Primary Tumor Location Found to Impact Prognosis and Response to Therapy in Patients With Metastatic Colorectal Cancer

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—John Marshall, MD

A recent article has reported that patients with left-sided colorectal cancers (CRCs) have a strikingly better prognosis than those with right-sided malignancies, and derive more benefit from standard therapy (JAMA Oncol. 2017;3:194-201.)

Right-sided tumors (those arising in the appendix, ascending colon, hepatic flexure, or first two-thirds of the transverse colon) and left-sided tumors (those arising in or distal to the latter one-third of the transverse colon) originate from different embryonic tissue and have unique molecular profiles, with right-sided tumors associated with the more frequent occurrence of poor prognostic gene expression profiles. In previous research, right-sided tumors typically have been found to demonstrate a poorer prognosis, but this clinical factor traditionally has not been included in disease stratification in clinical trials, nor has the effect of tumor side of origin been studied very often as a predictive factor for particular treatments.

Sabine Tejpar, MD, PhD, head of the molecular digestive oncology unit at the University Hospital of Gasthuisberg in Leuven, Belgium, and colleagues from several cancer centers (mostly in Europe) set out to investigate whether right-sidedness versus left-sidedness of primary tumors had any effect on the likelihood of response to therapy for metastatic disease. “We have known for some time that right versus left are prognostically different, but only more recently has sidedness been linked to treatment response,” says John Marshall, MD, chief of hematology and oncology at Lombardi Cancer Center at Georgetown University in Washington, DC, who was not affiliated with this study.

Study Details
The Cetuximab Combined With Irinotecan in First-line Therapy for Metastatic Colorectal Cancer (CRYSTAL) trial was a phase 3 study originally published in 2009 that demonstrated that adding cetuximab to infusional 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) significantly improved the overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) when administered as a first-line therapy for patients with KRAS wild-type metastatic CRC (mCRC). The FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab as First-Line Treatment For Patients With Metastatic Colorectal Cancer (FIRE-3) trial was a phase 3 study published in 2014 demonstrating that in patients with KRAS wild-type mCRC, FOLFIRI with cetuximab as first-line therapy conferred an increase in OS versus FOLFIRI with bevacizumab, although the PFS and ORR were not significantly different between the treatment groups. The current study evaluated the patients with KRAS wild-type mCRC from these 2 trials in terms of prognosis and response according to tumor side of origin. It was not a pooled analysis because the control arms were different.

Of the patients in the CRYSTAL trial with KRAS wild-type mCRC, 280 (77%) had left-sided tumors and 84 (23%) had right-sided tumors. Of the patients in the FIRE-3 trial with KRAS wild-type mCRC, 306 (78%) had left-sided tumors and 88 (22%) had right-sided tumors. Three patients from the CRYSTAL trial and 6 patients from the FIRE-3 trial were excluded because the tumor side of origin was unknown. A higher percentage of patients with right-sided tumors were women and had multiple metastatic sites and those with left-sided tumors were men and had fewer metastatic sites.

KEY POINTS
- Patients with mCRC with a left-sided primary tumor carry a better prognosis than patients with tumors originating on the right side.
- Adding cetuximab to chemotherapy improves outcomes for patients with left-sided tumors, but not for those with right-sided ones.
- Side of origin should be considered when deciding on therapeutic regimens for patients with mCRC.
tumors more often had liver-only metastases in both study populations.

The PFS, OS, and ORR were significantly greater in patients with left-sided versus right-sided tumors in the CRYSTAL trial of patients treated with FOLFIRI plus cetuximab. In patients treated with FOLFIRI alone, the median PFS, median OS, and ORR were numerically higher, although not reaching statistical significance, in patients with left-sided versus right-sided tumors. Patients with left-sided tumors in the FOLFIRI plus cetuximab arm of the FIRE-3 trial had significantly better PFS and OS than patients with right-sided tumors and a numerically (but not statistically significantly) higher ORR. In patients treated with FOLFIRI plus bevacizumab, those with left-sided tumors also had improved outcomes, but the differences were less prominent and only the OS difference reached statistical significance.

Among patients in the CRYSTAL trial with RAS wild-type left-sided tumors, adding cetuximab to FOLFIRI was found to significantly improve the PFS, OS, and ORR, which is in keeping with the overall study results. However, no significant benefit was noted with the addition of cetuximab in patients with right-sided tumors. Similarly, in the FIRE-3 trial, patients with left-sided tumors who were treated with FOLFIRI plus cetuximab were found to have a significantly longer OS compared with patients treated with FOLFIRI plus bevacizumab, with no significant differences noted with regard to PFS or ORR, in accordance with the overall study findings. However, among patients with right-sided tumors, no significant differences were noted between treatment groups. Dr. Tejpar and her colleagues note that the right-sided population was small in both studies, which may limit their findings.

“This article shows similar results to a retrospective study presented at the American Society of Clinical Oncology meeting last year by Alan Venook and colleagues. Further research now has to address why these treatment differences occur and to find better treatments tailored to the patient. We believe that there are molecular characteristics that will track right versus left, but they are not well described as yet,” says Dr. Marshall.

**Implications**

The current study found that patients with left-sided tumors not only had a better prognosis than those with right-sided tumors, but also that chemotherapy with FOLFIRI plus cetuximab improved outcomes in these patients (versus FOLFIRI alone in the CRYSTAL trial and versus FOLFIRI plus bevacizumab in the FIRE-3 trial), although the addition of cetuximab had little effect on patients with right-sided tumors. The study authors state that this suggests a need to find better therapy for patients with mCRC and right-sided primary tumors, and argue for stratification by tumor location in clinical trials. Furthermore, better elucidating the biological differences between tumors of different locations may help to develop more efficacious therapies. Multiple prior studies have provided mixed results when analyzing treatment benefit and side of tumor origin, but the authors of the current study state that the bulk of evidence does suggest primary tumor location as impacting the response to therapy.

“This study, along with other studies showing similar findings, is practice-changing. We should be taking sidedness into account, and in fact the NCCN guidelines now recommend against using first-line EGFR [epidermal growth factor receptor] inhibitors in patients with colorectal cancer that originated on the right, regardless of KRAS status. Unfortunately, community uptake is slow. I talk to many community oncology providers and uptake is not good—there is not a high level of awareness so education is in order,” says Dr. Marshall.

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