University of Groningen

Adjuvant Systemic Chemotherapy vs Active Surveillance Following Up-front Resection of Isolated Synchronous Colorectal Peritoneal Metastases

Rovers, Koen P.; Bakkers, Checca; van Erning, Felice N.; Burger, Jacobus W. A.; Nienhuijs, Simon W.; Simkens, Geert A. A. M.; Creemers, Geert-Jan M.; Hemmer, Patrick H. J.; Punt, Cornelis J. A.; Lemmens, Valery E. P. P.

Published in:
JAMA oncology

DOI:
[10.1001/jamaoncol.2020.2701](https://doi.org/10.1001/jamaoncol.2020.2701)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Rovers, K. P., Bakkers, C., van Erning, F. N., Burger, J. W. A., Nienhuijs, S. W., Simkens, G. A. A. M., Creemers, G.-J. M., Hemmer, P. H. J., Punt, C. J. A., Lemmens, V. E. P. P., Tanis, P. J., & de Hingh, I. H. J. T. (2020). Adjuvant Systemic Chemotherapy vs Active Surveillance Following Up-front Resection of Isolated Synchronous Colorectal Peritoneal Metastases. *JAMA oncology*, 6(8), [202701]. <https://doi.org/10.1001/jamaoncol.2020.2701>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Adjuvant Systemic Chemotherapy vs Active Surveillance Following Up-front Resection of Isolated Synchronous Colorectal Peritoneal Metastases

Koen P. Rovers, MD; Checca Bakkers, MD; Felice N. van Erning, PhD; Jacobus W. A. Burger, PhD; Simon W. Nienhuijs, PhD; Geert A. A. M. Simkens, PhD; Geert-Jan M. Creemers, PhD; Patrick H. J. Hemmer, MD; Cornelis J. A. Punt, PhD; Valery E. P. P. Lemmens, PhD; Pieter J. Tanis, PhD; Ignace H. J. T. de Hingh, PhD

[+ Supplemental content](#)

IMPORTANCE To date, there are no data on the value of adjuvant systemic chemotherapy following up-front resection of isolated synchronous colorectal peritoneal metastases.

OBJECTIVE To assess the association between adjuvant systemic chemotherapy and overall survival following up-front resection of isolated synchronous colorectal peritoneal metastases.

DESIGN, SETTING, AND PARTICIPANTS In this population-based, observational cohort study using nationwide data from the Netherlands Cancer Registry (diagnoses between January 1, 2005, and December 31, 2017; follow-up until January 31, 2019), 393 patients with isolated synchronous colorectal peritoneal metastases who were alive 3 months after up-front complete cytoreductive surgery with hyperthermic intraperitoneal chemotherapy were included. Patients allocated to the adjuvant systemic chemotherapy group were matched (1:1) with those allocated to the active surveillance group by propensity scores based on patient-, tumor-, and treatment-level covariates.

EXPOSURES Adjuvant systemic chemotherapy, defined as systemic chemotherapy without targeted therapy, starting within 3 months postoperatively.

MAIN OUTCOMES AND MEASURES Overall survival was compared between matched groups using Cox proportional hazards regression analysis adjusted for residual imbalance. A landmark analysis was performed by excluding patients who died within 6 months postoperatively. A sensitivity analysis was performed to adjust for unmeasured confounding by major postoperative morbidity.

RESULTS Of 393 patients (mean [SD] age, 61 [10] years; 181 [46%] men), 172 patients (44%) were allocated to the adjuvant systemic chemotherapy group. After propensity score matching of 142 patients in the adjuvant systemic chemotherapy group with 142 patients in the active surveillance group, adjuvant systemic chemotherapy was associated with improved overall survival compared with active surveillance (median, 39.2 [interquartile range, 21.1-111.1] months vs 24.8 [interquartile range, 15.0-58.4] months; adjusted hazard ratio [aHR], 0.66; 95% CI, 0.49-0.88; $P = .006$), which remained consistent after excluding patients who died within 6 months postoperatively (aHR, 0.68; 95% CI, 0.50-0.93; $P = .02$) and after adjustment for major postoperative morbidity (aHR, 0.71; 95% CI, 0.53-0.95).

CONCLUSIONS AND RELEVANCE Findings of this study suggest that in patients undergoing up-front resection of isolated synchronous colorectal peritoneal metastases, adjuvant systemic chemotherapy appeared to be associated with improved overall survival. Although randomized trials are needed to address the influence of potential residual confounding and allocation bias on this association, results of this study may be used for clinical decision-making in this patient group for whom no data are available.

JAMA Oncol. 2020;6(8):e202701. doi:10.1001/jamaoncol.2020.2701
Published online July 16, 2020.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Ignace H. J. T. de Hingh, PhD, Department of Surgery, Catharina Cancer Institute, Michelangelolaan 2, 5623 EJ Eindhoven, the Netherlands (ignace.d.hingh@catharinaziekenhuis.nl).

