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Early-Onset Colorectal Adenocarcinoma in the IDEA Database: Treatment Adherence, Toxicities, and Outcomes With 3 and 6 Months of Adjuvant Fluoropyrimidine and Oxaliplatin

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abstract

PURPOSE Early-onset (EO) colorectal cancer (CRC, age < 50 years) incidence is increasing. Decisions on optimal adjuvant therapy should consider treatment adherence, adverse events, and expected outcomes in a population with life expectancy longer than later-onset (LO) CRC (age ≥ 50 years).

MATERIALS AND METHODS Individual patient data from six trials in the International Duration Evaluation of Adjuvant Chemotherapy database were analyzed. Characteristics, treatment adherence, and adverse events in stage II or III EO-CRC and LO-CRC were compared. To reduce confounders of non–cancer-related deaths because of age or comorbidities, time to recurrence (3-year relapse-free rate) and cancer-specific survival (5-year cancer-specific mortality rate) were considered.

RESULTS Out of 16,349 patients, 1,564 (9.6%) had EO-CRC. Compared with LO-CRC, EO-CRC had better performance status (86% *v* 80%, $P < .01$), similar T stage (% T1-3/T4: 76/24 *v* 77/23, $P = .97$), higher N2 disease rate (24% *v* 22%, $P < .01$), more likely to complete the planned treatment duration (83.2% *v* 78.2%, $P < .01$), and received a higher treatment dose intensity, especially with 6-month regimens. Gastrointestinal toxicity was more common in EO-CRC; hematologic toxicity was more frequent in LO-CRC. Compared with LO-CRC, significantly worse cancer-specific outcomes were demonstrated especially in high-risk stage III EO-CRC: lower 3-year relapse-free rate (54% *v* 65%; hazard ratio [HR] 1.33; 95% CI, 1.14 to 1.55; *P* value < .001) and higher 5-year cancer-specific mortality rate (24% *v* 20%; HR 1.21; 95% CI, 1.00 to 1.47; *P* value < .06). In this subgroup, no difference was observed with 3 or 6 months of therapy, with equally poor disease-free survival rates (57% *v* 56%; HR 0.97; 95% CI, 0.73 to 1.29; *P* value = .85).

CONCLUSION Young age is negatively prognostic in high-risk stage III CRC and associated with significantly higher relapse rate; this is despite better treatment adherence and higher administered treatment intensity, suggesting more aggressive disease biology.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Colorectal cancer (CRC) incidence and mortality have significantly increased in young individuals over the past 2 decades, in particular in Western countries.[1,2] Putative causes include increased exposure to risk factors like Western-style diet, obesity, physical inactivity, and prenatal and childhood antibiotic usage.[3] Although biologic characteristics such as distal tumor location, poor differentiation, and advanced stage at diagnosis seem more prevalent, stage-specific survival was reported to be comparable with older patients.[4] However, the current knowledge mainly derives from retrospective analyses and population-based cancer registries. Whether outcomes under the condition of specific contemporary interventions are different between early-onset (EO)-CRC and later-onset (LO)-CRC is largely unknown. Also, there is uncertainty whether EO-CRC should be managed with different approaches compared with LO-CRC. Limited evidence from randomized control trials is available in view of the relatively small number of cases compared with older population.

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration published a prospective, preplanned pooled analysis of six randomized phase III trials of 3 versus 6 months of adjuvant

CONTEXT

Key Objective

To compare clinical characteristics, treatment adherence, adverse events, and outcomes of patients with early-onset (EO) colorectal cancer (CRC) to those of patients with later-onset CRC included in the International Duration Evaluation of Adjuvant Chemotherapy pooled analysis.

Knowledge Generated

Patients with EO-CRC experience disease recurrence more frequently than patients with later-onset CRC despite receiving a higher adjuvant treatment intensity; cancer-specific mortality rate is higher in high-risk stage III EO-CRC.

Relevance

Early-onset colorectal cancer has a unique and generally more aggressive biology compared with late-onset disease, potentially warranting different adjuvant and surveillance strategies for this subgroup of patients.

fluoropyrimidine and oxaliplatin.[5] The noninferiority of a 3-month treatment was not confirmed in stage III patients. However, subgroup analyses demonstrated that 3 months of oxaliplatin and capecitabine (CAPOX) was as effective as 6 months in low-risk patients.

Here, we exploited the IDEA pooled analysis database to compare characteristics, treatment adherence, adverse events, and outcomes of patients with EO-CRC to those of patients with LO-CRC in the adjuvant setting.[5]

MATERIALS AND METHODS

Patients

Individual patient data from stage II and III patients from the IDEA database were included. Clinical characteristics of all randomly assigned patients were analyzed according to two age groups: EO-CRC with age at random assignment lower than 50 years and LO-CRC with age $\geq$ 50 years.

To reduce possible confounders, patients who did not start treatment, patients with metastatic disease at trial entry, or who received bevacizumab or celecoxib together with chemotherapy and/or with rectal cancer (possibly not treatment-naive) were excluded for treatment adherence, adverse events, and survival analyses (Appendix Fig A1, online only).

Objectives

The primary objectives of this work were to determine whether potential differences between EO-CRC and LO-CRC existed in terms of (1) clinical characteristics; (2) treatment adherence; (3) adverse events; and (4) survival outcomes.

First, disease-free survival (DFS) was analyzed, since this was previously chosen as the primary end point in the IDEA pooled analysis. To reduce the confounder of non–cancer-related deaths because of age or comorbidities, time to recurrence (TTR) and cancer-specific mortality (CSM) were evaluated. Overall survival (OS), overall mortality (1 – OS), mortality after recurrence (ar-overall mortality), and ar-CSM were secondary end points.

Duration (3 *v* 6 months) and type of regimen (CAPOX or infusional fluorouracil, leucovorin, and oxaliplatin) of adjuvant treatment in age groups were evaluated in an exploratory analysis.

Statistical Analysis

Clinical characteristics, treatment adherence, and adverse events were analyzed with descriptive statistics. T stage and N stage were described both independently and combined in a TN variable to define three risk groups: high-risk stage II (T1-4, N0), low-risk stage III (T1-3, N1) and high-risk stage III (T4, N any; T any, N2).

DFS and TTR end points (with associated 3-year DFS rate and 3-year relapse-free rate [3y-RF rate]) by age groups and stage were estimated with direct adjusted Kaplan-Meier curves, stratified by clinical trials, and compared using log-rank test and multivariable Cox models stratified by studies. Cancer-specific survival was compared by Gray k-sample test and multivariate competing risk models stratified by studies. Five-year CSM (5y-CSM) rate were estimated by adjusted cumulative incidence function.

The association of baseline characteristics and survival outcomes was assessed using univariate Cox analyses; variables with P values < 0.05 were included into multivariable Cox regression models with backward selection. Tumor location and risk groups were not included in multivariable models as already considered in other variables (sidedness and T and N stages).

