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Gastrointestinal Cancer

Location of Primary Tumor and Benefit From Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies in Patients With *RAS* and *BRAF* Wild-Type Metastatic Colorectal Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Metastatic colorectal cancer • Right-sided tumor • Left-sided tumor • Anti-EGFR monoclonal antibodies

Abstract

Introduction. Right- and left-sided colorectal cancers (CRCs) differ in clinical and molecular characteristics. Some retrospective analyses suggested that patients with right-sided tumors derive less benefit from anti-epidermal growth factor receptor (EGFR) antibodies; however, molecular selection in those studies was not extensive.

Patients and Methods. Patients with *RAS* and *BRAF* wild-type metastatic CRC (mCRC) who were treated with single-agent anti-EGFRs or with cetuximab-irinotecan (if refractory to previous irinotecan) were included in the study. Differences in outcome between patients with right- and left-sided tumors were investigated.

Results. Of 75 patients, 14 and 61 had right- and left-sided tumors, respectively. None of the right-sided tumors responded according to RECIST, compared with 24 left-sided tumors (overall response rate: 0% vs. 41%; $p = .0032$), and only 2 patients with right-sided tumors (15%) versus 47 patients with left-sided tumors (80%) achieved disease control ($p < .0001$). The median duration of progression-free survival was 2.3 and 6.6 months in patients with right-sided and left-sided tumors, respectively (hazard ratio: 3.97; 95% confidence interval: 2.09–7.53; $p < .0001$).

Conclusion. Patients with right-sided *RAS* and *BRAF* wild-type mCRC seemed to derive no benefit from single-agent anti-EGFRs. ***The Oncologist*** 2016;21:988–994

Implications for Practice: Right- and left-sided colorectal tumors have peculiar epidemiological and clinicopathological characteristics, distinct gene expression profiles and genetic alterations, and different prognoses. This study assessed the potential predictive impact of primary tumor site with regard to anti-epidermal growth factor receptor (EGFR) monoclonal antibody treatment in patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer. The results demonstrated the lack of activity of anti-EGFRs in *RAS* and *BRAF* wild-type, right-sided tumors, thus suggesting a potential role for primary tumor location in driving treatment choices.

Introduction

The proximal and distal colon differ in terms of embryological origin, microbial flora, and exposure to environmental mutagens. As a consequence, colorectal carcinomas (CRCs) show heterogeneous epidemiological and clinicopathological characteristics based on their anatomical location [1–3].

A growing amount of evidence has unveiled distinct gene expression profiles and genetic alterations in right- and left-sided CRCs. Whereas right-sided tumors (i.e., those originating from cecum to transverse colon) are more likely diploid, hypermutated, and CpG-island methylated, exhibit microsatellite instability, and contain *BRAF* mutations, left-sided tumors (i.e., those originating from splenic flexure to rectum) frequently present chromosomal instability, *EGFR* and *HER2-neu* amplifications, and gene expression patterns associated with epidermal growth factor receptor (EGFR) pathway activation [1–6].

