Comparison of Outcomes After Fluorouracil-Based Adjuvant Therapy for Stages II and III Colon Cancer Between 1978 to 1995 and 1996 to 2007: Evidence of Stage Migration From the ACCENT Database

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ABSTRACT

Purpose

With improved patient care, better diagnosis, and more treatment options after tumor recurrence, outcomes after fluorouracil (FU)-based treatment are expected to have improved over time in early-stage colon cancer. Data from 18,449 patients enrolled onto 21 phase III trials conducted from 1978 to 2002 were evaluated for potential differences in time to recurrence (TTR), time from recurrence to death (TRD), and overall survival (OS) with regard to FU-based adjuvant regimens.

Methods

Trials were predefined as old versus newer era using initial accrual before or after 1995. Outcomes were compared between patients enrolled onto old- or newer-era trials, stratified by stage.

Results

Within the first 3 years, recurrence rates were lower in newer- versus old-era trials for patients with stage II disease, with no differences among those with stage III disease. Both TRD and OS were significantly longer in newer-era trials overall and within each stage. The lymph node (LN) ratio (ie, number of positive nodes divided by total nodes harvested) in those with stage III disease declined over time. TTR improved slightly, with larger number of LNs examined in both stages.

Conclusion

Improved TRD in newer trials supports the premise that more aggressive intervention (oxaliplatin- and irinotecan-based chemotherapy and/or surgery for recurrent disease) improves OS for patients previously treated in the adjuvant setting. Lower recurrence rates with identical treatments in those with stage II disease enrolled onto newer-era trials reflect stage migration over time, calling into question historical data related to the benefit of FU-based adjuvant therapy in such patients.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and third leading cause of cancer death in Western countries.¹⁻³ From the late 1950s to the mid 1990s, fluorouracil (FU) was the only effective chemotherapeutic drug for the treatment of CRC. Modulation of FU by leucovorin (LV) enhances the therapeutic effect (response rate) to FU in metastatic colorectal carcinoma.^{4,5} Intergroup trial INT-0035 was the first large-scale study to demonstrate a significant benefit of adjuvant treatment in patients with stage III colon cancer (CC) with FU plus levamisole.⁶ FU bolus and LV⁶ administered as either the Mayo Clinic or Roswell Park regimen became standard chemotherapy for stage III colon cancer in

1996^{7,8} and is an option for the treatment of patients with stage II disease.⁹

The ACCENT (Adjuvant Colon Cancer Endpoints) Group previously assessed clinical outcomes for patients with FU-based therapy as compared with observation-only control patients with resected stage II or III CC, based on individual patient data from 18 randomized phase III trials. This pooled analysis revealed that FU-based regimens were associated with curative benefit, as opposed to only delaying recurrence, because the risk of recurrence in patients treated with adjuvant chemotherapy never exceeded that of patients in the control arms. This treatment benefit was reflected in improved disease-free survival, mostly within the first 2 years of receiving an FU-based regimen after surgery, which

translated into an overall survival (OS) benefit over the 8-year follow-up period.¹⁰

In the metastatic setting, combination chemotherapy with FU/LV and oxaliplatin^{11,12} or irinotecan¹³⁻¹⁶ has resulted in improved outcomes and prolonged survival when compared with FU/LV alone. Irinotecan received European approval in France in 1995 and accelerated approval by the US Food Drug Administration in 1996. Oxaliplatin received European approval in France in 1996 and approval by the US Food and Drug Administration in 2002. With these advances in treating advanced CC, patients with early-stage disease now have access to these agents on tumor recurrence. Concurrent to the introduction of these newer therapies for metastatic disease, in 2000, new standards for surgical resection and pathologic evaluation were implemented.¹⁷ In particular, the practice guideline of histopathologic examination of a minimum of 12 lymph nodes (LNs) as adequate to declare stage II disease became an accepted standard.

Individual patient data from large trials in the adjuvant setting, assembled by the ACCENT group, provide the opportunity to examine clinical outcomes over an extended time period (from 1978 to 2002) in patients with stage II or III CC receiving protocol-specified FU-based chemotherapy. The goal of the current analysis was to examine whether time to recurrence (TTR), time from recurrence to death (TRD), and OS have changed over decades in

patients treated with FU-based chemotherapy regimens. We further evaluated whether the outcomes over time were altered by stage (II v III) or other patient characteristics, including age, T stage, and number of LNs examined.

