Prognostic and predictive value of primary tumour location in metastatic colorectal cancer: will the side change our treatment?

V. de Weerdt, MD, E. van Cutsem, MD, PhD

SUMMARY

Metastatic colorectal cancer is a heterogeneous disease. Tumours arising from different regions of the colon are clinically and molecularly distinct. The differing molecular characteristics translate into a differential clinical outcome with right-sided tumours displaying a worse prognosis compared to left-sided tumours. Besides the prognostic relevance of the primary tumour location, several retrospective analyses suggest that the primary tumour location may also be predictive of treatment benefit from targeted therapy with anti-EGFR and anti-VEGF directed agents in the first-line treatment of RAS wild-type metastatic colorectal cancer.

(BELG J MED ONCOL 2018;12(6):271-274)

INTRODUCTION

Colorectal cancer is a clinically and molecularly heterogeneous disease.[1-3] A significant part of this heterogeneity is captured by the anatomic location of the tumour. Left-sided tumours (those originating in the rectum, sigmoid colon, descending colon, splenic flexure or one-third of the transverse colon) derive from the embryonic hindgut. In contrast, right-sided tumours (those originating in the caecum, ascending colon, hepatic flexure or two-thirds of the transverse colon) derive from the embryonic midgut. The right colon and left colon have different vascular supplies, the right colon being supported by the superior mesenteric artery and the left colon by the inferior mesenteric artery. Also, the physiological functions of both sides differ, and exposure to nutrients and carcinogens varies. Some recent studies also suggest potential differences in the microbiome in the right and left colon.

Consistent with these differences in embryological origin, left-sided and right-sided tumours have also molecular differences. The four consensus molecular subtypes (CMS) of colorectal cancer are present on both colon sides, though with different frequencies in the different colon subsegments. Right-sided tumours are more common in women and are more frequently characterised by mucinous histology, high microsatellite instability, CpG island methylation and *RAS* and *BRAF* mutations. Conversely, left-sided tumours are more commonly associated with chromosomal instability and a gene expression profile corresponding to an activation of the epithelial growth factor receptor (EGFR) pathway.[1,2,4] These molecular differences translate into a differential clinical outcome with right-sided tumours displaying worse prognosis. Nevertheless, the primary tumour location (PTL) has not been used as a stratification factor in clinical trials so far,

Department of Gastroenterology/Digestive Oncology, University Hospitals Gasthuisberg, Leuven, Belgium.

Please send all correspondence to: E. van Cutsem, MD, PhD, Department of Gastroenterology/Digestive Oncology, University Hospitals Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium, tel: +32 16 34 42 18, email: eric.vancutsem@uzleuven.be.

Conflict of interest: V. de Weerdt has nothing to disclose. E. van Cutsem has reported research grants from Bayer, Boehringer, Amgen, Celgene, Ipsen, Lilly, Merck, Novartis, Roche and Sanofi.

Key words: left-sided colon cancer, RAS wild-type metastatic colorectal cancer, right-sided colon cancer..

and it has not been a factor in guiding the selection of the most appropriate therapy for patients with metastatic colorectal cancer (mCRC).

IS TUMOUR SIDE PROGNOSTIC FOR SURVIVAL?

Petrelli *et al.* conducted a meta-analysis of 66 studies including 1,437,846 patients with a median follow-up of 65 months. Left-sided primary tumour location was associated with a significantly reduced risk of death (HR=0.82 [95% CI: 0.79-0.84]; p<0.001), and this was independent of stage, race, adjuvant chemotherapy, year of study, number of participants and quality of included studies.[5]

Another recent meta-analysis of fifteen studies that compared the prognosis of colon cancer according to tumour location showed that left-sided colon cancer was significantly associated with better overall survival (OS) versus right-sided colon cancer (HR=1.14 [95% CI: 1.06-1.22]; p<0.01).[6] Kerr *et al.* analysed tumour specimens plus histopathological and outcome data from two large adjuvant trials (VICTOR trial and QUASAR2 trial).[7] In the multivariate analysis, they found that OS was significantly improved in patients whose primary tumours were left-sided compared with those with right-sided tumours (n=1582; HR right side *vs* left side=1.40 [95% CI: 1.07-1.82]; p=0.013). Interestingly, sidedness had no significant effect on relapse-free survival, suggesting that rates of recurrence were not significantly lower in patients whose tumours were left sided. The difference in OS appears to be a consequence of an increased duration of survival after relapse for those patients with left-sided tumours compared with those with right-sided tumours (n=362; HR for right side *vs* left side=1.53 [95% CI: 1.14-2.06]; p=0.004). Another recent meta-analysis comprised thirteen first-line randomised, controlled trials (RCT) and one prospective pharmacogenetic study investigated the role of PTL.[3] OS in patients with right-sided tumours was generally poor and remained below twenty months in several studies investigating chemotherapy with and without targeted therapy. This effect was also evident with regard to progression free survival (PFS). Further, the prognostic effect was similarly evident when the differential effect of PTL on the outcome was considered for each treatment arm of the studies, where data were available.