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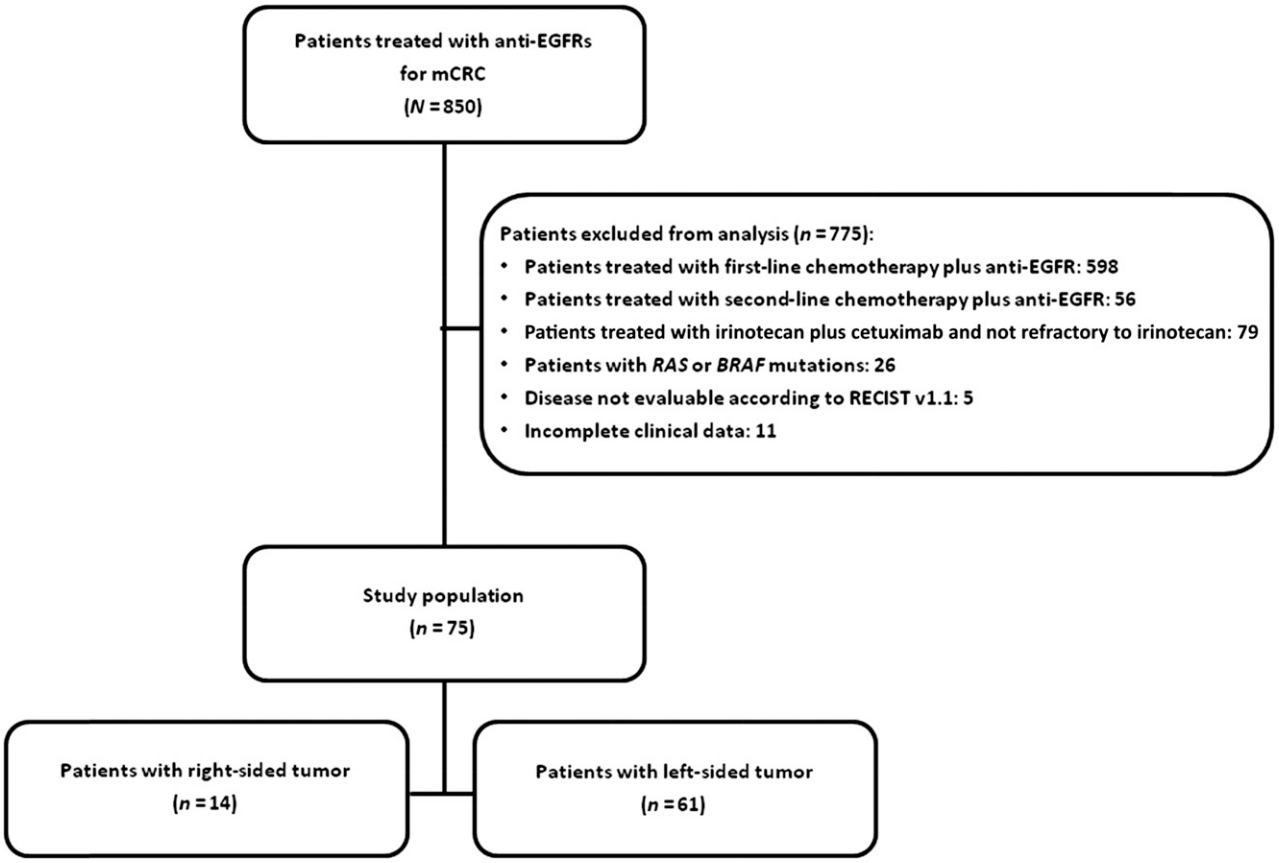

Figure 1. CONSORT diagram.
Abbreviations: EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer.

From a clinical perspective, it has been clearly demonstrated that the anatomical location also affects prognosis in patients with metastatic CRC (mCRC). Indeed, right-sided primary tumors are associated with shorter survival when compared with left-sided primary tumors [7, 8]. A relevant question is whether the primary tumor site may also predict differential benefit from available treatments.

Although the effect of the antiangiogenic bevacizumab is independent of tumor location [9], different retrospective analyses seem to suggest that patients with right-sided tumors derive less benefit from anti-EGFR monoclonal antibodies (moAbs) than those with left-sided tumors [6, 10, 11]. Moreover, in a subgroup analysis of patients with *KRAS* exon 2 wild-type mCRC included in CO.17, a phase III trial of cetuximab versus best supportive care in chemorefractory mCRC patients, primary tumor location showed a significant interaction with the outcome (p for interaction = .002) [12]. In particular, unlike patients with left-sided tumors, those with right-sided mCRCs seemed to derive no benefit from cetuximab monotherapy in terms of progression-free survival (PFS) [12]. A major limitation of this study was that extended *RAS* and *BRAF* mutation analyses were not taken into account; thus, independent of the primary tumor site, the study included patients with *KRAS* exon 3 and 4 and *NRAS* exon 2, 3, and 4 mutations, who do not derive benefit from anti-EGFR moAbs [13], and patients with *BRAF* mutation, who derive minimal benefit from the use of anti-EGFR moAbs [13, 14]. As recently confirmed in the new classification of mCRC molecular subtypes, *RAS* and *BRAF* mutations tend to occur more often in right-sided tumors [15]; therefore, the negative predictive impact of the proximal location with regard to the efficacy of cetuximab may be confounded by the higher percentage of mutations in this group.

Drawing from these considerations, we analyzed the potential predictive impact of primary tumor site with regard to the efficacy of anti-EGFR moAbs in a homogeneous population of patients with *RAS* and *BRAF* wild-type mCRC treated with anti-EGFR moAb monotherapy or in combination with irinotecan, if clearly refractory to irinotecan.

