Site of Recurrence and Survival After Surgery for Colorectal Peritoneal Metastasis

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Abstract

Background: Multimodal treatment, including systemic treatment and surgery, improved the prognosis of peritoneal metastasis (PM). Despite all efforts, recurrence rates remain high, and little data are available about clinical behavior or metastatic patterns of PM in comparison to hematogenous metastasis. Here, we aimed to analyze recurrence patterns after multimodal treatment for PM from colorectal cancer. **Methods:** Patients with colorectal PM undergoing multimodal treatment including systemic chemotherapy and cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) between 2005 and 2017 at 4 centers were analyzed retrospectively. **Results:** A total of 505 patients undergoing CRS/HIPEC were analyzed. Of the patients, 82.1% received preoperative chemotherapy. Median peritoneal cancer index was 6 (interquartile range = 3–11). Median disease-free and overall survival was 12 (95% confidence interval [CI] = 11 to 14) months and 51 (95% CI = 43 to 62) months, respectively. Disease recurred in 361 (71.5%) patients, presenting as isolated peritoneal recurrence in 24.6%, isolated hematogenous recurrence in 28.3%, and mixed recurrence in 13.9% of patients. Recurrence to the peritoneum was associated with an impaired time from recurrence to death of 21 (95% CI = 18 to 31) months for isolated peritoneal and 22 (95% CI = 16 to 30) months for mixed recurrence, compared with 43 (95% CI = 31 to >121) months for hematogenous recurrence (hazard ratio [HR] = 1.79, 95% CI = 1.27 to 2.53; *P* = .001; and HR = 2.44, 95% CI = 1.61 to 3.79; *P* < .001). On multiple logistic regression analysis, RAS mutational status (odds ratio [OR] = 2.42, 95% CI = 1.11 to 5.47; *P* = .03) and positive nodal stage of the primary (OR = 3.88, 95% CI = 1.40 to 11.86; *P* = .01) were identified as predictive factors for peritoneal recurrence. **Conclusions:** This study highlights the heterogeneity of peritoneal metastasis in patients with colorectal cancer. Recurrent peritoneal metastasis after radical treatment represents a more aggressive subset of metastatic colorectal cancer.

Peritoneal metastasis (PM) is an advanced stage of colorectal cancer and associated with a limited prognosis and often poor quality of life (1). Without treatment, PM is associated with a median overall survival (mOS) of only 6 months (2,3). Over the last years, however, multimodal strategies were developed for the treatment of PM, particularly enabled by refined systemic treatment regimens. Radical locoregional treatment of PM in selected patients, known as cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), was

associated with improved survival in many cohorts, who showed a mOS of more than 40 months (4–7).

Despite substantial progress in the treatment of metastatic disease, the clinical behavior and tumor biology that differentiate PM from hematogenous metastasis remain poorly investigated. Approximately 10% of colorectal cancer (CRC) patients develop PM, and in about half of them, PM remains the only metastatic site (8). Over the last decades, several observational studies indicated that peritoneal metastasis may differ from

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hematogenous metastasis to the liver or lung in terms of clinical behavior and prognosis. A subgroup analysis from several large trials treating patients with metastatic colorectal cancer observed a worse survival for PM compared with patients with hepatic or pulmonary metastasis only (9,10). The studies had a weakness: it remained unclear whether these findings reflect a different tumor biology or just different stages of the disease.

Here, we analyzed a large multicentric cohort of patients with PM from CRC after multimodal treatment and radical surgery (CRS/HIPEC), with a particular focus on recurrence patterns. Our aim was to identify independent risk factors predicting the pattern of disease recurrence after radical surgical resection.

Methods

Patients and Methods

Patients with CRC and PM after radical CRS/HIPEC (completeness of cytoreduction score 0) between January 2005 and December 2017 in 3 Swiss (University Hospital Zurich; University Hospital Lausanne; KSSG, St. Gallen) and 1 French (University Hospital Lyon) center were included in this retrospective analysis.

