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Development of a prediction model for recurrence in patients with colorectal peritoneal metastases undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Introduction: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) improves survival outcomes for selected patients with colorectal peritoneal metastases (PM), but recurrence rates are high. The aim of this study was to develop a tool to predict recurrence in patients with colorectal PM that undergo CRS-HIPEC.

Materials and methods: For this retrospective cohort study, data of patients that underwent CRS-HIPEC for colorectal PM from four Dutch HIPEC centers were used. Exclusion criteria were perioperative systemic therapy and peritoneal cancer index (PCI) ≥20. Nine previously identified factors were considered as predictors: gender, age, primary tumor characteristics (location, nodal stage, differentiation, and mutation status), synchronous liver metastases, preoperative Carcino-Embryonal Antigen (CEA), and peritoneal cancer index (PCI). The prediction model was developed using multivariable Cox regression and validated internally using bootstrapping. The performance of the model was evaluated by discrimination and calibration.

Results: In total, 408 patients were included. During the follow-up, recurrence of disease occurred in 318 patients (78%). Significant predictors of recurrence were PCI (HR 1.075, 95% CI 1.044–1.108) and primary tumor location (left sided HR 0.719, 95% CI 0.550–0.939). The prediction model for recurrence showed fair discrimination with a C-index of 0.64 (95% CI 0.62, 0.66) after internal validation. The model was well-calibrated with good agreement between the predicted and observed probabilities.

Conclusion: We developed a prediction tool that could aid in the prediction of recurrence in patients with colorectal PM who undergo CRS-HIPEC.

1. Introduction

Colorectal carcinoma (CRC) is the third most common malignancy worldwide and its burden is expected to increase in the upcoming years [1]. Approximately 10% of these patients develop peritoneal metastases (PM) at some point in the disease course [2,3]. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) improves the survival of selected patients with colorectal PM. This extensive treatment results in a median overall survival (mOS) up to four years, which is limited to about a year in patients treated with systemic chemotherapy [4–6].

To achieve these favorable outcomes, patient selection is of utmost

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importance. Despite careful patient selection, this extensive local treatment does not result in cure for all patients, which is reflected by high recurrence rates [5,7–9]. About half of the patients with disease recurrence are diagnosed with systemic metastases which are commonly diagnosed within a year after surgery [2,5,8,10]. For these patents, it is questionable whether CRS-HIPEC alone is the appropriate treatment. Systemic therapy, possibly (neo-)adjuvant around CRS-HIPEC, might be a better treatment option for these patients. Preoperative prediction of recurrence could therefore aid in the guidance of treatment choices. Identifying patients with an elevated risk of recurrence could help select patients who would benefit from additional systemic treatment.

Previous studies aimed to identify predictive factors for recurrence after CRS-HIPEC [5,6,11,12]. These studies included cohorts of patients in which the majority received perioperative systemic chemotherapy. We argue that a cohort of patients that did not receive any perioperative systemic therapy would be more suitable for the prediction of recurrence in a preoperative setting. The current study aimed to develop a tool to predict recurrence after CRS-HIPEC in a cohort of patients that were not treated with perioperative systemic therapy, which could help identify patients that would benefit from additional therapy.

2. Materials and Methods

2.1. Study design and data collection

This retrospective cohort study included patients who underwent a first CRS-HIPEC procedure for colorectal PM in the Erasmus MC Cancer Institute (EMC) in Rotterdam between 2014 and 2021, the Radboud University Medical Center in Nijmegen between 2010 and 2020, the University Medical Center Groningen between 2006 and 2019, and the Catharina Hospital Eindhoven (CHE) between 2013 and 2017. Exclusion criteria were treatment with perioperative systemic therapy to CRS-HIPEC, appendiceal carcinomas, a peritoneal cancer index (PCI) of 20 or higher, and no histologically proven PM. Patients that were included in the CAIRO-6 trial (NCT02758951) were also excluded from this study [13].

