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Original Research

Overweight is associated to a better prognosis in metastatic colorectal cancer: A pooled analysis of FFCD trials[☆]



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KEYWORDS

Overweight;
Prognostic factor;
Pooled analysis;
Colorectal cancer;
Bevacizumab

Abstract Background: Previous studies showed that high and low body mass index (BMI) was associated with worse prognosis in early-stage colorectal cancer (CRC), and low BMI was associated with worse prognosis in metastatic CRC (mCRC). We aimed to assess efficacy outcomes according to BMI.

Patients and methods: A pooled analysis of individual data from 2085 patients enrolled in eight FFCD first-line mCRC trials from 1991 to 2013 was performed. Comparisons were made according to the BMI cut-off: Obese (BMI ≥ 30), overweight patients (BMI ≥ 25), normal BMI patients (BMI: 18.5–24) and thin patients (BMI < 18.5). Interaction tests were performed between BMI effect and sex, age and the addition of antiangiogenics to chemotherapy.

Results: The rate of BMI ≥ 25 patients was 41.5%, ranging from 37.6% (1991–1999 period) to 41.5% (2000–2006 period) and 44.8% (2007–2013 period). Comparison of overweight patients versus normal BMI range patients revealed a significant improvement of median overall survival (OS) (18.5 versus 16.3 months, HR = 0.88 [0.80–0.98] $p = 0.02$) and objective response rate (ORR) (42% versus 36% OR = 1.23 [1.01–1.50] $p = 0.04$) but a comparable median progression-free survival (PFS) (7.8 versus 7.2 months, HR = 0.96 [0.87–1.05] $p = 0.35$). Subgroup analyses revealed that overweight was significantly associated with better OS in men. OS and PFS were significantly shorter in thin patients.

Conclusion: Overweight patients had a prolonged OS compared with normal weight patients with mCRC. The association of overweight with better OS was only observed in men. The pejorative prognosis of BMI < 18.5 was confirmed.

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1. Introduction

Obesity is a major health concern worldwide. The increased prevalence of overweight and obesity in most countries is described as a global pandemic. Globally, the proportion of adults with a body mass index (BMI) of 25 or greater increased from 28.8% in 1980 to 36.9% in 2013 for males and 29.8%–38% for females [1]. Worldwide, it is estimated that 3.6% of all new cancer cases in adults in 2012 were attributable to a high BMI. Colon cancer in males and postmenopausal breast cancer in females contributed the largest number of cancer cases attributable to high BMI [2]. Several plausible biological mechanisms could explain the association between adiposity and colon carcinogenesis [3]. It has never been determined whether obesity rates have increased in patients treated for metastatic colorectal cancer (mCRC) in the 2 last decades. A recent meta-analysis revealed that being obese before CRC diagnosis whatever the stage was associated with increased colorectal cancer-specific mortality and all-cause mortality [4]. Moreover, the analysis of the Adjuvant Colon Cancer End Points database revealed that patients with stage II or III disease who were either underweight or obese had worse overall survival (OS) and disease-free survival (DFS) compared to patients with a normal BMI [5]. Another large recent database analysis of patients treated for a stage I to III CRC stated that patients with normal weight, overweight, and

moderate obesity have a better prognosis compared to patients underweight or with severe or morbid obesity [6]. In a metastatic setting, conflicting data were reported for the prognostic effect of BMI. A post hoc analysis of two prospective randomised trials, CAIRO and CAIRO 2, revealed that a high BMI was associated with longer OS in the CAIRO trial, which evaluated chemotherapy alone, but not in the CAIRO 2 study, which evaluated chemotherapy in combination with antiangiogenic targeted therapy [7]. Thus, it has been hypothesised that antiangiogenic therapy may not be effective in obese patients due to the release of angiogenic factors by adipose tissue. Another retrospective study suggested that visceral fat area is a negative predictive factor for antiangiogenic efficacy [8]. Recently, the ARCAD analysis of patients from 25 first-line clinical trials in metastatic CRC (mCRC) showed that low BMI was associated with an increased risk of progression and death. No increased risk was found for elevated BMI in contrast to adjuvant setting [9]. In this study, BMI was not a predictor of progression or death by treatment type (targeted, mixing antiangiogenic and anti-EGFR versus non-targeted therapy). Nevertheless, a specific analysis of antiangiogenic therapy was not performed.

