Published in final edited form as:

J Geriatr Oncol. 2022 May ; 13(4): 469–479. doi:10.1016/j.jgo.2022.01.006.

Age and comorbidity association with survival outcomes in metastatic colorectal cancer: CALGB 80405 analysis

Nadine J. McCleary, MD, MPH[1,2,*], **Sui Zhang, MS, MPP**[1], **Chao Ma, MS**[1], **Fang-Shu Ou, PhD**[3], **Tiffany M. Bainter, MPH**[3], **Alan P. Venook, MD**[4], **Donna Niedzwiecki, PhD**[5], **Heinz-Josef Lenz, MD**[6], **Federico Innocenti, MD, PhD**[7], **Bert H. O'Neil, MD**[8], **Blase N. Polite, MD**[10], **Howard S. Hochster, MD**[11], **James N. Atkins, MD**[12], **Richard M. Goldberg, MD**[13], **Kimmie Ng, MD, MPH**[1,2], **Robert J. Mayer, MD**[1,2], **Charles D. Blanke, MD**[14], **Eileen M. O'Reilly, MD**[15], **Charles S. Fuchs, MD, MPH**[16], **Jeffrey A. Meyerhardt, MD, MPH**[1,2]

[1]Dana-Farber Cancer Institute, Boston, MA

[2]Harvard Medical School, Boston, MA

[3]Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN

[4]University of California, San Francisco, San Francisco, CA

[5]Duke University, Durham, NC

[6]USC Norris Comprehensive Cancer Center, Los Angeles, CA

[7]The University of North Carolina at Chapel Hill, Chapel Hill, NC

[8]Simon Cancer Center, Indiana University School of Medicine, Indianapolis, IN

[10]Pritzker School of Medicine, The University of Chicago, Chicago, IL

[11]Department of Medical Oncology, Rutgers Cancer Institute of New Jersey, Brunswick, NJ

[12]Southeast Cancer Control Consortium, CCOP, Goldsboro, NC

[13]West Virginia University Cancer Institute, Morgantown, WV

[14]SWOG and Oregon Health & Science University, Portland, OR

[*]**Corresponding author at:** Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02115, nj_mccleary@dfci.harvard.edu.

Authors' contributions: NJM contributed to study funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing of the manuscript. KN and JAM also contributed to funding acquisition. SZ and CM conducted all data curation and formal analyses. All authors aided in study conceptualization, investigation, and reviewing and editing the manuscript.

DECLARATIONS

Ethics approval and consent to participate: An IRB committee has reviewed the methodology used in this manuscript, and has determined that it meets the requirements for protection of human subjects.

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing interests: BHO is employed by Eli Lilly and Co. JAM has received institutional research funding from Boston Biomedical, has served as an advisor/consultant to Ignyta and COTA Healthcare and served on a grant review panel for the National Comprehensive Cancer Network funded by Taiho Pharmaceutical.

[15]Memorial Sloan-Kettering Cancer Center, New York, NY

[16]Yale Cancer Center and Smillow Cancer Hospital, Yale School of Medicine, New Haven, CT

Abstract

Background: Little is known about the interaction of comorbidities and age on survival outcomes in colorectal ancer (mCRC), nor how comorbidities impact treatment tolerance.

Methods: We utilized a cohort of 1,345 mCRC patients enrolled in CALGB/SWOG 80405, a multicenter phase III trial of fluorouracil/leucovorin + oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) plus bevacizumab, cetuximab or both. Endpoints were overall survival (OS), progression-free survival (PFS), and grade ≥3 toxicities assessed using NCI CTCAE v.3.0. Participants completed a questionnaire, including a modified Charlson Comorbidity Index. Adjusted Cox and logistic regression models tested associations of comorbidities and age on the endpoints.

Results: In CALGB/SWOG 80405, 1,095 (81%) subjects were <70 years and 250 (19%). Presence of ≥1 comorbidity was not significantly associated with either OS (HR 1.10, 95% CI 0.96–1.25) or PFS (HR 1.03, 95% CI 0.91–1.16). Compared to subjects <70 with no comorbidities, OS was non-significantly inferior for ≥70 with no comorbidities (HR 1.21, 95% CI 0.98–1.49) and significantly inferior for ≥70 with at least one comorbidity (HR 1.51, 95% CI 1.22–1.86). There were no significant associations or interactions between age or comorbidity with PFS. Comorbidities were not associated with treatment-related toxicities. Age ≥70 was associated with greater risk of grade ≥3 toxicities (OR 2.15, 95% CI 1.50–3.09, p<0.001).

Conclusions: Amongst participants in a clinical trial of combination chemotherapy for mCRC, presence of older age with comorbidities was associated with worse OS but not PFS. The association of age with toxicity suggests additional factors of care should be measured in clinical trials.

Keywords

Elderly; older adult; geriatric oncology; comorbidity; gastrointestinal cancer; colorectal cancer; treatment decision-making

INTRODUCTION

Age is a leading risk factor for colorectal cancer (CRC), with 43% of patients being diagnosed at age ≥70 .[1, 2] Despite the observation that older adults experience a higher rate of hospitalization and adverse events from cancer treatment,[1] we have surprisingly little data to guide the appropriate treatment selection for this population. Cancer in older adults may require distinct treatment strategies given their potential intolerance of specific therapies, particularly in the understudied subset of adults age ≥75. The prevalence of one or more comorbidities in patients diagnosed with colon cancer range from 14–68%, with up to 50% having at least three comorbid medical conditions beyond colon cancer.[3, 4] Further, the presence of comorbidity in patients with colon cancer portends a 1.2–4.8-fold increase in five-year mortality compared to patients without comorbidity.[4] Although comorbidity is associated with decreased survival and poor treatment tolerance among participants with

cancer in some,[5–9] but not all studies,[10] the degree to which comorbidity is associated with survival and tolerance to chemotherapy by age at diagnosis of metastatic CRC (mCRC) is poorly understood. We sought to determine how the association of age <70 vs. ≥70 years with survival and chemotherapy tolerance outcomes differs due to comorbidity.

METHODS

Participants

CALGB/SWOG 80405 evaluated the combination of cetuximab, bevacizumab or both with fluoropyrimidine-based chemotherapy [fluorouracil/leucovorin + oxaliplatin (FOLFOX) or irinotecan (FOLFIRI)], and is described in detail elsewhere.[11, 12] The study underwent major amendments twice: in October 2008 to restrict enrollment to *KRAS WT* tumors (codons 12 and 13), and in September 2009 to omit the dual antibody combination arm after the first 1,601 subjects were enrolled.[11, 12]

Participants were asked to complete a validated comprehensive diet and lifestyle questionnaire regarding diet, physical activity, medications and comorbid conditions using a modified Charlson Comorbidity Index (CCI) within one month after starting chemotherapy.[13] Weight change was derived using information from this questionnaire, (documenting weight at the time of questionnaire completion and weight at six months prior), with percent weight change defined as weight at the questionnaire's completion minus weight six months prior divided by weight 6 months prior. To document physical activity, participants were asked "During the past 2 months, what was your average time per week spent at each of the following recreational activities?" (ranging from 0 to 11 hours per week) about nine leisure activities. They were also asked about their regular walking pace and the number of flights of stairs climbed per day. Each activity was assigned a validated metabolic expenditure value (MET; 1 MET = 1 kcal·kg^{-1} body weight·h^{-1}).[14, 15] Total MET hours per week were calculated by totaling MET scores for each activity then multiplying by total hours per week. Participants who reported any history of the following were defined as having a comorbidity: heart attack, angina pectoris, angiogram, coronary artery bypass grafting (CABG), angioplasty, congestive heart failure, peripheral artery disease, peripheral vascular surgery, stroke, transient ischemic attack, carotid surgery, thrombosis, embolus, asthma, diabetes, and Crohn's disease. Participants who did not report at least one of these conditions were considered to not have a comorbidity. We have included the full distribution of comorbidities reported (Supp Table 3). Participants who completed the questionnaire were included in the cohort for this analysis, including those enrolled prior to the *KRAS* amendment and those on the dual antibody treatment arm, to be more generalizable to the broader mCRC population. We conducted sensitivity analyses excluding patients with KRAS mutant tumors who received dual antibody therapy in CALGB 80203, prior to transition to CALGB 80405.

