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▶ **To cite this version:**

Thibault Mazard, Eric Assénat, Marie Dupuy, Caroline Mollevi, Amandine René, et al.. Quantitative evaluation of liver metastases density on computed tomography: A new tool to evaluate early response to bevacizumab-containing chemotherapy. Digestive and Liver Disease, 2019, 51 (8), pp.1185-1191. 10.1016/j.dld.2019.03.028 . hal-02452602

HAL Id: hal-02452602
https://hal.umontpellier.fr/hal-02452602v1

Submitted on 25 Oct 2021

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Manuscript_c4ae85fa35305a2e8ffbef2fbd0cca4a

Quantitative evaluation of liver metastases density on computed tomography: a new tool to evaluate early response to bevacizumab-containing chemotherapy

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Funding: This study was supported by a grant from Roche and CHU Montpellier-Nîmes, France.

Word count: 2895 words

ABSTRACT

Background: Response Evaluation Criteria In Solid Tumors (RECIST) are used to assess tumour shrinkage after cytotoxic chemotherapy, but may be inadequate for efficacy evaluation of anti-angiogenic therapies.

Aims: This study aimed to identify novel radiologic tumour response criteria based on early changes in tumour size and density, observed on computed tomography (CT), in patients with colorectal liver metastases (CRLM) treated with bevacizumab-containing chemotherapy.

Methods: CT of 71 and 68 CRLM patients treated with bevacizumab and non-bevacizumab-based regimens, respectively, were retrospectively reviewed. Tumour size, tumour density, and tumour-to-liver density (TTLD) ratio were determined at baseline and at first restaging. We tested their correlation with progression-free (PFS) and overall survival (OS) using the log-rank test.

Results: In the bevacizumab group, neither RECIST response nor tumour density variation was correlated with PFS or OS. In contrast, PFS and OS were significantly longer in patients with tumour size reduction ≥15% (RECIST-$_{15\%}$) and/or decrease in TTLD ratio not exceeding -10% (TTLD-$_{10\%}$) than in patients who didn't reach any of those criteria, in univariate and multivariate analysis.
Only size-response criteria predicted clinical outcome in the non-bevacizumab group.

Conclusions: This study highlights new quantitative CT criteria that may early predict the efficacy of bevacizumab in CRLM patients.

Keywords: Bevacizumab; Contrast-enhanced computed tomography; Metastatic colorectal cancer; Tumour-to-liver density

1. Introduction

Bevacizumab is a humanised monoclonal antibody targeting the vascular endothelial growth factor (VEGF). By inhibiting its function on vascular endothelial cells, it blocks the angiogenesis of solid tumours needed for tumour growth, activating invasion and metastasis. The addition of bevacizumab to fluoropyrimidine-based chemotherapy, with irinotecan or oxaliplatin, as first- and second-line treatment for metastatic colorectal cancer (mCRC) significantly increased the median progression-free survival (PFS) in randomised controlled trials [1–3].

However, the absence of predictive biomarkers prevents the early identification of patients who will most likely benefit from bevacizumab therapy. Moreover, standard Response Evaluation Criteria in Solid Tumors (RECIST) based on long-axis measurements on axial computed tomography (CT) may be inadequate while assessing the efficacy of bevacizumab in each individual patient [4]. Indeed, bevacizumab-based regimen can induce morphological tumour changes without significant modification in their sizes. They have been well described by Chun et al. [5] in a cohort of patients with colorectal liver metastases (CRLM) before surgical resection and are characterised by a progressive transformation in lesions with homogeneous overall attenuation and sharp tumour-liver interface. In this study and a subsequent one [6], they reported that patients with those optimal changes exhibited better pathologic responses and outcomes, whereas RECIST responders did not. However, concerns arise about the inter-site reproducibility and transferability of such qualitative and therefore subjective criteria.

Tumour density variation measurement may represent an objective mean to consider intratumoural modifications in response to anti-angiogenic therapies. In metastatic gastro-intestinal tumour (GIST), where RECIST criteria also significantly underestimated the response to imatinib, Choi et al. developed new CT evaluation criteria measuring CT attenuation coefficient that provide a good correlation with outcome [7].

Several studies also suggest the relevance of using alternative methods of categorising changes in size to early discriminate on-treatment good versus poor responders. Early tumour shrinkage (ETS), using 20% reduction in the sum of the longest diameters of target lesions as a cut-off on the first CT scan restaging, is a good predictor of long-term outcomes in mCRC patients treated with cytotoxic chemotherapy alone or combined with cetuximab [8,9]. Cremolini et al. [10] showed similar correlations in patients treated with bevacizumab-based regimen.

In this context, this study aimed to further investigate the prognostic values of alternative CT-based quantitative assessment of early tumour response (size and density) in mCRC patients treated with a bevacizumab-containing regimen and in a similar population receiving regimens without anti-angiogenic therapies.