Relevant patient, disease, and perioperative characteristics, as well as postoperative outcomes were obtained from prospectively maintained databases from the aforementioned centers. Information on survival status was obtained from the national civil registry, when not available in the electronic patient file. Approval for the collection of these data was approved by the local Medical Ethics Review Committees of the Erasmus Medical Center (MEC-2018-1286). This study was conducted in compliance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement (checklist is provided in the **data supplement** [14].

2.2. Variable definitions and outcomes

Onset of colorectal PM was defined synchronous if PM was diagnosed at the time of presentation, during routine staging, or at surgery of the primary tumor. Metachronous onset was defined as PM diagnosed in the follow-up period after primary treatment. Nodal stage was determined by clinical staging for patients with synchronous PM and pathological staging for patients with metachronous PM. Disease-free survival (DFS) was defined as the time between CRS-HIPEC and the diagnosis of recurrence, death, or last follow-up in censored cases. Overall survival (OS) was defined as the time between CRS-HIPEC and death or last follow-up in censored cases.

The primary aim of this study was to develop a prediction model for recurrence, irrespective of location. Variables of interest for the development of the prediction model were selected based on previous studies reporting on risk factors for the development of metastases from CRC or recurrence after CRS-HIPEC (irrespective of location) [5,6,8,11,12,15–18]. Nine predictors were selected for the development of the model. Patient-related characteristics: sex (dichotomous) and age (continuous). Disease-related characteristics: location (right or left-sided), differentiation (good/moderate or poor), and nodal stage (positive or negative) of the primary tumor (all dichotomous), synchronous liver metastases (dichotomous), PCI (continuous), preoperative Carcino-Embryonal Antigen (CEA, continuous), mutational status (categorical, BRAF or KRAS or no BRAF/KRAS mutation).

2.3. Perioperative course

The perioperative course of these patients has been described earlier [8]. In summary, all patients were screened by preoperative imaging and if possible a diagnostic laparoscopy (DLS) to determine the extent of the disease, assessed by the PCI [19]. Patients were eligible for CRS-HIPEC if they were fit for major surgery, had an estimated PCI below 20, and no or limited systemic metastases (maximum of three liver metastases). CRS-HIPEC procedures were performed by a specialized surgical team, in accordance with the Dutch CRS-HIPEC protocol [20,21]. Patients were postoperatively treated following standard of care for CRS-HIPEC procedures.

2.4. Follow-up

Follow-up was performed in the outpatient clinic according to a local protocol. In general, during the first two years of follow-up, CT scans were performed every six months, or in case of rising CEA levels or clinical suspicion of recurrent disease. Follow-up was completed after a disease-free interval of five years following CRS-HIPEC. For patients treated in the EMC, CHE, and UMCG, CEA was determined every three months in the first two postoperative years and every six months thereafter. The interval between CT scans increased to 12 months if no recurrence was detected after two years in the EMC and UMCG or three years in the CHE. In the Radboud University Medical Center, CEA measurements and CT scans were performed every six months during the complete five years of follow-up.

2.5. Statistical analysis

Descriptive statistics were used to summarize patient, disease, and treatment-related characteristics. Categorical variables were presented as counts with percentages and continuous variables as median with interquartile range (IQR). The reversed Kaplan–Meier method was used to calculate median follow-up and median time to recurrence for patients that were diagnosed with recurrent disease within follow-up. The Kaplan–Meier method was used to estimate the median DFS and OS. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM Corporation, Armonk, NY) and R (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

2.6. Model development

The sample size was calculated according to the methods described by Riley et al. [22,23] Input for the sample size calculation was obtained using data from the development cohort. We used estimated event ratios of 0.45 and 0.22, for recurrence, respectively, and a median follow-up of 12.5 months. We selected our time-point of interest for prediction at 12 months. An r-squared value of 0.15 was used as suggested [22]. With 10 parameters to be estimated (nine predictors) this resulted in a sample size of ~500 patients. To reduce bias in results due to missing data, multiple imputation by chained equations was used. Additional information about handling of missing data can be found in Data Supplement 1. Predictors were entered into a Cox proportional hazards regression model. Nonlinear associations between continuous predictors (e.g. PCI) and the outcomes were assessed using restricted cubic splines. Plausibility of nonlinear associations was evaluated graphically and benefit for model fit was assessed using likelihood-ratio testing. In the final models no nonlinear associations were modeled. Statistical analysis was

performed in each imputed dataset and the resulting estimates were subsequently pooled using Rubin's rule.

