18.3%), overestimated 57 times (43.5%), and underestimated 50 times (38.2%).

The overall PPV for the different anatomical structures ranged between 33.3 and 87.8% (**Table 3a** and **b**, **Figure 2**). The anatomical sites in which the surgeon predicted reasonably well where the appendix (100%), rectum (87.8%), and sigmoid (81.3%). On the other hand, to predict a resection of especially the bladder (41.7%), jejunum (40.0%), peritoneum (34.2%), transverse colon (33.3%), or lymph nodes (32.1%) turned out to be very difficult. In contrast, the overall PPV for the presence of a stoma post−HIPEC was overall high (88.1%). In the 24 ES forms including the patients in whom a stoma was already present prior to CRS+HIPEC, a PPV of 100% was found.

The overall NPV for the different anatomical structures ranged between 54.9 and 100%, including 12 anatomical structures with an NPV greater than 90%. The lowest scores were found for the rectum (54.9%) and sigmoid (59.0%). In addition, the NPV for the absence of a stoma post−HIPEC was 56.2%. This means that surgeons incorrectly predicted the absence of a stoma in 56.2% of the cases, as in these patients a stoma was created during CRS+HIPEC. In the 24 ES forms including the patients in whom a stoma was already present prior to CRS+HIPEC, a NPV of 62.5% was found.

The sensitivity for resection of the different gastrointestinal anatomical structures was overall low with a range of 0.0 to 85.0%. Especially, overall sensitivity for the small bowel resections (i.e., jejunum, ileum, and ileocecal) was only 28.6, 40.7, and 21.9%, respectively. For the other anatomical structures sensitivity was the highest for the left peritoneum (96.2%) and the right peritoneum (73.3%). Overall sensitivity for the presence of a stoma post−HIPEC was found to be 51.3%.

The specificity for the preservation of the different anatomical structures was overall high and ranged from 75.5 to 100%.

Individual ability to predict the extent of surgery

The individual ability to predict the ES is outlined in **Supplementary Table 1** and **2**. Major differences in PPVs between the surgeons were observed for most of the anatomical structures, with exception of the appendix. For nine anatomical structures, the range between individual PPVs even exceeded 50% (i.e., jejunum,

ileum, left colon, transverse colon, spleen, gallbladder, bladder, lymph nodes, and uterus). The largest differences were observed for the transverse colon (range 100%), uterus (range 87.5%), and ileum (range 83.3%).

In contrast, the NPVs for the majority of the anatomical structures were similar between surgeons and differences ranged between 1.5 and 66.7%. The largest difference was observed for the sigmoid (range 31.8%).

Impact of radiological examinations on the ability to predict the extent of surgery

According to the preoperative evaluation for CRS+HIPEC, 87 ES forms (66.4%) included patients in whom only CT was performed and 44 ES forms (33.6%) included patients in whom both CT and MRI were performed. Combining CT with MRI significantly improved the overall PPV for the sigmoid (85.2 vs 76.2%, $p < 0.0001$), rectum (100 vs 73.9%, $p < 0.0001$), and ureter (100 vs 40.0%, $p = 0.024$), and the overall NPV for the jejunum (100 vs 85.4%, $p = 0.001$). For the other anatomical structures no significant differences were found for the overall PPV and overall NPV.

Postoperative morbidity and mortality

Major postoperative complications (i.e., grades III–IV) occurred in 12 patients (37.5%) (**Table 2**). The most common surgical complications in these patients were intra−abdominal abscesses (15.6%) and wound infections (15.6%). Reoperation was necessary in seven patients (21.9%). The overall 90−days postoperative mortality rate (i.e., grade V) was 3.1%.

Table 3a | Overall positive and negative predictive values for the different gastro–intestinal anatomical structures and presence of a stoma post–HIPEC.

Anatomical structure	Surgeon's prediction	Resected during CRS+HIPEC	*In situ* after CRS+HIPEC	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Stomach, n	Resection	0	0	*	96.2	0.0	100
	Remains *in situ*	5	126				
Duodenum, n	Resection	0	0	*	100	¥	100
	Remains *in situ*	0	131				
Jejunum, n	Resection	8	12	40.0	89.2	28.6	89.2
	Remains *in situ*	12	99				
Ileum, n	Resection	11	9	55.0	85.6	40.7	91.3
	Remains *in situ*	16	95				
Ileocecal, n	Resection	7	8	46.7	78.4	21.9	91.9
	Remains *in situ*	25	91				
Appendix, n	Resection	9	0	100	93.4	52.9	100
	Remains *in situ*	8	114				
Right colon, n	Resection	17	12	58.6	97.1	85.0	89.2
	Remains *in situ*	3	99				
Transverse colon, n	Resection	2	4	33.3	98.4	50.0	96.9
	Remains *in situ*	2	123				
Left colon, n	Resection	15	12	55.6	83.7	46.9	87.9
	Remains *in situ*	17	87				
Sigmoid, n	Resection	39	9	81.3	59.0	53.4	84.5
	Remains *in situ*	34	49				
Rectum, n	Resection	43	6	87.8	54.9	53.8	88.2
	Remains *in situ*	37	45				

	Surgeon's prediction	Stoma after CRS+HIPEC	No stoma after CRS+HIPEC	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Stoma post–HIPEC, n	Yes	37	5	88.1	56.2	51.3	90.9
	No	39	50				

***** In none of the 131 ES forms removal of the anatomical structure was predicted and therefore the overall PPV could not be calculated.
¥ In none of the 131 ES forms the anatomical structure was resected during CRS+HIPEC and therefore the overall sensitivity could not be calculated.

Table 3b | Overall positive and negative predictive values for the other anatomical structures.

Anatomical structure	Surgeon's prediction	Resected during CRS+HIPEC	*In situ* after CRS+HIPEC	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Right diaphragm, n	Resection	10	9	52.6	91.1	50.0	91.9
	Remains *in situ*	10	102				
Left diaphragm, n	Resection	8	6	57.1	95.7	61.5	94.9
	Remains *in situ*	5	112				
Right peritoneum, n	Resection	22	18	55.0	91.2	73.3	82.1
	Remains *in situ*	8	83				
Left peritoneum, n	Resection	25	48	34.2	98.3	96.2	45.7
	Remains *in situ*	1	57				
Lymph nodes, n	Resection	9	19	32.1	93.2	56.3	83.5
	Remains *in situ*	7	96				
Spleen, n	Resection	6	3	66.7	95.1	50.0	97.5
	Remains *in situ*	6	116				
Pancreas, n	Resection	0	0	*	100	¥	100
	Remains *in situ*	0	131				
Gallbladder, n	Resection	4	3	57.1	85.5	18.2	97.2
	Remains *in situ*	18	106				
Bladder, n	Resection	5	7	41.7	96.6	55.6	94.3
	Remains *in situ*	4	115				
Ureter, n	Resection	6	3	66.7	94.3	46.1	97.5
	Remains *in situ*	7	115				
Uterus, n €	Resection	11	13	45.8	76.9	47.8	75.5
	Remains *in situ*	12	40				

***** In none of the 131 ES forms removal of the anatomical structure was predicted and therefore the overall PPV could not be calculated.
¥ In none of the 131 ES forms the anatomical structure was resected during CRS+HIPEC and therefore the overall sensitivity could not be calculated.
€ Only based on 76 ES forms as these forms included information about female patients.

Figure 2 | Overall positive and negative predictive values for all anatomical structures divided into good PPV/NPV (i.e., >80%), moderate PPV/NPV (i.e., 50−80%), and poor PPV/NPV (i.e., <50%)

DISCUSSION

In this prospective observational cohort study, consisting of 131 ES forms, the surgeons' ability to predict the ES prior to CRS+HIPEC was evaluated for the first time. Overall, the surgeons seemed to be able to predict better the anatomical structures that remain *in situ* after CRS+HIPEC, rather than predict the resections that were necessary to achieve a complete cytoreduction with an underestimation of the ES in almost 40% of the cases.

Over the past decades, CRS+HIPEC has improved survival outcomes for patients with PM from various primary tumours.[1–7] This potential survival benefit needs to be in balance with the associated risks of treatment−related morbidity and

mortality. HIPEC surgeons attempt to make this estimation for their patients in advance of planning an CRS+HIPEC procedure, but the complex interplay of patient characteristics, tumour characteristics, and treatment−related characteristics makes this task almost impossible. In recent years, various risk factors for the occurrence of major postoperative complications after CRS+HIPEC (i.e., grades III–V) have been identified.[17,20,26,27] The ES—including the number of resected anatomical structures—has repeatedly been described as an independent risk factor for treatment−related morbidity.[20,26,27] A surgeon's ability to correctly predict the ES in advance of CRS+HIPEC seems to be one of the key elements to estimating the individual risk for treatment−related morbidity, which is of importance for informing patients in the outpatient clinic and patient−shared decision making. In our current study, we show that surgeons—despite the presence of different state−of−the−art imaging modalities such as multidetector CT, PET−imaging, and MRI—predicted the number of resections correctly in only 18.3% of the cases. Furthermore, in 38.2%, an underestimation of the number of anatomical resections occurred, subsequently the associated risk for treatment−related morbidity might also be underestimated prior to surgery. The high PPV for the presence of a stoma (88.1%) and the low NPV for the absence of a stoma (56.2%) post−HIPEC supports our protocol with stoma counselling and education for every patient prior to CRS+HIPEC.

To our knowledge, no previous studies have reported on surgeon's ability to predict the ES prior to CRS+HIPEC. However, the large number of publications about the limitations of current imaging modalities in detecting PM and the occurrence of an open–close procedure in up to 50% of the patients, confirm that in most patients surgeons despite having performed extensive imaging will only discover the true extent of peritoneal disease during the exploratory laparotomy itself.[28–35] This has major logistical consequences as for instance an open−close procedure is not only a patient tragedy, but also a drawback for the other patients waiting on the list. This is also reflected by our current study showing both an overestimation and underestimation of the number of resected anatomical structures during CRS+HIPEC in 43.5 and 38.2% of the cases, respectively.

Interestingly, for some specific anatomical structures we found high PPVs for each of the individual surgeons. For the appendix, this might be explained by the clear indication to remove this organ during CRS+HIPEC standardly. The PPVs for sigmoid and rectum were also high, which might be explained by the relatively high number of patients with synchronous onset of colorectal PM from sigmoid or rectal cancer (25.0 and 18.8%, respectively), and where the surgeon knows in advance

that this part of the colon will have to be removed. Overall, NPVs for the different anatomical structures were higher and showed less variation between surgeons compared to the PPVs. This suggests that surgeons were better able to predict the anatomical structures that remained *in situ* after CRS+HIPEC than to predict the anatomical structures that would be resected during CRS+HIPEC to achieve a complete cytoreduction.

From a clinical perspective, PPVs and NPVs are the most interesting outcomes reflecting the ability to predict the ES according to our daily practice. The ES that seems to be necessary to achieve a complete cytoreduction plays a crucial role in the selection process for CRS+HIPEC. This estimation per anatomical structure in advance is expressed by the PPV and NPV. However, our study results should be interpreted with some caution, as from a statistical point of view it is known that both values are influenced by the prevalence of the performed resections during CRS+HIPEC. For example, in our study cohort, there is a relatively high number of patients with rectal cancer, making it easier for surgeons to predict a rectum resection, resulting in a higher PPV. On the other hand, it is more difficult to predict the preservation of the rectum resulting in a lower NPV. In summary, the PPVs and NPVs provide specific information about the ability from our surgeons to predict the ES in this specific study population.

This study has certain strengths and limitations. This is the first study that describes the ability of experienced surgeons to predict the ES prior to CRS+HIPEC. These results have been collected in a way that fully reflects our daily clinical practice by having only experienced surgeons complete the standardised ES forms prior to surgery for a group of patients who represent our average HIPEC population. Gathered knowledge from this study made us aware of the still−existing challenge of predicting the ES, and future research should focus on optimising the detection of PM during the preoperative workup. There is not one CRS+HIPEC procedure; these procedures are very different in extent and burden and thus outcomes and a better estimation of the ES prior to surgery will improve our preoperative decision making especially when we are dealing with patients that are older or have extensive comorbidity. Our study has some limitations due to the single−centre approach and the already−mentioned limitations of the PPV and NPV from a statistical point of view. Our surgeons are extensively trained to perform gastrointestinal procedures and CRS+HIPEC procedures and therefore these results might not be extrapolated to all centres, although most CRS+HIPEC procedures are performed in highly experienced centres. The limitations of the PPV and NPV have been partly overcome

by also presenting the sensitivity and the specificity for the different anatomical structures, as these outcomes are not influenced by the number of resections. However, sensitivity and specificity seems less useful for surgeons because they do not reflect daily practice, as the predictions for the ES are always made prior to surgery.

CONCLUSIONS

The ES during CRS+HIPEC is a well−known risk factor for the occurrence of major postoperative morbidity, and therefore essential to know prior to surgery. Surgeons with extensive experience in performing these procedures have the ability to predict in advance which of the anatomical structures can be preserved during CRS+HIPEC but in most cases fail to predict the actual ES, including the resections that are necessary to achieve a complete cytoreduction. This phenomenon has not been described before and emphasises that future research should focus even more on optimising the detection of the extent of disease prior to surgery.

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SUPPLEMENTARY DATA

Supplementary Table 1 | Positive and negative predictive values for all anatomical structures divided per surgeon.

Anatomical structure	Surgeon I *n = 21*		Surgeon II *n = 28*		Surgeon III *n = 30*		Surgeon IV *n = 30*		Surgeon V *n = 22*	
	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)
Stomach	*	95.2	*	96.4	*	96.7	*	96.7	*	95.5
Duodenum	*	100	*	100	*	100	*	100	*	100
Jejunum	*	90.5	60.0	91.3	28.6	87.0	28.6	82.6	100	95.2
Ileum	0.0	84.2	83.3	90.9	25.0	80.8	60.0	80.0	66.7	94.7
Ileocecal	*	66.7	*	82.1	60.0	80.0	33.3	74.1	42.9	93.3
Appendix	*	90.5	100	92.3	100	96.4	100	96.4	100	89.5
Right colon	75.0	100	60.0	100	75.0	92.3	44.4	100	57.1	93.3
Transverse colon	*	95.0	0.0	100	0.0	96.6	100	100	50.0	100
Left colon	100	94.1	66.7	84.0	60.0	80.0	27.3	84.2	75.0	77.8
Sigmoid	87.5	53.8	75.0	56.3	75.0	50.0	88.9	60.0	81.8	81.8
Rectum	100	50.0	83.3	50.0	80.0	50.0	100	40.0	75.0	64.3
Right diaphragm	66.7	88.9	40.0	95.7	33.3	88.9	66.7	88.9	60.0	94.1
Left diaphragm	66.7	100	75.0	100	*	92.9	50.0	96.2	100	90.5
Right peritoneum	62.5	100	44.4	84.2	50.0	90.0	62.5	90.9	60.0	94.1
Left peritoneum	33.3	91.7	50.0	100	46.2	100	27.3	100	36.4	100
Lymph nodes	75.0	100	80.0	100	20.0	90.0	*	81.8	0.0	95.2
Spleen	100	100	100	96.3	*	90.0	25.0	96.2	100	95.0
Pancreas	*	100	*	100	*	100	*	100	*	100
Gallbladder	100	90.0	100	92.6	40.0	88.0	*	80.0	*	77.3
Bladder	*	95.2	*	92.9	100	100	22.2	100	100	95.2
Ureter	50.0	94.7	100	96.3	66.7	96.3	66.7	92.6	*	90.9
Uterus	40.0	75.0	60.0	81.8	100	80.0	12.5	60.0	75.0	87.5
Stoma post–HIPEC	100	53.8	90.0	55.6	87.5	54.5	66.7	50.0	90.0	75.0

***** In none of the ES forms from this surgeon removal of the anatomical structure was predicted and therefore the PPV could not be calculated.