2. Materials and Methods

2.1 Study design

We conducted a retrospective study reviewing the contrast-enhanced CT (CECT) images of a prospectively accrued cohort of patients with unresectable CRLM treated with a first-line therapy in three French multicentre clinical trials.

This work was performed in collaboration with the UNICANCER group and was approved by our institutional review board.

Written informed consent was obtained from each patient before joining the main study.

2.2 Patient selection

To be included in this study, patients had to have at least one liver metastasis larger than 1.5 cm, a baseline CT evaluation and a restaging CT study of sufficient quality to allow scoring of density response. Images acquisition needs to be obtained after intravenous contrast injection during the

portal venous phase with a slice thickness less than 3 mm. The quality of contrast enhancement was assessed by analyzing attenuation of portal and hepatic veins. All CECT with a density of less than 100 Hounsfield Unit (HU) were excluded from analysis.

Bevacizumab group

Patients were selected from a randomised non-comparative Phase II trial (ACCORD 13 trial, NCT00423696) evaluating the efficacy and safety of bevacizumab in combination with XELIRI or FOLFIRI as first-line therapy [11]. Amongst the 145 patients enrolled in this trial, data from 71 patients were used in the present study. Reasons for exclusion from the analysis are detailed in Fig. 1.

Non-bevacizumab group

The non-bevacizumab group included 21 out of the 42 patients enrolled in the ERBIRINOX trial (NCT00556413) and 47 out of the 122 patients enrolled in the METHEP trial (NCT00208260) [12,13]. They were all treated according to different chemotherapy regimens without bevacizumab. Reasons for exclusion from the analysis are detailed in Fig. 1.

2.3 Image analysis

All the CT scans used in this study were anonymised. Liver target lesions were chosen on the pre-treatment CT scan by a senior abdominal radiologist. He manually measured their long-axis diameters according to RECIST 1.1 criteria. Volumetric segmentations of the tumour were then performed using semi-automated edge detection software (Myrian®, Intrasense, Montpellier, France) by the same radiologist. Tumour edges were adjusted until satisfactory three-dimensional selection of a target lesion was obtained, and tumour mean volumetric attenuations were measured. The software also automatically segmented healthy liver, excluding the metastases and liver vessels, to calculate its

mean density. To compensate the intra- and inter-individual heterogeneity in liver contrast enhancement, the tumour-to-liver density (TTLD) ratio was determined, that is, the mean tumour density divided by the mean healthy liver density. Same analyses were repeated on the first CT restaging, 2 weeks after the CT baseline review, and this was performed in a random order. The radiologist was not informed about the patients' clinical data and patients' baseline CT examination results.

2.4 Statistical analysis

Imaging parameters were dichotomised to ensure the best discrimination between patients with late (time until progression > 10 months) and early disease progression (time until progression ≤ 10 months). Using the receiving operator characteristic (ROC) curve methodology, optimal threshold values were calculated to maximise Youden's index.

Data were categorised according to frequency values for categorical variables and median and range values for continuous variables.

The primary endpoint for this study was PFS, calculated from the baseline CT scan date to disease progression or death from any cause. Patients who were alive without disease progression were censored at the date of last contact. Overall survival (OS) was the secondary endpoint and was calculated from same start point to death from any cause. Survival rates were estimated using the Kaplan–Meier method.

In univariate analysis, the log-rank test was used to identify the prognostic variables. Significant clinical and imaging parameters for PFS in a univariate analysis ($p < 0.10$) were included in a multivariate Cox proportional hazards model. A weight, proportional to the coefficient of the Cox model, was attributed for each significant variable and then added to obtain an overall score. The

number of prognostic score modalities was reduced by regrouping non-significant adjacent categories. Finally, the obtained prognostic score was evaluated in the non-bevacizumab population.

3. Results

3.1 Patient and responses

Bevacizumab group

The analysed sample did not significantly differ from the whole clinical trial population (ACCORD 13 trial) in terms of age, sex, and PFS and OS (data not shown). Patient characteristics are detailed in Table 1.

Median time from pretreatment to first restaging CT scan was 2.1 months (range, 1–3.4 months). The pretreatment mean density of target lesions ranged from 32.4 to 107.02 HU with a median of 64.05 HU. At first restaging, the mean tumor density ranged from 30.5 to 111.16 HU with a median of 55.05 HU. The median mean healthy liver attenuation at baseline and at first restaging, was 105.69 HU and 98.45 HU, respectively (Supplementary table).