Patients and Methods

Patient Population

Consecutive patients with *RAS* and *BRAF* wild-type mCRC who were referred to three Italian institutions (Azienda Ospedaliero-Universitaria Pisana, Pisa; National Cancer Institute, Milan; and Veneto Institute of Oncology, Padua) from 2008 to 2015 and treated with panitumumab, cetuximab, or cetuximab plus irinotecan (only if refractory to irinotecan) were included. Refractoriness to irinotecan was defined as documented disease progression during or within 3 months from the last irinotecan-containing therapy. Only patients not previously treated with anti-EGFRs, with measurable disease according to RECIST version 1.1, and who underwent tumor reassessments during the treatment every 8 weeks were eligible.

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Table 1. Patients' characteristics

Characteristics	Right-sided tumor ($n = 14$), no. (%)	Left-sided tumor ($n = 61$), no. (%)	p value
Median age (range), years	73 (43–88)	73 (36–89)	.73[a]
Sex			.92
Male	8 (57.1)	34 (55.7)	
Female	6 (42.9)	27 (44.3)	
ECOG PS at the beginning of anti-EGFR-containing treatment			.31
0	4 (28.6)	25 (41.0)	
1–2	7 (50.0)	31 (50.8)	
NA	3 (21.4)	5 (8.2)	
Time between diagnosis of primary tumor and metastases			.04
Synchronous (≤3 months)	12 (85.7)	35 (57.4)	
Metachronous (>3 months)	2 (14.3)	26 (42.6)	
Primary tumor resected			.32
Yes	11 (78.6)	54 (88.5)	
No	3 (21.4)	7 (11.5)	
Pathologic T stage			.49
1	0 (0)	3 (4.9)	
2	0 (0)	3 (4.9)	
3	7 (50.0)	38 (62.3)	
4	4 (28.6)	10 (16.4)	
x	3 (21.4)	7 (11.5)	
Pathologic N stage			.53
0	1 (7.2)	14 (22.9)	
1	5 (35.7)	22 (36.1)	
2	5 (35.7)	17 (27.9)	
x	3 (21.4)	8 (13.1)	
Grading			.0097
1	1 (7.2)	1 (1.6)	
2	3 (21.4)	38 (62.3)	
3	7 (50.0)	9 (14.8)	
x	3 (21.4)	13 (21.3)	
Previous adjuvant treatment			.37
No	13 (92.9)	48 (78.7)	
Fluoropyrimidine	0 (0)	7 (11.5)	
Fluoropyrimidine + oxaliplatin	1 (7.1)	6 (9.8)	
Previous lines of treatment for metastatic disease, no.			.33
0	2 (14.3)	17 (27.9)	
1	3 (21.4)	18 (29.5)	
2	9 (64.3)	26 (42.6)	
Anti-EGFR-containing regimen			.68
Cetuximab	0 (0)	3 (4.9)	
Panitumumab	10 (71.5)	43 (70.5)	
Cetuximab + irinotecan	4 (28.5)	15 (24.6)	
Metastatic sites at the beginning of anti-EGFR-containing treatment, no.			.27
1	4 (28.6)	14 (22.9)	
>1	7 (50.0)	42 (68.9)	
NA	3 (21.4)	5 (8.2)	

[a]Wilcoxon test; all other p values are for chi-square test.
Abbreviations: anti-EGFR, anti-epidermal growth factor receptor monoclonal antibody; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, not available.

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Table 2. Response and survival parameters

Parameter	Right-sided tumor	Left-sided tumor	*p* value	Overall population
Evaluable for response, no.	13	59		72
CR	0 (0)	0 (0)		0 (0)
PR	0 (0)	24 (40.7)		24 (33.3)
SD	2 (15.4)	23 (39.0)		25 (34.7)
PD	11 (84.6)	12 (20.3)		23 (31.9)
ORR, %	0	41	.0032	33
DCR, %	15	80	<.0001	68
PFS, no.	14	61		75
Events	13 (92.9)	56 (91.8)		69 (92.0)
Median PFS, months	2.3	6.6		5.7
HR (95% CI)	3.97 (2.09–7.53)		<.0001	
OS				
Events	12 (85.7)	46 (75.4)		58 (77.3)
Median OS, months	6.0	15.3		12.9
HR (95% CI)	1.51 (0.79–3.74)		.17	
PPS, no.	13	56		69
Events	12 (92.3)	46 (82.1)		58 (84.0)
Median PPS, months	3.2	9.6		9.6
HR (95% CI)	0.99 (0.44–2.22)		.99	

Data given as no. (%) unless otherwise indicated.
Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; HR, hazard ratio; OR, odds ratio; ORR, overall response rate; OS, overall survival; PD, progression of disease; PFS, progression-free survival; PPS, postprogression survival; PR, partial response; SD, stable disease.