The prognostic effect of age with respect to DFS, OS, and survival after recurrence was assessed in various subgroups using univariate Cox models and visualized in forest plots including interaction P values (type-3 likelihood ratio test of the interaction term). Three subgroups (other race, mixed race, and rectum) were excluded because of limited number of patients with consequent model instability.

Analyses were performed using SAS software (version 9.4M7; SAS Institute Inc, Cary, NC).

RESULTS

Population Characteristics

A total of 16,349 patients enrolled in six clinical trials were included in this analysis; 1,564 patients with EO-CRC (9.6%) and 14,785 with LO-CRC (90.4%) (Appendix Fig A1 and Data Supplement, online only).

Overall, patients with EO-CRC were more frequently male (51.3%), although the proportion of male patients was lower in EO-CRC than in LO-CRC (57%); most patients with EO-CRC had a performance status (PS) of 0 and a distal, low-grade tumor; a higher number of lymph nodes was examined. The stage distribution between EO-CRC and LO-CRC was similar but with a 3% more high-risk stage II young patients.

Treatment Adherence

Overall, 14,518 patients were included in the following analyses: 1,311 patients with (9%) EO-CRC and 13,207 patients with (91%) LO-CRC. A significantly higher proportion of patients with EO-CRC was able to complete the planned duration of treatment compared with older patients with LO-CRC; of note, in the 6-month CAPOX group, 76% of EO-CRC reached full therapy duration versus 65% of older patients (P value $< .001$; Table 1). Conversely, this difference was less substantial among patients who received 3 months of treatment (89% EO-CRC *v* 87% LO-CRC, $P = .06$ with CAPOX; 93% EO-CRC *v* 92% LO-CRC, $P = .03$ with infusional fluorouracil, leucovorin, and oxaliplatin).

Dose intensity was significantly different between age groups; this may suggest that it was more likely for patients with EO-CRC to continue at least the fluoropyrimidine to complete the preplanned number of cycles, rather than discontinue the treatment. This was more substantial in the 6-month CAPOX therapy group, where 16% of patients with EO-CRC versus 12% of patients with LO-CRC had > 30% difference between fluoropyrimidine and oxaliplatin dose delivered.

Adverse Events

Overall, the number of adverse events was not significantly different between age groups (Table 2). Grade ≥ 3 adverse events were 36% and 39% in EO-CRC and LO-CRC groups, respectively. One patient with EO-CRC (0.1%) and 16 patients with LO-CRC (0.2%) died during treatment. Peripheral neuropathy incidence and degrees were similar in the overall comparison and also within comparisons of different treatment regimens (Data Supplement). The incidence of gastrointestinal symptoms, specifically nausea and vomiting but not diarrhea and mucositis, was higher in patients with EO-CRC. Conversely, hematologic toxicities were significantly more frequent in LO-CRC (62% for EO-CRC and 69% LO-CRC, P value $< .001$). Rates of febrile neutropenia were 1.4% in EO-CRC and 2.8% in LO-CRC. Fatigue and hand-foot syndrome were similar.

Survival

DFS and TTR. At a median follow-up of 69 (EO-CRC) and 72 (LO-CRC) months, no significant difference in DFS was demonstrated in the overall population (3-year rates: 76% [95% CI, 73 to 78] for EO-CRC and 78% [95% CI, 77 to 79] for LO-CRC [hazard ratio (HR), 1.01; 95% CI, 0.91 to 1.13; P value $= .81$]; Fig 1A). Similarly, no significant DFS difference was demonstrated in stage II and stage III subgroups (Figs 1B and 1C). However, by only examining disease relapse, a significantly lower 3y-RF rate was demonstrated overall (75% [95% CI, 72 to 77] *v* 79% [95% CI, 78 to 80] in LO-CRC; HR 1.13 [95% CI, 1.01 to 1.27]; P value $= .04$) and in stage III EO-CRC compared with older patients (69% [95% CI, 66 to 73] *v* 76% [95% CI, 75 to 77] in LO-CRC; HR 1.21 [95% CI, 1.07 to 1.37]; P value $= .003$; Figs 1D-1F).

OS and CSM. In keeping with fitter patients, OS was significantly higher in EO-CRC (5y-OS rates: 86% [95% CI, 84 to 88] *v* 83% [95% CI, 83 to 84]; HR 0.84 [95% CI, 0.73 to 0.97; P value 0.02]). No difference was demonstrated in stage III patients with cancer, whereas OS difference was significantly evident in stage II disease (Figs 2A-2C). However, when considering CSM, opposite results were demonstrated: no difference was observed overall and in stage II patients; conversely, a significantly higher CSM rate was demonstrated in stage III EO-CRC compared with older patients (5y-CSM rates: 15% [95% CI, 12 to 17] *v* 12% [95% CI, 12 to 13]; HR 1.20 [95% CI, 1.02 to 1.42; P value $= .03$]; Figs 2D-2F).

In univariate analyses, young age was not associated with poorer outcomes (Data Supplement). In the adjusted model, female patients, patients with PS = 0, low T stage, no lymph node involvement, with appropriate number of lymph nodes resected (> 12), and patients who completed adjuvant treatment had better DFS and OS.

Mortality and arCSM. After recurrence (ar), EO-CRC had a significantly lower mortality (median time to death 3.2 years [95% CI, 2.7 to 3.8] *v* 2.5 years [95% CI, 2.4 to 2.6]; HR 0.82 [95% CI, 0.71 to 0.96]; P value $= .01$). Similar to OS outcomes, ar-mortality difference was no longer observed when considering ar-CSM (Appendix Figs A2A-A2F, online only). After adjustment, PS, sidedness, and time to recurrence remained significantly associated with survival after recurrence (Data Supplement).

Prognostic Effect of Age in Patient Subgroups

No interaction for DFS nor for OS (Appendix Fig A3, online only) was observed between age groups and sex, race, PS, sidedness, histologic grade, node examined, and treatment regimen. However, age had different prognostic effects on the basis of risk groups (interaction P value for

TABLE 1. Treatment Adherence According to Age Groups, Duration, and Type of Therapy

