

Comment on Prognostic Relevance of Primary Tumor Sidedness in Early-Stage Colorectal Cancer

An Integrated Analysis of Four Randomized Controlled Trials (JCOG2003A)

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It was a delightful experience to read the article by Ouchi et al¹ showcasing their dedication and hard work. We extend our sincere congratulations to them for successfully conducting a well-executed study on the prognostic relevance of tumor sidedness in early-stage colorectal cancer patients. However, upon conducting a comprehensive analysis, there are certain areas that necessitate further elucidation and clarification.

First, the author categorized colon cancer stages II and III as early-stage, which seems to be inappropriate as we have a controversial aspect regarding the classification of colon cancer stages. As we know, the current National Comprehensive Cancer Network guidelines classify stages based on tumor, node, metastasis (TNM) staging. Additionally, adjuvant treatment is typically recommended for stages III and IV patients due to the presence of nodal involvement, while stage I and II patients generally do not require adjuvant treatment unless they fall into the high-risk stage II category. However, in our humble opinion, we believe it is more suitable to classify stages I and II as early stages and stage III as an advanced stage when considering a clinical context.² Along with this, receiving information about being diagnosed with early-stage colon cancer may provide some reassurance, since the uncertainty regarding the

specific stage may leave patients unsure about their prognosis and the most suitable treatment options.

Second, this study showed that overall survival (OS) was not significant in patients with right-sided and left-sided stage II tumors. Nevertheless, it is crucial to acknowledge that disparities in OS could arise when studying different races or geographical locations. Our perspective emphasizes the importance of considering the potential differences in outcomes between patients from the United States and Asia. Notably, a study conducted by Warschkow et al³ involving a large cohort of 91,416 patients from the United States with resected, stage I–III colon cancer from the Surveillance, Epidemiology, and End Results (SEER) database (2004–2012) found that OS was more favorable in stage I and II right-sided colon cancer (RCC), with hazard ratio of 0.89 [95% confidence interval (CI) = 0.84–0.94] and 0.85 (95% CI = 0.81–0.89), respectively. The patients with early-stage RCC experienced improved OS, contradicting the findings of this study. This outcome was primarily driven by a strong association between stage I and II disease, as laterality did not impact survival among patients with stage III disease. These conflicting results underscore the necessity for further investigation and research to gain a better understanding of the various underlying factors such as geographical location, that might contribute to these variations in survival rates.

Third, the conclusion made by the author regarding the lack of necessity to consider tumor sidedness for treatment stratification in early-stage colon cancer does not align with our perspective. To substantiate our standpoint, we intend to present findings from a study by Yang et al⁴ that highlight the significance of incorporating tumor sidedness into the treatment plan, emphasizing its comparable importance to TNM staging in clinical practice. The study included a cohort of 87,355 patients from the SEER database (2004–2017) and found that right-sidedness was a positive prognostic factor in the early stages (stage I/II) and revealed consistently lower rates of chemotherapy usage in RCC compared with left-sided colon cancer (LCC). Specifically, for stage II, the rates were 16.2% in RCC versus 28.5% in LCC ($P < 0.001$); for stage III, 69.8% versus 74.7% ($P < 0.001$); and for stage IV, 73.2% versus 78.5% ($P < 0.001$). The largest difference was observed in stage II, with a 12.3% disparity between RCC and LCC, followed by stage III (4.9%) and stage IV (5.3%).

Last but not least, significant progress in the field of colon cancer treatment has been driven by advancements in research over the years. It is widely recognized that adjuvant chemotherapy is extremely effective for patients with stage III colon cancer. However, the effectiveness of this treatment for individuals with stage II disease remains a topic of ongoing debate and disagreement among experts.⁵ Monitoring the levels of circulating tumor DNA (ctDNA) after surgery has been shown in multiple research studies to be a useful approach for early detection of recurrence and gaining valuable insights into the efficacy

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of chemotherapy treatment. The ctDNA Analysis Informing Adjuvant Chemotherapy in Stage II Colon Cancer (DYNAMIC) trial⁶ was a randomized trial specifically designed to investigate whether a ctDNA-guided approach could reduce the need for adjuvant treatment without compromising the risk of recurrence in patients with stage II colon cancer. The results of this trial suggest that the ctDNA-guided approach reduced the number of patients who received adjuvant therapy and did not alter the risk of recurrence. Interestingly, the trial also showed that ctDNA-positive patients who received chemotherapy exhibited a lower recurrence rate, suggesting a potential survival benefit from adjuvant therapy. Additionally, untreated ctDNA-negative patients demonstrated a very low risk of recurrence, further emphasizing the potential of ctDNA monitoring in guiding treatment decisions.

To conclude, the study conducted by Ouchi et al¹ is an exceptional piece of research that deserves acknowledgment and commendation. Nevertheless, the management of colon cancer should take into account not only TNM staging, but also some other factors such as tumor sidedness, the innovative

ctDNA-guided approach, and so on that demonstrate advancements in research and clinical practice.

REFERENCES

1. Ouchi A, Sadachi R, Hamaguchi T, et al; JCOG Colorectal Cancer Study Group. Prognostic relevance of primary tumor sidedness in early-stage colorectal cancer. *Ann Surg*. 2024;279:283–289.
2. Ha GW, Kim JH, Lee MR. Oncologic effects of primary tumor-sidedness on patients with stages 1–3 colon cancer: a meta-analysis. *Ann Surg Oncol*. 2019;26:1366–1375.
3. Warschkow R, Sulz MC, Marti L, et al. Better survival in right-sided versus left-sided stage I - III colon cancer patients. *BMC cancer*. 2016;16:1–14.
4. Yang Y, Yang X, Bai Z, et al. Unraveling the role of tumor sidedness in prognosis of stage II colon cancer. *Gastroenterol Rep (Oxf)*. 2024;12:goae028.
5. Rebutti SE, Pesola G, Martelli V, et al. Adjuvant chemotherapy for stage II colon cancer. *Cancers*. 2020;12:2584.
6. Tie J, Cohen JD, Lahouel K, et al; DYNAMIC Investigators. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. *N Engl J Med*. 2022;386:2261–2272.