Supplementary Table 2 | Sensitivity and specificity for all anatomical structures divided per surgeon.

Anatomical structure	Surgeon I *n = 21*		Surgeon II *n = 28*		Surgeon III *n = 30*		Surgeon IV *n = 30*		Surgeon V *n = 22*	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Stomach	0.0	95.2	0.0	100	0.0	100	0.0	100	0.0	100
Duodenum	¥	100	¥	100	¥	100	¥	100	¥	100
Jejunum	0.0	100	60.0	91.3	40.0	80.0	33.3	79.2	50.0	100
Ileum	0.0	88.9	71.4	95.2	16.7	87.5	37.5	90.9	66.7	94.7
Ileocecal	0.0	100	0.0	100	37.5	90.9	12.5	90.9	75.0	77.8
Appendix	0.0	100	50.0	100	66.7	100	66.7	100	60.0	100
Right colon	100	94.4	100	92.0	60.0	96.0	100	80.8	80.0	82.4
Transverse colon	0.0	95.0	¥	100	0.0	96.6	100	100	100	95.2
Left colon	80.0	100	33.3	95.5	37.5	90.9	50.0	66.7	42.9	93.3
Sigmoid	53.8	87.5	56.3	75.0	35.2	84.6	50.0	92.9	81.8	81.8
Rectum	60.0	100	55.6	80.0	44.4	83.3	55.6	100	54.5	81.8
Right diaphragm	50.0	94.1	66.7	88.0	25.0	92.3	40.0	96.0	75.0	88.9
Left diaphragm	100	94.7	100	96.0	92.9	0.0	66.7	92.6	33.3	100
Right peritoneum	100	81.3	57.1	76.2	71.4	78.3	62.5	87.0	75.0	88.9
Left peritoneum	75.0	64.7	100	72.7	100	45.8	100	33.3	100	61.1
Lymph nodes	100	94.4	100	95.8	50.0	69.2	0.0	75.0	0.0	95.2
Spleen	100	100	50.0	100	0.0	100	50.0	89.3	66.7	100
Pancreas	¥	100	¥	100	¥	100	¥	100	¥	100
Gallbladder	33.3	100	33.3	100	40.0	88.0	0.0	100	0.0	100
Bladder	0.0	100	0.0	100	100	100	100	75.0	50.0	100
Ureter	50.0	94.7	50.0	100	66.7	96.3	50.0	96.2	0.0	100
Uterus	50.0	66.7	60.0	81.8	40.0	100	20.0	46.2	75.0	87.5
Stoma post–HIPEC	57.1	100	52.9	90.9	41.2	92.3	25.0	85.7	75.0	90.0

¥ In none of the ES forms from this surgeon this anatomical structure was resected during CRS+HIPEC, and therefore sensitivity could not be calculated.

PART II

NEW AVENUES FOR RESEARCH

7

Impact and risk factors for clinically relevant surgery–related muscle loss in patients after major abdominal cancer surgery

Study protocol for a prospective observational cohort study (MUSCLE POWER)

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ABSTRACT

Background

Surgery−related muscle loss (SRML) occurs in at least one out of three cancer patients within one week after major surgery. Though, this important phenomenon has hardly been investigated.

Methods

The MUSCLE POWER is a prospective, observational cohort study that investigates the presence, impact, and predictors for clinically relevant SRML in 178 cancer patients after major abdominal surgery using ultrasound measurements, squeeze and force measurements, and QoL questionnaires. Primary endpoint is the proportion of patients with clinically relevant SRML defined as ≥5% muscle loss within one week after surgery, measured by the cross−sectional area (CSA) of three different muscles: m. biceps brachii, m. rectus femoris, and m. vastus intermedius. Possible correlation with QoL and fatigue up to six months after surgery will be investigated. Daily physical activity during hospital stay will be monitored by a motility tracker, and protein intake will be monitored by a dietician. Possible predictors for clinically relevant SRML—consisting of age ≥65 years, preoperative diabetes, preoperative sarcopenia, major postoperative complications (Clavien−Dindo ≥III), insufficient physical activity, and insufficient postoperative protein intake—will be investigated with a multivariable logistic regression analyses with a backward stepwise approach. Variables with a $p < 0.05$ will be retrained in the final multivariable model.

Discussion

The MUSCLE POWER investigates the presence and impact of clinically relevant SRML in cancer patients after major abdominal surgery. Crucial information regarding possible predictors for clinically relevant SRML can be used in future intervention studies to prevent postoperative muscle loss and subsequently improve postoperative outcome and QoL.

Trial registration

Medical Ethics Committee of the University Medical Center Groningen, the Netherlands (METc2018/361, version 3.0, January 21, 2019), and Netherlands Trial Register ([NTR], NTR NL7505, version 1.0, February 7, 2019).

INTRODUCTION

Acute muscle loss has been studied extensively in critically ill patients in the intensive care unit (ICU) and is recognized as a common problem.[1-7] At least 25% of the patients will develop ICU−acquired paresis, which is associated with significant mortality and morbidity and predicts long−term functional disability.[5-9]

In contrast to the growing amount of knowledge about the impact of muscle loss in ICU patients, there have been only a few studies reporting the amount of muscle loss in patients after major surgery.[10-13] In patients who underwent elective high−risk cardiothoracic surgery, 55% developed quadriceps atrophy seven days after surgery.[10] In another study, one out of three cancer patients developed clinically relevant surgery−related muscle loss (SRML) within one week after curative gastric cancer surgery.[11] Clinically relevant SRML was associated with postoperative complications and a longer length of hospital stay. These findings were also confirmed in a study including 254 patients who underwent major hepatectomies with extrahepatic bile duct resections.[12] In this study, patients with clinically relevant SRML within one week after surgery had a significantly higher rate of major postoperative complications and an increased surgery−related mortality risk. Quality of life (QoL) and fatigue were decreased up to three months after surgery. Postoperative fatigue is one of the main complaints after surgery and its presence prevents patients from returning to work. Only one study investigated and identified two independent predictors for clinically relevant SRML (age ≥65 years and preoperative diabetes).[11] These few studies demonstrate that clinically relevant SRML might be a major problem for our current healthcare system based on its impact on several short−term postoperative problems and its postoperative impact on QoL and fatigue.

Prevention of clinically relevant SRML can be a promising strategy to improve morbidity and mortality and increase QoL after major surgery. Unfortunately, these days, there is still a lack of scientific knowledge regarding this topic. Therefore, we made the design of the MUSCLE POWER study to further investigate the presence, impact, and possible predictors for clinically relevant SRML in cancer patients who underwent major abdominal cancer surgery. With this obtained knowledge, future intervention studies can focus on the prevention of postoperative muscle loss and minimise its impact on different postoperative outcomes and QoL in the long term.

METHODS

Study design

The MUSCLE POWER study is an observational single−centre prospective cohort study in an academic setting that evaluates the proportion of cancer patients with clinically relevant SRML after major abdominal cancer surgery by using bedside ultrasound measurements of the arms and legs. Clinically relevant SRML is defined as ≥5% muscle loss within one week after surgery measured by the cross−sectional area (CSA) of the different muscles. In addition, we explore the effects of clinically relevant SRML on different life domains of QoL and fatigue after surgery. Furthermore, we investigate six possible predictors for clinically relevant SRML, identified by current literature or expert opinion, to provide essential information for future intervention studies to prevent clinically relevant SRML and reduce the possible associated impact on short− and long−term outcomes after surgery. We hypothesize that 50% of our patient population will have clinically relevant SRML within one week after major abdominal cancer surgery. Predictors for developing clinically relevant SRML will be preoperative sarcopenia, preoperative diabetes, age ≥65 years, occurrence of major postoperative complications, insufficient physical activity, and insufficient protein intake during the first week after surgery. Clinically relevant SRML will also be associated with fatigue and a reduced QoL three and six months after surgery.

This trial will run in the University Medical Center Groningen (UMCG) from April 2019 until the target sample size of 178 patients has been reached (probably at the end of 2020). Other hospitals might be invited to collaborate, depending on the recruitment rate during the first year of patient inclusion.

Patient selection

Adult patients scheduled for major abdominal cancer surgery based on an underlying malignancy of the liver, pancreas, bile duct, colon, rectum, or pseudomyxoma peritonei are eligible for this study. Potential eligible patients will be identified at the weekly multidisciplinary oncology meeting and screened and informed about the study by their surgeon in the outpatient clinic during standard preoperative visits. Patients who meet the inclusion and exclusion criteria and are interested to participate in the study will receive a patient information letter describing the aims, content, duration, and objections of the study as well as the risks of participating. The investigator will contact these patients within one week by telephone to provide further information and answer remaining questions. After this conversation,

patients have two weeks to decide whether they would like to participate. For patients who want to participate, an informed consent form has to be signed prior to the surgical procedure. During the study period, patients can leave the study at any time for any reason without any consequences. The investigator can decide to withdraw a patient from the study for urgent medical reasons.

Inclusion criteria

To be eligible to participate in this study, a patient must meet all of the following inclusion criteria:

- Age ≥18 years;
- Able to read and understand the Dutch language;
- Diagnosed with or suspicion of a liver tumour (primary cancer or colorectal liver metastases), pancreatic malignancy, bile duct malignancy, colon tumour, rectum tumour, or pseudomyxoma peritonei;
- Scheduled for open major abdominal cancer surgery at UMCG, consisting of the following surgical procedures:
    - cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy (CRS+HIPEC);
    - (sub)total pelvic exenteration;
    - (sub)total colon resection;
    - pylorus preserving pancreaticoduodenectomy (PPPD);
    - whipple procedure (classic pancreaticoduodenectomy);
    - (sub)total pancreatectomy;
    - major liver resection defined as ≥3 liver segments.
- Undergone a preoperative computed tomography (CT) of the abdomen to determine preoperative sarcopenia;
- Given written informed consent to participate in the study.

Exclusion criteria

A potential eligible patient who meets any of the following exclusion cannot participate in this study: scheduled to undergo emergency resection; scheduled to undergo laparoscopic surgery; scheduled to undergo robotic surgery; and unable to co−operate and give informed consent.

Study endpoints

The primary endpoint of this study is the proportion of patients who have clinically relevant SRML, defined as ≥5% muscle loss within one week after surgery measured

by the CSA of the different muscles with bedside ultrasound measurements. The secondary endpoints are related to the amount of loss of muscle mass per day after surgery and during hospital stay and to the amount of decrease in muscle strength per day after surgery and during hospital stay. Six possible predictors for clinically relevant SRML—consisting of age ≥65 years, preoperative diabetes, preoperative sarcopenia, major postoperative complications (Clavien−Dindo ≥III), insufficient physical activity, and postoperative protein intake—will be explored. In addition, we will evaluated the amount of unplanned readmissions within 30 days after discharge, and the QoL and fatigue three and six months after surgery between patients with and without clinically relevant SRML.

Sample size calculation

The sample size calculation is based on the primary endpoint, the proportion of patients with clinically relevant SRML defined as ≥5% muscle loss within one week after surgery measured by the CSA of the different muscles. To determine the appropriate sample size (SS) for estimating the proportion of patients with clinically relevant SRML, we used the following formula:

$$SS = (Z\text{−score})^2 * \text{proportion} * (1 - \text{proportion}) / (\text{margin of error})^2$$

For a confidence level of 95%, α is 0.05 and the corresponding Z−value is 1.96. The sample proportion is unknown. We chose the number 0.50 (50%) because it takes the maximum spread into account. Consensus about the margin of error was achieved by joint discussion of the research group; a margin error of 0.075 (7.5%) was accepted. In total, 178 patients will be enrolled in the study to reach the target sample size.

Measurements

Figure 1 shows an overview of the different types of measurements during the study period.

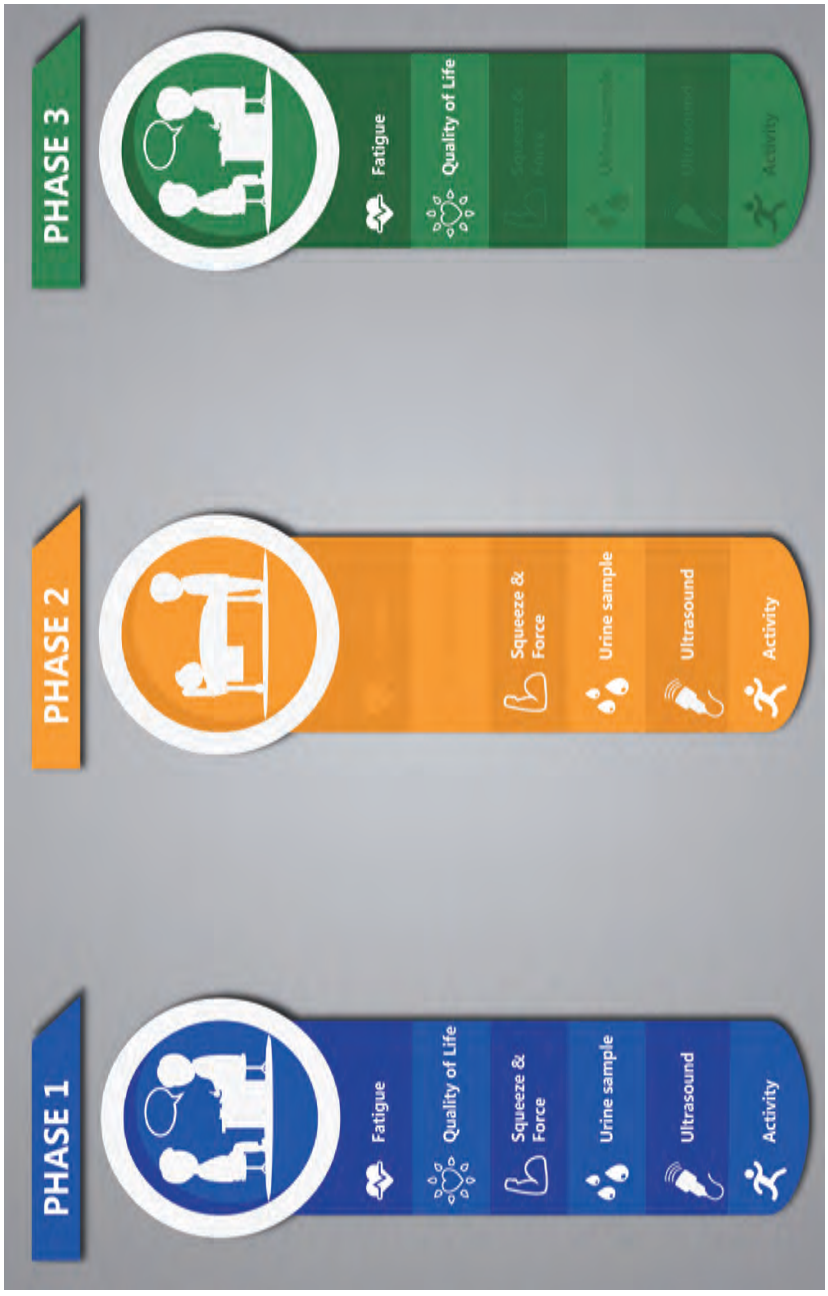

Figure 1 | Study design.