Ethics

Written informed consent was obtained from each patient. For Swiss centers, the study was approved by the ethics committee of the canton of Zurich, Switzerland (KEK-ZH-Nr. 2017-01656). Data of patients from Lyon were extracted from a prospectively maintained database, registered by the National Data Protection Commission under the Nr. DR-2016-002 in accordance with the French Law 78-17 (January 6, 1978) and approved by the ethical committee CPP Lyon Sud Est IV on April 15, 2015 (ClinicalTrials.gov Identifier: NCT02823860).

Study Endpoints

Primary endpoint was disease-free survival (DFS), defined as the time from CRS/HIPEC to disease recurrence or death from any cause. Secondary endpoints include disease-specific overall survival (OS), location of recurrence, and identification of factors predicting recurrence patterns. Data on DFS and OS were censored at the date of the last contact for patients who remained alive and had no evidence of disease recurrence. The cutoff date was set at December 31, 2017.

Patient Management

All patients were discussed in a multidisciplinary tumor board and received perioperative chemotherapy according to current treatment protocols. The peritoneal cancer index (PCI), a score to determine the extent of peritoneal metastasis, was determined at the time of laparotomy. CRS/HIPEC was performed as described previously (6). HIPEC was performed with mitomycin C (15-30 mg/m² body surface area for 90 minutes) or oxaliplatin (300 mg/m² body surface area for 30 minutes) at 42°C-43°C. Follow-up included computed tomography scans every 6 months or earlier in case of clinical suspicion and/or patient-reported symptoms. Hematogenous or peritoneal recurrence was either diagnosed by imaging or second-look laparoscopy.

Clinical Samples and Sanger Sequencing

Mutational status was retrieved from the pathology reports, or DNA was extracted as described previously (11). Genotyping of KRAS, NRAS, and BRAF was performed by polymerase chain reaction-based amplification of the respective open-reading frames (Exon 2, 3, and 4 for KRAS and NRAS and Exon 15 for BRAF; primer sequences, see [Supplementary Table 5](#), available online) and Sanger sequencing. Mismatch-repair proteins were analyzed by immunohistochemistry using the following antibodies: MLH1 (PharMingen, Becton Dickinson, San Diego, CA, G168-15, 1:100), MSH2 (Cell Marque Lifesciences Ltd, Rocklin, CA, G219-1129, 1:100), MSH6 (Cell Marque Lifesciences Ltd, Rocklin, CA, SP93.1:30), and PMS2 (PharMingen, Becton Dickinson, San Diego, CA, G168-15, 1:100). The OptiView DAB visualization technique (Ventana Medical Systems, Tucson, AZ) was used.

Statistical Analysis

Baseline characteristics of numerical variables are reported as mean and standard deviation for variables with symmetric distribution and as median and interquartile range for variables with asymmetric distribution. Comparison of numerical variables with respect to recurrence is done with the student t test and Mann-Whitney test, respectively. Categorical variables are reported with counts and percentages and compared with respect to recurrence with the χ^2 test. Tests calculated in the descriptive parts of the analysis are considered exploratory. Multiple logistic regression analysis with a backward selection process for stepwise exclusion of variables was used to find confounders for recurrence at different locations, yielding odds ratios (ORs), 95% confidence intervals (CIs), and respective P values. Time-to-event endpoints were visualized with Kaplan-Meier plots, a cumulative incidence plot of competing risks of recurrence at different locations, and a Simon-Makuch survival plot with recurrence considered in a time-dependent way. OS and DFS were calculated as the time from recurrence to the date of cancer-related death and the time from CRS/HIPEC to the first evidence of recurrence, respectively. The Mantel-Cox log-rank test was used to compare Kaplan-Meier curves, and multivariable analyses were performed by Cox regression to estimate hazard ratios (HRs), the corresponding 95% confidence intervals, and respective P values. Variable selection was performed by stepwise exclusion of variables. The starting set of variables used for this process was sex, age, primary tumor sidedness, histology, nodal stage, grading, systemic chemotherapy, PCI, syn- or metachronous metastases, hospital stay, intensive care unit stay, RAS mutations, and mismatch-repair status. The proportional hazard assumption was assessed by looking at the scaled Schoenfeld residuals. The assumption was fulfilled for all covariates, so the standard Cox model could be used. Backward selection was performed with a conditional likelihood ratio model. Missingness of variables is reported in [Table 1](#). Four covariates in the logistic models are not completely observed (nodal stage 41% missingness, RAS mutations 23% missingness, primary tumor sidedness 8% missingness, PCI 8% missingness). In the Cox model, 5 variables have missing values (nodal stage, systemic chemotherapy, syn-/metachronous metastases, hospital stay, and RAS or RAF mutations). The missing values of the model variables are imputed by multiple imputation with chained equations. One single dataset is used for modeling, and the results are considered as a sensitivity analysis and reported in [Supplementary Tables 6 and 7](#) (available online). Results of

