How We Treat Left-Sided vs Right-Sided Colon Cancer

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Learning Objectives

- To understand the biological and clinical differences between left-sided and right-sided colon cancer;
- To identify appropriate therapies for patients with metastatic colon cancer according to the primary tumor site and molecular profile.

Introduction

Cancers arising from different regions of the colorectum are clinically and molecularly distinct.[1-5] Right-sided tumors, which include those of the cecum, the ascending colon, and the proximal two-thirds of the transverse colon, arise embryologically from the midgut. Left-sided tumors, which comprise those of the distal one-third of the transverse colon, the descending colon, the sigmoid colon, and the rectum, arise from the hindgut. Right-sided and left-sided cancers are commonly defined as proximal and distal to the splenic flexure, respectively. Vascular support systems are also unique according to location, with the left and right sides of the colon supported by the inferior and superior mesenteric arteries, respectively. Left-sided and right-sided colorectal cancers (CRCs) differ extensively in terms of gene expression, DNA mutations, and methylation profile.[5] Clinically, left-sided and right-sided CRCs differ in epidemiologic trends and outcomes. Approximately two-thirds of sporadic colon cancers are left-sided and harbor traditional Vogelgram alterations,[6] whereas one-third are right-sided and follow different carcinogenic pathways. Moreover, individuals with the driver germline genetic alterations of hereditary syndromes show a propensity toward the development of right-sided tumors. Primary tumor site has been correlated with survival in a stage-dependent fashion, as well as with response to targeted agents in patients who have metastatic disease.[7] In addition to *RAS* mutation and microsatellite instability (MSI) status, tumor site has recently been incorporated into the National Comprehensive Cancer Network guidelines[8] for making treatment decisions. Importantly, emerging evidence suggests that CRC represents a biological continuum,[9] rather than a dichotomy defined by anatomical or embryonic landmarks.[10]

Genetic and Molecular Landscape by Tumor Location

Left-sided and right-sided CRCs exhibit unique profiles at the genetic, epigenetic, transcriptomic, and proteomic levels, as well as differences within the microbiome. Although certain alterations are common to the majority of CRCs, such as *APC* mutations and WNT pathway aberrations, at least 1300 genes have been identified with distinct expression patterns in left-sided and right-sided CRCs.[3] Data from The Cancer Genome Atlas demonstrate that right-sided tumors display a hypermutated genotype that is largely diploid and in which MSI is relatively prevalent,[2] whereas left-sided tumors more frequently show loss of heterozygosity and chromosomal instability.[11,12] Left-sided tumors are enriched for *KRAS* mutations, *EGFR/HER2* amplifications, and a high level of amphiregulin and epiregulin expression.[5,13] Conversely, right-sided tumors are enriched for *BRAF*, *PI3KCA*, and *TGFBR2* mutations.[14] Differences in DNA methylation between left-sided and right-sided CRCs have been well documented; most notably, the CpG island methylator phenotype (CIMP), or DNA hypermethylation at a unique set of gene regions that remain unmethylated in non-CIMP tumors, is more prevalent in right-sided CRCs. In addition, right-sided tumors are characterized by several adverse prognostic factors, including the serrated pathway signature and mucinous, undifferentiated histology. The distribution of the consensus molecular subtypes (CMS) differs across the colon and rectum,

with a greater proportion of CMS1 (immune/MSI) and CMS3 (metabolic) tumors in the right side of the colon, and a greater proportion of CMS2 (canonical) and CMS4 (mesenchymal) tumors in the left side of the colon.[15] Differences within the microbiome across subsites have been illustrated, with *Fusobacterium*, *Escherichia-Shigella*, and *Leptotrichia* more abundant in left-sided tumors, and *Prevotella*, *Peptostreptococcus*, and *Selenomonas* more prevalent in right-sided tumors.[16]

The interactions between tumor subsite, molecular profile, and outcomes continue to be explored. For example, in stage III colon cancer, the favorable prognostic benefit of deficient mismatch repair (dMMR) status has been shown to be restricted to patients who have right-sided tumors[9,17]; patients who have left-sided dMMR tumors fare worse in regard to disease-free survival (DFS)[17] and overall survival (OS)[9] than patients with right-sided dMMR cancers. Moreover, the presence of a *KRAS* mutation has been associated with poorer OS in left-sided (hazard ratio [HR], 1.98; 95% CI, 1.49-2.63; *P*<.0001) than in right-sided colon cancer (HR, 1.25; 95% CI, 0.97-1.60; *P*=.079) among patients with stage III disease.[9] A significant interaction between *KRAS* status and tumor site has also been demonstrated in patients with metastatic CRC.[18]

Clinically, proximal tumors more often present at later stages[19] and are associated with worse OS[20] relative to distal cancers. On the basis of these molecular and clinical differences, left-sided and right-sided colorectal tumors are increasingly being recognized as unique cancers that may respond to different therapeutic strategies.

