Article:
Yin, J, Cohen, R, Jin, Z et al. (23 more authors) (2021) Prognostic and Predictive Impact of Primary Tumor Sidedness for Previously Untreated Advanced Colorectal Cancer. Journal of the National Cancer Institute. ISSN 0027-8874

https://doi.org/10.1093/jnci/djab112

Prognostic and Predictive Impact of Primary Tumor Sidedness for Previously Untreated Advanced Colorectal Cancer

Jun Yin, PhD,[1], Romain Cohen, MD, [2], Zhaohui Jin, MD, [3], Heshan Liu, MS,[1], Levi Pederson, MS,[1], Richard Adams, MD,[4], Axel Grothey, MD,[5], Timothy S. Maughan, MD,[6], Alan Venook, MD,[7], Eric Van Cutsem, MD,[8], Cornelis Punt, MD,[9], Miriam Koopman, MD,[10], Alfredo Falcone, MD,[11], Niall C. Tebbutt, MD,[12], Matthew T. Seymour, MD,[13], Carsten Bokemeyer, MD,[14], Eduardo Diaz Rubio, MD,[15], Richard Kaplan, MD,[16], Volker Heinemann, PhD,[17], Benoist Chibaudel, MD,[18], Takayuki Yoshino, MD, PhD,[19], John Zalcberg, MBBS, PhD,[20], Thierry Andre, MD,[21], Aimery De Gramont, MD,[22], Qian Shi, PhD,[1], Heinz-Josef Lenz, MD,[23]

Affiliations:

1. Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN, USA.

2. Sorbonne University, Department of Medical Oncology, Saint-Antoine Hospital, AP-HP, F-75012 Paris, France.

3. Department of Oncology, Mayo Clinic, Rochester, MN, USA.

4. Cardiff University and Velindre Cancer Centre, Cardiff, UK.

5. West Cancer Center and Research Institute, OneOncology, Germantown, TN.

6. CRUK/MRC Oxford Institute for Radiation Oncology, Oxford, United Kingdom St James's Hospital and University of Leeds, Leeds, UK.

7. Department of Medicine, The University of California San Francisco, San Francisco, California, United States of America.

8. Digestive Oncology, University Hospitals Gasthuisberg Leuven and University of Leuven Leuven, Belgium.

9. Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center , Utrecht University, The Netherlands.

10. Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, The Netherlands.

11. Department of Oncology, University of Pisa, Italy.

12. Department of Medical Oncology, Austin Health, Melbourne.

13. NIHR Clinical Research Network, Leeds UK. St James's Hospital and University of Leeds, Leeds, United Kingdom.

14. Department of Oncology, Haematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

15. Universidad Complutense Instituto de Investigacion Sanitaria del Hospital Clinico San Carlos, Madrid, Spain.

16. MRC Clinical Trials Unit at UCL, University College London, London, UK.

17. University Hospital Grosshadern, Ludwig Maximilian University of Munich, Munich, Germany.

18. Institut Franco-Britannique, Levallois-Perret, France.

19. National Cancer Center Hospital East, Japan.

20. Monash University, Melbourne, Australia.

21. Hôpital Saint-Antoine, Paris, France.

22. Department of Medical Oncology, Franco-British Institute, Levallois-Perret, France.

23. Department of Gastrointestinal Onocology, Keck School of Medicine at USC, Los Angeles, CA, USA.

Correspondence:

Dr. Jun Yin, Department of Health Sciences Research, Mayo Clinic, 200 First Street, SW, Rochester, MN, 55905 Phone: 507-538-6252; Email: yin.jun@mayo.edu

Abstract

Background: Unplanned subgroup analyses from several studies have suggested primary tumor sidedness (PTS) as a potential prognostic and predictive parameter in metastatic colorectal cancer (mCRC). We aimed to investigate the impact of PTS on outcomes of mCRC patients.

Methods: PTS data of 9,277 mCRC patients from 12 first-line randomized trials in the ARCAD database were pooled. Overall survival (OS) and progression-free survival (PFS) were assessed using Kaplan-Meier and Cox models adjusting for age, sex, performance status, prior radiation/chemo, and stratified by treatment arm. Predictive value was tested by interaction term between PTS and treatment (cetuximab plus chemotherapy *vs*. chemotherapy alone). All statistical tests were 2-sided.

Results: Compared to right-sided metastatic colorectal cancer patients (n = 2421, 26.1%), left-sided metastatic colorectal cancer patients (n = 6856, 73.9%) had better OS (median = 21.6 v 15.9 months; adjusted hazard ratio [HR_{adj}] = 0.71, 95% confidence interval [CI] = 0.67-0.76, P<.001) and PFS (median = 8.6 v 7.5 months; HR_{adj} = 0.80, 95% CI = 0.75-0.84, P<.001). Interaction between PTS and *KRAS* mutation was statistically significant ($P_{interaction}$<.001): left-sidedness was associated with better prognosis among *KRAS* wild-type (WT) (OS HR_{adj} = 0.59, 95% CI = 0.53-0.66; PFS HR_{adj} =0.68, 95% CI = 0.61-0.75), but not among *KRAS* mutated tumors. Among *KRAS*-WT tumors, survival benefit from anti-EGFR was confirmed for left-sidedness (OS HR_{adj} = 0.85, 95% CI = 0.75-0.97, P=0.01; PFS HR_{adj} = 0.77, 95% CI = 0.67-0.88, P<.001), but not for right-sidedness.

Conclusions: The prognostic value of PTS is restricted to the *KRAS*-WT population. PTS is predictive of anti-EGFR efficacy, with a statistically significant improvement of survival for left-sidedness mCRC patients. These results suggest treatment choice in mCRC should be based on both PTS and *KRAS* status.

The prognostic and predictive values of primary tumor location in metastatic colorectal cancer (mCRC) have been increasingly recognized in the past several years. Post hoc analyses of multiple clinical trials showed an association between left-sidedness and better prognosis [1-3]. However, the relationship between the prognostic impact of primary tumor sidedness and *RAS*/*RAF* mutational status is not fully elucidated, with discrepant results between studies [1,4-8].