Table 1. Patient and recurrence characteristics

Variables	Overall No. (%)	No recurrence No. (%)	Recurrence No. (%)	P ^a	Missing ^b
Total	505 (100)	144 (28.5)	361 (71.5)		
Sex				.70	0.0
Male	254 (50.3)	70 (48.6)	184 (51.0)		
Female	251 (49.7)	74 (51.4)	177 (49.0)		
Age, mean (SD), y	57.72 (11.16)	58.51 (11.47)	57.40 (11.03)	.31	0.0
Primary tumor site				.06	9.7
Right colon	154 (33.8)	35 (26.7)	119 (36.6)		
Left and transverse colon	302 (66.2)	96 (73.3)	206 (63.4)		
Histology				.34	17.4
Intestinal	332 (79.6)	77 (81.9)	255 (78.9)		
Signet ring	28 (6.7)	8 (8.5)	20 (6.2)		
Mucinous	57 (13.7)	9 (9.6)	48 (14.9)		
Timing of PM				.29	0.0
Synchronous	280 (55.4)	74 (51.4)	206 (57.1)		
Metachronous	225 (44.6)	70 (48.6)	155 (42.9)		
pN stage				.002	38.6
N0	72 (23.2)	33 (34.7)	39 (18.1)		
N1/2	238 (76.8)	62 (65.3)	176 (81.9)		
Grading				.07	26.7
G1 (well diff.)	90 (24.3)	14 (15.2)	76 (27.3)		
G2 (moderately diff.)	208 (56.2)	61 (66.3)	147 (52.9)		
G3 (poorly diff.)	70 (18.9)	17 (18.5)	53 (19.1)		
G4 (dediff.)	2 (0.5)	0 (0.0)	2 (0.7)		
Chemotherapy—pre HIPEC				.002	0.2
No chemotherapy	90 (17.9)	26 (18.1)	64 (17.8)		
Conventional chemotherapy only	192 (38.1)	71 (49.3)	121 (33.6)		
Chemotherapy + targeted therapy	222 (44.0)	47 (32.6)	175 (48.6)		
No. of precycles, mean (SD)	6.21 (3.20)	6.00 (2.60)	6.29 (3.41)	.41	21.8
Chemotherapy—post HIPEC				.001	13.5
No chemotherapy	153 (35.0)	42 (38.9)	111 (33.7)		
Conventional chemotherapy only	142 (32.5)	46 (42.6)	96 (29.2)		
Chemotherapy + targeted therapy	142 (32.5)	20 (18.5)	122 (37.1)		
No. of cycles, mean (SD)	6.83 (3.43)	6.92 (2.70)	6.80 (3.63)	.82	55.2
Surgery					
Intraoperative PCI, median (IQR)	6.00 [3, 11]	4.00 [2, 9]	7.00 [4, 12.25]	< .001	8.3
Min operation time, median (IQR)	319.50 [240, 420]	350 [220, 430]	300 [240, 420]	.75	38.2
ICU stay, mean (SD), d	2.74 (8.14)	3.68 (14.21)	2.47 (5.27)	.22	22.2
Hospital stay, mean (SD), d	21.00 (13.14)	19.18 (15.22)	21.58 (12.38)	.11	15.2
KRAS				.04	24.4
Wild-type	246 (64.4)	78 (72.9)	168 (61.1)		
Mutated	136 (35.6)	29 (27.1)	107 (38.9)		
NRAS				.98	36.0
Wild-type	300 (92.9)	73 (93.6)	227 (92.7)		
Mutated	23 (7.1)	5 (6.4)	18 (7.3)		
BRAF				1.00	38.4
Wild-type	286 (92.0)	70 (92.1)	216 (91.9)		
Mutated	25 (8.0)	6 (7.9)	19 (8.1)		
Mismatch repair status				.28	54.1
MSS	50 (90.9)	218 (94)	168 (94.9)		
MSI-H	5 (9.1)	14 (6.0)	9 (5.1)		
Year of CRS/HIPEC				<.001	0.0
2005	12 (2.4)	0 (0.0)	12 (3.3)		
2006	11 (2.2)	1 (0.7)	10 (2.8)		
2007	13 (2.6)	2 (1.4)	11 (3.0)		
2008	13 (2.6)	3 (2.1)	10 (2.8)		
2009	17 (3.4)	3 (2.1)	14 (3.9)		
2010	26 (5.1)	6 (4.2)	20 (5.5)		
2011	30 (5.9)	7 (4.9)	23 (6.4)		
2012	47 (9.3)	12 (8.3)	35 (9.7)		
2013	44 (8.7)	7 (4.9)	37 (10.2)		
2014	59 (11.7)	6 (4.2)	53 (14.7)		