METHODS

This analysis focused on patients treated with similar FU-based regimens (eg, FU/LV $\pm$ levamisole or FU/levamisole) over time from 21 trials included in the ACCENT database. Patients undergoing surgery alone or receiving oxaliplatin, irinotecan, or oral fluoropyrimidines were excluded. Approval for this analysis was granted by the Mayo Clinic Investigational Review Board; individual trials were approved through local mechanisms at the time trials were conducted. Patients enrolled onto adjuvant trials after 1995 likely had oxaliplatin and irinotecan as treatment options on tumor recurrence, and therefore, we prespecified the time cutoff of January 1, 1995, for initiation of trial accrual to define newer- versus old-era trials. OS was defined as time from random assignment to death resulting from any cause. For the purpose of this analysis, TTR was defined as time from random assignment to disease recurrence (first local, regional, or distant relapse and second primary colon cancer), with death without recurrence censored at time of death. Other non-CCs were not considered as events for TTR. TRD was defined as time from first recurrence to death as a result of any cause.

The distributions of time-to-event outcomes were estimated using Kaplan-Meier methods and compared between newer- and old-era trials using

Fig 1. In patients with (A, B) stage II and (C, D) stage III disease, (A, C) recurrence and (B, D) mortality rates by time since random assignment. Risk of recurrence was calculated as the number of recurrences within each of the 6-month windows divided by the number of patients at risk (recurrence free) at the start of each interval. Risk of mortality was calculated in the same fashion.

a log-rank test. Hazard ratios (HRs) and 95% CIs were estimated using the Cox proportional hazards model. Multivariate Cox proportional hazards models were used to assess the adjusted associations, with adjustment for age and sex. Median follow-up for living patients was 10.2 and 6.0 years for old- and newer-era trials, respectively. All analyses were conducted with two-sided tests and a significance level of .05.

RESULTS

Thirteen trials with 10,269 patients were included in the old-era category, with eight trials with 8,180 patients in the newer-era set (Appendix Table A1, online only); 2,334 patients (13%) received FU/

Fig 2. Comparison of clinical outcomes between newer- and old-era trials. In patients with (A, C, E) stage II and (B, D, F) stage III disease, (A, B) time to recurrence, (E, F) time from recurrence to death, and (C, D) overall survival. HR, hazard ratio; KM Est, event-free rate at given time point (36 or 60 months) estimated based on Kaplan-Meier method.

levamisole, 12,792 (69%) received FU/LV, and 3,323 (18%) received FU/levamisole and LV. In both eras, 54% of patients were male. The median age was 62 and 61 years for old- and newer-era trials, respectively. A total of 6,054 patients experienced disease recurrence, and 6,177 patients died.

Overall, those who received an FU-based regimen in newer-era trials experienced significantly longer OS than patients in old-era trials (stage-adjusted HR, 0.78; 95% CI, 0.74 to 0.82; $P < .001$). This association was explained by significantly prolonged TRD for newer- versus old-era trials (stage-adjusted HR, 0.63; 95% CI, 0.60 to 0.67; $P < .001$). The median TRD was 20.5 months for newer- versus 12.9 months for old-era trials. TTR did not differ between eras (stage adjusted HR, 0.97; 95% CI, 0.92 to 1.02; $P = .25$).

Analyses by Stage

Interaction testing demonstrated a significant interaction between trial era and stage for both TTR ($P < .001$) and OS ($P = .0029$). Additional analyses were therefore performed by stage.

Patients With Stage II Disease

The pattern of recurrence and mortality in the newer- versus old-era trials was estimated by 6-month intervals (Figs 1A to 1D). Overall, 74% of recurrences occurred within 3 years after surgery for those with stage II disease. Over the entire period, the recurrence rate at each time point was lower in newer- than old-era trials (Fig 1A). Larger differences were observed during first 2 years after surgery, compared with later years (> 4 years) after surgery. Consistent with the recurrence rate, the mortality rate (Fig 1B) in patients in the newer era was always lower than that in patients in the old era over the estimation time period.

