

World Journal of *Clinical Cases*

World J Clin Cases 2022 March 16; 10(8): 2363-2659



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The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Hua-Ge Yin, Production Department Director: Xu Guo, Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

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<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

March 16, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Clinical Trials Study

Prognostic significance of peritoneal metastasis from colorectal cancer treated with first-line triplet chemotherapy

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Specialty type: Medicine, research and experimental

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Díez M, Wan XH

Received: September 16, 2021

Peer-review started: September 16, 2021

First decision: November 17, 2021

Revised: December 3, 2021

Accepted: January 22, 2022

Article in press: January 22, 2022

Published online: March 16, 2022



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Abstract

BACKGROUND

Peritoneal metastasis from colorectal cancer (CRC) carries a poor prognosis in most studies. The majority of those studies used either a single-agent or doublet chemotherapy regimen in the first-line setting.

AIM

To investigate the prognostic significance of peritoneal metastasis in a cohort of patients treated with triplet chemotherapy in the first-line setting.

METHODS

We retrospectively evaluated progression-free survival (PFS) and overall survival (OS) in 51 patients with metastatic CRC treated in a prospective clinical trial with capecitabine, oxaliplatin, irinotecan, and bevacizumab in the first-line setting according to the presence and absence of peritoneal metastasis. Furthermore, univariate and multivariate analyses for PFS and OS were performed to assess the prognostic significance of peritoneal metastasis at the multivariate level.

RESULTS

Fifty-one patients were treated with the above triplet therapy. Fifteen had peritoneal metastasis. The patient characteristics of both groups showed a significant difference in the sidedness of the primary tumor (left-sided primary tumor in 60% of the peritoneal group *vs* 86% in the nonperitoneal group, $P = 0.03$) and the presence of liver metastasis (40% for the peritoneal group *vs* 75% for the nonperitoneal group, $P = 0.01$). Univariate analysis for PFS showed a statistically significant difference for age less than 65 years ($P = 0.034$), presence of liver metastasis ($P = 0.046$), lung metastasis ($P = 0.011$), and those who underwent metastasectomy ($P = 0.001$). Only liver metastasis and metastasectomy were

statistically significant for OS, with *P* values of 0.001 and 0.002, respectively. Multivariate analysis showed that age (less than 65 years) and metastasectomy were statistically significant for PFS, with *P* values of 0.002 and 0.001, respectively. On the other hand, the absence of liver metastasis and metastasectomy were statistically significant for OS, with *P* values of 0.003 and 0.005, respectively.

CONCLUSION

Peritoneal metastasis in patients with metastatic CRC treated with first-line triple chemotherapy does not carry prognostic significance at univariate and multivariate levels. Confirmatory larger studies are warranted.

Key Words: Colorectal cancer; Peritoneal carcinomatosis; Triplet chemotherapy; Survival; Prognostic factors; Metastasectomy

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Core Tip: The established poor prognostic indicator of peritoneal metastasis in metastatic colorectal cancer (CRC) has been in patients treated with single agent or doublet chemotherapy. In our study, we retrospectively demonstrated that in patients treated with triplet chemotherapy in the first-line setting, the significance of peritoneal metastasis as a poor prognostic factor was lost. This might suggest a beneficial therapeutic effect of triplet chemotherapy in the first-line setting in patients with metastatic CRC and peritoneal metastasis.

Citation: Bazarbashi S, Alghabban A, Asefan M, Aljubran AH, Alzahrani A, Elhassan TA. Prognostic significance of peritoneal metastasis from colorectal cancer treated with first-line triplet chemotherapy. *World J Clin Cases* 2022; 10(8): 2429-2438

URL: <https://www.wjgnet.com/2307-8960/full/v10/i8/2429.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i8.2429>

INTRODUCTION

Globally, colorectal cancer (CRC) is the third most-common cancer and the second-most-common cause of cancer death in males and third in females[1]. There has been a significant improvement in overall survival (OS) for patients with metastatic CRC secondary to the introduction of several new chemotherapy and targeted agents[2-5]. Although no major improvement in survival was observed with first-line doublet chemotherapy regimens compared to single-agent regimens[6-8], triplet chemotherapy apparently resulted in improved OS compared to doublets in the first-line setting[9-12].

