For years the role of primary tumor sidedness (ie, left/right) as a prognostic factor in metastatic colorectal cancer was overlooked, but it has recently regained importance. In this section, Anelisa K. Coutinho, Jakob Eberhard, Juan Manuel O’Connor, and Cornelis J. A. Punt present the current evidence about the impact of tumor sidedness in metastatic disease and discuss what they believe are the implications in clinical practice of taking tumor sidedness into account or not.

**Is primary tumor sidedness relevant in deciding how to treat metastatic colorectal cancer?**

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For many years, the side location of a primary colorectal tumor was almost only ever mentioned as a prognostic curiosity. However, in May 2016, after three consecutive oral presentations at the American Society of Clinical Oncology Meeting, this simple perspective changed. An analysis of the CALGB/SWOG 80405 trial showed that the primary tumor location affected overall survival with a 14-month difference between left-sided and right-sided tumors (33 months and 19 months, respectively; *P* < 0.0001). In addition, the authors made an exploratory analysis of outcomes between sidedness and the monoclonal antibody used, showing that anti-EGFR treatments (cetuximab) had the best overall survival rate in patients with RAS wild-type left-sided tumors (39 months) vs patients with right-sided tumors (13 months). Differences also existed for an anti-vascular endothelial growth factor (VEGF) treatment, the first-line treatment arm (bevacizumab); however, it was smaller (32 months in left-sided tumors vs 29 months in right-sided tumors) than anti-EGFR treatments.

Following this analysis, other retrospective analyses evaluated the sidedness effect with data from important randomized trials, such as FIRE-3, PRIME, PEAK, and CRYSTAL. All of these trials obtained the same findings, ie, a huge prognostic difference between left-sided and right-sided tumors and an impressive discrepancy in the results, especially when anti-EGFRs were used for left-sided vs right-sided tumors.

FIRE-3 showed a better overall survival with FOLFIRI + cetuximab in RAS wild-type patients with left-sided vs right-sided primary tumors (38 months vs 18 months) and with FOLFIRI + bevacizumab (28 months vs 23 months) (Table I). In the PRIME study, the RAS wild-type patients with left-sided tumors had a better overall survival with FOLFOX + panitumumab vs patients treated with FOLFOX alone (30.3 months vs 23.6 months; HR, 0.73; *P* = 0.0112). However, in patients with right-sided tumors, there was no significant difference in overall survival with the addition of panitumumab (11.1 months vs 15.4 months with and without panitumumab, respectively [HR, 0.87; *P* = 0.5398]).

However, what is so different in the anatomy of each side to explain these findings? The embryological origins of the sides of the colon are diverse; the left side is derived from the embryonic hindgut and the right side from the embryonic midgut. Each side also has different blood supplies, innervations, and vascularization. The results obtained in the different trials are summarized in Table I.
lymphatic drainage pathways. Looking at the molecular features, some alterations, such as a BRAF mutation, microsatellite instability (MSI high), and hypermutation, are found more frequently in the right side of the colon than in the left side. In addition, an active EGFR signaling pathway and a high gene expression of epiregulin are more frequent in patients with left-sided tumors. Thus, the anatomical distinction in sides is probably just a surrogate marker for many biological and molecular alterations that can be predictive of benefit from the choice of monoclonal antibody regarding sidedness.6

So now, with the acquisition of this data, should we take into account the sidedness of the primary tumor in daily practice to choose the ideal first-line treatment for metastatic colorectal cancer? Alternatively, is it reasonable to leave the information aside and continue to choose regardless of the sidedness until prospective randomized trials clarify this point? The main arguments against considering sidedness as an important decision-making tool include the fact that all of the data was based on exploratory retrospective analyses, which need to be confirmed, and the lack of statistical significance in the reviewed trials for most of the right-sided outcome results, which is probably secondary to the small proportion of patients in this group. However, the arguments in favor of considering sidedness for clinical decisions include: (i) the similar results obtained from many retrospective analyses that showed big differences in overall survival and progression-free survival depending on the class of monoclonal antibody used; (ii) the proposed correlation with molecular characteristics for each side, which suggest a biological origin; and (iii) the fact that we already have the option to choose between a double or even triple chemotherapy regimen (oxaliplatin and/or irinotecan) combined with an anti-EGFR or anti-VEGF treatment as first-line options for RAS wild-type patients. The current regimen selection is based on a collection of information, including the intention of the treatment, volume of the disease, performance status, comorbidities, patient’s desire, and other molecular characteristics, such as BRAF mutational status. Therefore, we will not cause “harm” by including laterality as another item in the decision-making process.