Up to one-quarter of patients with isolated synchronous colorectal peritoneal metastases undergo cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) in an estimated 430 treatment centers worldwide.^{1,2} In several countries, including the Netherlands,^{2,3} these patients routinely undergo up-front CRS-HIPEC according to the protocol of the pioneer study by Verwaal et al.⁴ Unlike some national and international guidelines,³ neoadjuvant systemic therapy is not recommended by the Dutch guideline⁵ and therefore is given only in cases of an advanced primary tumor, initially unresectable peritoneal metastases, or a poor general condition.⁶ Following up-front CRS-HIPEC, an internationally debated topic is whether patients with isolated synchronous colorectal peritoneal metastases should receive adjuvant systemic chemotherapy. Several experts and guidelines recommend routine use of adjuvant systemic chemotherapy in this setting,^{2,3} while others recommend adjuvant systemic chemotherapy only in cases of lymph node positivity,² and some only state that adjuvant systemic chemotherapy could be considered.^{2,3} These inconsistent recommendations reflect an absence of data on the association between adjuvant systemic chemotherapy and overall survival in this particular group.⁷ To address this evidence gap, the present study aimed to assess the association between adjuvant systemic chemotherapy and overall survival in patients undergoing up-front complete CRS-HIPEC for isolated synchronous colorectal peritoneal metastases in the Netherlands after publication of the pioneer study in 2003.⁴

Methods

Data Source

For this observational cohort study, data were extracted from the nationwide Netherlands Cancer Registry. Trained data managers of the Netherlands Cancer Registry routinely collect information on tumor, patient, and treatment characteristics from medical records. Primary tumor location, histologic characteristics, and location of synchronous metastases are registered according to the *International Classification of Diseases for Oncology*. Pathologic stage is registered according to the tumor-node metastasis classification valid at the time of diagnosis. The vital status of patients is obtained by linkage to the Municipal Records Database, which records all deaths in the Netherlands. All data of the Netherlands Cancer Registry are anonymized and deidentified. According to the Central Committee on Research Involving Human Subjects in The Hague, the Netherlands, this study type does not require ethics approval in the Netherlands. The study was approved by the privacy review board of the Netherlands Cancer Registry. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Surgery

In the Netherlands, CRS-HIPEC is performed according to the standardized Dutch protocol in 9 acknowledged, high-volume tertiary referral centers.⁸ For colorectal peritoneal me-

Key Points

Question Is adjuvant systemic chemotherapy associated with improved overall survival compared with active surveillance in patients undergoing up-front resection of isolated synchronous colorectal peritoneal metastases?

Findings In this Dutch nationwide propensity score-matched cohort study including 393 patients, adjuvant systemic chemotherapy was associated with improved overall survival (median, 39 months) compared with active surveillance (median, 25 months). This difference in survival rates was statistically significant.

Meaning In this study, adjuvant systemic chemotherapy was associated with improved overall survival following up-front resection of isolated synchronous colorectal peritoneal metastases; however, randomized trials are needed to address the influence of potential residual confounding and allocation bias on this association.

tastases, CRS is performed only if macroscopically complete cytoreduction is deemed achievable after explorative laparotomy. Only after macroscopically complete CRS, HIPEC is performed with use of either mitomycin C or oxaliplatin at the physician's discretion.⁸

Cohort Selection

The initial selection identified all Dutch patients with colorectal cancer diagnosed from January 1, 2005, through December 31, 2017, with synchronous peritoneal metastases undergoing complete CRS-HIPEC (eTable in the [Supplement](#)). Patients were excluded in cases of an appendiceal primary tumor, an unspecified primary tumor location, histologic characteristics other than adenocarcinoma, concomitant extraperitoneal metastases, participation in the CAIRO6 trial,⁹ no histologically proven peritoneal metastases, systemic therapy or radiotherapy before CRS-HIPEC, unknown date of CRS-HIPEC, and unknown start date of systemic chemotherapy after CRS-HIPEC (eTable in the [Supplement](#)). In addition, to account for immortal time bias, patients were excluded if they died within 3 months postoperatively.¹⁰

Treatment Allocation

In the Netherlands, adjuvant treatment following up-front resection of isolated synchronous colorectal peritoneal metastases has been based on evidence in high-risk colon cancer. Following the Dutch national guideline,⁵ the European Society for Medical Oncology consensus guideline,¹¹ and several trials on adjuvant targeted therapy published thereafter,¹²⁻¹⁶ patients were allocated to the adjuvant systemic chemotherapy group if they started systemic chemotherapy (a fluoropyrimidine with oxaliplatin, fluoropyrimidine monotherapy, or a not-otherwise-specified chemotherapy regimen) (eTable in the [Supplement](#)) without targeted therapy within 3 months postoperatively. All other patients were allocated to the active surveillance group, including those receiving targeted therapy within or starting systemic chemotherapy later than 3 months postoperatively, because these therapies were considered to be given as palliative rather than adjuvant treatment.

Primary Outcome

The primary outcome was overall survival, defined as the time between the date of CRS-HIPEC and the date of death or the date of last follow-up in censored patients. Follow-up was conducted until January 31, 2019.

Covariates

Covariates included sex, age at diagnosis, period of diagnosis, primary tumor location, pathologic T category, pathologic N category, histologic characteristics, differentiation, weeks between cancer diagnosis and CRS-HIPEC, and initial length of hospital stay after CRS-HIPEC (≤ 21 or > 21 days) (eTable in the [Supplement](#)).

Statistical Analysis

Continuous variables were compared between adjuvant systemic chemotherapy and active surveillance groups using unpaired *t* test or Mann-Whitney test as appropriate. Categorical variables were compared between both groups using χ^2 test or Fisher exact test as appropriate.

