

# Impact of relative dose intensity of FOLFOX adjuvant chemotherapy on risk of death among stage III colon cancer patients

**Meijiao Zhou**

Louisiana State University Health Sciences Center

**Trevor D. Thompson**

Centers for Disease Control and Prevention

**Hui-Yi Lin**

Louisiana State University Health Sciences Center

**Vivien W. Chen**

Louisiana State University Health Sciences Center

**Jordan J. Karlitz**

Southeast Louisiana Veterans Health Care System

**Elizabeth T.H. Fontham**

Louisiana State University Health Sciences Center

**Katherine P. Theall**

Tulane University School of Public Health and Tropical Medicine

**Lu Zhang**

Clemson University

**Lori A. Pollack**

Centers for Disease Control and Prevention

**Xiao-Cheng Wu** (✉ [xwu@lsuhsc.edu](mailto:xwu@lsuhsc.edu))

Louisiana State University Health Sciences Center New Orleans <https://orcid.org/0000-0003-3663-5027>

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## Research article

**Keywords:** Relative dose intensity, FOLFOX, High-risk stage III, Low-risk stage III, Colon cancer

**Posted Date:** January 9th, 2020

**DOI:** <https://doi.org/10.21203/rs.2.20511/v1>

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# Abstract

Background Clinical trials have indicated high-risk (T4 and/or N2) and low-risk (T1-T3 and N1) stage III colon cancer patients might need different doses of FOLFOX to reserve a similar survival probability. Observational studies have investigated the effect of relative dose intensity (RDI) of FOLFOX on cancer survival for patients with stage III colon cancer, but nonetheless, the studies focused on very specific populations, and none performed stratified analysis by risk profiles. This study aims to identify the optimal RDI of FOLFOX administered for high-risk and low-risk stage III colon cancer patients.

Methods Data on 407 eligible patients, diagnosed with stage III colon cancer in 2011 who received FOLFOX, were collected by the eight population-based cancer registries for a CDC National Program of Cancer Registries (NPCR) project focused on Comparative Effectiveness Research. We employed Kaplan-Meier method, cumulative incidence function (CIF), Multivariable Cox model and Fine-Gray competing risks model to explore Optimal Relative Dose Intensity (RDI) defined as the lowest RDI administered without significant differences in either overall or cause-specific death.

Results Among the 168 high-risk patients, the optimal RDI cut-off point was 70% where there was no statistically significant difference in overall mortality (HR=1.87; 95% CI: 0.84-4.19) and cause-specific mortality (HR=1.72; 95% CI: 0.61-4.85) when  $RDI < 70\%$  vs.  $RDI \geq 70\%$ , adjusting for sociodemographic and clinical covariates. When the RDI cut-off was lower than the optimal one ( $<55\%$  vs.  $\geq 55\%$ ,  $<60\%$  vs.  $\geq 60\%$ , or  $<65\%$  vs.  $\geq 65\%$ ), the overall and cause-specific mortalities were significantly statistically different between the two groups of each comparison. Among the 239 low-risk patients, none of the evaluated cut-offs were associated with statistically significant differences in overall and cause-specific mortalities between comparison groups. The lowest RDI we assessed was 45%, HR=0.79; 95% CI: 0.23-2.67 for the overall mortality and HR=0.49; 95% CI: 0.05-4.84 for the cause-specific mortality, when  $RDI < 45\%$  vs.  $RDI \geq 45\%$ .

Conclusions To best utilize health care resources while maintaining efficacy, RDI can be maintained at a minimum of 70% in high-risk stage III colon cancer patients. For low-risk patients, we found that RDI as low as 45% did not impact risk of death.

## Background

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer, and the second leading cause of cancer death for males and females combined in the United States (US).<sup>1</sup> For patients with stage III colon cancer, the National Comprehensive Cancer Network (NCCN) has recommended 6 months of adjuvant chemotherapy with fluoropyrimidines and oxaliplatin after primary surgical treatment.<sup>2</sup> FOLFOX (Oxaliplatin, fluorouracil aka 5-FU, and leucovorin) is one of the standard adjuvant therapies commonly administered.<sup>2-4</sup>

Despite the efficacy of FOLFOX, this regimen usually results in significant toxicities, such as 5-FU-induced small bowel toxicity<sup>5,6</sup> and oxaliplatin-induced sensory peripheral neuropathy (SPN),<sup>7,8</sup> which is cumulative dose-dependent. Six randomized phase III clinical trials have been conducted in 12 countries to evaluate the non-inferiority of adjuvant therapy with either FOLFOX or CAPOX (capecitabine and oxaliplatin) administered for 3 months, as compared with 6 months.<sup>9</sup> The meta-analysis of these six trials showed that for stage III colon cancer patients, 3-month FOLFOX therapy resulted in a lower disease-free survival rate, particularly for the high-risk subgroup (patients with T4, N2, or both) (definitions of T and N are in Supplemental Material 1), whereas among patients with low-risk cancers (T1, T2, or T3 and N1), the non-inferiority with the 3-month chemotherapy use was not proven.<sup>9</sup>

In addition to clinical trials, previous observational studies have also found that patients who failed to complete the standard cycles of 5-FU chemotherapy had worse colon cancer-specific survival,<sup>10,11</sup> or overall survival<sup>10</sup>. Due to data limitations, these studies didn't consider dose intensity or cumulative dose. Dose intensity is defined as the amount of drug delivered per unit time per square meter of body surface area, and relative dose intensity (RDI) is the ratio of delivered dose intensity to the standard dose intensity.<sup>12,13</sup> Aspinall et al. investigated the effect of RDI of multiple chemotherapy regimens (FOLFOX included) on survival among US veterans, and found that stage III colon cancer patients who received greater than 70% of standard dose intensity adjuvant chemotherapy had higher 5-year overall survival.<sup>14</sup> A study based on data from Korea found that for patients with stage II/III CRC receiving adjuvant chemotherapy of FOLFOX,<sup>15</sup> more than 60% of the standard dose of oxaliplatin was necessary to achieve similar 5-year disease-free survival or overall survival to those of the standard dose group. However, both of studies used data from healthcare facilities with limited generalizability, and neither of these studies considered the effect of RDI by the tumor risk, as defined in clinical trial studies.