Measurement of Treatment Adherence	3-Month CAPOX			6-Month CAPOX			3-Month FOLFOX			6-Month FOLFOX		
	Age < 50 Years (n = 295)	Age ≥ 50 Years (n = 3,212)	*P*	Age < 50 Years (n = 319)	Age ≥ 50 Years (n = 3,144)	*P*	Age < 50 Years (n = 350)	Age ≥ 50 Years (n = 3,415)	*P*	Age < 50 Years (n = 347)	Age ≥ 50 Years (n = 3,436)	*P*
Completion of cycles, No. (%)			.0619[a]			.0004[a]			.0284[a]			.0472[a]
Reached full duration	257 (88.9)	2,737 (86.5)		239 (75.6)	1995 (64.6)		326 (93.4)	3,099 (91.5)		253 (74.9)	2,371 (69.7)	
Did not reach full duration	27 (9.3)	402 (12.7)		77 (24.4)	1,091 (35.3)		18 (5.2)	270 (8.0)		85 (25.1)	1,032 (30.3)	
Exceeded full duration	5 (1.7)	24 (0.8)		0 (0.0)	1 (0.0)		5 (1.4)	19 (0.6)				
Missing	6	49		3	57		1	27		9	33	
Percentage of fluorouracil									< .0001[b]			.0016[b]
Mean							96.2	93.2		85.4	81.6	
Median							100.0	100.0		94.9	90.4	
Range							16.7-200.0	14.7-357.1		8.3-196.4	1.2-194.7	
Missing							1	29		10	37	
Percentage of capecitabine			.0885[b]			< .0001[b]						
Mean	93.7	91.1		85.3	77.8							
Median	100.0	100.0		100.0	87.5							
Range	25.0-200.0	3.0-393.8		12.5-247.5	2.9-352.8							
Missing	7	59		6	67							
Percentage of oxaliplatin			.5016[b]			.0080[b]			.0077[b]			.1385[b]
Mean	91.4	89.6		74.0	69.3		94.4	92.6		75.6	73.5	
Median	100.0	100.0		82.1	75.0		100.0	100.0		81.8	80.4	
Range	25.0-169.2	25.0-252.9		12.5-132.3	10.9-146.3		16.7-200.0	14.7-284.4		8.1-155.0	6.7-171.9	
Missing	0	9		1	3		0	3		0	4	
Difference between cape or FU and oxaliplatin % of dose delivered, No. (%)			.6668[a]			.0073[a]			.0004[a]			.0176[a]
< 0	45 (15.6)	588 (18.7)		45 (14.4)	667 (21.7)		79 (22.6)	989 (29.2)		54 (16.0)	826 (24.3)	
0-10	210 (72.9)	2,243 (71.3)		159 (51.0)	1,560 (50.7)		237 (67.9)	2,207 (65.2)		174 (51.6)	1,603 (47.2)	
10-20	17 (5.9)	151 (4.8)		38 (12.2)	270 (8.8)		14 (4.0)	96 (2.8)		40 (11.9)	340 (10.0)	
20-30	7 (2.4)	62 (2.0)		21 (6.7)	211 (6.9)		10 (2.9)	28 (0.8)		26 (7.7)	247 (7.3)	
> 30	9 (3.1)	100 (3.2)		49 (15.7)	367 (11.9)		9 (2.6)	63 (1.9)		43 (12.8)	382 (11.2)	
Missing	7	68		7	69		1	32		10	38	

Abbreviations: CAPOX, oxaliplatin and capecitabine; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil.

[a]Chi-square *P* value.

[b]Kruskal-Wallis *P* value.

TABLE 2. Adverse Events According to Age Groups

Adverse Event	Age < 50 Years (n = 1,311)	Age ≥ 50 Years (n = 13,207)	P
All adverse events, No. (%)			.1067[a]
Grade 0-2	626 (63.6)	5,669 (61.0)	
Grade 3+	358 (36.4)	3,627 (39.0)	
Peripheral sensory neuropathy, No. (%)			.2400[a]
None	244 (24.9)	2,333 (25.2)	
Grade 1-2	658 (67.2)	6,316 (68.3)	
Grade 3+	77 (7.9)	597 (6.5)	
Gastrointestinal symptoms,[b] No. (%)			.0436[a]
Any GI any grade	423 (68.7)	3,822 (64.6)	
No GI symptoms	193 (31.3)	2095 (35.4)	
Nausea, No. (%)			< .0001[a]
None	321 (41.7)	4,200 (55.2)	
Grade 1	274 (35.6)	2,360 (31.0)	
Grade 2	156 (20.3)	888 (11.7)	
Grade 3+	18 (2.3)	161 (2.1)	
Vomiting, No. (%)			< .0001[a]
None	598 (77.8)	6,382 (83.9)	
Grade 1-2	159 (20.7)	1,118 (14.7)	
Grade 3+	12 (1.6)	105 (1.4)	
Diarrhea, No. (%)			.3765[a]
None	569 (57.9)	5,344 (57.6)	
Grade 1-2	362 (36.9)	3,344 (36.1)	
Grade 3+	51 (5.2)	585 (6.3)	
Mucositis, No. (%)			.8214[a]
None	491 (79.7)	4,685 (79.2)	
Grade 1-2	121 (19.6)	1,182 (20.0)	
Grade 3+	4 (0.6)	52 (0.9)	
Hematologic toxicities,[c] No. (%)			.0002[a]
Any hematologic toxicity any grade	383 (62.2)	4,107 (69.4)	
No hematologic toxicity	233 (37.8)	1812 (30.6)	
Febrile neutropenia, No. (%)			.0117[a]
None	969 (98.6)	9,011 (97.2)	
Grade 1-5	14 (1.4)	258 (2.8)	
Neutropenia, No. (%)			.0018[a]
None	404 (52.5)	3,566 (46.8)	
Grade 1-2	257 (33.4)	2,642 (34.7)	
Grade 3+	108 (14.0)	1,404 (18.4)	
Thrombocytopenia, No. (%)			< .0001[a]
None	468 (60.9)	3,885 (51.1)	
Grade 1-2	290 (37.7)	3,560 (46.8)	
Grade 3+	11 (1.4)	164 (2.2)	
Fatigue, No. (%)			.2234[a]
None	435 (60.6)	4,293 (60.1)	
Grade 1-2	272 (37.9)	2,671 (37.4)	
Grade 3+	11 (1.5)	185 (2.6)	
Hand-foot syndrome, No. (%)			.5684[a]
None	177 (66.5)	1759 (66.2)	
Grade 1-2	88 (33.1)	872 (32.8)	
Grade 3+	1 (0.4)	28 (1.1)	

[a]Chi-square *P* value.
[b]Nausea, vomiting, diarrhea, and mucositis.
[c]Neutropenia, febrile neutropenia, and thrombocytopenia.

DFS = 0.009, for OS < 0.001). The positive prognostic value of young age in stage II disease (HRs for DFS = 0.75, for OS = 0.44) shrunk in low-risk stage III (HRs for DFS = 0.92, for OS = 0.73) and completely reverted into a negative or no prognostic value in the high-risk stage III subgroup (T4 and/or N2 disease; HRs for DFS = 1.22, for OS = 1.04).

No significant difference in 3y-RF rates and 5y-CSM rates was observed in stage II and low-risk stage III patients; conversely, high-risk stage III EO-CRC had significantly lower 3y-RF rate (54% *v* 65%, HR 1.33 [95% CI, 1.14 to 1.15], *P* value < .001) and higher 5y-CSM rate (24% *v* 20%, HR 1.21 [95% CI, 1.00 to 1.47], *P* value < .06) compared with older patients (Figs 3A and 3B).