Several studies have shown that patients with peritoneal carcinomatosis in metastatic CRC have poor survival, and this was an independent poor prognostic factor[13,14]. However, the majority of those studies used either single-agent or doublet chemotherapy with or without targeted therapy[13,14]. It is unclear whether peritoneal carcinomatosis continues to be a poor prognostic factor in patients with metastatic CRC treated with triplet regimens.

We have previously reported the results of our phase I/II trial of triplet chemotherapy using capecitabine, oxaliplatin, and irinotecan with bevacizumab in patients with advanced CRC[15]. Here, we report the post hoc analysis of the efficacy of the above combination in patients with and without peritoneal metastasis and examined the different prognostic factors for progression-free survival (PFS) and OS in these groups of patients.

MATERIALS AND METHODS

Study design

The present study represents a post hoc analysis of the previously published phase I/II trial of triplet therapy in patients with unresectable metastatic or locally advanced CRC. Efficacy data were analyzed according to the presence *vs* the absence of peritoneal metastasis.

Patients

Patients with metastatic CRC not amenable to surgical resection were enrolled in a phase I/II trial of triplet chemotherapy consisting of capecitabine, oxaliplatin, irinotecan, and bevacizumab. The study procedures have been published earlier[15]. Briefly, patients were eligible for inclusion if they were

more than 18 years old, had histologically confirmed CRC adenocarcinoma with no prior chemotherapy or targeted therapy for metastatic disease, had Eastern Cooperative Oncology Group performance status 0-2, had measurable disease [defined by response evaluation criteria in solid tumors (RECIST) V1.1] [16], and had adequate organ function (defined as absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, normal serum bilirubin, serum transaminases ≤ 2.5 times the upper limits of normal, normal serum creatinine, and urine dipstick for proteinuria $\leq 2+$). Patients who had prior adjuvant oxaliplatin or fluoropyrimidine chemotherapy were eligible if the last chemotherapy was ≥ 12 mo. Exclusion criteria included central nervous system metastasis, severe cardiovascular dysfunction, prior malignancy within 5 years (except for adequately treated nonmelanoma skin cancer or in situ cervical cancer), active infection, bleeding diathesis, major surgery within 28 d of starting therapy, uncontrolled hypertension, prior history of dihydropyrimidine deficiency, and pregnancy or breastfeeding. The study was approved by the institutional review board under the number RAC2081068 and was listed on clinical trials.gov (NCT01311050). All patient signed informed consent.

Treatment

The phase I part of the trial has been described earlier in a previous publication[15]. According to phase I, the recommended doses for phase II were capecitabine 1000 mg/m² orally on days 1 to 14, oxaliplatin 130 mg/m², irinotecan 150 mg/m², and bevacizumab at 7.5 mg/kg of body weight, all on day 1 of each cycle. Treatment cycles were repeated every 21 d. Patients were given 5-8 cycles of a triplet regimen with bevacizumab. Responding patients were placed on maintenance capecitabine and bevacizumab at the above doses until disease progression or unacceptable toxicity.

Statistics and efficacy endpoints

The statistical design of the phase I and II parts of this study was described earlier[15]. The number of patients planned for the phase II part of the trial was 46. All patients were assessed for response according to RECIST criteria V1.1 by computed tomography scans or magnetic resonance imaging performed after the second, fifth, and eighth cycles of chemotherapy and every 2 mo thereafter.

Patient characteristics were summarized using frequencies with percentages, while continuous variables were summarized using medians with interquartile ranges. Patient characteristics were further retrospectively compared according to the presence or absence of peritoneal metastasis. Categorical variables were compared using the chi-square test, while continuous variables were compared using the Mann-Whitney test.

OS was defined as the time to death of any cause, while PFS was defined as the time to disease progression, recurrence, or death from any cause. Surviving patients were censored at last follow-up. Probabilities of OS and PFS were calculated using the Kaplan-Meier estimator with variance calculated using the Greenwood formula. Survival curves were compared using log-rank test. Multivariate analysis was performed using the cox proportional hazard regression model. The proportional hazards assumption was tested, and covariates that violated the proportional hazards assumption were added as time-dependent covariates. *P* value < 0.05 was considered significant. Analysis was conducted using RStudio. Version 1.4.1106 © 2009-2021 RStudio, PBC. The statistical methods of this study were performed and reviewed by Tusneem Elhassan from King Faisal Specialist Hospital and Research Center.