Considering the large numeric differences in overall survival when using an anti-EGFR treatment (either cetuximab or panitumumab) as a first-line therapy for RAS wild-type patients with left-sided vs right-sided tumors, it seems like there is no benefit, based on retrospective observations, for the addition of anti-EGFR for right-sided tumors. Both the CRYSTAL trial and the PRIME trial, which compared FOLFIRI + cetuximab with FOLFIRI and FOLFOX + panitumumab with FOLFOX, respectively, for first-line therapy in RAS wild-type patients, showed similar or even worse results for overall survival with anti-EGFR in patients with right-sided tumors (18.5 months vs 15.0 months in CRYSTAL [HR, 1.08; P=0.76] and 11.1 months vs 15.4 months in PRIME [HR, 0.87]).

For the anti-VEGF treatment bevacizumab, the imbalance between the two sides of the colon also favors the left side, although with a smaller difference. Even though an anti-EGFR treatment achieved a better numeric overall survival in left-sided tumors, a retrospective comparison with an anti-VEGF treatment showed that bevacizumab reached reasonable overall survival rates (over 23 months for both left-sided and right-sided tumors) and it showed no detrimental effects in either side. However, the effects of both anti-EGFR and anti-VEGF treatments in second-line therapy, as related to the site of primary tumor, cannot be predicted yet.

In conclusion, in light of the current data, I personally would cautiously favor inclusion of laterality as one of the variables to be considered for treatment selection for first-line treatment in RAS wild-type patients, while using common sense, coherence, and observing individual context, until prospective data becomes available.

References
The answer to this specific question is yes, primary tumor sidedness matters or should matter in the decision-making process of how to treat metastatic colorectal cancer. However, it is—of course—not the sidedness per se that matters, but more that it is the surrogate marker for a different biology, and left-sided cancers and right-sided cancers should perhaps be considered as different diseases.

There may be a solution, or at least a partial solution, to this difficult riddle. In 2014, Heinemann et al presented data from the FIRE-3 study, which randomized patients with metastatic colorectal cancer to FOLFIRI + cetuximab or FOLFIRI + bevacizumab as a first-line treatment. While no between-group differences were observed in the primary end point, ie, an objective response, there was a significant difference in survival in favor of the FOLFIRI + cetuximab in patients with KRAS wild-type tumors, indicating that the FOLFIRI + cetuximab regime would be preferable.

The results from FIRE-3 could not be confirmed in the phase 3 CALGB/SWOG 80405 study, which compared FOLFIRI or leucovorin/5-FU/oxaliplatin (FOLFOX) with bevacizumab or cetuximab in the same patient population as in FIRE-3. There was no difference in survival between patients receiving chemotherapy + cetuximab and those receiving chemotherapy + bevacizumab; therefore, both regimens were considered adequate first-line treatments for patients with metastatic, palliative colorectal cancer and RAS wild-type tumors.2

