Peritoneal Carcinomatosis and Multi-Organ Metastases are Prognostic Factors in Colorectal Cancer: A Retrospective Analysis

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Abstract: *Background*: Peritoneal carcinomatosis and multi-organ metastases might be prognostic factors in patients with advanced colorectal cancer and inoperable metastases at diagnosis.

Methods: A retrospective study was performed to examine the relationship between patient clinical characteristics and prognosis in patients with colorectal cancer and indication for first-line systemic chemotherapy.

Results: One hundred and twelve patients were accrued. According to univariate analysis, peritoneal carcinomatosis, lack of primary tumour resection and multi-organ metastases were associated with poor overall survival. According to multivariate analysis, patients with peritoneal carcinomatosis and patients with multi-organ metastases had a shorter overall survival (12 vs 27.0 months, p<0.001 and 14,6 vs 27 months, p=0.007, respectively).

Conclusions: Our results indicate that presence of peritoneal carcinomatosis and multi-organ metastases are independent predictors of poor outcome for patients with colorectal cancer undergoing first line treatment with standard chemotherapy.

Keywords: Colorectal cancer, prognostic factors, peritoneal carcinomatosis, first line chemotherapy, multi-organ metastases.

INTRODUCTION

Colorectal cancer (CRC) is one of the most frequently observed forms of cancer and one of the principal causes of cancer-related death in Western countries. Approximately 20% of patients present advanced disease the time of diagnosis and 50% of the patients diagnosed at an early stage develop metastasis and die from the disease [1-3]. The standard approach for advanced CRC with inoperable metastasis has been systemic treatment with chemotherapy for over 40 years. First approved agent was 5-fluorouracil (5-FU), which provided response rates (RR) between 10-20% as a single agent [4], followed by combinations with oxaliplatin, that increased both RR and overall survival (OS) [5], and finally with the addition of bevacizumab (Avastin®) a humanized monoclonal antibody that blocks tumour angiogenesis by binding to vascular endothelial growth factor [6-8]. Data from several studies in CRC suggest that the addition of targeted agents, such as bevacizumab, may be even more effective than irinotecan- or oxaliplatin-based chemotherapy alone. Bevacizumab has shown in several randomized clinical trials a clear benefit when it is used in combination with various standard chemotherapy regimens [9-12]. The combined use of XELOX plus bevacizumab provides a median progression free survival (PFS) of 9.4 months and a median OS of 21.3 months [12], and this combination is currently the most commonly used first-line treatment in patients with advanced CRC.

Despite these improvements in modern chemotherapeutic and targeted agents for treating CRC, long-term survival in patients with stage IV CRC is still limited, with most of these patients having a poor 5-year survival rate (<15 %) [13]. Surgery remains an important treatment option for advanced CRC, especially since it offers a curative option for select groups: patients with metastatic disease confined to a

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single organ, patients with a local recurrence only, or patients with limited intra-abdominal disease. In such cases, an aggressive and multimodal management integrating both surgical resection and systemic chemotherapy treatment allows achieving long-term surviving rates of 50% [14]. Different factors may influence the initial resectability status of metastases, such as the size and number of metastases, synchronous/metachronous presentation, tumour marker levels, poor/clear location, and presence/ absence of extrahepatic disease. Unfortunately, in most cases of CRC, treatment is palliative rather than curative, and the main objectives are to increase OS and maintain quality of life for as long as possible.

Surgical approach has been widely studied for liver metastases, but there are less solid data for other locations. From 10 to 25% of the patients who present liver metastasis are eligible for complete primary surgical resection, with a cure rate of about 30%, a 5-year survival of 40-60% and acceptable perioperative morbidity and mortality rates.

From 75 to 90% of patients with metastatic CRC are not candidates for initial complete resection, and in those cases the selected treatment is palliative chemotherapy [15].

Different clinical and pathological characteristics have been proposed as prognostic factors for patients with non resectable CRC undergoing first line systemic chemotherapy, such as the presence of peritoneal carcinomatosis [16], number of metastatic locations, elevated tumoural markers, the presence of KRAS mutations [17] and site of primary tumour [18]. However, to date there is no reliable strategy for predicting the survival of individual patients undergoing chemotherapy. This has led to an increased interest in identifying prognostic factors that could permit more accurate patient stratification. Such prognostic factors would help oncologists and their patients to making treatment decisions, and could be key for better designed and focused clinical trials.