On the other hand, some concern has arisen about the dose intensity of chemotherapy delivered to obese patients as body-surface area (BSA) is frequently limited to 2 m². A recent review of the literature pointed out

that up to 40% of obese patients received limited chemotherapy doses not based on real body weight. New guidelines recommend that full weight-based cytotoxic chemotherapy doses have to be used to treat obese patients with cancer [10]. Nevertheless, in a pooled analysis of two CCR adjuvant trials, 5-fluoropyrimidine dose capping in obese patients was not associated with an increased recurrence rate [11]. There are no data for stage IV patients.

We aimed to assess two questions in our study. First, has the proportion of overweight patients among patients enrolled in mCCR clinical trials increased over time? Second, do overweight patients have a better prognosis compared to normal weight?

2. Materials and methods

2.1. Database

The FFCD database for mCRC contains individual data of eight FFCD first-line mCRC trials. In these trials, 2118 patients were randomised between 1991 and 2013 [12–19].

2.2. Statistical analyses

OS was defined as the time between randomisation and death, and progression-free survival (PFS) as the time between randomisation and first progression or death. The objective tumour response rate (ORR) was defined as complete or partial response with the rules used at the time

of the trial (defined by OMS or RECIST v1.1 criteria). Dose was determined at the first cycle of chemotherapy. A dose reduction was considered when the ratio between the administered dose and the theoretical dose was less than 95% (doses were calculated with real BSA).

For this pooled analysis, BMI was collected at inclusion before the first palliative chemotherapy. BMI categories were determined according to WHO criteria (BMI classification World Health Organisation. <http://apps.who.int/bmi>). Obese patients (BMI ≥ 30 kg/m²), overweight patients (BMI ≥ 25 kg/m²), and thin patients (BMI < 18.5 kg/m²) were compared with normal patients (BMI: 18.5–24 kg/m²). We also examined possible nonlinear relationships between BMI and survival by specifying a model with a cubic spline of BMI adjusted on trial, age, and sex.

Analyses were stratified by trials, and overall pooled hazard ratios (HR and 95% CI) were calculated using a fixed-effect model. Cochrane Q tests were used to study heterogeneity between the trials. For all analyses, there was no significant heterogeneity.

To study the interaction between BMI and the covariates sex, age (≤ 70 versus > 70 years), WHO performance status (0 versus 1–2) and chemotherapy with antiangiogenics (Yes versus No), a cox model, stratified by trial was done for each covariate, and hazard ratios were compared by a heterogeneity test. Unstratified Kaplan–Meier survival curves are presented, and median survival times were calculated. All analyses were done on an intent-to-treat basis using SAS software.

Table 1
FFCD mCRC first-line trials included in the analysis.

Trial (ref)	Inclusion period	Treatment arms	Patients analysed/randomised
FFCD 9101 [15]	1991–1994	LV5FU2	213/217
		FUFOL	212/216
FFCD 9601 [16]	1997–2001	LV5FU2	74/74
		ldLV5FU2	73/75
		HD-FU	73/73
		Raltitrexed	72/72
FFCD 2000-05 [17]	2002–2006	LV5FU2	203/205
		FOLFOX	201/205
FFCD 2001-02 [13]	2003–2010	LV5FU2	69/71
		LV5FU2 simplified	71/71
		LV5FU2 + irinotecan	68/70
		FOLFIRI	68/70
		FOLFIRI HD + bevacizumab	86/86
FFCD 0504 [19]	2007–2008	FOLFIRI + bevacizumab + G-CSF	19/20
FFCD 0604 [18]	2007–2012	LV5FU2 or FOLFOX or FOLFIRI	45/51
PRODIGE 20 [12]	2011–2013	Idem + bevacizumab	51/51
		FOLFIRI + bevacizumab then bevacizumab	244/246
PRODIGE 9 [14]	2010–2013	FOLFIRI + bevacizumab then observation	243/245