To help us understand why these well-designed and well-conducted studies gave divergent results, the goal is now to identify subgroups, both on a molecular and clinical basis, that can, in the long term, identify characteristics that will enable a better selection of patients who will obtain a greater benefit with one regime vs another. Due to differences in the biology and embryonic origin for each side of the colon, an analysis of the CALGB study was made by distinguishing between the right and left side of the colon; the transverse colon and rectum were excluded. The results, presented at the 2016 American Society of Clinical Oncology meeting, showed that there is a clinical difference in patients with KRAS wild-type tumors and there was a significantly longer total survival and progression-free survival in patients with a left-sided tumor than in patients with a right-sided tumor. In the KRAS wild-type patients with a left-sided tumor who received cetuximab, the overall survival and progression-free survival were extended, which was the same for KRAS wild-type patients with a right-sided tumor who received bevacizumab. It also appeared that KRAS wild-type patients with a right-sided tumor who received cetuximab had poorer outcomes than did patients with a right-sided tumor and a KRAS mutation. Venook et al, who made the compilation, also had access to the data from FIRE-3 and also presented merged results from both studies. The outcome was the same in both trials; therefore, it could at least partially explain the differences in the results between the CALGB and FIRE-3 studies.

A meta-analysis, recently published by Holch et al,2 analyzed all first-line randomized controlled trials and prospective clinical trials that evaluated the importance of tumor location. The analysis shows that we can say clearly and beyond a doubt that sidedness is an obvious prognostic marker with an inferior prognosis for right-sided tumors and vice versa for left-sided tumors. There is also strong evidence that the addition of an anti-EGFR therapy provides a clear survival benefit for patients with left-sided tumors, whereas this is more controversial and doubtful for patients with right-sided tumors. It also seems that sidedness could be a selector and predictor of treatment choice, considering that an anti-EGFR treatment is more beneficial in left-sided tumors in terms of overall survival and progression-free survival than an anti-VEGF treatment. When it comes to objective risk reduction, it could be different when using an anti-EGFR to shrink the tumor in both left-sided and right-sided tumors, which is relevant mainly in patients with a curative intent of the treatment where maximum shrinkage is a requirement for additional surgery.3 All of this information has already been taken into consideration in most treatment proposals and algorithms.

All of these results continue to suggest that tumor localization matters. From a biological point of view, it is important to be aware of the different distributions, prognoses, and frequencies of microsatellite unstable / microsatellite stable tumors and tumors with BRAF mutations in the right vs the left side of the colon. Additional subgroup analyses are ongoing, indicating that the distinction goes further than deciding whether treatment with anti-EGFR or anti-VEGF is most suitable. In addition to having the worst prognosis, patients with right-sided tumors have more BRAF mutations and a higher extent of microsatellite instability, and they are more likely to develop in patients who have a genetic predisposition. Sidedness and the different biology between the sides of the colon will probably have an impact on the choice of other targeted drugs as well as new immunotherapies, such as PD1/PDL1 inhibitors.
The sidedness difference is a surrogate marker for different tumor biology, which is important. In the future, all studies should take into account the location of the tumor in the colorectum and secure tumor samples for extended biomarker analysis.