RESULTS

A total of 53 patients with metastatic or locally advanced unresectable CRC were enrolled in a phase I/II trial of combination chemotherapy with capecitabine, oxaliplatin, irinotecan, and bevacizumab (6 in the phase I part and 47 in the phase II part). Among those, two withdrew. Therefore, a total of 51 patients were available for evaluation. Patient characteristics are illustrated in Table 1. Fifteen patients (29.4%) had peritoneal metastasis. Forty (78.4%) had left-sided colon cancer. Thirty-three (64.7%) had liver metastasis; 20 (39.2%) had lung metastasis, and 32 (62.7%) patients had more than one site of metastasis.

The characteristics of patients with peritoneal metastasis *vs* no peritoneal metastasis are illustrated in Table 1. Of note, 31 (86%) patients with no peritoneal metastasis had left-sided primary tumors, while only 9 (60%) patients in the peritoneal metastasis group had left-sided primary tumors (*P* = 0.03). Additionally, 25 (75%) of the patients with no peritoneal disease had liver metastasis, while only 6 (40%) of the patients with peritoneal metastasis had liver metastasis (*P* = 0.01).

The median PFS and OS for the whole group were 10.8 mo [95% confidence interval (CI): 5.1-16.5] and 31.3 mo (95%CI: 16.9-45.6), respectively. The median PFS for the peritoneal metastasis group *vs* the group without peritoneal metastasis was 9.4 (95%CI: 8.6-10.1) mo *vs* 13.7 (95%CI: 4.4-22.9) mo (*P* = 0.401). The median OS for the group with peritoneal metastasis *vs* the group without peritoneal metastasis was not reached *vs* 31.3 (95%CI: 19.5-43.1) mo (*P* = 0.368) (Figures 1 and 2).

Univariate analysis of known prognostic factors is shown in Table 2. Age (less than 65 years), presence of liver/lung metastasis, and metastasectomy were statistically significant for PFS, with *P* values of 0.034, 0.046, 0.011, and 0.001, respectively. Only liver metastasis and metastasectomy were

Table 1 Characteristics of 51 patients with metastatic colorectal cancer, with and without peritoneal metastasis treated with triplet chemotherapy

	Whole group	Peritoneal metastasis <i>N</i> (%)	No peritoneal metastasis <i>N</i> (%)	<i>P</i> value
Age in years	52 (23-74)	52 (23-74)	50 (32-73)	0.97
Gender				0.97
Male	27 (52.9%)	8 (53.3%)	19 (52.8%)	
Female	24 (47.1%)	7 (46.7%)	17 (47.1%)	
Site of primary				0.03
Left	40 (78.4%)	9 (60%)	31 (86.1%)	
Right	11 (21.6%)	6 (40%)	5 (13.9%)	
Performance status				0.8
0-1	40 (78.4%)	12 (80%)	28 (77.8%)	
2	11 (21.6%)	3 (20%)	8 (22.2%)	
Liver metastasis				0.01
Yes	33 (64.7%)	6 (40%)	27 (75%)	
No	18 (35.3%)	9 (60%)	9 (25%)	
Lung metastasis				0.07
Yes	20 (39.2%)	3 (20%)	17 (47.2%)	
No	31 (60.8%)	12 (80%)	19 (52.8%)	
KRAS status				0.14
Wild	20 (39.2%)	3 (20%)	17 (47.2%)	
Mutant	21 (41.2%)	9 (60%)	12 (33.3%)	
Unknown	10 (19.6%)	3 (20%)	7 (19.4%)	
Prior surgery to primary				0.3
Yes	29 (55.9%)	10 (66.7%)	19 (52.8%)	
No	22 (43.1%)	5 (33.3%)	17 (47.2%)	
No of metastatic sites				0.39
1	19 (37.2%)	4 (28.6%)	13 (41.9%)	
> 1	32 (62.7%)	10 (71.4%)	18 (58.1%)	
Metastasectomy				0.4
Yes	13 (25.5%)	5 (33.3%)	8 (22.2%)	
No	38 (74.5%)	10 (66.7%)	28 (77.8%)	

statistically significant for OS, with *P* values of 0.001 and 0.002, respectively.

Multivariate analysis showed that age (less than 65 years) and metastasectomy were statistically significant for PFS, with *P* values of 0.002 and 0.001, respectively. On the other hand, the absence of liver metastasis and metastasectomy were statistically significant for OS, with *P* values of 0.003 and 0.005, respectively (Table 3).