Hence, we used data collected by population-based cancer registries covering all patients in selected U.S states to identify the optimal RDI of FOLFOX for high-risk and low-risk stage III colon cancer, respectively, regarding the effect of FOLFOX RDI on overall and cause-specific mortality in these two patient populations.

## Methods

### Data Source and Study Population

Data were obtained state central cancer registries participating in the Enhancing Cancer Registry Data for Comparative Effectiveness Research (CER) Project, a special project funded by the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries (NPCR). Details of the CER study have been described elsewhere.<sup>16</sup> Of specific interest and valuable information collected by the CER project were detailed information on the first course of chemotherapy, including: names of chemotherapy agents, numbers of planned and received cycles, cumulative planned and received doses, units planned

and received, starting and ending dates of chemotherapy, and whether chemotherapy was completed as planned.<sup>16</sup>

Men and women diagnosed with colon cancer (the International Classification of Diseases for Oncology 3rd edition codes of C18.0, C18.2-C18.9) in 2011 at American Joint Committee on Cancer (AJCC) 7th edition<sup>17</sup> stage III who received colon resection and chemotherapy of FOLFOX4 or FOLFOX6 were eligible for this study. To maintain the sample size, we included all colon cancer cases whether that was the first and only cancer present or the patient had multiple cancers. Out of the 10 states participating in the NPCR CER study, only eight states (i.e. Alaska, Colorado, Florida, Idaho, Louisiana, North Carolina, New Hampshire, and Rhode Island) were included based on having complete chemotherapy data. Additional exclusion criteria included: cases with histology codes of 9050–9055, 9140, or 9590–9992 which were hematopoietic and lymphoid colon cancers, died within 30 days of colon resection, received neoadjuvant chemotherapy; and had missing data on vital status or date of last contact. Among 509 cases, 102 of them had an unknown value in RDI due to missing data on the related variables of received cycles (n = 20), received doses (n = 76), chemotherapy starting date (n = 2), chemotherapy ending date (n = 25), height (n = 22) and weight (n = 23), which results in 407 cases for final analyses.

## Outcomes

Two outcomes were defined in this study: all-cause and cause-specific mortality. State cancer registries linked their data with state death certificate data files and National Death Index (NDI) database to obtain data on vital status and causes of death. Not all state cancer registries do NDI linkages every year. Death data obtained for Alaska and Florida were up to December 2014; North Carolina was up to June 2013. However, the remaining 5 states obtained death information up to November 2016 from the NDI. We used the Surveillance, Epidemiology, and End Results Program (SEER) cause-specific death classification to define the death due to colon cancer, which took into account causes of death in conjunction with tumor sequence, the primary site of the cancer diagnosis, and comorbidities (e.g., AIDS or site-related diseases).<sup>18</sup> For patients with colon cancer as the second or later primary cancer, we defined the colon cancer death as the death that was attributed to the particular cancer of C18.0, C18.2-C18.9.

The survival time was measured in months from colon cancer diagnosis to the date of death or last follow-up if a participant was still alive. The observations were censored if patients were alive during the time of clinical follow up.

## Exposure

Chemotherapy dose intensity was defined as the amount of drug administered per unit time (week or day) per square meter of body surface area (BSA).<sup>12,13,19</sup> Chemotherapy RDI was the ratio of delivered dose intensity (DDI) to the standard dose intensity (SDI)<sup>2</sup>. The details of RDI calculation are described in Supplemental Material 2.

Based on clinical trials showing that a high dosage of chemotherapy was needed for high-risk stage III colon cancer patients,<sup>9</sup> we defined the low and high RDI groups by using the cut-off points of 55%, 60%, 65%, 70%, 75%, and 80% for high-risk patients. For low-risk patients, we used the cut-off points of 45%, 50%, 55%, 60%, 65%, and 70%. For each cut-off point, patients receiving RDI greater than or equal to the predefined cut-off point were compared with patients receiving RDI lower than the predefined cut-off point, on their overall and cause-specific mortality. The optimal RDI was defined as the lowest RDI administered without significant increase in either overall mortality or cause-specific mortality.

## Covariates

Covariates included age at colon cancer diagnosis (< 50, 50–59, 60–69, and ≥ 70 years), race/ethnicity (Non-Hispanic white, Non-Hispanic black, Hispanics and others),<sup>20</sup> health insurance (private insurance including Medicare with private supplement, Medicare/other public, Medicaid, and not insured), census-tract residence (100% urban, 100% rural, and urban/rural mixed), census-tract population below the federal poverty level (< 20% and ≥ 20%), census-tract adults with less than high school education (< 25% and ≥ 25%).<sup>21,22</sup> census-tract population percentage of married (≤ 50% and > 50%),<sup>23</sup> tumor size (≤ 4 cm and > 4 cm),<sup>24,25</sup> lymph nodes retrieved (< 12 and ≥ 12),<sup>26</sup> tumor grade (well/moderately differentiated, and poor/undifferentiated), Charlson comorbidity index (0, ≥ 1),<sup>27</sup> anatomic subsites (proximal, distal, and others),<sup>28</sup> colon cancer classification (only with colon cancer, multiple cancers with colon as the first primary cancer, multiple cancers with colon as the non-first cancer), and number of positive lymph nodes (continuous variable).

## Statistical analysis

Socio-demographic and clinical characteristics of the patients were summarized using descriptive statistics.

The overall survival probability was estimated using the Kaplan-Meier method. The differences of all-cause mortality between various levels of chemotherapy RDI groups were compared using the log rank test. The competing risk approach was applied to analyze RDI level impact on cause-specific mortality. The probabilities of cause-specific mortalities were estimated using the cumulative incidence function (CIF), which were compared among the various RDI groups using the Gray's test.<sup>29</sup> Cox proportional hazards model and the competing risks model developed by Fine and Gray were applied to estimate the hazard ratio for overall mortality and cause-specific mortality, respectively.

In sensitivity analyses, we restricted our sample to patients with colon cancer as the only or the first primary tumor, to exclude the effects of previously diagnosed cancers on survival or on chemotherapy use.

All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). A P-value < 0.05 was considered statistically significant.