The aim of this study was to identify predicting factors of short-term survival in patients with stage IV CRC treated with first line chemotherapy based in fluoropyrimidine and oxaliplatin chemotherapy with or without bevacizumab.

MATERIAL AND METHODS

This was a multicenter and retrospective study of patients with advanced CRC at time of diagnosis, who had been treated with fluoropyrimidine and oxaliplatin combination chemotherapy regimens (with or without bevacizumab), at four different hospitals in Valencia (Spain). The chemotherapy regimen used, as well as the number of cycles, varied depending on response and patients' profile.

The study was approved by the institution's independent ethics committee and performed in accordance with the Helsinki Declaration of Good Clinical Practices, as well as local ethical and legal requirements. All patients (or relatives) provided written informed consent according to local ethical committee regulations.

Patient Characteristics

The medical records of patients diagnosed with advanced CRC were reviewed. Patients presented histologically confirmed CRC and were treated between January 2010 and December 2013 with a first-line chemotherapy regimen involving FOLFOX or XELOX with or without bevacizumab.

Treatment and Follow-Up

All enrolled patients were treated with fluoropyrimidine and oxaliplatin combination chemotherapy regimens (with or without bevacizumab). A complete review of the medical history was performed, including age, sex, primary tumour location, synchronous or metachronous diagnosis of metastases, presence of symptoms related to the tumour (weight loss, tumour bleeding, or bowel occlusion), comorbidity, Eastern Cooperative Oncology Group performance status, number of organs with metastatic involvement and resection of primary tumour, primary tumor resection, presence of extrahepatic disease and baseline measures of the tumour at baseline. Diagnosis and treatment evaluation were carried out with computed axial tomography, according to RECIST 1.1 criteria. Analytical data was also collected at baseline, including hematologic cell counts, lactate dehydrogenase (LDH) and carcinoembryonic antigen (CEA) levels. Therapy data was also collected (chemotherapy regimen, OR); time to progression disease (PD) and OS.

Treatment toxicity was assessed according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. OS was calculated as the time elapsed from diagnosis to the date of death; PFS as considered as the time elapsed from the start of treatment to the date of PD.

Statistical Analysis

All statistical analyses were performed using the SPSS statistical package version 16. A descriptive statistics analysis, including measures of central tendencies and dispersions of quantitative variables, as well as absolute and relative frequencies for categorical variables, was also carried out. T-test was used to compare two independent samples of continuous variables.

The chi-square test was used to compare two or more independent groups of subjects with respect to a given categorical variable. Univariate Cox proportional-hazards models were used for all potential baseline predictors to compute hazard ratios (HR) and their 95 % confidence intervals (CI), and a multivariate Cox proportional-hazards model to identify independent prognostic factors by multivariate analysis. A P-value of <0.1 was considered to be statistically significant.

RESULTS

Between January 2010 and December 2013, 112 patients with advanced CRC at time of diagnosis were treated with fluoropyrimidine and oxaliplatin combination chemotherapy regimens (XELOX or FOLFOX) with or without bevacizumab. Patient's characteristics are summarized in Table **1**. Median age was 65 years, most patients had a good ECOG-PS 0-1 (79,8%), had been treated with primary tumour resection (55,4%), presented one site of metastases (53,6 %), and received combination treatment with chemotherapy plus bevacizumab (67,6%). Median OS was 23 months and median PFS 12.2 months. Three patients achieved complete response (CR) (2,7%), and 60 patients partial response (PR) (53,6%), with an overall response rate (ORR) of 56,3%. Sixteen patients presented stable disease (SD) and 14 progressed during first line treatment.