Right-sidedness has been associated with resistance to anti-EGFR antibodies in *RAS*/*BRAF* wild-type (WT) tumors [2,3,9-11], whereas the efficacy of antiangiogenics does not depend on this clinical feature [1,12,13]. In the CALGB/SWOG 80405 trial comparing chemotherapy plus bevacizumab or cetuximab [8], *KRAS*-WT tumors with left-sided tumors benefited more from cetuximab than bevacizumab, while *KRAS*-WT patients with right-sided tumors experienced better outcomes with bevacizumab than cetuximab. Similarly, among *RAS*-WT FIRE-3 study patients with left-sided mCRC, those treated with 5FU, folinic acid and irinotecan (FOLFIRI) plus cetuximab had statistically significantly longer Overall Survival (OS) than patients receiving FOLFIRI plus bevacizumab, whereas no statistically significant differences in Overall Response Rate , Progression Free Survival (PFS), or OS was observed with FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for those with right-sided tumors[3]. Although these analyses are limited by small sample sizes, international guidelines recommend a cytotoxic doublet plus an anti-EGFR antibodies as the preferred option for patients with newly diagnosed left-sided *RAS*–WT mCRC, and conversely chemotherapy plus an antiangiogenic agent for right-sided *RAS*- WT tumors ASCO Guidelines[12]).

Although the primary tumor location is now incorporated into our daily clinical

practice to choose an appropriate first-line treatment, more evidence is needed to validate our practice. In this analysis, using pooled individual patient data from randomized phase III first line clinical trials in the ARCAD database, we aim to investigate prognostic and predictive values for cetuximab of primary tumor sidedness (left versus right). To our knowledge, this is the largest pooled mCRC population with primary tumor sidedness data, which enabled us to investigate potential interactions between sidedness, classes of targeted treatments, and modification effects by molecular features.

Methods

Data

Individual patient data (IPD) on primary tumor sidedness from 12 first-line randomized trials in mCRC in the ARCAD database were pooled (AGITG, COIN, FOCUS2, OPUS, CRYSTAL, COIN-B, C80405, 03-TTD-01, FIREII, TRIBE, CAIRO, CAIRO2) (**Supplementary Table 1**). Primary tumors originating in the splenic flexure, descending colon, sigmoid colon, or rectum were classified as left-sided mCRC. Primary tumors originating in the cecum, ascending colon, hepatic flexure were classified as right-sided mCRC. Transverse colon cancers were not included in the primary analysis. Patients who had multiple primary tumors identified in both right-sided and left-sided locations were excluded. KRAS mutation available in IPD are mutation on exon 3 (codon 59 and 61) and exon 4 (codon 117 and 146); Status concerning NRAS mutation were not available in IPD.

Individual trials were approved through countries' mechanisms at the time trials

were done. All patients provided written, informed consent at enrolment in the respective trials. The ARCAD database collaboration research protocol was approved by Mayo Clinic Institution Review Board.

Statistical Analysis

OS was defined as time from randomization to death from any causes. Progression-free survival PFS was defined as time from randomization to disease progression or death, whichever occurred first. OS and PFS were assessed using Kaplan-Meier analysis and Cox models adjusting for age, sex, performance status, prior radiation/chemo, number of metastatic sites, and stratified by treatment arms within trials. Subgroup analyses were done by age, sex, performance score, metastases, synchronous disease, mutational features, including an interaction term in the statistical models. Predictive value was tested by interaction between tumor sidedness and treatment (cetuximab plus chemotherapy vs. chemotherapy alone, with head-to-head randomizations, stratified by *KRAS* mutation status), after adjusting for age, sex, performance status, prior radiation/chemo, and stratified by comparison units. Sensitivity analyses were conducted to evaluate the predictive effect of chemotherapy plus bevacizumab compared with chemotherapy alone (chemotherapy ± bevacizumab), or chemotherapy plus cetuximab (chemotherapy + bevacizumab vs. chemotherapy + cetuximab). No head-to-head randomized comparisons are available in the current ARCAD database for chemotherapy ± bevacizumab, and only one trial (C80405) with concurrent randomization between chemotherapy + bevacizumab and chemotherapy + cetuximab. Therefore, propensity matching methods were applied, and multivariable

Cox proportional hazards model was then used to investigate the interaction between tumor sidedness and treatment effect. Specifically, propensity score matching with replacement (control units can be reused and matched to 5 treated units) was conducted with a nearest-neighbor algorithm, allowing a maximum tolerated difference between propensity scores of no larger than 20% of the propensity scores standard deviation[14]. Two-sided P values are reported; $P<0.05$ was considered statistically significant and was not adjusted for multiple comparisons. Analyses were carried out using SAS software (version 9.4; SAS Institute Inc).

Results

Patient characteristics

Among the 11,207 patients enrolled in the 12 first-line mCRC trials, 1,930 (17.2%) patients were excluded due to missing sidedness data, screen failures, having tumors sited on both the left and right sides, or having transverse colon primary tumors (see CONSORT diagram in **Figure 1**). This resulted in a total of 9,277 patients included in the present analysis; among them, 6,856 (73.9%) had left-sided tumors and 2,421 (26.0%) had right-sided tumors. Patient characteristics by sidedness are included in **Table 1**. A higher proportion of patients with right-sided tumors were women, had multiple metastatic sites, and had synchronous disease; whereas patients with left-sided tumors more frequently had liver-only metastases and lung-involved metastases, and had metachronous disease. Among patients with available molecular marker data, right-sided tumors were more likely to have *KRAS* (49.4% vs 37.5%, P<.001) and *BRAF* mutations (14.0% vs 4.5%, P<.001).

The baseline characteristics were relatively balanced for patients with *KRAS*-WT left-sided tumors between those treated with chemotherapy only vs. cetuximab (**Supplementary Table 2**). Similarly, the baseline characteristics were relatively balanced for patients with *KRAS*-WT right-sided tumors, except that those treated with cetuximab were more likely to be elderly (age >70 years) (**Supplementary Table 3**).