## Results

### Patient characteristics

There were 168 patients with high risk (T4 and/or N2) and 239 with low risk (T1-3/N1) stage III colon cancer included in this study (Table 1). In the high-risk group, patients aged 60 years or older accounted for more than half of the cases. Most patients were male, two-thirds were non-Hispanic Whites, and over a half were privately insured (56%). Sixty percent of patients resided in urban areas, 71% lived in low poverty areas, 78% were in high education areas, 51% were in high married census tracts, and more than 70% were from the states of Florida, Louisiana and North Carolina. More than half of patients had tumor size greater than 4 cm (57%). Most patients had 12 or greater lymph nodes examined (92%), well or moderately differentiated tumors (65%), no comorbid conditions (67%), cancer located in proximal colon (62%), and colon cancer as the only cancer (82%). The mean number of positive lymph nodes was 6. About 80% of the patients were alive at the end of follow up, with the mean follow up time of 35 months. Among deceased patients with a known cause of death, 16% died from non-colon cancer causes.

Table 1

Demographic and clinical characteristics of patients with stage III colon cancer by different risk groups

Characteristics	High risk (T4 and/or N2)	Low risk (T1-3/N1)
	N (%)	N (%)
All	168	239
Age at diagnosis		
< 50	31 (18.5)	48 (20.1)
50–59	37 (22.0)	60 (25.1)
60–69	56 (33.3)	75 (31.4)
≥ 70	44 (26.2)	56 (23.4)
Sex		
Male	92 (54.8)	126 (52.7)
Female	76 (45.2)	113 (47.3)
Race/Ethnicity		
Non-Hispanic white	113 (67.3)	161 (67.4)
Non-Hispanic black	31 (18.5)	44 (18.4)
Hispanics	21 (12.5)	29 (12.1)
Other	3 (1.8)	5 (2.1)
Insurance coverage		
Private	94 (56.0)	130 (54.4)
Medicare/ Other public	48 (28.6)	71 (29.7)
Medicaid	15 (8.9)	21 (8.8)
Not insured	9 (5.4)	16 (6.7)
Unknown	2 (1.2)	1 (0.4)
Census tract residence		
100% Urban	101 (60.1)	126 (52.7)
100% Rural	10 (6.0)	16 (6.7)
Mixed	55 (32.7)	95 (39.8)

Characteristics	High risk (T4 and/or N2)	Low risk (T1-3/N1)
	N (%)	N (%)
Unknown	2 (1.2)	2 (0.8)
Census tract poverty		
< 20%	120 (71.4)	184 (77.0)
≥ 20%	45 (26.8)	53 (22.2)
Unknown	3 (1.8)	2 (0.8)
Census tract education		
< 25% (high)	131 (78.0)	186 (77.8)
≥ 25% (low)	35 (20.8)	51 (21.3)
Unknown	2 (1.2)	2 (0.8)
Census tract marital status		
≤ 50% married	81 (48.2)	104 (43.5)
> 50% married	85 (50.6)	133 (55.7)
Unknown	2 (1.2)	2 (0.8)
State of residence		
AK	2 (1.2)	1 (0.4)
CO	21 (12.5)	42 (17.6)
FL	48 (28.6)	54 (22.6)
ID	7 (4.2)	15 (6.3)
LA	45 (26.8)	64 (26.8)
NC	38 (22.6)	58 (24.3)
NH	6 (3.6)	4 (1.7)
RI	1 (0.6)	1 (0.4)
Tumor size (cm)		
≤ 4	69 (41.1)	130 (54.4)
> 4	96 (57.1)	97 (40.6)
Unknown	3 (1.8)	12 (5.0)

Characteristics	High risk (T4 and/or N2)	Low risk (T1-3/N1)
	N (%)	N (%)
Lymph nodes examined		
< 12	13 (7.7)	34 (14.2)
≥ 12	155 (92.3)	205 (85.8)
Tumor grade		
Well/moderately differentiated	109 (64.9)	194 (81.2)
Poor/Undifferentiated	58 (34.5)	39 (16.3)
Unknown	1 (0.6)	6 (2.5)
Charlson Comorbidity Index		
0	113 (67.3)	176 (73.6)
≥ 1	55 (32.7)	63 (26.4)
Anatomic subsite		
Proximal colon (C18.0, C18.2-C18.5)	104 (61.9)	141 (59.0)
Distal colon (C18.6-C18.7)	63 (37.5)	92 (38.5)
Other (C18.8-C18.9)	1 (0.6)	6 (2.5)
Colon cancer classification		
Only with colon cancer	138 (82.1)	197 (82.4)
Multiple cancers, first primary colon	12 (7.1)	16 (6.7)
Multiple cancers, non-first colon	18 (10.7)	26 (10.9)
Number of positive lymph nodes	6.4 ± 4.5	2.0 ± 1.7
Vital status		
Alive	135 (80.4)	210 (87.9)
from colon cancer	21 (12.5)	15 (6.3)
Death from other causes	4 (2.4)	8 (3.3)
Death reasons unknown	8 (4.8)	6 (2.5)
Follow up time among alive patients (mean ± standard deviation)	34.6 ± 21.9	35.0 ± 22.8

The low-risk stage III colon cancer cases had similar distributions of sociodemographic characteristics as those high-risk stage III colon cancer. However, their clinical characteristics were less advanced and aggressive compared to high-risk stage III colon cancer cases; the majority of low-risk patients had tumor size less than or equal to 4 cm (54%), a higher percentage of well or moderately differentiated tumor grade (81%), no comorbid conditions (74%), slightly lower percentage of 12 or greater lymph nodes examined (86%) and cancer located in proximal colon (59%). The mean number of positive lymph nodes was 2. There were 88% of the patients alive at the end of follow up, with the mean follow up time of 35 months. Among deceased patients with a known cause of death, 35% died from competing risks.

Regression analysis for all-cause and cause-specific mortality in high-risk stage III colon cancer patients

Kaplan-Meier crude survival curves and cumulative incidence function (CIF) plots showed that among the high-risk stage III colon cancer cases, those receiving lower RDI had statistically significantly (borderline significant in CIF plots for cutoff point of 65%) lower overall survival probability and a higher risk of colon-cancer death than those receiving higher RDI, when the cut off points were 55%, 60%, 65% (Fig. 1. and Fig. 2). The survival probability and risk of death were not statistically significantly different for other RDI comparisons: RDI < 70% vs. RDI  $\geq$  70%, RDI < 75% vs. RDI  $\geq$  75%, and RDI < 80% vs. RDI  $\geq$  80%. The univariable analysis showed consistent results with hazard ratios (Supplemental Material 3).

