Outcome of patients with metastatic colorectal cancer depends on the primary tumor site (midgut vs. hindgut): analysis of the FIRE1-trial (FuFIRI or mIROX as first-line treatment)

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The aim of this study was to investigate the impact of midgut versus hindgut as the primary tumor site in patients with metastatic colorectal cancer (mCRC) receiving chemotherapy with FuFIRI or mIROX. We analyzed 423 patients from a phase III trial that randomized patients in a 1 : 1 fashion to either FuFIRI or mIROX. The cohort was grouped into midgut ($n=82$) and hindgut ($n=341$) primary tumors. The primary tumor site (midgut vs. hindgut) was correlated with parameters of treatment efficacy and survival. Our cohort comprised 82 patients presenting with primary midgut tumors and 341 with primary hindgut tumors. Tumors of midgut origin compared with hindgut origin were associated with inferior outcome. Objective response rate was 37 versus 43% ($P=0.34$), median progression-free survival was 6.0 versus 8.2 months ($P=0.024$, hazard ratio: 0.75), and median overall survival was 13.6 versus 21.8 months ($P=0.001$, hazard ratio: 0.65). Patients with midgut mCRC showed a clear trend toward inferior outcome in both study arms. However, the effect appeared less pronounced in the mIROX arm. Further datasets from large trials with various regimens are required as confirmation. *Anti-Cancer Drugs* **25:212–218** © **2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

In metastatic colorectal cancer (mCRC) various prognostic factors have been introduced to clinical practice in recent years. In addition to clinical characteristics or prognostic scores such as Köhne's score [1] and similar scores for early mortality [2], molecular markers correlating with poor outcome have been identified. Of those, *BRAF* mutation, especially, has proven its prognostic power in mCRC patients in a number of reports [3–6]. *KRAS*/*NRAS* mutation as a frequent event in mCRC can be seen as a likely prognostic factor because of fewer treatment options when compared with *KRAS*/*NRAS* wild-type mCRC [3,7]. *KRAS* mutation is an established negative predictive marker to guide anti-EGFR antibody treatment such as cetuximab and panitumumab in mCRC [4,8–12] and will be complemented by further, rare *KRAS* and *NRAS* mutations [3].

Interestingly, many publications over recent decades have suggested that cancers arising at different sides of the colon (right vs. left) may represent different subtypes of disease [13–18]. Most of these reports used the splenic flexure as the demarcation line of proximal (right-sided, midgut) and distal (left-sided, hindgut) colorectal tumors. However, the resulting two-colon concept was widely ignored by clinical trials in the following years. Therefore, data from large randomized trials are lacking, while data from registries provide unclear results [19,20].

In the light of more and more molecular markers and personalized medicine being the major goal of clinical oncology, some recent reports have again addressed the question as to whether patients with colorectal cancer whose primary tumor was located at the right side of the colon have a different (worse) prognosis compared with patients with primary tumor site in the remaining left part of the colon when relapsing after surgery [21]. Furthermore, reports have associated the localization of the primary tumor with the efficacy of cetuximab [21,22]. These abstracts have raised the question as to whether

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the localization of the primary tumor in colorectal cancer can serve as prognostic and/or predictive marker. To date, it is unclear whether the poor prognostic effect of right-sided (midgut) colorectal cancer depends on the therapeutic situation (adjuvant or palliative treatment) and the respective treatment line. In particular, effects may differ between chemotherapy-naive patients and populations with chemotherapy-refractory tumors. To our knowledge, the effect of primary tumor localization on outcome has not been shown in an mCRC study population receiving first-line treatment.

This exploratory analysis aims to investigate the impact of primary tumor site (midgut vs. hindgut tumors) on prognosis and therapeutic efficacy in patients with mCRC receiving either FuFIRI or mIROX as first-line treatment. This study allows the investigation of the effect of primary tumor site in patients receiving chemotherapy alone, without the addition of monoclonal antibodies. Moreover, as one treatment arm is free of oxaliplatin, while the other does not contain 5-FU, effects evaluated in this setting may generate hypotheses concerning interactions of primary tumor site and treatment.