Phase 1: one day prior to surgery; phase 2: weeks after surgery till discharge; and phase 3: three and six months after surgery.

Muscle mass

Baseline muscle mass for each patient will be measured by the investigator one day prior to surgery with a hand−held ultrasound system (Philips FUS6882 Lumify L12−4) and consist of ultrasound measurements of the following four muscles: m. biceps brachii, m. rectus abdominis, m. rectus femoris, and m. vastus intermedius. For each muscle, the cross-section (anterior−posterior diameter) and the CSA will be measured bilaterally three times. Patients will be positioned supine on the bed with arm and leg muscles relaxed. The transducer will be placed perpendicular to the long axis of the different muscles (i.e., perpendicular to the major axis of the limb). The location of the measurement of the arm will be at two−thirds of the length between the tip of the acromion and elbow fold with the elbow extended and the forearm in supine position. In the leg, the measurement will be at one−half the distance between spina iliaca anterior superior and the proximal border of the patella. The rectus will be measured halfway between the xiphoid and umbilicus on both sides of the abdomen. These different measuring points will be marked with a waterproof marker to ensure fixed points during the rest of the study period.

The muscle ultrasound measurements will be repeated on the third, seventh, and tenth day after surgery and on the day of discharge, with exception of the m. rectus abdominis, because of the laparotomy wound that will occur after surgery. Baseline measurements and measurements obtained on the seventh day after surgery will be used to investigate the primary endpoint. Other measurements will be used to investigate the amount of loss of muscle mass per day after surgery and during hospital stay.

Muscle strength

Squeeze and force measurements will be performed on the same days as the ultrasound measurements: one day prior to surgery; third, seventh, and tenth day after surgery; and on the day of discharge.

Isometric muscle force from grip strength of the hand, elbow flexion and extension, and knee flexion and extension will be measured with a hand−held dynamometer (HHD) using different break tests. A description of the body positions of the HHD and the patient during different measurements is described in **Table 1** and shown in **Figure 2** (**A** and **B**) and **Figure 3** (**A** and **B**). Patients will receive the instruction to build up maximal strength in one to two seconds. The researcher will gradually overcome the muscle force and stop at the moment the extremity gives away. Each measurement will be carried out three times in series with 20 seconds intervals between the contractions. This is a standardised method for performing a break test.[14]

By using multiple squeeze and force measurements at different time points, we can analyse the amount of decrease in muscle strength per day, discover specific patterns of decrease in muscle strength, and calculate the total amount of decrease in muscle strength during the hospital stay.

Table 1 | Body position of the hand−held dynamometer and the patient during different break tests.

	Joint/limb position	Localisation HHD	Position patient
Elbow flexion	Neutral shoulder, elbow flexed 90º, upper arm against trunk	Just proximal to styloid process of radius	Lying supine
Elbow extension	Same as in flexion	Just proximal to ulnar head	Same as in flexion
Knee flexion	Hip and knee flexed 90º	Just proximal to calcaneus	Sitting in a chair
Knee extension	Same as in flexion	Just proximal to talis	Same as in flexion

Physical activity

Insufficient physical activity post operation might be a possible predictor for clinically relevant SRML. Therefore, each patient will wear a motility tracker (Actigraph wGT3X−BT [Actigraph, Pensacola, FL, USA]) during the first week after surgery except on the day of operation and during water−based activities. The Actigraph WGT3X−BT is a small and lightweight device that will be worn on the left or right ankle with an elastic belt to prevent discomfort for the patient and to measure physical activity data as reliably as possible. The device does not provide direct feedback to the patient.

The Actigraph provides high raw acceleration data to capture physical activity intensity, activity bouts, and sedentary bouts. The information from the activity tracker will be downloaded to ActiLife. This program automatically provides total activity counts and time per intensity level per day. Existing cut−off points for moderate (2020−5999 counts/min) and vigorous intensity physical activity (>5999 counts/min) will be used. A valid monitoring day will be defined as having 10 or more hours of monitor wear. Wear time is determined by subtracting non−wear time from 24 hours. Non−wear time is as defined by an interval of at least 60 consecutive min of zero activity intensity counts.

A

B

Figure 2 | Positions of the hand−held dynamometer for elbow flexion and extension.
(A) Elbow flexion. (B) Elbow extension.

A

B

Figure 3 | Positions of the hand–held dynamometer for knee flexion and extension. *(A) Knee flexion. (B) Knee extension.*

The total amount of moderate and vigorous intensity physical activity in the first seven days after surgery will be calculated. If a patient's activity is less than 150 min of moderate/vigorous intensity physical activity within the first week after surgery, it will be registered as 'insufficient physical activity'. We will than investigate if insufficient physical activity is associated with clinically relevant SRML.

Protein intake

We suspect that malnutrition prior to surgery and insufficient protein intake during the first week after surgery might be possible predictors for clinically relevant SRML. According to the European Society for Clinical Nutrition and Metabolism guidelines, surgical patients need 1.5 g/kg protein per day after major surgery.[15] Patients will fill in the patient−generated subjective global assessment (PG−SGA) questionnaire one day prior to surgery. This validated questionnaire for nutritional assessment focuses on four elements: (1) dietary intake change, (2) gastrointestinal symptoms, (3) short−term weight loss, and (4) changes in functional capacity.[16] Each element can be scored from zero to four. The higher the total score from the PG−SGA, the greater the risk for malnutrition, in which a score of nine or higher indicates a critical need for nutritional interventions.

The first seven days after surgery, daily protein and energy intake will measured by a dietician by using a nutrition dairy. The intake on the day of the surgical procedure itself will be excluded. Afterwards, we will calculate the number of days that the protein intake was not adequate (e.g., <1.5 g/kg). We will register the protein intake as 'insufficient' if the patient received less than 1.5 g/kg for two or more days within the first week after surgery. Next we investigate if an insufficient amount of protein intake during the first week after surgery is associated with clinically relevant SRML.

Sarcopenia preoperatively

We suspect that preoperative sarcopenia might be a possible predictor for clinically relevant SRML. The presence of preoperative sarcopenia will be measured on preoperative workup CT scans by an experienced musculoskeletal radiologist. Cross−sectional skeletal muscle surface (cm^2) will be assessed at the level of the third lumbar vertebra (L3) to determine the sarcopenia index. Measurements of the psoas and abdominal wall will be obtained and compared. Skeletal muscle cut−off values for sarcopenia will be corrected for height, age, and ethnic group according to the consensus diagnostic criteria for sarcopenia, developed by the European Working Group on Sarcopenia in Older People (EWGSOP).[17] These measurements will be used to investigate if preoperative sarcopenia is associated with clinically relevant SRML.

Other possible predictors

In addition to the presence of insufficient physical activity, insufficient protein intake, and preoperative sarcopenia, we identified three other possible predictors for clinically relevant SRML: age ≥65 years, preoperative diabetes, and occurrence of major postoperative complications. Data about these possible predictors will be collected from digital patient records. Postoperative complications will be registered using the Clavien−Dindo classification system.[18] Major postoperative complications are defined as Clavien−Dindo ≥III. All possible predictors will be dichotomized (presence or absence of the predictor) for further analyses.

Urine collection

Urinary creatinine excretion rate (CER) measured from a 24−hour sample is an established non−invasive marker of total body muscle mass and seems to predict long−term outcomes in patients after liver transplantation.[19] We suspect that CER might be an interesting marker in predicting clinically relevant SRML. Therefore, collection of 24−hour urine samples will take place at baseline and be repeated on the seventh day after surgery.

Questionnaires

Patients will receive three different questionnaires at baseline and three and six months after surgery to compare scores over time to identify the impact of clinically relevant SRML on QoL and fatigue. Patients will receive the questionnaires by e−mail or on paper.

The WHOQOL−Bref (version 1.0, December 1996) and RAND−36 (version 2.0, 2007) will be used to assess QoL. The WHOQOL−Bref contains a total of 26 questions including the following four domains: physical health, psychological, social relationships, and environment.[20,21] The RAND−36 Item Health Survey cover eight concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, role emotional well−being, social functioning, energy/fatigue, and general health perceptions.[22] It also includes a single item that provides an indication of perceived change in health. Both questionnaires are available in Dutch.

The multidimensional fatigue inventory (Dutch version MFI−20, 2003) will be used to assess fatigue. The MFI−20 is a 20−item self−report instrument designed to measure fatigue and is well−established in cancer patients.[23] It covers the following dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.

Data handling

All data will be handled confidentially and stored in an electronic case record form designed in the software program Open Clinica (TRAIT BV, the Netherlands), a program especially designed for clinical trial data recording and monitoring. Only the principal investigators will have access to the stored data.

Data analysis plan

All statistical analyses will be conducted using SPSS® Statistics version 24.0 (IBM Corporation, Armonk, NY, USA). Continuous variables will be expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) and categorical variables will be described as count (*n*) and percentage (%) with 95% confidence intervals (CI). Patient characteristics will be compared using the student *t*−test or Mann Whitney U−test for continuous variables and differences between nominal variables will be determined using Pearson chi−square test or Fisher's exact test. Distribution will be assessed with the Shapiro−Wilk normality test.

The different possible predictors for clinically relevant SRML will be investigated with a multivariable logistic regression analyses to calculate odds ratios (ORs) with 95% CI. A backwards stepwise selection methodology will be used to identify independent predictors for clinically relevant SRML. Variables with $p < 0.1$ in the univariate analysis will be included in the multivariate analysis, and variables significant at $p < 0.050$ will be retrained in the final multivariable model. All tests will be two−sided and $p \leq 0.05$ will be considered statistically significant.

Dissemination policy

Both positive and negative research results will be disclosed and submitted to peer−reviewed scientific journals. The principal investigator and steering committee will prepare the manuscripts together with the statistician and other active writing committee members. Co−authorship is reserved for all investigators and in addition to those who constructively contributed to the study at the discretion of the project leader and steering committee. Finally, disputes on the interpretation of the results may not lead to an unnecessary delay in publication.

DISCUSSION

The results from the MUSCLE POWER study will provide important clinical knowledge on the presence, impact, and possible predictors for clinically relevant SRML after major abdominal cancer surgery. This obtained scientific knowledge, will fill in

important gaps in the current literature and may give leads how to prevent clinically relevant SRML and improve morbidity and mortality and QoL after surgery in this vulnerable patient population.

The primary aim of this study is to identify the proportion of patients who have clinically relevant SRML, defined in this study as ≥5% muscle loss within one week after surgery measured by the CSA of three different muscles by ultrasound. Our primary endpoint is clear and relatively easy to measure, although there is currently no global consensus about what amount of muscle loss is clinically relevant (e.g., harmful for the patient). The definition of clinically relevant SRML is therefore based on combining data from three previous published studies that examined acute muscle loss in surgical patients.[10-12]

In most previous clinical studies, changes in skeletal muscle mass were investigated by CT scans at different time points.[3,4,11,12] In the meantime, muscle ultrasound has emerged as a common, inexpensive, reliable, and valid imaging technique for measuring skeletal muscle at the bedside in patients with different clinical conditions, without exposing patients to harmful ionizing radiation.[1,9,24-27] Therefore, in the present study, we will investigate changes in skeletal muscle mass by using bedside ultrasound measurements instead of routinely performing additional CT scans at different time points.

In the MUSCLE POWER study, additional important information about two factors that may extensively influence skeletal muscle loss will be collected as well. To maintain skeletal muscle tissue, food intake and muscle contraction are crucial.[28] Previous published papers show that in the majority of patients after surgery, daily protein intake is much lower than the recommended guidelines of 1.5 g/kg/day.[13,17,18,29] In the present study, protein intake will be monitored daily by a dietician during the first week after surgery to explore its impact on clinically relevant SRML. Additionally, all patients will wear a motility tracker to calculate daily moderate and vigorous physical activity, as hospitalisation is known to be associated with reduced levels of physical activity. Recent studies with older patients show that nutritional and physical interventions should be combined to minimise loss of muscle mass and muscle strength.[30-32] To the best of our knowledge, continuous monitoring of both factors in patients in the first week after abdominal cancer surgery has not yet been performed. We suspect that in the near future, data from the MUSCLE POWER study may play an important role in the development of new nutritional and physical strategies to prevent postoperative muscle loss.

Of course, our study protocol may bear some limitations. First of all, the sample size calculation was based on the scarcely available scientific data about clinically relevant SRML.[10-12] Our hypothesis that 50% of our patient population will have clinically relevant SRML after major abdominal cancer surgery will take the limited amount of previous available data and the maximum spread into account. Despite this, the present study may not be powered enough to investigate all six possible predictors for clinically relevant SRML that were identified by current literature or expert opinion. Another limitation is the fact that we do not perform echo−intensity assessments of the different muscles to investigate muscle quality. Specific trainings are necessary to reliably reproduce these measurements and software that is necessary for echogenicity analysis is not available on our ultrasound system.[33,34] To partially solve this problem, we will perform squeeze and force measurements to obtain some information about muscle function (e.g., muscle strength).

DECLARATIONS

Funding

This work is supported by a grant from the UMCG Cancer Research Foundation (Institutional Foundation for Cancer Research and Development). The study protocol has not undergone any peer−review by this funding body, nor will they play a role in the analysis and interpretation of the data.

Ethical approval

The study protocol has been approved by the Medical Ethics Committee of the University Medical Center Groningen, the Netherlands (METc2018/361, version 3.0, January 21, 2019), and the study protocol was registered with the Netherlands Trial Register ([NTR], NTR NL7505, version 1.0, February 7, 2019).