In multivariable analysis, age, sex, race/ethnicity, insurance coverage (private insurance vs. non-private insurance), number of positive lymph nodes, tumor grade, Charlson comorbidity index, anatomic subsite and colon cancer classification (colon as the only cancer vs. multiple primary cancers), were included as confounders or significant factors for cancer survival (Table 2). Compared to the higher RDI groups, the lower RDI groups had a higher risk of overall mortality: RDI < 65% vs. RDI  $\geq$  65% (HR = 2.72 (1.22, 6.04); HR = 2.87 (1.30, 6.36) for RDI < 60% vs. RDI  $\geq$  60%; and HR = 3.90 (1.68, 9.08) for RDI < 55% vs. RDI  $\geq$  55%). A similar trend was found in cause-specific mortality. In the sensitivity analysis which included cases with colon cancer as the only or the first primary tumor, results followed a similar pattern (data not shown). The survival probability and risk of death showed no statistically significant difference for RDI comparisons: RDI < 70% vs. RDI  $\geq$  70%, RDI < 75% vs. RDI  $\geq$  75%, and RDI < 80% vs. RDI  $\geq$  80%.

Table 2

Impact of RDI Levels of FOLFOX Chemotherapy on All-cause Mortality and Cause-Specific Mortality in High-Risk Stage III Colon Cancer— Multivariable Analysis

RDI	All-cause mortality (N = 161)			Cause-specific mortality (N = 153)		
	Low RDI% (RDI < selected cutoffs)	Adjusted HR* (95% CI)	P	Adjusted HR* (95% CI)	P	
RDI < 55% vs. RDI ≥ 55%	20.5	3.90 (1.68, 9.08)	0.002	3.89 (1.44, 10.47)	0.007	
RDI < 60% vs. RDI ≥ 60%	26.7	2.87 (1.30, 6.36)	0.009	2.83 (1.13, 7.06)	0.03	
RDI < 65% vs. RDI ≥ 65%	31.1	2.72 (1.22, 6.04)	0.01	2.61 (1.06, 6.45)	0.04	
RDI < 70% vs. RDI ≥ 70%	39.8	1.87 (0.84, 4.19)	0.13	1.72 (0.61, 4.85)	0.3	
RDI < 75% vs. RDI ≥ 75%	47.8	1.99 (0.91, 4.34)	0.08	1.90 (0.73, 4.92)	0.19	
RDI < 80% vs. RDI ≥ 80%	59.6	1.52 (0.63, 3.63)	0.35	1.47 (0.49, 4.36)	0.49	
*Models adjusted for age, sex, race/ethnicity, insurance coverage, number of positive lymph nodes, tumor grade, Charlson comorbidity index, anatomic subsite and colon cancer classification (colon as the only cancer vs. multiple primary cancers).						

To avoid loss from risk of death, this study showed a minimum RDI of 70% may be administered.

Regression analysis for all-cause and cause-specific mortality in low-risk stage III colon cancer patients

Kaplan-Meier crude survival curves and cumulative incidence function plots were not significantly different at any of the RDI cut-off points from 45–70% (Figs. 3 and 4). The univariable analysis showed consistent results with hazard ratios (Supplemental Material 4).

In multivariable analysis, we adjusted for age, sex, race, insurance coverage (private insurance vs. non-private insurance), number of positive lymph nodes, tumor grade, Charlson comorbidity index, anatomic subsite, and colon cancer classification (colon as the only cancer vs. multiple primary cancers), which were confounders or significant factors for cancer survival (Table 3). Similar to results in Figs. 3 and 4, no cut-off points were found for significant hazard ratios in either all-cause or cause-specific mortality. Because of the small sample size, we did not explore the mortality influence of RDI < 40%. Results were similar in the sensitivity analysis which included cases with colon cancer as the only or the first primary tumor (data not shown).

Table 3

Impact of RDI Levels of FOLFOX Chemotherapy on All-cause Mortality and Cause-Specific Mortality in Low-Risk Stage III Colon Cancer— Multivariable Analysis

RDI	All-cause mortality (N = 225)			Cause-specific mortality (N = 220)	
	Low RDI% (RDI < selected cutoffs)	Adjusted HR* (95% CI)	P	Adjusted HR* (95% CI)	P
RDI < 45% vs. RDI ≥ 45%	16.0	0.79 (0.23, 2.67)	0.71	0.49 (0.05, 4.84)	0.54
RDI < 50% vs. RDI ≥ 50%	19.6	1.37 (0.53, 3.54)	0.52	0.81 (0.18, 3.66)	0.79
RDI < 55% vs. RDI ≥ 55%	21.8	1.34 (0.52, 3.47)	0.54	0.80 (0.18, 3.61)	0.78
RDI < 60% vs. RDI ≥ 60%	26.7	1.21 (0.47, 3.08)	0.7	0.49 (0.11, 2.11)	0.34
RDI < 65% vs. RDI ≥ 65%	31.1	1.16 (0.46, 2.90)	0.76	0.93 (0.26, 3.37)	0.91
RDI < 70% vs. RDI ≥ 70%	40.0	0.99 (0.42, 2.34)	0.98	1.07 (0.34, 3.38)	0.91
*Models adjusted for age, sex, race/ethnicity, insurance coverage, number of positive lymph nodes, tumor grade, Charlson comorbidity index, anatomic subsite and colon cancer classification (colon as the only cancer vs. multiple primary cancers).					

## Discussion

To our knowledge, this is the first population-based study to examine the association of FOLFOX RDI with the risk of overall and cause-specific deaths in two subgroups of patients diagnosed with stage III colon cancer. We found that in high-risk (T4 and/or N2) stage III colon cancer patients, lower RDI was related to higher risk of all-cause or cause-specific mortality when the cutoff points were 55%, 60%, or 65%. The risk of deaths was not statistically significantly different for the RDI comparisons of RDI < 70% vs. RDI ≥ 70%, RDI < 75% vs. RDI ≥ 75%, and RDI < 80% vs. RDI ≥ 80%. Therefore, to preserve the survival benefits, the lowest RDI from this study is 70%. For low-risk (T1-T3 and N1) stage III colon cancer, we did not find a significant difference in overall and cause-specific mortalities at any predefined RDI cutoff points from 45–70%, suggesting that 45% of standard FOLFOX administration did not harm to patients' survival for low-risk stage III colon cancer patients.