Each patient's propensity score (ie, the conditional probability of being allocated to the adjuvant systemic chemotherapy group) was estimated using a multivariable logistic regression model in which allocation to the adjuvant systemic chemotherapy group was regressed on all variables listed in the Covariates section.¹⁷ The propensity score was used to match patients of both treatment groups in a 1:1 ratio using the greedy nearest-neighbor method without replacement within calipers of width equal to 0.2 of the SD of the logit of the propensity score.¹⁸ Balance in covariates in the matched population was evaluated using standardized differences.¹⁹ A standardized difference between -0.10 and 0.10 indicated an adequate balance. Several covariates (ie, pathologic T category, pathologic N category, differentiation, and initial length of hospital stay) had missing data that could not be considered missing (completely) at random, limiting the use of multiple imputation methods.²⁰ Therefore, dummy variables of missing data were included in the propensity score estimation model to ensure that the proportions of patients with missing data were balanced between matched groups.

The overall survival of matched adjuvant systemic chemotherapy and active surveillance groups was estimated with the Kaplan-Meier method and compared between both groups using the log-rank test and Cox proportional hazards regression analysis. The hazard ratio (HR) was adjusted (aHR) for covariates with a standardized difference greater than 0.10 or smaller than -0.10 to account for residual imbalance between matched groups.¹⁹ To address the sensitivity of the HR to selection and allocation bias, these analyses were repeated after excluding patients who died within 6 months postoperatively, patients receiving targeted therapy within 3 months postoperatively, patients starting systemic chemotherapy between 3 and 4 months postoperatively, and all 3 of these groups. Cox proportional hazards regression analysis was used to assess the association between adjuvant systemic chemotherapy and overall survival across different levels of the following covariates: sex, age, period of diagnosis, pathologic T category, pathologic N category, histologic characteristics, dif-

ferentiation, and initial length of hospital stay. Tests for interaction were used to evaluate the heterogeneity of this association across different levels of these covariates.²¹

The Netherlands Cancer Registry does not record major postoperative morbidity, which may be a source of bias owing to its potential association with postoperative performance status, the probability of receiving adjuvant systemic chemotherapy, and overall survival.²² Moreover, although the matching process aimed to balance missing data between treatment groups, data on initial hospital stay (a surrogate marker for major postoperative morbidity) were missing in a relevant number of patients. Therefore, a sensitivity analysis using the formula described by Lin et al²³ was performed to quantify potential unmeasured confounding by major postoperative morbidity. The proportions of major postoperative morbidity in both treatment groups and its mortality HR were derived from a systematic search of Dutch literature on this topic after 2005. The estimated major postoperative morbidity rate was 15% based on, to the knowledge of the authors, the only study reporting major postoperative morbidity following up-front resection of synchronous colorectal peritoneal metastases.⁶ The proportion of major postoperative morbidity was estimated to be ± 2.3 times higher in the active surveillance group (21%) than in the adjuvant systemic chemotherapy group (9%) based on, to the knowledge of the authors, the only study reporting these proportions.²² Together with the highest reported mortality HR (1.75),^{24,25} the estimated proportions were included in the formula to assess whether adjustment for major postoperative morbidity would have eliminated the association between adjuvant systemic chemotherapy and overall survival.²³

All analyses were performed using 2-sided testing, with findings considered significant at $P < .05$. Analyses were conducted with SAS, version 9.4 (SAS Institute Inc).

Results

Of 930 initially identified patients, 393 were included (mean [SD] age, 61 [10] years; 181 [46%] male), of whom 172 individuals (44%) were allocated to the adjuvant systemic chemotherapy group (**Figure 1**). These 172 patients had a mean (SD) of 8 (2) weeks between CRS-HIPEC and the start of adjuvant systemic chemotherapy. The median duration of adjuvant treatment was 21 (interquartile range [IQR], 14-22) weeks in 102 patients with available data.

The **Table** presents a comparison of baseline variables between both treatment groups. The adjuvant systemic chemotherapy and active surveillance groups differed regarding period of diagnosis (eg, 2014-2017: 65 [38%] vs 134 [61%], $P < .001$), primary tumor location (eg, distal colon: 85 [49%] vs 81 [37%], $P = .03$), and initial length of hospital stay (eg, > 21 days: 6 [3%] vs 37 [17%], $P < .001$).

Following propensity score matching, 142 patients of the adjuvant systemic chemotherapy group were matched with 142 patients of the active surveillance group (**Figure 1**), leaving no statistically significant baseline differences between matched groups. After propensity score matching, the adjuvant systemic chemotherapy and active surveillance group had re-

Figure 1. Patient Selection, Treatment Allocation, and Propensity Score Matching

CRS-HIPEC indicates cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

sidual imbalance regarding period of diagnosis (eg, 2014-2017: 65 [46%] vs 77 [54%], standardized difference, -0.17), primary tumor location (ie, rectum: 7 [5%] vs 4 [3%], standardized difference, 0.11), histologic characteristics (ie, signet ring cell adenocarcinoma: 11 [8%] vs 6 [4%], standardized difference, 0.15), and initial length of hospital stay (ie, >21 days: 6 [4%] vs 16 [11%], standardized difference, -0.27) (Table).