Integrating Tumor Sidedness Into the Management of Metastatic Colorectal Cancer

Patients with metastatic CRC have longer OS, longer progression-free survival (PFS), and lower mortality rates if their tumors are left-sided rather than right-sided.[21-23] Although the prognostic effect of tumor location on metastatic disease has been established, its predictive effect on benefit from systemic therapy is an area of active investigation. Given the differences in gene expression between left-sided and right-sided CRC in angiogenesis and endothelial growth factor receptor (EGFR)–associated pathways and current standard practice, attention naturally has been directed toward understanding the differential benefit of cetuximab (Erbitux, Lilly) or bevacizumab across primary tumor sites.

Data from pivotal phase 2 and phase 3 trials support the notion that patients with wild-type *RAS* cancers are far more likely derive benefit from EGFR inhibition if their cancers are left-sided rather than right-sided.[18,24] A pooled analysis[25] of 5 randomized first-line trials (FIRE-3, CRYSTAL, PRIME, PEAK, and CALGB/SWOG 80405) and 1 randomized second-line study (20050181) examined the predictive effect of tumor side on outcomes in patients treated with cetuximab or panitumumab (Vectibix, Amgen) in combination with chemotherapy. The findings were consistent across studies and treatment lines. Only patients with left-sided tumors had a significant improvement in PFS (hazard ratio [HR], 0.78; *P* for interaction=.002) and OS (HR, 0.75; *P* for interaction <.001) when treated with cetuximab or panitumumab plus chemotherapy, rather than with chemotherapy alone or chemotherapy plus bevacizumab. Comparatively, no such benefit was seen in those with right-sided tumors (HR, 1.12 for OS and PFS). A trend toward improved response rates with anti-EGFR therapy was also observed in left-sided (odds ratio, 2.12) vs right-sided (odds ratio, 1.47) tumors (*P* for interaction=.07).[25] Others have reported similar findings[26-28] with both oxaliplatin- and irinotecan-based backbones when the analysis was restricted to panitumumab-based regimens.[29] In the FIRE-3 trial (FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab as First-Line Treatment for Patients With Metastatic Colorectal Cancer), an OS benefit was achieved with FOLFIRI/cetuximab compared with FOLFIRI/bevacizumab (38.3 vs 28.0 months; HR, 0.63; *P*=.002) in the patients who had left-sided CRC; no significant difference was seen in the patients with right-sided CRC (*P*=.28). Likewise, in the CRYSTAL study (Cetuximab Combined With Irinotecan in First-line Therapy for Metastatic Colorectal Cancer), no benefit was seen for the addition of cetuximab to FOLFIRI in patients with right-sided tumors, but cetuximab was shown to improve PFS (12.0 vs 8.9 months; HR, 0.50; *P* <.001) and OS (28.7 vs 21.7 months; HR, 0.65; *P*=.002) in those with left-sided tumors.

In the second-line setting and beyond, evidence suggests that the benefit of cetuximab remains limited to patients with left-sided tumors.[25,30,31] In a retrospective analysis of the FIRE-3 trial,[32] second-line therapy was found to be significantly more effective in delaying time to second progression in patients with left-sided vs right-sided tumors (6.0 vs 3.8 months; HR, 0.61; *P* <.001), and the benefit was greater in those receiving cetuximab- vs bevacizumab-containing regimens. In patients with disease refractory to standard chemotherapy, an analysis of the phase 3 NCIC CO.17 trial (Cetuximab and Best Supportive Care Compared With Best Supportive Care Alone in Treating Patients With Metastatic Epidermal Growth Factor Receptor-Positive Colorectal Cancer) showed a significant difference between cetuximab and best supportive care in improving PFS (3.6 vs 1.8 months; HR, 0.53; *P* <.0001) and OS (6.8 vs 4.2 months; HR, 0.60; *P*=.0003) in those with left-sided tumors; however,