DISCUSSION

To our knowledge, this is the first study to evaluate the prognostic significance of peritoneal metastasis in patients with metastatic CRC treated primarily with triplet first-line chemotherapy. Historically, the presence of peritoneal carcinomatosis in patients with metastatic CRC has resulted in poor prognosis[13, 14]. The median OS in patients treated with modern chemotherapy regimens, including targeted therapy, has ranged from 8 to 12 mo[17]. Bakkers *et al*[17] reported a population-based study with 7233 patients with metastatic CRC, of which 743 had peritoneal carcinomatosis. The median OS for the 409

Table 2 Univariate analysis of progression-free survival and overall survival in 51 patients with metastatic colorectal cancer treated with triplet therapy

	PFS		OS	
	Mo (95% CI)	P value	Mo (95% CI)	P value
Age		0.034		0.157
< 65	12.4 (5-19.9)		31.3 (14.9-47.6)	
≥ 65	5.7 (5-6.3)		20.9 (0-45.2)	
Gender		0.429		0.439
Male	10.8 (4.3-17.3)		31.3 (13.2-49.3)	
Female	9.4 (0-19.3)		29.1 (0-58.5)	
Site of primary		0.823		0.844
Left	10.8 (4.1-17.5)		31.3 (14.8-47.7)	
Right	9.1 (0.5-17.8)		20.9 (0-82.8)	
Performance status		0.068		0.532
0-1	15.9 (7-24.8)		38.2 (22.9-53.5)	
2	6.9 (2.8-11)		31.3 (5.7-56.8)	
Liver metastasis		0.046		0.001
Yes	8.9 (7-10.9)		24.7 (10.9-38.5)	
No	15.9 (5.7-26.1)		NR	
Lung metastasis		0.011		0.087
Yes	8.9 (6.4-11.4)		24.7 (17.6-31.9)	
No	13.7 (5.8-21.6)		40 (0-84.7)	
Peritoneum metastasis		0.401		0.368
Yes	9.4 (8.6-10.1)		NR	
No	13.7 (4.4-22.9)		31.3 (19.5-43.1)	
KRAS		0.957		0.851
Wild	13.7 (0-30.7)		38.2 (23.3-53)	
Mutant	10.8 (5.2-16.4)		29.1 (20.8-37.3)	
Unknown	9.4 (8.2-10.5)		22.1 (0-44.4)	
Prior surgery to primary		0.928		0.764
Yes	10.8 (3-18.6)		29.1 (23.7-34.4)	
No	10.2 (3.4-17)		40 (14.8-65.2)	
No of metastatic sites		0.565		0.278
1	12.4 (6.7-18.2)		61.7 (0-127.7)	
> 1	8.9 (6.6-11.3)		27.6 (21.9-33.4)	
Metastasectomy		0.001		0.002
Yes	18.6 (0-NR)		NR	
No	8 (5.4-10.6)		27.6 (20.8-34.4)	

PFS: Progression-free survival; OS: Overall survival; CI: Confidence interval; NR: Not reached.

patients with synchronous peritoneal carcinomatosis was 8.1 mo compared to 12 mo for those with metachronous peritoneal metastasis. This difference was not statistically significant in multivariate analysis, with a hazard ratio of 1.03 (95%CI: 0.83-1.27). Since this was a population-based study, treatment consisted of palliative chemotherapy, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) and best supportive care. The percentage of patients who had CRS-

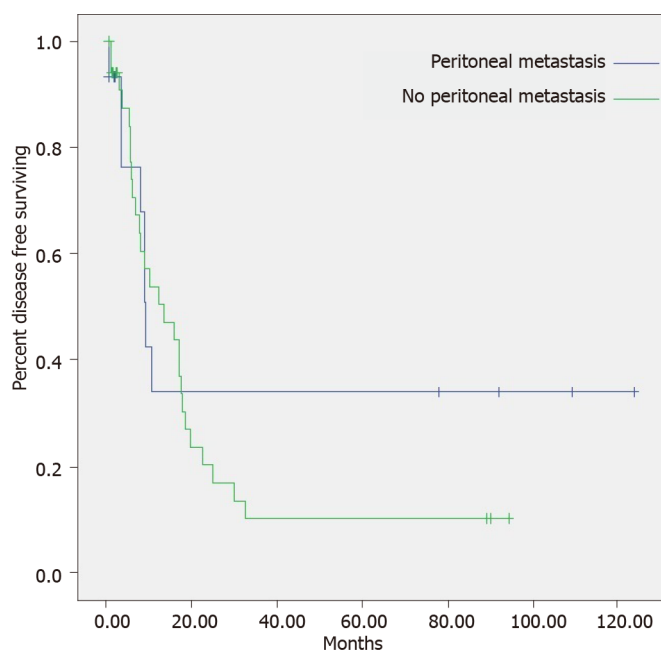


Figure 1 Kaplan–Meier curve for progression-free survival for patients with metastatic colorectal cancer with (blue curve) and without (green curve) peritoneal carcinomatosis ($P = 0.401$).