In the entire matched population, the median follow-up was 25.9 (IQR, 15.7-46.8) months and 186 patients (65%) died. Corresponding numbers were 35.9 (IQR, 20.8-51.5) months and 91 deaths (64%) in the adjuvant systemic chemotherapy group and 21.3 (IQR, 12.5-34.7) months and 95 deaths (67%) in the active surveillance group. The median overall survival was 35.2 (IQR, 18.0-64.9) months in the entire matched population, 39.2 (IQR, 21.1-111.1) months in the adjuvant systemic chemotherapy group, and 24.8 (IQR, 15.0-58.4) months in the active

surveillance group (Figure 2). Overall survival rates were 86% (1 year), 49% (3 years), and 29% (5 years) in the entire matched population; 92% (1 year), 55% (3 years), and 35% (5 years) in the adjuvant systemic chemotherapy group; and 81% (1 year), 41% (3 years), and 22% (5 years) in the active surveillance group (Figure 2). Adjuvant systemic chemotherapy was associated with improved overall survival compared with active surveillance (HR, 0.64; 95% CI, 0.48-0.86; $P = .003$; aHR, 0.66; 95% CI, 0.49-0.88; $P = .006$). This association remained consistent after excluding 13 patients who died within 6 months postoperatively (aHR, 0.68; 95% CI, 0.50-0.93; $P = .02$), 4 patients starting systemic chemotherapy with targeted therapy within 3 months postoperatively (aHR, 0.68; 95% CI, 0.50-0.91; $P = .01$), 13 patients starting systemic chemotherapy between 3 and 4 months postoperatively (aHR, 0.65; 95% CI, 0.48-0.87; $P = .004$), and after excluding all 3 of these groups

Table. Comparison of Baseline Variables Between Treatment Groups in the Unmatched and Matched Population

Characteristic	Unmatched population (n = 393)			Matched population (n = 284)			Standardized differences ^a	
	Adjuvant systemic chemotherapy (n = 172)	Active surveillance (n = 221)	P value	Adjuvant systemic chemotherapy (n = 142)	Active surveillance (n = 142)	P value	Unmatched	Matched
Sex, No. (%)								
Male	82 (48)	99 (45)	.57	68 (48)	68 (48)	>.99	0.06	0.00
Female	90 (52)	122 (55)		74 (52)	74 (52)		-0.06	0.00
Age at diagnosis, mean (SD), y	60.1 (10.5)	61.7 (9.8)	.12	61.0 (10.4)	61.1 (10.4)	.97	-0.16	0.00
Period of diagnosis, No. (%)								
2005-2009	25 (15)	28 (13)	<.001	24 (17)	17 (12)	.29	0.05	0.14
2010-2013	82 (48)	59 (27)		53 (37)	48 (34)		0.44	0.07
2014-2017	65 (38)	134 (61)		65 (46)	77 (54)		-0.47	-0.17
Weeks from diagnosis to CRS-HIPEC, median (IQR)	10 (7-13)	10 (7-14)	.78	10 (7-14)	10 (7-14)	.86	0.01	-0.03
Primary tumor location, No. (%)								
Proximal colon	80 (47)	125 (57)	.03	76 (54)	75 (53)	.62	-0.20	0.01
Distal colon	85 (49)	81 (37)		59 (42)	63 (44)		0.26	-0.06
Rectum	7 (4)	15 (7)		7 (5)	4 (3)		-0.12	0.11
Pathologic T category, No. (%)								
T0-3	46 (27)	62 (28)	.71	40 (28)	40 (28)	>.99	-0.03	0.00
T4	124 (72)	154 (70)		100 (70)	100 (70)		0.05	0.00
Missing data	2 (1)	5 (2)		2 (1)	2 (1)		-0.08	0.00
Pathologic N category, No. (%)								
N0	31 (18)	41 (19)	.88	28 (20)	26 (18)	.99	-0.01	0.00
N1	57 (33)	67 (30)		49 (35)	49 (35)		0.06	-0.03
N2	81 (47)	107 (48)		62 (44)	64 (45)		-0.03	0.00
Missing data	3 (3)	6 (3)		3 (2)	3 (2)		-0.07	-0.01
Histologic characteristics, No. (%)								
Adenocarcinoma	96 (56)	131 (59)	.53	84 (59)	88 (62)	.46	-0.07	-0.06
Mucinous adenocarcinoma	63 (37)	79 (36)		47 (33)	48 (34)		0.02	-0.01
Signet ring cell adenocarcinoma	13 (8)	11 (5)		11 (8)	6 (4)		0.11	0.15
Differentiation, No. (%)								
Well/moderately	99 (58)	125 (57)	.96	79 (56)	80 (56)	.89	0.02	-0.01
Poor/undifferentiated	30 (17)	41 (19)		27 (19)	24 (17)		-0.03	0.06
Missing data	43 (25)	55 (25)		36 (25)	38 (27)		0.00	-0.03
Initial length of hospital stay after CRS-HIPEC, No. (%)								
≤21 d	95 (55)	116 (52)	<.001	82 (58)	77 (54)	.08	0.06	0.07
>21 d	6 (3)	37 (17)		6 (4)	16 (11)		-0.45	-0.27
Missing data	71 (41)	68 (31)		54 (38)	49 (35)		0.22	0.07

Abbreviations: CRS-HIPEC, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; IQR, interquartile range.

^a A standardized difference between -0.10 and 0.10 indicated an adequate balance.

(aHR, 0.70; 95% CI, 0.50-0.97; $P = .03$). Adjustment for unmeasured confounding by major postoperative morbidity did not eliminate the association between adjuvant systemic chemotherapy and improved overall survival (aHR, 0.71; 95% CI, 0.53-0.95). The association between adjuvant systemic chemotherapy and overall survival was homogeneous across different levels of all covariates except for pathologic T category (eFigure in the Supplement).

Discussion

In this nationwide observational cohort study in patients who were alive 3 months after up-front resection of isolated synchro-

nous colorectal peritoneal metastases, adjuvant systemic chemotherapy was associated with improved overall survival compared with active surveillance.