For patients with stage II disease treated with FU-based chemotherapies, the HR for TTR comparing newer- with old-era trials was 0.76 (95% CI, 0.67 to 0.87; $P < .001$; Fig 2A). Of note, patients who experienced recurrence in newer-era trials had longer TRD than patients in old-era trials (HR, 0.62; 95% CI, 0.52 to 0.73; $P < .001$; Fig 2E). There was an 18% absolute increase in the 3-year survival rate after recurrence in newer- (43%) compared with old-era trials (25%). The significant gains in TTR and TRD translated into OS improvement. Patients with stage II disease treated with an FU-based regimen in newer-era trials showed a 6% absolute reduction in 5-year mortality rate compared with patients in old-era trials (11% v 17%), with an HR of 0.67 (95% CI, 0.58 to 0.76; $P < .001$; Fig 2C).

Patients With Stage III Disease

The pattern of recurrence (Fig 1C) over time was substantially different for patients with stage III compared with those with stage II disease. For both newer- and old-era trials, the risk of recurrence was clearly highest in the year after surgery, with a rapid reduction until approximately the fourth year of follow-up. The recurrence-rate curves by era were virtually superimposable within 1 year and subsequently crossed over at several time points. For old- and newer-era trials, 81% and 83% of recurrences occurred within 3 years after surgery, respectively. However, the mortality-rate pattern over time (Fig 1D) showed that patients enrolled onto newer-era trials with FU-based regimens had improved OS over the entire time period.

A significant prolongation of OS was observed in patients with stage III cancers in newer-era trials, with an HR of 0.80 (5-year rate, 71% and 64% in newer- and old-era trials, respectively; $P < .001$; Fig

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Old-Era Trials (1987 to 1994)		Newer-Era Trials (1995 to 2002)		<i>P</i> *
	No.	%	No.	%	
Total No. of trials	13		8		
Total No. of patients	10,269		8,180		
Regimens	FU/LV; FU + levamisole; FU/LV + levamisole		FU/LV; FU/LV + levamisole		
Age, years					$< .001$
Missing	0		1		
Median	62		61		
Range	15-90		19-85		
Age group, years					.4143
Missing	0		1		
≥ 75	1,833	17.8	1,498	18.3	
< 75	8,436	82.2	6,681	81.7	
Sex					.4368
Missing	0		3		
Male	5,527	53.8	4,448	54.4	
Female	4,742	46.2	3,729	45.6	
Stage					$< .001$
Missing	1		16		
II	3,205	31.2	2,158	26.4	
III	7,063	68.8	6,006	73.6	
T stage					$< .001$
Missing	144		932		
T1/2/is	2,111	20.8	677	9.3	
T3	6,862	67.8	5,770	79.6	
T4	1,152	11.4	801	11.1	
No. of LNs examined					$< .001$
Missing	603		1,068		
≥ 12	4,263	44.1	4,041	56.8	
< 12	5,403	55.9	3,071	43.2	

Abbreviations: FU, fluorouracil; LV, leucovorin; LN, lymph node.

*Two-sample *t* test for continuous age; χ^2 test for categorical factors.

2D). There was no significant evidence of differences in TTR between newer- and old-era trials (5-year recurrence rate, 62% for both newer- and old-era trials; $P = .64$; Fig 2B). However, patients with stage III cancers enrolled after 1995 treated with an FU-based regimen survived longer after disease recurrence than patients enrolled before 1995 (HR, 0.64; 95% CI, 0.60 to 0.68; $P < .001$; Fig 2F).

Analyses by LN

A higher proportion of patients in newer-era trials (57%) had ≥ 12 LNs examined than those in old-era trials (44%; $P < .001$; Table 1). For all three outcomes, when patients with stages II and III disease were pooled, HRs for patients in newer- versus old-era trials were similar among those with ≥ 12 LNs and < 12 LNs examined (Appendix Figs A1A to A1C, online only). Figures 3A and 3B show comparisons of TTR by ≥ 12 LNs versus < 12 LNs examined, further stratified by stage. Among patients with stage II disease, there was a clear separation in the Kaplan-Meier curves between newer- versus old-era trials for those with ≥ 12 LNs examined and for those with < 12 LNs examined ($P < .001$). However, in patients with stage III disease, there were no statistically significant differences in TTR between newer- and old-era patients with either ≥ 12 or < 12 LNs examined ($P = .11$).

