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ORIGINAL REPORT

Impact of Young Age on Treatment Efficacy and Safety in Advanced Colorectal Cancer: A Pooled Analysis of Patients From Nine First-Line Phase III Chemotherapy Trials

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ABSTRACT

Purpose
Colorectal cancer predominantly occurs in the elderly, but approximately 5% of patients are 50 years old or younger. We sought to determine whether young age is prognostic, or whether it influences efficacy/toxicity of chemotherapy, in patients with advanced disease.

Methods
We analyzed individual data on 6,284 patients from nine phase III trials of advanced colorectal cancer (aCRC) that used fluorouracil-based single-agent and combination chemotherapy. End points included progression-free survival (PFS), overall survival (OS), response rate (RR), and grade 3 or worse adverse events. Stratified Cox and adjusted logistic-regression models were used to test for age effects and age-treatment interactions.

Results
A total of 793 patients (13%) were younger than 50 years old; 188 of these patients (3% of total patients) were younger than 40 years old. Grade 3 or worse nausea (10% *v* 7%; $P = .01$) was more common, and severe diarrhea (11% *v* 14%; $P = .001$) and neutropenia (23% *v* 26%; $P < .001$) were less common in young (younger than 50 years) than in older (older than 50 years) patients. Age was prognostic for PFS, with poorer outcomes occurring in those younger than 50 years (median, 6.0 *v* 7.5 months; hazard ratio, 1.10; $P = .02$), but it did not affect RR or OS. In the subset of monotherapy versus combination chemotherapy trials, the relative benefits of multiagent chemotherapy were similar for young and older patients. Results were comparable when utilizing an age cut point of 40 years.

Conclusion
Young age is modestly associated with poorer PFS but not OS or RR in treated patients with aCRC, and young patients have more nausea but less diarrhea and neutropenia with chemotherapy in general. Young versus older patients derive the same benefits from combination chemotherapy. Absent results of a clinical trial, standard combination chemotherapy approaches are appropriate for young patients with aCRC.

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INTRODUCTION

The 2010 estimates in the United States identified 142,570 new occurrences of colorectal cancer and 51,370 deaths as a result of that malignancy.[1] Colorectal cancer is predominantly a disease of the elderly; the median age is 72 years, and 28% of patients are older than 80 years.[2,3] A higher proportion of older patients present with locoregional disease.[4] Treatment does benefit at least some older patients; indeed, fit elderly with advanced colorectal cancer (aCRC) experience approximately the same benefits from systemic therapy as those in the more common age demographics.[5]

In young patients, colorectal cancer tends to present more commonly with stage III or IV disease.[6] Stage for stage, the prognosis is similar in younger patients, though overall survival (OS) is clearly worse in the youngest subgroups. The predictive effect of younger age as related to systemic therapy, especially with newer agents, is unknown. Because of an inherited defect in DNA mismatch repair (Lynch syndrome), young patients tend to have a higher proportion of tumors demonstrating microsatellite instability, which are associated with a better prognosis but which may predict for lower benefit from fluorouracil-based chemotherapy, at least in the adjuvant setting.[7,8]

We studied a number of phase III chemotherapy trials in patients with aCRC, assessing outcomes in younger versus older patients. Herein, we describe analyses of the pooled results of nine randomized trials and subsets of those treated with oxaliplatin- and irinotecan-containing regimens. We also looked specifically at monotherapy versus combination chemotherapy (in a subset of the randomized trials) in the young and older patients to gauge potential differential treatment effects.

METHODS

The Adolescent and Young Adult Oncology Progress Review group, funded by the National Institutes of Health in conjunction with the Livestrong Foundation, recommended a systematic review of available clinical trials data, originally aiming to determine whether there were biologic and/or outcome differences according to age in select common cancers (including colorectal neoplasms). They approached authors of large-scale randomized trials that were expected to harbor significant numbers of young patients, ages 15 to 39 years. When colorectal cancer was determined to be of interest, nine studies testing fluorouracil-based chemotherapy in advanced disease were selected for additional analysis on the basis of data availability and relevance to current practice. Details regarding the individual clinical trials and patient characteristics are listed in Appendix Table A1 (online only).[9-17] The individual trials were approved by local investigational review boards at the time the studies were conducted, and our pooled analyses were approved by the Mayo Clinic investigational review board.

