CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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Right-Sided vs Left-Sided Colorectal Cancer

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H&O What is the definition of right-sided vs left-sided colon cancer?

AV In the analysis of the Cancer and Leukemia Group B (CALGB)/SWOG 80405 trial that we presented at the 2016 annual meeting of the American Society of Clinical Oncology (ASCO), we defined right-sided colon cancer as cancer of the cecum and the ascending colon up to the hepatic flexure. Left-sided colon cancer comprises cancer of the splenic flexure and cancer in regions distal to the splenic flexure, including the rectum. The transverse colon connects the left and right sides and on average is appreciably shorter than the right and left sides. Fewer cancers occur there, and for clarity, we omitted patients with cancer of the transverse colon from our analysis. In fact, the addition of these cases to either the left side or the right side did not change our results.

H&O What are the distinct characteristics of right-sided vs left-sided tumors?

AV If we think about it embryologically, the right side of the colon arises from the midgut, and the left side arises from the hindgut. The transverse colon is composed of parts of both structures. It is thought that more of the transverse colon comes from the midgut than from the hindgut, although this is quite variable.

We have only recently, over the past 5 to 10 years, determined that the parts of the colon derived from the midgut and the hindgut are different. For example, we have observed that flat polyps are more likely to occur on the right side than on the left side. These are different from the garden-variety polyps that typically give rise to cancer.

Right-sided tumors are more likely to develop in patients who have a genetic predisposition to colorectal cancer, including those with Lynch syndrome or microsatellite instability. Furthermore, tumors with *BRAF* mutations, which are a poor prognostic sign in colorectal cancer, also are more likely to occur on the right side.

Another difference between right-sided and left-sided cancers is that right-sided colon cancers tend to be diagnosed much later than left-sided colon cancers. This clinical observation reflects the tendency for right-sided colon cancers to produce symptoms only when they are relatively advanced. Stool is liquid on the right side of the colon, and the cecum is a large and wide structure, so the bowel symptoms that typically herald the presence of colon cancer—such as pain, cramps, or blockage—do not occur until an extensive mass has formed, sometimes over many years.

H&O What differences in gene expression profiles have been found?

AV We are only now beginning to investigate and sort out the molecular differences between the tumors in the 2 sides. Several different groups have come up with their own version of the molecular subtypes. Guinney and colleagues published the leading study on this subject in 2015 in *Nature Medicine*. By looking at various expression arrays, they came up with 4 well-defined subtypes (some groups have defined 5 subtypes) that reflect the ways in which colorectal cancer behaves biologically. These types are not randomly distributed across the colon; they tend to be on one side or the other. Ultimately, what matters is not the sidedness of the tumor because sidedness is simply a surrogate for the types of tumors that tend to occur on that side.

H&O What studies have looked at the prognostic or predictive value of tumor sidedness?

AV To my knowledge, the first study that found differences in outcome was an Eastern Cooperative Oncology Group/CALGB study by O'Dwyer and colleagues, which appeared in the *Journal of Clinical Oncology* in 2001. A total of 1120 patients with metastatic colorectal cancer were randomly assigned to 1 of 5 arms. The researchers found that survival was 15.8 months in the patients with left-sided primary tumors and 10.9 months in those with right-sided tumors, a difference of approximately 5 months. Was that because treatment worked better in the patients with left-sided tumors, or did these patients have a better underlying prognosis? The study was not able to answer that question.

In the CALGB/SWOG 80405 trial that we analyzed, we showed that tumor sidedness has both prognostic and predictive value in metastatic colorectal cancer. One of the advantages of this trial was that overall survival (OS) and progression-free survival (PFS) did not differ depending on whether the patients received bevacizumab (Avastin, Genentech) or cetuximab (Erbitux, Lilly) in addition to chemotherapy with 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX) or with 5-FU, leucovorin, and irinotecan (FOLFIRI). We found that tumors of the right side were clinically different from tumors of the left side. Among patients with *KRAS* wild-type disease, OS and PFS were better in those with left-sided primary tumors. In addition, OS and PFS were better with bevacizumab than with cetuximab in patients with right-sided primary tumors. Therefore, bevacizumab may be a better first-line treatment for patients with right-sided primary tumors regardless of their *KRAS* status.