(continued)

Table 1. (continued)

Variables	Overall No. (%)	No recurrence No. (%)	Recurrence No. (%)	P ^a	Missing ^b
2015	64 (12.7)	20 (13.9)	44 (12.2)		
2016	91 (18.0)	36 (25.0)	55 (15.2)		
2017	78 (15.4)	41 (28.5)	37 (10.2)		
Center				.01	0.0
Center A	405 (80.2)	110 (76.4)	295 (81.7)		
Center B	52 (10.3)	11 (7.6)	41 (11.4)		
Center C	33 (6.5)	17 (11.8)	16 (4.4)		
Center D	15 (3.0)	6 (4.2)	9 (2.5)		

^aPearson χ^2 test or Mann-Whitney U test was used to compare data. Tests are considered exploratory. All tests were 2-sided. CRC = colorectal carcinoma; CRS = cytoreductive surgery; dediff = dedifferentiated; diff = differentiated; HIPEC = hyperthermic intraperitoneal chemotherapy; ICU = intensive care unit; IQR = interquartile range; MSI-H = microsatellite instable (high); MSS = microsatellite stable; PCI = peritoneal cancer index; PM = peritoneal metastasis.

^bThe column "Missing" shows the percentage of missing values per variable.

the study were reported according to the STROBE guidelines. All statistical tests are 2-sided, and a P value less than .05 is considered to be statistically significant. Statistical analysis was performed using R version 4.0.2 (2020-06-22) and IBM SPSS (version 25, Chicago, IL).

Results

Patient Characteristics

Overall, 505 patients with CRC and PM underwent radical CRS/HIPEC between January 2005 and December 2017 in 1 French and 3 Swiss centers. Patients had a mean age of 57.7 (SD = 11.16) years with a balanced sex ratio of 50.3% male and 49.7% female patients. Of the patients, 82.1% received preoperative chemotherapy. Synchronous PM was found in 280 (55.4%) patients, 238 (76.8%) patients had a node-positive primary tumor (pN1/N2), and the median PCI was 6 (interquartile range = 3-11). Table 1 summarizes patient characteristics; a STROBE flow chart is provided in [Supplementary Figure 1](#) (available online), and treatment details are specified in [Supplementary Figure 2](#) (available online).