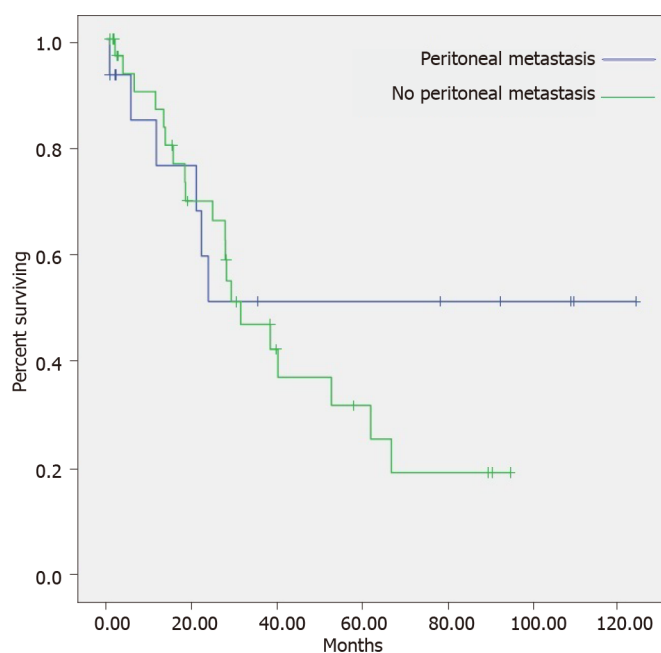


Figure 2 Kaplan–Meier curve for overall survival for patients with metastatic colorectal cancer with (blue curve) and without (green curve) peritoneal carcinomatosis ($P = 0.368$).

HIPEC in the above study was 16% in the metachronous group and 8% in the synchronous group. Palliative chemotherapy was given to 55% and 69% of patients in the metachronous and synchronous groups, respectively.

A more similar cohort to our study was the pooled analysis reported by Franko *et al*[13], wherein they looked at the survival and prognostic significance of patients with peritoneal metastasis *vs* other organ metastasis from two large north central cancer treatment group phase III studies (N9741 and N9841). Since those patients were entered in a prospective clinical trial, all had good performance status from 0 to 1 and expected survival of more than 3 mo with no negative prognostic factors such as ascites or malignant bowel obstruction. All patients were treated with doublet regimens (FOLFOX *vs* IFL *vs* IROX). There was no differential impact of the type of systemic chemotherapy used on the basis of the presence or absence of peritoneal carcinomatosis. Expectedly, peritoneal carcinomatosis in this pooled

Table 3 Multivariate analysis of progression-free survival and overall survival in 51 patients with metastatic colorectal cancer treated with triplet therapy

	PFS		OS	
	HR (95%CI)	P value	HR (95%CI)	P value
Age		0.002		
≥ 65	1 ^a			
< 65	0.22 (0.08-0.57)			
Liver metastasis		0.076		0.003
Yes	1 ^a		1 ^a	
No	0.5 (0.23-1.07)		0.21 (0.07-0.6)	
Metastasectomy		0.001		0.005
Yes	1 ^a		1 ^a	
No	0.23 (0.09-0.57)		0.18 (0.05-0.61)	

^aRepresent the reference group.

PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

analysis had a negative prognostic impact on survival, with a hazard ratio (HR) of 1.316 (95%CI: 1.152-1.504, $P < 0.0001$). Other investigators at an earlier date found no benefit of infusional 5-fluorouracil (5-FU) as opposed to bolus 5-FU in patients treated for CRC with peritoneal metastasis[18].

Our cohort was treated uniformly with the combination of capecitabine, oxaliplatin, irinotecan, and bevacizumab. The PFS was 9.4 mo for patients with no peritoneal metastasis *vs* 13.7 mo in patients with peritoneal carcinomatosis. A difference was not statistically significant in univariate and multivariate analyses. Similarly, OS in our cohort was not reached for patients with peritoneal carcinomatosis compared to 31.3 mo in the no peritoneal metastasis group ($P = 0.0368$, univariate analysis). The median follow-up for the whole group was 89 mo.