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8

Molecular fluorescence guided surgery of colorectal peritoneal metastases

A narrative review

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ABSTRACT

Patients with peritoneal carcinomatosis (PC) from colorectal origin may undergo cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) as a curative approach. One major prognostic factor that affects survival is completeness of cytoreduction. Molecular fluorescence guided surgery (MFGS) is a novel intraoperative imaging technique that may improve tumour identification in the future, preventing over– and under–treatment in these patients. This narrative review outlines a chronological overview of MFGS development in patients with PC of colorectal origin.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide, with an incidence of 40 patients per 100.000 population and a mortality rate of 15 per 100.000 persons.[1,2] Of these patients, 8–25% develop peritoneal carcinomatosis (PC).[3-6] Over the past decades, the treatment of PC of colorectal origin has evolved considerably, from palliative care towards a more successful treatment approach with curative intent.[7,8] In particular, the introduction of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has contributed significantly to this change.[9,10] After surgical cytoreduction of all macroscopic tumour tissue, the abdominal cavity is perfused with heated chemotherapy in order to eliminate remaining microscopic disease. Up to date, only one randomised clinical trial has been performed studying patients with PC of colorectal origin. A median overall survival of 22 months was seen for patients after undergoing CRS in combination with HIPEC, compared to 13 months for patients receiving only systemic chemotherapy with or without palliative surgery.[11,12] The authors report a 5–years survival of 43% for patients in whom all macroscopic tumour was removed, compared to 0% for patients in whom residual lesions of more than 2.5 mm were left behind.[11] These findings emphasize the importance of patient selection and a macroscopically complete cytoreduction, mainly because incomplete cytoreduction followed by HIPEC does not contribute to a prolonged survival, but potentially does introduce a high risk of postoperative complications, an extensive rehabilitation period and subsequently decreased quality of life.[12-15]

Although the technical quality of the complete CRS+HIPEC procedure has improved, still up to 88% of the patients undergoing CRS+HIPEC for PC of CRC develop recurrent disease within 2 years.[16] Currently, many imaging modalities are available for preoperative staging, such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scans. Unfortunately, all of these imaging modalities are insufficient for the preoperative assessment of tumour load, or determination of a preoperative peritoneal cancer index (PCI), the most important staging system in PC. CT, MRI and fluorodeoxyglucose (FDG–) PET scans have a poor sensitivity and specificity to estimate PCI by detection of individual tumour deposits, due to the limited spatial resolution.[17] For example, the detection of individual peritoneal deposits using a CT–scan varies from 9.1 to 24.3% for tumor sizes <1 cm, to up to 59.3–66.7% for tumour size of over 5 cm.[18] These results are in accordance with other previous studies.[19-21] Current hybrid PET/CT scanners have a limited spatial resolution of 5–8 mm, whereas MRI seems to be more promising in detecting peritoneal lesions.[22,23]

For intraoperative differentiation between benign and malignant lesions, surgeons currently depend on visual and tactile inspection only. Unfortunately, the human eye and palpation are not competent enough to detect molecular changes in intra−abdominal lesions that have the same colour and physical properties, or to distinguish tumour lesions from benign scar tissue originating from previous surgery. Today, to the best of our knowledge, no intraoperative imaging modalities provided by the more classical modalities like PET, are available to assist in the real−time identification of peritoneal cancer deposits, loco−regional metastases and tumor−positive resection margins.

Considering the high tumour recurrence rates after the CRS+HIPEC procedure, there is a clear need for an imaging modality that can aid the oncological surgeon in the differentiation between tumour and benign tissue intraoperatively. In recent years, optical molecular imaging using tumour−targeted fluorescence tracers has emerged as a promising imaging technique for real−time guidance in oncological surgery.[24-26] This technique can be applied intraoperatively to serve as a 'red−flag' imaging technique to assist in optimal tumour identification. Improved detection of tumour tissue could not only help attain a more complete cytoreduction, but might also facilitate tailored surgery, avoiding unnecessary resections of benign lesions and organs.

This narrative review explains the principles of intraoperative optical molecular imaging and provides a chronological overview of the development of molecular fluorescence guided surgery (MFGS) in patients with PC of colorectal origin.

PRINCIPLES OF INTRAOPERATIVE OPTICAL MOLECULAR IMAGING

In colorectal surgery, as in surgical oncology in general, radical surgery and tumour−free resection margins are essential for optimising patient prognosis. Optical molecular imaging using fluorescence imaging agents can provide real−time intraoperative feedback with high resolution, that is in concordance with the natural surgical field of view of a surgeon and based on the molecular characteristics of the tissue (**Figure 1**). The technique makes use of non−ionising imaging agents and can be implemented relatively easily in the current surgical workflow.

Over the past decades, there has been an increased interest in the clinical application of optical molecular imaging using fluorescence imaging agents. Fluorescence occurs when a photon or fluorescent dye absorbs light at a certain wavelength,

subsequently triggering the release of a photon with a longer wavelength.[27] The quality of fluorescence imaging is influenced by different factors such as changes in photon directions (i.e., scattering) and absorption of photons by the tissue. Multiple tissue components play an important role in fluorophore absorption, with the most relevant being haemoglobin, water, and lipids. As the scattering and absorption properties of tissue are lower in light with longer wavelengths, the near–infrared (NIR) light spectrum (700–900 nm) is considered the optimal clinical diagnostic window for fluorescence imaging.[28]

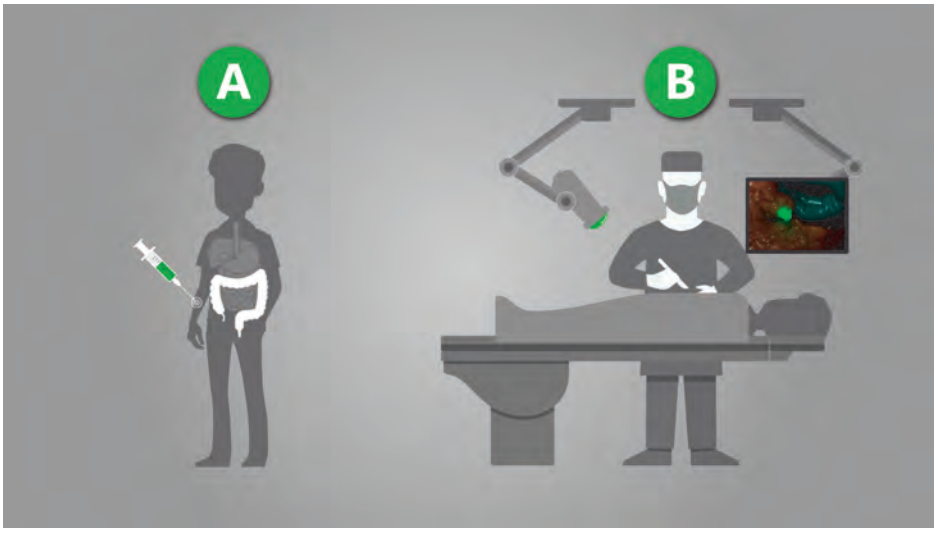

Figure 1 | Concept of molecular fluorescence guided surgery (MFGS).
(A) Prior to surgery a fluorescent target tracer is injected intravenously. (B) During the operation the surgeon will receive real–time feedback by a molecular fluorescence camera in the detection of tumour tissue. Unpublished figure from previously published study Harlaar et al.[107]

These characteristics result in deeper penetration depths of up to one to three centimetres that can be obtained in the NIR light spectrum, leading to higher signal–to–background (SBR) ratios compared to the visible light spectrum (i.e., red–green–blue white–light, 380–700 nm).[29,30]

NIR fluorescence light is invisible to the human eye and therefore special imaging devices are required to visualise fluorescence during surgery. In general, these camera systems are equipped with two different light sources: a white–light source and a NIR fluorescence light source. Due to the use of a dichroic mirror and specific filters installed in the camera system itself, the visible light derived from the tissue can be separated from NIR fluorescence light, which enables simultaneous imaging

of both visible and NIR fluorescence light. Next to that, an overlay of fluorescence signals can be projected on the 'normal' white−light images by use of computer software.[27] In the operating theatre, all three images can be displayed on monitors at the same time, providing real−time imaging related to the natural surgical field of view (**Figure 2**). Currently, there are several different intraoperative NIR fluorescence imaging devices available for research and clinical use.[31-38]

Fluorescence signals in tissue arise by either an endogenous tissue component (i.e., autofluorescence), or an intravenously administered exogenous optical contrast agent. At present, various types of optical contrast agents are available enabling intraoperative imaging, which can roughly be divided into non−targeted and targeted imaging agents.

The effect of non−targeted imaging agents is mainly based on vascularisation and perfusion (i.e., also the so−called enhanced permeability and retention [EPR] effect), whereas targeted imaging agents specifically bind to a receptor or protein that is present in a tumour cell. Due to genetic alterations that occur in cancer development, various receptors and proteins become upregulated, which can potentially be used as targets for imaging purposes.[39] Prior to developing such targeted imaging agents, it is essential to identify which genes or proteins become upregulated for each specific tumour type.[40,41]

UPREGULATED GENES AND PROTEINS RELATED TO CRC

The potential application of targeted imaging agents for intraoperative tumour visualisation is dependent on the expression levels of biomarkers. A biomarker is a specific component present on or secreted by the tumour cell itself.

Most colorectal cancers are thought to develop via the 'adenoma−to−carcinoma sequence', arising from normal cells through the stepwise asset of different genetic alterations.[42,43] In these expressed genes different functional categories can be identified: genes related to proliferation and metabolic rates, to cell adhesion and communication, to transcription and mitosis regulation, or to apoptosis.[44,45] Knowing which biomarkers are encoded by which genes is important when searching for which target to develop a fluorescence imaging agent for.

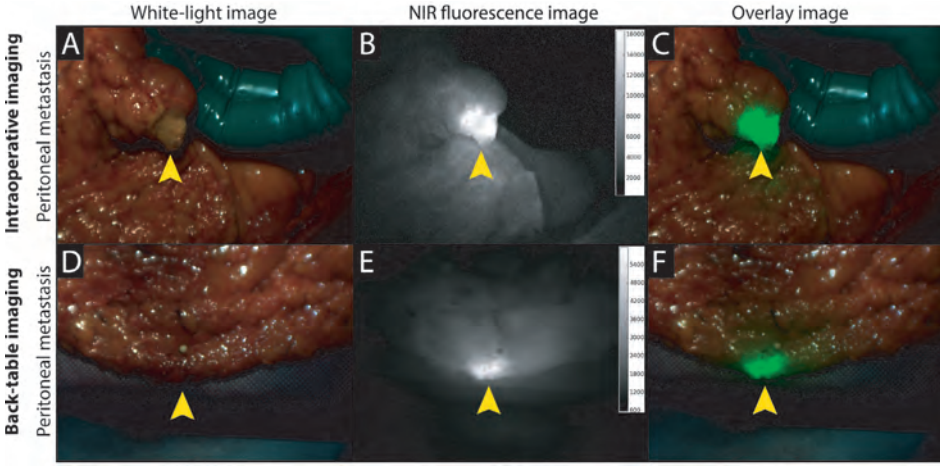

Figure 2 | Intraoperative imaging with white−light, NIR fluorescence and the overlay of both. *Intraoperative imaging of a patient with PC of colorectal origin following intravenous administration of 4.5 mg of the fluorescent tracer bevacizumab−800CW targeting VEGF−A. A white−light image (A), NIR fluorescence image (B) and overlay of both (C) clearly show fluorescent signals at the location of a clinically suspect peritoneal lesion. Back−table imaging directly after surgery of a different peritoneal lesion of the same patient is depicted (D−F). Both peritoneal lesions proved to be tumour metastasis upon final histopathology. Unpublished figures from previously published study Harlaar et al.*[107]

Cardoso et al. presented a list of 128 different genes that were found to be upregulated in CRC compared to normal colorectal tissue.[44] Since protein expression is not always synchronously upregulated, not all of these genes result in overexpression of the related proteins or receptors. Previously, an extensive literature search has been performed on this specific list of genes, in order to identify which genes gave an upregulation of the related proteins or receptors as confirmed by immunohistochemical analysis.[46] As a result, 29 targets were identified, that could be used for imaging purposes during surgery.

TARGET SELECTION CRITERIA (TASC)

To select the most optimal target for imaging purposes from this large set of upregulated biomarkers, the TArget Selection Criteria (TASC) scoring system was developed.[46] The aim of the TASC was to improve the selection of suitable biomarkers for tumour−targeted imaging of all types of cancer. Seven of the most relevant target characteristics were identified based on literature, that each could be scored with 0–6 points. The following characteristics were identified by which a biomarker is validated: I) extracellular biomarker localisation – either on

the cell membrane or in close proximity of the tumour cell; II) expression pattern; III) tumour−to−healthy tissue ratio (T/N); IV) percentage of positive tumours; V) reported successful use of the biomarker in *in vivo* imaging studies; VI) enzymatic activity; and VII) internalisation.[46] Based on extensive testing of the TASC on a variety of biomarkers, cut−off values were determined for target selection. A total score of 18 or more indicates that a biomarker can be considered a potential candidate for tumour−targeted imaging.

As mentioned before, 29 targets were identified that may be used as potential targets for intraoperative imaging of CRC.[46] Using the TASC−scoring system, six biomarkers were considered the most promising: Epithelial Cell Adhesion Molecule (EpCAM), CXC Chemokine Receptor 4 (CXCR4), Mucin 1 (Muc1), Matrix MetalloProteinases (MMPs), Epidermal Growth Factor Receptor (EGFR), and Carcino-Embryonic Antigen (CEA). Although the Vascular Endothelial Growth Factor−A (VEGF−A) scored a total of 17 points, it was still considered a suitable potential target as well, given the extensive experience there already is in VEGF−A targeted imaging. For the clinical translation of these seven suitable biomarkers, specific fluorescence imaging agents need to be available to facilitate MFGS of CRC and PC of colorectal origin.

FLUORESCENCE IMAGING ANGENTS

As stated before, fluorescence imaging agents or probes that can be used for MFGS can roughly be divided into two categories: non−targeted fluorescent probes and targeted fluorescent probes. The main difference between these two categories is based on their mechanism of action (MOA).

Non−targeted fluorescent probes

Non−targeted fluorescent probes accumulate ‘passively’ in solid tumours due to physiological properties such as increased angiogenesis, pressure differences and high metabolic activity (**Figure 3A**). It is commonly known that the majority of solid tumour cells stimulate angiogenesis and therefore are highly vascularised. This feature combined with the lack of efficient lymphatic drainage results in more accumulation in tumour tissue compared to normal surrounding tissue, thereby enhancing contrast and enabling a differentiation between the tumour and surrounding tissue. This phenomenon is also known as the enhanced permeability and retention (EPR) effect.

Many non−targeted fluorescent probes have already been used in humans to enhance contrast during surgery in a variety of different indications, such as for example fluorescein for retinal fluorescein angiography, indocyanine green (ICG) for liver perfusion and lymph node detection, or methylene blue for sentinel lymph node detection in breast cancer patients.[47-53]

ICG is the most commonly known fluorescent probe, which was already approved by the Food and Drug Administration (FDA) back in 1959. ICG has several advantages over to fluorescein as it only fluoresces in the NIR light spectrum (instead of the visible light spectrum) and therefore is less influenced by tissue optical properties such as scattering and absorption. As ICG binds to plasma proteins, it has a negligible toxicity and is excreted rapidly by the liver into the bile, with a plasma half−life of only 3−4 min.[54-55] These features make ICG a very attractive contrast agent for assessment of macro− and micro−circulatory status of different organs based on its intravascular distribution.[56]

Ever since its first clinical application in hepatology for liver condition monitoring in 1957, it has been widely applied and studied to visualise perfusion in ophthalmology for identification of retinal blood vessels, in cardiac bypass surgery for evaluation of anastomoses and for monitoring cardiac output.[57-62] More recent studies have reported the potential application of ICG for intraoperative fluorescence angiography in a broad range of other indications such as neuro−, coronary−, reconstructive− , liver− and vascular surgery.[59,63-70]

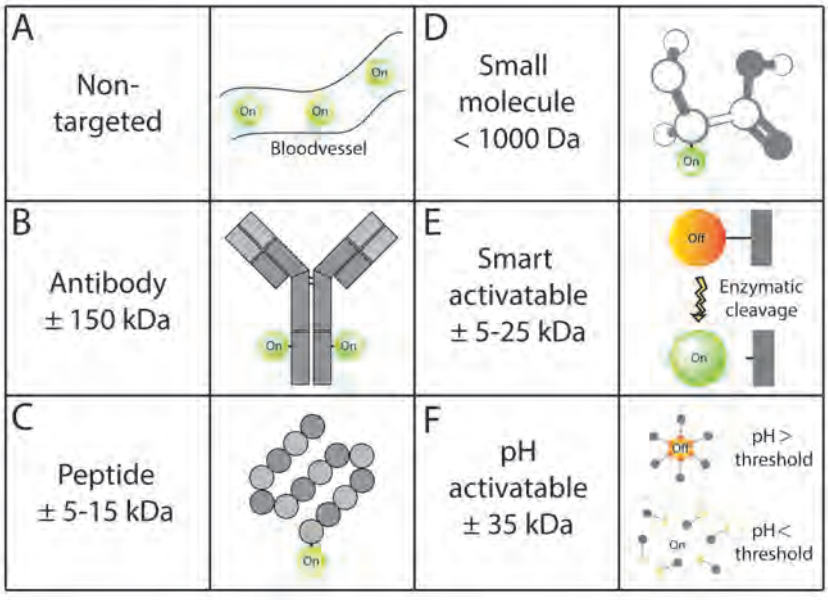

Figure 3 | Fluorescence imaging probes. Overview of fluorescent imaging probes with different mechanisms of action.