Abbreviations: FFCD, Fédération Francophone de Cancérologie Digestive; LV5FU2, fluorouracil and leucovorin bimonthly; FUFOL, bolus fluorouracil and leucovorin monthly; ldLV5FU2, fluorouracil and low dose leucovorin bimonthly; HD-FU, weekly high dose fluorouracil; FOLFOX, fluorouracil, leucovorin and oxaliplatin; FOLFIRI, fluorouracil, leucovorin and irinotecan; FOLFIRI HD, FOLFIRI high dose; G-CSF, granulocyte-colony stimulating factor; PRODIGE, Partenariat de Recherche en Oncologie Digestive.

3. Results

3.1. Descriptive and time analysis

The first-line mCRC FFCD trials used in the pooled analysis are listed and described in Table 1. A total of 33 randomised patients were not included in the pooled analysis because of missing data. The pooled analysis was performed on 2085 patients. BMI distribution according to the trial is presented in Table S1 (supplementary file). Patients with BMI of 25 and above represented 41.5% of all patients. The global obesity rate was 12%, and the rate of severe and morbid obesity was 2.6%. The rate of patients with BMI of 25 and above varied from 37.6% during the period 1991–1999 to 41.5% during the period 2000–2006 and 44.8% during the period 2007–2013 (p = 0.006) (Table S2 supplementary file). This variation was

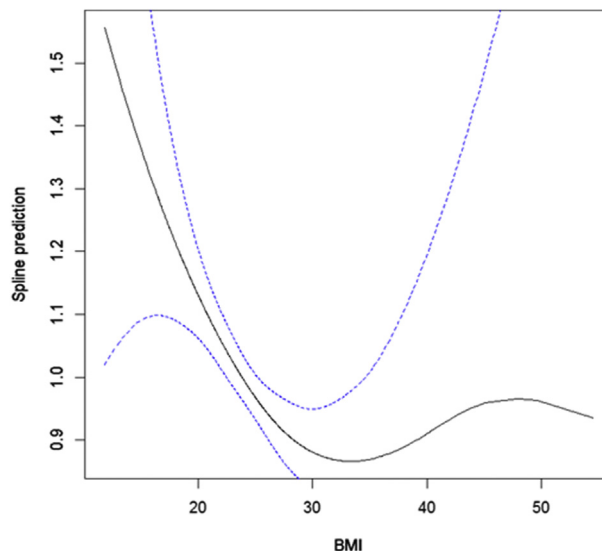


Fig. 2. Spline curve of BMI and overall mortality.