Generally, survival in patients with peritoneal carcinomatosis from CRC metastasis has improved with the introduction of CRS-HIPEC. The benefit of CRS-HIPEC has been proven in randomized controlled clinical trials using older chemotherapy regimens (fluoropyrimidine alone)[19]. There are, however, multiple prospective phase II and retrospective studies reporting a 3-year survival of 30% to 60% in patients with isolated peritoneal carcinomatosis treated with CRS-HIPEC[20-24]. In our cohort, the percentage of metastasectomy that could have influenced the efficacy of our therapy was 33.3% in the peritoneal carcinomatosis group *vs* 22.2% in the no peritoneal carcinomatosis group, a difference that did not reach statistical significance. We accordingly believe that surgery played a partial role in the good results seen in the group of peritoneal metastases.

The presence of other site involvement in patients with CRC peritoneal metastasis has been examined by Franko *et al*[14]. A total of 10553 patients treated with systemic therapy in prospective randomized trials were reported by the ARCAD database. Of those, 9178 (87%) had nonperitoneal metastasis, 194 (2%) had isolated peritoneal metastasis, and 1181 (11%) had peritoneal and other organ metastases. Survival was better in the nonperitoneal metastasis group (adjusted HR 0.75, 95%CI: 0.63-0.91, $P = 0.003$). Patients with peritoneal metastasis and one other site had similar survival to those with isolated peritoneal metastasis (adjusted HR 1.10, 95%CI: 0.89-1.37, $P = 0.37$). Two of 14 trials reported in the above pooled analysis used triplet regimens as an investigational arm; however, none of them reported a subgroup analysis based on peritoneal metastasis[11,25]. In our study, the patients with peritoneal metastasis had a higher percentage of more than 1 metastatic site involvement (71.4%) than the nonperitoneal metastasis group (58.1%), a difference that was not statistically significant ($P = 0.39$).

Our study has several limitations, firstly the retrospective nature of the study. Additionally, the small number of patients included makes interpretations of the data difficult. On the other hand, our patient cohort was treated in a prospective phase I/II study with a uniform treatment plan.

CONCLUSION

In conclusion, our data showing equal survival in metastatic CRC patients with peritoneal metastasis *vs* no peritoneal metastasis and the absence of a negative prognostic impact of peritoneal carcinomatosis when patients are treated with a triplet chemotherapy regimen as a first-line therapy is hypothesis-generating. These data need to be confirmed in large prospective studies.

ARTICLE HIGHLIGHTS

Research background

Peritoneal metastasis has been shown to be a poor prognostic factor in metastatic colorectal cancer (CRC). In all published literature citing the above, the patients were treated with either single or doublet first-line chemotherapy. There are no data on the prognostic significance of peritoneal carcinomatosis in patients treated with first-line triplet chemotherapy.

Research motivation

We have shown before that triplet first-line chemotherapy in metastatic CRC overcomes the poor prognosis of right-sidedness. We wanted to examine whether the same applies to peritoneal metastasis in CRC.

Research objectives

We wanted to examine the progression-free survival (PFS) and overall survival (OS) of patients with peritoneal *vs* no peritoneal metastasis treated with first-line triplet chemotherapy and to confirm the lack of a statistically significant difference in the two groups on univariate and multivariate analysis.

Research methods

This was a post hoc analysis of a phase I/II trial evaluating the efficacy and toxicity of triplet chemotherapy in the first-line treatment of metastatic CRC. Patient characteristics, PFS, and OS were examined for the groups with and without peritoneal metastasis. Univariate and multivariate analyses were performed to include other known prognostic factors in metastatic CRC.

Research results

No statistically significant difference was found in the PFS and OS in the group with or without peritoneal metastasis. Peritoneal metastasis was confirmed not to be an independent prognostic factor in patients with metastatic CRC treated with first-line triplet chemotherapy based on multivariate analysis.

Research conclusions

The study suggests that first-line triplet chemotherapy overcomes the poor prognostic significance of patients with metastatic CRC. This needs to be confirmed in large prospective trials.

Research perspectives

Treatment of patients with metastatic CRC should be personalized based on prognostic clinical and molecular factors. The benefit of triplet chemotherapy might outweigh the excess toxicity in certain subgroups, such as those with peritoneal carcinomatosis.