Methods

Study design

Data for this analysis were obtained from the FIRE1 trial. This study was a randomized, multicenter phase III trial to investigate the efficacy of FuFIRI versus mIROX as first-line chemotherapy in patients with mCRC and was carried out between 2000 and 2004. The study was conducted according to the Declaration of Helsinki and was approved by the local ethics committee. Regular site visits were performed. Tumor assessments were performed preferably by computed tomography scans, but also by MRI, radiograph, and ultrasound. During therapy, tumor assessments were carried out after the first and second cycle, and thereafter every two cycles. Response was evaluated by the WHO criteria. The study was funded by Aventis and Pfizer [23].

Assessment of primary tumor site

The FIRE1 trial recorded primary tumor site by rectum versus colon tumors. The present evaluation was performed based on retrospective assessment of primary tumor site that was conducted according to guidelines provided by the ethics committee of the University of Munich (No. 545-11). All data were acquired and analyzed anonymously.

Definition of midgut versus hindgut tumors

In the present analysis, all tumors located in the rectum, sigma, descending colon, and left flexure were defined as hindgut tumors (= left colon). All tumors from the cecum to the distal part of the transverse colon were defined as midgut tumors (= right colon).

Treatment schedule

FuFIRI: irinotecan 80 mg/m^2 as a 0.5-h infusion followed by folinic acid 500 mg/m^2 applied over 2 h and 5 fluorouracil 2000 mg/m^2 administered as a 24-h infusion. mIROX-regimen (mIROX): irinotecan 80 mg/m^2 as a 0.5-h infusion six times weekly plus oxaliplatin 85 mg/m^2 as 2-h infusion on days 15 and 29 of each cycle. In both arms, treatment was repeated every 49 days. In the case of isolated resectable liver metastases, resection was recommended after completion of two treatment cycles. Patients achieving complete remission (CR) received one further cycle of therapy, and treatment was stopped only after confirmation of CR. Patients achieving partial remission or stable disease continued therapy until progression or toxicity. At the time of disease progression or treatment intolerability, cross-over from FuFIRI to mIROX and vice versa was recommended and subsequently performed in about 69% of the study population [23].

Patients

Patients aged 18–75 years with histologically proven metastatic adenocarcinoma of the colon or rectum without prior chemotherapy for metastatic disease were eligible. Prior adjuvant chemotherapy was allowed with a treatment-free interval of 6 months and did not include topoisomerase I inhibitors or platinum compounds [23].

End points

The present investigation was performed as an exploratory analysis using response rates (complete remission = CR; partial remission = PR; stable disease = SD; progressive disease = PD), progression-free survival (PFS), and overall survival (OS) as reference for outcome in patients with tumors of midgut vs. hindgut origin. PFS was regarded as the interval between randomization and first documentation of progression or death; OS was calculated as the time between randomization and death because of any reason. Patients who were alive were censored at the last time point of patient contact. A final update on OS was conducted in 2012.

Statistical analysis

OS and PFS stratified by primary tumor site were estimated using the Kaplan–Meier method, and differences were evaluated by log-rank test and Cox regression model. Response rates were compared by χ^2-tests. A *P*-value less than 0.05 (two-sided tests) was regarded as significant. A backward elimination from a set of candidate predictors was performed at a significance level of 0.05. Simultaneously to this backward elimination, possible nonlinear relationships between a continuous covariate and the log hazard were evaluated by fractional polynomials. In addition, graphically based residual analyses were performed to evaluate the assumption of proportional hazards in the Cox regression model. SPSS PASW 21.0 (SPSS Inc., Chicago, Illinois, USA) and R, version 2.13.0 (the R Foundation for Statistical Computing/R Development

Core Team, GNU General Public License) software were used for statistical analysis.

Results

Study population

The exact localization of the primary tumor was assessable in 423 patients representing 88.3% of the whole study population. The primary tumor site could not be assessed in 56 patients. Of these 423 patients, 82 had primary midgut tumors, whereas 341 presented hindgut tumors. In detail, tumors were located in the rectum ($n = 189$), sigma ($n = 121$), descending colon ($n = 22$), left flexure ($n = 9$), transverse colon ($n = 15$), right flexure ($n = 12$), ascending colon ($n = 25$), and cecum ($n = 30$).

Baseline characteristics

In patients with midgut mCRC compared with the hindgut group, a trend towards more female patients was observed (37 vs. 28%). Moreover, performance status, assessed by Karnofsky performance status, might have been less favorable in the midgut cohort as compared with the hindgut group. Comparable frequencies of metastases, prior adjuvant treatment, and treatment arms were observed in midgut and hindgut tumors. The median age was 64 years in both cohorts (Table 1).