According to RECIST 1.1 criteria, 26.8%, 71.8%, and 1.4% of patients presented with a partial response (PR), stable disease (SD), and progression disease (PD), respectively, at first restaging. The median tumour density was reduced by 11.3% (range, -62.7 – +39.8%) and the TTLD ratio by 5.7% (range -38.0 – +43.4%). With a median follow-up of 34.1 months (range, 2.8–47.5 months), median PFS and OS were 9.6 months (95%CI: 9.1–10.1 months) and 22.1 months (95%CI: 20.2–24.8 months), respectively.

Non-bevacizumab group

Median time from pretreatment to first restaging CT assessments was 2.0 months (range, 1.6–3.2 months).

The pretreatment mean density of target lesions ranged from 43.2 to 117.3 HU with a median of 76.73 HU. At first restaging, the mean tumor density ranged from 43.2 to 113.4 HU with a median of 76.07 HU. The median mean healthy liver attenuation at baseline and at first restaging, was 111.63 HU and 106.79 HU, respectively (Supplementary table).

According to RECIST 1.1 criteria, 48.5%, 50.0%, and 1.5% of the patients exhibited a PR, SD, and PD, respectively, at first restaging. The median tumour density was reduced by 1.1% (range -37.7 – +48.3%), and the TTLD ratio increased by 3.1% (range, –40.9 – +54.4%). With a median follow-up of 45.4 months (range, 3.5–67.8 months), median PFS and OS were 11.8 months (95% CI, 10.5–16.7 months) and 48.8 months (95% CI, 27 months–not reached), respectively.

3.2 Association between radiologic parameters and outcomes

Bevacizumab group

Optimal ROC-determined cut-off points were -15% for RECIST 1.1 measurements (RECIST$_{-15\%}$), 0% for tumour variation density, and -10% for TTLD (TTLD$_{-10\%}$) ratio.

On univariate analysis, measurements according to these RECIST$_{-15\%}$ and TTLD$_{-10\%}$ thresholds were significantly associated with both PFS and OS (Table 2). Size response measurements according to standard RECIST threshold (-30%), ETS threshold (-20%), and tumour variation density according to 0% threshold were not significantly correlated with survival.

The multivariate Cox regression confirmed that RECIST$_{-15\%}$ and TTLD$_{-10\%}$ are strong independent prognostic factors. RECIST$_{-15\%}$ responders (measurements < threshold) had significantly longer PFS (HR, 0.46; 95% CI, 0.27–0.80; p=0.007) and OS (HR, 0.46; 95% CI, 0.26–0.82; p=0.010) than RECIST$_{-15\%}$ non-responders (measurements ≥ threshold). Similarly, PFS and OS in TTLD$_{-10\%}$ responders (measurements ≥ threshold) was significantly greater (HR, 0.44; 95% CI, 0.26–0.76;

p=0.003 and HR, 0.48; 95% CI, 0.27–0.84; p=0.012, respectively) as compared to $TTLD_{-10\%}$ non-responders (measurements < threshold) (Table 3).

Non-bevacizumab group

Patients with size response according to RECIST 1.1 criteria had longer PFS and OS. Size response according to a lower threshold (-15% and -20%) was only significantly correlated to OS. None of the tumour density variation criteria could predict outcomes in this group (Table 2 and Table 3).

3.3 Development of a prognostic score for bevacizumab-treated patients

The variables used to derive the prognostic scores were determined using multivariate analysis. We combined the two relevant factors, $RECIST_{-15\%}$ and $TTLD_{-10\%}$ thresholds, into a single prognostic index with values of 0 and 1 (Table 4). The index sums provided an overall score with values ranging from 0 to 2. We subsequently defined two prognostic classes by grouping together populations of poor and intermediate prognosis (PIP= scores 1 and 2) versus good prognosis (GP= score 0).

In the bevacizumab group, patients classified in the GP group had a significantly better PFS (10.3 months; 95% CI, 9.4–11.3 months) and OS (30.7 months; 95% CI, 21.9 months–not reached) than those classified in the PIP group (9.1 months; 95% CI, 8.0–9.8 months and 20.4 months; 95% CI, 14.9–22.2 months for PFS and OS, respectively) (Table 4).

In the non-bevacizumab group, the prognostic score was neither correlated with PFS (p=0.89) nor with OS (p=0.27). Kaplan–Meier survival curves by prognostic category are shown in Fig. 2.

4. Discussion

We report new radiologic response criteria that combine measurements of tumour size and density ratio variations on bevacizumab-containing chemotherapy in CRLM patients. Using ROC-

determined cut-off points, we established 15% decrease in the maximum diameters of target lesions according to RECIST 1.1 criteria (RECIST$_{-15\%}$) and 10% decrease in TTLD ratio (TTLD$_{-10\%}$) at the first restaging CT scan as optimal thresholds to predict long-term outcomes. Indeed, patients with a tumour size reduction superior or equal to 15% and a decrease in TTLD ratio not exceeding -10% had longer PFS and OS compared to the ones who had no tumour reduction. Moreover, that correlation was only noticed in the bevacizumab group, suggesting a better ability of those criteria to identify bevacizumab-specific anti-tumour effect.