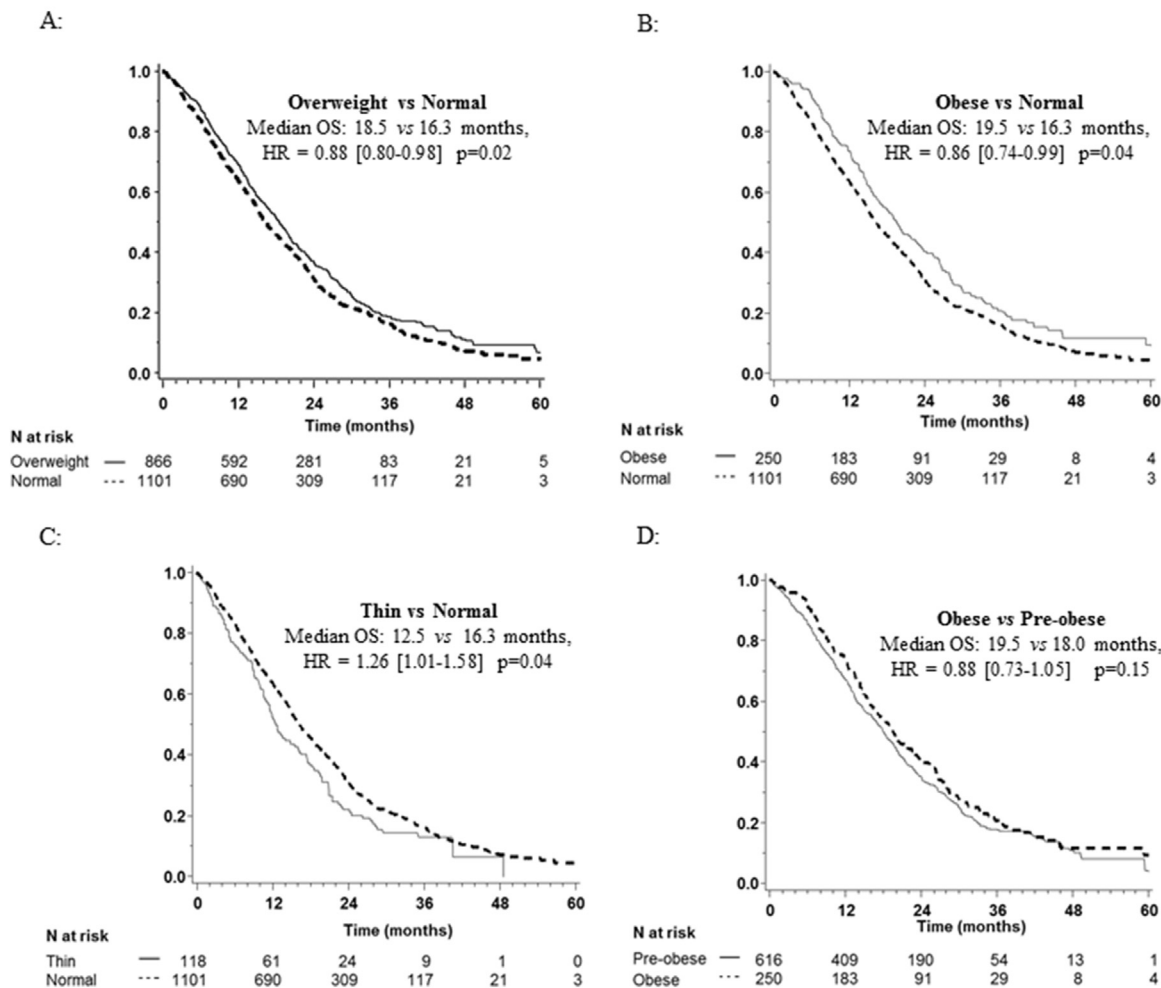


Fig. 1. Kaplan–Meier curves for overall survival (OS) according to the body mass index (BMI). (A) Comparison of OS: Overweight patients versus normal. (B) Comparison of OS: Obese patients versus normal. (C) Comparison of OS: Thin patients versus normal. (D) Comparison of OS: Preobese versus obese.

significant over time according to the Cochran–Armitage test.

3.2. Effect of overweight on overall survival

Overweight patients had a median OS of 18.5 months versus 16.3 months in normal patients HR = 0.88 [0.80–0.98] p = 0.02 (Fig. 1A). OS was significantly longer in obese patients: 19.5 versus 16.3 months in normal patients, HR = 0.86 [0.74–0.99] p = 0.04 (Fig. 1B). OS was significantly shorter in thin patients: 12.5 versus 16.3 months in normal patients, HR = 1.26 [1.01–1.58] p = 0.04 (Fig. 1C). There is no significant difference of OS between preobese and obese patient (Fig. 1D). OS in severe and morbid obesity was 26.6 months. The spline curve analysis showed that a BMI of around 33 kg/m² was associated with the lowest

mortality (Fig. 2). Cochran Q tests revealed homogeneity according to trials for OS (forest plot of BMI effect is presented in the supplementary file).