Our findings from population-based cancer registry data confirmed that higher chemotherapy RDI was needed in high-risk stage III colon cancers, compared with low-risk cancers, and are consistent with the conclusions from six randomized, phase 3 clinical trials conducted by the International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration, which found that a higher dosage of FOLFOX particularly benefited high-risk stage III colon cancers. These clinical trials evaluated whether 3 months of FOLFOX or CAPOX (capecitabine and oxaliplatin) is non-inferior to 6 months of therapy in the rate of disease-free survival at 3 years.<sup>4,9,30,31</sup> Results from a pooled analysis of six trials showed that in stage III colon cancer patients treated with FOLFOX, 6-month therapy had a higher rate of disease-free survival than 3-month therapy, particularly in the high-risk group.<sup>9</sup> Data from the IDEA France suggested that for FOLFOX6 regimen, patients with high-risk stage III colon cancer need 6-month chemotherapy for a maximal relapse risk reduction, for low-risk cancer patients, the absolute difference in the 3-year disease free survival rate between 6 and 3 months of chemotherapy was clinically less relevant (2%).<sup>31</sup> Older clinical trials have also shown that the efficacy of oxaliplatin is more significant in stage III N2 tumors, compared to stage III N1 tumors<sup>32,33</sup> (10-year overall survival advantage of 12.9% ( $p = 0.013$ ) in those with N2 tumors, and 6% ( $p = 0.248$ ) in those with N1 tumors, when adding oxaliplatin to fluorouracil plus leucovorin<sup>33</sup>). André et al. suggested defining a low-risk subset of patients with stage III colon cancer to spare the toxicity of oxaliplatin.<sup>33</sup>

Oxaliplatin can induce sensory peripheral neuropathy (SPN), which can be long-lasting or even permanent.<sup>7,8,34</sup> Reduced chemotherapy RDI to a minimal effective dose may spare neurotoxicity and maintain quality of life in cancer survivors. Our results found that the optimal cut-off point of RDI was 70% in the high-risk stage III colon cancer patients, and RDI of 45% has no significant adverse influence on risk of death for low-risk stage III colon cancer. A few other observational studies have investigated the effect of RDI on colon cancer survival. Aspinall et al. found that patients from Veterans medical centers with stage III colon cancer who received > 70% RDI adjuvant chemotherapy had improved 5-year overall survival, compared to the ones receiving RDI ≤ 70%; and the survival benefits were only seen in the first year after the completion of chemotherapy.<sup>14</sup> However, unlike the chemotherapy regime in our study, the

regimens in their study included 5-FU/LV (30.8%), FOLFOX (34.3%), oxaliplatin plus capecitabine (5.4%), capecitabine monotherapy (12.5%), and mixed/others chemo (16.9%). Given that the toxicity of oxaliplatin is more severe than 5-FU, the optimal RDI of FOLFOX may be lower than 70% in combined high-risk and low-risk stage III colon cancer as the defined population in Aspinall's study.<sup>14</sup> Another study performed in Korea University Anam Hospital, with patients receiving FOLFOX as the only chemotherapy regimen, suggested that more than 60% of the standard dose of oxaliplatin was necessary to achieve similar 5-year disease free survival or overall survival to those of the standard dose group, for patients with stage II/III CRC patients.<sup>15</sup> Both of the studies from Veterans medical centers and Korea University Anam Hospital had restricted population, and they didn't take into consideration risk features in stage III colon cancers. Those are some reasons that may contribute to the discrepancies about optimal RDI cut off points.

There are several strengths in this study. The study cohort is from the CER study, which includes ten population-based cancer registries covering about 27% of the United States population.<sup>16</sup> Our analytical data from eight of the ten cancer registries with complete chemotherapy data represents patients from different geographic regions and reflects clinical practice in the community. The collection of detailed chemotherapy data, including chemotherapy regimens, dosage and duration by NPCR cancer registries met CDC's objective to support CER, such as this RDI study. While the reported survival outcomes in the paper are short-term, this cohort of CER colon patients will continue to be followed by the registries and be able to present long-term survival and recurrence in the future.

Although our study was comprehensive in its evaluation of acceptable RDI to maintain efficacy in a relatively homogenous population, there are potential limitations. First, there was limited sample size restricted determination of the exact optimal RDI cut off points for low-risk stage III colon cancer. Second, there were substantial differences in the survival time or follow up time for different states, which resulted in a low percentage of events in the survival analysis and short-term survival outcome. Third, the data may underestimate the comorbid conditions, since patients with unknown comorbidity were categorized as no comorbidity according to the Facility Oncology Registry Data Standard (FORDS) coding manual.<sup>20,35</sup> In addition, information about comorbidity severity was not available. Furthermore, our study had incomplete data on microsatellite instability (MSI) status, which may affect the adjuvant therapy benefits in stage II or III colon cancer patients.<sup>36</sup>

## Conclusion

In conclusion, among patients with stage III colon cancer who were receiving adjuvant therapy of FOLFOX, the acceptable relative dose intensity (RDI) was 70% for high-risk stage III colon cancer, and RDI of 45% has no influence on risk of death for low-risk group. These results can be considered with the findings from clinical trials performed by the International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration. Our findings add new evidence on the quality of cancer therapy, including how to

administer FOLFOX to reduce side-effects and the use of health care resources if efficacy were maintained.

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## List Of Abbreviations

5-FU – Fluorouracil; AJCC - American Joint Committee on Cancer; BSA - Body Surface Area

CAPOX - Capecitabine and Oxaliplatin; CDC - Centers for Disease Control and Prevention

CER - Enhancing Cancer Registry Data for Comparative Effectiveness Research

CI - Confidence Interval; CIF - Cumulative Incidence Function; CRC - Colorectal Cancer

DDI - Delivered Dose Intensity; DI - Dose Intensity

FOLFOX - Oxaliplatin, 5-FU, and Leucovorin

FORDS - Facility Oncology Registry Data Standard; HR - Hazard Ratio

IDEA - International Duration Evaluation of Adjuvant Therapy; MSI - Microsatellite Instability

NCCN - National Comprehensive Cancer Network

NPCR - National Program of Cancer Registries; RDI - Relative Dose Intensity

SDI - Standard Dose Intensity; SEER - Surveillance, Epidemiology, and End Results Program

SPN - Sensory Peripheral Neuropathy; US - United States

## Declarations

## **Ethics approval and consent to participate**

This study used the de-identified data collected by eight population-based cancer registries for a CDC-funded project. The Institutional Review Board (IRB) of the Louisiana State University Health Sciences Center-New Orleans approved the use of the data for this study.