This study illustrates again an inadequacy of conventional RECIST-defined response to early identify anti-angiogenic-based treatment responders. That can be partly corrected by the use of a smaller cut-off value size reduction than the traditional 30%. Before this study, several studies have shown that reaching a tumour shrinkage greater than or equal to ≥ 15-20% at first restaging was correlated with improved PFS and OS in first-line anti-angiogenic plus chemotherapy-treated patients [10,14,15].

In order to circumvent size measurement shortcomings, CECT can also provide other non-invasive quantitative parameters to more specifically characterise and quantify the effect of bevacizumab on tumour angiogenesis. Indeed, effective inhibition of that process must logically lead to changes in tumour perfusion, blood volume, and capillary permeability, resulting in post-contrast attenuation (or density) changes that can be sequentially measured on CT follow-up [16]. Additionally, reduction in tumour density has already been shown to be an additional indicator of early response to anti-angiogenic therapy in a variety of non-colorectal tumours. The first illustration was obtained by Choi et al. in patients with GIST treated with imatinib, where a decrease greater than or equal to 15% of mean tumour density on first restaging of CECT could identify patients with more favourable outcomes [7]. An early decrease in tumour attenuation, alone or in combination with size and/or morphologic criteria, was also found to be correlated with survival outcomes in patients with metastatic renal cell carcinoma treated with anti-angiogenic targeted therapy [17]. In colorectal cancer,

a retrospective study carried out by Chung et al. demonstrated that in 59 patients with liver metastases, evaluating treatment response at 2 months, with tumour size and density changes on CT, was a better predictor of time to tumour progression than changes in tumour size or density alone in two populations treated or not with bevacizumab [18]. In our study, reduction in tumour density was more pronounced in the bevacizumab group than in the non-bevacizumab group. Nevertheless, regardless of the applied threshold, we could not correlate that reduction with survival outcomes because absolute tumour density may have been influenced by variations in scanning parameters such as time of slice acquisition, dose and flow rate of injected iodinated contrast media from one CT examination to another one. As a result, we decided to normalise tumour density by the surrounding liver tissue density and called it TTLD assessment. Surprisingly, bevacizumab improved the survival outcomes in patients whose on-treatment ratio at 2 months did not decrease more than 10%, that is, in patients with the maintenance of a certain degree of tumour enhancement and hence a certain degree of tumour blood supply compared to the healthy liver. This finding supports the vasculature 'normalization' hypothesis developed by Jain et al. [19] to explain the anti-tumour effect of anti-vascular agents. Indeed, he argues that rather than inducing tumour vessel regression to starve the tumour, they were effective by correcting tumour vascular abnormalities thereby alleviating tumour hypoxia, facilitating tumour delivery of associated cytotoxic drugs, or reprogramming the immunosuppressive tumour micro-environment to an immunosupportive one.

Through this ratio, we also investigate the potential impact of surrounding healthy liver modifications under anti-angiogenic treatment on the whole treatment anti-tumour effect. In patients treated for liver metastases from neuroendocrine tumours, bevacizumab did not modify the perfusion parameters in normal liver tissue [20]. However, it was also found that bevacizumab attenuated hepatic fibrosis in rats [21] and could protect against the occurrence of sinusoidal obstruction syndrome [22], thereby perhaps facilitating tumour drug access.

Over the past few years, other alternative radiologic criteria have been studied to address issues encountered with the efficacy assessment of anti-angiogenic therapies. We recently confirmed that MD Anderson morphologic criteria were able to early predict PFS in patients with unresectable CRLM treated with bevacizumab-containing chemotherapy and offered to add their evaluation to the established RECIST criteria [23]. Functional imaging has also the potential to give a greater insight of early changes of the vascular network in response to anti-VEGF pathway therapies. Contrast-enhanced liver ultrasound has been the most studied modality in metastatic colorectal patients receiving first-line bevacizumab-based treatment. Several haemodynamic parameters were found to correlate with response and/or survival rates, but, most of the time, only in a small sample of patients and with the lack of control group without anti-angiogenic therapies [24–26].

Furthermore, a major obstacle to the widespread use of those techniques is their reproducibility. Our method, although dependent on imaging quality, has the advantages of being easily and quickly applied, even by a non-radiologist physician, and the software used ensures continued accuracy and reduces inter-observer variability. Those different methods should actually be seen as complementary rather than competing, and a joint cross-validation study should be performed to optimise both approaches.

