Editorial Commentary

# Is the transverse colon the new right?—similarities in EGFR drug response and prognosis

**Soledad Cameselle-García^, Ana Fernández Montes^**

Gastrointestinal Cancer Unit, Medical Oncology Department, Complexo Hospitalario Universitario de Ourense, Ourense, Spain

*Correspondence to:* Ana Fernández Montes, MD. Gastrointestinal Cancer Unit, Medical Oncology Department, Complexo Hospitalario Universitario de Ourense, Ramón Puga S/N, 32005 Ourense, Spain. Email: afm1003@hotmail.com.

*Comment on:* Solar Vasconcelos JP, Chen N, Titmuss E, *et al.* Transverse Colon Primary Tumor Location as a Biomarker in Metastatic Colorectal Cancer: A Pooled Analysis of CCTG/AGITG CO.17 and CO.20 Randomized Clinical Trials. Clin Cancer Res 2024;30:1121-30.

**Keywords:** Colon; anti-epidermal growth factor receptor (anti-EGFR); laterality; transverse

Submitted Apr 16, 2024. Accepted for publication Aug 12, 2024. Published online Oct 10, 2024.
doi: 10.21037/jgo-24-272
**View this article at:** https://dx.doi.org/10.21037/jgo-24-272

There is currently no clear definition regarding the exact division point between right-sided and left-sided colon cancer. The most widely-accepted definition establishes the right colon as the region of the large intestine extending from the ileocecal valve to the proximal two-thirds of the transverse colon, while the left colon includes the distal third of the transverse colon, descending colon, and sigmoid colon (1). This differentiation is supported by the different embryonic origins of these regions. More recently, the colon was dichotomized, with the right colon including the ileocecal valve to the splenic flexure, and the left colon from the splenic flexure to the rectum (2). It is now known that these anatomical differences are complemented by clinical and molecular differences that confer unique characteristics to each location.

Right-sided colon carcinomas account for a third of all colorectal cancer (CRC). They are more common in women, often have a mucinous component, with a signet ring cell histology, and tend to be more undifferentiated tumors. Additionally, cancers on the right side tend to spread peritoneally, while those on the left side are more likely to metastasize to the lungs and liver (3,4). This different biological behavior reflects the existence of distinct carcinogenesis pathways on each side, which has served as a rational basis to explain the differences in response to anti-epidermal growth factor receptor (EGFR) treatments, as proposed in the recent article by Solar Vasconcelos *et al.* (4).

Tumors on the right side are characterized by being associated with mutations in the *BRAF* and *RAS* genes, as well as microsatellite instability and an increased hypermethylation of cytosine-phosphate-guanine (CpG) islands (5). Forty percent of CRC harbor *KRAS* missense mutations in codons 12, 13, or 61 which confer a lack of response to anti-EGFR therapies (6). *KRASG12C* is detected in 2–4% of metastatic CRC (mCRC) and depicts an aggressive disease with a disappointing response to standard treatments (7). Recent studies however, have evaluated the combination of small oral inhibitory molecules, as sotorasib or adagrasib, with anti-EGFR therapies achieving promising results (8,9).

Tumors on the left side are typically associated with chromosomal instability (CIN), high DNA copy number variation (CNV), and high dependence on the *WNT* and *MYC* pathways. Left-sided tumors also present more mutations in *RAS*, *APC* and *p53*, *HER1* and *HER2* amplifications, as well as gene expression profiles that confer greater sensitivity to EGFR-targeted therapies (10,11).

Retrospective analyses of randomized studies have evaluated the efficacy of anti-EGFR therapies in patients with *RAS* wild-type CRC based on laterality. One such study addressed the prognostic and predictive value of tumor laterality and RAS wild-type status in patients

^ ORCID: Soledad Cameselle-García, 0000-0002-2678-7230; Ana Fernández Montes, 0000-0003-4630-5830.

treated with chemotherapy and anti-EGFR therapy across six phase III studies, CALGB 80405, CRYSTAL, PRIME, PEAK, FIRE 3, and 200501819 (12). This retrospective analysis showed that left-sided tumors had greater benefit in overall survival (OS), objective response rate (ORR), and progression-free survival (PFS) with the addition of an anti-EGFR drug to chemotherapy compared to chemotherapy alone or chemotherapy plus bevacizumab in first-line treatment of mCRC. However, the benefit is not as clear in tumors located on the right side. These results are consistent with data from the PARADIGM10 study (13). In the phase III PARADIGM study, 823 patients with *RAS* wild-type mCRC were randomized to receive panitumumab or bevacizumab in combination with standard first-line chemotherapy. This study showed greater benefit in OS in patients treated with the anti-EGFR combination and with tumors located on the left side, as well as in the overall population. On the other hand, this benefit was not achieved in patients with right-sided tumors. In this context, the value of associating an anti-EGFR in patients with left-sided *RAS* wild-type CRC is clearly established, while its use in right-sided colon cancer remains controversial.