FOOTNOTES

Author contributions: Bazarbashi S contributed to designing the study; Bazarbashi S, Alghabban A and Asefan M contributed to data analysis; Bazarbashi S, Alghabban A, Asefan M, Aljubran AH and Alzahrani A contributed to write the manuscript; Elhassan TA has contributed to the statistical analysis.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board at King Faisal Specialist Hospital and Research Center under the number RAC2081068.

Clinical trial registration statement: This study is registered at <https://clinicaltrials.gov/ct2/show/NCT01311050?term=bazarbashi&draw=2&rank=4>. The registration identification number is: NCT01311050.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors have nothing to disclose.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and since the study is not randomized trial, the CONSORT 2010 statement do not apply.

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Wang JJ

REFERENCES

- 1 Segal NH, Saltz LB. Evolving treatment of advanced colon cancer. *Annu Rev Med* 2009; **60**: 207-219 [PMID: 19630571 DOI: 10.1146/annurev.med.60.041807.132435]
- 2 Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-1417 [PMID: 19339720 DOI: 10.1056/NEJMoa0805019]
- 3 Hurwitz H, Tebbutt NC, Kabbinavar F, Giantonio BJ, Guan ZZ, Mitchell L, Waterkamp D, Tabernero J. Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. *Oncologist* 2013; **18**: 1004-1012 [PMID: 23881988 DOI: 10.1634/theoncologist.2013-0107]
- 4 Grothey A. Medical treatment of advanced colorectal cancer in 2009. *Ther Adv Med Oncol* 2009; **1**: 55-68 [PMID: 21789113 DOI: 10.1177/1758834009343302]
- 5 Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Williams R, Rong A, Wizezorek J, Sidhu R, Patterson SD. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013; **369**: 1023-1034 [PMID: 24024839 DOI: 10.1056/NEJMoa1305275]
- 6 Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, Smith DB, Shepherd S, Maraveyas A, Ferry DR, Meade AM, Thompson L, Griffiths GO, Parmar MK, Stephens RJ; FOCUS Trial Investigators; National Cancer Research Institute Colorectal Clinical Studies Group. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007; **370**: 143-152 [PMID: 17630037 DOI: 10.1016/S0140-6736(07)61087-3]
- 7 Ducreux M, Malka D, Mendiboure J, Etienne PL, Texereau P, Auby D, Rougier P, Gasmi M, Castaing M, Abbas M, Michel P, Gargot D, Azzedine A, Lombard-Bohas C, Geoffroy P, Denis B, Pignon JP, Bedenne L, Bouché O; Fédération Francophone de Cancérologie Digestive (FFCD) 2000-05 Collaborative Group. Sequential vs combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2011; **12**: 1032-1044 [PMID: 21903473 DOI: 10.1016/S1470-2045(11)70199-1]
- 8 Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Loosveldt OJ, van Bochove A, Sinnige HA, Creemers GM, Tesselaar ME, Slee PHTJ, Werter MJ, Mol L, Dalesio O, Punt CJ. Sequential vs combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; **370**: 135-142 [PMID: 17630036 DOI: 10.1016/S0140-6736(07)61086-1]
- 9 Cremolini C, Antoniotti C, Stein A, Bendell J, Gruenberger T, Rossini D, Masi G, Ongaro E, Hurwitz H, Falcone A, Schmolli HJ, Di Maio M. Individual Patient Data Meta-Analysis of FOLFOXIRI Plus Bevacizumab Versus Doublets Plus Bevacizumab as Initial Therapy of Unresectable Metastatic Colorectal Cancer. *J Clin Oncol* 2020; JCO2001225 [PMID: 32816630 DOI: 10.1200/JCO.20.01225]
- 10 Gruenberger T, Bridgewater J, Chau I, García Alfonso P, Rivoire M, Mudan S, Lasserre S, Hermann F, Waterkamp D, Adam R. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol* 2015; **26**: 702-708 [PMID: 25538173 DOI: 10.1093/annonc/mdl580]
- 11 Masi G, Vasile E, Loupakis F, Cupini S, Fornaro L, Baldi G, Salvatore L, Cremolini C, Stasi I, Brunetti I, Fabbri MA, Puglisi M, Trenta P, Granetto C, Chiara S, Fioretto L, Allegrini G, Crinò L, Andreuccetti M, Falcone A. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. *J Natl Cancer Inst* 2011; **103**: 21-30 [PMID: 21123833 DOI: 10.1093/jnci/djq456]
- 12 Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, Mezi S, Tomasello G, Ronzoni M, Zaniboni A, Tonini G, Carlomagno C, Allegrini G, Chiara S, D'Amico M, Granetto C, Cazzaniga M, Boni L, Fontanini G, Falcone A. FOLFOXIRI plus bevacizumab vs FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol* 2015; **16**: 1306-1315 [PMID: 26338525 DOI: 10.1016/S1470-2045(15)00122-9]
- 13 Franko J, Shi Q, Goldman CD, Pockaj BA, Nelson GD, Goldberg RM, Pitot HC, Grothey A, Alberts SR, Sargent DJ. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. *J Clin Oncol* 2012; **30**: 263-267 [PMID: 22162570 DOI: 10.1200/JCO.2011.39.2632]