Prognostic Value of Primary Tumor Sidedness

In the overall population (N=9277), median follow-up was 46.4 months (95% confidence interval [CI] = 45.2–47.3). Patients with left-sided tumors had better OS and PFS than patients with right-sided tumors after accounting for age, sex, performance status, prior radiation or adjuvant chemotherapy, with stratification by treatment arm within trials, with a 29% lower risk of death and 20% lower risk of either progression or death (median OS = 21.6 vs. 15.9 months, HR_{adj} = 0.71 [95% CI = 0.67-0.76, P<.001]; median PFS = 8.6 vs. 7.5 months, HR_{adj} = 0.80 [95% = CI 0.75-0.84, P<.001]) (**Table 2, Figure 2, Supplementary Table 4**).

A statistically significant interaction between sidedness and *KRAS* mutation ($P_{interaction}$ <.001 for both OS and PFS) was found. Primary tumor sidedness was prognostic among *KRAS*-WT patients only (OS: HR_{adj} = 0.59, 95%CI = 0.53-0.66, P<.001; PFS: HR_{adj} = 0.68, 95%CI = 0.61-0.75, P<.001), but not among *KRAS*-mutated (MT) patients (OS: HR_{adj} = 0.94, 95%CI = 0.84-1.05, P=0.726; PFS: HR_{adj} = 0.97, 95%CI = 0.86-1.09, P=0.705) (**Table 2, Figure 3**). No interaction was detected between primary tumor sidedness and chemotherapy backbone.

Predictive Value of Primary Tumor Sidedness

Primary tumor sidedness was predictive of cetuximab efficacy compared to chemotherapy alone (OS: $P_{interaction}$ = 0.008; PFS: $P_{interaction}$ = 0.13). Among *KRAS*-WT left-sided tumors, statistically significant improvements in OS and PFS were observed for patients treated with cetuximab (median OS = 22.3 vs 20.5 months, HR_{adj} = 0.85 [95% CI = 0.75-0.97], P=0.01; median PFS = 9.3 vs 8.5 months, HR_{adj} = 0.77 [95% CI = 0.67-0.88], P<.001) (**Table 2**). In contrast, among *KRAS*-WT right-sided tumors, there was no statistically significant benefit of cetuximab in either OS or PFS. However, there was a trend towards detrimental effects of cetuximab in first line setting for right-sided *KRAS*-WT tumors (HR_{adj} = 1.26, 95% CI = 0.98-1.63) which support the current practice guideline recommendation of limiting EGFR inhibitor in the first line setting for left-sided KRAS-WT mCRC.

Among *KRAS*-WT and *BRAF*-WT tumors, OS and PFS benefits from cetuximab were observed for left-sided tumors (n=1100), but not for right-sided tumors (n=200) (**Figure 4**). Among *KRAS*-WT and $BRAF^{V600E}$ mutated mCRC, no benefit from cetuximab was observed in either left-sided (n=72) or right-sided tumors (n=81).

Sensitivity Analyses with Propensity Score Matching

Primary tumor sidedness was not predictive of bevacizumab efficacy compared to chemotherapy alone (OS: $P_{interaction}$ = 0.18; PFS: $P_{interaction}$ = 0.19) (**Table 3**). However, primary tumor sidedness was predictive of bevacizumab efficacy compared to cetuximab among *KRAS*-WT tumors (OS: $P_{interaction}$ = 0.005; PFS: $P_{interaction}$ = 0.05) (**Table 4**), with chemotherapy plus bevacizumab superior to chemotherapy plus

cetuximab in patients with *KRAS*-WT right-sided tumors but no statistically significant treatment difference in patients with *KRAS*-WT left-sided tumors. Among *KRAS*-MT tumors, primary tumor sidedness was not predictive of bevacizumab efficacy compared to cetuximab (OS: $P_{interaction} = 0.565$; PFS: $P_{interaction} = 0.071$).

Discussion

Here we present a study of 9,277 individual patients with known primary tumor sidedness, which constitutes the largest study population as we know. We show that the statistically significant positive prognostic impact of left-sidedness is restricted to the *KRAS-WT* population, while *KRAS-MT* population exhibits poor outcomes irrespective of the primary tumor sidedness. We confirm that the efficacy of cetuximab is limited to the left-sided *KRAS* wild-type population.

The prognostic and predictive values of primary tumor sidedness in mCRC have been brought to light by post hoc analyses of clinical trials. The unplanned and retrospective nature of these works, their lack of statistical power given the small number of patients with right-sided tumors and the lack of adjustment for major prognostic parameters prevented the drawing of any definitive conclusions [2,3,11]. Primary tumor sidedness information is available for 83% of the patients from 12 large randomized studies included in the present work, which constitute the largest study thus far to our best knowledge. Rigorous statistical analyses were used to estimate primary tumor sidedness effect in the present work, while adjusting for main prognostic factors, and stratifying by treatment arms within trials (for prognostic analyses) and by comparison unit (for predictive analyses). In a sensitivity analysis where we included the

transverse colon cancers, transverse tumors had similar OS and PFS with right-sided tumors (**Supplementary Figure 1**).