The principle investigators of the trial supplied individual patient data. Cox proportional hazards models stratified by study, and logistic-regression models adjusting for trial, were used to test for age effects using two prespecified cut points: age younger than 40 years versus 40 years or older and age younger than 50 years versus 50 years or older.[18,19] Age by treatment interactions were assessed as well by using a likelihood ratio test. Objective response rates (RRs), progression-free survival (PFS), and OS were compared by using data from all nine trials, as were rates of grade 3 or greater adverse events (by using National Cancer Institute Common Toxicity Criteria, version 2.0[20]). These analyses were subsequently conducted in the eight trial-specific treatment arms that contained a fluoropyrimidine and oxaliplatin regimen. A similar analysis was also performed on the six treatment arms that consisted of a fluoropyrimidine/irinotecan combination. Finally, to gauge the relative benefit of multidrug chemotherapy in the two age groups, similar efficacy analyses were carried out in the subset of five trials comparing monotherapy to combination chemotherapy. Details of the oxaliplatin- and irinotecan-containing trials, as well as those included in the combination chemotherapy analyses, are supplied online. All analyses were carried out with the Linux release of SAS, version 9.2 (SAS Institute, Cary, NC); *P* values reported are two sided, and *P* values less than .05 denote statistical significance.

RESULTS

The nine trials included in the primary analyses were conducted from August 1995 to August 2004, and they included 6,286 patients. Two patients were missing age data, so 6,284 were eligible for our analyses. One hundred eighty-eight (3% of patients) were younger than age 40 years, and 793 (13%) were younger than age 50 years (Appendix Table A2, online only). Two thousand, one hundred fifty-three patients were treated with oxaliplatin-containing chemotherapy, of whom 2% were younger than 40 years of age and 11% were younger than 50 years of age (Appendix Tables A3 and A4, online only). One thousand, four hundred ninety-five patients received irinotecan-containing therapy, of whom 4% were younger than 40 years of age and 16% were younger than 50 years of age (Appendix Tables A5 and A6, online only).

Table 1. Grade 3 or Worse Toxicity Rates in All Trials

Toxicity by Age Group Comparison	Age Group (%)		Analysis		
	Young	Old	OR	95% CI	*P**
Younger than 40 years *v* 40 years or older					
Nausea	14	7	1.74	1.13 to 2.69	.01
Vomiting	15	6	2.23	1.45 to 3.43	< .001
Diarrhea	12	14	0.71	0.46 to 1.12	.14
Stomatitis	1	2	0.51	0.12 to 2.10	.35
Neutropenia	26	26	0.67	0.47 to 0.96	.03
Younger than 50 years *v* 50 years or older					
Nausea	10	7	1.38	1.07 to 1.78	.01
Vomiting	9	6	1.33	1.00 to 1.77	.05
Diarrhea	11	14	0.68	0.54 to 0.86	.001
Stomatitis	2	2	0.85	0.48 to 1.50	.57
Neutropenia	23	26	0.64	0.53 to 0.78	< .001

*Multivariate *P* value from logistic regression adjusted for trial.

Toxicity

All trials. Patients younger than 40 years versus those 40 years or older had more grade 3 or worse nausea (14% *v* 7%; odds ratio [OR], 1.74; $P = .01$) but less neutropenia (26% *v* 26%; OR, 0.67; $P = .03$; Table 1). Rates of diarrhea and stomatitis were similar between the two age groups. When comparing those patients younger than 50 years to those 50 years or older, younger patients had more nausea (10% *v* 7%; OR, 1.38; $P = .01$) but less diarrhea (11% *v* 14%; OR, 0.68; $P = .001$) and neutropenia (23% *v* 26%; OR, 0.64; $P < .001$). Rates of stomatitis were similar between age groups.

Oxaliplatin-Containing Arms

When assessing just those treatment arms containing oxaliplatin, no significant differences were seen in grade 3 or worse adverse event rates comparing either age group to older patients (Appendix Table A7, online only). Patients younger than 50 years had borderline increased rates of nausea compared with those age 50 years or older (10% *v* 6%; OR, 1.59; $P = .06$).

Irinotecan-Containing Arms

When a similar subset analysis was carried out to evaluate treatment arms containing irinotecan and fluorouracil regimens, no significant differences were seen in grade 3 or worse adverse event rates when comparing patients younger than 40 years with those age 40 years or older (Appendix Table A8, online only). Patients younger than 50 years, however, had lower rates of diarrhea (16% *v* 22%; OR, 0.58; $P = .006$) and neutropenia (29% *v* 36%; OR, 0.62; $P = .006$) than did those age 50 years or older.