Even though data were prospectively collected, limitations of our study were as follows: its retrospective nature and the heterogeneity of the non-bevacizumab control group. The quality of CT images was also not homogeneous amongst the study cohorts, and because of the low quality of some CT scan images, we had to exclude many CT scans from the analysis. Another limitation is the lack of data exploring the correlation between our radiologic response criteria and pathological response that has consistently been found as a strong predictor of survival in patients with CRLM that was resected after chemotherapy [27–29]. Moreover, the coarse assessment performed by the software is not able to capture some pathological features described as predictive of patient outcomes in a context of

bevacizumab-based treatment as the residual tumour thickness at the interface between the tumour and the non-neoplastic liver or the growth patterns (replacement/pushing/desmoplastic histopathologic growth pattern) also defined from pathological characteristics noticed at this interface [30,31].

In conclusion, we report new quantitative radiologic parameters able to early identify patients with a more favourable outcome in a liver metastatic colorectal population treated with bevacizumab. Further validation in other cohorts is underway.

Acknowledgments

The study was partly funded by a grant from Roche laboratory and Montpellier Universitary

Hospital.

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Figure legends

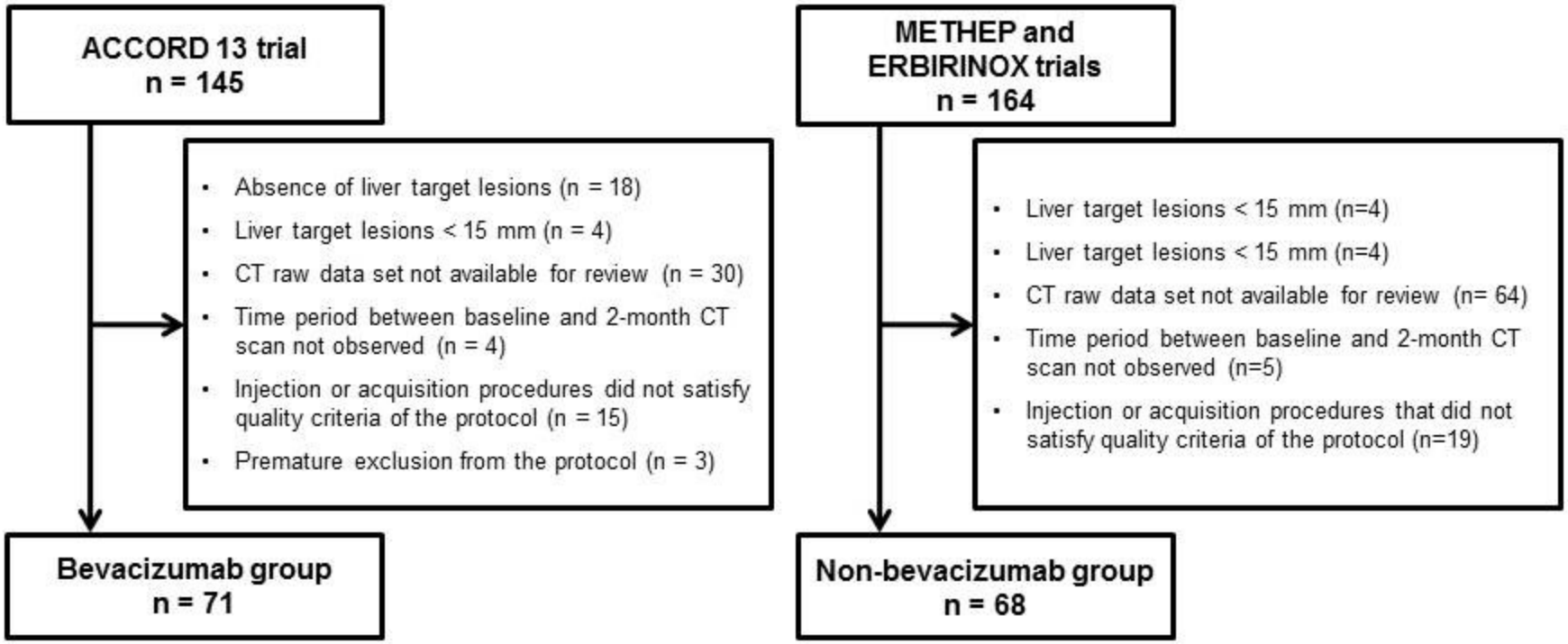
Figure 1. Study flowchart

ACCORD 13 Actions Concertées dans les Cancers COloRectaux et Digestifs n°13 – *Concerted Actions in COlorectal and Digestive Cancers* n°13 (NCT00423696), *CT* computed tomography, *ERBIRINOX* ERBitux IRINotecan OXaliplatin (NCT00556413), *METHEP* METastases HEPatic (NCT00208260).