References
2. Venook AP, Nesbitrecke D, Innocenti F et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). Presented at American Society of Clinical Oncology 2014.
Since 2016, the role of sidedness has regained importance as a prognostic factor in colorectal cancer. The results of a subanalysis of the CALGB/SWOG 80504 study were presented at the 2016 American Society of Clinical Oncology meeting. This subanalysis compared chemotherapy + bevacizumab with chemotherapy + cetuximab in patients with advanced colorectal cancer and RAS wild-type tumors, and it showed that there was a median survival of 36 months for patients with left-sided tumors vs 16 months for patients with right-sided tumors. A recent systematic review and meta-analysis of 68 clinical trials, which included more than 1,400,000 patients, demonstrated a significant impact on survival, with a 20% reduction in mortality for patients with left-sided tumors (HR, 0.82; 95% CI, 0.79-0.84; P < 0.001), regardless of the initial stage, race, year of the study, number of subjects, adjuvant therapy, and the quality of the studies. However, the question remaining concerned whether sidedness was also a predictive factor for treatment response. In this respect, several analyses were conducted in an attempt to prove the interaction between sidedness and prediction of a response to biological treatment. Although no interaction was initially observed in the efficacy between different anti-angiogenic agents, such as bevacizumab, the location of the primary tumor seems to play a role in the effect of anti-EGFR therapy, such as cetuximab or panitumumab. A subgroup analysis of six randomized controlled trials, which included patients with a diagnosis of advanced colorectal cancer, showed that, for the patients with RAS wild-type tumors, there were differences in the efficacy of anti-EGFR treatments according to the location of the primary tumor. While anti-EGFR-based treatments showed a significant benefit for patients with left-sided tumors (HR, 0.69; 95% CI, 0.58-0.83), no differences were seen for patients with right-sided tumors (HR, 0.96; 95% CI, 0.68-1.35) (P interaction <0.001). These analyses have some limitations, eg, the inclusion of the phase 2 trial PEAK, the retrospective analysis of the data, using definitions of primary tumor location that were not prespecified, including only patients with a RAS wild-type genotype, and not including the triple combination therapy with or without bevacizumab, as clearly shown by the study design. A retrospective analysis of the CRYSTAL and FIRE-3 trials, which assessed the location of the primary colorectal tumor as a predictive factor, showed that, although the treatment arms compared were different, there were differences observed for progression-free survival, overall survival, and objective response rate in favor of the combined therapy with cetuximab in left-sided tumors. For example, FIRE-3 reported that, for patients with left-sided tumors, the median survival was 38 months when they were treated with FOLFIRI + cetuximab vs 28.3 months in those treated with FOLFIRI + bevacizumab (P = 0.002). However, the median survival for patients with right-sided tumors treated with FOLFIRI + bevacizumab was 18.3 months vs 23 months for those treated with FOLFIRI + cetuximab (P = 0.28). The simplest conclusion based on the analysis of these two studies shows that right-sided primary tumor location is a negative predictive factor for a response to anti-EGFR therapy.

How can these differences be explained?

Left-sided tumors show more dependency on EGFR, including a higher number of EGFR copies, a larger number of endogenous EGFR ligands, such as amphiregulin (AREG) and epiregulin (EREG), and a canonical phenotype that is based on the new consensus molecular subtype 2 (CMS2) classification. Moreover, there are some molecular alterations that might account for resistance to treatment with anti-EGFR in right-sided tumors, such as the BRAF V600E mutation, a CpG island, mutations in phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit α isoform (PIK3CA), and a higher representation of the immune subtype CMS1 with the phenotype of microsatellite instability.

Is primary tumor sidedness (left – right) relevant in deciding how to treat metastatic disease?

The short answer is “yes.” We should consider that, although the analysis of the CRYSTAL and FIRE-3 trials was retrospective and not prespecified, the findings were consistent with first-line therapies, mainly in patients with advanced colorectal cancer with RAS, BRAF, and wild-type tumors. Some changes have already been made in the 2017 National Comprehensive Cancer Network guidelines, which exclude the possibility of using anti-EGFR therapy as a first-line therapy for RAS wild-type patients with right-sided tumors. The combined analysis of different studies shows that patients with right-
sided tumors have a poor prognosis and that right-sided tumors have a negative predictive value in terms of response to anti-EGFR treatment. Moreover, it is clear that tumor location must be considered as a stratification factor in future clinical trials. The challenge is to identify the molecular pattern accounting for these differences in the sensitivity to anti-EGFR therapy according to the primary tumor location.

References
Is primary tumor sidedness relevant in deciding how to treat metastatic colorectal cancer?

Established prognostic markers are the RAS and BRAF mutational status of the tumor in mCRC, and mismatch repair status in the early stages of the disease. The RAS and BRAF mutational status is also predictive for the use of anti-epidermal growth factor receptor (EGFR) treatments (cetuximab, panitumumab). Promising predictive markers include the HER2 and mismatch repair status in mCRC for treatment with anti-HER2 antibodies and immune checkpoint inhibitors, respectively. These markers may not only provide targets for novel drugs, but may also allow for a better selection of patients for treatment with established drugs to prevent unnecessary exposure to their toxicity and to reduce costs. Therefore, with most research being focused on molecular subtypes, it came somewhat as a surprise that a clinical characteristic, such as sidedness of the primary tumor, resurfaced last year as a topic of intense debate in mCRC.