The effect of non−targeted fluorescent probes is based on tissue distribution by perfusion (A), whereas antibody−based (B), peptide−based (C) and small molecule−based (D) imaging enables targeted fluorescence imaging through binding to specific receptors or proteins overexpressed by the tumour. Smart activatable fluorescent probes are activated upon cleavage by specific enzymes or proteases secreted by the tumour (E), whereas pH activated probes becomes fluorescent through a change in molecular structure due to the characteristic acidotic environment of a tumour (F).

The first potential application of ICG−based fluorescence imaging in patients with peritoneal metastases of colorectal origin was demonstrated in 2016.[71] In this study, peritoneal metastases from non−mucinous adenocarcinoma were accurately identified following the intravenous administration of free ICG during surgery, leading to an adjustment in clinical decision making in 29% of patients. However, the benefit was minimal in patients with mucinous adenocarcinoma. Despite the positive results demonstrated in this study, the main disadvantage still lies in the fact it is not tumour−specific and therefore leads to a low sensitivity and specificity.

Targeted fluorescent probes

Due to the low sensitivity and specificity of non−targeted fluorescence probes, its application in surgical oncology is still limited. Therefore, to increase contrast, this resulted in a shift towards the development and clinical translation of targeted optical imaging agents enhancing surgical vision based on the molecular characteristics of cancer cells.

The MOA of targeted fluorescent probes is based on the concept of a carrier molecule that is conjugated to a fluorescent dye, specifically binding to a certain tumour target. Carrier molecules can either be monoclonal antibodies, (small) peptides, small molecules or other molecules that specifically target certain cell surface markers that become overexpressed due to genetic variances that occur in every tumour (**Figure 3B**).[72] Moreover, the increased metabolic activity that characterises certain tumour types can be used as a target.[40]

Besides a suitable carrier molecule, the fluorescent dye itself also plays an important role. The development of new fluorescence probes is challenging since each agent needs separate regulatory approval, which is an expensive and time−consuming process.[73] As mentioned before, fluorescent dyes that emit light in the NIR light spectrum provide several advantages over dyes that emit light in the visible light spectrum. Although there is a wide variety of fluorescent dyes available for conjugation to carrier molecules, the most preclinical and clinical experience has been obtained with the NIR fluorescent dye IRDye800CW, developed by LI-COR Biosciences Inc. (Lincoln, NE, USA). The IRDye800CW has a peak emission wavelength at 794 nm and is ideal for protein and antibody labelling, as conjugation to a carrier molecule is relatively easy and extensive toxicity studies have been performed.[74]

The increasing clinical application of therapeutic monoclonal antibodies specifically targeting certain biomarkers of cancer is an interesting development in the perspective of optical molecular imaging. Targeting certain tumour−specific receptors with fluorescently labelled antibodies seems to have great potential for visualisation of cancer during interventions, also in CRC.[72,75-78] Multiple targeted probes have already been testes successfully in several preclinical studies.[75,77-84]

The first in−human proof−or−principle of targeted optical molecular imaging using a fluorescent probe was provided by van Dam et al. in 2011, demonstrating the potential of MFGS in patients with PC originating from ovarian cancer using the fluorescent tracer folate−FITC, targeting the folate receptor a.[24] Ever since, targeted optical imaging has been applied for many different indications.

POTENTIAL FLUORESCENCE IMAGING AGENTS FOR DETECTION OF COLORECTAL CANCER

As mentioned before, using the TASC scoring system, seven potential targets for optical molecular imaging of PC of colorectal origin have been identified: CXCR4, EpCAM, EGFR, CEA, Muc1, MMPs and VEGF−A.[46] The specifics of these proteins and receptors are summarised in **Table 1**.[85-109] Several fluorescent imaging probes targeting these biomarkers have already been investigated in humans in a broad variety of indications.

For example, the NIR fluorescent tracer cetuximab−800CW targeting EGFR has been applied in humans for surgical navigation in head−and−neck squamous cell carcinoma.[92] Moreover, cetuximab-800CW is being used in a phase−I clinical trial in the University Medical Center Groningen in patients with head and neck squamous cell carcinoma (NCT03134846).

Besides, the NIR fluorescent tracer bevacizumab−800CW targeting VEGF−A has been applied for detection of a variety of different tumour types, among which locally advanced rectal cancer (NCT01972373), pancreatic cancer (NCT02743975), breast cancer (NCT02583568) and oesophageal cancer.[108,109] The feasibility of MFGS using bevacizumab−800CW is also being investigated for intraoperative guidance in benign diseases such as endometriosis (NCT02975219) or for endoscopic detection of familial adenomatous polyposis (NCT02113202).

In CRC and specifically peritoneal metastases of colorectal origin, so far two phase−I feasibility studies have been performed in humans.

Table 1 | Potential targets for optical molecular imaging in PC of colorectal origin using the TASC scoring system.

Target	Name	Location	Function	Over−expression in CRC	Carrier molecule clinically available	GMP-labelled fluorescent tracer	Clinical trials in humans
CXCR4	Chemokine Receptor 4	Cell surface	Homing of hematopoietic stem cells to the bone−marrow	± 70%[85]	AMD3100 (molecule)[86] SDF−1a (peptide)[86] 12G5 (mAb)[86]	-	-
EpCAM	Epithelial Cell Adhesion Molecule	Cell surface	Cell adhesion	> 80%[87,88]	Edrecolomab Catumaxomab	323/A3−800CW[89]	-
EGFR	Epidermal Growth Factor Receptor	Cell surface	Cell proliferation, differentiation, adhesion and migration	± 80%[90,91]	Cetuximab Panitumumab	Cetuximab−800CW Panitumumab−800CW	NCT03134846[92]
CEA	Carcino−embryogenic antigen	Cell surface	Cell adhesion	> 90%[93-95]	Arcitumomab	SGM−101[96]	-
Muc1	Mucin−1	Cell surface	Forming protective mucous barriers on epithelial surfaces, intracellular signaling (cell adhesion and anti−adhesion)	± 50%[97,98]	Muc1−targeting peptide C595 (mAb) Bispecific anti−Muc1 antibody	-	-
MMP	Matrix Metalloproteinases	Tumour micro−environment	Degrading proteins in extracellular matrix	30-95% depending on the type[97,99-102]	-	-	-
VEGF-A	Vascular Endothelial Growth Factor−A	Tumour micro−environment	Angiogenesis	Up to 96%[103,104]	Bevacizumab	Bevacizumab−800CW[105]	NCT02113202 NCT01972373 NCT02583568 NCT02975219 NCT02743975 NCT01691391 [106-109]

FEASABILITY STUDIES IN PC OF COLORECTAL ORIGIN

In 2016, Harlaar et al. used the NIR fluorescent tracer bevacizumab−IRDye800CW targeting VEGF−A for MFGS in seven patients with PC from CRC origin, that were scheduled to undergo CRS+HIPEC.[107] Intravenous administration of bevacizumab-800CW 3 days prior to surgery proved to be safe, as no (serious) adverse events that were related to tracer administration occurred in any of the patients. Fluorescence signals were observed in all patients during surgery. Additional tumor tissue that had not been identified by the surgeons using only visual and tactile inspection was detected in two patients using fluorescence imaging. The fresh surgical specimens were imaged back−table at the operating theatre. A total of 80 peritoneal areas were imaged using the intraoperative camera system and analysed by a pathologist. All 29 resected, but non−fluorescent areas proved to be benign on final histopathology, thus potentially indicating a sensitivity of 100%. In 27 out of 57 fluorescent areas in the fresh surgical specimen, tumour tissue was identified. Although the authors state that their study was not powered to investigate the sensitivity and specificity, the results are very promising. In conclusion, in this study MFGS using bevacizumab-800CW was safe and feasible and could potentially improve CRS and patient selection.

The second feasibility study was performed in 2018 by Boogerd et al., in which SGM−101, a fluorescent anti−CEA monoclonal antibody, was administered intravenously 2−4 days before surgery, to investigate the feasibility of MFGS in CRC and PC of colorectal origin.[96] Patients with PC of colorectal origin that were scheduled for open surgical removal were included. First, a dose−finding study was performed in the first nine patients. Subsequently, the most optimal dose of SGM−101 was investigated in another 17 patients. SGM−101 showed no treatment−related (serious) adverse events. However, a total of eight possibly related mild adverse events occurred throughout the study. Using MFGS, in six patients a total of 19 additional peritoneal lesions were identified as potentially tumour−positive, and therefore treatment strategies were changed. The authors report a sensitivity of 98% and a specificity of 62%.

Interestingly, although both studies used different fluorescent tracers, more or less the same conclusions were drawn. Most importantly, both bevacizumab−800CW and SGM−101 were deemed safe in combination with MFGS. Moreover, it appeared that with both fluorescent tracers, a very high sensitivity could be obtained. If these results are validated in a larger patient cohort and indeed clinically suspect, but

non−fluorescent lesions turn out to be benign, non−fluorescent lesions may be left in situ in the future and subsequently decrease morbidity. Interestingly, this might also imply that currently visual and tactile inspection−based surgery leads to unnecessary resections when compared to MFGS. The majority of complications and revalidation time is probably related to the extent of the cytoreduction itself. This might also improve the current morbidity of 22−34% and mortality of 0.8−4.1%.[110-115]

The specificity in these two feasibility studies appears to be relatively low, with a substantial amount of false positive lesions when applying intraoperative fluorescence imaging. This might be due to technical limitations of the fluorescence camera system that still need to be improved, such as the multispectral substration techniques. Currently, quantification of fluorescence with most of the present generation of clinically approved fluorescence camera systems is still limited, making the interpretation of fluorescence signals subjective. If a threshold could be set to give the surgeon a 'yes' or 'no' answer to the question whether a peritoneal lesion is tumour−positive with a certain sensitivity and specificity, this could potentially improve interpretation of fluorescence signals. Last, for some tracers, the optimal dose might still needs further optimisation.[107]

Additional research and studies need to be performed to investigate novel fluorescence imaging agents in humans for MFGS of PC of colorectal origin. Theoretically, multiple fluorescence imaging agents can be intravenously administered to the same patients simultaneously, a so−called "tracer cocktail", in order to improve sensitivity and specificity. Therefore, novel fluorescence imaging agents need to be validated in a standardised way, with the emphasis on the determination of the safety, feasibility, optimal agent dose, and optimal timing for surgical intervention in phase−I feasibility studies.

FUTURE PERSPECTIVES

Target selection for MFGS

Currently, there are many carrier molecules that seem promising for potential validation in phase−I feasibility studies according to the TASC scoring system.[46] Additionally, new strategies have been developed recently to identity biomarkers that are upregulated in cancer development, such as functional genomic mRNA (FGM) profiling.[116] This method corrects expression data of numerous genes for relevant non−genetic variables. It is likely that in the near future new promising targets will be identified by this gene expression analysis, that may be used as targets, providing new possibilities for imaging of PC of colorectal origin.

Novel fluorescence imaging probes

Next to the validation of potential targets for imaging, novel fluorescent probes are being developed.[72,117] Different types of carrier molecules have different pharmacokinetics. The substantial molecular weight of monoclonal antibodies (generally ± 150 kDa, **Figure 3B**) results in a relatively long blood circulation time of several days up to weeks. Although there is extensive experience with the use of monoclonal antibodies, even smaller molecules may provide favourable pharmacokinetic properties, such as nanobodies.[118] A faster clearance from background tissue results in sufficient signal−to−background ratios that occur within a much shorter period of time. Therefore, peptides or small molecules might be logistically favourable compared to antibodies for MFGS (**Figure 3C** and **D**).[118] On the other hand, smaller molecules are in general more difficult to conjugate to a fluorescence dye, as even small structural changes can influence pharmacokinetics and binding efficacy significantly.[118,119]

Another subgroup of imaging probes has come forward in recent years: targeted smart−activatable probes (**Figure 3E**).[119] The working mechanism of these probes is based on the principle of photochemical quenching or ligand−targeted activation. Smart activatable probes only fluoresce when bound to the tumour or cleaved by specific proteases or peptidases excreted by the tumour, which improves signal−to−background ratios due to limited background fluorescence.[118,120] The first clinical studies to investigate smart activatable probes have been performed already.[117] However, to the best of our knowledge, this has not yet been done for intraoperative imaging of CRC or PC of colorectal origin.

A similar 'on−or−off' concept has been applied in the development of a pH−activatable fluorescent probe. This probe becomes activated upon contact with a certain threshold pH (pH ≤ 6.9), as the majority of solid tumours are acidotic. Although this probe does not target a tumour biomarker, it is still highly specific due to the pH transistor concept.[121] The benefit of such a probe is that it can be applied in a broad range of oncological indications. However, the first proof−of−concept in human study using a pH−activated probe still needs to be conducted.

Phase II/III clinical studies

Although different fluorescent probes are being developed, so far only two phase−I feasibility studies have been finalised in relatively small numbers of patients with PC of colorectal origin.[96,107] The ability of fluorescence imaging to detect peritoneal metastases that are missed by visual and tactile inspection and to aid in the

differentiation between malignant and benign tissue, may have the potential to change clinical decision making. Although these results seem promising, further validation in phase−II clinical studies is required, with larger patient cohorts that are sufficiently powered to estimate the diagnostic accuracy. Eventually, in phase−III studies, the impact of MFGS in CRS+HIPEC surgery on clinical endpoints such as progression−free and overall survival need to be evaluated, hoping to improve the current median progression−free survival of only 12.6 months.[11]

Photodynamic therapy

Although current clinical studies are mainly aimed to investigate the feasibility of optical imaging for cancer detection, in the future intraoperative imaging may also be used as a therapeutic modality. Carrier molecules that specifically target the tumour can also be labelled to a photoactive dye (i.e., photosensitiser), to allow targeted photodynamic therapy (tPDT). When excited with light of a specific wavelength, photosensitisers not only fluoresce, but also form reactive oxygen species that oxidise the cells they target, thereby killing them.[122] Potentially, tPDT may be applied after CRS, to assist in the elimination of microscopic peritoneal lesions. As there is only superficial activation of the targeted photosensitisers, side−effects are estimated to be limited. The first clinical trials have already been performed to investigate the safety and feasibility of tPDT using a variety of different photosensitisers. Phase I and II clinical trials have been conducted for treatment of colorectal cancer, pelvic recurrence of CRC, colorectal liver metastases (NCT00068068), and locally advanced rectal cancer.[123-126] Moreover, tPDT has also been applied for the treatment of peritoneal metastases originating from ovarian cancer and sarcomas, and different gastrointestinal tumours with promising results.[127,128] These studies demonstrate that tPDT could potentially be used as an effective treatment for both CRC and PC. However, future studies are required to determine the effect on PC of colorectal origin, when combined with MFGS.