Table 1 Patient characteristics

	Hindgut tumors [*n* (%)]	Midgut tumors [*n* (%)]
Patients	341 (81)	82 (19)
Age		
Median	64	64
Range	25–80	22–76
Sex		
Female	97 (28)	30 (37)
Male	244 (72)	52 (63)
Performance status (Karnofsky)		
100	144 (42)	25 (30)
90	94 (27)	23 (28)
80	76 (22)	18 (22)
70	25 (7)	15 (18)
60	0 (0)	1 (1)
Not reported	2 (1)	0 (0)
Prior therapy		
Chemotherapy	100 (29)	25 (30)
Tumor characteristics		
Liver	290 (86)	68 (85)
Liver only metastasis	177 (52)	44 (55)
Lung	99 (29)	18 (23)
Lymph node	49 (14)	13 (16)
Peritoneum	7 (2)	2 (3)
Not reported	2	2
Treatment arm		
FuFIRI	172 (50)	42 (51)
mIROX	169 (50)	40 (49)

Characteristics of patients, percentages based on nonmissing data.

Consistency with whole study population

In the current cohort response rates reached 43% in patients treated with FuFIRI and 40% in patients receiving mIROX. These rates are comparable to 41% in the whole study population that was observed in both treatment arms. Median PFS was 8.2 months (FuFIRI) versus 7.2 months (mIROX), respectively, in the presented subpopulation and 8.2 and 7.2 months in the whole study population. Median OS – following the final update – in the present cohort was 21.8 months (FuFIRI) versus 18.9 months (mIROX). Survival in the full study population reached 21.0 versus 18.7 months in the respective treatment arms.

Effect of primary tumor site on response

Objective response rate (CR, PR) was 37% in midgut tumors, compared with 43% in hindgut tumors across both study arms ($P = 0.34$). This difference was pronounced in the FuFIRI arm (33 vs. 46%, $P = 0.03$) but not present in the mIROX arm (40 vs. 40%, $P = 0.94$) (Table 2).

Effect of primary tumor site on progression-free survival

Median PFS was 6.0 months in patients with midgut and 8.2 months in patients with hindgut tumors [$P = 0.024$, hazard ratio (HR): 0.75]. Taking treatment arms into account, 6.0 versus 8.7 months ($P = 0.02$, HR: 0.66) was observed in the FuFIRI arm in midgut versus hindgut tumors, whereas 6.0 versus 7.8 months ($P = 0.35$, HR: 0.84) was reached in the mIROX arm, respectively (Fig. 1a–c).

Effect of primary tumor site on overall survival

Median OS was 13.6 months in patients with midgut tumors and 21.8 months in patients with tumors of hindgut origin ($P = 0.001$, HR: 0.65). Specifically, 12.5 versus 25.0 months ($P = 0.001$, HR: 0.55) was observed in the FuFIRI arm, whereas 14.0 versus 20.4 months ($P = 0.12$, HR: 0.74) was reached in the mIROX arm in midgut versus hindgut mCRC (Fig. 2a–c).

Effect of treatment arm on outcome in midgut versus hindgut tumors

The outcome of patients with mCRC of midgut origin was similar in both treatment arms (FuFIRI vs. mIROX) concerning response rates (33 vs. 40%, $P = 0.7$), PFS [6.0 vs. 6.0 months, $P = 0.79$; HR: 0.94 (0.60–1.489)] and OS [12.5 vs. 14.5 months, $P = 0.65$; HR: 0.90 (0.57–1.43)]. In patients with hindgut mCRC a slight trend toward better outcome in the FuFIRI arm was observed. Response rates were 46 versus 40% ($P = 0.04$), PFS was 8.7 versus 7.8 months [$P = 0.17$; HR: 1.17 (0.94–1.46)], and OS was 25.0 versus 20.4 months [$P = 0.19$; HR: 1.17 (0.93–1.47)].