Effect of Treatment Duration in Age Groups

In this exploratory analysis, the impact of 3 versus 6 months of adjuvant therapy in stage III disease on DFS was assessed separately in the two age groups and according to low-risk or high-risk stage. DFS was chosen as the end point for this analysis, given this was the primary end point of IDEA and also because this is a comparison within same age groups, thus not affected by non–cancer-related deaths confounders. In the LO-CRC group, the results were in line with the previous findings.[5] Conversely, low-risk stage III EO-CRC had significantly lower 3y-DFS rate with 3 months of treatment compared with 6 months (81% *v* 87%; HR 1.49 [95% CI, 1.00 to 2.20], *P* value < .05); in the high-risk stage III EO-CRC group, no difference was observed, with equally poor

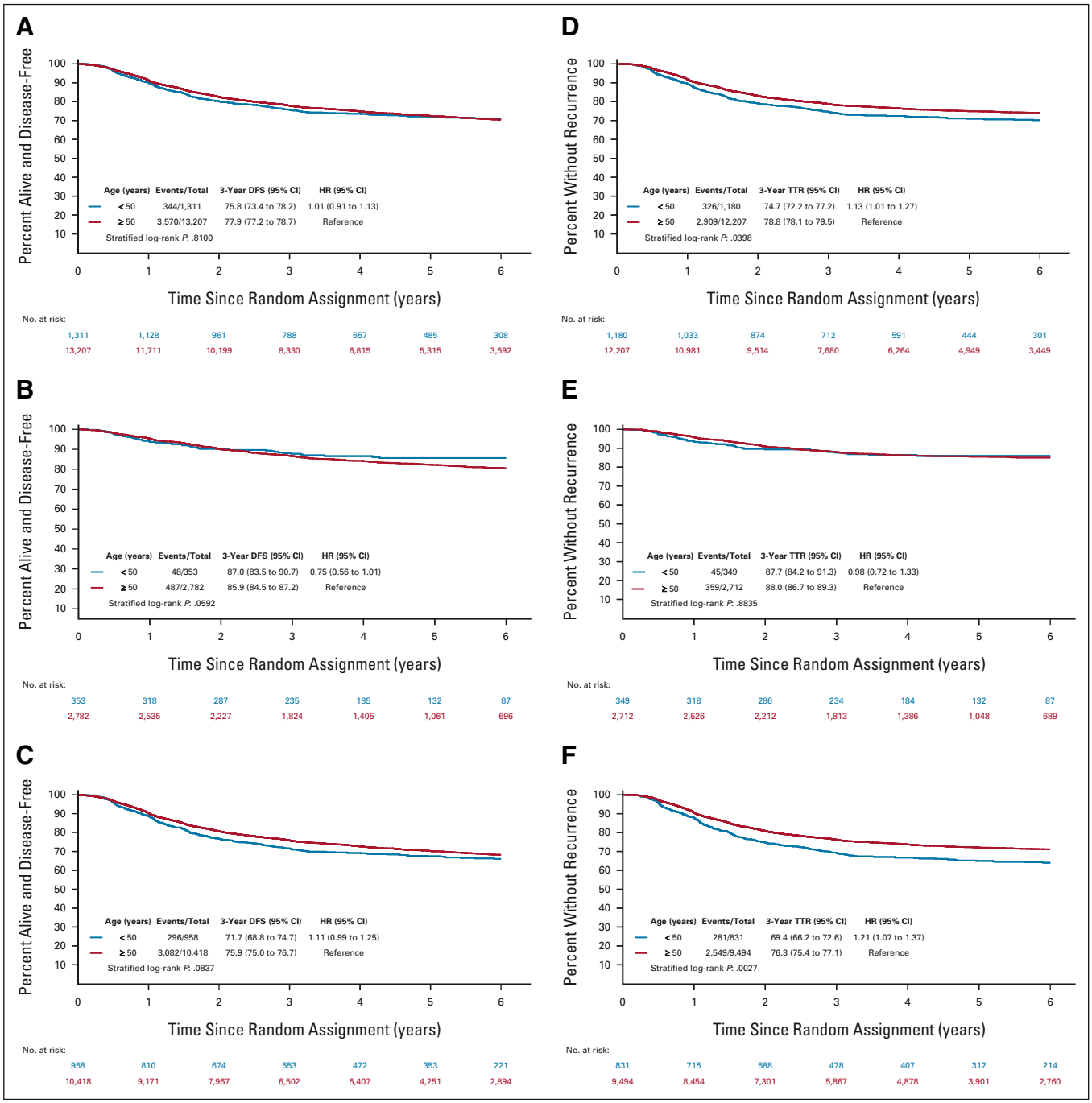

FIG 1. DFS and TTR according to age groups and disease stage. DFS in (A) all stages, (B) high-risk stage II patients, and (C) stage III patients. TTR in (D) all stages, (E) high-risk stage II patients, and (F) stage III patients. DFS, disease-free survival; HR, hazard ratio; TTR, time to recurrence.

DFS rates of 57% and 56% (HR 0.97 [95% CI, 0.73 to 1.29; *P* value = .85]) with 3 and 6 months, respectively (Fig 4). The Data Supplement includes 3y-DFS and 5y-CSM comparisons in EO-CRC and LO-CRC according to TN stages and chemotherapy regimen.

DISCUSSION

In this comprehensive analysis including six multicenter, randomized clinical trials of adjuvant chemotherapy, patients with EO-CRC have been evaluated and compared with older patients for the first time.

Clinically, young patients have better PS and more frequently a distal tumor, in line with known higher prevalence of proximal and *BRAF*-mutant/MMRd tumors in older patients.[6]

A better PS and likely lower comorbidities in young patients may allow for a more aggressive treatment approach, suggested here by the higher number of stage II young