2.7. Internal validation

To address potential overfitting, internal validation using bootstrapping was performed. For bootstrapping, 500 random samples were drawn from the development dataset (with replacement). A shrinkage factor was then calculated and used to adjust the regression coefficients of the prediction model. Calibration was assessed with a calibration plot for predictions at six months, one year, and two years. Harrell's C was used to determine the discriminatory performance of the model [24]. A Harrell's C of 1.0 indicates perfect discrimination, whereas 0.5 suggests poor discriminative ability (≤0.6 poor, 0.6–0.7 fair, 0.7–0.8 good, 0.8–0.9 very good, 0.9 excellent).

3. Results

In total, 465 patients underwent a first CRS-HIPEC procedure for colorectal PM in one of the four HIPEC centers and did not receive neoadjuvant and/or adjuvant systemic therapy. A total of 47 patients were excluded because the location of recurrence was not reported, or they had a PCI of 20 or higher. In total, 408 patients were included in the development cohort. Baseline characteristics are provided in Table 1.

The median follow-up time for all patients was 14 months (7–37). Median DFS was 8 months [5–16] for the complete cohort. A total of 318 patients (78%) had recurrence of disease with a median time to recurrence of 7 months [4–12]. Out of these patients, 182 (57%) were diagnosed with extra-peritoneal metastases and 79 patients (25%) were diagnosed with extra-peritoneal metastases only (without local recurrence, Table 2). Extra-peritoneal metastases most commonly involved the liver in 62 patients (40%), lungs in 41 patients (27%), or both in 20 patients (13%). A total of 218 patients deceased during follow-up, resulting in a median OS of 34 months (IQR 18–56).

3.1. Prediction of disease recurrence

Table 3 displays regression coefficients and hazard ratio's (HR) of the predictors for recurrence. There was no evidence for multicollinearity between the predictors. Through bootstrapping by internal validation a shrinkage factor of 0.90 was estimated. Significant predictors for recurrence of disease in multivariable analysis were PCI (HR 1.075, 95% CI 1.044–1.108) and left-sided primary tumor location (HR 0.719, 95% CI 0.550–0.939). After shrinkage, the model demonstrated a C-index of 0.64 (95% CI 0.62, 0.66) for the development cohort, which is defined as fair discriminative capacity. Calibration of this model was satisfactory, with a tendency towards an underestimation of probabilities in low-risk patients at six months after surgery and in high-risk patients at two years after surgery (Fig. 1). Supplementary Fig. 1 shows the risk-prediction nomogram.

3.2. Additional prediction of extra-peritoneal recurrence

We hypothesized that specifically patients with extra-peritoneal recurrence (with or without peritoneal recurrence) could gain benefit from systemic perioperative therapy. For this reason, we developed a second prediction model to predict extra-peritoneal recurrence as shown in Supplementary Table 1. The only significant predictor for extra-peritoneal recurrence in multivariable analysis was PCI (internally validated HR 1.698 (1.254–2.298). Internal validation resulted in a shrinkage factor of 0.84 with a C-index of 0.64 (95% CI 0.62, 0.66) also defined as fair discriminative capacity. The calibration plots showed good agreement between the predicted and observed probabilities of systemic recurrence at six months, one year, and two years after surgery (Supplementary Fig. 2). Supplementary Fig. 3 displays the risk-prediction nomogram.

Table 1
Baseline characteristics.