Statistical Analysis

In this retrospective analysis, data for all participants in all treatment arms were combined and analyzed according to the presence and number of comorbidities. Survival endpoints are defined as: (1) progression free survival (PFS), defined as the time from randomization

to disease progression or death and (2) overall survival (OS), defined as the time from randomization to death from any cause. Adverse events were assessed according to the National Cancer Institute Common Toxicity Criteria version 3.0, where the presence of adverse event was defined in the current analysis as the occurrence of any CTCAE grade 3 or higher symptomatic adverse event. We evaluated the association of the presence and number of comorbidities with PFS and OS within two age groups defined by age at diagnosis (<70 vs. ≥70 years) using Cox proportional hazards. The age threshold of <70 vs. ≥70 was selected for its clinical relevance regarding median age of diagnosis for CRC and consistency with prior analyses,[16] though this a priori categorization may fail to capture the biologic and phenotypic diversity of older adults, the assumption of proportional hazards was met. We adjusted for the following participant and clinical characteristics: sex, body mass index (BMI), prior surgery, Eastern Cooperative Oncology Group (ECOG) performance status, sidedness, prior adjuvant therapy, prior radiotherapy, protocol chemotherapy, treatment arm, KRAS status, physical activity and weight change. We included solicited symptomatic adverse events if (1) grade 2 or above and within the FOLFOX arms for neuropathy, or grade 3 or above for other selected adverse events (AEs); (2) relation to treatment was deemed possible, probable, or definite; and (3) AE occurred after study registration. Chi-square tests or Fisher's exact tests were used to test differences in categorical variables. Missing variables were coded with indicator variables and included as a category in modeling; except for BMI, physical activity and weight change where missing values were recoded into the majority category. All analyses were performed on de-identified data. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). Two-sided statistical significance was defined as $P < 0.05$ and not adjusted for multiple comparisons.

All analyses were performed with approval from the local Institutional Review Board in accordance with the precepts of the Helsinki Declaration.

RESULTS

Between November 2005 and March 2012, 3,058 unselected participants enrolled in CALGB 80405 (Figure 1), of which 2,326 were randomized and 1,575 consented to the diet and lifestyle questionnaire. The majority completed the questionnaire (86%), resulting in a final sample size of 1,345 for this analysis. Median follow-up time was 6.1 years, with 1146 (85%) deaths and 1158 (86%) having disease progression. Baseline characteristics between those completing the questionnaire and those enrolled in 80405 who did not complete questionnaire were reported in Supplemental Table 1. Age was not statistically different between two groups.

Baseline characteristics

Table 1 depicts baseline characteristics by comorbidities and age. We did not observe any statistically significant difference in frequency of comorbidities by treatment arm (Table 1). Eighty-one percent of subjects were age <70 (n=1,095) and 19% (n=250) were age ≥70. Enrollment of subgroups of older adults enrolled in this study are as follows: age 70–74 (144(57.6%)), 75–79 (82(32.8%)), 80–84 (22(8.8%)), 85+ (2(0.8%)). The median age of the

overall questionnaire cohort was 59 years [interquartile range (IQR) 51–68 years]. Absence of comorbidities and younger age were associated with increased physical activity. FOLFOX was more frequently used as the chemotherapy backbone for subjects without comorbidities and those <70 years old. The lower rate of resection on the primary tumor among older adults does seems to suggest that surgeons are less likely to operate on older patients; further exploration of this trend was beyond the scope of this manuscript.

Survival Outcomes

After a median follow-up of 6.10 years, 85% (n=1146) participants have died and 94% (n=1263) had progressed or died. We observed a statistically significant association in OS by age ≥70 vs. age <70 (adjusted HR 1.32, 95% CI 1.13–1.53, p<0.001) but not for PFS (adjusted HR 1.09, 95% CI 0.94–1.26, p=0.25). When limited to CRC-related overall survival events, defined as death attributed to colorectal cancer, we did not demonstrate a statistically significant association by age (HR 1.18, 95% CI 0.99–1.39, p=0.06). Similarly, after sensitivity analyses we did not observe a statistically significant difference in OS by any vs. no comorbidity (adjusted HR 1.21, 95% CI 0.99–1.27, p=0.08) or PFS (HR 1.03, 95% CI 0.91–1.16, p=0.63) (Supp Table 2). Figure 2 demonstrates survival curves for age and comorbidity. Figure 3 demonstrates survival outcomes in subgroups of patient/disease characteristics by age and by comorbidity.

Compared to subjects < 70 with no comorbidities (Table 2), OS was not statistically significantly worse for patients ≥70 with no comorbidities (HR 1.21, 95% CI 0.98–1.49) but OS was significantly worse for those ≥70 with at least one comorbidity (HR 1.51, 95% CI 1.22–1.86). However, the P for interaction between age and comorbidity with OS was not significant (p=0.29). There were no significant associations between age or comorbidity and PFS.

We explored other potential modifiers of comorbidities and outcomes, including sex, baseline performance status, chemotherapy backbone, treatment arm, *KRAS* tumor status, and *BRAF* tumor status (Figure 3). We did not observe significant interactions of any of these factors with comorbidity (P > 0.05). We did observe a statistically significant interaction between age and sidedness (OS p-interaction = 0.01, PFS p-interaction = 0.002). For left side tumor, patients ≥70 were more likely to experience cancer progression or death. The interaction between age and *KRAS* tumor status was statistically significant (OS p-interaction = 0.005, PFS p-interaction = 0.08), patients ≥70 with wild type *KRAS* mutation had higher probability to experience the event. *BRAF* tumor status was also statistically significant in regard to OS for patients ≥70 with wild type *BRAF* mutation (p-interaction = 0.001).

Ten percent of patients had two or more comorbidities. When we stratified comorbidities into three categories (none, 1, 2 or greater), we continued to observe that there were no associations between comorbidities and OS or PFS. However, certain comorbidities were significantly associated with OS, including a history of heart catherization (OS HR 1.59, 95% CI 1.01–2.51, p=0.04), diabetes (OS HR 1.20, 95% CI 1.03–1.41, p=0.02), and Crohn's disease (OS HR 1.61,1.04–2.47, p=0.03). Samples sizes by specific comorbidities became too small to test for interaction by age.

Solicited adverse events

After sensitivity analyses, the presence of any comorbidities did not predict for a likelihood of treatment-related adverse events (Table 3). However, age ≥ 70 was associated with increased likelihood of neutropenia, diarrhea, dehydration, anorexia, nausea, fatigue, weight loss, pain and any grade 3 or higher toxicity. When considering the interaction of age and comorbidity, compared to subjects < 70 with no comorbidities, patients ≥70 without comorbidity had increased likelihood of grade 3 or higher toxicities (OR 1.89, 95% CI 1.18 – 3.03). Compared to subjects <70 with no comorbidities, patients ≥70 with any comorbidity had a significantly increased likelihood of toxicity (OR 2.69, 95% CI 1.57 – 4.59); however, P for interaction between age and comorbidity was not significant (p=0.49). In Table 4, for symptomatic adverse events with >10 occurrences, we noted a statistically significant interaction between age and comorbidity for fatigue (p-interaction=0.03).

DISCUSSION

Within a large, community and academic center-based NCI-sponsored clinical trial for metastatic colorectal cancer, CALGB 80405, we evaluated the association of comorbidity on survival outcomes and treatment tolerance by adults age <70 vs. ≥70 receiving cytotoxic chemotherapy and antibody therapy. While analyses were limited by power, the presence of any comorbidity in older adults compared to younger adults without comorbidity predicted for worse overall survival, but not progression-free survival, suggesting that older adults experience similar PFS benefit with systemic therapy regardless of presence of comorbidity. This indicates that older patients with no comorbidity are biologically similar to younger patients.

Our study supports prior observational studies showing limited association of age with toxicity and survival outcomes for older adults. For example, evaluation of adults age <75 and ≥75 in four cancer registries - the Surveillance, Epidemiology, and End Results registry linked to Medicare claims (SEER-Medicare), the New York State Cancer Registry linked to Medicaid and Medicare claims (NYSCR), the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) and the National Comprehensive Cancer Network (NCCN) - demonstrated no statistically significant association between age and survival outcomes or tolerance among those receiving oxaliplatin-based chemotherapy.[17] However, the association between comorbidity and survival outcomes are less consistent.[4, 18, 19] Most, [4, 20] but not all studies,[18] report inferior survival outcomes among patients with comorbidities, even after accounting for the potential confounding effects of older age, cancer stage and cancer treatment. In a pooled analysis of four early stage colon cancer clinical trials, Haller et al showed no statistically significant association of comorbidity on disease-free survival, overall survival or moderate-severe treatment-related adverse event among older adults age ≥70 receiving oxaliplatin-based therapy.[21] However, that study differed from the present analysis in that the cohort included patients with surgically resectable disease and few patients age > 75 years. We did not observe a statistically significant association of comorbidity with survival outcomes or toxicity in a mCRC population. Future prospective clinical trials for metastatic colorectal cancer should include

full measures of comorbidity, in addition to functional status or disability, to increase the generalizability and consistency of study findings.

Implications for routine oncology practice

Our study suggests that while older adults (≥ 70 years of age) have inferior overall survival to younger adults (≤ 70), the presence of comorbidities does not modify the association between age and overall survival or tolerance of combination chemotherapy with antibody therapy for mCRC regardless of CCI score. Yet, up to 47% of older adults diagnosed with colon cancer are not offered cancer treatment due to presence of one or more comorbidity. Of those offered cancer treatment, 24–70% are not treated according to established guidelines, possibly due to concerns about toxicity.[4] We recommend considering the impact of age ≥ 70 years as applied in this study to consideration of treatment complexity for older adults. Specifically, fit older adults with few to no concurrent medical condition are anticipated to tolerate multiagent chemotherapy like younger counterparts. Further prospective study is needed to understand tolerance, disability and survival outcomes of octogenarians, a rapidly rising subset of older adults diagnosed with mCRC but not adequately reflected in historical trials (including this one).