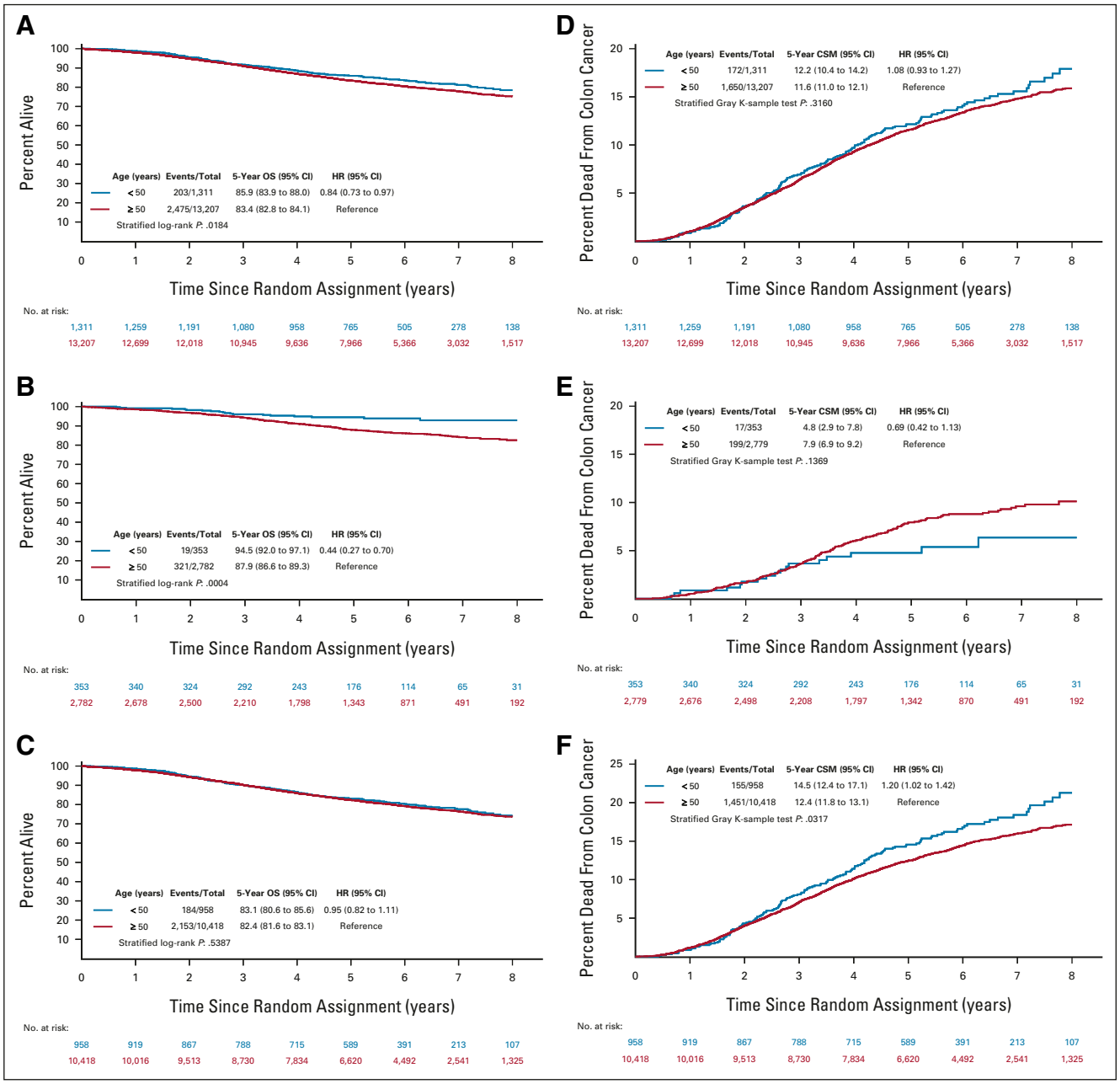

FIG 2. OS and cancer-specific survival according to age groups and disease stage. OS in (A) all stages, (B) high-risk stage II patients, and (C) stage III patients. CSM in (D) all stages, (E) high-risk stage II patients, and (F) stage III patients. CSM, cancer-specific mortality; HR, hazard ratio; OS, overall survival.

patients included, higher number of lymph nodes examined, and higher chemotherapy dose intensity.

This is in line with previous evidence highlighting how young patients are more likely to receive more intense treatment approaches.[7]

A higher incidence of nausea and vomiting in young patients was observed; this confirmed similar findings previously reported in patients with CRC included in the ACCENT database and also in other cancer types.[8-10] Whether these are anticipatory, acute or delayed nausea, and vomiting is not documented in the IDEA database and should be prospectively investigated for treatment optimization. Conversely, the lower incidence of hematologic toxicities despite higher chemotherapy doses received may open opportunities for further treatment intensification. Information on whether granulocyte colony-stimulating factors (GCSFs) were more frequently used in EO-CRC to maintain dose intensity is not available; upfront GCSFs are not standard with fluoropyrimidine and oxaliplatin, thus the incidence of neutropenic events should well represent the reality, while lower dose reductions compared with older

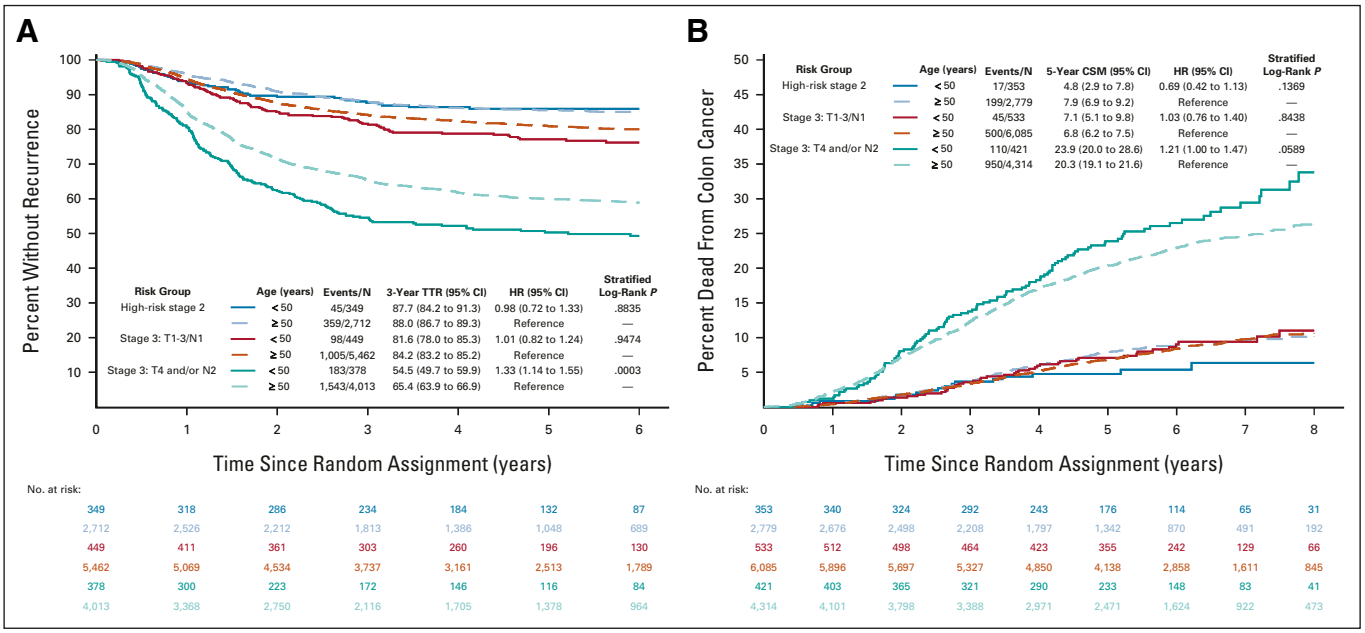

FIG 3. (A) TTR and (B) cancer-specific survival according to age and risk groups. CSM, cancer-specific mortality; HR, hazard ratio; TTR, time to recurrence.

patients may also be explained by a different GCSF usage. Although peripheral neuropathy rates looked similar between age groups, the long-term impact and persistency of low-grade neurotoxicity were not assessed in this study. Similarly, cardiovascular, psychologic, and gonadal toxicities were not documented; these should be prospectively assessed in cancer survivors.