	Total N = 408
Gender	
Male	193 (47.3)
Age **(years)**	65 (56–71)
ASA-classification	
1–2	322 (80.3)
3–4	79 (19.7)
Missing	*7 (1.7)*
Primary tumor location	
Right-sided	189 (46.3)
Left-sided	219 (53.7)
T stage primary tumor	
T1-2	17 (4.2)
T3-4	385 (95.8)
Missing	*6 (1.5)*
N stage primary tumor [a]	
N-	111 (29.9)
N+	260 (70.1)
Missing	*37 (9.1)*
M stage primary tumor	
M0	164 (46.6)
M1	188 (53.4)
Missing	*78 (18.1)*
Location metastases [b]	
Local/PM	140 (83.3)
Systemic	14 (7.4)
Local/systemic	14 (7.4)
Missing	*20 (10.6)*
Differentiation primary tumor	
Good/moderate	267 (65.4)
Poor	64 (15.7)
Missing	77 (18.9)
Histology primary tumor	
Adenocarcinoma	204 (72.1)
Mucinous	50 (17.7)
Signet cell	29 (10.2)
Missing	*125 (30.6)*
Mutation status [c]	
BRAF [d]	13 (3.2)
KRAS [e]	31 (7.6)
Prior chemotherapy [f]	
Yes	117 (28.7)
Time of onset of PM	
Synchronous	154 (37.7)
Synchronous liver metastases	
Yes	36 (8.8)
PCI at DLS [g]	4 [3–8]
Preoperative CEA [h]	7.2 (3.6–16.5)
HIPEC chemotherapy	
MMC	342 (84.0)
Oxaliplatin	65 (16.0)
Missing	1 (0.2)
PCI at HIPEC [i]	9 [5–13]
R score	
R1	405 (99.3)
R2a	2 (0.5)
R2b	0 (0.0)
Missing	1 (0.2)
Severe postoperative complications [j]	
Yes	111 (27.2)
Reoperation [k]	
Yes	47(12.1)

Continuous variables are shown as median [IQR]. Frequencies are shown as N (%). ASA, American association for anesthesiology; BRAF, B-Raf proto-oncogene; CEA, carcinoembryonic antigen; CCR, completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; KRAS, kirsten rat sarcoma viral; MMC mitomycin-C; PCI, peritoneal cancer index; PM, peritoneal metastasis.

[a] Nodal stage was determined by clinical staging for patients with synchronous PM and pathological staging for patients with metachronous PM [b] Location of metastases synchronous to primary tumor [c] Data available for 73 patients (17.9%) [d] Most common type of BRAF mutation p.V600E in 12 patients (92.3%) [e] Most common type of KRAS mutation pG12D in 12

patients (38.7%) [f] Data available for 378 patients (92.6%) [g] Data available for 170 patients (41.7%) [h] Data available for 155 patients (62.0%) [i] Data available for 390 patients (95.6%) [j] According to Clavien–Dindo classification ≥ III (i.e., reintervention, extended ICU stay/readmission to ICU, or treatment-related death); available for 397 patients (97.3%) [k] Data available for 388 patients (95.1%).

Table 2
Location of recurrence.

	Total N = 318	Median time to recurrence **(months)**
Recurrence location‘		
Peritoneal	132 (41.5)	8 [5–12]
Extra-peritoneal	79 (24.8)	6 [4–11]
Peritoneal and extra-peritoneal	103 (32.4)	7 [4–9]
Systemic location [a]		
Liver	62 (40.0)	6 [3–9]
Lung	41 (26.5)	7 [4–8]
Liver and lung	20 (12.9)	5 [4–8]
Other	32 (20.6)	6 [4–12]
Missing	*27 (14.8)*	

[a] For all patients (n = 182) with systemic recurrence.

Table 3
Predictors for recurrence after CRS-HIPEC.