Backward elimination algorithm for other factors impacting outcome

The effect of midgut versus hindgut tumor site was adjusted for several potential predictors (performance status, age, sex, adjuvant chemotherapy, number of metastases, liver metastasis, liver-only metastasis, lung metastasis, lymph node metastasis, pelvic tumor lesions,

Table 2 Response to treatment

Parameters	Hindgut (all patients)	Midgut (all patients)	Hindgut FuFIRI	Midgut FuFIRI	Hindgut mIROX	Midgut mIROX
Number of patients	341	82	172	42	169	40
CR [*n* (%)]	23 (7)	9 (11)	13 (8)	3 (7)	10 (6)	6 (15)
PR [*n* (%)]	123 (36)	21 (26)	66 (38)	11 (26)	57 (34)	10 (25)
SD [*n* (%)]	119 (35)	23 (28)	69 (40)	13 (31)	50 (30)	10 (25)
PD [*n* (%)]	33 (10)	14 (17)	10 (6)	6 (14)	23 (14)	8 (20)
Not assessable [*n* (%)]	43 (13)	15 (18)	14 (8)	9 (21)	29 (17)	6 (15)
ORR (%)	43	37	46	33	40	40

CR, complete remission; Not assessable, not assessable because of any reason; ORR (CR + PR), overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease.

and peritoneal metastasis), by using the backward elimination algorithm. No predictor was selected when PFS and OS were stratified by midgut versus hindgut tumor site. Thus, the final model consisted of the predictor midgut versus hindgut tumor site.

Discussion

This investigation concerning the impact of primary tumor site in mCRC on the outcome of patients was motivated by recent reports concerning differences between tumors of the right versus left colon.

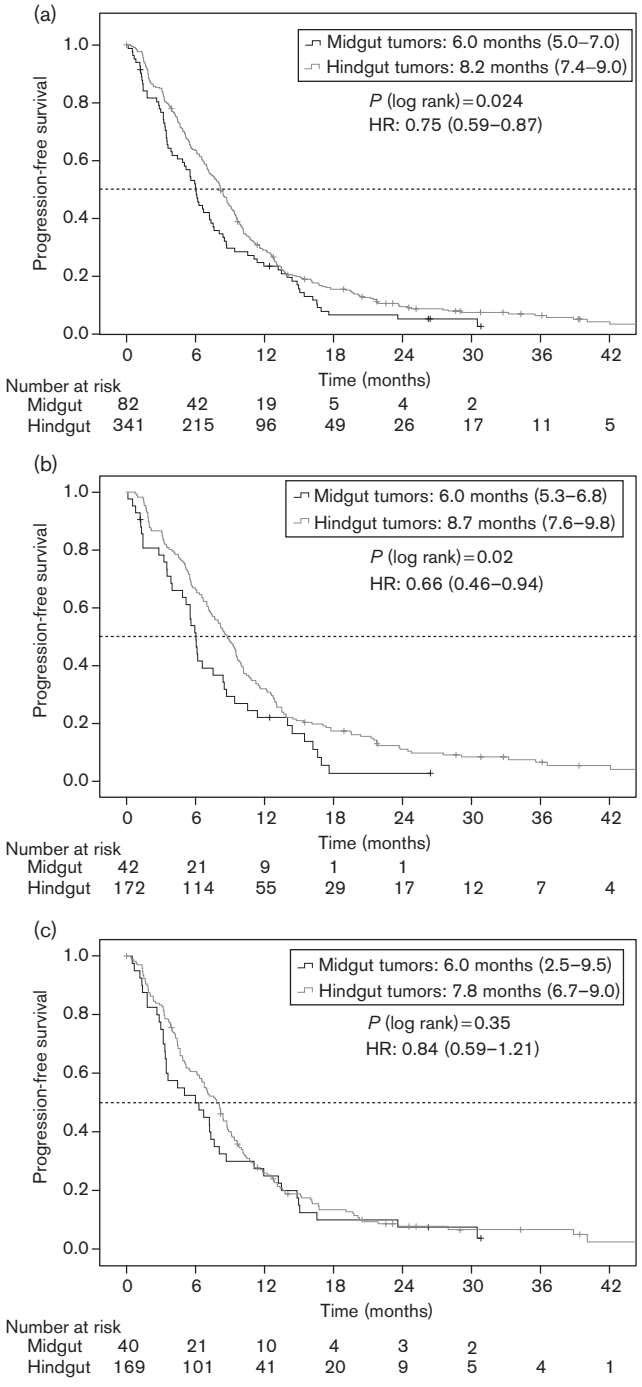
A general issue by addressing differences between right and left colon tumors occurs in terms of the definition of right versus left colon that differs between the respective cohorts and abstracts [21,22,24]. We grouped tumors into right versus left tumors by modified midgut versus hindgut definition. Our modification concerns the distal third of the colon transversum, which we counted as 'right colon'. A more precise separation of midgut versus hindgut localization in tumors of the colon transversum could not be deducted based on pathology reports. In our cohort, a small number of patients presented with primary tumors of the transverse colon (15 patients, accounting for 3.5% of all patients). From our perspective, a bias of potentially 'left-colon' tumors with regard to the negative prognostic effect of midgut tumors seemed unlikely. In addition, further heterogeneity between the recently published abstracts is caused by the role of the rectum within the definition of right versus left colon tumors. Whereas some authors differentiate right colon versus left colon versus rectum tumors [24], we analyzed midgut versus hindgut tumors. Rectum tumors were not evaluated separately. Furthermore, the strict dichotomous separation of left versus right/midgut versus hindgut may undergo critical re-evaluation in the light of reports that suggest a 'continuum hypothesis' [18,25].