In terms of survival outcomes, in this work, we highlight the importance of evaluating cancer-specific outcomes instead of traditional end points when comparing groups with significantly different life expectancies. In fact, young patients had similar DFS and longer OS than older patients; however, these results may be confounded by an expected higher mortality rate for competing causes in older patients. Cancer-specific outcomes highlighted how young patients have the same risk of dying of cancer than older patients overall, whereas in high-risk stage III disease, younger age is a significant poor prognostic factor. This might be explained by a more aggressive disease biology. Interestingly, comprehensive genomic profiling demonstrated only minor genomic differences between younger and older patients with CRC, with *TP53* and *CTNNB1* more frequently found in young patients, and *APC*, *BRAF*, and *KRAS* more frequently altered in older patients.[11,12] Whether post-transcriptional differences exist or meaningful differences can be found in the tumor microenvironment, leading to more immune escape in younger patients, needs to be assessed.

After disease recurrence, the risk of dying of cancer in young patients was not different compared with that of older patients, despite higher likelihood of receiving more aggressive treatments including more intense chemotherapy, wider use of surgery for metastatic disease, or more frequent inclusion in clinical trials.[7]

Treatment duration should be carefully considered in patients with EO-CRC. On the basis of the inferiority of 3 versus 6 months shown in the IDEA pooled analysis in high-risk stage III disease, 3 months of therapy should not be standard in this specific group of patients.[5] Importantly, this study further highlights poor overall completion rates of adjuvant therapy, especially with 6-month regimens even in young clinical trial patients with expected excellent PS. Here, in patients with EO-CRC with high-risk stage III cancer, the benefit of 6 months of treatment is more likely overcome by the overall poor outcome of this subgroup, with nearly half of the patients experiencing disease recurrence with either 3 or 6 months of treatment. This highlights the unmet need for early detection and possibly completely novel strategies to be developed in this group of patients.

Three months of adjuvant fluoropyrimidine and oxaliplatin therapy is now standard in low-risk stage III disease[5]; the current analysis demonstrates a significant 6% incremental benefit in 3y-DFS rate in patients assigned to 6 months of treatment over 3 months of treatment in patients with EO-CRC, despite completion rates in 6-month groups being lower than in 3-month groups. However, this age group–specific analysis was ad hoc with a relatively small sample size. Thus, cautions are needed to interpret the results, especially in conjunction with toxicity data. A minimum of 3 months of treatment is recommended in all stage III patients with cancer; longer duration of therapy may have a minimal effect in this subgroup at a clear cost of increased toxicity.

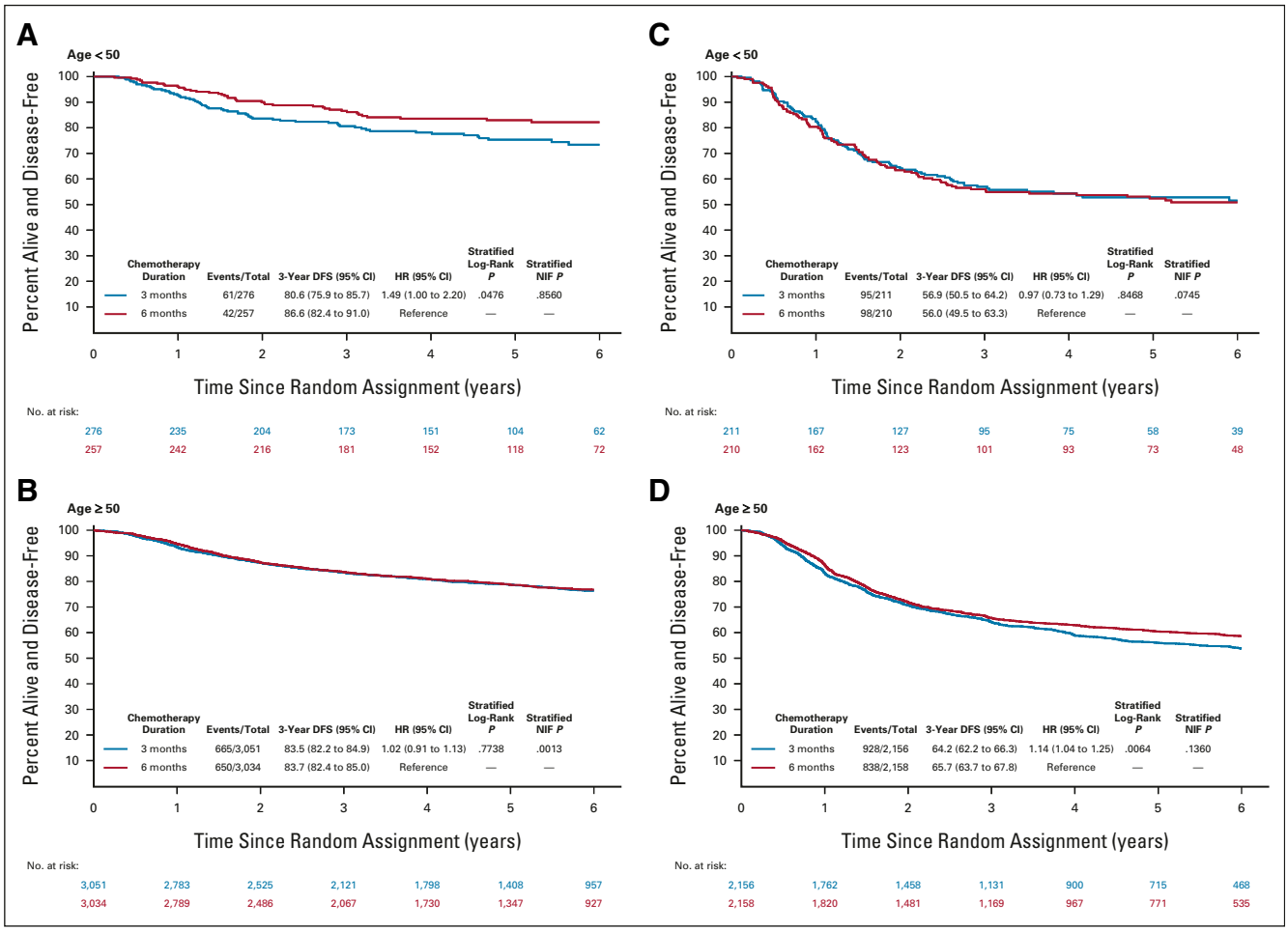

FIG 4. DFS in stage III low and high risk according to age groups and treatment duration. DFS in (A) low-risk stage III patients age < 50 years, (B) low-risk stage III patients age ≥ 50 years, (C) high-risk stage III patients age < 50 years, and (D) high-risk stage III patients age ≥ 50 years. DFS, disease-free survival; HR, hazard ratio; NIF, non-inferiority.