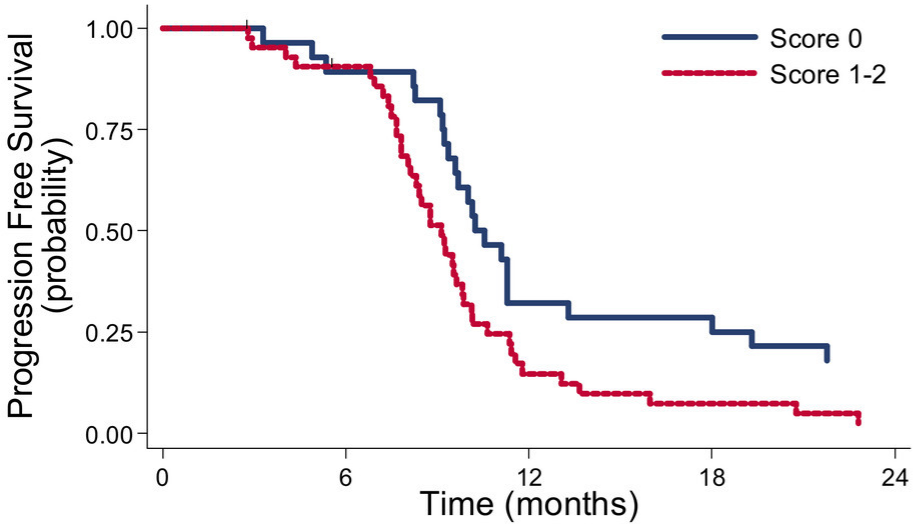
Figure 2. Kaplan–Meier survival curves according to the prognostic score category in the bevacizumab (A + B) and the non-bevacizumab (C + D) groups

Prognostic scores according to RECIST (-15% threshold) and tumour-to-liver density (-10% threshold) ratio variations at first restaging compared to baseline measurement: score 0=good prognosis, score 1=intermediate prognosis, score 2=poor prognosis

Abbreviations: *OS* overall survival, *PFS* progression-free survival

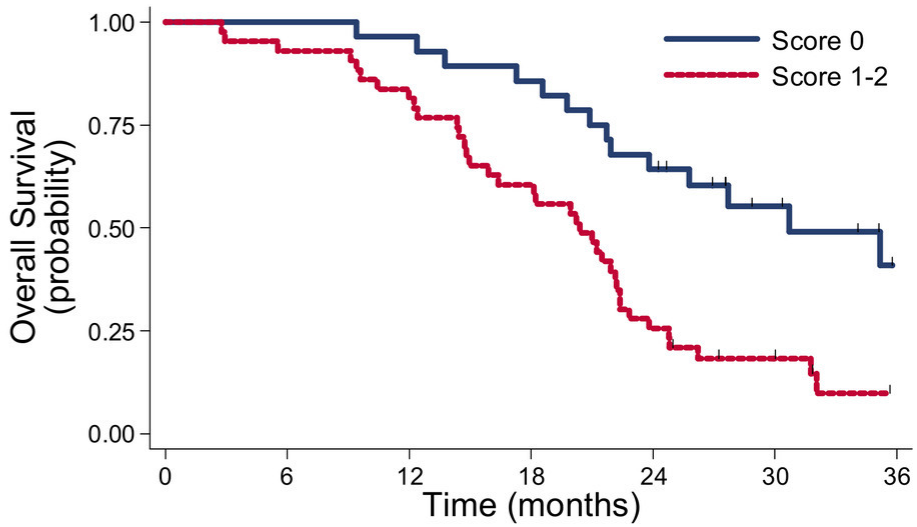

ACCORD 13 trial
n = 145
Absence of liver target lesions (n = 18)
Liver target lesions < 15 mm (n = 4)
CT raw data set not available for review (n = 30)
Time period between baseline and 2-month CT scan not observed (n = 4)
Injection or acquisition procedures did not satisfy quality criteria of the protocol (n = 15)
Premature exclusion from the protocol (n = 3)
Bevacizumab group
n = 71
METHEP and
ERBIRINOX trials
n = 164
Liver target lesions < 15 mm (n=4)
Liver target lesions < 15 mm (n=4)
CT raw data set not available for review (n= 64)
Time period between baseline and 2-month CT scan not observed (n=5)
Injection or acquisition procedures that did not satisfy quality criteria of the protocol (n=19)
Non-bevacizumab group
n = 68