Other observational studies have analyzed the association between adjuvant systemic chemotherapy and overall survival after CRS-HIPEC for colorectal peritoneal metastases.²⁶⁻³⁷ However, in their analyses, these studies included patients with metachronous peritoneal metastases,²⁶⁻³⁷ incomplete cytoreductions,^{26-32,35,36} extraperitoneal metastases,^{26,28-30,32-37} appendiceal tumors,^{26,35,36} or systemic therapy before CRS-HIPEC.^{26,28-37} Moreover, most other studies did not account for immortal time bias,^{26,27,29-36} did not define time frames of adjuvant systemic chemotherapy,^{26-30,32-36} or did not primarily assess the association between adjuvant systemic chemo-

Figure 2. Overall Survival of Adjuvant Systemic Chemotherapy and Active Surveillance Groups in the Matched Population

Association between adjuvant systemic chemotherapy and improved survival (hazard ratio, 0.64; 95% CI, 0.48-0.86; $P = .003$).

therapy and overall survival.²⁶⁻³⁶ Only one study accounted for immortal time bias and primarily addressed the association between adjuvant systemic chemotherapy and overall survival.³⁷ This French multicenter study revealed no overall survival benefit of adjuvant systemic chemotherapy in 231 patients who underwent complete CRS-HIPEC for colorectal peritoneal metastases and did not die due to early postoperative complications. In contrast to the present study, nearly all patients in this study received systemic chemotherapy before CRS-HIPEC, most of whom had a response or stable disease. Altogether, the results of the present study could not be meaningfully compared with previously published studies.

The present study reports a marked decrease in the proportion of patients receiving adjuvant systemic chemotherapy following up-front resection of isolated synchronous colorectal peritoneal metastases in the Netherlands in recent years. Before 2014, the Dutch colorectal cancer guideline did not include a statement on the use of adjuvant systemic chemotherapy in this setting, while the updated guideline of 2014 states that its use could be considered.⁵ Therefore, the decision to administer adjuvant systemic chemotherapy largely depended on the preference of physicians and patients. However, after review of the available evidence on this topic in 2016,⁷ the use of adjuvant systemic chemotherapy was no longer advised given the absence of supporting evidence. This change in recommendation may explain the relatively short follow-up of the active surveillance group compared with the adjuvant systemic chemotherapy group.

What is the rationale for giving adjuvant systemic chemotherapy in this setting? Similar to other institutional and popu-

lation-based studies,^{6,38} the present study suggests that synchronous colorectal peritoneal metastases predominantly arise from advanced (mostly pT₄ and pN₂ category) primary tumors. Systemic failure is common after CRS-HIPEC,³⁹ probably because these tumors are at substantial risk of systemic spread.⁴⁰ Particularly in such high-risk tumors, adjuvant systemic chemotherapy may improve oncologic outcomes by preventing systemic spread through elimination of micrometastases. In addition to prevention of systemic spread, adjuvant systemic chemotherapy could also decrease or delay locoregional recurrences by eradication of postsurgical residual disease since visualization and palpation may not adequately detect all malignant tissue during CRS.⁴¹⁻⁴³ On the other hand, the administration of adjuvant systemic chemotherapy could decrease the systemic treatment options for recurrent disease, which occurs in most patients with resected colorectal peritoneal metastases.³⁹ Thereby, it could be hypothesized that adjuvant systemic chemotherapy predominantly prolongs recurrence-free survival without significantly improving overall survival.

As in any observational cohort study, survival outcomes of the present study may have been affected by selection bias. Despite the use of propensity score-based methods and a conditional landmark analysis, differences in unmeasured covariates could have led to systematically different treatment groups. These differences are illustrated by comparing the overall survival curve of the present study with the intention-to-treat overall survival curves of landmark studies addressing the same topic in stage III colon cancer and pancreatic, gastric, and biliary tract cancer.⁴⁴⁻⁴⁷ In these studies, the overall survival curves diverge after approximately 10 to 18 months. The overall survival curve of the present study already diverges after 3 months (when adjuvant systemic chemotherapy is still administered), which may suggest an influence of residual selection bias due to unmeasured confounding (eg, due to major postoperative morbidity). Although a sensitivity analysis was used to adjust for unmeasured confounding, the HR and proportions of the unmeasured confounder were derived from Dutch institutional series. Variations in these measures could have underestimated or overestimated the confounder's possible role in the association between adjuvant systemic chemotherapy and improved overall survival.

The potential presence of residual confounding in the present study highlights the importance of randomized clinical trials on this topic. However, previous randomized clinical trials in the adjuvant setting following resection of colorectal metastases have been preliminarily terminated owing to poor accrual.^{48,49} Moreover, feasible accrual and positive results were observed in previous studies in the neoadjuvant or perioperative setting in esophageal and gastric cancer.^{50,51} Thereby, it seems preferable to conduct a randomized clinical trial on resectable colorectal peritoneal metastases in the neoadjuvant or perioperative setting. The Dutch Peritoneal Oncology Group designed the ongoing multicenter randomized CAIRO6 trial to assess the intention-to-treat superiority of neoadjuvant and adjuvant systemic therapy and CRS-HIPEC compared with up-front CRS-HIPEC alone for resectable colorectal peritoneal metastases.⁹