Efficacy

All trials. RRs were virtually identical when comparing patients younger than 40 years of age to those age 40 years or older (41% *v* 43%; OR, 1.01; $P = .96$) and those younger than 50 years to those age 50 years or older (42% *v* 43%; OR, 1.02; $P = .84$). The median PFS did not significantly differ for patients age younger than 40 years and those 40 years or older (5.9 *v* 7.4 months; hazard ratio [HR], 1.05; $P = .54$; Fig 1A). The median PFS was worse when comparing patients younger

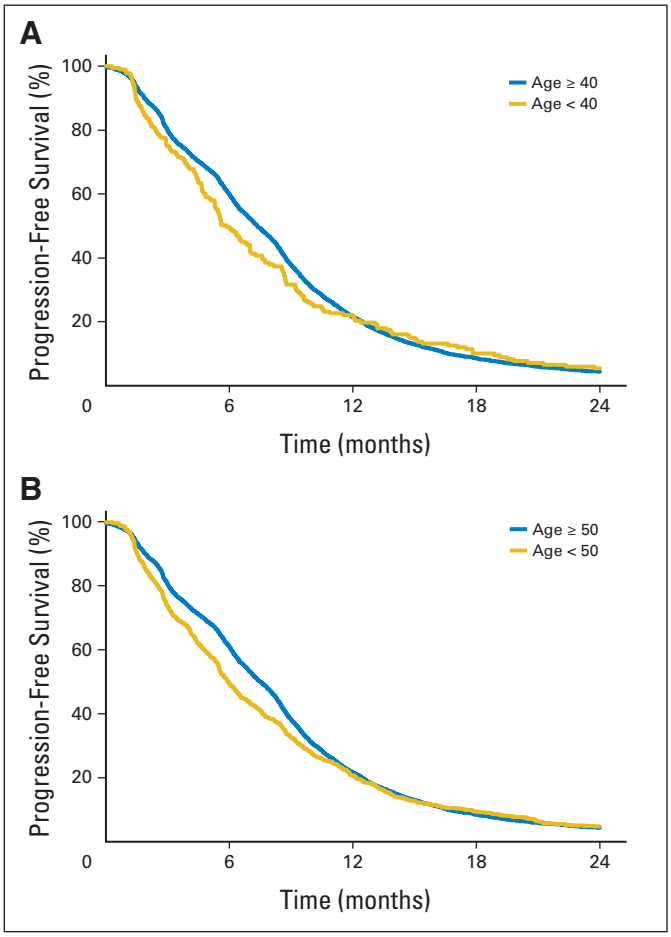

Fig 1. Progression-free survival in all trials (N = 6,284). (A) Younger than 40 years old versus 40 years or older. (B) Younger than 50 years old versus 50 years or older.