Time to Recurrence and Death After Multimodal Treatment of PM

After radical treatment, the cohort had a median DFS of 12 (95% CI = 11 to 14) months and a mOS of 51 (95% CI = 43 to 62) months ([Figure 1](#)). Overall, positive nodal stage (pN1/2) was associated with a shorter time to recurrence compared with patients with negative nodes (11 vs 22 months, HR = 2.14, 95% CI = 1.29 to 3.56; $P = .003$). Independently, a higher PCI (HR = 1.03, 95% CI = 1.00 to 1.06; $P = .07$) and the presence of KRAS or NRAS-mutations (HR = 2.30, 95% CI = 1.58 to 3.33; $P < .001$) were associated with shorter DFS. These numbers also translate into impaired survival. [Supplementary Tables 1 and 2](#) (available online) show the independent association of different risk factors with time-to-disease recurrence and overall survival. In the next step, we assessed the pattern and different sites of recurrent disease.

Pattern of Recurrence After Multimodal Treatment of PM

After a median follow-up time of 25 months, 71.5% (n = 361) of patients presented with recurrence, diagnosed during regular follow-up imaging or imaging performed because of patients' complaints about disease-specific symptoms. Recurrence was limited to the peritoneum in 124 (24.6%) patients, and 143 (28.3%) patients had isolated hematogenous metastasis to the lung (n = 45, 8.9%), the liver (n = 38, 7.5%), combined in lung and liver (n = 20, 3.9%), or other distant organs (n = 5, 1.0%). No patients had isolated lymph node metastases. In 70 (13.9%) patients, recurrence was multifocal, resulting in a combination of peritoneal and hematogenous recurrence ([Figure 2](#)). Time to recurrence was analyzed according to the site of recurrence, separating peritoneal only, hematogenous only, and patients with mixed peritoneal and hematogenous recurrence. Competing risk estimates were plotted as cumulative incidence functions for the competing risk of recurrence at different locations ([Figure 3](#)).

Survival According to Recurrence Sites

The site of disease recurrence after CRS/HIPEC had a statistically and clinically significant impact on patient survival, shown in [Figure 4, A](#). To consider recurrence site as a time-dependent covariate, survival is shown from time of recurrence until death. Median survival after recurrence is 21 (95% CI = 18 to 31) months for patients with isolated peritoneal recurrence and 22 (95% CI = 16 to 30) months for mixed recurrence, which is statistically significantly worse compared with 43 (95% CI = 31 to >121) months for patients with isolated hematogenous recurrence, which is also clinically significant (HR = 1.79, 95% CI = 1.27 to 2.53; $P = .001$, and HR = 2.44, 95% CI = 1.61 to 3.79; $P < .001$). Among patients with hematogenous recurrence, survival of those with hepatic recurrence (26 months, 95% CI = 19 to 33) was inferior to those with pulmonary recurrence (34 months, 95% CI = 30 to 38). In addition, we calculated a Simon-Makuch survival plot ([Figure 4, B](#)), where site of recurrence is considered in a time-dependent way. Presence of peritoneal recurrence was associated with a statistically and clinically significant shorter mOS of 13 (95% CI = 6 to 28) months, whereas patients with hematogenous recurrence only showed a better survival of 42 (95% CI = 30 to 71) months.

Figure 1. Time to recurrence and overall survival after multimodal therapy for peritoneal metastasis. **A)** Median disease-free survival after multimodal treatment including CRS/HIPEC ($n = 505$) was 12 (95% confidence interval [CI] = 11 to 14) months. **B)** Median overall survival was 51 (95% CI = 43 to 62) months. CRS/HIPEC = cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy.

Figure 2. Site of recurrence. After radical treatment, 71.5% ($n = 361$) of patients developed recurrence after an average follow-up time of 25 months. The peritoneum was involved in 194 (38.4%) patients, isolated in 124 (24.5%), and combined with hematogenous metastasis in 70 (13.9%) patients. Isolated hematogenous recurrence was observed in 143 (28.3%) patients. All percentages refer to the total number of operated patients ($n = 505$). In 24 (4.8%) patients, we do not have information about the site of recurrence.