Tejpar *et al.* performed a retrospective data analysis from patients with RAS wild-type (wt) mCRC treated in the CRYSTAL and FIRE-3 trials.[8] Patients were classified as having left-sided or right-sided mCRC. PFS, OS and the objective response rate (ORR) were significantly greater in left-sided *vs* right-sided tumours among RAS wt CRYSTAL-study patients treated with folfiri plus cetuximab. Furthermore, median PFS, median OS and the ORR were numerically superior in folfiri-treated CRYSTAL-study patients with left-sided tumours compared with patients with right-sided tumours. Similar results were found among folfiri plus cetuximab treated RAS wt patients in the FIRE-3 study. Although less pronounced, this effect was also observed in the folfiri plus bevacizumab treatment arm of FIRE-3 for PFS, OS and the ORR. A team of investigators and collaborators under the leadership of the European Society of Medical Oncology (ESMO) performed a large retrospective analysis including 2159 patients (515 with right-sided and 1644 with left-sided tumours) with unresectable RAS wt mCRC in six randomised trials (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK and 20050181), comparing chemotherapy plus EGFR antibody therapy (experimental arm) with chemotherapy or chemotherapy and bevacizumab (control arms). A significantly worse prognosis was observed for patients with right-sided tumours compared with those with left-sided tumours in both the pooled control and experimental arms for OS (HRs=2.03 [95% CI: 1.69-2.42] and 1.38 [1.17-1.63], respectively), PFS (HRs=1.59 [1.34-1.88] and 1.25 [1.06-1.47]), and ORR (ORs=0.38 [0.28-0.50] and 0.56 [0.43-0.73]). [9]

As *BRAF* mutations are associated with worse outcome in mCRC, one might wonder whether this drives the prognostic effect of sidedness. However, multivariate analyses in the papers discussed above showed that the *BRAF* mutational status is an independent prognostic factor.[6,8]

IS TUMOUR SIDE PREDICTIVE FOR TREATMENT RESPONSE?

The CALGB/SWOG 80405 trial enrolled 1137 patients with RAS wt mCRC who were randomised to first-line bevacizumab or cetuximab combined with one of two chemotherapy doublets (folfox or folfiri).[10] The outcome by treatment arm was not statistically different. When patients were pooled according to PTL, patients with left-sided tumours receiving the anti-EGFR monoclonal antibody cetuximab had a median OS of 36 months compared with an OS of 16.7 months for those with right-sided tumours (HR=1.87 [95% CI:1.48-2.32]; p<0.001). Tejpar *et al.* found similar results in the retrospective analysis of the CRYSTAL and FIRE-3 trails.[8] Holch *et al.* also demonstrated sidedness as a predictive biomarker in the meta-analysis on the CRYSTAL and PRIME trials.[3] He further performed a meta-analysis on three trials evaluating PTL in the comparative setting of first-line anti-EGFR versus anti-VEGF antibody in combination with standard chemotherapy (FIRE-3, CALGB/SWOG 80405, PEAK). In RAS wt left-sided colorectal cancer, the meta-analysis revealed a significant benefit from first-line anti-EGFR treatment with regard to OS and ORR but not for PFS. In contrast, in right-sided colorectal cancer, PFS was significantly bet-

KEY MESSAGES FOR CLINICAL PRACTICE

1. Caveat: the recommendations are based on large retrospective analyses. They are in line with the European Society of Medical Oncology recommendations and consensus.
2. Right versus left colon cancer differences are reflected in epidemiology, etiological factors, pathogenesis, molecular alterations, embryology, clinical presentation and outcome.
3. Right-sided tumours have worse prognosis compared with left-sided tumours.
4. Patients with RAS wild-type left-sided tumours benefit most from anti-EGFR (epithelial growth factor receptor) therapies in the first-line treatment of metastatic colorectal cancer, especially if tumour response is warranted. This should, however, be put in perspective in the continuum of care of metastatic colorectal cancer treatment and in balance with the toxicity pattern of EGFR antibody therapy and of bevacizumab.
5. Patients with RAS wild-type right-sided tumours might be better treated with chemotherapy alone or probably chemotherapy plus bevacizumab – except if the goal is tumour size reduction as the objective response rates were higher.
6. There is no reason to avoid EGFR antibody therapy in later lines in cases of disease progression or treatment intolerance independent of the primary tumour location.
7. New randomised controlled trials should stratify patients according to the primary tumour location.