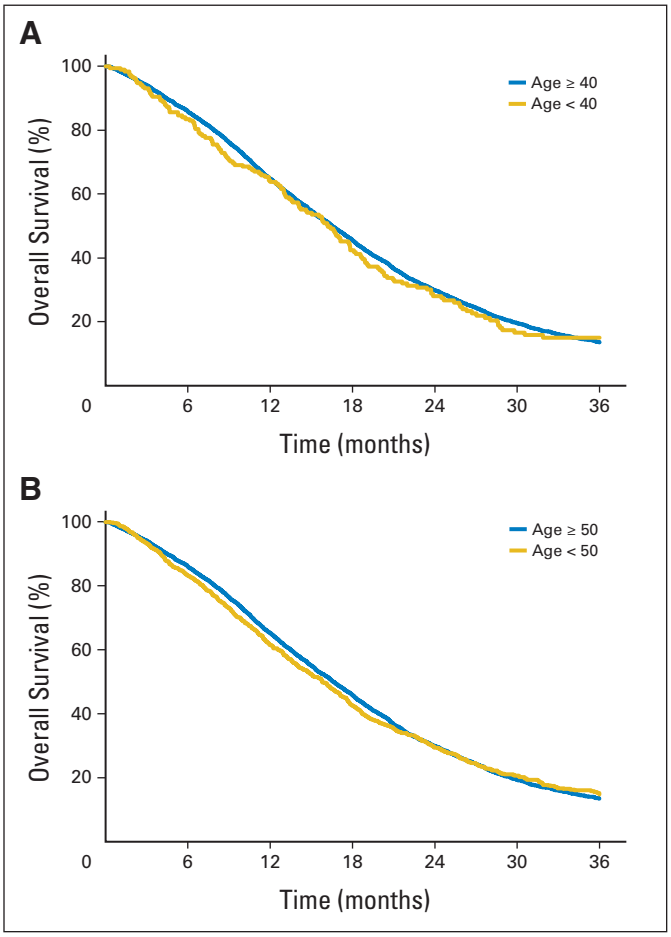

Fig 2. Overall survival in all trials (N = 6,284). (A) Younger than 40 years old versus 40 years or older. (B) Younger than 50 years old versus 50 years or older.

than 50 years to those age 50 years or older (6.0 *v* 7.5 months; HR, 1.10; $P = .02$; Fig 1B). The median OS did not differ in the cohort of patients younger than 40 years versus those age 40 years or older (16.2 *v* 16.5 months; HR, 1.04; $P = .61$; Fig 2A) or in those younger than 50 years versus those age 50 years or older (15.8 *v* 16.6 months.; HR, 1.03; $P = .48$; Fig 2B).

Oxaliplatin-Containing Arms

The RRs were numerically lower in patients who were younger than 40 years or age compared with those age 40 years or older, though the difference was not statistically significant (41% *v* 56%: OR, 0.58; $P = .08$). The RRs were similar for patients younger than 50 years or age versus those age 50 years or older (54% *v* 56%; OR, 0.94; $P = .66$). The median PFS was shorter for those patients younger than 40 years compared with those age 40 years or older (6.7 *v* 8.6 months; HR, 1.36; $P = .05$; Appendix Fig A1A, online only). The PFS in patients younger than 50 years or age versus those 50 years or older and the OS in both cohorts comparing young versus older ages did not differ (Appendix Figs A1B, A2A, and A2B, online only).

Irinotecan-Containing Arms

The RRs were comparable in young versus older patients for both age cut points of 40 years (45 *v* 46%; OR, 1.06; $P = .83$) and 50 years (48 *v* 46%; OR, 1.16; $P = .31$). The PFS and OS did not significantly different in young versus old patients when using either age cut point (survival curves not shown).

Monotherapy Versus Combination Chemotherapy Subset

We repeated our previous analyses in the subset of five trials that tested fluorouracil-based monotherapy and combinations of oxaliplatin or irinotecan with fluorouracil. The RR for monotherapy versus combination chemotherapy in patients younger than 40 years were 31% and 51%, respectively (OR, 2.79; 95% CI, 1.13 to 6.90; Table 2). The RR for the same comparison in patients age 40 years and older were 29% and 51%, respectively (OR, 2.69; 95% CI, 2.33 to 3.11). No evidence of an age-by-chemotherapy interaction emerged ($P = .78$), providing evidence that younger and older patients did not receive differential benefit from combination therapy in terms of RR. The RR for monotherapy versus combination chemotherapy in those patients younger than 50 years were 28% and 54%, respectively (OR, 3.29; 95% CI 2.18 to 4.96; Appendix Table A9, online only); the RR for the same comparison in those age 50 years or older were 29% and 51%, respectively (OR, 2.63; 95% CI 2.26 to 3.06). The age-by-chemotherapy interaction was again not significant, for which $P = .43$.

The median PFS for monotherapy versus combination chemotherapy was 4.7 versus 6.5 months in those patients younger than 40

Table 2. Relative Treatment Benefit in Five Monotherapy Versus Combination Chemotherapy Trials in Patients Younger Than 40 Years Versus 40 Years or Older

Treatment Benefit Variable	Age Group										
	Younger Than 40 Years					40 Years or Older					
	Mono	Combo	HR/OR†	95% CI	*P*	Mono	Combo	HR/OR†	95% CI	*P*	Interaction *P**
Median PFS, months	4.7	6.5	0.70	0.45 to 1.08	.10	6.1	8.3	0.73	0.68 to 0.78	< .001	.69
Median OS, months	13.3	15.0	0.95	0.62 to 1.47	.82	14.7	16.6	0.87	0.81 to 0.94	< .001	.84
RR, %	31	51	2.79	1.13 to 6.90	.03	29	51	2.69	2.33 to 3.11	< .001	.78