An univariate analysis was performed to evaluate the influence of clinical characteristics on OS (Table **2**). Variables that were significantly associated with shorter OS were the presence of PC (HR 1.78, 95% IC 1.6-2.41, p-value 0.001), number of metastases locations (2 or more organs vs 1 organ; HR 2.38, 95% IC 1.21-3.58, p-value 0.007), and absence of primary tumour resection (HR 1.44, 95% IC 0.94-2.75, p-value 0.08). Performance-Status 2 or more, weight-loss over 10%, and lack of bevacizumab showed a not-significant trend to worse prognosis (p-value <0.2). When those patients that had received bevacizumab were analyzed separately it was found that, for patients receiving bevacizumab, high CEA level was also a shorter survival predictor, while PC is the only prognostic factor that achieved statistical significance in our model for patients treated exclusively with chemotherapy. With those factors that presented high or medium significance (ie: Performance Status 2, Weight

Table 1: Clinicopathological Factors

Variable	Total n = 112
Age, years (range)	65 (39-83)
>70 years	46 (40.7%)
<70 years	66 (58.3%)
Sex	
Male	66 (58.9%)
Female	46 (41.1%)
Performance Status	
0-1	87 (79.8%)
2	22 (20,2%)
Tumour related symptoms	
Weight loss >10%	21 (18,6%)
Bleeding	35 (37.6%)
Occlusion	10 (10.9%)
Surgery of Primary Tumour	
Yes	62 (55,4%)
No	50 (44.6%)
Location of Metastases	
Liver	89 (79.5%)
Peritoneum	24 (21,4%)
Lung	32 (28.6%)
Bone	3 (2.7%)
Lymph node	27 (24.1%)
Number of Metastatic Locations	
1	60 (53.6%)
2 or more	52 (46.4%)
Serum Levels	
CEA (high)	76 (80.9%
LDH (high)	32 (49,2%)
Hemoglobine (low)	46 (54,1%)
Grade of differentiation	
1	15 (20%)
2	49 (65,3%)
3	10 (13,3%)
KRAS	
Mutated	42 (37,8%)
Wild-Type	40 (36%)
Unknown	29 (26,1%)
Chemotherapy scheme	
FOLFOX/XELOX	36 (32.3%)
FOLFOX/XELOX-B	76 (67.6%)

Table 2: Univariate Analysis of Factors Associated with Overall Survival in Patients with Stage IV Colorectal Cancer

Variable n= 112	Univariate analysis Hazard Radio 95% CI	Log-Rank test p-value	Significance
Age, years			
<70	1	0.269	NS
> or = 70	1.31 (0.37-1.319)		
Sex			
male	1		NS
Female	1,41 (0.58-1.73)	0,974	
Performance Status			
0-1	1		
2	1.202 (0.85-2.95)	0,142	Doubtful
Tumour related symptoms			
Weight loss >10%	1,77 (0.31-2.87)	0,188	Doubtful
Bleeding	1.624 (0.56-1.85)	0,942	NS
Occlusion	1.891 (0.474-3.7)	0,474	NS
Surgery of Primary Tumour			
Yes	1		
No	1.446 (0.942-2.754)	0,081	Significant
Location of Metastases			
Liver	1.205 (0.58-2.33)	0,662	NS
Peritoneum	1.786 (1.60-2.41)	0,002	Significant
Lung	0.86 (0.35-1.38)	0,160	NS
Lymph node	0.83 (0.38-1.28)	0,250	NS
Number of organs with metastases			
1	1	0,008	Significant
2 or more	2.38 (1.21-3.58)		
Serum Levels			
CEA (high)	1.19 (0.44-1.78)	0,746	NS
LDH (high)	1.50 (0.45-1.74)	0,723	NS
Hemoglobine (low)	1.45 (0.53-1.84)	0,991	NS
KRAS			
Mutated	1.488 (0.59-2.11)	0,726	NS
Bevacizumab treatment			
Yes	1		
No	1.321 (0.83-2.47)	0.189	Doubtful

This table provides the P-value of the statistician log-rank, for all predictive variables tested, and a qualitative evaluation of the result:
1. Significant, if p-value inferior to 0,1.
2. Doubtful if the p-value is superior to 0,1 but lower than 0,2.
3. Not-significant (NS), if p-value> 0,2.
In this study we will use 0.1 as a significance threshold. Although it is more common to use 0.05 instead, this is a convention, and we shouldn't forget that the final purpose is to develop a multivariate model, where some factors can play an important role although they are not strongly significant on their own.