CONCLUSION

In conclusion, treatment of PC of colorectal origin with curative intent consists of CRS followed by HIPEC. Up to date, surgeons still rely on visual and tactile inspection for intraoperative differentiation between tumour and benign tissue. The ultimate goal during cytoreduction is to obtain a macroscopically complete cytoreduction by resecting malignant tissue only. Therefore, there is a clear need for an intraoperative imaging technique improving tumour detection. The first phase−I clinical trials have been performed showing the potential benefit of MFGS for patients with

PC of colorectal origin. Even though no conclusions can be drawn with regard to the impact of these studies on clinical decision making, it appears MFGS has the potential to improve both cytoreduction and patient selection, facilitating patient–tailored surgery. However, to reliably determine the sensitivity and specificity of MFGS during CRS+HIPEC, subsequent phase–II studies are required.

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9

Summary, conclusions and future perspectives

SUMMARY AND CONCLUSIONS

Challenges in patient selection for CRS+HIPEC

In **Chapter 1**, the rationale behind this thesis was outlined. Carefully selected patients with limited and resectable colorectal peritoneal metastases (PM) can be treated with curative intent by combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC). This complex abdominal procedure is accompanied by substantial treatment−related morbidity and mortality, a diminished quality of life (QoL) up to one year after surgery, and high rates of early recurrence of disease. A complex interplay of patient, tumour, and treatment−related factors determines these postoperative outcomes. For clinicians and patients, it remains a serious challenge to weigh the potential survival benefit from this extensive treatment against the risk of substantial treatment−related morbidity, mortality, and potential diminished QoL and functional status. According to the available literature, the extent of peritoneal disease (i.e., peritoneal cancer index [PCI]), completeness of the performed cytoreduction (i.e., completeness of cytoreduction score [CC−score]), and signet ring cell histology especially have a great influence on the survival outcomes after CRS+HIPEC. These powerful prognostic factors for survival after CRS+HIPEC are determined at the time or even after the operative exploration rather than in a preoperative setting. The aim of this thesis is to identify new and promising preoperative factors in patients with colorectal PM to predict postoperative morbidity and survival outcomes after CRS+HIPEC in an earlier stage.

Part I – Biological and clinical prognostic factors to further optimise patient selection for CRS+HIPEC.

In **Chapter 2**, we investigated the impact of the time−of−onset of colorectal PM (synchronous or metachronous) on surgical morbidity and survival outcomes after CRS+HIPEC. For this chapter, the most common definitions used in the scientific literature for synchronous and metachronous colorectal PM were selected, as there is no worldwide consensus regarding this matter. Patients with synchronous colorectal PM were diagnosed with colorectal cancer at the time of presentation. Patients with metachronous colorectal PM developed colorectal PM after an initial 'curative' colorectal resection. The results from this multicentre observational cohort study—consisting of 433 consecutive patients who underwent CRS+HIPEC between February 2006 and December 2017 in two Dutch tertiary referral hospitals—showed that metachronous onset of colorectal PM was associated with early recurrence after CRS+HIPEC when compared to synchronous onset of colorectal PM. Remarkably,

overall survival (OS) and surgical morbidity were similar between both groups. Additional analyses revealed that especially patients with metachronous colorectal PM with a PCI above 10 had a markedly worse OS and disease−free survival (DFS) after CRS+HIPEC when compared to the other patients. Therefore, we recommend being extra careful in selecting patients with metachronous colorectal PM with a PCI above 10 for CRS+HIPEC.

The diagnostic laparoscopy (DLS) has been implemented in the preoperative workup for CRS+HIPEC in patients with suspicion of colorectal PM to prevent non−therapeutic laparotomies (i.e., open−close procedures) at the University Medical Center Groningen (UMCG). **Chapter 3** describes the feasibility and safety of routinely performing DLS in 184 consecutive patients with suspicion of colorectal PM. Good laparoscopic evaluation was possible in 75% of the patients, despite the fact that 84% of these patients had a history of prior abdominal surgery. Major postoperative complications occurred in only five patients (2.7%), who were all deemed not suitable for CRS+HIPEC, with no postoperative deaths. Another important finding was the unexpectedly high rate of 50.5% of patients who were potential candidates for CRS+HIPEC according to preoperative imaging but in the end were deemed not suitable for CRS+HIPEC during DLS. On the one hand, this reflects the low validity of imaging for colorectal PM to predict the presence and extent of peritoneal disease, and on the other hand, it supports the added value of DLS prior to CRS+HIPEC; almost half of the patients with suspicion of colorectal PM avoided a laparotomy by having a DLS performed.

Chapter 4 focuses on the evaluation of the implementation of DLS in the preoperative workup for CRS+HIPEC and the impact on preventing non−therapeutic laparotomies. DLS was introduced in 2012 for this specific indication; this provided the opportunity to compare a historical cohort of 48 consecutive patients with colorectal PM who were scheduled for CRS+HIPEC before the introduction of DLS to 124 consecutive patients with colorectal PM who were scheduled for CRS+HIPEC after DLS was part of the preoperative workup. The rate of non−therapeutic laparotomies significantly dropped from 35.4 to 21.0% after the introduction of DLS in our preoperative workup, despite the fact that only 68.5% of the patients underwent DLS in our academic centre after this introduction. In cases where surgeons refrained from performing DLS, in two out of three patients this was due to the patient having recently underwent abdominal surgery in the referring centre, resulting in an unexpectedly higher rate of non−therapeutic laparotomies (28.2%) in these patients. We suspect that surgeons from referral centres might

understage the extent of colorectal PM and overestimate the possibility of achieving a complete cytoreduction, because they have less experience in reporting these prognostic factors. With this obtained knowledge, we are paying more attention to early detection and referring of patients with colorectal PM to our academic centre. Patients will undergo laparoscopic evaluation by one of our HIPEC surgeons to investigate the extent and resectability of the colorectal PM, independently of prior abdominal surgery performed at the referral centre. With these adjustments, we suspect that the rate of non−therapeutic laparotomies in patients with colorectal PM will drop even further in our academic centre in the following years.

At this moment, the PCI scoring system is predominantly used worldwide as a static single−time−point scoring system during an exploratory laparotomy for potential CRS+HIPEC and as such does not include disease progression over time. With the introduction of DLS in our preoperative workup for CRS+HIPEC, the opportunity arose to investigate the impact of an increase in PCI in a short−time frame on survival outcomes after CRS+HIPEC. In **Chapter 5**, we developed the ΔPCI as an independent, more dynamic prognostic factor for OS in patients with colorectal PM. In our prospectively maintained institutional database, we identified 84 patients who underwent DLS and an exploratory laparotomy for potential CRS+HIPEC between 2012 and 2018, with the PCI being known for both procedures. The difference in PCI score between DLS and exploratory laparotomy (i.e., ΔPCI) was calculated. Patients were divided into three groups of rate progression: stable disease (ΔPCI 0–3), mild progression of disease (ΔPCI 4–9), or severe progression of disease (ΔPCI ≥10). The median OS after CRS+HIPEC was significantly decreased in patients with a ΔPCI of 4–9 (35.1 months) or ΔPCI ≥10 (24.1 months) when compared to patients with a ΔPCI of 0–3 (47.9 months). In multivariate regression analysis, ΔPCI remained an independent risk factor for OS. This prognostic factor appears to reflect on a more aggressive tumour biology and might serve as an adjunct tool for intraoperative clinical decision making beyond static PCI scoring at the time of exploratory laparotomy for potential CRS+HIPEC. HIPEC surgeons should be aware of a high−ΔPCI−associated diminished prognosis and should reconsider the execution of the CRS+HIPEC procedure when confronted with a high ΔPCI of ≥10 intraoperatively.

The extent of surgery (ES) during CRS+HIPEC is a well−known risk factor for the occurrence of major postoperative morbidity and is essential to know prior to surgery. Potential survival benefit from the CRS+HIPEC needs to be in balance with the associated risks of treatment−related morbidity and mortality. Every day, HIPEC

surgeons attempt to make this estimation for their patients in advance of planning a CRS+HIPEC procedure. **Chapter 6** describes a prospective, observational cohort study that investigated surgeons' abilities to correctly predict the ES in advance of CRS+HIPEC. Five surgeons with extensive experience in gastrointestinal surgery and CRS+HIPEC procedures predicted the ES prior to surgery. For each individual patient, all surgeons independently predicted the resection or preservation of 22 different anatomical structures according to a standardised ES form. The actual ES during CRS+HIPEC was extracted from the surgical procedure report and compared with the predicted ES. One hundred and thirty−one ES forms were collected from 32 patients who successfully underwent CRS+HIPEC. Positive and negative predictive values per anatomical structure (PPV and NPV, respectively) were calculated. A high PPV suggests that the surgeon is well able to predict if the anatomical structure will be resected, whereas a high NPV indicates that the surgeon is well able to predict if the anatomical structure will be preserved. The number of resections necessary to achieve a complete cytoreduction was predicted correctly 24 times (18.3%), overestimated 57 times (43.5%), and underestimated 50 times (38.2%). Overall, NPVs for the different anatomical structures were higher and showed less variation between surgeons compared to the PPVs. This suggests that surgeons with extensive experience in performing these procedures have the ability to predict in advance which of the anatomical structures can be preserved during CRS+HIPEC but in most cases fail to predict the resections that are necessary to achieve a complete cytoreduction with an underestimation of the ES in almost 40% of the cases. This phenomenon has not been described before and emphasises that future research should focus even more on optimising the detection of the extent of disease prior to surgery.

Part II – New avenues for research.

Surgery−related muscle loss (SRML) occurs in at least one out of three cancer patients within one week after major surgery. Prevention of clinically relevant SRML in cancer patients can be a promising strategy to improve morbidity and mortality and increase QoL after major surgery. These days, there is still a lack of scientific knowledge regarding this topic. **Chapter 7** extensively describes the design of the MUSCLE POWER study, an observational single−centre prospective cohort study that currently is investigating the presence, impact, and possible predictors for clinically relevant SRML in 178 cancer patients after major abdominal surgery using ultrasound measurements, squeeze and force measurements, and QoL questionnaires. Daily physical activity during the hospital stay is monitored by a motility tracker, and protein intake is monitored by a dietician. Crucial information

regarding possible predictors for clinically relevant SRML can be used in future intervention studies to prevent postoperative muscle loss and minimise its impact on different postoperative outcomes and QoL in the long term. The MUSCLE POWER study is open for inclusion and more than 50 patients have been enrolled over the past four months. Final results can be expected at the end of 2020.

Chapter 8 explains the principles of intraoperative optical molecular imaging and provides a chronological overview on molecular fluorescence guided surgery (MFGS) development in patients with colorectal PM. For intraoperative differentiation between benign and malignant lesions, surgeons currently depend on visual and tactile inspection only. Considering the high tumour recurrence rates after CRS+HIPEC, there is a clear need for an imaging modality that can aid the oncological surgeon in the differentiation between tumour and benign tissue intraoperatively. In recent years, MFGS has emerged as a promising real−time intraoperative imaging technique to improve tumour detection by using tumour−targeted fluorescence tracers. A tumour−targeted fluorescence tracer is based on the concept of a carrier molecule that is conjugated to a fluorescent dye, specifically binding to a certain tumour target. This technique can be applied intraoperatively to serve as a 'red−flag' imaging technique to assist in optimal tumour identification, thereby potentially enhancing surgical vision for the detection of small tumour deposits and enabling differentiation between benign and malignant tissue during surgery. Bevacizumab-IRDye800CW, one of the promising tumour−targeted fluorescence tracers targeting the vascular endothelial growth factor (VEGF), will be used in the near future for a new phase I trial at the UMCG to detect tumour tissue from colorectal PM during DLS (i.e., the SELECT trial). If bevacizumab-IRDye800CW is also feasible during DLS, it might provide a more accurate investigation of the extent of peritoneal disease at an earlier stage. Ultimately, these new strategies may reduce overtreatment, morbidity, and costs while maintaining the same or better effectiveness with a lower recurrence rate and improved QoL.

FUTURE PERSPECTIVES

There is no doubt that adequate patient selection for the treatment of colorectal PM is the main challenge in the field of CRS+HIPEC. The potential survival benefit must be in balance with the treatment−related morbidity, mortality, and impact on QoL. Hopefully, the results presented in this thesis will contribute to further understanding of the complex interplay of patient, tumour, and treatment−related factors that determines these postoperative outcomes. Improvement of the

preoperative selection of patients for CRS+HIPEC—including a more tumour– and patient–tailored approach—is crucial to gaining further progression in the field of CRS+HIPEC.

Tumour biology

Tumour biology is very likely to play an important role in the outcome after CRS+HIPEC, as we have shown in **Chapter 2** and **Chapter 5** of the present thesis. Strikingly, only the presence of signet ring cell histology is used during the preoperative selection process for CRS+HIPEC, as there are no known biomarkers that are capable of predicting chemotherapeutic efficacy and outcome after CRS+HIPEC. Four molecular subtypes of colorectal cancer have been identified on the basis of the gene expressions levels and combined to a new classification system, the consensus molecular subtypes (CMS) classification including CMS1 to CMS4. The majority of the colorectal PM belong to the CMS4 subtype (75%), which represents a particular class of highly aggressive tumours that seems to be associated with worse survival outcomes and poor response to current anticancer therapy. Identification of the molecular subtype of colorectal PM can have therapeutic consequences and might serve as an additional selection criterion for CRS+HIPEC in the future. Highly experienced HIPEC centres can make an important contribution by storing tissue and blood samples from their patients in an institutional or national biobank for translational research.

Improvement of tumour detection

Preoperative imaging modalities

Accurate preoperative assessment of the PCI would be extremely useful in differentiating patients who are candidates for CRS+HIPEC from those who are not in an earlier stage. Many imaging modalities are available for preoperative staging in general, such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) scans. Unfortunately, all of these preoperative imaging modalities greatly underestimate the intraoperative PCI. Surgical oncologists are still discovering the real extent and potential resectability of colorectal PM during an exploratory laparotomy, which causes patient selection to take place in the operating room rather than in an outpatient setting. **Chapter 3** and **Chapter 4** describe the added value of DLS in the preoperative workup for CRS+HIPEC to prevent non–therapeutic laparotomies in patients with extensive disease. In the near future, it is possible that DLS will play a smaller role in patient selection because detection rates of colorectal PM from current preoperative imaging modalities are slowly improving. The first small series with diffusion–

weighted MRI images (DW−MRI) shows that it seems possible to distinguish patients with extensive disease from patients with resectable disease (i.e., PCI ≤20), and therefore might be used as a non−invasive tool to select patients with colorectal PM for CRS+HIPEC. An accurate preoperative assessment of the PCI allows not only excluding patients with extensive disease and predicting the likelihood of complete cytoreduction but also confers several other advantages. As described in **Chapter 6** of the present thesis, experienced HIPEC surgeons are still struggling to predict the extent of surgery (ES) prior to CRS+HIPEC despite the presence of current preoperative imaging modalities. A more accurate preoperative assessment of the PCI will provide crucial additional information for the oncologic surgeon to determine the true extent and length of surgery in advance. This information is useful in the outpatient clinic to inform patients and their families in a more patient−tailored way as well as for logistic optimisation of staff planning and operating room time.