Fig 3. Comparison of time to recurrence stratified by time era and lymph nodes (LNs) examined in patients with (A) stage II and (B) stage III disease. KM Est, event-free rate at given time point (36 or 60 months) estimated based on Kaplan-Meier method.

We further examined LN-related measures in a continuous form. Overall, the mean and median numbers of histopathologically evaluated LNs increased by 16% and 30%, respectively, between old- and newer-era trials (Table 2). However, in patients with stage III disease, the number of positive LNs increased by only 6%, and the ratio of positive to evaluated nodes declined (Table 2). TTR improved slightly with larger number of LNs examined in both patients with stage II and

III disease, but it declined in patients with stage III disease with increasing numbers of positive LNs and with higher LN ratios (Table 3).

Analyses by Other Factors

Appendix Figures A1A to A1C (online only) show comparisons of TTR, TRD, and OS in newer- versus old-era trials by subpopulation defined by T stage, number of LNs examined, and age group. P values

Table 2. Comparisons of LN-Related Measures Between Newer- and Old-Era Trials

LNs	All Patients				Patients With Stage III Disease			
	Newer Era (n = 7,097)	Old Era (n = 9,609)	Total (N = 16,706)	P^*	Newer Era (n = 7,097)	Old Era (n = 9,609)	Total (N = 16,706)	P^*
Total evaluated LNs				$< .001$				$< .001$
No.	7,097	9,609	16,706		4,972	6,693	11,665	
Mean	15.0	12.9	13.7		14.9	12.8	13.7	
SD	10.1	9.6	9.9		10.0	9.5	9.8	
Median	13.0	10.0	11.0		13.0	10.0	11.0	
Range	1.0-99.0	1.0-116.0	1.0-116.0		1.0-99.0	1.0-116.0	1.0-116.0	
Total positive LNs				.0035				.0024
No.	7,091	9,608	16,699		4,967	6,692	11,659	
Mean	2.5	2.4	2.4		3.6	3.4	3.5	
SD	3.5	3.1	3.3		3.6	3.2	3.4	
Median	1.0	1.0	1.0		2.0	2.0	2.0	
Range	0.0-38.0	0.0-44.0	0.0-44.0		1.0-38.0	1.0-44.0	1.0-44.0	
LN ratio (positive to evaluated)				$< .001$				$< .001$
No.	7,091	9,608	16,699		4,967	6,692	11,659	
Mean	0.21	0.24	0.23		0.30	0.34	0.32	
SD	0.25	0.27	0.26		0.25	0.27	0.26	
Median	0.13	0.14	0.13		0.22	0.25	0.25	
Range	0.00-1.00	0.00-1.00	0.00-1.00		0.01-1.00	0.01-1.00	0.01-1.00	

Abbreviations: LN, lymph node; SD, standard deviation.

*Unequal variance t test.

Table 3. Univariate Association Between LN Variables and Time to Recurrence

Patient Population	No. of LNs Examined*			No. of Positive LNs*			LN Ratio†		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
All patients	0.992	0.989 to 0.995	< .001	1.114	1.109 to 1.119	< .001	1.184	1.174 to 1.194	< .001
Patients with stage II disease	0.975	0.967 to 0.983	< .001	NA			NA		
Patients with stage III disease	0.996	0.993 to 0.999	.0192	1.096	1.090 to 1.103	< .001	1.152	1.141 to 1.164	< .001

Abbreviations: HR, hazard ratio; LN, lymph node; NA, not applicable.

*One LN increase.