## **Availability of data and materials**

The analytic dataset available from the corresponding author on reasonable request.

## **Competing interest**

The authors declare that they have no competing interests.

## **Funding**

This work was supported in part under CDC Cooperative Agreements of the National Program of Cancer Registries: #U58/DP000792 in conjunction with the participating states and a CDC Comparative Effectiveness Research contract to ICF: #200-2008-27957.

## **Authors' Contributions**

This study was part of MZ's PhD's dissertation, and HL, VWC, JJK, ETHF, KPT, and XW were committee members. MZ devised the study, performed the data analysis, and prepared the first draft of the manuscript. TDT acquired data and assisted in data analysis. HL provided guidance in the analysis plan. VWC was involved in study concept and design. JJK, ETHF, and KPT provided constructive suggestions about the study. LZ aided in interpreting the results and providing consultation for relative dose intensity calculation. LAP acquired data. XW contributed to the design and implementation of the study and oversaw the whole study. TDT, HL, VWC, JJK, ETHF, KPT, LAP, LZ, and XW made critical revisions of the manuscript. All authors have reviewed and approved the final manuscript.

## **Acknowledgments**

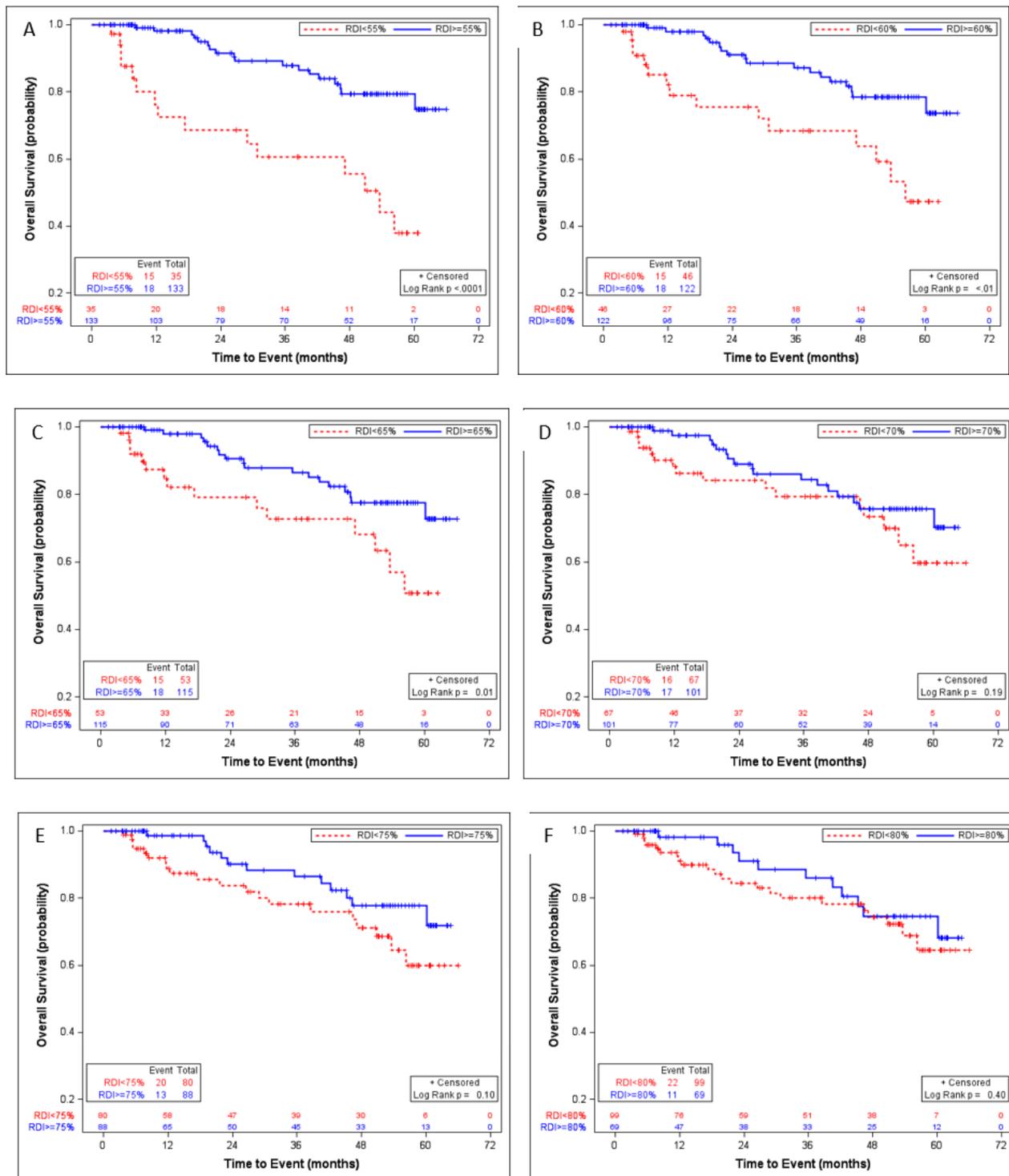
We would like to acknowledge the project investigators at the participating central cancer registries, as well as other organizations, and individuals, including the registrars, that supported the collection of the

data to enhance NPCR for Comparative Effectiveness Research: Alaska Cancer Registry (Judy Brockhouse); Cancer Registry of Greater California (Dee W. West); Colorado Central Cancer Registry (Randi K. Rycroft); Cancer Data Registry of Idaho (Christopher J. Johnson); Florida Cancer Data System (Monique N. Hernandez); Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (Christie R. Eheman, David Butterworth); ICF International (Kevin B. Zhang); Louisiana Tumor Registry and Epidemiology Program (Xiao-Cheng Wu); Rhode Island Cancer Registry (David Rousseau); New Hampshire State Cancer Registry (Maria O. Celaya); CDC-NPCR Contractor, DB Consulting (Jennifer M. Wike); North Carolina Cancer Registry (Melissa Pearson); and Texas Cancer Registry (Anne M. Hakenewerth).