In our study cohort, objective response rate did not indicate great differences when midgut and hindgut tumors were compared. By contrast, PFS and OS were markedly shorter in patients with midgut tumors when compared with hindgut tumors. An overall survival of about 14 months in patients with midgut mCRC is well comparable to survival data of patients with established factors of poor prognosis such as *BRAF* mutation [3,4,6,7]. Although recent reports suggest that *BRAF* mutation might be present at a higher frequency in midgut versus hindgut CRC, this may explain the great effect on OS only to a certain extent [21]. The inferior outcome of patients with right-sided CRC as compared with left-sided CRC was also observed in the PETACC3 trial (adjuvant treatment) with no difference in relapse-free survival, but a significant difference in survival after relapse (HR: 1.97, $P < 0.001$) [21]. By contrast, in chemorefractory patients with mCRC receiving best supportive care (BSC) the tumor site did not impact PFS or OS. Taking these observations together, it might be suspected that the primary tumor site (right vs. left or midgut vs. hindgut) is not a prognostic marker in general but is associated with treatment sensitivity in patients with metastatic/recurrent disease receiving active treatment. However, more datasets of trials in adjuvant and metastatic settings need to be analyzed before conclusions concerning the prognostic power of tumor site in colorectal cancer can be drawn.

In addition, a second effect was demonstrated in patients with mCRC receiving cetuximab therapy: patients with left-sided mCRC had a significantly longer PFS compared with patients presenting with right-sided mCRC. Therefore, Missiaglia *et al.* [21] concluded that left-sided mCRC might also have a predictive value for cetuximab therapy. This hypothesis is supported by an analysis of the NCIC CTG CO.17 trial that investigated cetuximab plus BSC versus BSC alone in chemorefractory patients with mCRC. In patients receiving cetuximab therapy longer PFS and OS in favor of patients with left-sided compared with right-sided tumors were observed. Accordingly, when tumor sites were analyzed separately, a clear treatment effect of cetuximab was described in patients with *KRAS* wild type, left-sided tumors, whereas less striking treatment effects were demonstrated in *KRAS* wild type, right-sided tumors [22]. As the FIRE1-trial did not contain treatment with an anti-EGFR antibody, no conclusions can be made here. It remains an interesting question as to whether tumor site correlates with treatment benefit in general, with certain chemotherapeutic regimens, and with anti-EGFR antibody use alone or in combination with chemotherapy.