†0.1 unit increase.

for interaction testing between trial era and patient characteristics of interest are listed in Appendix Table A2 (online only) for TTR, TRD, and OS. Patients with T1/2/cancers had substantially longer TTR in both univariate and multivariate models (Fig 3), with a 3-year recurrence-free rate of 86.6% (95% CI, 83.8% to 89.0%) versus 76.8% (95% CI, 74.9% to 78.6%) in newer- compared with old-era trials. In T3 cancers, the 3-year recurrence-free rates were similar between newer- and old-era trials (72.9%; 95% CI 71.7% to 74.0% v 73.0%; 95% CI, 71.9% to 74.0%). However, patients with T4 cancers in newer-era trials had a higher recurrence risk compared with those in old-era trials, with a 3-year recurrence-free rate of 57.4% (95% CI, 53.8% to 60.8%) versus 62.1% (95% CI, 59.2% to 64.9%).

DISCUSSION

In this analysis, we compared OS and its components, TTR and TRD, in patients who received FU-based chemotherapy in adjuvant CC trials before and after 1995, proximal to the time that irinotecan and/or oxaliplatin became available for the subsequent treatment of recurrent disease. OS was clearly improved in newer- compared with old-era trials, with significantly longer TRD but not longer TTR. Variations in schedule of FU administration were unlikely to have substantially contributed to this difference, because multiple trials have demonstrated no significant differences in efficacy among variations of FU-based regimens.^{7,8,18,19} Our results support the concept that access to better salvage treatments, including irinotecan, oxaliplatin, and/or surgery, for recurrence provides benefit to OS by prolonging survival after recurrence.

Patients with stage II disease enrolled onto newer-era trials had longer TTR than patients in old-era trials. However, there was no difference in TTR between patients with stage III disease enrolled onto old- and newer-era trials. If within stage, the patients were indeed homogeneous in terms of recurrence risk at initiation of adjuvant therapy and then received the same chemotherapy, presumably the TTR would not differ between old- and newer-era trials. This seems to be true for patients with stage III disease but not for those with stage II disease. One of the most important determinants of prognosis in patients with CC is the extent of LN involvement. As early as 1991, it was recommended that at least 12 nodes be sampled to stage a patient adequately.²⁰ Among patients included in our analysis, we found that more LNs were examined in newer- versus old-era trials, resulting in stage migration through the Will Rogers phenomenon.²¹ Although the resection technique has not changed substantially, staging is more accurate because of the increased number of LNs examined by pathologists in newer- versus old-era trials. In essence, in the old-era trials, a

higher proportion of patients classified as having stage II disease actually had undiagnosed LN involvement (stage III disease) because of suboptimal nodal staging.²¹ This finding brings into question the validity of some of the conclusions derived from older trials in stage II CC with regard to the reported efficacy of FU-based adjuvant therapy, because the results were conceivably compromised by a proportion of patients with undiagnosed stage III disease who therefore received stage III–like benefit from adjuvant therapy. Subgroup analyses restricted to just those patients in prior trials considered adequately staged by present criteria demonstrating a benefit of FU-based adjuvant therapy in patients with stage II disease are unfortunately not available. However, these data further emphasize the need for improved decision-making tools for adjuvant therapy in patients with stage II disease. The better prognosis of T1/2 disease in newer- versus old-era trials and of T4 disease in old- versus newer-era trials may be explained by the evolution of TNM classification and better definition of T stage over time.

An intriguing finding is that in patients with stage II disease with ≥ 12 LNs examined, TTR was still significantly prolonged in newer- versus old-era trials. This likely indicates the presence of undetected stage III disease in old-era trials even in patients with ≥ 12 LNs examined. The changing definition of LN metastasis without evidence of lymphoid tissue as compared with extranodal tumor deposit in TNM classification may be one of the possible explanations. Nonetheless, this finding supports the notion that the quality of LN evaluation matters, and the increasing numbers of LNs examined in the newer-era trials certainly reflect the more modern pathology practices resulting from the emphasis of professional organizations on the importance of LN harvesting.