## **Disclaimer**

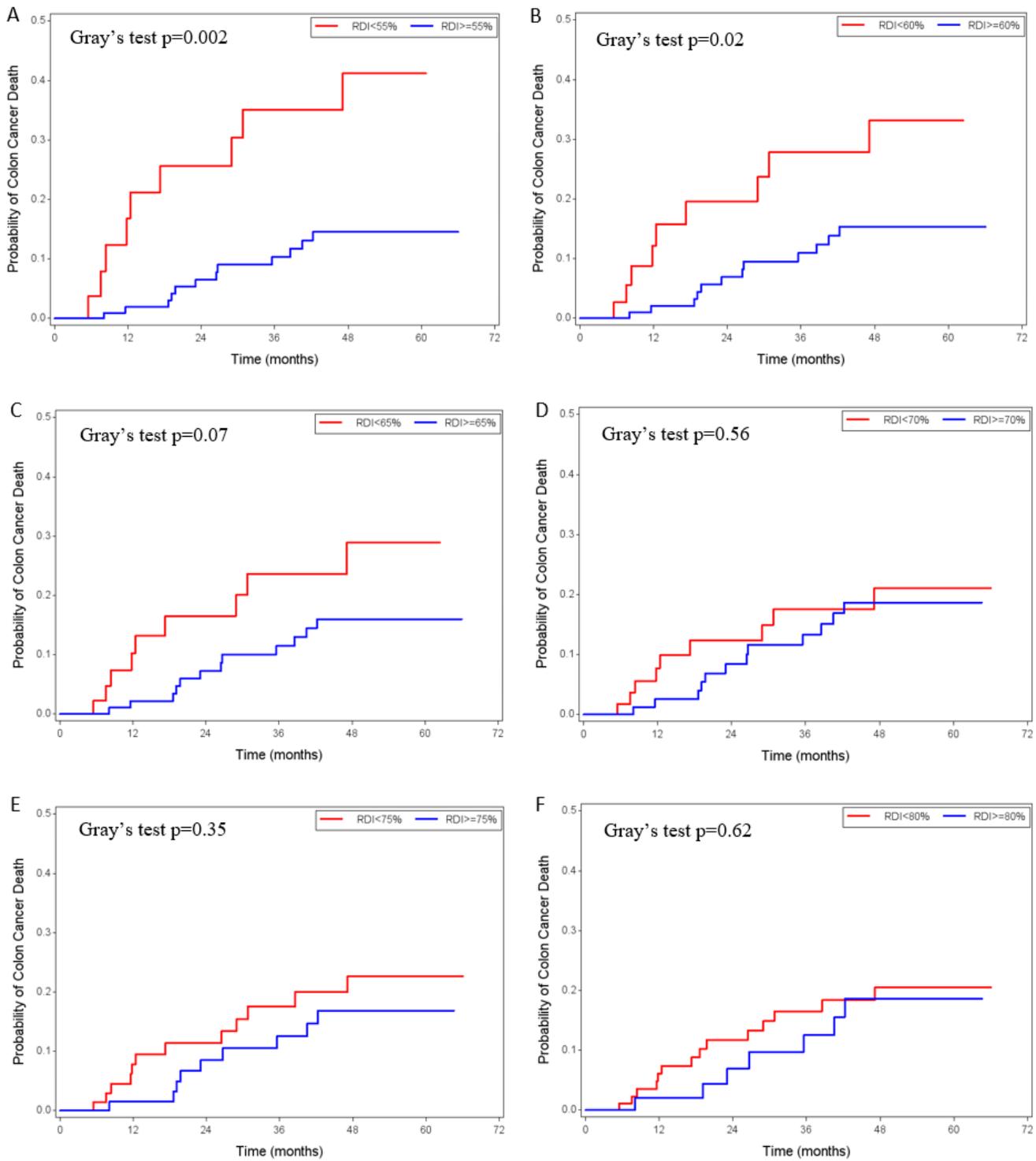
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