3.3. Effect of overweight on progression-free survival and objective response

Analysis of PFS and ORR are presented in Table 2. PFS was significantly shorter in thin patients. ORR was evaluated in 1771 patients. The ORR was significantly better in overweight patients than that in normal patients (OR = 1.23 [1.01–1.50] p = 0.04).

3.4. Subgroup analysis for survival

Subgroup analyses are presented in Table 3. Obesity was significantly associated with better OS in men but not in

Table 2
Progression-free survival and objective tumour response rate according to BMI.

BMI (kg/m ²)	Objective response			Progression-free survival		
	Rate	OR [CI 95%]	p Mantel Haenszel	Median (months)	HR [CI 95%]	p Logrank
Obese versus normal	42.0%	1.11 [0.82–1.50]	0.50	7.9	0.93 [0.81–1.07]	0.33
	36.4%	–		7.2	–	
Overweight versus normal	42.1%	1.23 [1.01–1.50]	0.04	7.8	0.96 [0.87–1.05]	0.35
	36.4%	–		7.2	–	
Thin versus normal	37.4%	1.18 [0.75–1.84] ^a	0.48	5.7	1.31 [1.06–1.63]	0.01
	36.4%	–		7.2	–	

^a In this analysis, FFCD 0504 was not used because the number of objective response/number of patients was too small: there was no objective response in 3 thin patients.

Table 3
Subgroup analysis according to sex, age, WHO performance status and chemotherapy for overall survival and progression-free survival.

	N	Obese versus normal		Overweight versus normal		
		HR [95% CI]	p interaction	N	HR [95% CI]	p interaction
Overall survival						
Sex						
Male	784	0.76 [0.63–0.91]	0.02	1235	0.84 [0.74–0.95]	0.07
Female	567	1.09 [0.84–1.41]		732	1.02 [0.85–1.21]	
Age						
≤70 years	806	0.88 [0.73–1.07]	0.71	1160	0.94 [0.82–1.07]	0.19
>70 years	545	0.83 [0.66–1.05]		807	0.82 [0.70–0.95]	
WHO performance status						
0	510	0.97 [0.76–1.24]	0.64	772	1.00 [0.85–1.18]	0.28
1–2	669	0.89 [0.72–1.11]		931	0.89 [0.77–1.02]	
Chemotherapy						
Without bevacizumab	934	0.83 [0.69–0.99]	0.56	1352	0.89 [0.79–1.00]	0.94
With bevacizumab	417	0.91 [0.70–1.18]		615	0.88 [0.73–1.06]	
Progression-free survival						
Sex						
Male	784	0.83 [0.70–0.99]	0.06	1235	0.92 [0.82–1.03]	0.35
Female	567	1.11 [0.87–1.42]		732	1.01 [0.86–1.19]	
Age						
≤70 years	806	0.93 [0.78–1.11]	0.98	1160	1.02 [0.91–1.15]	0.11
>70 years	545	0.94 [0.75–1.17]		807	0.88 [0.76–1.01]	
WHO performance status						
0	510	0.99 [0.80–1.23]	0.74	772	1.06 [0.91–1.22]	0.23
1–2	669	0.94 [0.77–1.16]		931	0.93 [0.82–1.07]	
Chemotherapy						
Without bevacizumab	934	0.90 [0.76–1.07]	0.47	1352	0.94 [0.85–1.05]	0.68
With bevacizumab	417	1.01 [0.79–1.28]		615	0.99 [0.84–1.16]	

