ANNALS OF SURGERY OPEN

OPEN

Response to Comment on: "Prognostic Relevance of Primary Tumor Sidedness in Early-Stage Colorectal Cancer: An Integrated Analysis of 4 Randomized Controlled Trials (JCOG2003A)"

Akira Ouchi, MD, PhD,* Shunsuke Tsukamoto, MD, PhD,† Atsuo Takashima, MD, PhD,‡ Yasuhiro Shimada, MD,§ Tetsuya Hamaguchi, MD, PhD,‖ Masafumi Inomata, MD, PhD,¶ Yasumasa Takii, MD,# Ryo Sadachi, PhD,** and Yukihide Kanemitsu, MD†

We thank Shah et al[1] for their interest in our study.[2] In their letter, the authors called into question the classification of "early-stage" and "advanced" colorectal cancer (CRC) in relation to our description of "early-stage" for stage II and III CRC. They also suggested the possibility of different impacts of primary tumor sidedness (PTS) on prognostic outcomes between patients in Western and Asian countries and even between patients in other Asian countries and Japan. Further, they proposed the potential for a circulating tumor DNA-guided treatment strategy in addition to PTS.

First, we described our cohort of stage II to III CRC as "early-stage" CRC for convenience in our article; however, categorizing "early-stage" and "advanced" CRC can be very ambiguous. In recent National Comprehensive Cancer Network (NCCN) guidelines for colon cancer,[3] the term "early-stage" appears two times in the text, both instances of which are used with the meaning of "stage I to III." Then, what is early and what is advanced? Stage IV CRC, which involves distant organs, distant lymph nodes, or peritoneal metastasis, has long been considered incurable. Recently, however, some of these patients have been shown to have oligometastasis rather than systemic disease, which has a better chance of being curable. Drawing the line between curable and incurable diseases is becoming more challenging when relying only on TNM classification. Therefore, now might be a good time to change how we say "early-stage" and "advanced" CRC.

Second, Shah and colleagues cited an epidemiological study by Warschkow et al,[4] which revealed statistically better overall survival (OS) of patients with right-sided colon cancer in stage II based on data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute in the United States. Similar results were reported in a recent study by Huang et al.[5] In JCOG2003A, survival of patients with right-sided tumors also tended to be better in stage II CRC, with unadjusted and adjusted hazard ratios of left-sided tumors to right-sided tumors of 1.298 (0.663–2.545) and 1.517 (0.738–3.115), respectively. This means that the trend of survival in stage II CRC in Japan is similar to that reported in Western epidemiological studies. Furthermore, JCOG2003A showed no difference in risk of recurrence after primary surgery according to PTS, which means the discrepancy in OS according to PTS in the previous studies was due only to the difference in OS after recurrence. Although we do not object that the true endpoint is survival rather than recurrence when developing a treatment for CRC, we conclude that treatment stratification before primary surgery based on PTS is unnecessary for stage II and III CRC receiving no significant difference in relapse-free survival in our study.

In their third point, Shah and colleagues provided a new perspective regarding the impact of PTS in stage II CRC. They cited an epidemiological study by Yang et al[6] which showed that, although significantly better survival of right-sided CRC was observed in both cohorts, PTS seemed to have a more significant impact on survival in T4N0M0 compared with T3N0M0 patients. The most crucial difference in patient characteristics in these 2 groups is the pathological invasion of tumor cells to the serosa, which is the well-known risk of peritoneal dissemination. In addition, there are several differences in genetic characteristics between right-sided and left-sided CRC which are known.[7] These differences might affect the recurrent sites of CRC, including hematogenous spread, lymphatic spread, and peritoneal dissemination, which affect OS after recurrence. Unfortunately, JCOG2003A did not have information regarding recurrent sites and genetic profiles, and the problem regarding the impact of PTS on recurrent sites remains.

*From the *Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Aichi, Japan; †Department of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan; ‡Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; §Clinical Oncology Division, Kochi Health Sciences Center, Kochi, Japan; ‖Department of Medical Oncology, Saitama Medical University International Medical Center, Saitama, Japan; ¶Department of Gastroenterological and Pediatric Surgery, Oita University Faculty of Medicine, Oita, Japan; #Department of Gastroenterological Surgery, Niigata Cancer Center Hospital, Niigata, Japan; and **Japan Clinical Oncology Group Data Center, National Cancer Center Hospital, Tokyo, Japan.*