KRAS and NRAS Mutational Status Defines Site of Recurrence

As a first step, we analyzed the frequencies of RAS mutations in the overall cohort. To reduce the bias from missing data, we additionally sequenced the complete ($n = 52$) cohort from 1 center and compared it with the current literature (Supplementary Tables 3 and 4, available online). RAS/RAF mutation frequencies (Supplementary Figure 3, available online) and recurrently altered loci of somatic KRAS mutations (Supplementary Figure 4, available online) presented with a similar distribution as found in the literature (12-19). Finally, we performed a multivariable

analysis of factors predicting peritoneal and hematogenous site of recurrence, summarized in Table 2. Positive nodal status (OR = 3.88, 95% CI = 1.40 to 11.86; $P = .01$) and the presence of RAS mutation (OR = 2.42, 95% CI = 1.11 to 5.47; $P = .03$) were identified as predictive factors of peritoneal recurrence after CRS/HIPEC. After multiple imputation of missing variables, KRAS or NRAS mutational status remained a statistically significant factor for recurrence to the peritoneum, together with the PCI. This finding is of clinical significance. Nodal status was associated with peritoneal and hematogenous recurrence (Supplementary Table 6, available online).

Figure 3. Competing risk estimates for recurrence according to site of recurrence. Cumulative incidence is shown per competing event type. Incidences after 24 months are 23.3% (95% confidence interval [CI] = 19.4% to 27.1%) for peritoneal, 29.6% (95% CI = 25.4% to 33.8%) for hematogenous, and 14.3% (95% CI = 11.1% to 17.5%) for mixed recurrence. A recurrence with unknown location occurred for 4.2% (95% CI = 2.3% to 6.0%), and 0.1% (95% CI = 0.01% to 1.9%) died of other causes. Confidence intervals are estimated with the Greenwood-type of variance.

Discussion

This study confirms excellent outcomes for selected patients with PM from CRC after multimodal systemic and radical locoregional treatment and underlines the different behavior and biologic background of PM in comparison with hematogenous metastasis. For the first time, we observed that the site of recurrence after radical treatment, thus in patients without detectable disease, depends also on tumor biology. In addition, peritoneal recurrence was associated with a worse survival than isolated hematogenous recurrence. In contrast to hematogenous metastasis, peritoneal recurrence was associated with a positive KRAS or NRAS mutational status and a positive nodal stage.

Solid evidence in the literature, from randomized controlled trials and multiple national and international registry studies, supports an aggressive surgical approach in selected patients with colorectal PM (20–23). Optimal selection criteria have been defined based on multiple retrospective analyses and include the amount of peritoneal disease, reflected by the PCI, and tumor biology (6,24,25). Despite the clinical overall success in the treatment of PM, many open questions regarding the clinical behavior, tumor biology, and differences compared with hematogenous metastasis remain unanswered (26).

In this study, overall recurrence rates after CRS/HIPEC were comparable with those known in the literature, and hematogenous recurrence was detected about 2 months earlier than peritoneal recurrence. This is not surprising because of the lower sensitivity of imaging modalities to detect small peritoneal

disease on cross-sectional imaging (27). It is unlikely that later detection of recurrent disease in the peritoneum is the only cause of the observed dramatically reduced survival.

Growing evidence about the diverse molecular background of CRC contributed to the increasing understanding that tumor biology determines not only survival but also the metastatic potential and, possibly, the site of recurrence (17,28–33). Some authors, after analyzing the phylogenetic data of the primary tumor and its metastases, hypothesize that distant metastases arise independently of lymph node metastasis (33). For example, Yaeger et al. (17) examined the genomic landscape of 1134 colorectal adenocarcinomas and found a high level of genomic concordance between primary tumors and metastases, suggesting that genetic variants are already present in the primary and do not develop at the site of metastasis. In their analysis, mutations in NRAS, KRAS, BRAF, and APC were associated with worse survival, confirming the known detrimental effect of these mutations (34,35). Additionally, RAS/RAF as well as some other mutations like PIK3CA, PTEN, AKT1, SMAD2, and SMAD4 were associated with a higher risk of peritoneal metastases (17).

