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EDITORIAL – COLORECTAL CANCER

Does Sidedness Matter in Unresectable Colorectal Cancer?

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Emerging evidence during the last 5 years has shown that right-sided metastatic colorectal cancer has a very different biology and a poorer prognosis than left-sided disease (Table 1). This difference in outcomes by sidedness appears to extend to benefit from systemic therapy as well. Treatment directed against the epidermal growth factor receptor (EGFR) pathway appears to be significantly less effective for right-sided tumors than for left-sided tumors.[1,2]

The study by Shida et al.[3] in this issue is an interesting addition to the literature because it demonstrates that the known association of right-sided metastatic colorectal cancer with a poorer prognosis appears to be independent of treatment strategy. The study included 678 patients with unresectable stage 4 colorectal cancer. Of these 678 patients, 193 (28%) had right-sided primary tumors and 485 (72%) had left-sided primary tumors. The results demonstrated a significant difference in median overall survival between right- and left-sided tumors (16.4 vs 23.4; $p < 0.01$). An analysis of 188 propensity score-matched pairs showed a similar difference in median overall survival between right- and left-sided tumors (16.4 vs 21.5 months; $p < 0.01$).

It should be noted that patient characteristics differed between those with left-sided and those with right-sided tumors. In particular, the patients with right-sided tumors were older, had worse Eastern Cooperative Oncology Group (ECOG) performance status, and had higher percentages of M1b/M1c disease and poorly differentiated tumors. They also were less likely to receive a targeted therapy in addition to chemotherapy. These differences in patient and tumor characteristics and treatment regimen may have confounded the observed differences in survival based on tumor sidedness. However, in a multivariate analysis that adjusted for ECOG performance status, sites of metastatic disease, tumor differentiation, preoperative carcinoembryonic antigen carcinoembryonic antigen (CEA) levels, type of surgery, and type of chemotherapy regimen, right-sided disease remained an independent prognostic factor associated with worse survival [hazard ratio (HR) 1.26, 95% confidence interval (CI) 1.03–1.53]. These results are particularly important because they are independent of both surgical and systemic therapy strategy. The study findings are limited by its single-center, retrospective cohort design. As the authors acknowledge, patients were enrolled during 16 years. During this time, the standard of care changed repeatedly, so earlier patients likely received suboptimal therapy by current standards. Although the results of the multivariate analysis are compelling, the imbalance toward poorer prognostic features in the right-sided tumor group raises the possibility of residual confounding. Screening also might have had a smaller effect for right-sided tumors than for left-sided tumors if more patients in this population had undergone flexible sigmoidoscopy instead of colonoscopy.

Nevertheless, this study contributes important and novel findings for the understanding and treatment of metastatic colorectal cancer. The data align well with the retrospective analyses of the phase 3 randomized CALGB/SWOG 80405 and FIRE-3 trials conducted in the United States and Europe, respectively.[2,4] The CALGB/SWOG 80405 data showed worse overall survival for patients with right- versus left-sided tumors (19.4 vs 34.2 months; HR 1.56; 95% CI 1.32–1.84).[2] The FIRE-3 data also showed significantly worse overall survival for patients with right- versus left-sided tumors that was most pronounced for patients treated with anti-EGFR therapy (16.1 vs

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TABLE 1 Summary of pivotal clinical trials showing overall survival stratified by primary tumor location

Trial	Treatment arms	Left-sided tumors				Right-sided tumors			
		No. of patients	Median OS (months)	HR (95% CI)	*p* value	No. of patients	Median OS (months)	HR (95% CI)	*p* value
CALGB/SWOG 80405[2]	FOLFOX/FOLFIRI + bev	152	32.6	–	–	78	29.2	–	–
	FOLFOX/ FOLFIRI + cetux	173	39.3	0.77 (0.59–0.99)	0.04	71	13.7	1.36 (0.93–1.99)	0.10
FIRE-3[11]	FOLFIRI + bev	149	28.0	–	–	50	23.0	–	–
	FOLFIRI + cetux	157	38.3	0.63 (0.48–0.85)	0.002	38	18.3	1.31 (0.81–2.11)	0.28
CRYSTAL[11]	FOLFIRI	138	21.7	–	–	51	15.0	–	–
	FOLFIRI + cetux	142	28.7	0.65 (0.50–0.86)	0.02	33	18.5	1.08 (0.65–1.81	0.76
PEAK[12]	FOLFOX + bev	54	32.0	–	–	14	21.0	–	–
	FOLFOX + pani	53	43.4	0.84 (0.22–3.27)	NR	22	17.5	0.45 (0.08–2.49)	NR
PRIME[12]	FOLFOX	159	23.6	–	–	49	15.4	–	–
	FOLFOX + pani	169	30.3	0.73 (0.57–0.93)	NR	39	11.1	0.87 (0.55–1.37)	NR