Limitations of our analysis are mainly because of its post hoc nature and the absence of important prognostic biomarkers like microsatellite instability (MSI), including whether germline (Lynch syndrome) or sporadic status. Recently, the effect of MSI status was explored in a similar setting in the ACCENT pooled analysis of 12 adjuvant trials.[13] Up to 11% of patients had an MSI-high tumor; however, the germline status was not available. The higher prevalence of MSI-high in older patients with associate positive prognostic value in early-stage disease may further explain the poorer outcomes observed in patients with EO-CRC. Although a higher incidence of Lynch syndrome could be expected in younger patients, it is not clear whether the prognostic value of germline or sporadic MSI is significantly different. This information should be systematically and prospectively collected in future studies.

Previous findings showed how young patients are more likely to have a cancer of the rectum and metastatic disease at diagnosis compared with older patients; these patients were not included in the current analysis. Finally, an arbitrary cutoff at 50 years was used to define the two age groups. This cutoff has been consistently used in recent epidemiologic studies and identifies a population of patients diagnosed before screening programs.[1,2] Although different age cutoffs or age as continuous variable could be further explored, statistical power could be lost in smaller subgroup analyses. Our pragmatic approach may help informing decisions related to changes of surveillance strategies.

In conclusion, in this post hoc analysis of the IDEA database, we demonstrated how age is prognostic with significant negative value for early-onset colon cancer in stage III. Young patients with high-risk stage III cancer experience disease recurrence more frequently than older patients despite receiving a higher adjuvant treatment intensity. These findings should inform the design of future clinical trials and the optimization of surveillance strategies in light of the challenging, increased incidence of CRC in young adults.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Early-Onset Colorectal Adenocarcinoma in the IDEA Database: Treatment Adherence, Toxicities, and Outcomes With 3 and 6 Months of Adjuvant Fluoropyrimidine and Oxaliplatin

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APPENDIX

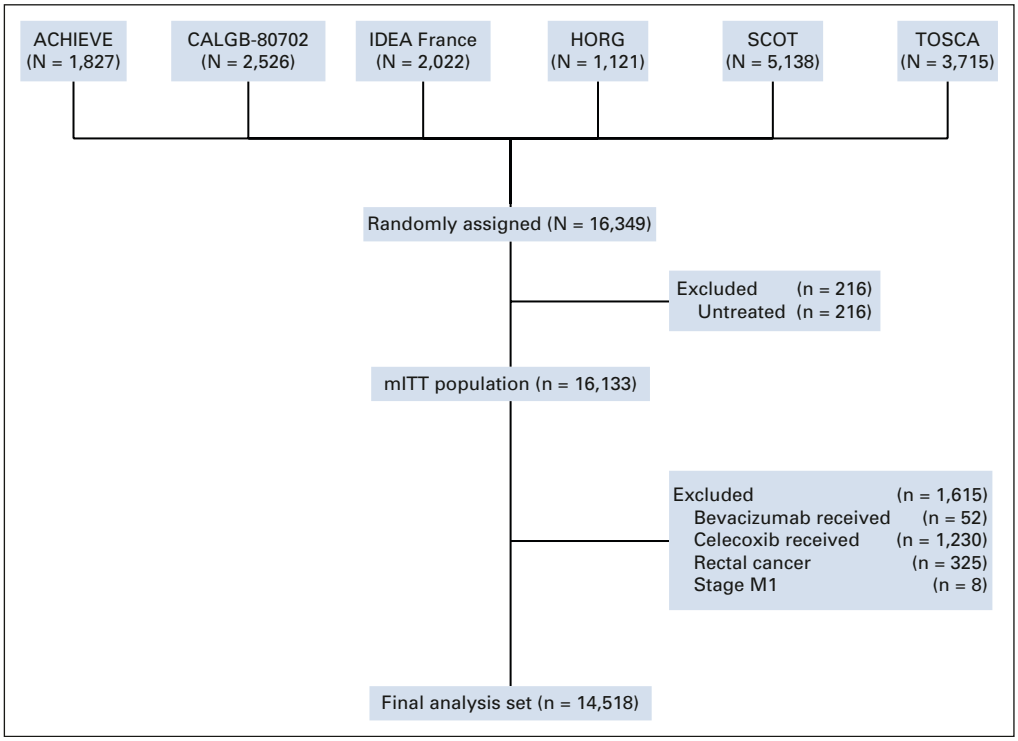

FIG A1. Flow diagram. CALGB, Cancer and Leukemia Group B; HORG, The Hellenic Oncology Research Group; IDEA, International Duration Evaluation of Adjuvant Chemotherapy; mITT, modified intention-to-treat; SCOT, 3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer; TOSCA, The Three or Six Colon Adjuvant.