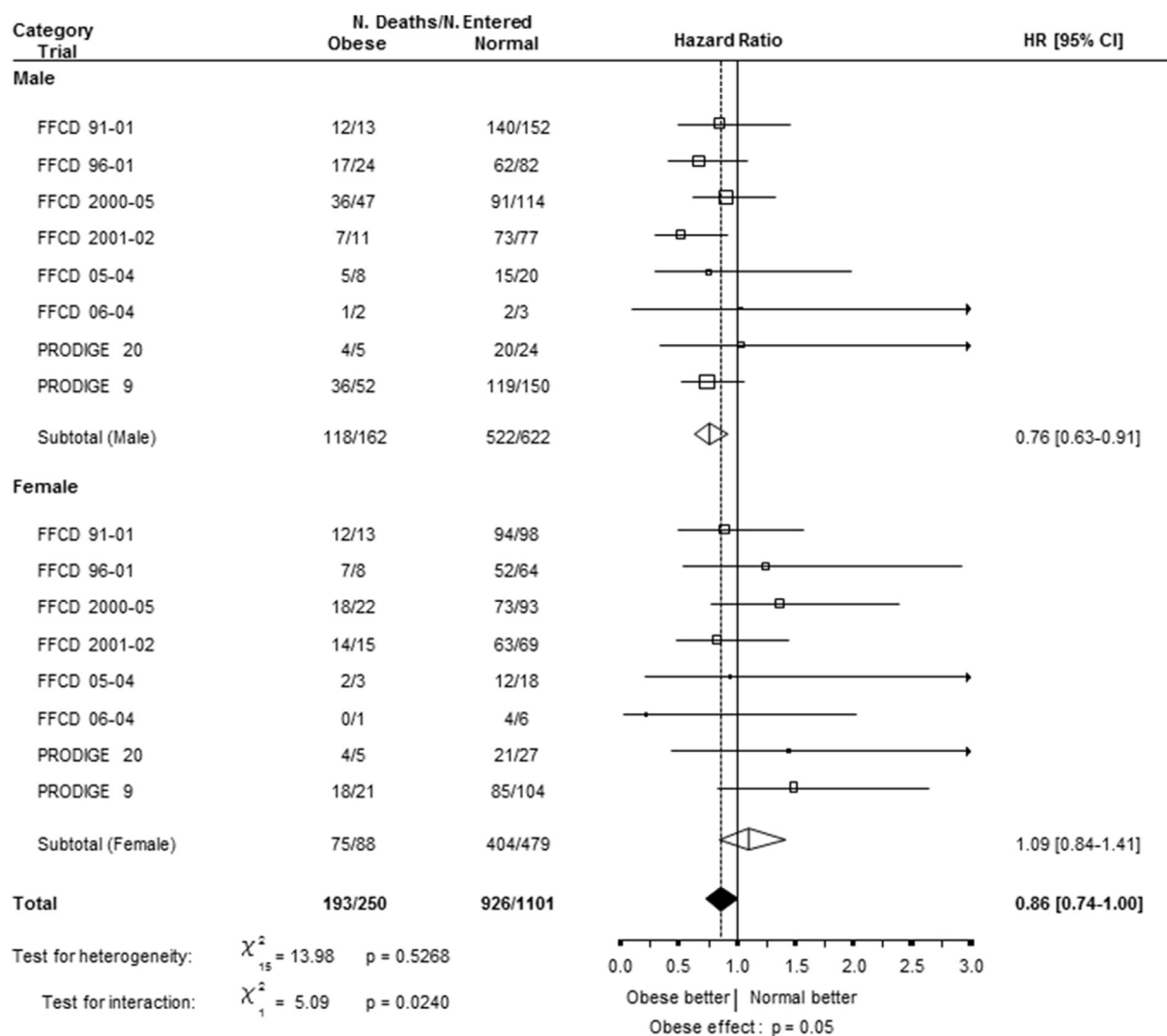


Fig. 3. Forest plot of overall survival by sex and trial—Obese versus Normal, HR = hazard ratio.

women (Fig. 3). A better PFS was also observed in obese men than in normal weight men (forest plot in supplementary file). There was no interaction between the effect of obesity (or overweight) and age or WHO performance status or bevacizumab treatment on OS and PFS.