Although results of CAIRO6 will become available within a few years and observational studies are generally primarily hypothesis generating, results of the present study may be used for clinical decision-making in the understudied and increasing group of patients undergoing up-front resection of isolated synchronous colorectal peritoneal metastases for whom, to the knowledge of the authors, no data are available.⁵² Current guidelines are based on low-quality observational studies in heterogeneous populations without subgroup analyses of this particular patient group.²⁶⁻³⁷ Moreover, if CAIRO6 does not show superiority of a neoadjuvant strategy, up-front surgery will remain standard care and the international debate on adjuvant systemic chemotherapy will continue. In addition, even if neoadjuvant treatment becomes standard care, there will still be patients undergoing up-front resection of isolated synchronous colorectal peritoneal metastases (eg, during emergency surgery). In both situations, data reported from the present study may be used for adjuvant treatment decisions until data obtained in randomized adjuvant trials (if these will ever be conducted) become available. In addition, randomized clinical trials generally assess the efficacy of an intervention (ie, the effect under selected conditions), whereas population-based studies, such as the present investigation, may provide additional information on the possible real-world benefit in the general population.

Limitations

In addition to limitations associated with selection bias, the present study has several other limitations. The peritoneal cancer index is not registered in the Netherlands Cancer Registry.⁵³ Although unlikely to play a role in selection for adjuvant treatment by itself, unmeasured differences in the peritoneal cancer index may have been associated with survival outcomes. No

data were available on the date and treatment of recurrence. This lack of data could have led to allocation bias because patients starting systemic chemotherapy within 3 months postoperatively (now allocated to the adjuvant systemic chemotherapy group) probably received palliative treatment for very early recurrent disease, while patients starting systemic chemotherapy more than 3 months postoperatively (now allocated to the active surveillance group) probably received late adjuvant treatment. Although excluding patients starting systemic chemotherapy between 3 and 4 months postoperatively did not change the association between adjuvant systemic chemotherapy and overall survival, allocation bias could theoretically have affected study results. Insufficient data on adjuvant regimens, adjuvant treatment duration, and disease recurrence impeded regimen-specific, duration-specific, and recurrence-free survival analyses. While the present study did not aim to analyze such outcomes, it may be valuable to assess these outcomes in future multicenter observational studies using more detailed institutional databases.

Conclusions

In patients undergoing up-front resection of isolated synchronous colorectal peritoneal metastases, adjuvant systemic chemotherapy appeared to be associated with improved overall survival compared with active surveillance. Although randomized clinical trials are needed to address the influence of potential residual confounding and allocation bias on this association, results of the present study may be used for clinical decision-making in this increasing, understudied patient group for whom, to the knowledge of the authors, no data are available at this time.

ARTICLE INFORMATION

Accepted for Publication: May 8, 2020.

Published Online: July 16, 2020.

doi:10.1001/jamaoncol.2020.2701

Author Affiliations: Department of Surgery, Catharina Cancer Institute, Eindhoven, the Netherlands (Rovers, Bakkers, Burger, Nienhuijs, Simkens, de Hingh); Department of Research, Netherlands Comprehensive Cancer Organization, Utrecht, the Netherlands (van Erning, Lemmens, de Hingh); Department of Medical Oncology, Catharina Cancer Institute, Eindhoven, the Netherlands (Creemers); Department of Surgery, University Medical Centre Groningen, Groningen, the Netherlands (Hemmer); Department of Medical Oncology, Amsterdam University Medical Centers, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands (Punt); Department of Public Health, Erasmus University Medical Centre, Rotterdam, the Netherlands (Lemmens); Department of Surgery, Amsterdam University Medical Centers, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands (Tanis); GROW-School for Oncology and Development Biology, Maastricht University, Maastricht, the Netherlands (de Hingh).

Author Contributions: Drs Rovers and de Hingh had full access to all of the data in the study and

take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Rovers, Bakkers, van Erning, Burger, Nienhuijs, Creemers, Hemmer, Punt, Tanis, de Hingh.

Acquisition, analysis, or interpretation of data: Rovers, Bakkers, van Erning, Simkens, Lemmens, Tanis, de Hingh.

Drafting of the manuscript: Rovers, Bakkers, van Erning, Tanis, de Hingh.

Critical revision of the manuscript for important intellectual content: Burger, Nienhuijs, Simkens, Creemers, Hemmer, Punt, Lemmens, de Hingh.

Statistical analysis: Rovers, van Erning, Simkens.

Administrative, technical, or material support: Lemmens, de Hingh.

Supervision: Burger, Simkens, Punt, Tanis, de Hingh.

Conflict of Interest Disclosures: Dr Punt reported serving as an advisor for Servier and Nordic Pharma. Dr de Hingh reported receiving grants from Roche, QP&S, and RaD Biotech outside the submitted work. No other disclosures were reported.

Additional Contributions: The authors thank the registration team of the Netherlands Comprehensive Cancer Organization for the collection of data.