	Univariable HR (95% CI)	Regression coefficient (β) [a]	Multivariable HR (95% CI) [a]
Gender			
Male	Ref	Ref	Ref
Female	1.052 (0.845–1.309)	0.139	1.149 (0.801–1.647)
Age (years)	0.995 (0.988–1.002)	−0.009	0.991 (0.978–1.005)
Primary tumor location			
Right sided	Ref	Ref	Ref
Left sided	0.845 (0.678–1.054)	−0.330	0.719 (0.550–0.939)
N stage primary tumor [b]			
N-	Ref	Ref	Ref
N+	1.158 (0.899–1.489)	0.117	1.124 (0.866–1.459)
Synchronous liver metastases [c]			
Yes	0.988 (0.653–1.497)	−0.123	0.884 (0.543–1.440)
Differentiation primary tumor			
Good/ moderate	Ref	Ref	Ref
Poor	1.211 (0.890–1.647)	0.130	1.139 (0.773–1.678)
PCI at HIPEC	1.088 (1.062–1.116)	0.072	1.075 (1.044–1.108)
CEA	1.005 (1.001–1.008)	0.003	1.0035 (1.000–1.007)
Mutational status			
No	Ref	Ref	Ref
BRAF	1.837 (0.650–5.194)	0.654	1.923 (0.611–6.048)
KRAS	1.596 (0.643–3.961)	0.502	1.653 (0.686–3.980)

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; KRAS, kirsten rat sarcoma viral; MMC mitomycin-C; PCI, peritoneal cancer index.

[a] After internal validation, adjustment with shrinkage factor 0.901.

[b] Nodal stage was determined by clinical staging for patients with synchronous PM and pathological staging for patients with metachronous PM.

[c] Synchronous to colorectal peritoneal metastases.

3.3. Prediction web application

The prediction model for recurrence was implemented in a web application to estimate a patient’s recurrence probability after CRS-HIPEC at different time points. The application is available at https://colorectalpm.shinyapps.io/recurrence_colorectal_pm/.

4. Discussion

In the current study, we developed a prediction tool for recurrence after cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colorectal peritoneal metastases (PM) that could aid in clinical decision making. PCI and right primary tumor location were the most important significantly associated factors with an increased risk of recurrence. The prediction model that was developed showed fair discriminatory capacity and was well-calibrated, providing accurate risk predictions.

High recurrence rates after CRS-HIPEC in patients with PM underscore the need for the optimization of perioperative treatment strategies. Additional perioperative systemic therapy might reduce the risk of recurrence in these patients. In most countries, perioperative systemic chemotherapy, either in neo- or adjuvant setting, is standard of care in patients undergoing CRS-HIPEC for colorectal PM [25]. The evidence supporting the benefit of this additional therapy is however scarce and randomized controlled trials (RCTs) are missing [26]. In the Netherlands, due to this lack of evidence, systemic therapy is not used as a standard perioperative regimen [27]. This provided the opportunity to initiate the ongoing CAIRO-6 trial, in which patients with isolated colorectal PM are randomized to receive either CRS-HIPEC alone, or CRS-HIPEC with perioperative systemic therapy [13]. The results from this trial will provide valuable information on the benefit of systemic therapy for these patients.

However, not all patients with PM likely benefit from systemic therapy or the addition of this treatment to CRS-HIPEC. Due to associated toxicity and patient burden, it would be preferred to select patients that most likely gain survival benefit. Patients at low risk of recurrence may not derive significant benefit from systemic therapy and could potentially be spared additional treatment. A previous study by Rieser et al. (2021) developed a prediction model to specifically predict early recurrence after CRS-HIPEC (i.e. within eight months) [11]. The authors did not specify location of recurrence, but identified BMI, liver lesions, progression on chemotherapy, positive nodal stage, and PCI as predictors of early recurrence. This model showed fair discriminatory power and has not yet been externally validated but might have added value in patient selection for additional therapy or CRS-HIPEC in general.

An important limitation of this study and most previous studies evaluating risk factors for recurrence after CRS-HIPEC is that a substantial proportion of patients received perioperative systemic therapy, which could have affected the risk of recurrence. For the utility in perioperative patient selection, one would preferably identify risk factors in a cohort of patients that did not receive perioperative systemic therapy. Since perioperative systemic therapy is not standard of care in the Netherlands, the current study presents a relatively large cohort of patients that did not receive additional perioperative therapy. In this cohort, only PCI and primary tumor location were strong predictors for recurrence in this cohort. In contrast to the study of Rieser et al., prognostic factors like nodal stage and synchronous liver metastases were not significantly associated with recurrence [11]. This might be due to selection bias, as these patients might have been treated with perioperative chemotherapy more often.