Intraoperative imaging modalities

Chapter 8 of the present thesis provides an overview of the developments in molecular fluorescence guided surgery (MFGS) in patients with colorectal PM. Oncologic surgeons still rely heavily on visual and tactile inspection alone for intraoperative differentiation between tumour and benign tissue. Considering the high tumour recurrence rates after CRS+HIPEC and unnecessary resections of benign lesions or organs, there is a clear need for an intraoperative imaging technique improving tumour detection. The ultimate goal during cytoreduction is to obtain a macroscopically complete cytoreduction by resecting malignant tissue only. In recent years, optical molecular imaging using tumour−targeted fluorescence tracers has emerged as a promising imaging technique for real−time guidance in oncological surgery. The first phase I clinical trials have been performed in patients with colorectal PM who underwent an exploratory laparotomy for potential CRS+HIPEC and showed high sensitivities for two different fluorescent tracers for the detection of colorectal PM lesions. This suggests that clinically suspect but non−fluorescent lesions during CRS+HIPEC may be safely left in situ in the future and subsequently decrease postoperative morbidity after CRS+HIPEC, as the majority of the complications and revalidation time seems to be related to the ES itself. Although these results seem promising, further validation in phase II clinical studies is required, with larger patient cohorts that are sufficiently powered to estimate the diagnostic accuracy. Eventually, in phase III studies, the impact of MFGS in CRS+HIPEC surgery on survival outcomes need to be evaluated.

MFGS may also be useful in an earlier stage; in patients with suspicion of colorectal PM who undergo DLS to assess the presence and extent of colorectal PM. Assessment of the PCI during DLS remains challenging, as small tumour lesions could be easily missed and clinically suspicious lesions could be benign, leading to underestimating or overestimating the extent of colorectal PM. In 2016, our research group proved the feasibility of colorectal PM by using bevacizumab−IRDye800CW in patients who underwent an exploratory laparotomy for potential CRS+HIPEC. Meanwhile, a new fluorescent camera has been designed by *SurgVision BV* to be used during DLS. Currently, we are completing the study design of the SELECT trial; a non−randomised, non−blinded, prospective, single−centre phase I feasibility study with bevacizumab−IRDye800CW for patients with suspicion of colorectal PM who are scheduled for DLS. If bevacizumab−IRDye800CW is also feasible during DLS, which is a very different setting compared to open surgery, it might provide a more accurate investigation of the extent of colorectal PM. Ultimately, all of these strategies may reduce overtreatment, morbidity, and costs while maintaining the same or better effectiveness with a lower recurrence rate and improved QoL.

PCI cut−off value for the curative treatment of colorectal PM

Many attempts have been made to discover the PCI cut−off value beyond which CRS+HIPEC should be contra−indicated in patients with colorectal PM, because the potential small survival benefit does not outweigh the treatment−related morbidity and mortality. This cut−off has been set at various levels without any worldwide consensus. In the current scientific literature, cut−off values between 15 and 25 are reported. Most HIPEC teams perform CRS+HIPEC only in patients with a PCI ≤20; this cut−off value is also stated in our national Dutch HIPEC protocol. **Chapter 2** of the present thesis—including survival data from 433 Dutch HIPEC patients—shows an unexpectedly poor survival benefit for patients with a PCI between 11 and 20 when compared to survival outcomes with modern systemic therapies. The 2−year survival rate after CRS+HIPEC is less than 50% in this group of patients with relatively extensive colorectal PM. We hope these survival data will provide an increased awareness among HIPEC surgeons, which may even lead to a lower PCI cut-off value in the Netherlands in the near future.

Early detection and treatment of patients at risk for colorectal PM

Prevention is better than cure

Proactive strategies have been developed in an attempt to prevent or diagnose colorectal PM at an earlier stage in patients with high risk of developing colorectal PM. The first studies on second−look surgery and prophylactic or adjuvant HIPEC

show some promising results, although these results need to be confirmed by various currently recruiting clinical trials. Patient selection for these approaches is based on independent risk factors for the development of colorectal PM, including pT4 stage tumours, mucinous subtype, emergency surgery, positive cytology of peritoneal lavage, lymph node metastases, and non−radical resections during primary tumour resection.

Second−look surgery

Second−look surgery is based on routinely performing a reoperation in asymptomatic patients with high risk of developing colorectal PM after an initial curative primary tumour resection. In pilot studies, up to 71% of the asymptomatic high−risk patients have pathologically confirmed colorectal PM during routine second−look surgery within one year after primary tumour resection, with most patients being eligible for CRS+HIPEC at that moment. Current and future randomised clinical trials are required to evaluate the optimal timing of second−look surgery and its relationship to adjuvant systemic chemotherapy after primary tumour resection, and most importantly, to ascertain the role on long−term survival benefit. A treatment shift in our standard of care may occur from conventional surgery to a more aggressive, early radical approach in the near future.

Prophylactic HIPEC

Prophylactic HIPEC is an even more proactive strategy as this strategy focuses on the prevention of metachronous onset of colorectal PM. In patients with high−risk colorectal tumours, HIPEC is administered simultaneously as an adjuvant treatment to primary tumour resection. Currently, several phase III trials are recruiting high−risk patients to investigate the influence of prophylactic HIPEC on survival outcomes. Recently, the results from the Dutch COLOPEC trial have been published; a multicentre, open−label, randomised controlled trial that assessed the added value of prophylactic HIPEC with oxaliplatin in 204 patients with a pT4 stage or performed colon tumour. Treatment with prophylactic HIPEC with oxaliplatin did not improve the peritoneal metastasis−free survival 18 months after surgery. Results from other phase III clinical trials must be awaited before conclusions can be drawn. Even if a significant survival benefit can be achieved by using another therapeutic drug to perform HIPEC, other issues such as optimal patient selection and timing of prophylactic HIPEC should be further investigated in the future.

A

APPENDICES

NEDERLANDSE SAMENVATTING EN CONCLUSIES

Uitdagingen bij het selecteren van patiënten voor CRS+HIPEC

De motivering voor dit proefschrift wordt in **hoofdstuk 1** toegelicht. Zorgvuldig geselecteerde patiënten met beperkte en resectabele colorectale peritoneale metastasen (PM) kunnen in opzet curatief behandeld worden met cytoreductieve chirurgie gecombineerd met hyperthermische intraperitoneale chemotherapie (CRS+HIPEC). Deze complexe abdominale procedure gaat gepaard met een aanzienlijke postoperatieve morbiditeit en mortaliteit, een vermindering van de kwaliteit van leven tot één jaar na de ingreep, met daarnaast een hoog risico op het vroegtijdig terugkeren van de ziekte. Een complex samenspel van patiënt gerelateerde factoren, tumor gerelateerde factoren en behandeling gerelateerde factoren bepalen deze postoperatieve uitkomsten. Voor medici en patiënten is het bijna een onmogelijke opgave om de potentiële overlevingswinst van deze uitgebreide procedure af te zetten tegenover het bijkomende risico op het optreden van postoperatieve morbiditeit, mortaliteit, en de kans op vermindering van kwaliteit van leven en functionele gesteldheid. Volgens de huidige beschikbare literatuur worden overlevingsuitkomsten na CRS+HIPEC met name sterk beïnvloed door de uitgebreidheid van de aanwezige peritoneale ziekte (beschreven met de PCI−score), de volledigheid van de uitgevoerde cytoreductie (beschreven met de CC−score) en het aanwezig zijn van zegelring cel pathologie in het tumorpreparaat. Deze essentiële prognostische overlevingsfactoren worden op het moment van de operatieve exploratie of zelfs pas na afloop van de procedure bepaald en zijn daarmee dus helaas niet geschikt om adequaat patiënten in de preoperatieve poliklinische setting te selecteren voor CRS+HIPEC. Dit proefschrift besteed aandacht aan het identificeren van nieuwe en mogelijk veelbelovende preoperatieve factoren die in een eerder stadium het individuele risico op het optreden van postoperatieve morbiditeit en de mogelijke overlevingswinst na CRS+HIPEC kunnen voorspellen.

Deel I – Biologische en klinische prognostische factoren om patient-selectie voor CRS+HIPEC verder te optimaliseren

We onderzochten in **hoofdstuk 2** of postoperatieve morbiditeit en overlevings-uitkomsten na CRS+HIPEC beïnvloed worden door het moment van het ontstaan van colorectale PM (synchroon of metachroon). Wereldwijd zijn er geen eenduidige definities voor synchrone en metachrone colorectale PM en daarom werden voor dit hoofdstuk de meeste gebruikte definities in de wetenschappelijke literatuur geselecteerd. Patiënten met synchrone colorectale PM bleken reeds al colorectale PM te hebben bij de primaire diagnose van colorectale kanker. Patiënten met

metachrone colorectale PM ontwikkelden colorectale PM na een initiële 'curatieve' colorectale resectie. De resultaten van deze observationele multicenter−studie, bestaande uit 433 patiënten die tussen februari 2006 en december 2017 CRS+HIPEC ondergingen in twee Nederlandse tertiaire verwijzingscentra, toonden aan dat patiënten met metachrone colorectale PM significant vaker een vroeg recidief van ziekte kregen na CRS+HIPEC. Opvallend genoeg bleek de algehele overleving na CRS+HIPEC vergelijkbaar tussen patiënten met synchrone en metachrone colorectale PM. Met aanvullende analyses bleek dat de groep van patiënten met metachrone colorectale PM zeer heterogeen was en dat een subgroep van patiënten met een PCI boven de 10 de slechtste algehele en ziektevrije overleving na CRS+HIPEC had. Wij raden dan ook aan om extra voorzichtig te zijn bij het selecteren van patiënten voor CRS+HIPEC wanneer er sprake is van de aanwezigheid van metachrone colorectale PM met een PCI boven de 10.

De diagnostische laparoscopie (DLS) is geïmplementeerd in het gestandaardiseerde preoperatieve selectieproces voor CRS+HIPEC In het Universitair Medisch Centrum Groningen (UMCG) om niet−therapeutische laparotomieën (open−dicht procedures) bij patiënten met vermoeden op colorectale PM te voorkomen. **Hoofdstuk 3** beschrijft de haalbaarheid en veiligheid van het routinematig verrichten van DLS bij 184 patiënten met verdenking op colorectale PM. Een goede laparoscopische evaluatie van het abdomen was mogelijk bij 75% van de patiënten, terwijl 84% van de patiënten al eerdere buikoperatie(s) hadden ondergaan. Grote postoperatieve complicaties (Clavien−Dindo III−IV) traden op bij slechts vijf patiënten (2.7%) die allemaal tijdens DLS niet geschikt bleken voor CRS+HIPEC. Een andere belangrijke bevinding was het onverwacht hoge percentage van patiënten (50.5%) die potentiële kandidaten waren voor CRS+HIPEC volgens preoperatieve beeldvorming, maar uiteindelijk tijdens DLS niet geschikt werden geacht voor CRS+HIPEC. Enerzijds benadrukt dit de beperkingen van de huidige beeldvormende technieken in het detecteren van de aanwezigheid en omvang van peritoneale ziekte en anderzijds ondersteunt dit de toevoegde waarde van DLS voorafgaand aan CRS+HIPEC. In bijna de helft van de patiënten met verdenking op colorectale PM kon de DLS een onnodige laparotomie voorkomen.

De implementatie van DLS in het gestandaardiseerde preoperatieve selectieproces voor CRS+HIPEC wordt geëvalueerd in **hoofdstuk 4**, waarbij ook aandacht wordt besteed aan de impact op het voorkomen van niet−therapeutische laparotomieën. In 2012 werd de DLS voor deze specifieke indicatie geïntroduceerd in het preoperatieve selectieproces voor CRS+HIPEC. Hierdoor kon een historisch cohort van 48 patiënten

met colorectale PM die een laparotomie ondergingen voor mogelijke CRS+HIPEC worden vergelijken met 124 patiënten met colorectale PM die een laparotomie ondergingen voor mogelijke CRS+HIPEC na de introductie van de DLS in het preoperatieve selectieproces voor CRS+HIPEC. Het aantal niet−therapeutische laparotomieën daalden significant van 35.4 naar 21.0% na de introductie van de DLS, ondanks dat na deze introductie slechts 68.5% van de patiënten een DLS in ons academisch centrum ondergingen. Bij twee van de drie patiënten bleek een recente abdominale ingreep uitgevoerd in het verwijzend centrum de reden om af te zien van een DLS. Bij deze patiënten werd een onverwachts hoger percentage niet−therapeutische laparotomieën (28.5%) gevonden. We vermoeden dat chirurgen van verwijzende centra de uitgebreidheid van de peritoneale ziekte eerder onderschatten en de mogelijkheid om een volledige cytoreductie te bereiken eerder overschatten, omdat zij minder ervaring hebben met het exact rapporteren van deze twee belangrijke prognostische factoren. Met deze verkregen kennis besteden we nu meer aandacht aan het vroeg detecteren en laagdrempelig laten verwijzen van patiënten met colorectale PM naar ons academisch centrum. Patiënten ondergaan een DLS door één van onze HIPEC chirurgen om de uitgebreidheid en resectabiliteit van colorectale PM vast te stellen, onafhankelijk van recente abdominale chirurgie in het verwijzend centrum. Met deze aanpassingen verwachten wij in de komende jaren dat het percentage niet−therapeutische laparotomieën bij patiënten met colorectale PM nog verder zal gaan dalen.

Op dit moment wordt wereldwijd het PCI scoring systeem gebruikt als statische eenmalige meting tijdens een exploratieve laparotomie voorafgaand aan een mogelijke CRS+HIPEC procedure en bevat als zodanig dus geen informatie over eventuele progressie van peritoneale ziekte. Door de introductie van de DLS in het preoperatieve selectieproces voor CRS+HIPEC ontstond de mogelijkheid om te onderzoeken wat de invloed is van een snelle toename van de PCI in een kort tijdsbestek op overlevingsuitkomsten na CRS+HIPEC. In **hoofdstuk 5** presenteren we de ΔPCI als een onafhankelijke, en met name meer dynamische, prognostische factor voor algehele overleving bij patiënten met colorectale PM. We identificeerden, vanuit onze prospectief bijgehouden institutionele database, 84 patiënten die tussen 2012 en 2018 zowel een DLS als een exploratieve laparotomie voor mogelijke CRS+HIPEC procedure ondergingen, waarbij de PCI voor beide procedures bekend was. Het verschil in PCI score tussen de DLS en de exploratieve laparotomie (ΔPCI) werd berekend. Patiënten werden verdeeld in drie categorieën ten aanzien van progressie van peritoneale ziekte: (1) stabiele ziekte (ΔPCI 0–3); (2) milde progressie van ziekte (ΔPCI 4–9); en (3) ernstige progressie van ziekte (ΔPCI ≥10). De gemiddelde

overleving na CRS+HIPEC lag significant lager bij patiënten met een ΔPCI van 4–9 (35 maanden) of een ΔPCI van ≥10 (24 maanden) dan bij patiënten met een ΔPCI van 0–3 (48 maanden). Bij de multivariate regressie analyse bleef de ΔPCI een onafhankelijke risicofactor voor algehele overleving. Deze prognostische factor is waarschijnlijk een uiting van agressievere tumor biologie en zou mogelijk aanvullend gebruikt kunnen worden in de klinische beslissing voor het uitvoeren van de CRS+HIPEC procedure dan alleen de statische PCI score ten tijde van de exploratieve laparotomie. HIPEC chirurgen moeten zich bewust worden van deze ΔPCI geassocieerde afname van overleving na CRS+HIPEC en dienen als zij geconfronteerd worden met een ΔPCI ≥10 tijdens exploratieve laparotomie het uitvoeren van de CRS+HIPEC procedure te heroverwegen.