Decision making may benefit from risk-stratification tools to assess patient readiness for cancer treatment and potential toxicity. The comprehensive geriatric assessment captures comorbidity, functional status, polypharmacy, and other factors in order to aid clinical decision-making, treatment selection and predict treatment-associated symptomatic adverse events among older adults [22, 23,24]. While it is acceptable to apply the current study findings to similarly fit older and younger adults diagnosed with mCRC in routine oncology practice, the association of comorbidity among unselected patients is not well known. As such, it may be useful to consider applying the comprehensive geriatric assessment and adverse event risk-stratification tool to all CRC patients under consideration for therapy for advanced disease regardless of age to determine and potentially mitigate risks of chemotherapy treatment.

Strengths and Limitations

We utilized a validated modified CCI to assess the presence and number of comorbid conditions at the initiation of first-line chemotherapy for mCRC.[13, 25] We did not use the CCI score for analysis as it fails to capture the severity or duration of illness,[26] the presence of psychiatric comorbidity, (which can mask cancer symptoms),[27, 28] and can limit the breadth of comorbidities reported. Nevertheless, comorbidity remains a robust predictor of cancer survival outcomes based on medical record or claims review.[29]

It may be noted that there were some distinctions between those patients who documented comorbidity through completion of the CCI and those who did not – those who completed the questionnaire generally had better performance status and were less likely to be underweight. Patients who completed the questionnaire were also less likely to have developed recurrent cancer after adjuvant chemotherapy and less likely to have their primary tumor left unresected. This may have limited the generalizability of our findings, as patients

included in the analysis may be generally healthier than those excluded due to their absence of questionnaire response.

Another limitation is that study participants were derived from a cohort enrolled in a clinical trial, that may by definition only include adults age 70+ that are younger (age 70–75), fitter, or those with fewer and less severe comorbidities. Further study is warranted to specifically enroll older adults in cancer clinical trials and overcome barriers previously experienced by the authors.[30]

Nonetheless, we did find associations for overall survival and toxicities related to age and comorbidity that have implications in clinical practice and may be more relevant in a more general mCRC population. While chronologic age is an imprecise proxy for functional status, the observed association of age with toxicity may be due to unmeasured factors not available for analysis, including measures of functional status and disability. Comorbidities were self-reported and not verified with medical records, however self-reported CCI has been validated in the past.[31]

Conclusions

Based on the lack of association of comorbidity with progression-free and overall survival, our study supports offering similar combination cytotoxic chemotherapy with a targeted biologic to both younger and older adults diagnosed with mCRC regardless of presence of comorbidity. However, older adults experienced more toxicities overall and better instruments to predict and reduce toxicity in this non-curative population remain important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

Not applicable

Funding:

This work was supported by the Anonymous Family Fund for Innovations in Colorectal Cancer (to JAM), Dana-Farber/Harvard Cancer Center (GI Spore Career Development Award 5P50CA127003–08 to NJM), Douglas B Marshall Jr Family Foundation (to JAM), George Stone Family Foundation (to JAM), Guo Shu Shi Fund (to JAM), Project P Fund (to KN), National Cancer Institute (R01CA205406 to KN and R01CA149222 to JAM), and the US Department of Defense (CA 160344 to KN).

List of Abbreviations

AE	adverse event
CAGB	coronary artery bypass grafting
CanCORS	Cancer Care Outcomes Research and Surveillance Consortium
CCI	Charlson Comorbidity Index

CRC	colorectal cancer
ECOG	Eastern Cooperative Oncology Group
FOLFOX	chemotherapy regimen of fluorouracil/leucovorin + oxaliplatin
FOLFIRI	chemotherapy regimen of fluorouracil/leucovorin + irinotecan
IQR	interquartile range
mCRC	metastatic colorectal cancer
MET	metabolic expenditure value
NCCN	National Comprehensive Cancer Network
NYSCR	New York State Cancer Registry linked to Medicaid and Medicare claims
OS	overall survival
PFS	progression free survival
SEER-Medicare	Surveillance, Epidemiology, and End Results registry linked to Medicare claims
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology

REFERENCES

1. McCleary NJ, Dotan E, Browner I. Refining the chemotherapy approach for older patients with colon cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology Aug 20 2014;32(24):2570–80. doi:10.1200/JCO.2014.55.1960 [PubMed: 25071118]
2. U.S. Cancer Statistics. Centers for Disease Control and Prevention Accessed September 18, 2018. https://gis.cdc.gov/cancer/USCS/DataViz.html
3. Yoon SJ, Kim EJ, Seo HJ, Oh IH. The Association between Charlson Comorbidity Index and the Medical Care Cost of Cancer: A Retrospective Study. BioMed research international 2015;2015:259341. doi:10.1155/2015/259341 [PubMed: 26347086]
4. Sogaard M, Thomsen RW, Bossen KS, Sorensen HT, Norgaard M. The impact of comorbidity on cancer survival: a review. Clinical epidemiology Nov 1 2013;5(Suppl 1):3–29. doi:10.2147/CLEP.S47150 [PubMed: 24227920]
5. Firat S, Byhardt RW, Gore E. Comorbidity and Karnofksy performance score are independent prognostic factors in stage III non-small-cell lung cancer: an institutional analysis of patients treated on four RTOG studies. Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys Oct 1 2002;54(2):357–64. [PubMed: 12243808]
6. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. Jama May 26 2004;291(20):2441–7. [PubMed: 15161894]
7. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med Jan 15 1994;120(2):104–10. [PubMed: 8256968]

8. Janssen-Heijnen ML, Szerencsi K, van de Schans SA, Maas HA, Widdershoven JW, Coebergh JW. Cancer patients with cardiovascular disease have survival rates comparable to cancer patients within the age-cohort of 10 years older without cardiovascular morbidity. Crit Rev Oncol Hematol Dec 2010;76(3):196–207. doi:S1040–8428(09)00228–5 [pii] 10.1016/j.critrevonc.2009.11.004 [PubMed: 20036574]
9. van Eeghen EE, Bakker SD, van Bochove A, Loffeld RJ. Impact of age and comorbidity on survival in colorectal cancer. Journal of gastrointestinal oncology Dec 2015;6(6):605–12. doi:10.3978/j.issn.2078-6891.2015.070 [PubMed: 26697191]
10. Houterman S, Janssen-Heijnen ML, Hendrikx AJ, van den Berg HA, Coebergh JW. Impact of comorbidity on treatment and prognosis of prostate cancer patients: a population-based study. Crit Rev Oncol Hematol Apr 2006;58(1):60–7. doi:S1040–8428(05)00167–8 [pii] 10.1016/j.critrevonc.2005.08.003 [PubMed: 16213153]
11. Lieu CH, Messersmith WA. Cetuximab or Bevacizumab With First-Line Chemotherapy in Advanced KRAS Wild-Type Colorectal Cancer: No Difference, but Not the Same. JAMA Jun 20 2017;317(23):2376–2378. doi:10.1001/jama.2017.6673 [PubMed: 28632850]
12. Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA Jun 20 2017;317(23):2392–2401. doi:10.1001/jama.2017.7105 [PubMed: 28632865]
13. Meyerhardt JA, Heseltine D, Campos H, et al. Assessment of a dietary questionnaire in cancer patients receiving cytotoxic chemotherapy. J Clin Oncol Nov 20 2005;23(33):8453–60. doi:10.1200/JCO.2005.02.5460 [PubMed: 16293876]
14. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25(1):71–80. [PubMed: 8292105]
15. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol 2006;24(22):3535–3541. [PubMed: 16822843]
16. McCleary NJ, Meyerhardt JA, Green E, et al. Impact of Age on the Efficacy of Newer Adjuvant Therapies in Patients With Stage II/III Colon Cancer: Findings From the ACCENT Database. Journal of Clinical Oncology 2013/07/10 2013;31(20):2600–2606. doi:10.1200/JCO.2013.49.6638 [PubMed: 23733765]
17. Sanoff HK, Carpenter WR, Sturmer T, et al. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. J Clin Oncol Jul 20 2012;30(21):2624–34. doi:10.1200/JCO.2011.41.1140 [PubMed: 22665536]
18. Haller D, O'Connell M, Cartwright T, et al. Impact of age and medical comorbidity (MC) on adjuvant treatment outcomes for stage III colon cancer (CC): A pooled analysis of individual patient data from four randomized controlled trials (abstract 3522). J Clin Oncol 2012;30(suppl)
19. Sarfati D, Hill S, Blakely T, et al. The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study. BMC Cancer 2009;9:116. doi:1471–2407-9–116 [pii] 10.1186/1471-2407-9-116 [PubMed: 19379520]
20. Sarfati D, Tan L, Blakely T, Pearce N. Comorbidity among patients with colon cancer in New Zealand. The New Zealand medical journal Jul 8 2011;124(1338):76–88.
21. Haller DG, O'Connell MJ, Cartwright TH, et al. Impact of age and medical comorbidity on adjuvant treatment outcomes for stage III colon cancer: a pooled analysis of individual patient data from four randomized, controlled trials. Annals of oncology : official journal of the European Society for Medical Oncology Apr 2015;26(4):715–24. doi:10.1093/annonc/mdv003 [PubMed: 25595934]
22. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol Sep 1 2011;29(25):3457–65. doi:10.1200/JCO.2011.34.7625 [PubMed: 21810685]
23. Extermann M, Boler I, Reich R, et al. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score: Design and validation. J Clin Oncol 2010;28(7S):(suppl; abstr 9000).

24. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet Oct 23 1993;342(8878):1032–6. [PubMed: 8105269]

25. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. American journal of epidemiology Jul 1985;122(1):51–65. [PubMed: 4014201]

26. Sarfati D. Review of methods used to measure comorbidity in cancer populations: no gold standard exists. Journal of clinical epidemiology Sep 2012;65(9):924–33. doi:10.1016/j.jclinepi.2012.02.017 [PubMed: 22739245]

27. Hoeben KW, van Steenbergen LN, van de Wouw AJ, Rutten HJ, van Spronsen DJ, Janssen-Heijnen ML. Treatment and complications in elderly stage III colon cancer patients in the Netherlands. Annals of oncology : official journal of the European Society for Medical Oncology Apr 2013;24(4):974–9. doi:10.1093/annonc/mds576 [PubMed: 23136227]

28. Gupta SK, Lamont EB. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. J Am Geriatr Soc Oct 2004;52(10):1681–7. [PubMed: 15450045]

29. Kehl KL, Lamont EB, McNeil BJ, Bozeman SR, Kelley MJ, Keating NL. Comparing a medical records-based and a claims-based index for measuring comorbidity in patients with lung or colon cancer. Journal of geriatric oncology May 2015;6(3):202–10. doi:10.1016/j.jgo.2015.01.005 [PubMed: 25662785]

30. McCleary NJ, Hubbard J, Mahoney MR, et al. Challenges of conducting a prospective clinical trial for older patients: lessons learned from NCCTG N0949 (alliance). Journal of geriatric oncology 2018;9(1):24–31. [PubMed: 28917648]

31. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? Medical care Jan 1996;34(1):73–84. [PubMed: 8551813]

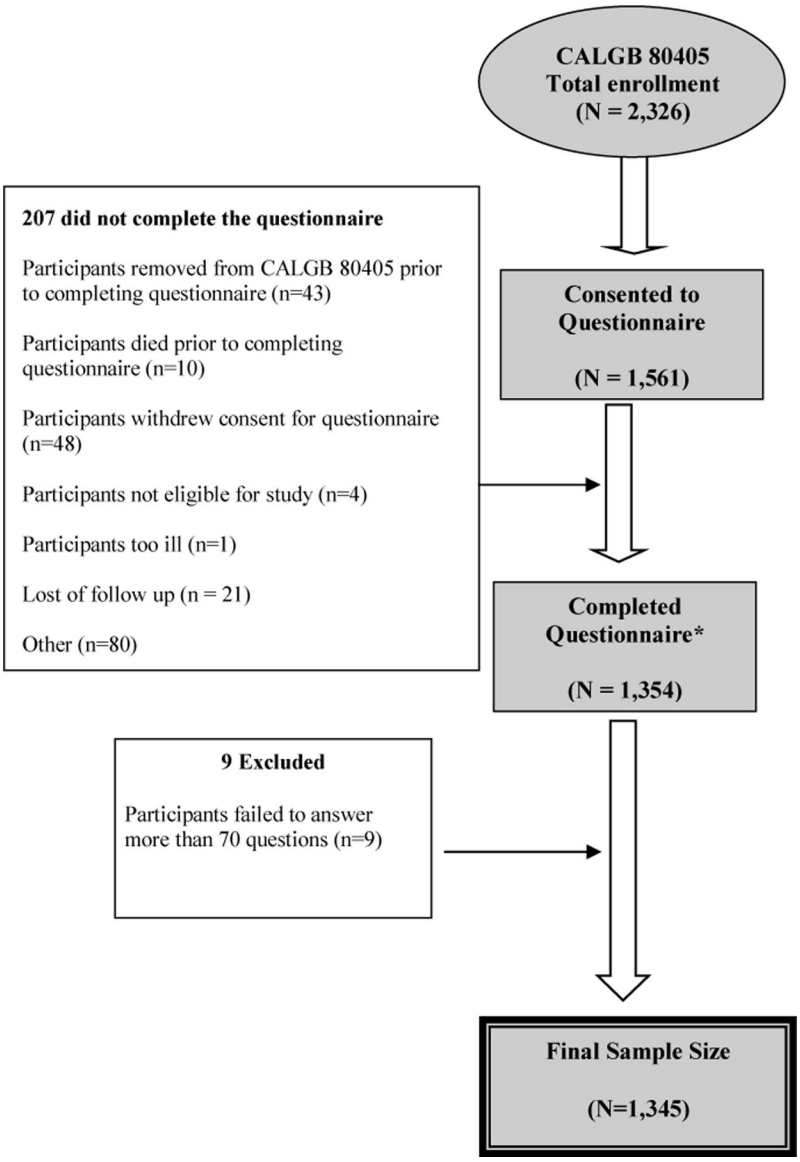
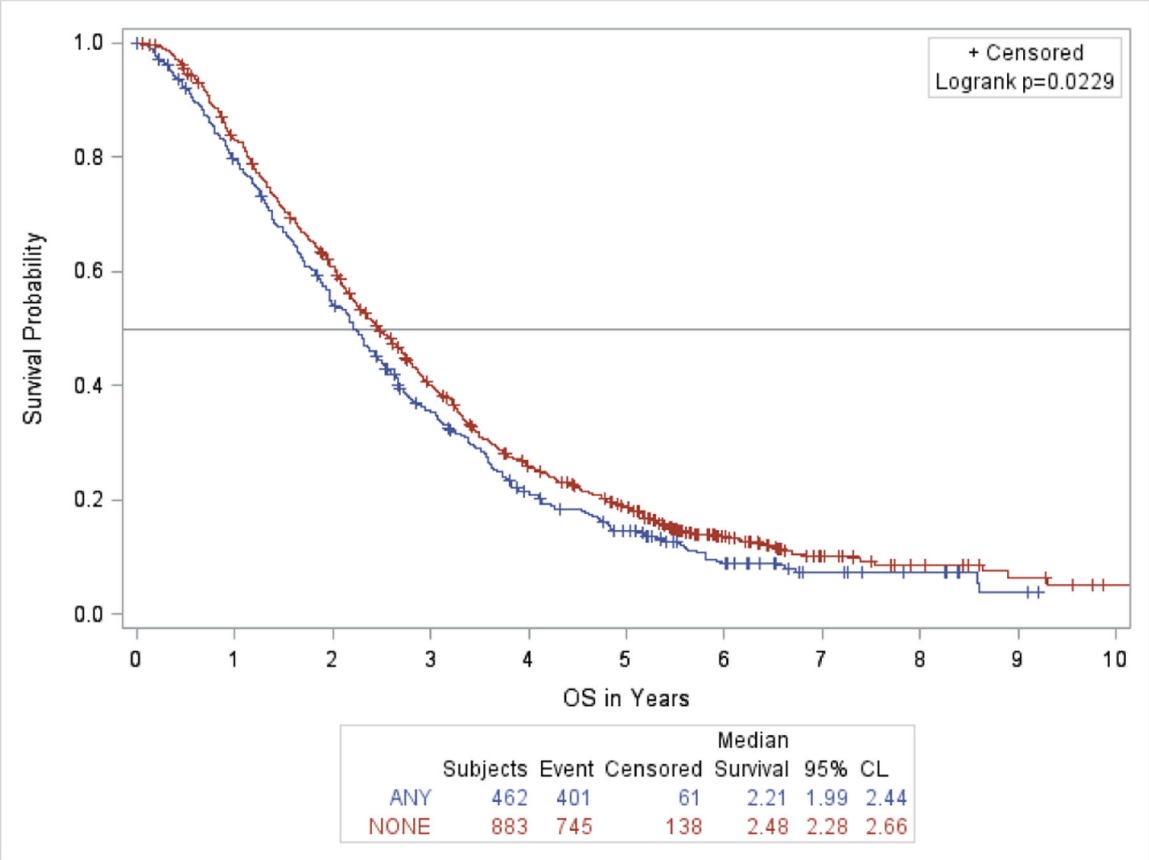
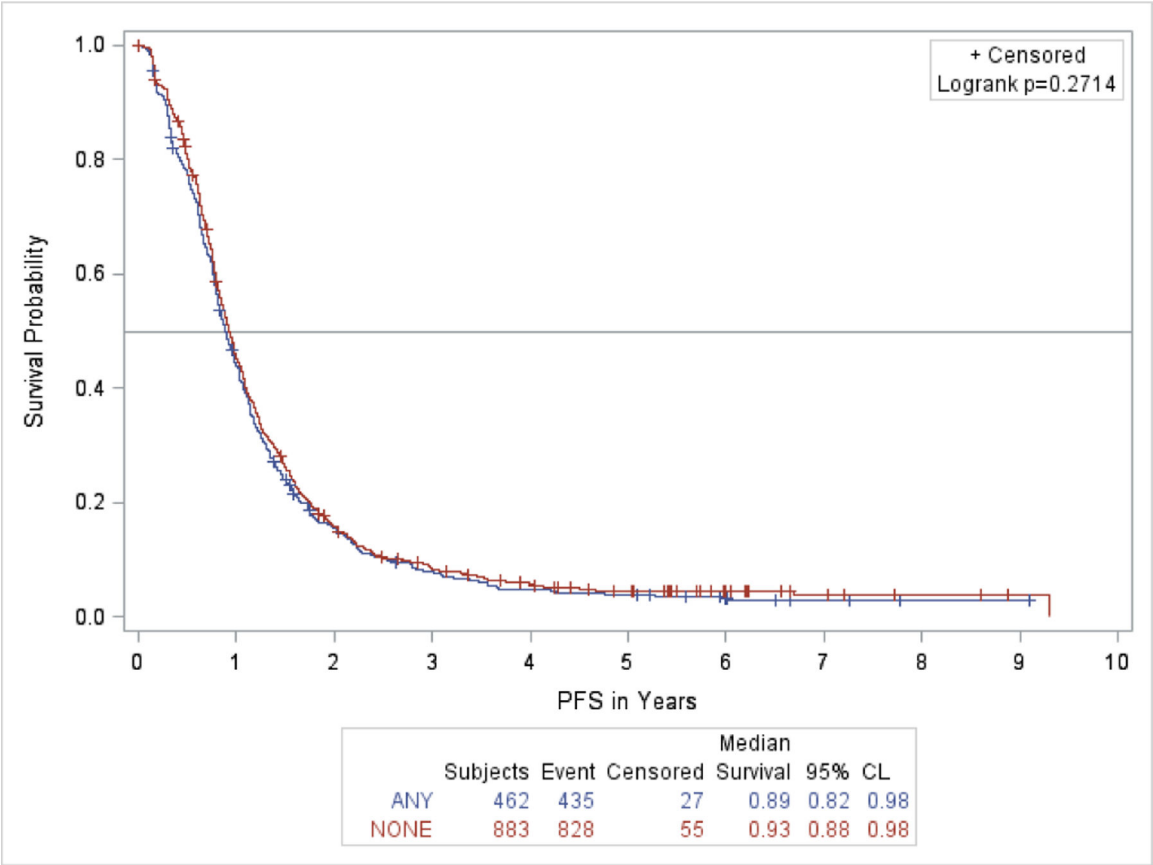


