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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
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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 $\geq$30), overweight patients (BMI $\geq$ 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 $\geq$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.

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