loss>10%, Primary Tumour not operated, Peritoneal Carcinomatosis, 2 or more organs with metastases and Not bevacizumab treatment), we conducted a multivariate Cox analysis, with Enter method (every variable is introduced). The results of this first approach suggest that Peritoneal Carcinomatosis and 2 or more organs with metastases should be the two only variables on the next analysis, which was a new Cox regression with Enter method but with just those two factors. According to multivariate Cox analysis, PC (HR 1.764, 95% CI 1.67-2.60, *P*= 0.017), and multi-organ metastases (HR 1.438, 95% CI 1.13-4.57, *P* = 0.02) were independently associated with short-term OS (Table **3**).

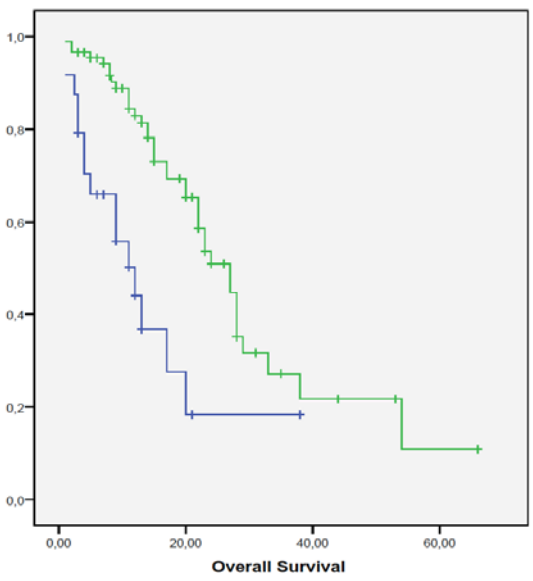
Clinicopathological characteristics of patients by presence of PC and single vs multi-organ metastases are summarized in Table **4**. There were not reached significant differences in age, gender, Performance Status, histology, KRAS mutation status or use of

Table 3: Multivariate Analysis of Factors Associated with Overall Survival in Patients with Stage IV CCR

Variable	Multivariate analysis Hazard Radio, 95% CI	p-value
Performance Status 2	1.202 (0.44-2.2)	0,982
Weight loss >10%	1,787 (0.285-2.07)	0,2
Primary Tumour not operated	1.438 (0.570-2.234)	0,730
Peritoneal Carcinomatosis	1.764 (1.67-2.60)	0,017*
2 or more organs with metastases	1.438 (1.13-4.57)	0,02*
Not bevacizumab treatment	1.326 (0.68-2.49)	0,418

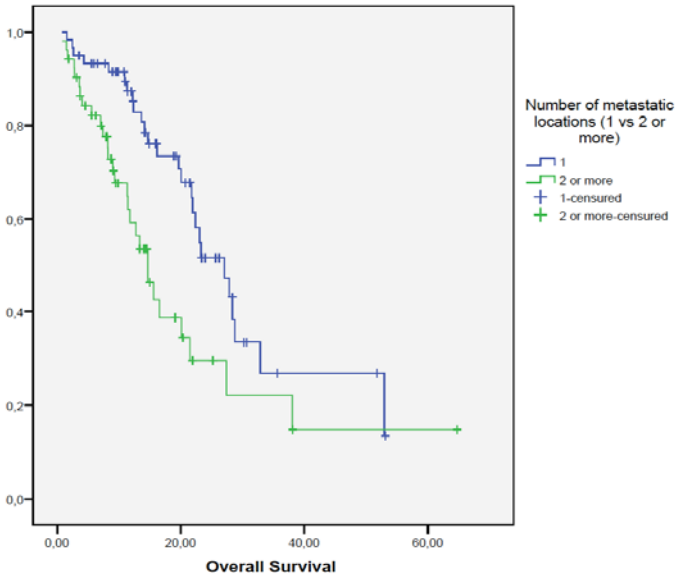
Table 4: Clinico-Pathological Factors by Presence of Peritoneal Carcinomatosis (PC) and Multi vs Single-Organ Metastases

