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Original Research

Surgical treatment options following chemotherapy plus cetuximab or bevacizumab in metastatic colorectal cancer—central evaluation of FIRE-3

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Abstract ***Background:*** The FIRE-3 trial investigated combination chemotherapy plus either cetuximab or bevacizumab in patients with untreated metastatic colorectal cancer (mCRC) not scheduled for upfront surgery. We aimed to determine the number of patients who present with potentially resectable disease during systemic first-line therapy and to compare the findings with study reports concerning resections and outcome.

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Cetuximab;
Bevacizumab;
Surgery

Patients and methods: This evaluation of 448 patients was performed as central review blinded for treatment, other reviewers' evaluations and conducted interventions. Resectability was defined if at least 50% of the reviewers recommended surgical-based intervention. Overall survival was assessed by Kaplan–Meier method.

Results: Resectability increased from 22% (97/448) at baseline before treatment to 53% (238/448) at best response ($P < 0.001$), compared with an actual secondary resection rate for metastases of 16% (72/448). At baseline (23% versus 20%) and best response (53% versus 53%), potential resectability of metastases in this molecular unselected population was similar in cetuximab-treated patients versus bevacizumab-treated patients and not limited to patients with one-organ disease. The actual resection rate of metastases was significantly associated with treatment setting ($P = 0.02$; university hospital versus hospital/practice). Overall survival was 51.3 months (95% confidence interval [CI] 35.9–66.7) in patients with resectable disease who received surgery, 30.8 months (95% CI 26.6–34.9) in patients with resectable disease without surgery and 18.6 months (95% CI 15.8–21.3) in patients with unresectable disease ($P < 0.001$).

Conclusions: Our findings illustrate the potential for conversion to resectability in mCRC, certain reluctance towards metastatic resections in clinical practice and the need for preplanned and continuous evaluation for metastatic resection in high-volume centres.

ClinicalTrials.gov-identifier: NCT00433927.

1. Introduction

Surgical resection of metastases from colorectal cancer (mostly in the liver) is potentially curative and has become the standard of care when applicable [1–7]. Recent studies have also explored a role for liver resection in selected patients with extrahepatic disease [8]. The optimal strategy and treatment sequence in resectable metastatic disease is unclear but may include perioperative chemotherapy [3,9]. As most patients with metastatic colorectal cancer (mCRC) present with initially unresectable lesions, intensive systemic therapy is used to downstage unresectable disease and enable resection [1,3,4,10,11]. Recent studies have reported secondary resection rates of about 15% [12–15], but higher rates have been reported in studies focussing on the resection of metastases [10,11].

FIRE-3 (AIO KRK-0306) was a phase III study, recruiting patients in universities, local hospitals and physician practices across Germany and Austria. Patients received first-line treatment for mCRC and were not scheduled for upfront surgery [16]. This review—based on high-volume centre experience—aims to offer a proactive perception of treatment options and estimates the proportion of patients that are eligible (or becoming eligible) for resection of metastases. Therefore, the number of patients who would have been candidates for surgery up front is compared with the number of patients who were considered 'resectable' at best response following systemic treatment. Potential interventions are also characterised for technical difficulty and anticipated clinical benefit. We explore the correspondence between our review and documented interventions in FIRE-3 as well as the impact on outcome of patients with resectable disease undergoing surgery or not. This is the largest of such analyses performed to date and the first to include a broad study population with multiple patterns of disease spread.

2. Methods

Patients in FIRE-3 received fluorouracil, folinic acid and irinotecan (FOLFIRI) plus either cetuximab or bevacizumab. Liver resection was a secondary endpoint. For details, (including follow-up therapy) refer to ClinicalTrials.gov-identifier NCT0043392 and previous publications [16–18].

Eight experienced surgeons (JP, HL, MB, TB, MR, DS, CJB and UPN) and three medical oncologists (DPM, GF and SS) participated actively in the central review. They were unaware of patients' personal information, treatment allocation, other reviewers' evaluations and whether patients actually underwent interventional treatment.

Tumour resectability was evaluated for each patient at baseline and at best response, which was defined as the tumour nadir according to Response Evaluation Criteria in Solid Tumours, version 1.1, and had previously been identified as part of an independent radiological review of response in FIRE-3 [18]. Best response in this population occurred after a median time of 3.5 months (range 0.6–22.1) (cetuximab arm) versus 3.8 months (range 0.4–30.4) (bevacizumab arm) after randomisation and had previously been identified, centrally [18]. Data of the computed tomography and/or magnetic resonance imaging (MRI) examination were uploaded in Digital Imaging and Communications in Medicine (DICOM) format to a central server for