3.5. Dose intensity according to BMI

This analysis was performed only on five trials: FFCD 0504 and FFCD 0604 patients were excluded from this analysis due to the small number of patients per group, and FFCD 9101 patients were excluded because dose intensity data were not available. Dose reduction at the first cycle was more frequently observed in obese patients than in overweight patients (34% versus 19%, $p < 0.0001$) and in obese patients than in normal patients (34% versus 16%, $p < 0.0001$) (Table S3 supplementary file). In obese patients, no significant difference was observed for OS comparing dose

reduction patients to patients with no dose reduction, HR: 1.28 [95% CI 0.88–1.87] $p = 0.19$) and for PFS (HR: 1.03 [0.74–1.45] $p = 0.85$).

4. Discussion

The prognostic value of obesity in CCR is controversial. Our pooled analysis, using data from a large panel of patients with mCRC enrolled in randomised clinical trials, revealed that obesity and overweight compared with normal weight had a positive effect for OS and that a low BMI was associated with a worse prognosis. In contrast to our results, obesity has been associated with recurrence and poor survival in early-stage colon cancer [5]. Nevertheless, in a metastatic setting, a pooled analysis of two trials suggested that obesity was associated with a better prognosis in mCCR [7]. A large meta-analysis performed with other trials showed that low BMI was associated with a poor prognosis but did

not demonstrate a protective effect for obesity compared with normal weight [9]. It must be pointed out that in the Renfro *et al.* study, [9] BMI was analysed as a continuous variable, whereas in the Simkens *et al.* study, [7] BMI was analysed according to WHO categories and in our study by both methods. Analyses by category could have amplified the differences in prognostic values according to the category. In the ARCAD study, [9] risk of death decreases as BMI increases to approximately 28 kg/m² and then it plateaued, in contrast from our database, the spline curve is U-shaped as in the Kroenke *et al.* study [6]. One explanation of the discrepancy of the result from our study and the ARCAD study [9] is the difference of patient's weight distribution. In the latter study, overweight and obesity rate were higher than in our study, and normal weight patients represented 42.8% in the ARCAD study but 52.8% in our study. Moreover, in our study, few patients had a severe or morbid obesity that impaired to draw conclusion for this subgroup of patients. A pooled analysis with other database for this subgroup of patients will be of interest. It must be pointed out that our data are from first-line trials. Results may change as patients with metastatic CRC progress along continuum because they may have a greater loss of muscle mass and an increase in sarcopenic obesity.

Our study confirmed that low BMI is a strong negative prognostic factor. Low BMI could reflect cachexia, which is a surrogate marker of tumour aggressiveness [20]. BMI is easy to calculate and a reliable tool to assess cachexia and malnutrition, but more precise data, independent of BMI, such as weight history just before diagnosis, albumin plasma level [21,22] and CT scan sarcopenia, have a prognostic value [23,24]. Lean muscle mass is likely greater in patients with overweight and moderate obesity and may account for improved outcomes [25]. Unfortunately, these specific data were missing in our studies. We therefore performed two comparisons: obese versus normal patients and overweight versus normal patients. In both comparisons, we found that a high BMI was a prognostic factor for a better outcome. These results and the discrepancy for the impact of obesity in early- and late-stage CCR generate new clinical hypotheses to test in the future.