Objectives and Definitions

The objective of this analysis was to examine potential differences in response and survival parameters between patients with right- and left-sided tumors (i.e., proximal or distal to the splenic flexure). Overall response rate (ORR) was defined as the proportion of patients achieving partial or complete response according to RECIST version 1.1. Disease control rate (DCR) was defined as the proportion of patients achieving partial or complete response or stable disease according to RECIST version 1.1. PFS was defined as the time from the first administration of anti-EGFR MoAbs to the evidence of disease progression according to RECIST version 1.1, or death from any cause. Postprogression survival (PPS) was defined as the time from evidence of disease progression to anti-EGFR MoAb treatment to death from any cause. Overall survival (OS) was defined as the time from the first administration of anti-EGFR moAbs to death from any cause.

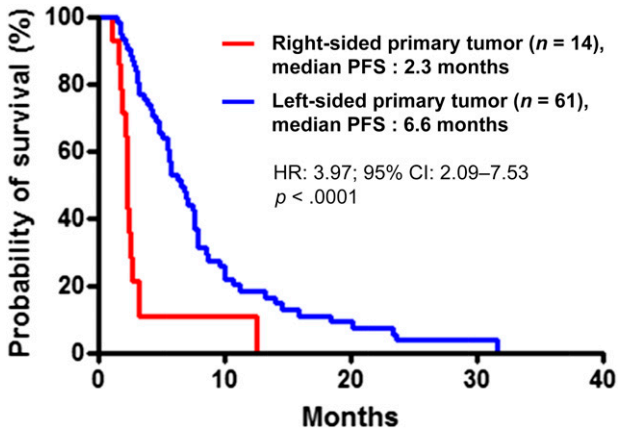

Figure 2. Kaplan-Meier analyses of PFS comparing patients with right-sided (red line) and left-sided (blue line) tumors.
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

RAS and *BRAF* Analyses

DNA was extracted from formalin-fixed, paraffin-embedded blocks. Hematoxylin- and eosin-stained slides were reviewed by expert pathologists who macrodissected proper representative areas of tumor tissue to obtain an amount containing at least 50% neoplastic cells. Genomic DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany, https://www.qiagen.com) with overnight proteinase K digestion, and DNA concentration was determined by the NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific Life Sciences, Waltham, MA, http://www.thermofisher.com). *KRAS* (exons 2, 3, and 4), *NRAS* (exons 2, 3, and 4), and *BRAF*V600E mutational status were tested by pyrosequencing on the PyroMarkQ96 ID instrument (Qiagen) with commercially available kits (Diatech Pharmacogenetics, Jesi, Italy, http://www.diatechpharmacogenetics.com) or by mass spectrometry using the matrix-assisted laser desorption ionization-time of flight MassARRAY system (Sequenom, San Diego, CA, https://www.sequenom.com). The sensitivity (detectable percentage of mutant alleles) of pyrosequencing and mass spectrometry techniques is approximately 5%.

Statistical Analysis

The chi-square test, Wilcoxon test, and Fisher exact test were used, when appropriate, to compare clinical and biological features, ORR, and DCR between right- and left-sided tumor

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groups. PFS, PPS, and OS analyses were determined according to the Kaplan-Meier method, and survival curves were compared using the log-rank test. Statistical significance was set at $p = .05$ for a bilateral test. All analyses were carried out with GraphPad Software (La Jolla, CA, http://www.graphpad.com).

Results

From a common data set including 850 mCRC patients treated with anti-EGFRs, we extracted 75 with *RAS* and *BRAF* wild-type mCRC who fulfilled the inclusion criteria (Fig. 1). Of these, 14 (18.7%) and 61 (81.3%) had right- and left-sided tumors, respectively.