OS overall survival, *mon* months, *HR* hazard ratio, *CI* confidence interval, *FOLFOX* 5-fluorouracil, leucovorin, and oxaliplatin, *FOLFIRI* 5-fluorouracil, leucovorin and irinotecan, *bev* bevacizumab, *cetux* cetuximab, *pani* panitumumab, *NR* not reported

38.7 months, HR 0.26; $p < 0.0001$ for cetuximab-treated patients and 22.7 vs 28.0 months; HR 0.63; $p = 0.034$ for bevacizumab-treated patients).[1]

A summary of these data and additional data from other pivotal trials is shown in Table 1. The current study confirmed these data while adding that right-sided disease has a significantly poorer prognosis than left-sided disease regardless of chemotherapy regimen or whether primary tumor resection was performed.[3] Together, these findings suggest that although tumor biology likely differs across populations worldwide, the prognostic significance of right- versus left-sided primary tumors remains consistent.

The mechanisms mediating the differences in tumor biology and prognosis between right- and left-sided tumors are active areas of investigation. The embryologic origin of the proximal colon through the first two thirds of the transverse colon (right side) is the midgut, whereas the remaining one third of the transverse colon, sigmoid colon, and rectum arise from the hindgut.[5] This difference may explain the distinct molecular patterns seen in right- versus left-sided tumors. Right-sided tumors are more likely to be microsatellite instability-high (MSI-H) and to have BRAF mutations, low chromosomal instability, and high CpG island methylator phenotype (CIMP), whereas left-sided tumors are more likely to be microsatellite stable and to have high chromosomal instability and low CIMP.[6] Left-sided tumors also are associated with overexpression of EGFR ligands, including epiregulin and amphiregulin, which could explain the improved efficacy seen with anti-EGFR therapy in left-sided disease.[2,4,6]

In the consensus molecular subtypes (CMS) classification system, right-sided tumors are predominantly the CMS1 subtype (MSI-H, CIMP-high, BRAF mutations, immune infiltration, and activation), whereas left-sided tumors are mainly the CMS2 or canonical subtype (somatic copy number alteration high with WNT and MYC activation).[7] Findings show that BRAF-mutant colorectal cancer is especially associated with a very poor prognosis.[7] Because the current study did not report on genomic alterations, it is unknown whether these differences in molecular patterns fully explain the prognostic differences observed or whether right-sided disease is an independent, poor prognostic factor. It would be interesting to see whether differences in CMS subtypes and molecular alterations in the current cohort were the primary drivers of the prognostic differences. More work is needed to understand the molecular underpinnings of right- versus left-sided colorectal cancer.

Overall, this study has important implications for both clinical practice and trial development. Patients with right-sided primary tumors should generally be considered to have more aggressive disease. This could mean starting with systemic chemotherapy rather than upfront surgery more often for patients with oligometastatic disease and right-sided tumors. For fit patients, an intensive combination regimen such as FOLFOXIRI with bevacizumab could be considered more strongly for right-sided disease.[8] It also is known that patients with right-sided tumors have inferior survival with anti-EGFR therapy than those with left-sided tumors and those with right-sided tumors treated with anti-vascular endothelial growth factor (anti-VEGF) therapy.[2]

In future trials, right-sided disease should be considered an important subgroup for stratification. Sidedness may become not only a prognostic marker but also a predictive biomarker for novel therapeutic agents. Clearly, more research is needed to understand the biologic differences between right- and left-sided disease. The disparate molecular signatures certainly are a major factor, but there are likely other important factors. Relevant differences may exist in the tumor immune microenvironment between the right and left sides. The CMS classification system captures some aspects of the differences in immune activation based on sidedness,[7] but likely other immune checkpoints and biomarkers remain to be discovered. Studies of the colonic microbiome have shown enriched levels of *Fusobacteria* and *Bacteroidetes* species in right-sided tumors, with more *Selenomonas* and *Prevotella* species in left-sided tumors.[6,9,10] Whether these differences have prognostic and/or predictive significance or not is unknown. Further investigations are needed for development of strategies to abrogate the negative effects of right-sided colon cancer.

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