no benefit was seen in those with right-sided tumors.[1] Similarly, a study examining patients who received third- or later-line cetuximab showed significant improvements in time to treatment discontinuation and OS in patients with left-sided compared with right-sided cancers.[33] In a small study of patients receiving cetuximab or irinotecan plus cetuximab, no meaningful clinical benefit (in response rate or PFS) was seen in those with right-sided tumors.[34] In addition to *RAS* mutations, human epidermal growth factor receptor 2 (*HER2*) status has emerged as a predictive marker not only of benefit from *HER2*-directed therapy, such as trastuzumab, lapatinib (Tykerb, Novartis), or pertuzumab (Perjeta, Genentech), but also of lack of benefit from anti-EGFR therapy. In a study of patients with wild-type *RAS/BRAF* tumors, the administration of anti-EGFR therapy in the second-line setting was associated with inferior PFS among those who had *HER2*-amplified tumors compared with those who had tumors that were not *HER2*-amplified.[35]

In contrast to the data for EGFR-based therapy, most evidence supports clinical benefit with the addition of bevacizumab to chemotherapy that is independent of the primary tumor site.[36,37] A few studies have suggested a preferential benefit for certain subsites[38] or left-sided tumors,[39,40] but these data have yet to be confirmed in additional studies.

Our understanding of the influence of tumor location on responsiveness to specific therapies continues to evolve as sidedness is included prospectively as a stratification factor in clinical trials.

Effect of Tumor Location in Early-Stage Colorectal Cancer

Although studies have yielded mixed findings, evidence suggests a prognostic role of tumor subsite that may vary by stage in nonmetastatic CRC. Among patients with stage I CRC, having a right-sided tumor has been associated with significantly better 5-year DFS,[41] cancer-specific survival, and OS,[42] although not all studies have demonstrated a significant difference[43] (albeit in a population with a generally excellent prognosis regardless of tumor site). Similarly, in patients with stage II disease, some studies have demonstrated lower recurrence rates[44] and superior survival in those with proximal primary tumors,[20,42,45] whereas others have shown the opposite effect of sidedness on outcomes.[43,46] Within stage III CRC, the finding of improved outcomes in patients with distal tumors has been more consistent across studies,[20,43,46] although one Surveillance, Epidemiology, and End Results (SEER) study found no significant difference in rates of cancer-specific survival and OS between patients with left-sided and those with right-sided colon cancer.[42]

Less is known about the predictive effect of tumor location on benefit from adjuvant chemotherapy. A retrospective study of stage III CRC[47] suggested a selective survival benefit for adjuvant chemotherapy in patients with right-sided tumors and women, but not in men with left-sided cancers. However, this study predated the introduction of oxaliplatin (patients received 5-fluorouracil/levamisole) and there was no interaction test reported, so the findings cannot be applied to current practice. A more recent Medicare-SEER analysis of patients with stage II/III CRC[48] demonstrated a 5-year OS benefit for adjuvant chemotherapy among those with stage III tumors that was independent of sidedness. Presently, insufficient evidence exists to support the use of tumor location in making decisions about chemotherapy for stages I through III CRC.

Conclusions

The biological and clinical distinctions between right-sided and left-sided CRC, and their effect on outcomes, have been recognized for more than 50 years,[49,50] although they have only recently been assimilated into clinical practice[8] and trial design. Presently, tumor subsite influences how we treat patients with metastatic wild-type *RAS* CRC in the first-line, second-line, and refractory settings; in these patients, anti-EGFR therapy benefits primarily those with left-sided or distal tumors. Looking forward, using molecular signatures related to CRC sidedness will be important for the discovery of effective target drugs and clinically meaningful predictive and prognostic biomarkers. Further study is needed to determine how left- vs right-sidedness influences the efficacy of cytotoxic, targeted, and immune therapies, as well as how tumor location affects the benefit of adjuvant therapy in earlier-stage disease. Investigations are ongoing into the interaction between tumor subsite and molecular profile (which includes MSI and *RAS/RAF/HER2* status, CMS classification, and the metabolome, microbiome, and immunome) as well as the interaction between tumor subsite, patient characteristics (eg, gender, ethnicity), and germline and pharmacogenetic markers. Although tumor sidedness has become increasingly important in translational and clinical studies, diversity within a given subsite remains, and this must be considered when novel findings are being interpreted. A more comprehensive and prospective approach linking location-specific pathways with drug and clinical trial development will advance our understanding and utilization of left-vs-right classification in the management of patients with CRC.