A recent meta-analysis analyzing the PEAK, CALGB/SWOG 80405, FIRE-3, PARADIGM, and CAIRO5 studies showed a benefit in PFS when associating an anti-vascular endothelial growth factor (VEGF) versus an anti-EGFR in *RAS* wild-type mCRC patients with right-sided tumors (14). Given the results of previous studies and the limited efficacy of anti-EGFR agents in this patient subgroup, National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines now recommend in first-line treatment of advanced or mCRC, combining an anti-VEGF agent with chemotherapy for tumor harboring proficient mismatch repair/microsatellite stable (pMMR/MSS) and wild-type *RAS* and *RAF*; combining an anti-EGFR agent with chemotherapy for left-sided tumor harboring pMMR/MSS and wild-type *RAS* and *RAF* (15,16).

Further questions are raised in the case of patients diagnosed with RAS wild-type colon cancer located in the transverse colon. Patients with a tumor located in the transverse colon are not well represented in clinical studies due to their low frequency and lack of previous consensus in terms of a definition. Indeed, the CALGB 8040513 study excluded these patients (17), while other studies [CRYSTAL (18), PRIME (19), PEAK (20), FIRE-3 (21), and 20050181 (22)] included this population with those patients having disease in the right colon. Thus, the fact that characteristics associated with the most distal third of the colon may more closely reflect characteristics of left-sided tumors based on embryonic origin was not taken into account.

Both the prognostic and predictive value of response to anti-EGFR drugs diminish with more advanced treatment lines, and location may not be relevant in the advanced setting due to the acquisition of new resistance mutations. Many trials, such as CORRECT or SUNLIGHT have reported significantly improved outcomes beyond second line in unselected patients. The use of multikinase inhibitors as regorafenib has been useful in this setting despite its limited clinical benefit (8). Improvements in the understanding of underlying mechanisms of resistance, as *ERBB2* amplification or *PIK3CA* (23), will change this approach in the future.

In this context, the study by Solar Vasconcelos *et al.* shows interesting results regarding the predictive value of response to anti-EGFR drugs and prognosis of tumors located in the transverse colon, aiming to confirm similar outcomes for the transverse colon and the right colon, justifying the existing dichotomy between the right and left colon (4). The analysis included a pool of 553 patients from the CO.20 (24) and eCCTG/AGIT CO.17 (25) clinical trials. These studies included mCRC patients treated with anti-EGFR in advanced lines of therapy. The CCTG/AGIT CO.17 trial included 572 patients. After excluding patients with unknown *BRAF* and *RAS* status, data from 201 patients were analyzed. The CO.20 study included 750 patients, and data from 352 patients were analyzed, including only those who had received cetuximab monotherapy treatment and excluding those with a mutation in *KRAS* exon 2. Of the 553 patients included, up to 352 presented a mutation in *NRAS*, *BRAF* V600E, or *KRAS* exons 3 or 4; these data were however not analyzed but nonetheless could have impacted the data. Ninety percent of patients were heavily pretreated, having received at least two lines of treatment, and may have developed resistance mutations that were not tested for.

When evaluating patients by laterality, only 32 of the 553 patients were classified as having a tumor located in the transverse colon, limiting representativeness for drawing solid conclusions. The results showed interesting outcomes when analyzing the efficacy of anti-EGFR (cetuximab) treatment. Cetuximab treatment compared to best supportive care did not increase OS or PFS in patients with tumors located in the transverse colon or right colon, reinforcing the similarity between these locations. It also did not result in an increase in ORR, which was 0% in patients

 

with tumors located in the transverse colon and 3.4% in those with right-sided tumors. However, statistically significant differences were found in tumors located on the left side compared with transverse, with a response rate of around 10%, median OS of 9.7 *vs.* 5.9 months [hazard ratio (HR) =0.42; 95% confidence interval (CI): 0.27–0.67; P=0.0002] and median PFS of 3.8 *vs.* 1.8 months (HR =0.49; 95% CI: 0.31–0.76; P=0.001) (4). These data are consistent with those of previous publications (12,14).

Despite the limitations, the data presented in this study indicate that there are multiple similarities between tumors located in the right colon and in the transverse colon from a prognostic standpoint, as a worse prognosis was observed in the placebo arm compared to the left colon (4). This reinforces the idea of the importance of colon laterality based on embryonic origin, and hence its dichotomization.