Clinical and pathological characteristics at baseline are summarized in Table 1. No significant differences between groups were observed in terms of sex ($p = .92$), Eastern Cooperative Oncology Group Performance Status 1–2 ($p = .31$), median age ($p = .73$), pathologic stage (pT: $p = .49$; pN: $p = .53$), number of metastatic sites at the beginning of the anti-EGFR-containing treatment ($p = .27$), and resection of the primary tumor ($p = .32$). Patients in the right-sided tumor group more frequently had synchronous metastases ($p = .04$) and poorly differentiated tumors when compared with patients in the left-sided tumor group ($p = .0097$). No significant differences were found with regard to prior adjuvant treatment ($p = .37$), the number of previous lines of treatment received for metastatic disease ($p = .33$), and which anti-EGFR-containing regimen was administered ($p = .68$).

Response and survival parameters are listed in Table 2. Of 72 evaluable patients, 24 (33%) achieved RECIST response. All 24 had a left-sided tumor. Therefore, the ORR in left-sided tumors was 41% compared with 0% in right-sided tumors ($p = .0032$). Of the patients with left-sided tumors, 47 (80%) achieved disease control compared with 2 patients (15%) with right-sided primary tumors ($p < .0001$).

In the overall population, disease progression and death occurred in 69 patients (92%) and 58 patients (77%), respectively. Median PFS was 2.3 months in the right-sided tumor group and 6.6 months in the left-sided tumor group (hazard ratio [HR]: 3.97; 95% CI: 2.09–7.53; $p < .0001$) (Fig. 2). Patients with right-sided tumors also had shorter OS, although not significantly so (6.0 vs. 15.3 months; HR: 1.51; 95% CI: 0.79–3.74; $p = .17$), whereas no difference was shown in PPS (3.2 vs. 9.6 months; HR: 0.99; 95% CI: 0.44–2.22; $p = .99$) (Fig. 3). OS from the diagnosis of metastatic disease was 21.0 and 35.4 months for patients with right-sided and left-sided tumors, respectively (HR: 0.99; 95% CI: 0.49–1.98; $p = .97$). A higher percentage of patients with left-sided tumors received at least one more treatment after disease progression (Table 3).

Discussion

This series underlines a significant difference in clinical outcome among patients with right- and left-sided primary tumors treated with anti-EGFR moAbs, thus confirming and reinforcing results of the retrospective subgroup analysis of the phase III randomized CO.17 study of cetuximab versus best supportive care [12].

A crucial question remained when interpreting results provided by Brulé et al. [12]: was the significant interaction observed in that subgroup analysis due to the higher incidence of *BRAF* and *RAS* mutated tumors in the right-side colon? To answer this question, our analysis was restricted to patients with extended *RAS* and *BRAF* wild-type mutations, as assessed

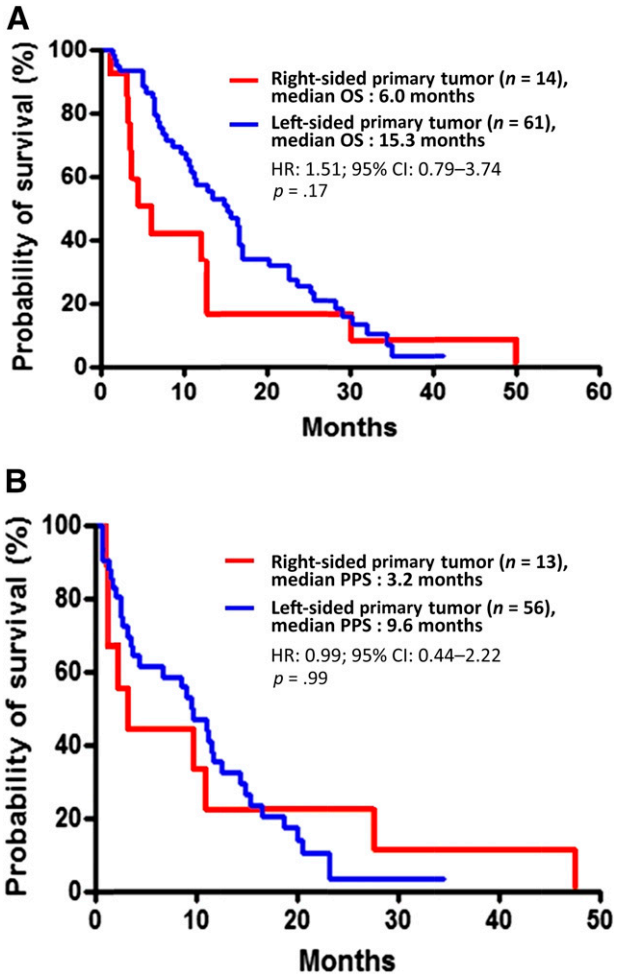

Figure 3. Kaplan-Meier analyses of **(A)** overall survival and **(B)** PPS, comparing patients with right-sided (red line) and left-sided (blue line) tumors.