While the main studies focused on the *KRAS*-WT population and the predictive effect of primary tumor sidedness for the efficacy of cetuximab, data concerning the *KRAS*-MT population are limited and controversial. In a retrospective cohort of 564 patients with *KRAS*-MT mCRC, sidedness was not associated with survival outcomes [7]. In a post hoc analysis of 358 patients from the TRIBE study, no interaction was reported between *RAS*/*RAF* mutations and sidedness, but statistical significance of the impact of sidedness on PFS was lost after adjustment for mutational status [6]. In our study, the median OS was 16.7 and 17.1 months for left-sided and right-sided KRAS-MT tumors, respectively (HR = 0.98; 95% CI = 0.86-1.11). Among the 1,939 patients with available *KRAS* mutational status in our IPD meta-analysis, we observed a statistically significant interaction between primary tumor sidedness and this molecular feature. More precisely, primary tumor sidedness had no prognostic impact in the *KRAS*-MT population. We acknowledge that the amount of missing data for *KRAS* status is a weakness (4561 of 9277, 49%). Nevertheless, this is counterbalanced by the size of our population and the robustness of the analysis. Our data confirmed the conclusion that the prognostic value of primary tumor sidedness is observed in the KRAS-WT population, but not in the KRAS-MT population. Note that, in the current analyses, extended RAS mutations beyond KRAS mutation were not included due to limited data availabilities. Given mCRCs harboring RAS mutation on exon 3 or 4 behave similarly as KRAS mutation on exon 2[15] in terms of biological and clinical consequences, the prognostic value of primary tumor location in RAS wild-type mCRC could be potentially more profound.

Concerning *BRAF*^{V600E} mutants, we did not detect any association between primary tumor sidedness and survival in patients with the *BRAF*^{V600E} mutated mCRC without any OS or PFS benefits of EGFR inhibition in *KRAS*-WT *BRAF*^{V600E} mutated mCRC while the benefits were seen in *KRAS*-WT / *BRAF*-WT patients. The limit of this study is largely due to its retrospective nature. Some of the data (including molecular markers without NRAS, Mismatch repair and HER2 status) were missing; the studies were conducted over a long period of time with different designs and treatment arms, with only one anti-EGFR antibody (cetuximab). However, by integrating IPD over 12 trials, the robustness and power for formally testing interaction effects were substantially increased compared to previous reports.

In relation to the predictive value of primary tumor sidedness, a limitation of our study is lack of head-to-head comparisons to address the question whether the treatment effect of bevacizumab depends on the sidedness of the primary tumor. This is because no studies in our database tested bevacizumab versus chemotherapy alone, and only one study in our database (CALGB 80405) tested bevacizumab versus cetuximab where we can make head-to-head comparison. Exploratory analyses using propensity score matching methods showed that primary tumor sidedness was not predictive of bevacizumab efficacy compared to chemotherapy alone, but primary tumor sidedness was predictive of bevacizumab efficacy versus cetuximab among *KRAS*-WT tumors, with bevacizumab superior to cetuximab in *KRAS*-WT right-sided tumors.

In summary, the present study clearly demonstrates that the prognostic value of primary tumor sidedness is restricted to the *KRAS*-WT mCRC population. Primary tumor sidedness is predictive of anti-EGFR efficacy, with a statistically significant

improvement of survival for left-sided mCRC. These results suggest integrating both primary tumor sidedness and *KRAS* status in the choice of treatment for mCRC.

Funding

This work was supported by ARCAD Foundation.

Notes

Role of the funder: The funder had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

Disclosures: There is no conflict of interest.

Author Contributions: JY conceptualized the study, performed the formal analysis, and wrote the original draft of the manuscript; RC & ZJ conceptualized the study, and wrote the original draft of the manuscript; HL & LP performed the formal analysis, and reviewed and revised the mansucript; RA, TM, AV, EC, CP, MK, AF, NT, MS, CB, ER, RK & VH provided & curated the data, and reviewed and revised the manuscript; AG, BC, TY, JZ, TA & AG reviewed and revised the manuscript; QS & HL conceptualized the study, coordinated data curation, and reviewed and revised the manuscript. All authors participated in the editing of the manuscript and approved the final version.

Data Availability

The data sharing of individual patient data from each participating trial will be subject to the policy and procedures of the institutions and groups who conducted the original study.

References

1. Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst* 2015; **107**(3).

2. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol* 2017; **28**(8): 1713-29.

3. Klingbiel D, Tejpar S. Microsatellite Instability and BRAF and KRAS Mutations in Stage III Colon Cancer: Requirements for Accurate Prognosis Assessment. *JAMA Oncol* 2016; **2**(5): 653-4.

4. Sunakawa Y, Ichikawa W, Tsuji A, et al. Prognostic Impact of Primary Tumor Location on Clinical Outcomes of Metastatic Colorectal Cancer Treated With Cetuximab Plus Oxaliplatin-Based Chemotherapy: A Subgroup Analysis of the JACCRO CC-05/06 Trials. *Clin Colorectal Cancer* 2017; **16**(3): e171-e80.

5. Chibaudel B, Andre T, Tournigand C, et al. Understanding the Prognostic Value of Primary Tumor Location and KRAS in Metastatic Colorectal Cancer: A Post Hoc Analysis of the OPTIMOX3 DREAM Phase III Study. *Clin Colorectal Cancer* 2020.

6. Cremolini C, Antoniotti C, Lonardi S, et al. Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Retrospective analysis of the TRIBE trial by GONO. *Ann Oncol* 2018; **29**(7): 1528-34.

7. Loupakis F, Schirripa M, Intini R, et al. Another Chapter of the Right Versus Left Story: Is Primary Tumor Location a Prognostic Feature in RAS Mutant Metastatic Colorectal Cancer? *Oncologist* 2019; **24**(2): e77-e9.

8. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *Journal of Clinical Oncology* 2016; **34**(15_suppl): 3504-.

9. Benavides M, Díaz-Rubio E, Carrato A, et al. Tumour location and efficacy of first-line EGFR inhibitors in KRAS/RAS wild-type metastatic colorectal cancer: retrospective analyses of two phase II randomised Spanish TTD trials. *ESMO open* 2019; **4**(6): e000599.

10. Peeters M, Price T, Taieb J, et al. Relationships between tumour response and primary tumour location, and predictors of long-term survival, in patients with RAS wild-type metastatic colorectal cancer receiving first-line panitumumab therapy: retrospective analyses of the PRIME and PEAK clinical trials. *British Journal of Cancer* 2018; **119**(3): 303-12.

11. Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. *Ann Oncol* 2017; **28**(8): 1862-8.

12. Yoshino T, Portnoy DC, Obermannova R, et al. Biomarker analysis beyond angiogenesis: RAS/RAF mutation status, tumour sidedness, and second-line ramucirumab efficacy in patients with metastatic colorectal carcinoma from RAISE-a global phase III study. *Ann Oncol* 2019; **30**(1): 124-31.