Abbreviations: Mono, monotherapy; combo, combination therapy; HR, hazard ratio; OR, odds ratio; PFS, progression-free survival; OS, overall survival; RR, response rate.
**P* value testing for age by chemotherapy interaction.
†HR of PFS/OS; OR for RR.

years (HR, 0.70; 95% CI 0.45 to 1.08) and 6.1 versus 8.3 months in those age 40 years or older (HR, 0.73; 95% CI, 0.68 to 0.78; Figs 3A and 3B). For the test for an age-by-chemotherapy interaction, $P = .69$. The median PFS for monotherapy versus combination chemotherapy was 4.7 versus 7.2 months in those younger than 50 years (HR, 0.64; 95% CI, 0.52 to 0.78) and 6.2 versus 8.4 months in those age 50 years or older (HR, 0.74; 95% CI, 0.69 to 0.80; Appendix Fig A3A and A3B, online only). For the age-by-treatment interaction, $P = .11$, which provided no evidence that younger patients received less PFS benefit from combination chemotherapy than did older patients.

The median OS for monotherapy versus combination chemotherapy was 13.3 versus 15 months in those patients younger than 40 years (HR, 0.95; 95% CI, 0.62 to 1.47) and 14.7 versus 16.6 months in those age 40 years or older (HR, 0.87; 95% CI, 0.81 to 0.94; Figs 4A and 4B). For the age-by-chemotherapy interaction, $P = .84$. The median OS for monotherapy versus combination chemotherapy was 13.5

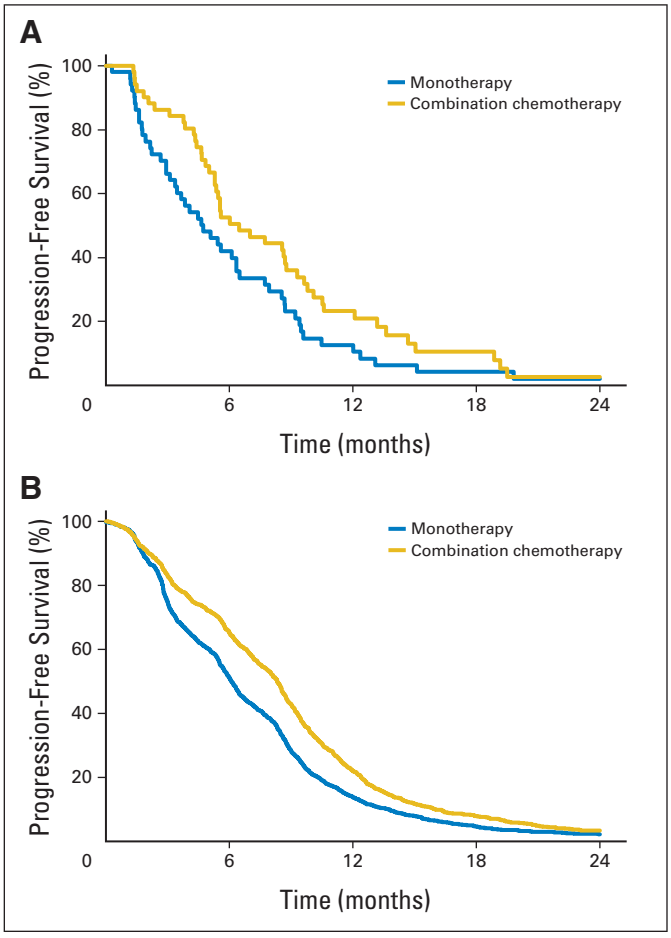

Fig 3. Relative treatment benefit (ie, progression-free survival) in five monotherapy versus combination chemotherapy trials (N = 3,813). (A) Younger than 40 years old. (B) Forty years or older.