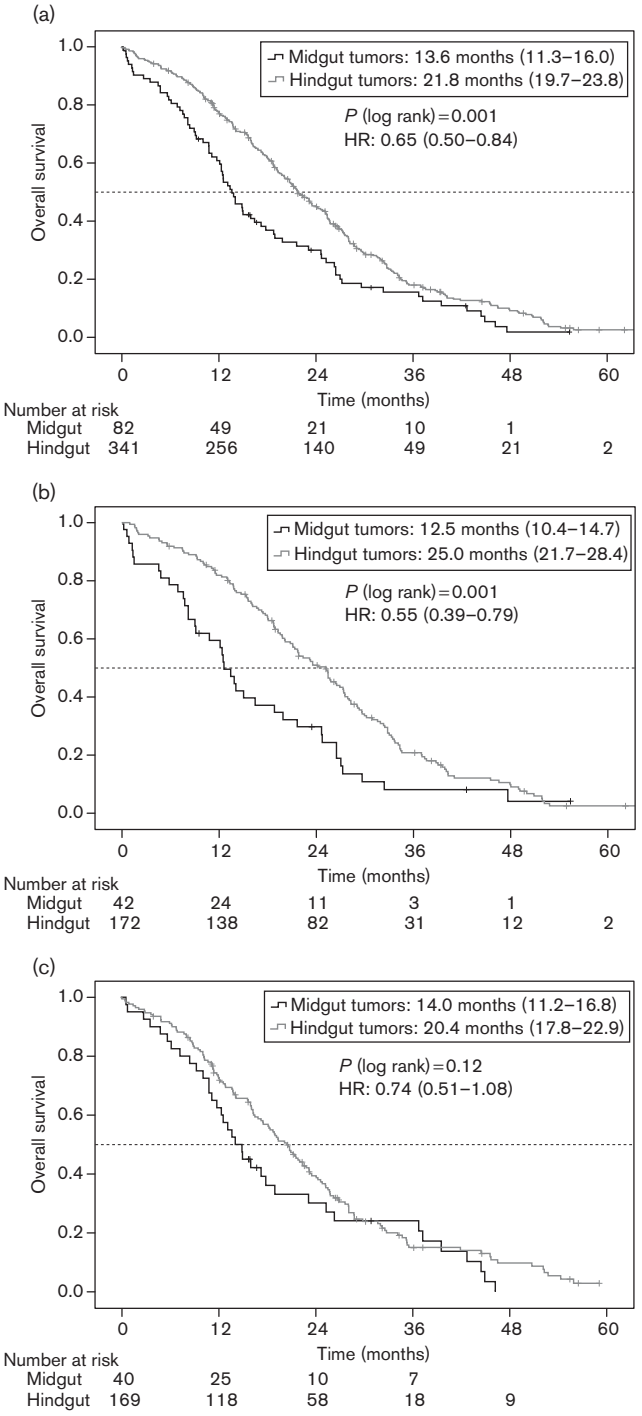
The prognostic or predictive effect of the primary tumor localization in CRC is suspected to be at least partly

Fig. 1



Progression-free survival according to localization of the primary tumor. (a) All patients; (b) patients receiving FuFIRI as first-line treatment; (c) patients receiving mIROX as first-line treatment. HR, hazard ratio.

Fig. 2



Overall survival according to localization of the primary tumor. (a) All patients; (b) patients receiving FuFIRI as first-line treatment; (c) patients receiving mIROX as first-line treatment. HR, hazard ratio.

influenced by the distinct occurrence of mutations and expressions of key markers including BRAF, KRAS, PI3KCA, MSI, EREG, EGFR, HER2, ERCC1, TS2, and VEGFR2 [13,16]. Specifically, a recent report suggested that ERCC1 and TS2 expression appears to be *KRAS* and primary tumor-site dependent [24]. Taking this into account, interaction of tumor side and treatment arm could have been suspected in our study cohort. In fact,

the survival of patients with midgut versus hindgut mCRC did not show a significant interaction with the respective treatment or with other subgroups in our population as shown in the backward elimination algorithm. Nevertheless, although not significant, the prognostic effect of primary tumor site appeared more pronounced in the FuFIRI arm compared with the mIROX arm. Hindgut tumors were associated with a slight trend toward better outcome in the FuFIRI arm compared with the mIROX arm, which is in accordance with the whole study population. By contrast, in patients with midgut tumors response rates were rather favorable in the mIROX arm, whereas PFS and OS were comparable in both arms. These hypothesis-generating trends in small subsets stress the need for further analysis of different therapeutic settings and various regimens.

Our results are limited by the number of patients included and in some ways by the absence of antibodies in first-line treatment as well as in second-line treatment [23]. This trial finished in 2004, and thus only a minority of patients might have been exposed to cetuximab or bevacizumab in later treatment lines; these data are not available. Nevertheless, the significant impact of midgut versus hindgut tumor on outcome of patients in a cohort treated without antibodies for at least two treatment lines in a clear majority of patients is an interesting finding.

Conclusion

On the basis of our findings and the limited data that have been published thus far, suspicion arises that compared with midgut tumors, hindgut tumors are associated with less favorable treatment effects in metastatic/recurrent CRC. In addition, this effect might partly depend on the treatment given. Further datasets from large trials with and without anti-EGFR antibodies are required before more conclusions can be drawn.

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Conflicts of interest

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