A: PFS in the bevacizumab group



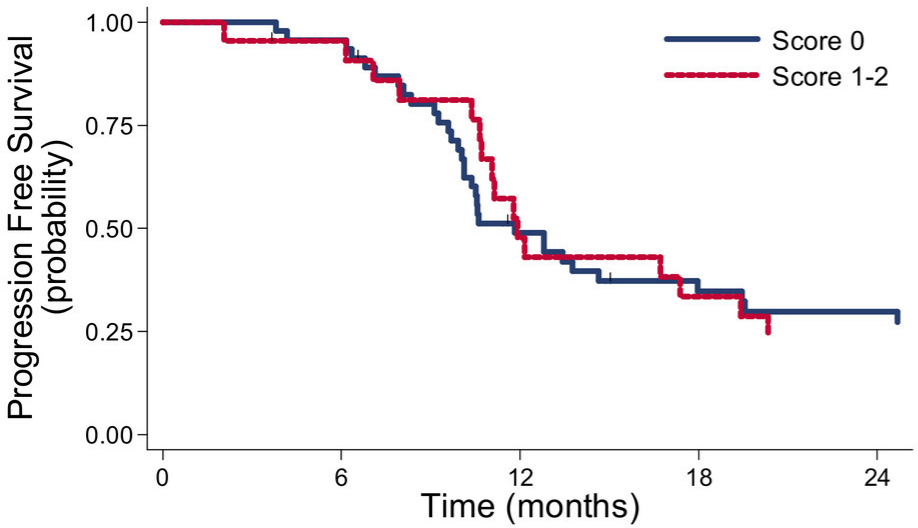
No. at risk					
Score 0	28	25	9	8	5
Score 1-2	43	37	6	3	1

B: OS in the bevacizumab group



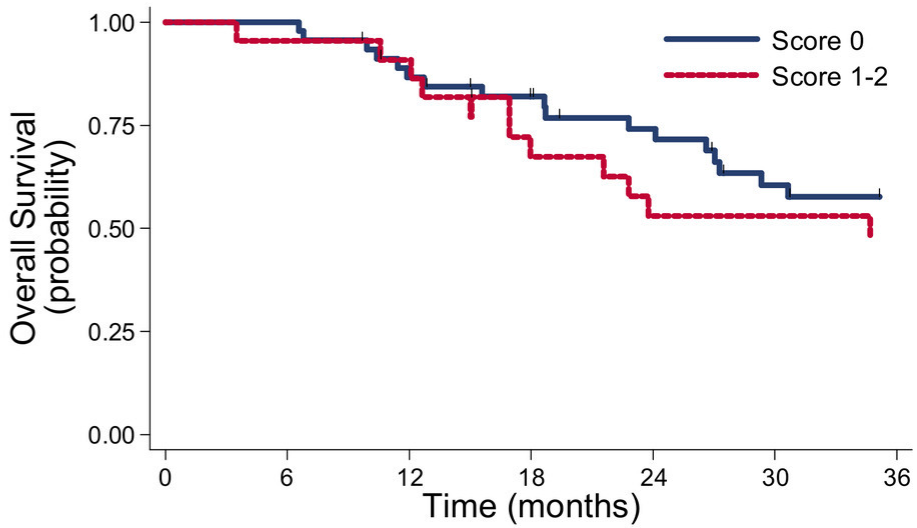
No. at risk							
Score 0	28	28	27	24	18	10	4
Score 1-2	43	40	35	26	11	6	1

C: PFS in the non-bevacizumab group



No. at risk					
Score 0	46	44	21	14	12
Score 1-2	22	20	10	7	5

D: OS in the non-bevacizumab group



No. at risk							
Score 0	46	46	38	33	28	21	18
Score 1-2	22	21	20	14	11	11	10

Table 1

Patient demographics and tumour characteristics

	BEV group (*N*=71)	**Non-BEV group** (*N*=68)
	N (%)	*N* (%)
Age (years), median [range]	62.0 [39–75]	60.5 [32–81]
< 60	28 (39)	31 (45)
[60–69]	27 (38)	29 (43)
[70–81]	16 (23)	8 (12)
Males	34 (48)	30 (44)
ECOG performance status		
0	38 (54)	49 (73)
1	28 (39)	18 (27)
2	5 (7)	– –
Missing		1
Number of metastatic sites		
1	30 (42)	49 (72)
2	33 (47)	11 (16)
≥ 3	8 (11)	8 (12)
Localisation of the primary tumour		
Right side	22 (31)	21 (31)
Left side	45 (63)	44 (65)
Transverse	4 (6)	3 (4)
Chemotherapy regimen		
FOLFIRI with bevacizumab	44 (62)	– –
XELIRI + bevacizumab	27 (38)	– –
FOLFIRI standard	– –	5 (7)
FOLFIRI high dose	– –	13 (19)
FOLFOX 4	– –	5 (7)
FOLFOX 7	– –	7 (11)
FOLFIRINOX	– –	17 (25)
FOLFIRINOX with cetuximab	– –	21 (31)

Abbreviations: *BEV* bevacizumab, *ECOG* Eastern Cooperative Oncology Group, *FOLFIRI* folinic acid + 5-fluorouracile + irinotecan, *FOLFIRINOX* folinic acid + 5-fluorouracile + irinotecan + oxaliplatin, *FOLFOX* folinic acid + 5-fluorouracile + oxaliplatin, *XELIRI* capecitabine + irinotecan