An effect of KRAS or NRAS mutated status on tumor recurrence site after surgery, as shown with a higher risk for peritoneal recurrence in this study, has so far not been described. The present study, based on a large and multicentric cohort of patients, supports the concept that the underlying genetic background primarily determines the patterns of metastatic dissemination and not the common mechanistic theory of sequential progression (metastatic cascade).

Figure 4. Median survival time from recurrence according to site of recurrence. **A)** Survival is considered from time of recurrence until death or last follow-up. Peritoneal recurrence, either isolated (median survival = 21 months, 95% confidence interval [CI] = 18 to 31 months; hazard ratio [HR] = 1.79, 95% CI = 1.27 to 2.53; $P = .001$) or in combination with other recurrence sites (median survival = 22 months, 95% CI = 16 to 30 months; HR = 2.44, 95% CI = 1.61 to 3.70; $P < .001$), is associated with a statistically and clinically significantly lower survival time compared with a median survival time of 43 months (95% CI = 31 to >121) of patients with hematogenous recurrence only. **B)** Simon-Makuch plot for overall survival with location of recurrence as time-dependent covariate. At time 0 (CRS/HIPEC), all patients are in the group “no recurrence.” Upon a recurrence event, each individual patient is removed from the risk set in the group “no recurrence” and added to the risk set of the corresponding recurrence group, in which he or she remains until death. Here, the median survival time after 1 year of survival after CRS/HIPEC was 13 months for peritoneal (95% CI = 6 to 28 months), 20 months for mixed (95% CI = 5 to 35 months), and 42 months for hematogenous recurrence (95% CI = 30 to 71 months). In 24 patients, recurrence localization is not known, and 144 patients showed no recurrence. CRS/HIPEC = cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy.

Table 2. Factors influencing site of recurrence^a

Variables	Peritoneal recurrence (n = 128)		Hematogenous recurrence (n = 128)	
	OR ^b (95% CI)	P	OR ^b (95% CI)	P
Age, y				
<50	1.00 (Referent)		1.00 (Referent)	
≥50	0.60 (0.24 to 1.45)	.26	1.25 (0.54 to 2.95)	.60
Primary tumor site				
Right colon	1.00 (Referent)		1.00 (Referent)	
Left colon	0.88 (0.39 to 2.04)	.77	1.06 (0.48 to 2.37)	.88
Primary pN stage				
N0	1.00 (Referent)		1.00 (Referent)	
N+	3.88 (1.40 to 11.86)	.01	1.44 (0.55 to 3.88)	.46
Preoperative chemotherapy				
FOLFOX/FOLFIRI/Capecitabine	1.00 (Referent)		1.00 (Referent)	
+ targeted therapy	1.11 (0.38 to 3.14)	.85	0.74 (0.26 to 2.05)	.56
Intraoperative PCI				
≤7	1.00 (Referent)		1.00 (Referent)	
>7	1.79 (0.84 to 3.86)	.13	1.54 (0.74 to 3.21)	.25
Syn-/metachronous PM				
Synchronous	1.00 (Referent)		1.00 (Referent)	
Metachronous	0.96 (0.31 to 2.95)	.94	1.48 (0.52 to 4.24)	.46
RAS-mutations				
Wild-type	1.00 (Referent)		1.00 (Referent)	
KRAS or NRAS	2.42 (1.11 to 5.47)	.03	1.92 (0.91 to 4.08)	.09

^aRecurrence was analyzed in all patients where a follow-up of the first 24 months was available. Odds ratios and respective 2-sided P values were estimated with a multiple logistic regression model. The same analyses with a single imputed dataset are provided in [Supplementary Table 6](#) (available online). CI = confidence interval; FOLFOX = leucovorin + 5-fluorouracil + oxaliplatin; FOLFIRI = leucovorin + 5-fluorouracil + irinotecan; OR = odds ratio; PCI = peritoneal cancer index; PM = peritoneal metastases.