13. Loupakis F, Hurwitz HI, Saltz L, et al. Impact of primary tumour location on efficacy of bevacizumab plus chemotherapy in metastatic colorectal cancer. *Br J Cancer* 2018; **119**(12): 1451-5.

14. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; **70**(1): 41-55.

15. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. *J Clin Oncol* 2016; **34**(2): 179-85.

Tables

Table 1. Patient Characteristics

Characteristic	Right Colon (n=2752)	Left Colon (n=6525)	Total (N=9277)	*P*
Age at enrollment				<.001[1]
No. (Missing)	2749 (3)	6519 (6)	9268 (9)	
Mean (SD), y	62.4 (10.69)	61.2 (10.73)	61.6 (10.73)	
Median (Range), y	64.0 (22.0, 89.0)	62.0 (18.0, 85.0)	63.0 (18.0, 89.0)	
IQR, y	56.0, 70.0	54.0, 69.0	55.0, 70.0	
Age Group, No. (%)				<.001[2]
Missing	3	6	9	
≤70 y	2091 (76.1)	5169 (79.3)	7260 (78.3)	
>70 y	658 (23.9)	1350 (20.7)	2008 (21.7)	
Gender, No. (%)				<.001[2]
Missing	4	12	16	
Female	1199 (43.6)	2337 (35.9)	3536 (38.2)	
Male	1549 (56.4)	4176 (64.1)	5725 (61.8)	
Performance Score, No. (%)				0.003[2]
Missing	3	9	12	
0	1572 (57.2)	3491 (53.6)	5063 (54.6)	
1	1039 (37.8)	2707 (41.5)	3746 (40.4)	
2+	138 (5.0)	318 (4.9)	456 (4.9)	
Liver Involvement, No. (%)				<.001[2]
Missing	290	1027	1317	
No Involvement	623 (25.3)	1235 (22.5)	1858 (23.3)	
Liver Involvement Only	636 (25.8)	1720 (31.3)	2356 (29.6)	
Liver and ≥ 1 non-Liver Involvement	1203 (48.9)	2543 (46.3)	3746 (47.1)	
Lung Involvement, No. (%)				<.001[2]
Missing	311	1086	1397	
No Involvement	1647 (67.5)	3246 (59.7)	4893 (62.1)	
Lung Involvement Only	85 (3.5)	363 (6.7)	448 (5.7)	
Lung and >= 1 non-Lung Involvement	709 (29.0)	1830 (33.6)	2539 (32.2)	
Number of Metastatic Sites, No. (%)				0.007[2]
Missing	292	1018	1310	
0-1	1021 (41.5)	2463 (44.7)	3484 (43.7)	
2+	1439 (58.5)	3044 (55.3)	4483 (56.3)	
Received Any Prior Surgery, No. (%)				0.14[2]
Missing	620	1348	1968	
No	570 (26.7)	1473 (28.5)	2043 (28.0)	
Yes	1562 (73.3)	3704 (71.5)	5266 (72.0)	
Received Any Prior Chemotherapy, No. (%)				<.001[2]
Missing	199	468	667	
No	2158 (84.5)	4788 (79.0)	6946 (80.7)	
Yes	395 (15.5)	1269 (21.0)	1664 (19.3)	
Received Any Prior Radiation, No. (%)				<.001[2]
Missing	57	156	213	
No	2634 (97.7)	5702 (89.5)	8336 (92.0)	
Yes	61 (2.3)	667 (10.5)	728 (8.0)	
Synchronous Disease Status, No. (%)				<.001[2]
Missing	2014	5607	7621	
Metachronous	170 (23.0)	352 (38.3)	522 (31.5)	
Synchronous Unresected	195 (26.4)	176 (19.2)	371 (22.4)	

Synchronous Resected	373 (50.5)	390 (42.5)	763 (46.1)	
KRAS, No. (%)				<.001[2]
Missing	1322	3239	4561	
MT	706 (49.4)	1233 (37.5)	1939 (41.1)	
WT	724 (50.6)	2053 (62.5)	2777 (58.9)	
BRAF, No. (%)				<.001[2]
Missing	1441	3587	5028	
MT	183 (14.0)	131 (4.5)	314 (7.4)	
WT	1128 (86.0)	2807 (95.5)	3935 (92.6)	
Includes Target Agent, No. (%)				<.001[2]
No	1000 (36.3)	3069 (47.0)	4069 (43.9)	
Cetuximab	648 (23.5)	1913 (29.3)	2561 (27.6)	
Bevacizumab	867 (31.5)	1016 (15.6)	1883 (20.3)	
Cet+Bev	237 (8.6)	527 (8.1)	764 (8.2)	
Treatment Type, No. (%)				<.001[2]
Missing	391	1071	1462	
OX-based chemo + biologics	1120 (47.4)	2300 (42.2)	3420 (43.8)	
IRI-based chemo + biologics	515 (21.8)	820 (15.0)	1335 (17.1)	
OX-based chemo (no biologics)	597 (25.3)	1890 (34.7)	2487 (31.8)	
IRI-based chemo (no biologics)	129 (5.5)	444 (8.1)	573 (7.3)	
Chemo backbone, No. (%)				<.001[2]
Missing	810	1640	2450	
Oxaliplatin-based	1298 (66.8)	3621 (74.1)	4919 (72.1)	
Irinotecan-based	644 (33.2)	1264 (25.9)	1908 (27.9)	

[a]Equal variance two sample t-test
[b]Two-sided Chi-Square p-value
[c]Although 40 patients were originally deemed eligible for the trials, the data showed 0 metastatic disease sites.