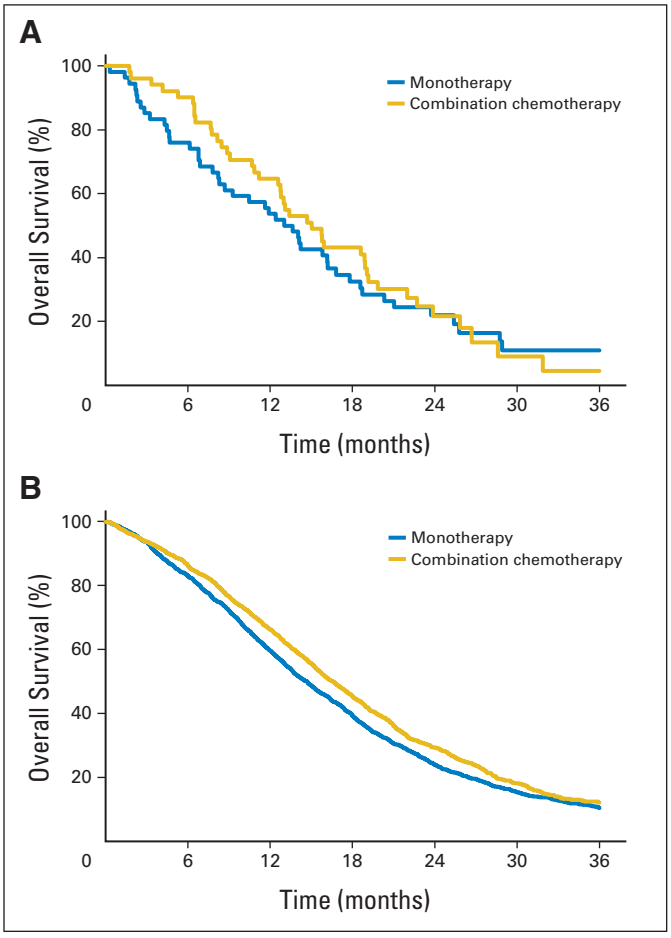

Fig 4. Relative treatment benefit (ie, overall survival) in five monotherapy versus combination chemotherapy trials (N = 3,813). (A) Younger than 40 years old. (B) Forty years or older.

versus 16.3 months in those patients younger than 50 years (HR, 0.82; 95% CI, 0.67 to 1.02) and 14.8 versus 16.5 months in those patients age 50 years or older (HR, 0.89; 95% CI, 0.82 to 0.96; Appendix Figs A4A and A4B, online only). Testing for an age-by-chemotherapy interaction yielded $P = .57$, which provided no evidence of a differential level of OS benefit of combination therapy in patients younger than 40 or younger than 50 years.

DISCUSSION

Although rare in young adults, colorectal cancer can occur before age 40 years, and the incidence in the younger population has increased recently, whereas it has remained fairly flat or has declined modestly in those of more elderly age.[3] Questions have been raised as to whether the biology of the disease is different in the young—specifically, whether the disease is inherently more aggressive, as well as whether the young respond differently to systemic therapy. Outcomes for adolescents and young adults with a variety of cancer types are worse, but usually these data apply to pediatric tumors (eg, sarcomas, leukemias) that affect a slightly older than usual population. In general, epithelial neoplasms have not been well studied.[21,22] Young patients with colorectal cancers tend to present at a more advanced stage (the majority at stage III or worse), which may reflect differing biology but which might also be explained by differing practice patterns before diagnosis according to the age of the patient (eg, elderly general population patients might be more likely to get screening colonoscopies, rectal exams, or stool guiac testing compared with younger patients). Stage-adjusted outcomes tend to be similar in the young versus older patients.[6]

Inherited syndromes, such as familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (HNPCC), are more common in the young, and at least HNPCCs tend to behave less aggressively, in that those with HNPCC-associated aCRCs have better survival.[7] The impact of potentially associated genetic factors complicates matters. Microsatellite instability (MSI) is a hallmark of HNPCCs, and recent data have suggested that fluorouracil-based chemotherapy does not benefit patients with high-MSI tumors.[7,8] However, the majority of these data were derived from patients in the adjuvant setting. The effect on patients with metastatic disease, especially when fluorouracil is also combined with modern drugs, is difficult to discern. There is a paucity of information regarding regimens that contain oxaliplatin, and some limited data suggest that MSI (not necessarily related to age) is a positive predictor of response to irinotecan-based regimens (data also derived from the adjuvant setting).[23] The percentage of patients with high-MSI disease on our study is not known; regardless, inherited syndromes still only account for a small fraction of large bowel neoplasms in the young.