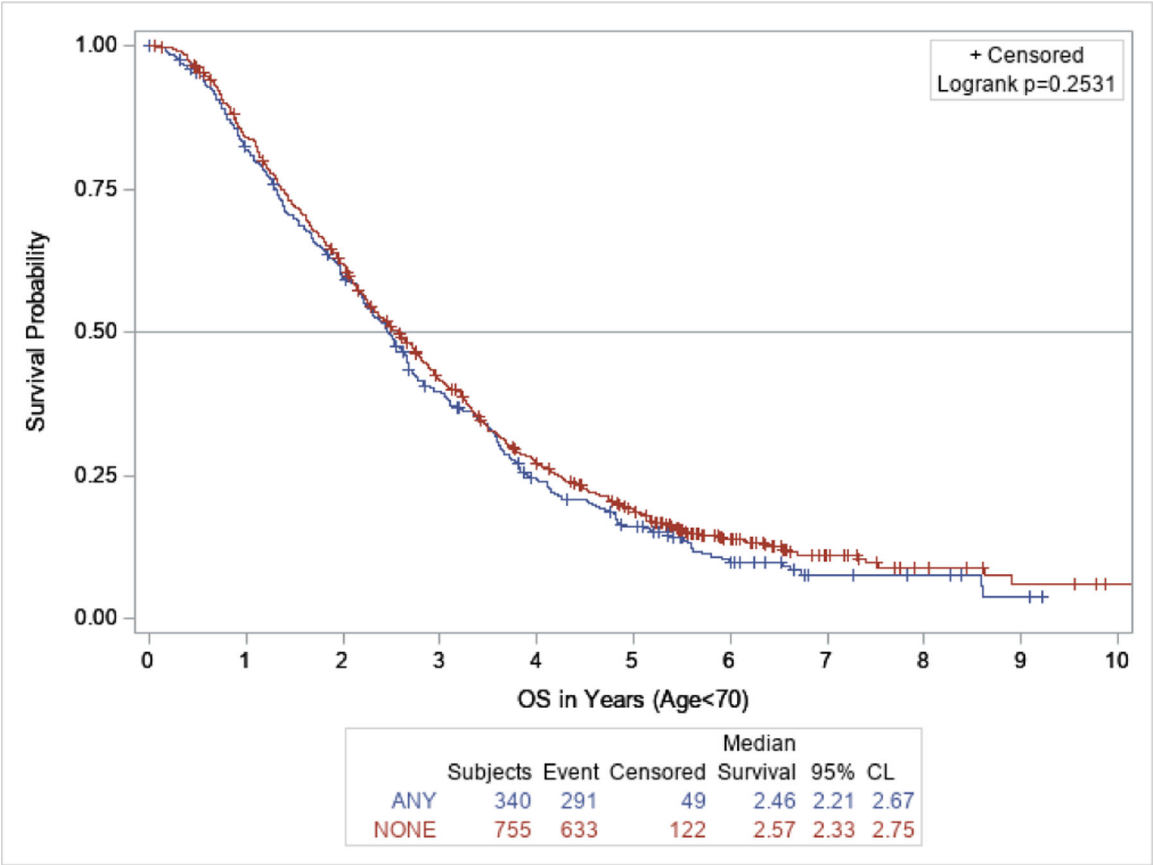
Figure 1:
Cohort Diagram



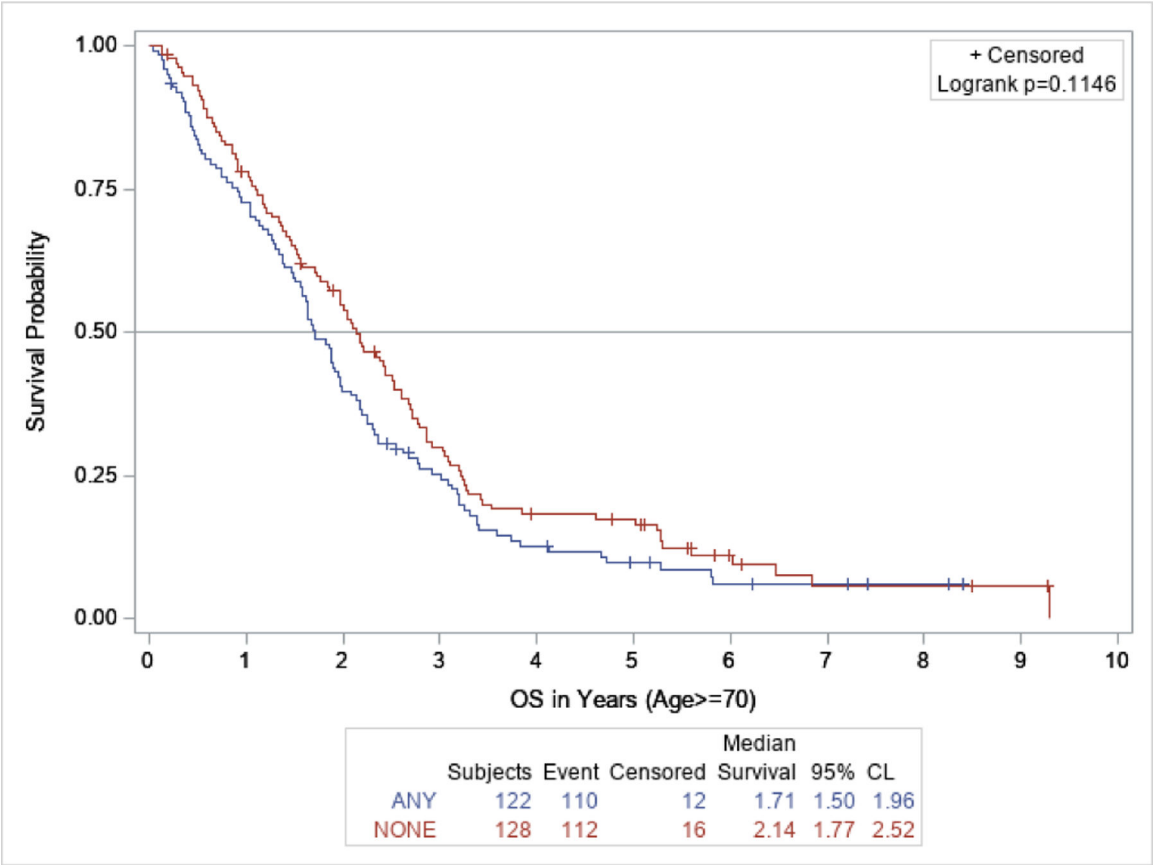
	Subjects	Event	Censored	Median Survival	95%	CL
ANY	462	401	61	2.21	1.99	2.44
NONE	883	745	138	2.48	2.28	2.66