Table 2. Efficacy Results

Prognostic impact					Predictive impact					
Variable	Left-sided, median mos	Right-sided, median mos	HR_{adj} (95% CI)	P^a	Variable	Cetuximab + chemotherapy, median mos	Chemotherapy alone, median mos	HR_{adj} (95% CI)	P^a	$P_{interaction}$
Overall survival					Overall survival					
All (N=9259)	21.6	15.9	0.71 (0.67-0.76)	<.001	*KRAS* WT					
KRAS WT (n=2773)	21.7	13.7	0.56 (0.49-0.64)	<.001	Left-sided (n=1211)	22.3	20.5	0.85 (0.75,0.97)	0.01	0.008
KRAS MT (n=1936)	16.7	17.1	0.98 (0.86-1.11)	0.73	Right-sided (n=290)	12.0	14.8	1.26 (0.98,1.63)	0.08	
Progression-free survival					*KRAS* MT					
All (N=9183)	8.6	7.5	0.80 (0.75-0.84)	<.001	Left-sided (n=739)	14.5	15.6	1.05 (0.90,1.23)	0.53	0.91
KRAS WT (n=2762)	8.5	6.9	0.64 (0.57-0.73)	<.001	Right-sided (n=313)	15.8	15.9	1.07 (0.84,1.37)	0.56	
KRAS MT (n=1933)	7.0	6.9	0.98 (0.86-1.11)	0.71	Progression-free survival					
—	—	—	—	—	*KRAS* WT					
—	—	—	—	—	Left-sided (n=1209)	9.3	8.5	0.77 (0.67,0.88)	<.001	0.13
—	—	—	—	—	Right-sided (n=287)	7.2	7.2	1.02 (0.77,1.34)	0.91	
—	—	—	—	—	*KRAS* MT					
—	—	—	—	—	Left-sided (n=736)	6.3	7.4	1.09 (0.92,1.29)	0.32	0.37
—	—	—	—	—	Right-sided (n=313)	6.8	7.4	1.21 (0.93,1.57)	0.15	

[a]Two-sided Wald test p values. CI = confidence interval; HR_{adj} = adjusted hazard ratio; MT = mutant; WT = wild-type.

Table 3. Propensity Score Analyses of treatment effect of CT + Bevacizumab vs. CT alone.

Variable	Bevacizumab + CT median (range), months	CT alone median (range), months	HR_{adj} (95% CI)	P^a	$P_{interaction}$
Overall survival					
Left-sided (n=1827)	27.0 (24.6-29.8)	18.7 (17.1-19.0)	0.60 (0.52-0.69)	<0.001	0.18
Right-sided (n=715)	25.5 (22.4-30.8)	13.4 (12.5-14.9)	0.55 (0.45-0.66)	<0.001	
Progression-free survival					
Left-sided (n=1827)	11.4 (10.7-12.5)	8.0 (7.6-8.3)	0.58 (0.51-0.65)	<0.001	0.19
Right-sided (n=715)	10.4 (9.4-11.5)	6.4 (6.1-7.2)	0.53 (0.44-0.63)	<0.001	

[a]P-values are from two-sided chi-square test. CI = confidence interval; CT = chemotherapy; HR_{adj} = adjusted hazard ratio.

Table 4. Propensity Score Analyses of treatment effect of CT + Cetuximab vs. CT + Bevacizumab

Variable	No.	Cetuximab + CT median (range), mos	Bevacizumab + CT median (range), mos	HR_{adj} (95% CI)	P^a	$P_{interaction}$
Overall survival						
KRAS WT						
Left-sided	255	25.5 (22.0-28.4)	24.6 (17.7-29.2)	1.10 (0.77-1.56)	0.61	0.005
Right-sided	300	12.5 (9.4-16.4)	26.0 (22.7-34.4)	1.89 (1.33-2.67)	<0.001	
KRAS MT						
Left-sided	199	13.1 (10.8-15.4)	24.8 (17.9-28.4)	2.09 (1.40-3.12)	<0.001	0.56
Right-sided	323	15.9 (11.5-19.1)	26.1 (21.5-30.8)	1.84 (1.37-2.47)	<0.001	
Progression-free survival						
KRAS WT						
Left-sided	254	9.0 (8.5-11.1)	11.7 (9.6-13.7)	1.23 (0.89-1.70)	0.21	0.05
Right-sided	300	6.7 (5.1-8.2)	10.7 (9.8-11.6)	1.84 (1.31-2.57)	<0.001	
KRAS MT						
Left-sided	198	6.4 (5.7-7.4)	13.1 (9.8-14.7)	3.16 (2.11-4.71)	<0.001	0.07
Right-sided	322	7.0 (6.3-8.2)	10.9 (9.5-11.9)	1.77 (1.35-2.33)	<0.001	

[a] Two-sided Wald test p values. CI = confidence interval; HR_{adj} = adjusted hazard ratio; MT = mutant; WT = wild-type.

Figure Legends

Figure 1. CONSORT diagram.

Figure 2. Overall survival and progression-free survival by primary tumor sidedness (left-sided vs. right-sided colon cancer), adjusted for age, sex, performance status, prior radiation/chemo, number of metastatic sites, and stratified by treatment arm within trials. A). Overall survival by left-sided vs. right-sided colon cancer. B). Overall survival by primary tumor sidedness and treatment arm within trials. C). Progression-free survival by left-sided vs. right-sided colon cancer. D). Progression-free survival by primary tumor sidedness and treatment arm within trials. All statistical tests were 2-sided. CT = chemotherapy. LS = left-sidedness. RS = right-sidedness.

Figure 3. Forest plots of the number of events, hazard ratio, and p-values of cox-regressions in each category of variable. A). Overall survival is stratified by categories of variables. B). Progression-free survival is stratified by categories of variables. All statistical tests were 2-sided. [a]Stratified type 3 likelihood-ratio P value was calculated. CI = confidence interval.

Figure 4. Overall survival and progression-free survival among KRAS wild-type by BRAFV600E mutation mCRC. A). Overall survival is stratified by the BRAF mutant and wild-type in the KRAS-wt left-sided tumors. B). Progression-free survival is stratified by the BRAF mutant and wild-type in the KRAS-wt left-sided tumors. C). Overall survival is

stratified by the BRAF mutant and wild-type in the KRAS-wt right-sided tumors. D). Porgression-free survival is stratified by the BRAF mutant and wild-type in the KRAS-wt right-sided tumors. All statistical tests were 2-sided. [a]Stratified type 3 likelihood-ratio P value was calculated. CI = confidence interval. MT = mutant. WT = wild=type.