The median time between relapse and death was 20.5 months for newer-era trials, which is both statistically and clinically significantly longer than the 12.9 months observed in old-era trials (data not shown). The era-based TRD in our analysis is almost identical to the OS reported in clinical trials for these eras in patients with advanced CRC. One possible explanation is that some patients with metastatic relapse in new trials underwent surgery for their metastasis with curative intent. Since 1990, and particularly after 1995, the use of postrecurrence metastasectomy has increased long-term survival in selected patients.²² Although in newer-era studies more patients had access to such surgery, use was still limited. The more broadly applicable explanation is likely that the newer-era patients had access to palliative therapy, including oxaliplatin and irinotecan, both of which have been shown to increase OS in patients with metastatic disease.²³ In old-era trials, all adjuvant studies were carried out before the approval of oxaliplatin and irinotecan. The observed median OS after relapse

(TRD) of 20.5 months in newer-era trials is now close to the OS observed for patients with an initial diagnosis of metastatic disease, which reflects progress in the management of metastatic CRC based on a multidisciplinary approach (surgery for metastasis, use of oxalip- latin and irinotecan, bevacizumab, cetuximab, and panitumumab). In the GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) C96-1 study, included in the group of newer-era trials in our analysis, the high proportion of patients (38%) undergoing surgery for meta- static relapse underscores the importance of routine follow-up after adjuvant therapy and of addressing recurrence.¹⁹ Finally, improved surveillance and imaging techniques may have introduced lead-time bias in newer-era trials, where recurrences were simply detected ear- lier. However, the studies included in our analysis used standard surveillance schedules that did not meaningfully evolve over the study period.

FU continues to serve as the backbone for combination regimens with targeted agents in both adjuvant and metastatic settings. The recognition of prolonged survival, especially prolonged TRD in the modern era, contributes valuable insights into the design of clinical trials testing innovative regimens, including better end point selection and more accurate projection of the treatment effect. De Gramont et al²⁴ showed that longer follow-up will be needed to demonstrate a treatment effect on OS in modern adjuvant trials because of the pro- longed TRD. Their results were based on simulations in which TRD of patients in both experimental and control arms was extended in the same fashion, without changing TTR. The results observed in our analysis clearly support that longer follow-up for OS is necessary, because OS was improved in newer-era trials, with most of the contri- bution from improved TDR. This prolonged OS in both arms may artificially reduce the apparent treatment effect of newer adjuvant agents if OS is chosen as the primary efficacy end point in future studies. This finding reinforces consideration of disease-free survival as the primary end point in adjuvant CC studies to capture the net benefit of a newer therapy in a timely fashion.²⁵ Our data also empiri- cally support that stage migration has occurred in clinical practice

among patients with stage II disease, so that the recurrence rate in current patients with stage II disease is low. Efficacy of FU-based adjuvant therapy in adequately staged patients with stage II disease requires further evaluation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(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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Appendix

The ACCENT (Adjuvant Colon Cancer Endpoints) Group consists of: D.J. Sargent, E. Green, A. Grothey, S.R. Alberts, B. Bot, M. Campbell, Q. Shi (Mayo Clinic, Rochester, MN); G. Yothers, M.J. O'Connell, N. Wolmark (NSABP [National Surgical Adjuvant Breast and Bowel Project] Biostatistical and Operations Centers, Pittsburgh, PA); A. de Gramont (Hôpital Saint Antoine, Paris, France); R. Gray, D. Kerr (QUASAR [Quick and Simple and Reliable] Collaborative Group, Birmingham and Oxford, United Kingdom); D.G. Haller (Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA); J. Benedetti (SWOG [Southwest Oncology Group] Statistical Center, Seattle, WA); M. Buyse (IDDI, [International Drug Development Institute], Louvain-la-Neuve, Belgium); R. Labianca (Ospedali Riuniti, Bergamo, Italy); J.F. Seitz (University of the Mediterranean, Marseilles, France); C.J. O'Callaghan (NCIC-CTG [National Cancer Institute of Canada Clinical Trials Group], Queens University, Kingston, Ontario, Canada); G. Francini (University of Siena, Siena, Italy); P.J. Catalano (ECOG [Eastern Cooperative Oncology Group] Statistical Center, Boston, MA); C.D. Blanke (Oregon Health Sciences University, Portland, OR); T. Andre (Hôpital Saint Antoine, Paris, France); R.M. Goldberg (Ohio State University Comprehensive Cancer Center, Columbus, OH); A. Benson (Northwestern University, Chicago, IL); C. Twelves (University of Bradford, West Yorkshire, United Kingdom); J. Cassidy (Bristol Meyers-Squibb, New York, NY); F. Sirzen (Roche, Basel, Switzerland); L. Cisar (Pfizer, New York, NY); E. Van Cutsem (University Hospital Gasthuisberg, Gasthuisberg, Belgium); and L. Saltz (Memorial Sloan-Kettering Cancer Center, New York, NY).