De uitgebreidheid van de cytoreductieve chirurgie tijdens CRS+HIPEC is een bekende risicofactor voor het optreden van ernstige postoperatieve morbiditeit en is dus essentieel om te weten voorafgaand aan de procedure. Potentiele overlevingswinst van de CRS+HIPEC procedure moet in evenwicht zijn met de bijkomende risico's voor het optreden van postoperatieve morbiditeit en mortaliteit. Elke dag proberen HIPEC chirurgen deze inschatting nauwkeurig voor hun patiënten te maken voordat patiënten worden ingepland voor CRS+HIPEC. **Hoofdstuk 6** beschrijft een prospectieve, observationele, cohortstudie die onderzocht hoe bekwaam vijf ervaren chirurgen zijn in het voorspellen van de uitgebreidheid van de cytoreductieve chirurgie voorafgaand aan CRS+HIPEC. Alle chirurgen voorspelden voor elke individuele patiënt onafhankelijk van elkaar het reseceren of *in situ* laten van 22 verschillende anatomische structuren volgens een gestandaardiseerd formulier voorafgaand aan CRS+HIPEC. De werkelijke uitgebreidheid van de cytoreductieve chirurgie tijdens CRS+HIPEC werd uit het operatieverslag geëxtraheerd en vergeleken met de vooraf voorspelde uitgebreidheid. Honderd eenendertig formulieren werden verzameld van 32 patiënten die succesvol CRS+HIPEC ondergingen. Voor iedere anatomische structuur werd de positief en negatief voorspellende waarde berekend (PVW en NVW, respectievelijk). Een hoge PVW suggereert dat de chirurg goed kan voorspellen of de anatomische structuur gereseceerd dient te worden, terwijl een hoge NVW aangeeft dat de chirurg goed kan voorspellen of een anatomische structuur veilig *in situ* kan worden gelaten. Het aantal resecties dat noodzakelijk bleek te zijn om een complete cytoreductie te bereiken werd slechts 24 keer correct ingeschat (18.3%), 57 keer overschat (43.5%) en 50 keer onderschat (38.2%). Over het algemeen lagen de NVW's voor de verschillende anatomische structuren hoger en toonden minder variatie tussen de chirurgen in vergelijking met de PVW's. Dit suggereert dat chirurgen met uitgebreide ervaring in het uitvoeren

van deze procedures het vermogen hebben om te voorspellen welke anatomische structuren gespaard kunnen worden tijdens CRS+HIPEC, maar in de meeste gevallen onvoldoende kunnen voorspellen welke resecties noodzakelijk zullen zijn om een complete cytoreductie te bereiken met een onderschatting in bijna 40% van de gevallen. Dit fenomeen benadrukt opnieuw dat toekomstig onderzoek zich nog meer moet focussen op het optimaliseren van het detecteren van de aanwezigheid en uitgebreidheid van colorectale PM voorafgaand aan chirurgie.

Deel II – Nieuwe wegen voor onderzoek.

Minstens één op de drie kankerpatiënten heeft binnen zeven dagen na complexe chirurgie klinisch relevant chirurgisch gerelateerd spierverlies (SRML). In de toekomst kan preventie van klinisch relevant SRML bij kankerpatiënten een veelbelovende strategie zijn om postoperatieve morbiditeit en mortaliteit te verminderen en de kwaliteit van leven na chirurgie te vergroten. Er is echter nog steeds een gebrek aan wetenschappelijke kennis over dit onderwerp. **Hoofdstuk 7** beschrijft daarom ook uitvoerig het design van de MUSCLE POWER studie; een observationele, mono−center, prospectieve, cohortstudie die momenteel de aanwezigheid, impact en mogelijke voorspellers voor klinisch relevant SRML na grote abdominale chirurgie bij 178 kankerpatiënten in kaart brengt met behulp van o.a. echometingen, krachtmetingen en kwaliteit van leven vragenlijsten. Fysieke activiteit gedurende de ziekenhuisopname wordt dagelijks gemonitord met een bewegingssensor en de eiwitintake wordt dagelijks gemonitord door een diëtist. Cruciale informatie over mogelijke voorspellers voor klinisch relevant SRML kan worden gebruikt voor toekomstige interventiestudies om postoperatief spierverlies te voorkomen en de impact op verschillende postoperatieve uitkomsten en kwaliteit van leven op de lange termijn te minimaliseren. De MUSCLE POWER studie is open voor inclusie en de afgelopen vier maanden zijn al meer dan 50 patiënten succesvol geïncludeerd. De eindresultaten worden eind 2020 verwacht.

Hoofdstuk 8 beschrijft de principes van intra−operatieve moleculaire beeldvorming en biedt een chronologische overzicht over de ontwikkelingen van moleculaire fluorescentie geleide chirurgie (MFGS) bij patiënten met colorectale PM. Momenteel zijn chirurgen volledig afhankelijk van hun visuele en tactiele inspectie tijdens een procedure om te differentiëren tussen benigne en maligne laesies. Het hoge percentage aan vroege recidieven na CRS+HIPEC laat zien dat er behoefte is aan een beeldvormende modaliteit die de oncologisch chirurg intra−operatief kan helpen bij het differentiëren tussen benigne en maligne weefsel. De afgelopen jaren heeft MFGS zich ontwikkeld tot een veelbelovende real−time intra−operatieve

beeldvormende techniek om tumordetectie te verbeteren door gebruik te maken van tumorgerichte fluorescerende tracers. Een tumorgerichte fluorescerende tracer is gebaseerd op het concept van een dragermolecuul dat is geconjugeerd aan een fluorescerende kleurstof die specifiek kan binden aan een bepaald tumor doelwit. Deze intra−operatieve beeldvormende techniek kan worden toegepast als een soort 'rode−vlag' techniek om zo te helpen bij optimale tumoridentificatie, waardoor de chirurg tijdens de procedure kleinere tumor laesies makkelijker kan identificeren en tegelijkertijd kan differentiëren tussen benigne en maligne weefsel. Bevacizumab-IRDye800CW, een veelbelovende tumorgerichte fluorescerende tracer gericht op de vasculaire endotheliale groeifactor (VEGF−A), zal in de nabije toekomst in het UMCG worden gebruikt voor een nieuwe fase−I studie om tumorweefsel van colorectale PM te detecteren tijdens DLS (de SELECT trial). Indien bevacizumab-IRDye800CW accuraat detecteerbaar is tijdens een DLS wordt het in de toekomst mogelijk om de uitgebreidheid van peritoneale ziekte in een eerder stadium nauwkeuriger te onderzoeken. Uiteindelijk kunnen dit soort nieuwe strategieën mogelijk overbehandeling, postoperatieve morbiditeit en kosten verminderen met behoud van dezelfde of zelfs betere effectiviteit van de procedure met een lagere recidiefkans en een verbetering van de kwaliteit van leven.

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** Shared first author position. Both authors contributed equally to this work.*

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Prof. dr. G.M. van Dam, lieve Go, wat ben ik een enorme geluksvogel geweest dat jij mijn professor was. Het schept natuurlijk al een band als je beide op dezelfde dag in februari 2018 de kliniek van het UMCG verlaat om aan nieuwe doelen te gaan werken. Ik krijg nog steeds een enorme lach op mijn gezicht als ik terugdenk aan mijn eerste EMIM congres in San Sebastián in Spanje. Ik had slechts enkele weken gesnuffeld aan de bijzondere wereld van fluorescentie en kwam er daar pas achter wat voor zeer gewaarde wereld−expert jij eigenlijk bleek te zijn op dit gebied! Als ik jouw naam liet vallen wilden iedereen opeens wel graag met mij praten. Laten we het maar een korte periode van onbewuste onbekwaamheid noemen. Ondertussen weet ik wel beter. Met jou heb ik een enorm enthousiaste, ambitieuze maar vooral ook gezellige professor aan mijn zijde gehad die op borrels vaak pas diep in de nacht vertrok om bijvoorbeeld nog even snel het vliegtuig te gaan halen. Jouw relaxte, no−nonsense houding beviel perfect en soms hoefde ik alleen te zeggen dat er 'even een paar grijze haren nodig waren' en dan wist je genoeg. Je hebt mij elke keer op het hart gedrukt om mijn proefschrift spoedig af te ronden, omdat tegelijkertijd promoveren en in opleiding zijn tot chirurg vanuit jouw eigen ervaring voor niemand aan te raden was. Niet alleen dit advies maar ook vele anderen heb ik in mijn oren geknoopt. Helaas hebben we weinig fluorescent licht samen gezien, maar lieve Go fluorescente geleide chirurgie gaat werkelijkheid worden in de dagelijkse kliniek en ik beloof je dat ik dan bij elke procedure even aan jou zal denken.

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geweest. Wat was het top om iemand te hebben die de statistiek wel begreep en alle 'losse klusjes' eventjes tussendoor deed. Succes met de laatste loodjes van je eigen proefschrift. Ik zal wat boeken weggooien om jouw proefschrift tegen die tijd in mijn boekenkast te kunnen plaatsen. **Steven** jij was de reddende engel aan het begin van mijn promotietijd. Jij gaf mij de zwembandjes die nodig waren om niet volledig te verzuipen bij het schrijven van een review over de ontwikkelingen die binnen de moleculaire fluorescente geleide chirurgie plaatsvonden. Altijd mooi om 'onze gepubliceerde figuren' weer terug te zien bij nationale en internationale congressen. Succes in het Martini ziekenhuis en ik ga onze (verhitte) discussies stiekem wel missen. **Laura**, heldin van de prehabilitatie poli, wat heb ik jou over de jaren zien groeien van semi−arts naar promovendus bij de HPB chirurgie. Jouw droge humor kan ik altijd enorm waarderen. Dank voor alle inclusies voor de MUSCLE POWER studie en in de toekomst bedenken we vast een studie waar de galblaas patiënten wel aan mogen deelnemen. **Alain**, wat was het leuk om samen te werken met een radioloog en te leren hoe je een goede echo maakt van spierweefsel! Jouw lach toen ik vertelde dat de spieren van het bovenbeen van mijn vriend wel 2.5 keer dikker waren dan die van mij vergeet ik niet snel. **Prof. dr. C.P. van der Schans**, beste Cees, dank voor het meedenken en uitlenen van alle belangrijke materialen die we nu nog steeds voor de MUSCLE POWER studie gebruiken. **Prof. dr. G.H. de Bock**, beste Truuske, dank voor je eindeloze uitleg over de statistische methodiek die we moesten gaan gebruiken voor de MUSCLE POWER studie. Ik moest soms erg worstelen met jouw kritische vragen over wat ik nu eigenlijk echt wilde onderzoeken, maar het is de opzet van de studie zeker ten goede gekomen. **Frederik**, Fredje, wat heb jij mij altijd enorm gesteund! Zowel tijdens mijn gehele promotietijd als ook in de aanloop naar mijn sollicitatie om een opleidingsplaats bij de chirurgie te bemachtigen. Je hebt een zeer goede indruk gemaakt als kerstman bij het jaarlijkse arts−assistentendiner en ik ben altijd blij als ik jou weer bij een borrel of op een congres zie staan. Toch moet hier zeker ook vermeld worden dat je met ieder manuscript actief meedacht en met veel enthousiasme elke keer weer de uitgebreidheid van chirurgie stond te voorspellen. Jouw 'extra' aantekeningen op het *extent of surgery* formulier paste helaas niet altijd in de database, maar ik heb enorm genoten om ze allemaal te lezen. De Zuid-Afrikaanse wijn *Pinnotage* komt nog jouw kant op. Dit is de wijn die ik destijds, toen ik hoorde dat ik was aangenomen voor de opleiding, al voor je wilde kopen maar waarbij ik uit puur enthousiasme per ongeluk de verkeerde fles bij de Gall & Gall had meegepakt. **Carlijn**, wat vind ik het altijd fijn om even met jou te kunnen sparren en het liefste dan met een goede cappuccino erbij. Ik heb veel bewondering voor hoe je alles altijd toch weer weet te combineren; van levertransplantatie in de nacht tot je gezinsleven overdag. Je

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CURRICULUM VITAE

Judith Eleonora Katharina Regina Hentzen werd op 17 mei 1989 geboren te Utrecht. Zij groeide op als jongste dochter van Ab Hentzen en Maria Verkleij samen met haar twee oudere broers Christiaan en Jasper en oudere zus Miriam. In 2007 behaalde zij haar gymnasium diploma aan het Leidsche Rijn College te Utrecht. Aansluitend volgde zij de HBO opleiding Verpleegkunde aan de Hogeschool van Utrecht en behaalde een jaar later haar propedeuse. In 2008 kon Judith beginnen aan de opleiding Geneeskunde aan de Universiteit van Utrecht. Tijdens haar opleiding Geneeskunde liep zij onder andere een coschap Kindergeneeskunde in het Muhimbili Hospital in Tanzania. Haar wetenschapstage vond plaats in het Academisch Medisch Centrum te Amsterdam, waarbij zij onder leiding van prof. dr. B.W. Mol en dr. W.M. van Ankum landelijk onderzoek verrichtte naar de behandeling van miskramen in Nederland. In het voorjaar van 2015 begon zij als arts-assistent niet in opleiding bij de afdeling chirurgie in de Isala klinieken te Zwolle. In dezelfde periode voltooide zij onder leiding van dr. G.A. Patijn haar wetenschappelijke onderzoek naar het optimaliseren van antibiotica profylaxe binnen de hepato-pancreato-biliaire chirurgie. Aansluitend werkte zij vanaf 2017 als arts-assistent niet in opleiding bij de afdeling chirurgie in het Universitair Medisch Centrum Groningen. In het voorjaar van 2018 is zij onder leiding van haar promotor prof. dr. G.M. van Dam en copromotor dr. S. Kruijff gestart met haar promotieonderzoek naar de chirurgische behandeling van uitgezaaide dikke darmkanker, dat resulteerde in dit proefschrift wat nu voor u ligt. Na twee jaar gewerkt te hebben als promovendus startte zij in januari 2020 met haar opleiding tot chirurg. De eerste drie jaar van haar opleiding vinden plaats in de Isala klinieken te Zwolle (Opleider V.B. Nieuwenhuijs). Vervolgens zal zij haar opleiding voort zetten in het Universitair Medisch Centrum Groningen (Opleiders dr. R.J. van Ginkel en prof. dr. J.M. Klaase).