Tumor sidedness also provided prognostic value in a study that Tejpar and colleagues published in *JAMA Oncology* in 2016. This retrospective analysis of patients with *RAS* wild-type metastatic colorectal cancer from CRYSTAL (Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) and FIRE-3 (FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab as First-Line Treatment of *KRAS* Wild-Type Metastatic Colorectal Cancer) found that those with left-sided cancer had a better prognosis regardless of treatment—their OS, PFS, and objective response rate were all better. The study also found that patients with left-sided tumors derived more benefit from first-line treatment with FOLFIRI plus cetuximab than from FOLFIRI alone or FOLFIRI plus bevacizumab. Patients with right-sided tumors derived only limited benefit from these standard treatments.

These studies from Europe consistently show that patients do much better with cetuximab than with bevacizumab, whereas our work here in the United States has not demonstrated any superiority of cetuximab vs bevacizumab. We have struggled to explain this difference in results.

> We showed that tumor sidedness has both prognostic and predictive value in metastatic colorectal cancer.

One difference is that approximately one-third of the population in our study—from the United States and Canada—had right-sided cancer, whereas only 22% of those in the FIRE-3 population—from Germany and Austria—had right-sided cancer. We hypothesized that the relative sidedness imbalance may have led to poorer outcomes in the US study in patients receiving cetuximab because of the higher percentage of right-sided tumors in this group. Therefore, we did a modeling study in which we weighted our patient sample to reflect the same distribution of left vs right as in the FIRE-3 population. We found that tumor sidedness accounted for some of the difference between the 2 studies, but not all of it.

Another important point about these 2 studies, and others that are similar, is that only first-line treatment was mandated. This means that the effects of subsequent treatments are virtually impossible to weed out, and that some of the differences may be attributed to such factors as patterns of care.

What all the studies have shown—CALGB/SWOG 80405, FIRE-3, and CRYSTAL—is that endothelial growth factor receptor (EGFR) antibodies do not, on average, provide meaningful benefit to patients with right-sided cancer, regardless of *RAS* status. Is this true for all patients, or might there be some patients who could benefit from these agents? Furthermore, are these data on the first-line use of cetuximab applicable to the use of cetuximab as a second-line agent?

There are 2 studies that have looked at how tumor sidedness may affect how well cetuximab works beyond first-line treatment. A study by Brulé and colleagues reanalyzed data from the National Cancer Institute of Canada (NCIC) Clinical Trials Group CO.17 (A Phase III Randomized Study of Cetuximab and Best Supportive Care Versus Best Supportive Care in Patients With

Pretreated Metastatic Epidermal Growth Factor-Positive Colorectal Carcinoma) and concluded that tumor location within the colon is strongly predictive of PFS benefit from cetuximab therapy in refractory metastatic colorectal cancer. Among patients with *KRAS* wild-type colorectal cancer, cetuximab improved PFS only in those with left-sided disease. Similar results were seen by Moretto and colleagues in a 2016 study in which single-agent anti-EGFR antibodies did not benefit patients with right-sided metastatic colorectal cancer without mutations in *RAS* or *BRAF*.

H&O Do these findings have any additional implications?

AV In theory, we may be able to explain some study results that we find confusing. For example, the New EPOC (Eloxatin Peri-Operative Chemotherapy) trial by Primrose and colleagues showed that patients with *KRAS* wild-type colorectal cancer who had resectable liver metastases did worse if they received an EGFR antibody plus chemotherapy than if they received chemotherapy alone. This was a finding that seemed illogical and was inconsistent with expectations. If this study had included a large percentage of patients with right-sided colorectal cancer, however—and I recently learned that it did not—that could explain the results. We obviously have been barking up the wrong tree when it comes to *RAS*. We thought it was the dominant oncogene overall, but on the right side it is not. There is a whole new line of research we need to do now.

H&O What ongoing research is looking at sidedness?

AV Our group has undertaken a molecular analysis of patients with metastatic colorectal cancer to help explain what is going on in these patients. Our work has been slowed by the unexpected death of our friend and colleague Daniel Sargent, who has been the major biostatistician for so many large oncology trials, so we may or may not have the results ready to present at the next ASCO annual meeting.

Disclosures

Dr Venook has received research funding from and served as an advisor to Genentech, Roche, Merck Serono, and Bristol-Myers Squibb.

Suggested Readings

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