REFERENCES

1. Razenberg LG, Lemmens VE, Verwaal VJ, et al. Challenging the dogma of colorectal peritoneal metastases as an untreatable condition: results of a population-based study. *Eur J Cancer*. 2016;65:113-120. doi:10.1016/j.ejca.2016.07.002
2. Bushati M, Rovers KP, Sommariva A, et al. The current practice of cytoreductive surgery and HIPEC for colorectal peritoneal metastases: results of a worldwide web-based survey of the Peritoneal Surface Oncology Group International (PSOGI). *Eur J Surg Oncol*. 2018;44(12):1942-1948. doi:10.1016/j.ejso.2018.07.003
3. Klaver CE, Groenen H, Morton DG, Laurberg S, Bemelman WA, Tanis PJ; Research Committee of the European Society of Coloproctology. Recommendations and consensus on the treatment of peritoneal metastases of colorectal origin: a systematic review of national and international guidelines. *Colorectal Dis*. 2017;19(3):224-236. doi:10.1111/codi.13593
4. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol*. 2003;21(20):3737-3743. doi:10.1200/JCO.2003.04.187

5. Colorectaalcarcinoom. Landelijke richtlijn, versie: 3.0. Gastro intestinale tumoren. Published April 16, 2014. Accessed June 8, 2020. <https://www.nhg.org/sites/default/files/content/nhg.org/uploads/colorectaalcarcinoom.pdf>
6. Devilee RA, Simkens GA, van Oudheusden TR, et al. Increased survival of patients with synchronous colorectal peritoneal metastases receiving preoperative chemotherapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2016;23(9):2841-2848. doi:10.1245/s10434-016-5214-3
7. Rovers KP, Simkens GA, Punt CJ, van Dieren S, Tanis PJ, de Hingh IH. Perioperative systemic therapy for resectable colorectal peritoneal metastases: sufficient evidence for its widespread use? a critical systematic review. *Crit Rev Oncol Hematol*. 2017;114:53-62. doi:10.1016/j.critrevonc.2017.03.028
8. Kuipers AM, Mirck B, Aalbers AG, et al. Cytoreduction and HIPEC in the Netherlands: nationwide long-term outcome following the Dutch protocol. *Ann Surg Oncol*. 2013;20(13):4224-4230. doi:10.1245/s10434-013-3145-9
9. Rovers KP, Bakkers C, Simkens GAAM, et al; Dutch Peritoneal Oncology Group (DPOG); Dutch Colorectal Cancer Group (DCCG). Perioperative systemic therapy and cytoreductive surgery with HIPEC versus upfront cytoreductive surgery with HIPEC alone for isolated resectable colorectal peritoneal metastases: protocol of a multicentre, open-label, parallel-group, phase II-III, randomised, superiority study (CAIRO6). *BMC Cancer*. 2019;19(1):390. doi:10.1186/s12885-019-5545-0
10. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. *J Clin Oncol*. 2013;31(23):2963-2969. doi:10.1200/JCO.2013.49.5283
11. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer: a personalized approach to clinical decision making. *Ann Oncol*. 2012;23(10):2479-2516. doi:10.1093/annonc/mds236
12. Allegra CJ, Yothers G, O'Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. *J Clin Oncol*. 2011;29(1):11-16. doi:10.1200/JCO.2010.30.0855
13. de Gramont A, Van Cutsem E, Schmoll HJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncol*. 2012;13(12):1225-1233. doi:10.1016/S1470-2045(12)70509-0
14. Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. *JAMA*. 2012;307(13):1383-1393. doi:10.1001/jama.2012.385
15. Taieb J, Tabernero J, Mini E, et al; PETACC-8 Study Investigators. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15(8):862-873. doi:10.1016/S1470-2045(14)70227-X
16. Kerr RS, Love S, Segelov E, et al. Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2016;17(11):1543-1557. doi:10.1016/S1470-2045(16)30172-3
17. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55. doi:10.1093/biomet/70.1.41
18. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biom J*. 2009;51(1):171-184. doi:10.1002/bimj.200810488
19. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107. doi:10.1002/sim.3697
20. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/bmj.b2393
21. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine—reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357(21):2189-2194. doi:10.1056/NEJMs077003
22. Simkens GA, van Oudheusden TR, Luyer MD, et al. Serious postoperative complications affect early recurrence after cytoreductive surgery and HIPEC for colorectal peritoneal carcinomatosis. *Ann Surg Oncol*. 2015;22(8):2656-2662. doi:10.1245/s10434-014-4297-y
23. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics*. 1998;54(3):948-963. doi:10.2307/2533848
24. van Eden WJ, Kok NF, Jóźwiak K, et al. Timing of systemic chemotherapy in patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Dis Colon Rectum*. 2017;60(5):477-487. doi:10.1097/DCR.0000000000000774
25. van Eden WJ, Kok NFM, Woensdregt K, Huitema AD, Boot H, Aalbers AGJ. Safety of intraperitoneal mitomycin C versus intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis of colorectal cancer undergoing cytoreductive surgery and HIPEC. *Eur J Surg Oncol*. 2018;44(2):220-227. doi:10.1016/j.ejso.2017.10.216
26. Culliford AT IV, Brooks AD, Sharma S, et al. Surgical debulking and intraperitoneal chemotherapy for established peritoneal metastases from colon and appendix cancer. *Ann Surg Oncol*. 2001;8(10):787-795. doi:10.1007/s10434-001-0787-9
27. Glehen O, Cotte E, Schreiber V, Sayag-Beaujard AC, Vignal J, Gilly FN. Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. *Br J Surg*. 2004;91(6):747-754. doi:10.1002/bjs.4473
28. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol*. 2004;22(16):3284-3292. doi:10.1200/JCO.2004.10.012
29. Gilly FN; International Registry of Colorectal Carcinomatosis. Phase II studies: international registry of colorectal carcinomatosis. *Eur J Surg Oncol*. 2006;32(6):648-654. doi:10.1016/j.ejso.2006.03.030
30. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol*. 2010;28(1):63-68. doi:10.1200/JCO.2009.23.9285
31. Passot G, Vaudoyer D, Cotte E, et al. Progression following neoadjuvant systemic chemotherapy may not be a contraindication to a curative approach for colorectal carcinomatosis. *Ann Surg*. 2012;256(1):125-129. doi:10.1097/SLA.0b013e318255486a
32. Cashin PH, Graf W, Nygren P, Mahteme H. Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: prognosis and treatment of recurrences in a cohort study. *Eur J Surg Oncol*. 2012;38(6):509-515. doi:10.1016/j.ejso.2012.03.001
33. Maggiori L, Goéré D, Viana B, et al. Should patients with peritoneal carcinomatosis of colorectal origin with synchronous liver metastases be treated with a curative intent? a case-control study. *Ann Surg*. 2013;258(1):116-121. doi:10.1097/SLA.0b013e3182778089
34. Ung L, Chua TC, David L M. Peritoneal metastases of lower gastrointestinal tract origin: a comparative study of patient outcomes following cytoreduction and intraperitoneal chemotherapy. *J Cancer Res Clin Oncol*. 2013;139(11):1899-1908. doi:10.1007/s00432-013-1517-y
35. Nikolic S, Dzodic R, Zegarac M, et al. Survival prognostic factors in patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy: a single institution experience. *J BUON*. 2014;19(1):66-74. doi:10.1016/j.ejso.2014.08.415
36. Ceelen W, Van Nieuwenhove Y, Putte DV, Pattyn P. Neoadjuvant chemotherapy with bevacizumab may improve outcome after cytoreduction and hyperthermic intraperitoneal chemoperfusion (HIPEC) for colorectal carcinomatosis. *Ann Surg Oncol*. 2014;21(9):3023-3028. doi:10.1245/s10434-014-3713-7
37. Mailet M, Glehen O, Lambert J, et al; BIG-RENAPE Working Group. Early postoperative chemotherapy after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for isolated peritoneal carcinomatosis of colon cancer: a multicenter study. *Ann Surg Oncol*. 2016;23(3):863-869. doi:10.1245/s10434-015-4914-4
38. Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer*. 2011;128(11):2717-2725. doi:10.1002/ijc.25596
39. van Oudheusden TR, Nienhuijs SW, Luyer MD, et al. Incidence and treatment of recurrent disease after cytoreductive surgery and intraperitoneal chemotherapy for peritoneally metastasized colorectal cancer: a systematic review. *Eur J Surg Oncol*. 2015;41(10):1269-1277. doi:10.1016/j.ejso.2015.05.018
40. van Gestel YR, de Hingh IH, van Herk-Sukel MP, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. *Cancer*