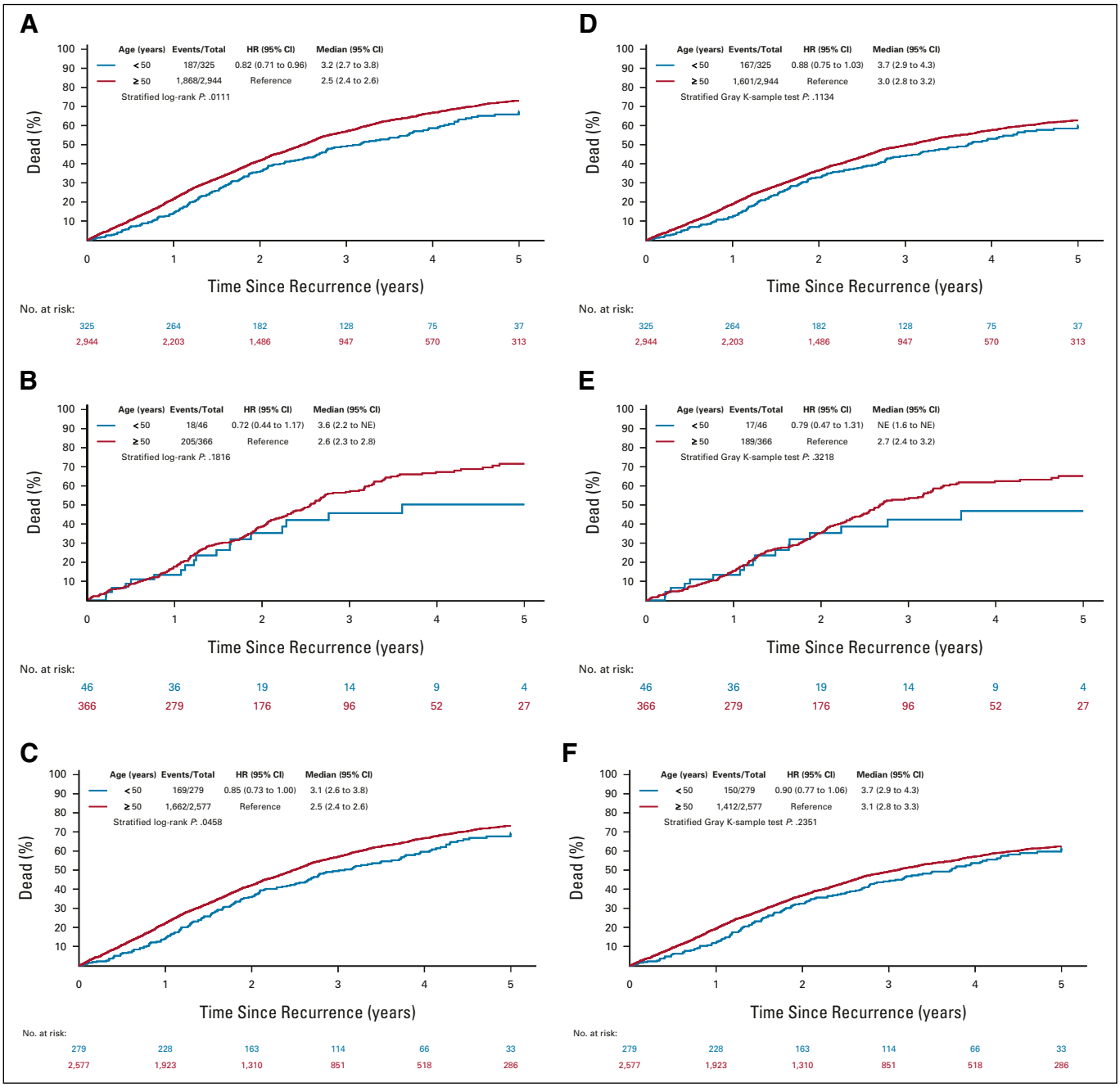

FIG A2. Mortality and ar-CSM according to age groups and disease stage at diagnosis. Overall mortality in (A) all stages, (B) high-risk stage II patients, and (C) stage III patients. Cancer-specific mortality in (D) all stages, (E) high-risk stage II patients, and (F) stage III patients. ar-CSM, cancer-specific mortality after recurrence; ar-CSS, cancer-specific survival after recurrence; ar-OM, overall mortality after recurrence; HR, hazard ratio; NE, not evaluable.

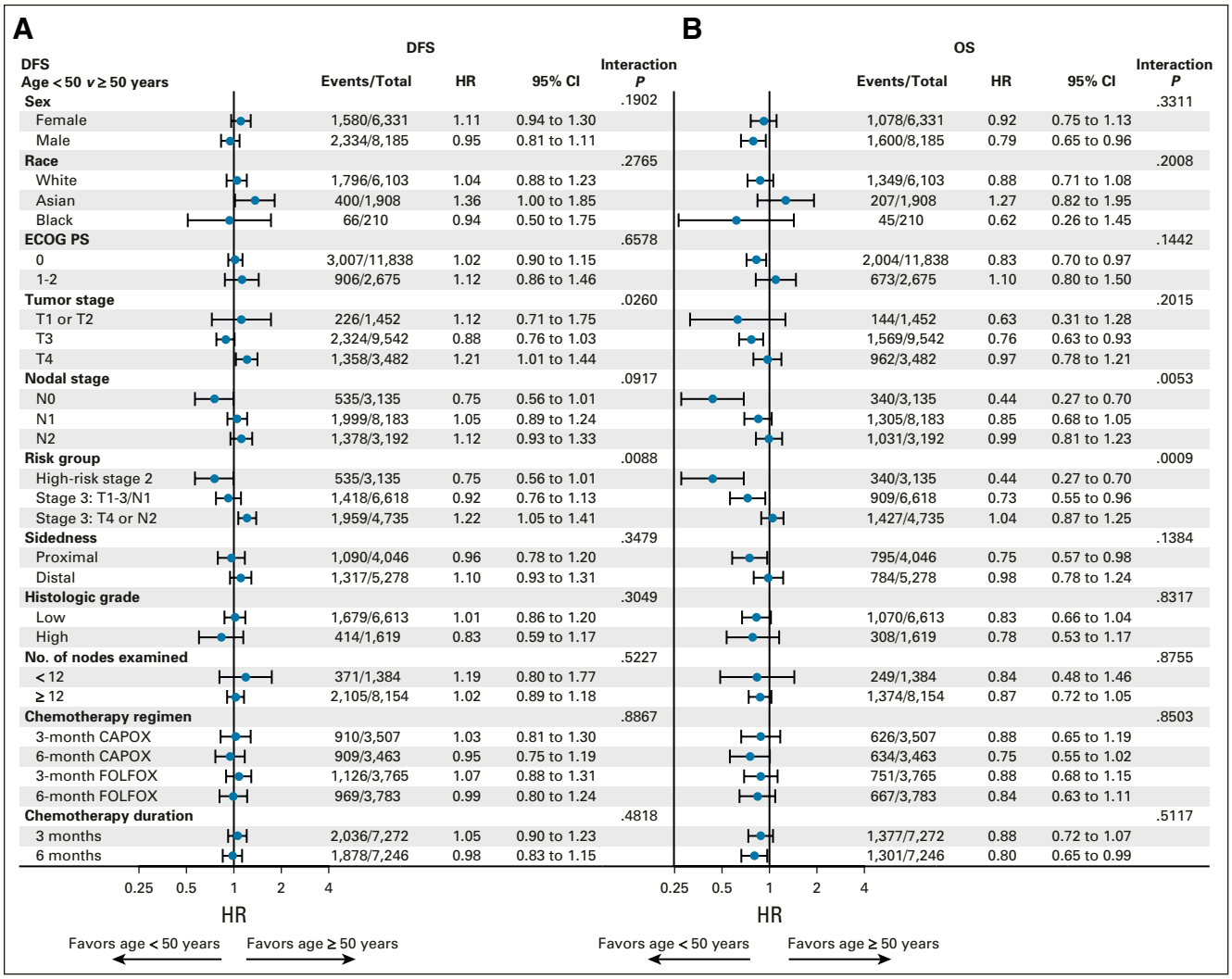

FIG A3. Forest plot for age group effect on (A) DFS and (B) OS by baseline factors. CAPOX, oxaliplatin and capecitabine; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; OS, overall survival.