Other important questions are whether or not young patients are well represented on clinical trials and, indirectly, whether trial results apply to the young population. Bleyer et al[22] suggested that the lack of improvement in outcomes for the adolescent and young adult population over the last 40 years may relate to lower rates of participation in clinical studies.[22] Patients age 50 years or younger represented 13% of all the patients entered onto the aCRC trials we studied. In the general population, patients younger than 50 years of age comprise only 4.6% of those with colorectal cancer[3]; thus, if anything, younger patients were over-represented in the individual studies and on our study as a whole. Although this could reflect the more advanced stage at presentation of adolescent and young adult patients with CRC, similar patterns have been observed in adjuvant colorectal cancer trials (Sargent et al, manuscript in preparation). This suggests that the lower rates of participation by adolescent and young adult patients with pediatric cancers in clinical trials are not recapitulated in clinical studies of adult cancers. The subtype-specific dependence on trial participation may reflect the fact that adolescent and young adult patients are overwhelmingly treated in adult cancer settings as well as reflect the relatively poor penetration of this market by pediatric trials compared with adult studies. It is also interesting to speculate whether the age-dependent disparity in outcomes for adolescents and young adults with colorectal cancer relative to pediatric cancers (stage for stage) is related to the relatively good participation of adolescent and young adult patients of in trials of the former but not in the latter.

In our analyses, younger and older patients in general had similar outcomes. RRs, PFS, and OS did not significantly differ for those younger than 40 years compared with those age 40 years or older. RR and OS were similar in those younger than 50 years and those age 50 years or older; PFS was minimally worse in the younger cohort (6.0 *v* 7.5 months; $P = .02$), which was likely a spurious finding arising from chance alone. When assessing oxaliplatin-containing chemotherapy in those younger than 40 years compared with those age 40 years or older and in those younger than 50 years versus those age 50 years or older, the only efficacy parameter that differed was PFS, which was shorter in the patients younger than 40 years of age (6.7 *v* 8.6 months in those age 40 years or older; $P = .05$). Given the large number of comparisons made, it is quite possible that these two significant findings were also a result of chance. The demonstration that OS did not significantly differ in any age comparison also minimizes the clinical relevance of the observed PFS differences. No efficacy differences were seen by age in assessing the potential effect of irinotecan-containing systemic therapy. Additionally, it should be noted patients at the youngest extreme are rare and were not well represented, even on our study.

Toxicity patterns varied mildly by age. The youngest (younger than 40 years of age) had more nausea but less neutropenia than older patients; those younger than 50 years, compared with those age 50 years or older, had similar patterns of relative toxicity as well as less diarrhea. No differences in the various age groups were seen when specifically assessing oxaliplatin-containing chemotherapy. In assessing the irinotecan-containing arms, patients younger than 50 years of age had less diarrhea and neutropenia than did those age 50 years and older. Other chemotherapy trials have shown higher rates of vomiting, diarrhea, and dehydration in elderly patients who received the irinotecan, bolus fluorouracil, and leucovorin regimen[12]; with oxaliplatin-based chemotherapy, the elderly experience more neutropenia and thrombocytopenia.[24] None of the differences we observed were of sufficient magnitude to influence clinical practice.

A key question is whether younger and older patients receive different benefits from the newer combination chemotherapy regimens. In our analyses, younger patients derived the same magnitude of benefit from combination chemotherapy and single-agent treatment. This was manifested by similar levels of improvements in RR, PFS, and OS in each age group. ORs for response (single-agent *v* combinations) and HRs for the comparison of PFS and OS were quite similar in the patients younger than 40 years of age and those age 40 years or older as well as in the patients younger than 50 years of age and

those age 50 years or older. Although there was no major differential effect seen with the regimens utilized in the studies included in our analysis, it remains possible that younger patients might be fitter and better able in general to tolerate more intense programs, such as fluorouracil, oxaliplatin, and irinotecan.[25] This could, theoretically, lead to better outcomes in younger patients.

In summary, this pooled analysis has demonstrated that younger age is not associated with meaningfully poorer outcomes in patients with aCRC. Younger patients also derive the same level of benefit from combination chemotherapy. Toxicity patterns do not vary sufficiently to change therapeutic recommendations on the basis of patient age. Young adult participation rates in aCRC clinical trials appears better than those seen in patients with pediatric cancer types, but only a small fraction of those with aCRC enter onto studies. In the absence of an applicable clinical trial, combination chemotherapy remains the appropriate standard of care for younger patients with aCRC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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