Epidemiol. 2014;38(4):448-454. doi:10.1016/j.canep.2014.04.004

41. Liberale G, Vankerckhove S, Caldon MG, et al; Group R&D for the Clinical Application of Fluorescence Imaging of the Jules Bordet's Institute. Fluorescence imaging after indocyanine green injection for detection of peritoneal metastases in patients undergoing cytoreductive surgery for peritoneal carcinomatosis from colorectal cancer: a pilot study. *Ann Surg.* 2016;264(6):1110-1115. doi:10.1097/SLA.0000000000001618
42. Harlaar NJ, Koller M, de Jongh SJ, et al. Molecular fluorescence-guided surgery of peritoneal carcinomatosis of colorectal origin: a single-centre feasibility study. *Lancet Gastroenterol Hepatol.* 2016;1(4):283-290. doi:10.1016/S2468-1253(16)30082-6
43. Boogerd LSF, Hoogstins CES, Schaap DP, et al. Safety and effectiveness of SGM-101, a fluorescent antibody targeting carcinoembryonic antigen, for intraoperative detection of colorectal cancer: a dose-escalation pilot study. *Lancet Gastroenterol Hepatol.* 2018;3(3):181-191. doi:10.1016/S2468-1253(17)30395-3
44. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med.* 1990;322(6):352-358. doi:10.1056/NEJM199002083220602

45. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA.* 2013;310(14):1473-1481. doi:10.1001/jama.2013.279201
46. Noh SH, Park SR, Yang HK, et al; CLASSIC Trial Investigators. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014;15(12):1389-1396. doi:10.1016/S1470-2045(14)70473-5
47. Primrose JN, Fox RP, Palmer DH, et al; BILCAP Study Group. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol.* 2019;20(5):663-673. doi:10.1016/S1470-2045(18)30915-X
48. Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol.* 2008;26(30):4906-4911. doi:10.1200/JCO.2008.17.3781
49. Snoeren N, van Hillegersberg R, Schouten SB, et al; Hepatica Study Group. Randomized phase III study to assess efficacy and safety of adjuvant

CAPOX with or without bevacizumab in patients after resection of colorectal liver metastases: HEPATICA study. *Neoplasia.* 2017;19(2):93-99. doi:10.1016/j.neo.2016.08.010

50. Cunningham D, Allum WH, Stenning SP, et al; MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355(1):11-20. doi:10.1056/NEJMoa055531
51. van Hagen P, Hulshof MC, van Lanschot JJ, et al; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366(22):2074-2084. doi:10.1056/NEJMoa1112088
52. Razenberg LG, van Gestel YR, Creemers GJ, Verwaal VJ, Lemmens VE, de Hingh IH. Trends in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of synchronous peritoneal carcinomatosis of colorectal origin in the Netherlands. *Eur J Surg Oncol.* 2015;41(4):466-471. doi:10.1016/j.ejso.2015.01.018
53. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res.* 1996;82:359-374. doi:10.1007/978-1-4613-1247-5_23