Variable	Peritoneal Carcinomatosis n=24 (%)	Non Peritoneal Carcinomatosis n=88 (%)	P value	Multi-organ metastases n 52 (%)	Single-organ Metastases n = 60 (%)	P value
Age, years (range)	62.3 (39-77)	66.5 (47-83)	0.867	67.5 (39-83)	68 (42-81)	0.827
Sex			0.437			0.327
Male	15 (62,5%)	51 (57.9%)		33 (63.4%)	33 (55%)	
Female	9 (37.5%)	37 (42%)		19 (36.6%)	27 (45%)	
Performance Status			0.067			0.250
0-1	16 (66.6%)	71 (83.5%)		38 (76%)	49 (83%)	
2	8 (33.3%)	14 (16.5%)		12 (24%)	10 (17%)	
Tumour related symptoms						
Weight loss >10%	6 (28.5%)	15 (21,1%)	0.329	12 (29.2%)	9 (17.6%)	0.142
Bleeding	4 (19%)	31 (43%)	0.038*	16 (38%)	19 (37.2)	0.552
Occlussion	1 (4.7%)	9 (12.6%)	0.281	2 (4.8 %)	8 (15.6%)	0.091
Surgery of Primary Tumour			0.462			0.105
Yes	14 (58.3%)	48 (54.5%)		25 (48%)	37 (61.6%)	
No	10 (41.7%)	40 (45.5%)		27 (52%)	23 (38.3%)	
Location of Metastases						
Liver	13 (54.1%)	76 (86.3%)	0.001*	41 (78.8%)	48 (80%)	0.532
Peritoneum				18 (34.6%)	6 (10%)	0.002*
Lung	4 (16.6%)	28 (31.8%)	0.112	29 (55.7%)	3 (5%)	0.001*
Bone	1 (4.1%)	2 (2.2%)	0.519	2 (3.8%)	1 (1.6%)	0.446
Lymph node	11 (45.8%)	16 (18.1%)	0.007*	25 (48%)	2 (3.3%)	0.001*
Number of Metastatic Locations			0.002*			
1	6 (25%)	54 (61.3%)				
2 or more	18 (75%)	34 (38.6%)				
Serum Levels						
CEA (high)	17 (77.2%)	59 (81.9%)	0.417	37 (82.2%)	39 (79.5%)	0.477
LDH (high)	5 (41.6%)	27 (50.9%)	0.398	15 (50%)	17 (48.5%)	0.553
Hemoglobine (low)	9 (45%)	37 (56.9%)	0.248	23 (57.5%)	23 (51.1%)	0.355
Grade of differentiation			0.56			0.254
1	5 (25%)	10 (18.1%)		7 (20.5%)	8 (19.5%)	
2	11 (55%)	38 (69%)		24 (70.5%)	25 (60.9%)	
3	4 (20%)	6 10.9%)		3 8.8%)	8 (19.5%)	
KRAS			0.539			0.568
Mutated	7 (29.1%)	35 (40.2%)		18 (34.6%)	24 (40.6%)	
Wild-Type	9 (37.5%)	31 (35.6%)		18 (34.6%)	22 (37.2%)	
Unknown	8 (33.3%)	21 (24.1%)		16 (27.1%)	13 (22%)	
Chemotherapy scheme			0.344			0.234
FOLFOX/XELOX	15 (62.5%)	61 (69.3%)		19 (36.6%)	17 (28.3%)	
FOLFOX/XELOX-B	9 (37.5%)	27 (30.7%)		33 (63.4%)	42 (71.6%)	