Figure 1

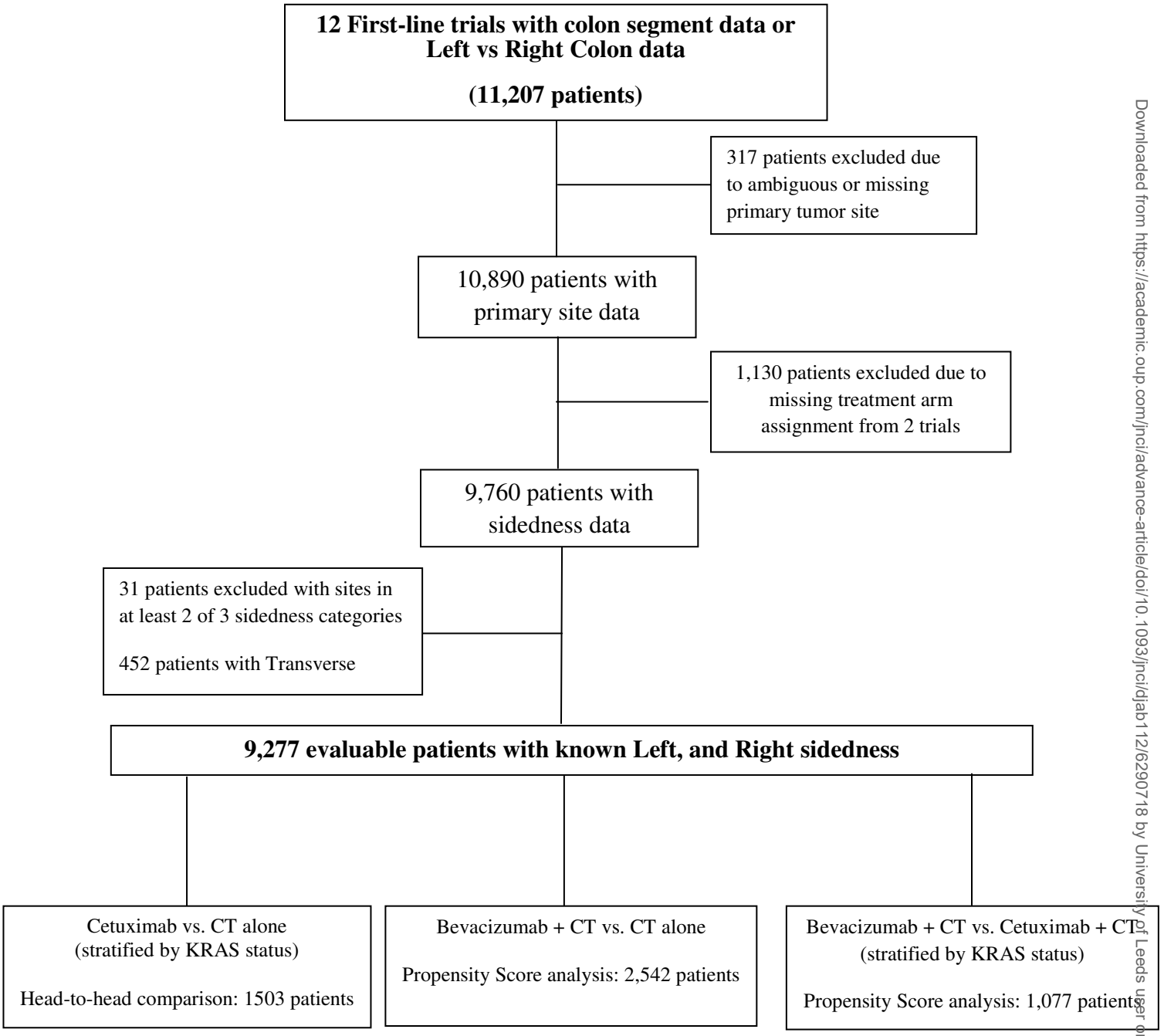

Figure 2