Obesity is associated with changes in the adipokine and insulin-IGF axis [26]. Leptin levels are increased in obese patients and associated with the onset of colorectal cancer [27]. Nevertheless, leptin seems to have a dual action in that it promotes early carcinogenesis but has no effect in more advanced cancer [28,29]. Moreover, leptin expression correlated with a better prognosis in one study [30]. Other hormones, such as insulin and insulin-like growth factor 1 (IGF1), have controversial effects on the development of colorectal cancer [3]. Thus, it could be speculated that obesity and hormonal changes may have different effects depending on the

tumour stage. It could also be of interest to evaluate the correlation between obesity-hormone levels and prognosis in a metastatic setting. Another hypothesis to explain the differences in OS could be a different metabolism of anticancer drugs in obese patients [31]. However, despite the great variability of chemotherapy regimens among the trials included in our study, there was no heterogeneity among the trials related to the effect of obesity. On other hand, obese patients are more likely to be treated with metformin due to diabetes. Metformin may improve outcomes in CRC patients [32]. Unfortunately, concomitant treatments were not collected in our trials.

We found no interaction between obesity and treatment with bevacizumab. Even though IGF1 and leptin could have a pro-angiogenic effect [3], the efficacy of bevacizumab was maintained in obese patients. Some concerns have arisen with regard to the efficacy of antiangiogenic drugs in obese patients [7]. Nevertheless, our results confirmed those of the ARCAD study [9], which reported no difference in the efficacy of targeted therapy according to BMI.

In our study, the association of obesity and better survival was observed in men but not in women. Previous studies have underlined the lack of effect or a minor effect of obesity for CCR occurrence [33] or prognosis [5,9] in women compared to men. The role of sex hormones is controversial [3]. Unfortunately, we have no data of menopausal status or hormonal dosage in our database to explore the prognostic role of sex hormone according to BMI. It has been suggested that in women, the localisation of the fat is a more important risk factor than BMI [34]. Abdominal obesity is better evaluated by waist circumference than BMI but was not assessed in our study. Thus, further study should investigate the differential effect of obesity according to sex and hormonal status.

One previous study suggested that dose capping in obese patients is associated with worse PFS and OS [35]. Our study did not confirm this result. Nevertheless, due to the small number of patients in our study, this point should be investigated further.

In conclusion, patients with BMI ≥ 25 had a prolonged OS compared with normal weight patients with mCRC enrolled in first-line chemotherapy clinical trials. We found no evidence of decreased efficacy of bevacizumab in obese patients. The association of overweight with better OS was only observed in men.

Author contributions

T.A., E.B. and P.R. contributed for conception and design. T.A., M.D., E.B., S.M., T.L., J-L.L., P.R. and O.B. contributed for data analysis and interpretation. All authors participated in provision of study materials or patients, collection and assembly of data, manuscript

writing and final approval of the manuscript. No financial support was obtained by the authors.

Conflict of interest statement

T.A. declared consultancy or advisory role for Roche, Sanofi and Novartis; travel, accommodation, and expenses from Ipsen. O.B. declared consultancy or advisory role for Amgen, Roche, Merck-Sereno, Teva, Novartis, Lilly, Hospira and Pierre Fabre. P-L.E. declared consultancy or advisory role for Sanofi, Ipsen and Novartis. J.B. declared consultancy or advisory role for Roche, Boehringer Ingelheim, Novartis and Pierre Fabre. J-M.P. declared consultancy or advisory role for Sanofi, Bayer, Celgene, Lilly, Ipsen, Novartis, Roche, Merck and Amgen. E.F. declared consulting or advisory role for Sanofi, Novartis, Roche, Merck and Celgene. P.M. declared consultancy or advisory role for Roche and Sanofi. J-L.L. declared consulting or advisory role for Sanofi, Novartis, Merck-Sereno, Lilly, Ipsen and Celgene. P.R. consulting or advisory role for Lilly, Celgene, Ipsen, Sanofi and Sirtex. C.L. declared consulting or advisory role for Ipsen. J-F.S. declared consulting or advisory role for Merck-Sereno, Amgen, Roche and Sanofi. M.D., E.B., S.M., T.L., L.B., M.G., R.F., G.B. and A.de.G. declared no conflicts of interests disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejca.2018.03.031>.

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