Although our prediction model shows fair discriminatory capacity, better discrimination would be preferred for individual patient selection and its utility in clinical decision making. Another strategy to identify patients that most likely benefit from systemic therapy would be to predict the development of extra-peritoneal recurrence (either with or

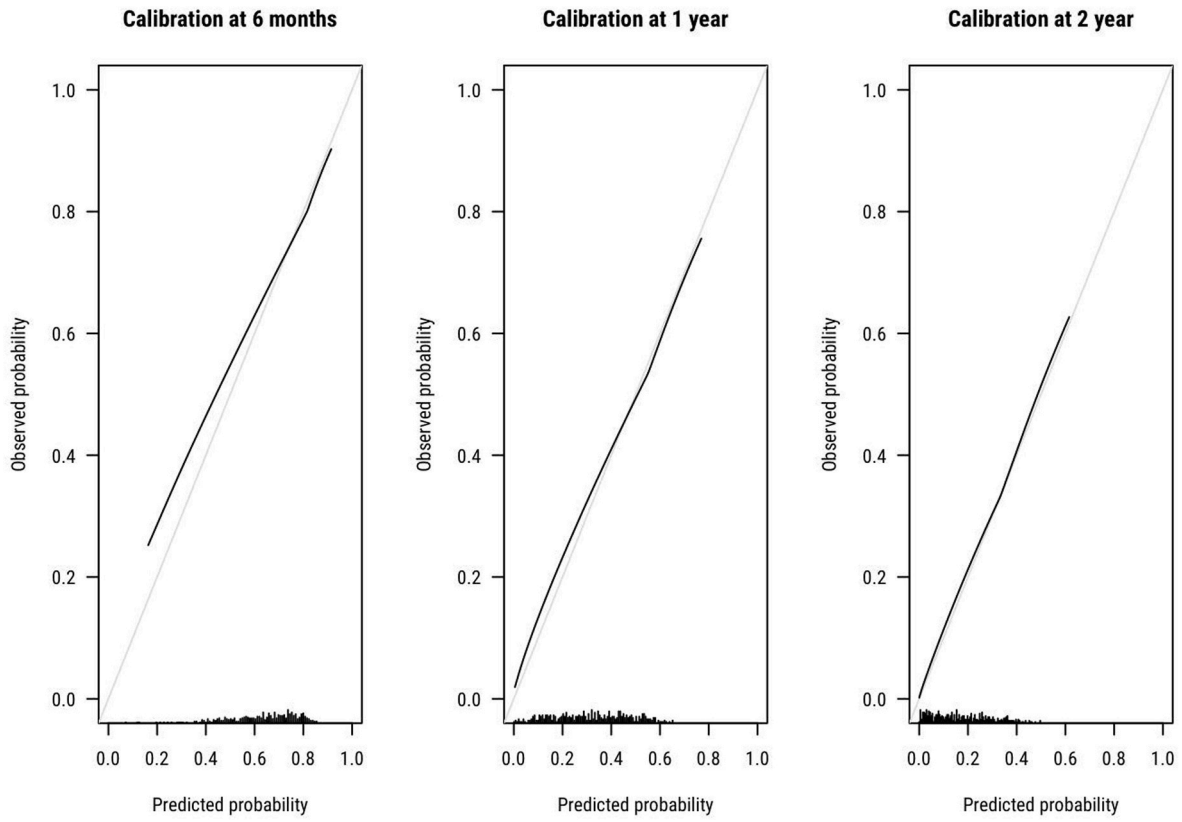

Fig. 1. Calibration plots for the predicted recurrence probability at six months (A), one year (B), and two years (C).

without peritoneal recurrence). Patients with 'systemic disease' are more likely to benefit from systemic treatment compared to patients with local disease only. An additional model predicting extra-peritoneal recurrence identified PCI as the only significant predictor and provided a similar performance compared with the model for any recurrence. Previous studies evaluating the site of recurrence after CRS-HIPEC were not able to establish any risk factor for extra-peritoneal recurrence [6,12]. This is probably explained by a difference in outcome measures. These previous studies used isolated extra-peritoneal recurrence as an outcome measure, whereas the current study included all extra-peritoneal metastases (with or without peritoneal recurrence), since we argued that both groups would benefit from the addition of systemic therapy. Due to similar performance and the limited ability to identify factors that specifically predict extra-peritoneal recurrence, we concluded that the additional value of this second model in clinical practice would be limited.