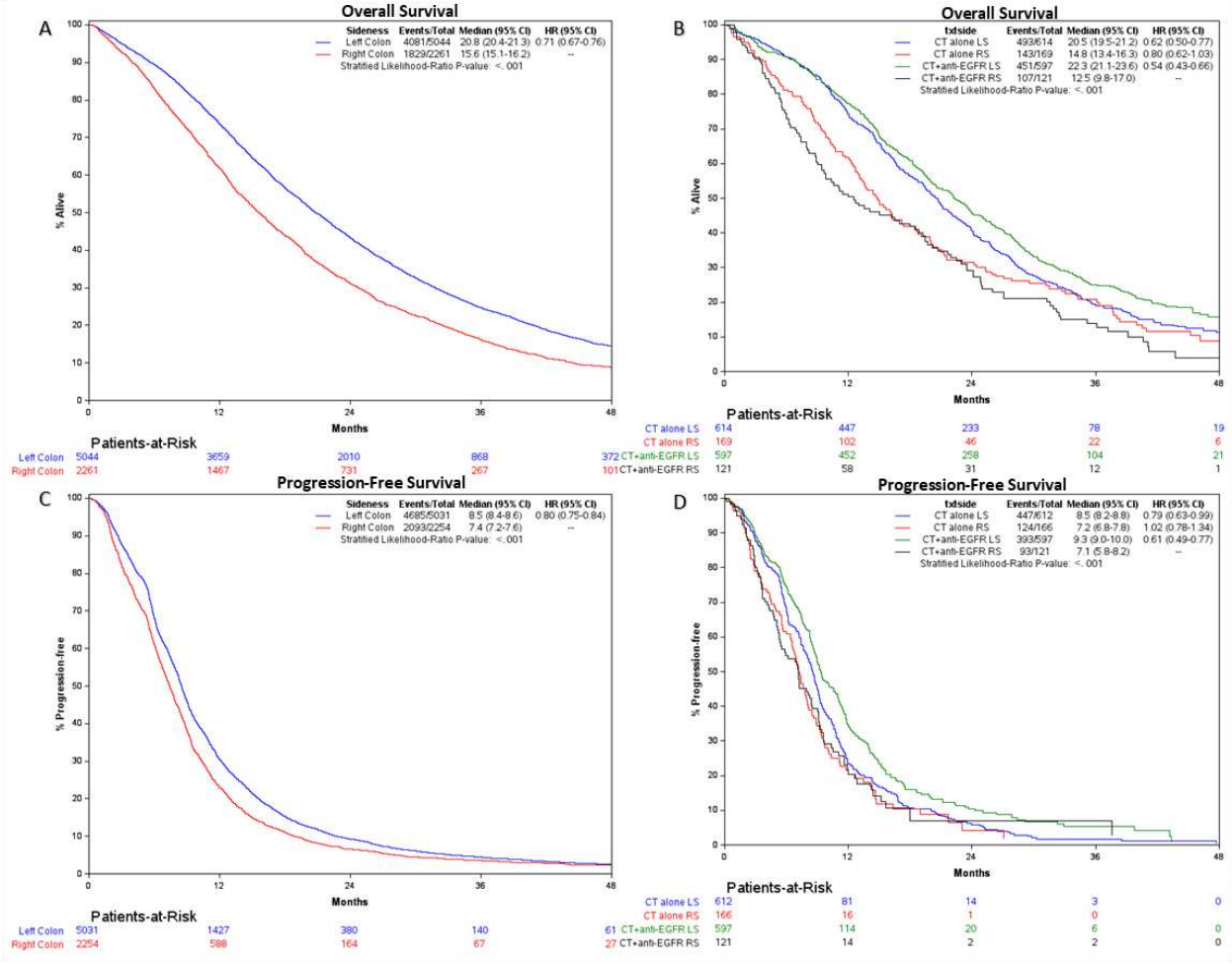

Figure 3

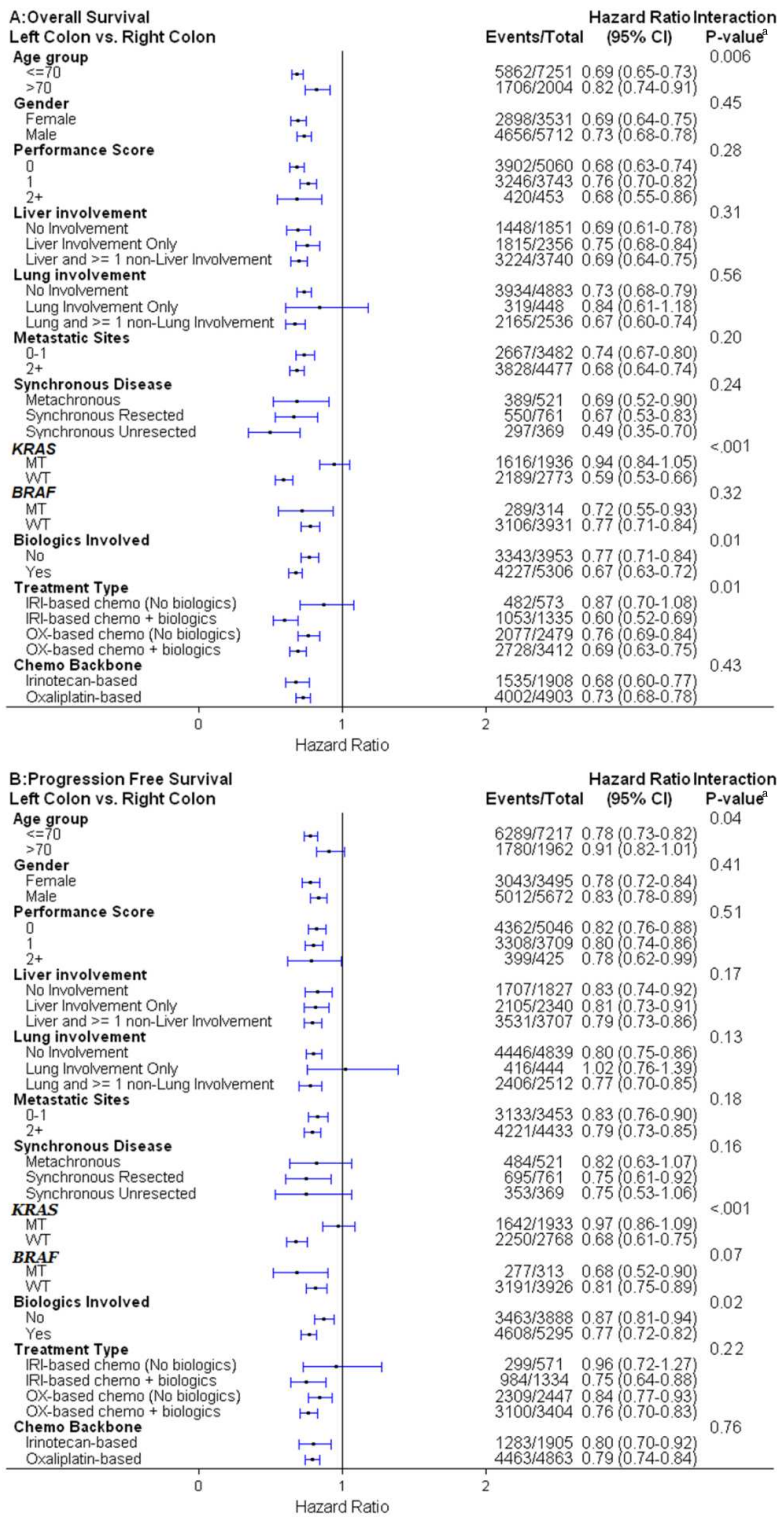

Figure 4