^bThe odds ratio is the exponential function of the regression coefficient, corresponding to a 1-unit change in the variable.

We would also like to acknowledge the limitations of our study. The study period covers a long interval and data from 4 centers. However, by performing a sensitivity analysis with imputed datasets (see the Methods above and [Supplementary Tables 6 and 7](#), available online), we could exclude a bias through center, period of treatment, or missing variables.

The analyzed cohort, however, represents a selection of patients with PM who were considered resectable, which may translate into a potential selection bias. For example, patients with rapid tumor progression may be underrepresented. Indeed, in this study, BRAF did show a significant difference in overall survival. Because of a limited number of affected individuals as well as the low frequency of BRAF mutated tumors, BRAF could not be included in the multivariable analysis. Previous studies including patients with metastatic CRC showed not only reduced survival, especially in patients with microsatellite instability low and microsatellite stability, but also a higher risk for peritoneal metastasis (36,37), and others reported a 3-fold higher rate of PM in patients with BRAF V600E mutations compared with BRAF wild-type tumors (38-40).

Mutations in RAS/RAF and PI3KCA activate epidermal growth factor receptor downstream signals and serve as predictive factors for targeted therapies like anti-epidermal growth factor receptor antibodies (37,41,42), which became evident only around 2008 (43,44). Consequently, patients in the earlier time period were not routinely tested for RAS/RAF mutations. As testing became more frequent over time, the ratio of confirmed KRAS or NRAS mutations to wild-type cases decreased. Because of hospital policies and federal regulations regarding long-term storage of biological samples, many tissue samples were no longer available for testing, which explains some missing data. To overcome this, we tested the complete cohort from 1 center and compared the frequencies and loci of mutations of the RAS/RAF pathway to preexisting datasets ([Supplementary Tables 3 and 4](#) and [Supplementary Figures 3 and 4](#), available online). Our results were comparable to these datasets (12-19), and we assume that our patient cohort therefore represents an adequate sample. Additionally, results of multivariable analyses were confirmed by doing sensitivity analyses with imputed datasets and taking time period of treatment into consideration ([Supplementary Table 6](#), available online). No indication for a bias due to increased KRAS and NRAS testing rates over the study time period could be found.

We also explored the potential effect of systemic treatment, which obviously advanced over the study period. A majority (>80%) of patients received perioperative FOLFOX (oxaliplatin, folinic acid, fluorouracil) or FOLFIRI (irinotecan, folinic acid, fluorouracil) in each period. Interestingly, targeted therapies did not improve the outcome of PM as one would probably expect, although all patients were formally in the same Union for International Cancer Control stage IV. Only in the latest period of 2015-2017, a relatively small subset of 18% received triplet therapy, which seemed to translate into better outcomes. However, this finding was not statistically significant, but we consider the effect potentially underestimated because of the short follow-up of these patients. This factor certainly needs further exploration.

This study in patients after radical treatment of PM identified tumor biology as a paramount prognostic factor for the site of recurrence. In addition, we confirmed the detrimental impact of PM on patient survival compared with hematogenous metastasis. Mutated RAS, a high PCI, and nodal status were identified as specific risk factors for peritoneal recurrence. These novel findings underline the heterogeneity of colorectal metastasis

and the more aggressive tumor biology behind peritoneal recurrence.

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Data Availability

The datasets generated during the current study are available from the corresponding author on reasonable request. The supplementary analyses were derived from data available in the public domain: cBioPortal for Cancer Genomics (<http://www.cbioportal.org/>) (17-19) and TCGA Research Network (<https://www.cancer.gov/tcga/>) (15).

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