Disclosure: Y.K. received a consulting or advisory role from Covidien, and honoraria from Chugai Pharma, Johnson and Johnson KK, Covidien, and Intuitive Surgical. S.T. received honoraria from Johnson and Johnson KK, Covidien, and Intuitive Surgical. Y.S. received honoraria from Ono Pharmaceutical, Novartis, Yakult Honsha, and Daiichi Sankyo/UCB Japan. T.H. received honoraria from Chugai Pharma, Merck Serono, Takeda, Taiho Pharmaceutical, Ono Pharmaceutical, Yakult Pharmaceutical, Lilly, Bristol-Myers Squibb Japan, Bayer, and Daiichi Sankyo/UCB Japan, and research funding from Taiho Pharmaceutical, Ono Pharmaceutical, Chugai Pharma, BeiGene, Astellas Pharma, AstraZeneca, and Pfizer. The remaining authors declare that they have nothing to disclose. This study was supported in part by the National Cancer Center Research and Development Funds (23-A-16, 23-A-19, 26-A-4, 29-A-3, 2020-J-3, and 2023-J-03), Grants-in-Aid for Clinical Cancer Research (11S-4, 14S-3, 14S-4, 17S-3, 17S-5, 20S-3, and 20S-5), and Health Sciences Research Grants (H13-21Century-15, H14Gann-015, H16Gann-031, H19Gann-021, H21Gann-027, HI5-018, H18-013, H21-017, H24-005, H19-021, and H22-027) from the Ministry of Health, Labour, and Welfare of Japan.

Reprints: Yukihide Kanemitsu, MD, Department of Colorectal Surgery, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo, Tokyo 104-0045, Japan. Email: ykanemit@ncc.go.jp.

Annals of Surgery Open (2024) 4:e505

Received: 19 September 2024; Accepted 21 September 2024

Published online 16 October 2024

DOI: 10.1097/AS9.0000000000000505

Last, we mention the possibility of PTS as a surrogate of genetic biomarkers. Previous studies for metastatic CRC showed that, not PTS itself, genetic differences between right-sided and left-sided CRC dominate patient outcomes.[7,8] However, it is impractical to perform genetic tests for all stage II to III CRC patients due to cost constraints and the limited time available from diagnosis to surgery. PTS is a simple marker without any associated costs for assessment. Therefore, we should investigate the relationship between PTS and innovative approaches such as preoperative circulating tumor DNA status for cost–benefit balanced treatment optimization for resectable CRC.

Once again, we extend our heartfelt thanks to Shah and colleagues for their insightful commentary. Their perspectives have sparked essential discussions and highlighted areas for further research. We sincerely appreciate their contribution, which is integral to advancing our understanding of CRC, and look forward to future studies that will clarify the impact of PTS on the recurrent sites of CRC and investigate the relationship between PTS and innovative approaches, ultimately optimizing treatment for stage II to III CRC.

ACKNOWLEDGMENTS

A.O., S.T., T.H., and Y.K. were responsible for the study concept. A.O., S.T., A.T., Y.S., T.H., M.I., Y.T., and Y.K. established the study design. R.S. collected, assembled, and analyzed the data. A.O. wrote the initial draft, and all authors revised and approved the final draft of the manuscript. All authors had full access to the data in this study and accept responsibility for submitting the manuscript for publication.

REFERENCES

1. Shah SR, Kevadiya MP, Salewala KS, et al. Comment on prognostic relevance of primary tumor sidedness in early-stage colorectal cancer: an integrated analysis of four randomized controlled trials (JCOG2003A). *Ann Surg Open*. 2024;5:e450.
2. Ouchi A, Sadachi R, Hamaguchi T, et al; JCOG Colorectal Cancer Study Group. Prognostic relevance of primary tumor sidedness in early-stage colorectal cancer: an integrated analysis of 4 randomized controlled trials (JCOG2003A). *Ann Surg*. 2024;279:283–289.
3. National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Treatment of Cancer by Site: Colon Cancer; 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed July 1, 2024.
4. 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;16:554.
5. Huang ZS, Wu JW, Li Y, et al. Effect of sidedness on survival among patients with early-stage colon cancer: a SEER-based propensity score matching analysis. *World J Surg Oncol*. 2021;19:127.
6. 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.
7. Shitara K, Muro K, Watanabe J, et al. Baseline ctDNA gene alterations as a biomarker of survival after panitumumab and chemotherapy in metastatic colorectal cancer. *Nat Med*. 2024;30:730–739.
8. Watanabe J, Muro K, Shitara K, et al. Panitumumab vs bevacizumab added to standard first-line chemotherapy and overall survival among patients with RAS wild-type, left-sided metastatic colorectal cancer: a randomized clinical trial. *JAMA*. 2023;329:1271–1282.