Abbreviations: CI, confidence interval; HR, hazard ratio; PPS, postprogression survival.

on archived tissue samples collected before any treatment. Based on our results, we can conclude that the lack of activity of anti-EGFRs in right-sided tumors cannot be attributed to the negative predictive impact of these mutations.

In our opinion, a point of strength of this study that makes it different from previous analyses [7, 11] lies in the choice to restrict the analysis to patients receiving anti-EGFR moAbs as single agents or in combination with irinotecan, only in strictly defined irinotecan-refractory patients. By excluding patients with potentially chemosensitive disease, we were able to focus on the true interaction of tumor site and outcome of anti-EGFR agents, at least in terms of response and PFS.

A clear limitation is the lack of a control arm including untreated patients. This prevented us from drawing definitive conclusions about the predictive role of the primary location. Nevertheless, the evidence of a significant difference in terms of response rate and PFS (i.e., outcome parameters more tightly related to the activity and efficacy of the study treatment, and not in terms of PPS and OS) might suggest a predictive, rather than prognostic, impact of the primary tumor site.

The reasons for such a different efficacy of anti-EGFRs in right- and left-sided mCRCs likely should be sought in a different

Table 3. Treatments after therapy with anti-epidermal growth factor receptor monoclonal antibody

Treatment	Right-sided tumor ($n = 14$), no. (%)	Left-sided tumor ($n = 61$), no. (%)	p value[a]
At least one treatment after PD			
Yes	1 (7.1)	24 (39.3)	.027
No	13 (92.9)	37 (60.7)	
5-Fluorouracil/capecitabine			.11
Yes	0 (0)	11 (18.0)	
No	14 (100)	50 (82.0)	
Oxaliplatin			1.0
Yes	0 (0)	4 (6.6)	
No	14 (100)	57 (93.4)	
Irinotecan			1.0
Yes	1 (7.1)	6 (9.8)	
No	13 (92.9)	55 (90.2)	
Bevacizumab			1.0
Yes	0 (0)	3 (4.9)	
No	14 (100)	58 (95.1)	
Regorafenib			.11
Yes	0 (0)	11 (18.0)	
No	14 (100)	50 (82.0)	
TAS-102			1.0
Yes	0 (0)	1 (1.6)	
No	14 (100)	60 (98.4)	
Other			1.0
Yes	0 (0)	3 (4.9)	
No	14 (100)	58 (95.1)	

[a]Fisher exact test.
Abbreviation: PD, progression of disease.

molecular phenotype underlying these two groups. In fact, translational studies showed distinct and specific genetic features and expression profiles according to primary tumor location [16]. Not only are left-sided tumors often present with gene signatures associated with EGFR and MAPK activation [6] but they are also characterized by higher levels of epiregulin and amphiregulin expression when compared with right-sided primary tumors. High levels of EGFR endogenous ligands have been associated with response to anti-EGFRs, whereas low levels have been related to resistance to EGFR inhibition [17].

CpG island methylation is an epigenetic mechanism of gene silencing more frequently observed in right- than left-sided tumors and the methylation of the *EGFR* promoter may be responsible for the loss of EGFR expression [18] and, thus, for inefficacy of anti-EGFRs. On the other hand, the "canonical" CMS2 subtype, characterized by epithelial activation, and, therefore, potentially more sensitive to EGFR inhibition, is highly represented among left-sided tumors [15].

Conclusion

Our results support the importance of considering the primary tumor site in tailoring the best treatment for every patient with mCRC. To this purpose, the data from this study deserve confirmation in subgroup analyses of clinical studies randomizing patients to receive, or not receive, an anti-EGFR moAb and they underline the importance of collecting this information in ongoing and future trials.

Acknowledgment

We thank the nonprofit ARCO Foundation for supporting the molecular and statistical analyses in this study.

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Disclosures

Sara Lonardi: Roche, Sanofi, Amgen, Eli Lilly, Bayer (C/A), Roche, Amgen (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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