Table 2

Univariate analysis for PFS and OS

	BEV group (*N*=71)		**Non-BEV group (*N*=68)**	
	PFS	OS	PFS	OS
	No. of events		No. of events	
Age, years				
< 60	26/28	19/28	24/31	15/31
[60–69]	25/27	19/27	21/29	14/29
[70–81]	15/16	13/16	4/8	4/8
p value	*.056*	*.086*	*.464*	*.954*
ECOG performance status				
0	34/38	25/38	35/49	24/49
1	27/28	21/28	14/18	9/18
2	5/5	5/5	–	–
p value	*.075*	*.414*	*.822*	*.661*
RECIST$_{-30\%}$				
< -30%	18/19	11/19	19/33	12/33
≥ -30%	48/52	40/52	30/35	21/35
p value	*.949*	*.262*	*.032**	*.020**
RECIST$_{-15\%}$				
< -15%	44/47	30/47	38/56	24/56
≥ -15%	22/24	21/24	11/12	9/12
p value	*.028**	*.009**	*.120*	*.040**
RECIST$_{-20\%}$				
< -20%	36/38	25/38	36/53	22/53
≥ -20%	30/33	26/33	13/15	11/15
p value	*.727*	*.265*	*.262*	*.030**
Tumour density variation$_{0\%}$				
< 0%	56/57	43/57	24/36	18/36
≥ 0%	10/14	8/14	26/32	15/32
p value	*.095*	*.289*	*.357*	*.880*
Tumour density variation$_{-10\%}$				
< -10%	39/40	32/40	14/20	11/20
≥ -10%	27/31	19/31	35/48	22/48
p value	*.099*	*.563*	*.588*	*.635*
Tumour density variation$_{-15\%}$				
< -15%	26/27	24/27	4/13	7/13
≥ -15%	40/44	27/44	41/55	26/55
p value	*.196*	*.163*	*.359*	*.802*
TTLD$_{-10\%}$				
< -10%	27/28	24/28	8/12	6/12
≥ -10%	39/43	27/43	41/56	27/56
p value	*.013**	*.012**	*.330*	*.977*

Abbreviations: *BEV* bevacizumab, *CR* complete response, *ECOG* Eastern Cooperative Oncology Group, *PFS* progression-free survival, *OS* overall survival, *PD* progressive disease, *PR* partial response, *TTLD* tumour-to-liver density

* $p \leq 0.05$

Table 3

Multivariate Cox regression analysis of relevant parameters (hazard ratios)

	BEV group (*N*=71)		**Non-BEV group (*N*=68)**	
	PFS	OS	PFS	OS
RECIST$_{-15\%}$				
< -15%	1 –	1 –	1 –	1 –
≥ -15%	2.15 (1.25–3.70)	2.67 (1.40–5.09)	1.69 (0.86–3.34)	2.22 (1.02–4.87)
p value	*0.007**	*0.010**	*0.325*	*0.915*
TTLD$_{-10\%}$				
≥ -10%	1 –	1 –	1 –	1 –
< -10%	2.25 (1.32-3.84)	4.14 (1.69-10.10)	0.69 (0.32–1.48)	1.05 (0.43–2.55)
p value	*0.003**	*0.012**	*0.148*	*0.059*

Data in parentheses are 95% confidence intervals. Abbreviations: *BEV* bevacizumab, *CI* confidence interval, *PFS* progression-free survival, *OS* overall survival, *TTLD* tumour-to-liver density

* *p value* ≤ 0.05

Table 4

Prognostic score

Score points	Variable	
	RECIST-15%	**TTLD-10%**
0 ⇒ Good prognosis	<-15%	≥-10%
1 ⇒ Intermediate prognosis	<-15% or ≥-15%	<-10% or ≥-10%
2 ⇒ Poor prognosis	≥-15%	<-10%

Survival according to the prognostic category

	BEV group (*N*=71)					**Non-BEV group (*N*=68)**				
		PFS		**OS**			**PFS**		**OS**	
	N (%)	Median (mo)	HR	Median (mo)	HR	*N* (%)	Median (mo)	HR	Median (mo)	HR
Intermediate (1) + poor prognosis (2)	43 (60.6)	9.1	1	20.4	1	22 (32.3)	11.9	1	34.7	1
Good prognosis (0)	28 (39.4)	10.3	0.52 (0.31–0.87)	30.7	0.35 (0.19–0.65)	46 (67.7)	11.8	0.96 (0.53–1.73)	48.9	0.67 (0.33–1.36)

Data in parentheses are 95% confidence intervals unless otherwise stated. Abbreviations: *BEV* bevacizumab, *CI* confidence interval, *HR* hazard ratio, *mo* months, *PFS* progression-free survival, *OS* overall survival, *TTLD* tumour-to-liver density