ter for bevacizumab based treatment compared with treatment with anti-EGFR antibody. The results for the OS did not reach the level of significance. Of note, the overall odds ratio (OR) for the ORR numerically favoured anti-EGFR based treatment in patients with right-sided tumours.[3] The largest and strongest data on the predictive effect of tumour sidedness came here also from the ESMO analysis.[9] A significant predictive benefit was demonstrated for chemotherapy plus EGFR antibody therapy in patients with left-sided tumours (HRs=0.75 [0.67-0.84] and 0.78 [0.70-0.87] for OS and PFS, respectively). However there was a trend, but no significant benefit for patients treated with chemotherapy with or without bevacizumab with right-sided tumours (HRs=1.12 [0.87-1.45] and 1.12 [0.87-1.44] for OS and PFS, respectively). For the ORR, there was a trend towards a greater benefit for chemotherapy plus EGFR antibody therapy in the patients with left-sided tumours (OR=2.12 [1.77-2.55]) compared with those with right-sided tumours (OR=1.47 [0.94-2.29]). Right sided seems to derive more benefit from bevacizumab compared with the EGFR antibodies.

CONCLUSION

Data across several studies clearly indicate that right-sided colon cancer is associated with worse prognosis compared with left-sided colon cancer. The clear prognostic effect is evident for first-line chemotherapy alone and chemotherapy plus targeted therapy. Furthermore, there are data showing that patients with left-sided Ras wild type primary tumours benefit most from adding EGFR antibody therapy to chemotherapy. Prior work has demonstrated an EGFR inhibitor-sensitive phenotype that appears to be more prevalent in left-sided tumours.[1,2,4] One older hypothesis states that PTL may simply be a surrogate marker for the *BRAF* mutational status, given the predominance of *BRAF* mutation in right-sided tumours. However, multivariate analyses in the papers discussed above showed that the *BRAF* mutational status is an independent prognostic factor.[6,8] Other studies revealed that even *BRAF* wt tumours may possess a *BRAF*-mutant-like gene expression signature, which is associated with a similar poor prognosis.[1,2,4] The molecular differences responsible for the different outcome in right-sided and left-sided metastatic colorectal cancer have still to be unravelled. The latest version of the National Comprehensive Cancer Network (NCCN) guidelines on treatment of metastatic colon cancer recommend anti-EGFR therapy only for RAS wt and left-sided tumours. Although the evidence is clearly growing, some experts say caution is warranted in drawing conclusions to change clinical practice as all data are derived

from retrospective analyses with relatively small sample sizes. Future randomised trials should stratify patients according to PTL. Also, a comprehensive evaluation of molecular features is necessary to better understand the prognostic and predictive effects of PTL and will contribute to improvements in treatment outcomes in the future.

REFERENCES

1. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015;21(11):1350-6.

2. Missiaglia E, Jacobs B, D'Ario G, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Onc. 2014;25(10):1995-2001.

3. Holch JW, Ricard I, Stintzing S, et al. The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials. Eur J Cancer. 2017;70:87-98.

4. Dienstmann R, Vermeulen L, Guinney J, et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer. 2017;17(2):79-92.

5. 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(2):211-219.

6. Yahagi M, Okabayashi K, Hasegawa H, et al. The worse prognosis of right-sided compared with left-sided colon cancers: a systematic review and meta-analysis. J Gastrointest Surg. 2016;20(3):648-55.

7. Kerr DJ, Domingo E, Kerr R. Is sidedness prognostically important across all stages of colorectal cancer? Lancet Oncol. 2016;17(11):1480-2.

8. Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: Retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol. 2017;3(2):194-201.

9. Arnold D, Lueza B, Douillard J-Y, 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(8):1713-29.

10. Venook A, Niedzwiecki D, Innocenti F, et al. Impact of primary tumor location on overall survival and progression free survival in patients with metastatic colorectal cancer: Analysis of CALGB/SWOG 80405 (Alliance). ASCO annual meeting 2016. J Clin Oncol. 34, 2016;34(15_suppl):3504.

11. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386-422.