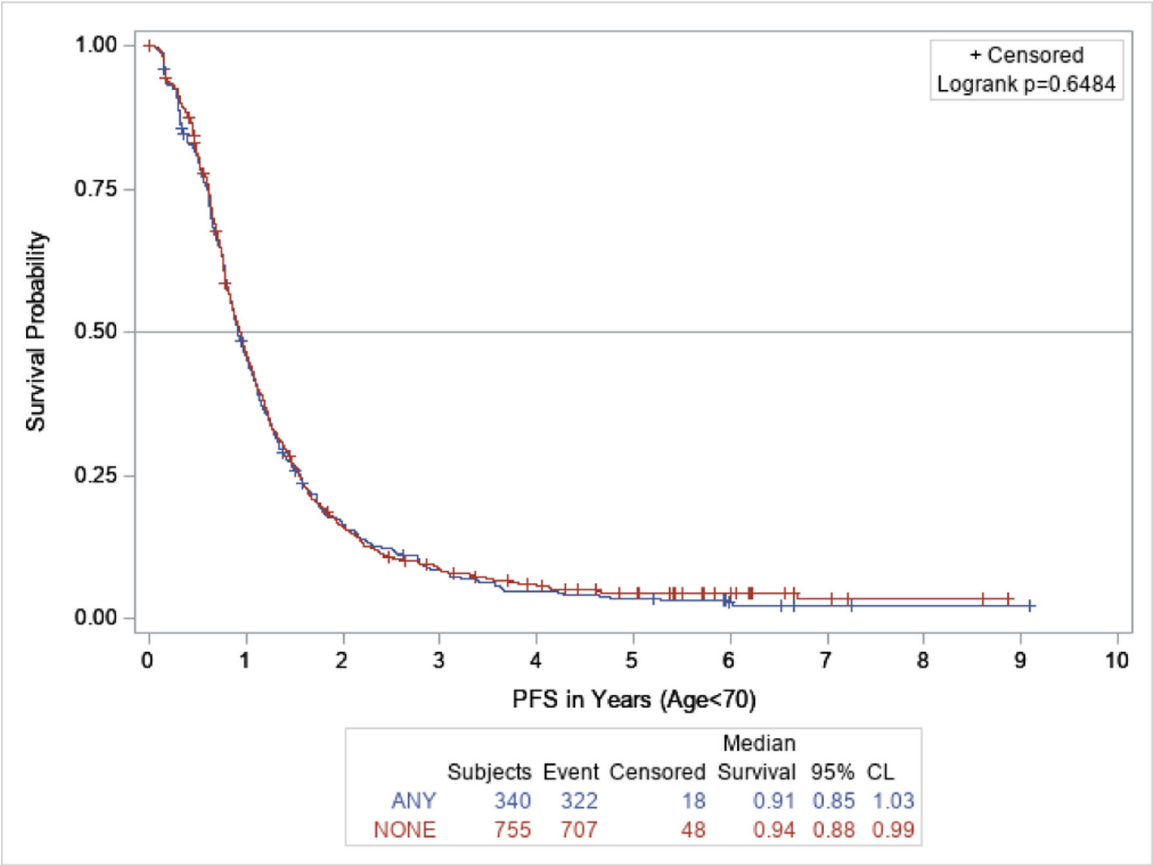
	Subjects	Event	Censored	Median Survival	95% CL	
ANY	462	435	27	0.89	0.82	0.98
NONE	883	828	55	0.93	0.88	0.98



	Subjects	Event	Censored	Median Survival	95%	CL
ANY	340	291	49	2.46	2.21	2.67
NONE	755	633	122	2.57	2.33	2.75



	Subjects	Event	Censored	Median Survival	95%	CL
ANY	122	110	12	1.71	1.50	1.96
NONE	128	112	16	2.14	1.77	2.52



	Subjects	Event	Censored	Median Survival	95%	CL
ANY	340	322	18	0.91	0.85	1.03
NONE	755	707	48	0.94	0.88	0.99

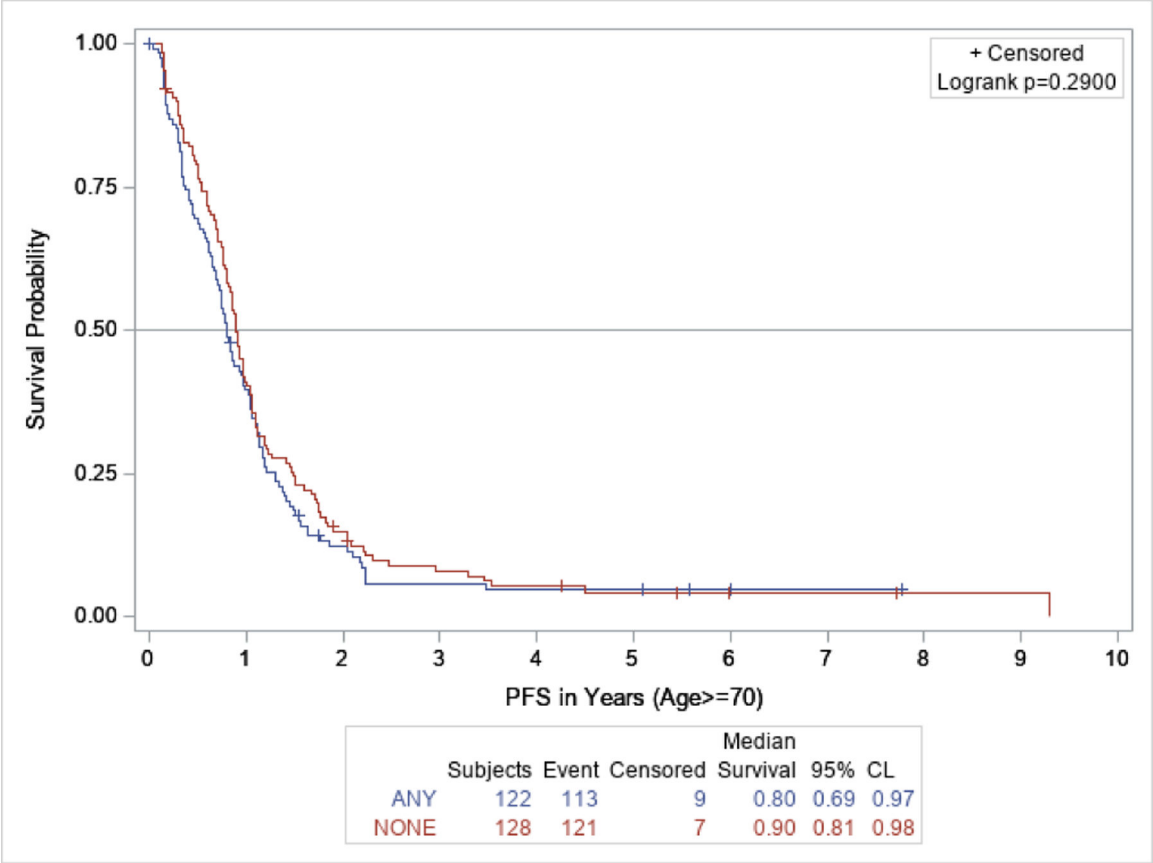


Figure 2:

KM Survival Curves

A. OS by any comorbidity vs. none

B. PFS by any comorbidity vs. none

C. OS by any comorbidity vs. none, among Age <70

D. OS by any comorbidity vs. none, among Age ≥70

E. PFS by any comorbidity vs. none, among Age <70

F. PFS by any comorbidity vs. none, among Age ≥70

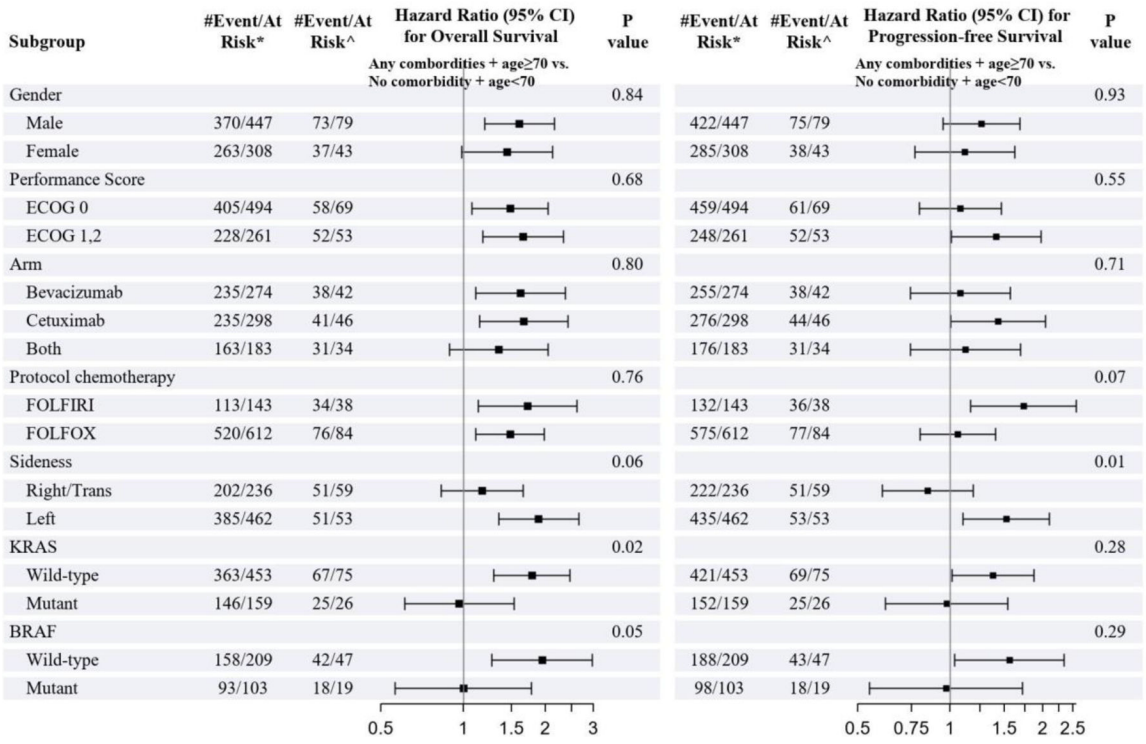


Figure 3:

Forest Plot of OS, PFS by any comorbidity + age ≥70 vs. no comorbidity + age <70

Note:

* #Event/At Risk for no comorbidity + age < 70.

^ #Event/At Risk for any comorbidity + age ≥ 70.

Hazard Ratio (HR) represents the effect of any comorbidity + age ≥ 70 vs. no comorbidity + age < 70. HR (95% CI) and P-values are based on the Cox model with the interaction term of comorbidity (none, any) and age (<70, ≥ 70) * selected subgroup, adjusted by female, BMI (min- 20.9, 21=24.9, 25–29.9, 30–34.9, 35+), primary tumor unresected, performance status (ECOG 0, ECOG 1 and 2), sidedness (left, right and transverse, multiple and missing), prior adjuvant therapy, prior radiotherapy, protocol chemotherapy, treatment arm, KRAS status (wild-type, mutation, indeterminant), BRAF status (wild-type, mutation, indeterminant), physical activities (0–2.9, 3–8.9, 9–17.9, 18+), and weight change (loss ≥5%, change <5%, gain ≥5%).

Table 1:

Participant characteristics

	Overall		No Comorbidity	Any Comorbidity	p-value		Age <70	Age ≥70	p-value
No. at risk	**1345**		**883**	**462**			**1095**	**250**	
Age at registration									
Median (interquartile range)	59.1 (51.1–67.5)		56.8 (48.8–65.5)	63.0 (54.9–70.5)	<0.001		55.9 (48.8–62.8)	74.1 (72.1–77.0)	<0.0010
Age <70	1095 (81.4%)		755 (85.5%)	340 (73.6%)	<0.001				
Age ≥70	250 (18.6%)		128 (14.5%)	122 (26.4%)					
Comorbidity									**<0.001**
No comorbidity	883 (65.7%)						755 (68.9%)	128 (51.2%)	
1 comorbidity	333 (24.8%)						254 (23.2%)	79 (31.6%)	
≥ 2 comorbidity	129 (9.6%)						86 (7.9%)	43 (17.2%)	
BMI at registration					**<0.0010**				**0.02**
min-20.9	122 (9.1%)		86 (9.7%)	36 (7.8%)			102 (9.3%)	20 (8.0%)	
21–24.9	300 (22.3%)		235 (26.6%)	65 (14.1%)			239 (21.8%)	61 (24.4%)	
25–29.9	495 (36.8%)		325 (36.8%)	170 (36.8%)			389 (35.5%)	106 (42.4%)	
30–34.9	275 (20.4%)		167 (18.9%)	108 (23.4%)			227 (20.7%)	48 (19.2%)	
35+	153 (11.4%)		70 (7.9%)	83 (18.0%)			138 (12.6%)	15 (6.0%)	
Sex					**0.23**				**0.51**
Male, N (%)	794 (59.0%)		511 (57.9%)	283 (61.3%)			651 (59.5%)	143 (57.2%)	
Female, N (%)	551 (41.0%)		372 (42.1%)	179 (38.7%)			444 (40.5%)	107 (42.8%)	
Protocol chemotherapy					**<0.0010**				**0.07**
FOLFIRI, N (%)	308 (22.9%)		173 (19.6%)	135 (29.2%)			240 (21.9%)	68 (27.2%)	
FOLFOX, N (%)	1037 (77.1%)		710 (80.4%)	327 (70.8%)			855 (78.1%)	182 (72.8%)	
Treatment Arm					**0.94**				**0.24**
Bevacizumab, N (%)	516 (38.4%)		339 (38.4%)	177 (38.3%)			409 (37.4%)	107 (42.8%)	
Cetuximab, N (%)	510 (37.9%)		337 (38.2%)	173 (37.4%)			425 (38.8%)	85 (34.0%)	
Bevacizumab+Cetuximab, N (%)	319 (23.7%)		207 (23.4%)	112 (24.2%)			261 (23.8%)	58 (23.2%)	
Prior adjuvant chemotherapy					**<0.0010**				**0.10**
No, N (%)	1172 (87.1%)		791 (89.6%)	381 (82.5%)			962 (87.9%)	210 (84.0%)	

J Geriatr Oncol. Author manuscript; available in PMC 2023 May 01.

	Overall		No Comorbidity	Any Comorbidity	p-value		Age <70	Age ≥70	p-value
Yes, N (%)	173 (12.9%)		92 (10.4%)	81 (17.5%)			133 (12.1%)	40 (16.0%)	
Prior Pelvic radiation					**0.02**				**0.61**
No, N (%)	1232 (91.6%)		820 (92.9%)	412 (89.2%)			1005 (91.8%)	227 (90.8%)	
Yes, N (%)	113 (8.4%)		63 (7.1%)	50 (10.8%)			90 (8.2%)	23 (9.2%)	
Primary tumor unresected					**<0.0010**				**<0.0010**
No, N (%)	1057 (78.6%)		670 (75.9%)	387 (83.8%)			837 (76.4%)	220 (88.0%)	
Yes, N (%)	288 (21.4%)		213 (24.1%)	75 (16.2%)			258 (23.6%)	30 (12.0%)	
ECOG Performance Status					**0.002**				**0.11**
ECOG 0, N (%)	824 (61.3%)		567 (64.2%)	257 (55.6%)			682 (62.3%)	142 (56.8%)	
ECOG 1–2, N (%)	521 (38.7%)		316 (35.8%)	205 (44.4%)			413 (37.7%)	108 (43.2%)	
Sidedness					**0.007**				**0.002**
Right or Transverse, N (%)	465 (34.6%)		285 (32.3%)	180 (39.0%)			357 (32.6%)	108 (43.2%)	
Left, N (%)	780 (58.0%)		536 (60.7%)	244 (52.8%)			653 (59.6%)	127 (50.8%)	
Multiple or Missing, N (%)	100 (7.4%)		62 (7.0%)	38 (8.2%)			85 (7.8%)	15 (6.0%)	
KRAS					**0.96**				**0.39**
WT, N (%)	805 (59.9%)		530 (60.0%)	275 (59.5%)			653 (59.6%)	152 (60.8%)	
MUT, N (%)	292 (21.7%)		192 (21.7%)	100 (21.6%)			233 (21.3%)	59 (23.6%)	
Missing, N (%)	248 (18.4%)		161 (18.2%)	87 (18.8%)			209 (19.1%)	39 (15.6%)	
Physical Activity, MET h/w					**<0.0010**				**<0.0010**
0–2.9	630 (46.8%)		378 (42.8%)	252 (54.5%)			493 (45.0%)	137 (54.8%)	
3–8.9	310 (23.0%)		208 (23.6%)	102 (22.1%)			252 (23.0%)	58 (23.2%)	
9–17.9	164 (12.2%)		111 (12.6%)	53 (11.5%)			132 (12.1%)	32 (12.8%)	
18+	241 (17.9%)		186 (21.1%)	55 (11.9%)			218 (19.9%)	23 (9.2%)	
Weight Change					**0.7343**				**0.7277**
Loss ≥ 5%, N (%)	861 (64.0%)		564 (63.9%)	297 (64.3%)			704 (64.3%)	157 (62.8%)	
Change < 5%, N (%)	439 (32.6%)		287 (32.5%)	152 (32.9%)			353 (32.2%)	86 (34.4%)	
Gain ≥5%, N (%)	45 (3.3%)		32 (3.6%)	13 (2.8%)			38 (3.5%)	7 (2.8%)	

Note: P-value is from Wilcoxon test for continuous variables, and Chi-squared test for categorical variables. P-value for performance status is based on ECOG 0 vs combination of ECOG 1 and ECOG 2. P-value for sidedness is based on left vs combination of right and transverse. P-value for KRAS is based on wild type vs mutant.