- 10.1200/JCO.2011.37.1039]
- 14 **Franko J**, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, Saltz L, Punt CJA, Koopman M, Tournigand C, Tebbutt NC, Diaz-Rubio E, Souglakos J, Falcone A, Chibaudel B, Heinemann V, Moen J, De Gramont A, Sargent DJ, Grothey A; Analysis and Research in Cancers of the Digestive System (ARCAD) Group. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol* 2016; **17**: 1709-1719 [PMID: 27743922 DOI: 10.1016/S1470-2045(16)30500-9]
- 15 **Bazarbashi S**, Aljubran A, Alzahrani A, Mohieldin A, Soudy H, Shoukri M. Phase I/II trial of capecitabine, oxaliplatin, and irinotecan in combination with bevacizumab in first line treatment of metastatic colorectal cancer. *Cancer Med* 2015; **4**: 1505-1513 [PMID: 26207614 DOI: 10.1002/cam4.497]
- 16 **Eisenhauer EA**, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]
- 17 **Bakkers C**, Lurvink RJ, Rijken A, Nienhuijs SW, Kok NF, Creemers GJ, Verhoef C, Lemmens VE, van Erning FN, De Hingh IH. Treatment Strategies and Prognosis of Patients With Synchronous or Metachronous Colorectal Peritoneal Metastases: A Population-Based Study. *Ann Surg Oncol* 2021; **28**: 9073-9083 [PMID: 34076807 DOI: 10.1245/s10434-021-10190-z]
- 18 **Folprecht G**, Köhne CH, Lutz MP. Systemic chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Cancer Treat Res* 2007; **134**: 425-440 [PMID: 17633071 DOI: 10.1007/978-0-387-48993-3_28]
- 19 **Verwaal VJ**, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy vs systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008; **15**: 2426-2432 [PMID: 18521686 DOI: 10.1245/s10434-008-9966-2]
- 20 **Lin EK**, Hsieh MC, Chen CH, Lu YJ, Wu SY. Outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer with peritoneal metastasis. *Medicine (Baltimore)* 2016; **95**: e5522 [PMID: 28033247 DOI: 10.1097/MD.0000000000005522]
- 21 **Goéré D**, Malka D, Tzanis D, Gava V, Boige V, Eveno C, Maggiori L, Dumont F, Ducreux M, Elias D. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? *Ann Surg* 2013; **257**: 1065-1071 [PMID: 23299520 DOI: 10.1097/SLA.0b013e31827e9289]
- 22 **Elias D**, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O, Giovannini M, Lasser P. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. *Ann Surg Oncol* 2004; **11**: 518-521 [PMID: 15123461 DOI: 10.1245/ASO.2004.09.008]
- 23 **Elias D**, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, Lorimier G, Dubé P, Glehen O. 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**: 63-68 [PMID: 19917863 DOI: 10.1200/JCO.2009.23.9285]
- 24 **Franko J**. Therapeutic efficacy of systemic therapy for colorectal peritoneal carcinomatosis: Surgeon's perspective. *Pleura Peritoneum* 2018; **3**: 20180102 [PMID: 30911652 DOI: 10.1515/pp-2018-0102]
- 25 **Souglakos J**, Androulakis N, Syrigos K, Polyzos A, Ziras N, Athanasiadis A, Kakolyris S, Tsousis S, Kouroussis Ch, Vamvakas L, Kalykaki A, Samonis G, Mavroudis D, Georgoulas V. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 2006; **94**: 798-805 [PMID: 16508637 DOI: 10.1038/sj.bjc.6603011]



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