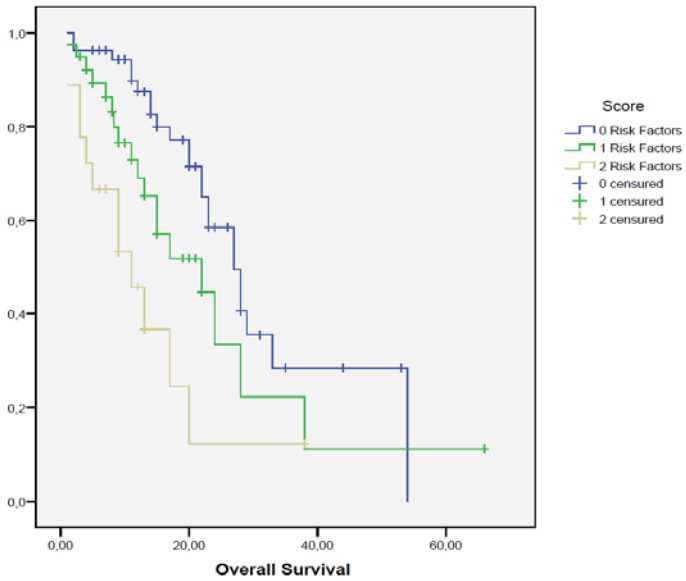
	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	12,964	1	,000

a



	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	7,352	1	,007

b



	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	14,654	2	,001

c

Figure 1: 1a. Kaplan-Meier survival curves according to Peritoneal Carcinomatosis. **1b**. Kaplan-Meier curves according to multi-organ metastases. **1c.** Kaplan-Meier curves according to number of risk factors 0 vs 1 vs 2.

bevacizumab between groups. Twenty-four patients had PC at the moment of diagnosis. Median OS was shorter in patients with PC as compared with those patient without this condition (12 vs 27.0 months, *P*<0.001) (Figure **1a**). Fifty-two patients (46.4%) presented metastases at two or more organs (multi-organ metastases), and they showed a significantly shorter OS compared with those with single-organ metastases (14,6 vs 27 months, *P*=0.007) (Figure **1b**). Median OS for patients who did not present any independent prognostic factor was 27.0 months (score 0), compared with 16.5 months for patients with one (score 1), and 11.4 months for patients with both of them (score 2) (log-rank *P* =0.001). Kaplan-Meier curves for three groups are shown in Figure **1c**.

Twenty-one patients (18%) were candidates for surgical metastasectomy after first line chemotherapy. The rate was significantly higher in patients with single vs multi-organ metastases (29.3 vs 9,7%, *P*=0.009), lower in patients with PC vs those without PC (10.5 vs 22.61, *P*=0.19), and higher in patients without any of those factors, vs patients with one of them, and patients with both (30.1 vs 11.1 vs 7.1%, *P*=0.038). Median OS for patients treated with metastasectomy has not been reached after a median follow up of thirty-six months vs 20 months for rest of patients (*P*<0.001).

DISCUSSION

This retrospective study was designed to identify predictive factors of short-term survival in patients presenting de novo metastatic CRC with no indication for a curative treatment, but receiving optimal chemotherapy with fluoropyrimidine and oxaliplatin with or without bevacizumab. Our results indicate that presence of PC and multi-organ metastases are independent predictors for a worse OS.

Our study, as the studies published to date that explore predictive factors of survival, has a retrospective nature and provides conflicting results. Yun *et al.* published data from a retrospective study involving 503 patients with different stages of CRC that underwent surgery, 376 of whom treated with palliative intention. They found that potential predictors of survival for the palliative operation group were CEA level, tumour differentiation, resection of primary tumour and treatment with chemotherapy; but for 131 patients with asymptomatic incurable disease, only chemotherapy was related to OS [18]. This data can hardly been compared with our results, since they studied a more heterogeneous population, with patients operated with different intentions (curative and palliative). Moreover, not all of them were treated with chemotherapy; what resulted in the only independent factor related with survival in the stage IV incurable population.

More recently, Mijamoto *et al.* published data from 161 patients treated in a single institution with advanced CRC treated with first line systemic chemotherapy. They observed that median OS was higher for patients with single-organ metastases when compared with those with multi-organ metastases (two or more locations), while there was no significant difference between patients with metastases in two versus three or more organs. According to their multivariate analysis, left-sided location of the primary tumour and R0 resection of metastatic lesions were independently associated with good prognosis. In this study patients could have received chemotherapy with 5-fluorouracil, leucovorin with or without oxaliplatin or irinotecan, with or without bevacizumab or anti-epidermal growth factor receptor (EGFR) antibodies, and 34% of them were suitable for metastasectomy after chemotherapy treatment. In their cohort of patients 18% of patients had peritoneal metastases (31% in the group of multi-organ metastases versus 6% in single-organ metastases subpopulation), but this factor was not related with OS in the univariate analysis and was not included in the multivariate analysis. It should be pointed out that 50% of patients did not receive targeted therapies combined with chemotherapy as first-line treatment, what is a lower rate than in our population (76%); and that they did not communicate data from others possible prognostic factors such as CEA serum levels or KRAS mutations that could also play a role in this setting. Again, all this heterogeneity in clinical and pathological characteristics makes very difficult the comparison of the results.