Missing values: 1 in BMI, 3 in physical activity, 21 in weight change, all recoded into the majority category.

Table 2:

Survival outcomes by comorbidity strata and age

		No Comorbidity	Any Comorbidity	P-value*	P-value#
Overall Survival					
Age <70	Deaths/At Risk	633/755	291/340		
	HR (95% CI)	Referent	1.06 (0.92 – 1.22)	0.45	0.29
Age ≥70	Deaths/At Risk	112/128	110/122		
	HR (95% CI)	1.21 (0.98 – 1.49)	1.51 (1.22 – 1.86)	0.11	
	Subgroup p2^	0.07	0.002		
Progression-free survival					
Age <70	Progression/At Risk	707/755	322/340		
	HR (95% CI)	Referent	0.99 (0.87 – 1.14)	0.92	0.35
Age ≥70	Progression /At Risk	121/128	113/122		
	HR (95% CI)	1.02 (0.84 – 1.25)	1.17 (0.95 – 1.44)	0.32	
	Subgroup p2^	0.83	0.15		

Abbreviations: HR = Hazard Ratio; CI = Confidence Interval.

Note:

^P-value compares the difference between age (<70, ≥70) within each comorbidity subgroup.

*P-value assesses the significance between no comorbidity and any comorbidity within each subgroup by age.

#P-value assesses the significance of comorbidity*age interaction for overall and progression- free survival.

HR (95% CI) and p-values are based on Cox model with the interaction term of comorbidity (none, any) * age (<70, ≥70), adjusting by following covariates: female, BMI (min-20.9, 21=24.9, 25–29.9, 30–34.9, 35+), primary tumor unresected, performance status (ECOG 0, ECOG 1 and 2), sidedness (left, right and transverse, multiple and missing), prior adjuvant therapy, prior radiotherapy, protocol chemotherapy, treatment arm, *KRAS* status (wild-type, mutation, indeterminant), physical activities (0–2.9, 3–8.9, 9–17.9, 18+), and weight change (Loss ≥5%, change <5%, gain ≥5%).

Table 3.

Frequency of moderate-severe toxicities by comorbidity and age strata

	Total		No Comorbidity	Any Comorbidity	OR for Any Comorbidity (95% CI)	p-value		Age <70	Age ≥70	OR for age ≥70 (95% CI)	p-value
Neutropenia	456 (33.9%)		295 (33.4%)	161 (34.8%)	1.15 (0.89 – 1.49)	0.29		347 (31.7%)	109 (43.6%)	1.56 (1.16 – 2.11)	0.004
Hemoglobin	23 (1.7%)		11 (1.2%)	12 (2.6%)	1.83 (0.74 – 4.55)	0.19		17 (1.6%)	6 (2.4%)	1.83 (0.67 – 5.04)	0.24
Diarrhea	161 (12.0%)		89 (10.1%)	72 (15.6%)	1.37 (0.96 – 1.96)	0.08		113 (10.3%)	48 (19.2%)	1.99 (1.34 – 2.94)	<0.001
Dehydration	59 (4.4%)		32 (3.6%)	27 (5.8%)	1.48 (0.85 – 2.60)	0.17		38 (3.5%)	21 (8.4%)	2.19 (1.22 −3.93)	0.01
Vomiting	46 (3.4%)		28 (3.2%)	18 (3.9%)	1.08 (0.57 – 2.05)	0.82		35 (3.2%)	11 (4.4%)	1.23 (0.59 – 2.53)	0.58
Anorexia	39 (2.9%)		18 (2.0%)	21 (4.5%)	1.74 (0.86 – 3.51)	0.13		26 (2.4%)	13 (5.2%)	2.24 (1.06 – 4.72)	0.03
Nausea	40 (3.0%)		24 (2.7%)	16 (3.5%)	1.08 (0.54 – 2.15)	0.82		26 (2.4%)	14 (5.6%)	2.43 (1.21 – 4.88)	0.01
Neuropathy	401 (38.7%)		280 (39.4%)	121 (37.0%)	0.87 (0.66 – 1.16)	0.35		335 (39.2%)	66 (36.3%)	0.91 (0.64 – 1.28)	0.57
Fatigue	146 (10.9%)		88 (10.0%)	58 (12.6%)	1.12 (0.77 – 1.64)	0.55		104 (9.5%)	42 (16.8%)	1.87 (1.23 – 2.83)	0.003
Severe Weight Loss	20 (1.5%)		10 (1.1%)	10 (2.2%)	1.80 (0.69 – 4.68)	0.23		11 (1.0%)	9 (3.6%)	3.67 (1.42 – 9.46)	0.007
Hypertension	45 (3.3%)		28 (3.2%)	17 (3.7%)	1.09 (0.56 – 2.11)	0.80		33 (3.0%)	12 (4.8%)	1.46 (0.71 – 3.01)	0.30
Pain	63 (4.7%)		40 (4.5%)	23 (5.0%)	0.95 (0.55 – 1.66)	0.87		44 (4.0%)	19 (7.6%)	2.18 (1.21 – 3.92)	0.01
Any above	960 (71.4%)		618 (70.0%)	342 (74.0%)	1.23 (0.94 – 1.61)	0.14		756 (69.0%)	204 (81.6%)	2.15 (1.50 – 3.09)	<0.001

Abbreviations: OR = odds ratio; CI = confidence interval;

Note:

OR (95% CI) and p-values are based on logistic model adjusting by following covariates: age (continuous, in model for comorbidity), female, BMI (min-20.9, 21=24.9, 25–29.9, 30–34.9, 35+), primary tumor unresected, performance status (ECOG 0, ECOG 1 and 2), sidedness (left, right and transverse, multiple and missing), prior adjuvant therapy, prior radiotherapy, protocol chemotherapy, treatment arm, *KRAS* status (wild-type, mutation, indeterminant), physical activities (0–2.9, 3–8.9, 9–17.9, 18+), and weight change (Loss ≥5%, change <5%, gain ≥5%).

Toxicities included if (1) grade 2 or above and within FOLFOX for neuropathy, or grade 3 or above for other selected AE; (2) relation = Possible, Probable, Definite; (3) occurrence after registration.

Table 4.

Frequency of moderate-severe toxicities by age within comorbidity strata *

	N(%) Total	N(%) <70, Comorbidity none	N(%) <70, Any comorbidity	N(%) ≥70, Comorbidity none	N(%) ≥70, Any comorbidity	OR, <70, Comorbidity none	OR <70, Any comorbidity	OR ≥70, Comorbidity none	OR ≥70, Any comorbidity	p-inter
N	**1345**	**755**	**340**	**128**	**122**					
Neutropenia	456 (33.9%)	243 (32.2%)	104 (30.6%)	52 (40.6%)	57 (46.7%)	ref	1.00 (0.74 – 1.35)	1.30 (0.86 – 1.95)	1.90 (1.25 – 2.88)	0.22
Diarrhea	161 (12.0%)	69 (9.1%)	44 (12.9%)	20 (15.6%)	28 (23.0%)	ref	1.24 (0.81 – 1.90)	1.87 (1.07 – 3.28)	2.42 (1.44 – 4.07)	0.91
Neuropathy	401 (38.7%)	241 (39.4%)	94 (38.7%)	39 (39.8%)	27 (32.1%)	ref	0.92 (0.67 – 1.26)	1.00 (0.64 – 1.56)	0.76 (0.46 – 1.25)	0.60
Fatigue	146 (10.9%)	74 (9.8%)	30 (8.8%)	14 (10.9%)	28 (23.0%)	ref	0.77 (0.48 – 1.24)	1.15 (0.61 – 2.15)	2.37 (1.40 – 4.02)	0.03
Any	960 (71.4%)	517 (68.5%)	239 (70.3%)	101 (78.9%)	103 (84.4%)	ref	1.10 (0.81 – 1.48)	1.89 (1.18 – 3.03)	2.69 (1.57 – 4.59)	**0.49**

Note:

OR (95% CI) and p-values are based on logistic model adjusting by following covariates: female, BMI (min-20.9, 21=24.9, 25–29.9, 30–34.9, 35+), primary tumor unresected, performance status (ECOG 0, ECOG 1 and 2), sidedness (left, right and transverse, multiple and missing), prior adjuvant therapy, prior radiotherapy, protocol chemotherapy, treatment arm, KRAS status (wild-type, mutation, indeterminant), physical activities (0–2.9, 3–8.9, 9–17.9, 18+), and weight change (Loss ≥5%, change <5%, gain ≥5%).

Symptomatic adverse event is included if (1) grade 2 or above and within FOLFOX for neuropathy, or grade 3 or above for other selected AE; (2) relation = Possible, Probable, Definite; (3) occurrence after registration.

* Modelling only if number of events in any 4 categories are more than 10.