Patient Cases

Case Presentation No. 1

A 72-year-old man presents with abdominal bloating and discomfort, anorexia, and fatigue. His past medical

history is significant for hypertension (well controlled with an angiotensin-converting enzyme inhibitor), diabetes mellitus (without baseline neuropathy), and chronic obstructive pulmonary disease (not on supplemental oxygen). He is independent with his activities of daily living but does not lead a very active lifestyle. He has no prior history of bleeding or thromboembolic events. His first colonoscopy reveals a nonobstructing mass within the ascending colon, with biopsy confirming moderately differentiated adenocarcinoma. Carcinoembryonic antigen (CEA) is elevated to 328 ng/mL, and computed tomography (CT) demonstrates multiple hepatic and pulmonary metastases. Molecular profiling is notable for wild-type *RAS*/*BRAF*, intact MMR proteins, and absence of *HER2* amplification.

Question: Which of the following would be considered an appropriate first-line regimen?

A. FOLFOX plus cetuximab
B. FOLFIRI plus cetuximab
C. FOLFOXIRI plus cetuximab
D. FOLFOX plus bevacizumab
E. FOLFOXIRI plus bevacizumab

Answer: The most appropriate first-line therapy for this patient is FOLFOX plus bevacizumab (option D). Although the tumor is *RAS/BRAF*–wild-type, on the basis of data from FIRE-3, CRYSTAL, and CALGB/SWOG 80405 (Cetuximab and/or Bevacizumab Combined With Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer), among other trials and pooled analyses, he would not be expected to derive clinical benefit from the addition of cetuximab to chemotherapy. Although FOLFOXIRI plus bevacizumab is another approved option for first-line therapy, it is associated with a significantly higher rate of toxicity and would not be the most appropriate choice in this older patient with multiple comorbidities, a suboptimal performance status, and disease that is unlikely to be converted to resectability.

Case Presentation No. 2

A 53-year-old woman presents with intermittent bloody bowel movements and iron deficiency anemia. She has no preceding significant medical history and maintains a good performance status. Subsequent workup reveals an obstructing rectosigmoid adenocarcinoma, in addition to multiple hepatic and subcentimeter pulmonary metastases. CEA is elevated to 572 ng/mL. The patient undergoes primary tumor resection and has an uneventful recovery. Tumor profiling is noteworthy for wild-type *RAS*/*BRAF* and microsatellite stable status, and the patient receives first-line treatment with FOLFOX plus bevacizumab. After 10 months of therapy, CT shows disease progression. More comprehensive molecular profiling of a fresh liver biopsy specimen and circulating tumor DNA confirms *RAS*–wild-type status and reveals *HER2* amplification without other actionable alterations. The patient is referred to you for further management.

Question: Which of the following would be the least appropriate option for this patient?

A. Clinical trial including HER2-directed therapy
B. FOLFIRI plus bevacizumab
C. FOLFIRI plus cetuximab
D. Trastuzumab plus pertuzumab or lapatinib
E. FOLFIRI

Answer: The least suitable option for this patient would be FOLFIRI plus cetuximab (option C). Approximately 5% to 10% of patients with metastatic CRC have tumors with *HER2* amplification or overexpression, which have a predilection for the distal colon/left side of the colon. Although the patient had a left-sided primary tumor and wild-type *RAS/BRAF* disease (suggesting benefit from anti-EGFR therapy), the presence of *HER2* amplification predicts resistance to and lack of benefit from anti-EGFR therapy. This case presentation underscores the importance of testing for *HER2* status and performing comprehensive molecular profiling at the initial diagnosis of metastatic disease to guide first-line and subsequent lines of therapy.

Disclosure

Dr Hanna has no relevant financial disclosures. Dr Lenz has served on the advisory boards of Merck KGaA and Genentech and has lectured for Merck KGaA.

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