Although the prognostic value of primary tumor sidedness in mCRC was recognized in 2001 and confirmed in 2015, it was rarely, if ever, used in clinical practice, eg, for stratification or subgroup analyses in prospective randomized trials. Early data from 2015 on its predictive value regarding the use of anti-EGFR antibodies as a late-line monotherapy had little clinical impact at the time. However, data from more recent analyses on the predictive value of primary tumor sidedness can no longer be ignored, and the implications of using expensive drugs probably played a role.

Although different definitions have been used for sidedness, right-sided tumors are commonly defined as tumors originating in the cecum, ascending colon, hepatic flexure, and transverse colon; whereas, left-sided tumors are commonly defined as tumors originating in the splenic flexure, descending colon, sigmoid, and rectum. As to its predictive value for anti-EGFR treatment in (K)RAS and BRAF wild-type tumors, all retrospective analyses that have been performed to date show that the benefit of anti-EGFR treatment is limited to mCRC patients with left-sided primary tumors, with no benefit being shown for mCRC patients with right-sided tumors. These results apply to anti-EGFR treatment + chemotherapy as a first- and second-line therapy and as a monotherapy in late-line treatment. The situation is more complex regarding the use of chemotherapy + bevacizumab, an antibody against vascular endothelial growth factor (VEGF), vs anti-EGFR treatment. Currently, the results of three randomized trials—PEAK, FIRE-3, and CALGB/SWOG 80405—on chemotherapy + bevacizumab vs chemotherapy + anti-EGFR are available for this analysis, where: (i) PEAK was a randomized phase 2 trial; (ii) FIRE-3 showed an unexpected benefit in median overall survival for the anti-EGFR treatment arm, which may be related to the use of salvage treatments and therefore not to the comparison of primary interest, while the results on response rate and median progression-free survival were highly comparable; and (iii) the results of CALGB 80405 did not confirm the overall survival benefit observed in FIRE-3. A meta-analysis of these trials showed a superior efficacy for chemotherapy + bevacizumab in right-sided tumors and a preference for chemotherapy + anti-EGFR treatment in left-sided tumors. However, this latter conclusion leans heavily on the effect of sidedness on median overall survival, which is strongly influenced by the FIRE-3 data, which, with respect to overall survival, is questionable.

While data on the predictive value for anti-EGFR treatment appear quite robust, it is not expected that tumor sidedness will tell the whole story. Embryologically, the right side of the colon is derived from the midgut, whereas the left side of the colon and rectum develop from the hindgut, and there are genomic differences between these tissues that might underlie the observed difference in outcome. Therefore, further studies on molecular-marker profiles should elucidate this issue. Since factors, such as BRAF mutational status, sex, and prior adjuvant therapy, have been included in multivariate analyses, they cannot account for the observed effect of sidedness. However, even BRAF wild-type tumors may contain a BRAF mutant-like gene expression signature, which is most often present in right-sided mCRC.

In conclusion, sidedness of the primary tumor in patients with mCRC has a strong prognostic value, which should be included in the design of future clinical trials. The predictive results on tumor sidedness should be interpreted with caution due to the retrospective nature of the analyses, which were per-
formed on subpopulations of patients included in these trials, and because none of these studies contemplated a full treatment sequence strategy. However, currently available data strongly suggest that mCRC patients with right-sided primary tumors should not be treated with anti-EGFR antibodies irrespective of RAS/BRAF mutational status. In these patients as well as in mCRC patients with left-sided RAS/BRAFV600E mutated tumors, chemotherapy + bevacizumab is the treatment of choice. In patients with left-sided RAS/BRAF wild-type tumors, both chemotherapy + bevacizumab and chemotherapy + anti-EGFR are valid treatment options, and any possible preference for the latter option should be confirmed in further trials.

References