## **Figures**



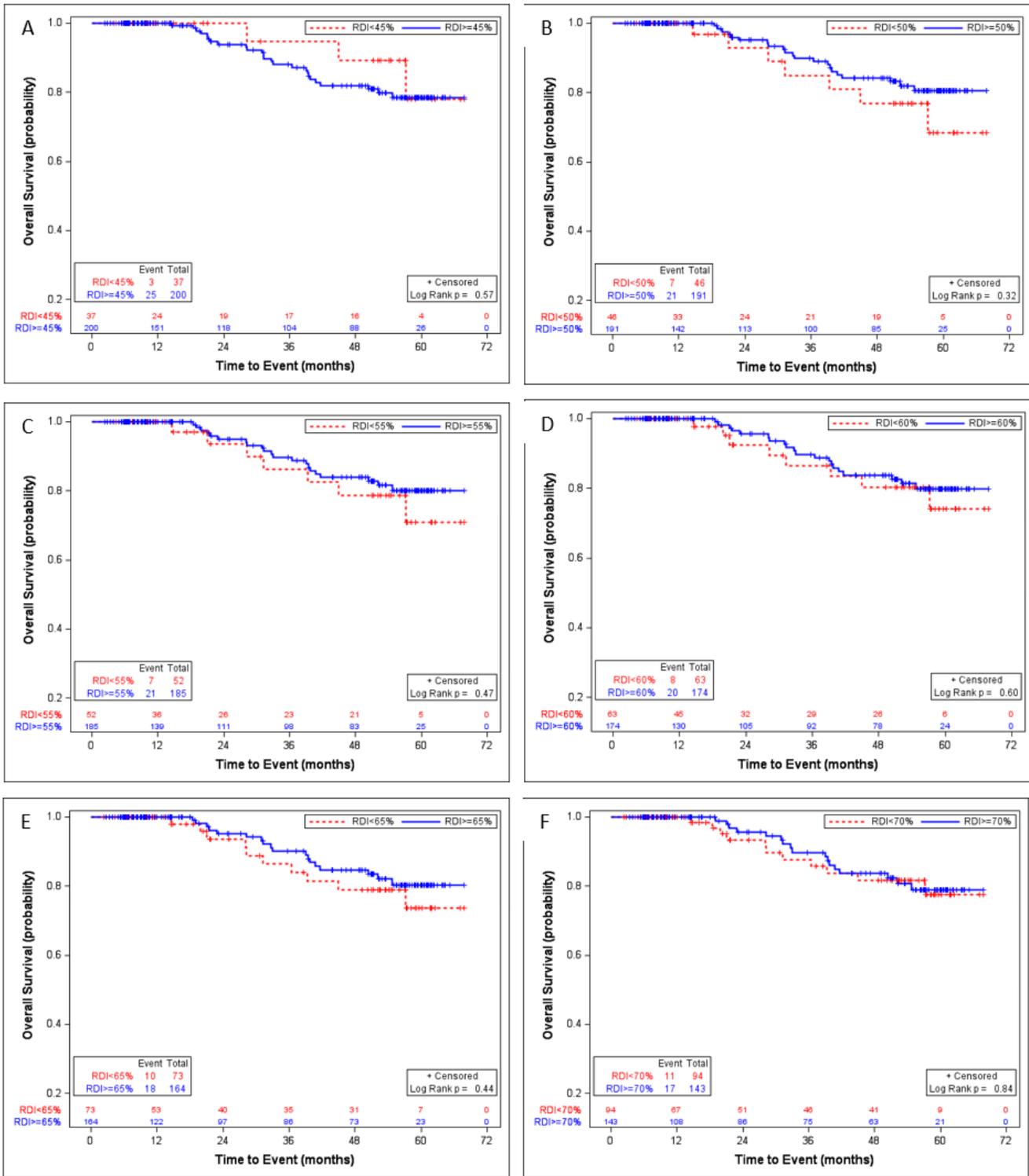
**Figure 1**

Overall survival in the high-risk stage III colon cancer patients with different relative dose intensity cut-off points of 55% (A), 60% (B), 65% (C), 70% (D), 75% (E), and 80% (F), using Kaplan-Meier method



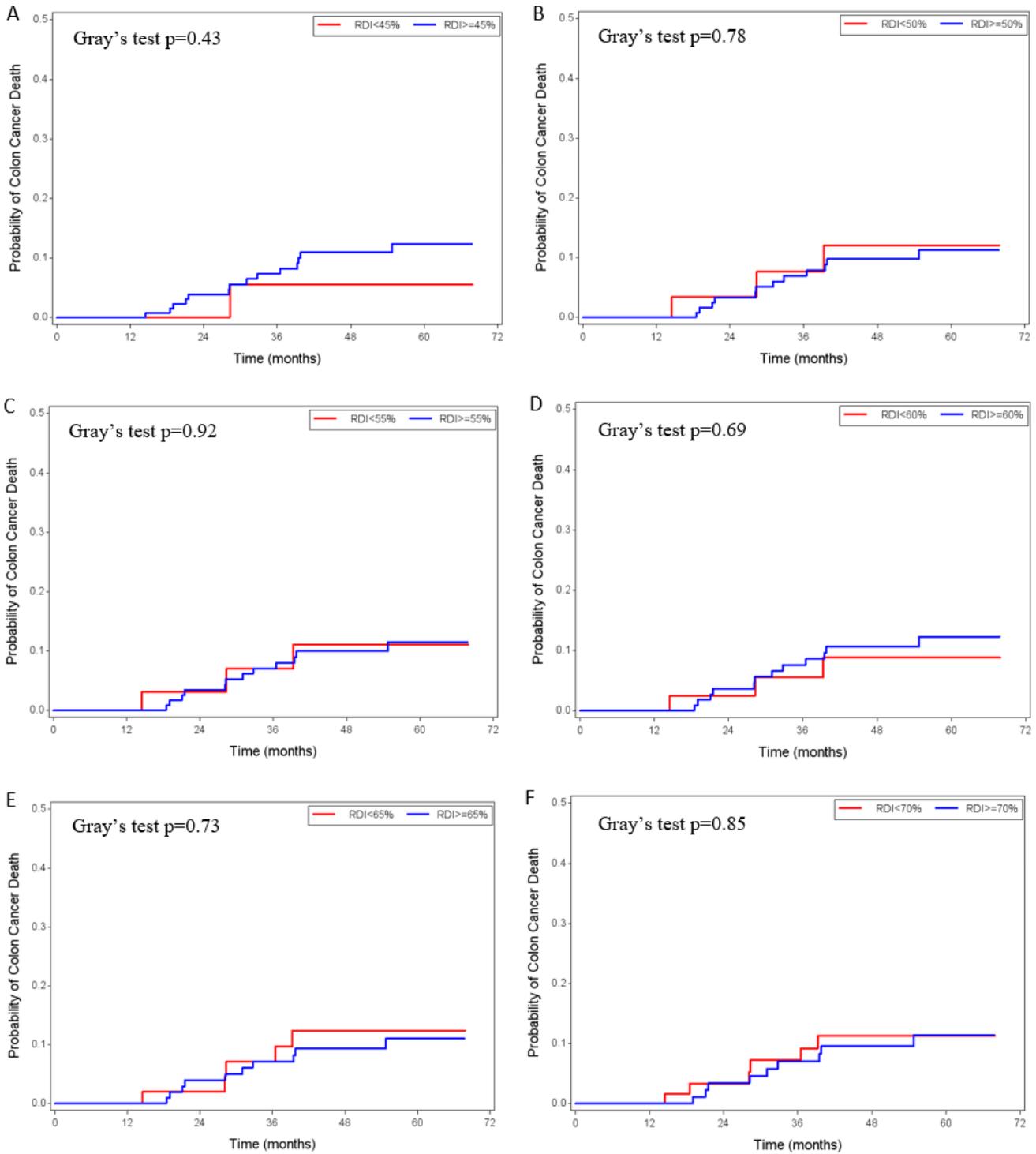
**Figure 2**

Cumulative Incidence Function plots in the high-risk stage III colon cancer patients with relative dose intensity cut-off points of 55% (A), 60% (B), 65% (C), 70% (D), 75% (E), and 80% (F).



**Figure 3**

Overall survival in the low-risk stage III colon cancer patients with relative dose intensity cut-off points of 45% (A), 50% (B), 55% (C), 60% (D), 65% (E), and 70% (F), using Kaplan-Meier method



**Figure 4**

Cumulative Incidence Function plots in the low-risk stage III colon cancer patients with relative dose intensity cut-off points of 45% (A), 50% (B), 55% (C), 60% (D), 65% (E), and 70% (F).

## Supplementary Files

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