Our study is focused on a more homogeneous cohort of patients, all of them with inoperable metastatic disease at diagnoses, and all of them treated with optimal first line chemotherapy regimens; reported results should be therefore only considered for patients in this situation. Nevertheless, our analysis point out multi-organ metastatic affection as an independent prognostic factor for OS. The difference (14 vs 27 months) is smaller than the reported by Miyamoto *et al.* (19.2 vs 42 months), probably due to the fact that in their cohort of patients 55% with single organ metastases were candidates for R0 metastasectomy vs only 18% in our study. The importance of surgical resection of metastases in stage IV CRC has been widely studied, and nowadays it is considered the gold standard for patients who are candidates for a complete resection of all metastatic sites. Chua *et al.* reviewed the outcomes of 1142 patients with colorectal liver metastases after hepatectomy and extrahepatic disease resection [19, 20] and they found a median OS of 30 months, and median PFS of 12 months, with a 5-year survival rate of patients with R0 hepatectomy of 25%, confirming that this procedure, when feasible, offers the most definitive treatment and achieves the longest survival rates for patients with advanced CRC. All our patients were considered to have inoperable metastases at diagnoses, and proposed for first line palliative

systemic chemotherapy. The aim of our study was to evaluate possible factors to predict patients outcome in this setting, and we decided not to include in the analysis furthers interventions such as surgical metastasectomy or second line chemotherapy treatments that patients might received further in their evolution. It is important to point out that even in patients considered by their clinicians to be inoperable, a considerable percentage (18%) could benefit from a radical treatment after systemic chemotherapy, mostly patients without PC and with single-organ metastases, what has undoubtedly influenced in our results, since this factor appears to be the strongest predictor of survival for patients after treatment.

In the other hand, PC has historically been associated with worse outcomes in terms of OS, PFS and treatment efficacy [21]. In addition, these patients suffer more frequently tumor-related symptoms such as abdominal pain, bowel occlusion and nausea and vomiting [22]. Our results suggest that this is still true in the era of modern therapies, and that in spite of the new chemotherapy regimens and the addition of targeted therapies such as bevacizumab, this factor remains important and predicts worse outcome for patients with advanced CRC. During the last years an important amount of clinical evidence has appeared, showing the role of peritoneal cytoreductive surgery with hyperthermic intraperitoneal chemoperfusion to improve survival of these patients [23,24]. Verwaal *et al.* [25] published data from a prospective randomized study were 105 patients were assigned to a systemic chemotherapy treatment with or without peritoneal cytoreduction surgery; they observed a significant difference in OS favouring the surgery arm (21.6 vs 12.6 months). Though it is true that this study was realized with suboptimal chemotherapy regimen, and before the incorporation of monoclonal antibodies targeting angiogenesis or the EGFR, we think that peritoneal cytoreductive surgery must be considered as an important option to improve outcomes in patients with PC, and must be integrated in the managing of the disease, as complementary procedure to systemic treatments.

In summary, these findings suggest that presence of PC and multi-organ metastases at the moment of advance inoperable CRC diagnosis, are independently related with worse OS, and they predict as well a lower probability of making the patient candidate for metastatectomy after systemic treatment. Further efforts should be made to study the associations between prognostic factors and CRC biology behaviour.

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INFORMED CONSENT

An informed consent form was reviewed and signed by every patient in order to publish information from clinical history.

Research Involving Human Participants and/or Animals

The research was carried out according to the principles set out in the Declaration of Helsinki 1964 and all subsequent revisions, informed consent was obtained, and the ethic committee approved the study.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

All authors certify that there is not any conflict of interest to be disclosed.

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