From the perspective of predicting response to anti-EGFR therapy, drawing conclusions for outcomes in the transverse colon is more complex, and these results should be considered as hypothesis-generating due to the low number of cases, retrospective nature, and absence of using location as a stratification criterion in both analyzed meta-analyses. As such, further in-depth data analyses are necessary to determine reliable conclusions regarding the predictive value in terms of response to anti-EGFR therapy in the transverse colon.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*. The article has undergone external peer review.

*Peer Review File:* Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-272/prf

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-272/coif). S.C.G. has received payment for lectures and presentations from Roche. A.F.M. has received consulting fees from Amgen, Merck, Astra Zeneca, MSD, and BMS. She has also received payment for lectures and presentations from Amgen, Servier, Lilly, Merck, BMS, MSD, Eisai, Daichi, Beigene, Roche, and Astra Zeneca. Additionally, she has received support for attending meetings and/or travel from Roche and Astra Zeneca. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



## References

1. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330-7.
2. Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer: A Systematic Review and Meta-analysis. JAMA Oncol 2017;3:211-9.
3. Benedix F, Meyer F, Kube R, et al. Right- and left-sided colonic cancer - different tumour entities. Zentralbl Chir 2010;135:312-7.
4. Solar Vasconcelos JP, Chen N, Titmuss E, et al. Transverse Colon Primary Tumor Location as a Biomarker in Metastatic Colorectal Cancer: A Pooled Analysis of CCTG/AGITG CO.17 and CO.20 Randomized Clinical Trials. Clin Cancer Res 2024;30:1121-30.
5. Mukund K, Syulyukina N, Ramamoorthy S, et al. Right and left-sided colon cancers - specificity of molecular mechanisms in tumorigenesis and progression. BMC Cancer 2020;20:317.
6. Koulouridi A, Karagianni M, Messaritakis I, et al. Prognostic Value of KRAS Mutations in Colorectal Cancer Patients. Cancers (Basel) 2022;14:3320.
7. Ciardiello D, Maiorano BA, Martinelli E. Targeting KRASG12C in colorectal cancer: the beginning of a new era. ESMO Open 2023;8:100745.
8. Fakih MG, Kopetz S, Kuboki Y, et al. Sotorasib for

previously treated colorectal cancers with KRASG12C mutation (CodeBreaK100): a prespecified analysis of a single-arm, phase 2 trial. Lancet Oncol 2022;23:115-24.
9. Yaeger R, Weiss J, Pelster MS, et al. Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated KRAS G12C. N Engl J Med 2023;388:44-54.
10. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350-6.
11. Bylsma LC, Gillezeau C, Garawin TA, et al. Prevalence of RAS and BRAF mutations in metastatic colorectal cancer patients by tumor sidedness: A systematic review and meta-analysis. Cancer Med 2020;9:1044-57.
12. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 2017;28:1713-29.
13. Watanabe J, Muro K, Shitara K, et al. Panitumumab vs Bevacizumab Added to Standard First-line Chemotherapy and Overall Survival Among Patients With RAS Wild-type, Left-Sided Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA 2023;329:1271-82.
14. Rossini D, Boccaccino A, Carullo M, et al. Primary tumour side as a driver for treatment choice in RAS wild-type metastatic colorectal cancer patients: a systematic review and pooled analysis of randomised trials. Eur J Cancer 2023;184:106-16.
15. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:10-32.
16. NCCN. Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 2.2024. April 30, 2024.
17. Lenz HJ, Ou FS, Venook AP, et al. Impact of Consensus Molecular Subtype on Survival in Patients With Metastatic Colorectal Cancer: Results From CALGB/SWOG 80405 (Alliance). J Clin Oncol 2019;37:1876-85.
18. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-17.
19. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697-705.
20. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 2014;32:2240-7.
21. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1065-75.
22. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:4706-13.
23. Bray SM, Lee J, Kim ST, et al. Genomic characterization of intrinsic and acquired resistance to cetuximab in colorectal cancer patients. Sci Rep 2019;9:15365.
24. Siu LL, Shapiro JD, Jonker DJ, et al. Phase III randomized, placebo-controlled study of cetuximab plus brivanib alaninate versus cetuximab plus placebo in patients with metastatic, chemotherapy-refractory, wild-type K-RAS colorectal carcinoma: the NCIC Clinical Trials Group and AGITG CO.20 Trial. J Clin Oncol 2013;31:2477-84.
25. van der Kruijssen DEW, van der Kuil AJS, Vink GR, et al. Time-varying prognostic value of primary tumor sidedness in metastatic colorectal cancer: A population-based study and meta-analysis. Int J Cancer 2023;152:1360-9.

**Cite this article as:** Cameselle-García S, Fernández Montes A. Is the transverse colon the new right?—similarities in EGFR drug response and prognosis. J Gastrointest Oncol 2024;15(5):2363-2366. doi: 10.21037/jgo-24-272