Table A1. Trials Included

Era	Study	Accrual Year	No. of Patients
Old	NCCTG 784852	1978-1984	121
	FFCD	1982-1993	127
	INT-0035	1984-1987	457
	Siena	1984-1990	118
	NSABP C-03	1987-1989	519
	NCIC	1987-1992	180
	NCCTG 874651	1988-1989	255
	INT-0089	1989-1992	3,363
	NSABP C-04	1989-1990	2,083
	NCCTG 894651	1989-1991	685
	GIVIO	1989-1992	413
	NSABP C-05	1991-1994	1,070
	NCCTG 914653	1993-1998	878
Newer	SWOG 9415	1995-1999	939
	GERCOR	1996-1999	905
	NSABP C-06	1997-1999	776
	MOSAIC	1998-2001	1,121
	XACT	1998-2001	983
	CALGB 89,803	1999-2001	629
	PETACC 3	1999-2002	1,605
	NSABP C-07	2000-2002	1,222

Abbreviations: CALGB, Cancer and Leukemia Group B; FFCD, Fédération Francophone de Cancérologie Digestive; GERCOR, Groupe Coopérateur Multidisciplinaire en Oncologie; GIVIO, Gruppo Interdisciplinare Valutazione Interventi in Oncologia; INT, Intergroup; MOSAIC, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer; NCCTG, North Central Cancer Treatment Group; NCIC, National Cancer Institute of Canada; NSABP, National Surgical Adjuvant Breast and Bowel Project; PETACC, Pan European Trial Adjuvant Colon Cancer; SWOG, Southwest Oncology Group; XACT, Xeloda in Adjuvant Colon Cancer Therapy.

Time Trends in Outcomes After Adjuvant FU-Based Chemotherapy

Table A2. Interaction Testing Between Trial Eras and Baseline Factors

Characteristic	TTR			TRD			OS		
	HR*	95% CI	Interaction <i>P</i>	HR	95% CI	Interaction <i>P</i>	HR	95% CI	Interaction <i>P</i>
T stage			< .001			.0647			< .001
T1/2/is	0.561	0.46 to 0.68		0.517	0.41 to 0.66		0.452	0.37 to 0.55	
T3	1.014	0.95 to 1.08		0.664	0.62 to 0.71		0.847	0.80 to 0.90	
T4	1.207	1.05 to 1.38		0.721	0.62 to 0.84		0.897	0.78 to 1.03	
Stage			< .001			.7590			.0029
II	0.761	0.67 to 0.87		0.618	0.53 to 0.73		0.649	0.57 to 0.74	
III	1.015	0.96 to 1.07		0.635	0.60 to 0.68		0.807	0.76 to 0.85	
No. of LNs examined			.9873			.6865			.3784
≥ 12	0.972	0.90 to 1.05		0.644	0.59 to 0.70		0.819	0.76 to 0.89	
< 12	0.971	0.90 to 1.05		0.660	0.61 to 0.72		0.780	0.72 to 0.84	
Age group, years			.0093			.2671			.0038
≥ 75	0.866	0.77 to 0.98		0.700	0.61 to 0.80		0.700	0.63 to 0.78	
< 75	1.033	0.98 to 1.09		0.644	0.60 to 0.69		0.838	0.79 to 0.89	

Abbreviations: HR, hazard ratio; LN, lymph node; OS, overall survival; TTR, time to recurrence; TRD, time from recurrence to death.

*Estimated based on models including all data and with main effect and interaction terms in the model, without adjusting for other factors.

Fig A1. Comparison of outcomes between time eras (newer v old) by subpopulation for (A) time to recurrence, (B) time from recurrence to death, and (C) overall survival.