If the CAIRO-6 trial shows that the addition of systemic therapy results in an overall survival benefit for patients with colorectal PM undergoing CRS-HIPEC, one could argue that this should become standard of care for all patients. The first results of the CAIRO-6 trial show that the addition of perioperative systemic therapy has acceptable tolerability, so the burden of this addition might be limited [28]. Nonetheless, we argue that the proposed model could potentially help guide clinical decision making in selected cases, since this is currently the only tool available for the preoperative prediction of recurrence in patients undergoing CRS- HIPEC. To establish its potential utility, the model should be externally validated, preferably on the CAIRO-6 data. Additionally, new predictors that might optimize patient selection are widely being investigated. A potential biomarker of interest, specifically for the prediction of extra-peritoneal recurrence, is ctDNA. A study by Beagan et al. showed that ctDNA could serve as a preoperative marker of recurrence in a small cohort of patients with colorectal PM [29]. In four out of five patients that experienced extra-peritoneal recurrence, ctDNA was detected preoperatively.

4.1. Strengths and limitations

A major strength of this study is that it includes a large cohort of patients with PM undergoing CRS-HIPEC that did not receive perioperative systemic therapy. Hence, the models presented in this study are currently the only available tools to select patients that potentially benefit from perioperative systemic therapy. Nonetheless, their utility in individual patient selection is limited as they do not show optimal discrimination. The sample size calculation to use nine predictors in the models resulted in a sample size of ~500 patients. Although relatively large, our cohort was limited to 408 patients which could have limited the power to find significant results. The retrospective nature of this study could have resulted in selection bias. Although perioperative systemic therapy is currently not standard of care for patients with PM undergoing CRS-HIPEC in the Netherlands, patients with potential risk factors for early recurrence could have received adjuvant systemic therapy more often. Likewise, although not standard of care, induction systemic therapy could have been considered in patients with extensive or borderline resectable disease. These patients were excluded from the current study, as the use of perioperative systemic therapy could have affected the risk of recurrence. Another important limitation due to the retrospective nature was missing data. Missing data was common for some potential predictors such as preoperative CEA and mutational status. To address missing data, multiple imputation was used. This is accompanied by a small risk of bias, but this was deemed to be higher with complete case analysis.

5. Conclusions

Based on the developed prediction model the ability to select patients that might benefit from perioperative systemic therapy around CRS-

HIPEC based on their risk of recurrence is limited. Since this model is currently the only available tool for pre-operative prediction of recurrence, it could aid in clinical decision making. The utility of this model must be further evaluated, and future studies should focus on the identification of new risk factors for recurrence to improve patient selection for perioperative systemic therapy.

CRediT authorship contribution statement

Michelle V. Dietz: Conceptualization, Data curation, Writing – original draft, Visualization. **Gerjon Hannink:** Methodology, Software, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Ibrahim Said:** Data curation, Writing – review & editing. **Femke A. van der Zant:** Data curation, Writing – review & editing. **Vincent C.J. van de Vlasakker:** Data curation, Writing – review & editing. **Alexandra R.M. Brandt-Kerkhof:** Resources, Writing – review & editing. **Cornelis Verhoef:** Conceptualization, Writing – review & editing, Supervision. **Andreas J.A. Bremers:** Resources, Writing – review & editing. **Johannes H.W. de Wilt:** Resources, Writing – review & editing. **Patrick H.J. Hemmer:** Resources, Writing – review & editing. **Ignace H.J.T. de Hingh:** Resources, Writing – review & editing. **Philip R. de Reuver:** Resources, Conceptualization, Writing – review & editing, Supervision. **Eva V.E. Madsen:** Resources, Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2024.108294.

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