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ORIGINAL ARTICLE

Evaluation of the change of outcomes over a 10-year period in patients with stage III colon cancer: pooled analysis of 6501 patients treated with fluorouracil, leucovorin, and oxaliplatin in the ACCENT database

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Background: Since 2004, adjuvant 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX or FLOX) have been the standard of care for patients with resected colon cancer. Herein we examine the change of outcomes over a 10-year period in patients with stage III colon cancer who received this regimen.

Patients and methods: Individual patient data from the ACCENT database was used to compare the outcomes in older (1998–2003) and newer (2004–2009) treatment eras for patients with stage III colon cancer who received adjuvant FOLFOX or FLOX. The outcomes were compared between the two groups by the multivariate Cox proportional-hazards model adjusting for age, sex, performance score, T stage, N stage, tumor sidedness, and histological grade.

Results: A total of 6501 patients with stage III colon cancer who received adjuvant FOLFOX or FLOX in six randomized trials were included in the analysis. Patients enrolled in the new era group experienced statistically significant improvement in time to recurrence [3-year rate, 76.1% versus 73.0%; adjusted hazard ratio (HR_{adj}) = 0.83 (95% CI, 0.74–0.92), $P = 0.0008$], disease-free survival (DFS) [3-year rate, 74.7% versus 72.3%; $HR_{adj} = 0.88$ (0.79–0.98), $P = 0.024$], survival after recurrence (SAR) [median time, 27.0 versus 17.7 months; $HR_{adj} = 0.65$ (0.57–0.74), $P < 0.0001$], and overall survival (OS) [5-year rate, 80.9% versus 75.7%; $HR_{adj} = 0.78$ (0.69–0.88), $P < 0.0001$]. The improved outcomes remained in patients diagnosed at 45 years of age or older, low-risk patients (T1–3 and N1), left colon, mismatch repair proficient (pMMR), *BRAF*, and *KRAS* wild-type tumors.

Conclusion: Improved outcomes were observed in patients with stage III colon cancer enrolled in clinical trials who received adjuvant FOLFOX/FLOX therapy in 2004 or later compared with patients in the older era. Prolonged SAR calls for revalidation of 3-year DFS as the surrogate endpoint of OS in adjuvant clinical trials and reevaluation of optimal follow-up of OS to confirm the trial findings based on the DFS endpoints.

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Key words: adjuvant, colon cancer, disease-free survival, FOLFOX, overall survival, stage III

INTRODUCTION

Patients with stage III colon cancer are a heterogeneous group with a wide range of 5-year overall survival (OS) rates.[1,2] In 2004 the MOSAIC trial investigators noted improved disease-free survival (DFS) with the addition of oxaliplatin to 5-fluorouracil (5-FU) and leucovorin (LV) (FOLFOX). The 3-year DFS rate was 72.2% in the FOLFOX group compared with 65.3% in the 5-FU/LV group.[3] The 10-year follow-up confirmed the observed OS benefit of adding oxaliplatin to the treatment of stage III colon cancer.[4] Hence the combination of oxaliplatin and 5-FU/LV or capecitabine (i.e. FOLFOX or CAPOX) became, and has remained, the standard of care for stage III colon cancer after surgical resection.[4,5]

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Using the ACCENT (Adjuvant Colon Cancer Endpoints) database, Shi et al.[6] previously demonstrated an increase in survival after recurrence (SAR) and OS over time in patients with stage II/III colon cancer who were treated with a 5-FU-based regimen. The same question was asked when the standard of care shifted to 5-FU/LV plus oxaliplatin with multiple newer therapeutic options available for advanced and recurrent diseases.[7] We now have nearly a decade of experience since 5-FU plus oxaliplatin regimens supplanted 5-FU plus LV as the standard of care in stage III disease leading us to examine the change of outcomes over a 10-year period of patients with stage III colon cancer who received oxaliplatin in addition to 5-FU plus LV adjuvant therapy.

PATIENTS AND METHODS

This analysis focuses on patients with stage III colon cancer from six adjuvant trials included in the ACCENT database who were treated with 5-FU/LV plus oxaliplatin (supplementary Table S1, available at *Annals of Oncology* online). Patients using biologic drugs were excluded. In this report we use 'FOLFOX' as an inclusive term to encompass the variations. Approval to perform the analysis was granted by the Mayo Clinic Investigational Review Board (IRB). IRBs at individual treatment sites approved patient enrollment at their institutions in the individual trials at the time that these trials were conducted. In the current analysis the patient enrollment period is dichotomized into two cohorts: older (1998–2003) versus newer (2004–2009) eras. The cutoff points were chosen to reflect the evolution of therapy and the introduction of biologic agents around 2004.

The outcomes included time to recurrence (TTR), DFS, SAR, and OS. DFS is defined as the time from randomization to recurrence or death from any cause. TTR is defined as the time from randomization to disease recurrence with death without recurrence censored at the time of death. SAR is defined as the time from the first documented recurrence to death from any cause. OS is defined as the time from randomization to death from any cause. To control for potential confounding effects, all analyses were adjusted for patient pretreatment characteristics: age, sex, performance score, T stage (AJCC version 4, 5 or 6), N stage, tumor sidedness, and histologic grade. The distribution of time-to-event outcomes was estimated using the adjusted Kaplan–Meier methods and the two eras were compared by multivariate Cox proportional-hazards modeling. All analyses were conducted using two-sided tests with a significance level of 0.05.

Table 1. Patient demographics and disease characteristics

	Enrollment time era		*P* value
	1998–2003 ($N = 1532$)	2004–2009 ($N = 4969$)	
Age (years), *n* (%)			0.0620[a]
<45	171 (11.2)	589 (11.9)	
45–65	912 (59.5)	3075 (61.9)	
>65	449 (29.3)	1305 (26.3)	
Sex, *n* (%)			0.0935[a]
Female	680 (44.4)	2327 (46.8)	
Male	852 (55.6)	2642 (53.2)	
Performance score, *n* (%)			0.0087[a]
Missing	4	75	
0	1293 (84.6)	3998 (81.7)	
1	235 (15.4)	896 (18.3)	
T stage, *n* (%)			0.0038[a]
Missing	2	14	
T1/2	191 (12.5)	656 (13.2)	
T3	1157 (75.6)	3553 (71.7)	
T4	182 (11.9)	746 (15.1)	
N stage, *n* (%)			0.0035[a]
Missing	1	0	
N1	993 (64.9)	3017 (60.7)	
N2	538 (35.1)	1952 (39.3)	
Total evaluated lymph nodes, *n* (%)			<0.0001[a]
Missing	10	1284	
<12	594 (39.0)	882 (23.9)	
12+	928 (61.0)	2803 (76.1)	
Tumor sidedness, *n* (%)			0.0166[a]
Missing	43	1044	
Right colon	589 (39.6)	1497 (38.1)	
Transverse	144 (9.7)	301 (7.7)	
Left colon	756 (50.8)	2127 (54.2)	
Differentiation grade, *n* (%)			0.0006[a]
Missing	34	58	
Low (grade 1–2)	1227 (81.9)	3820 (77.8)	
High (grade 3/4/anaplastic)	271 (18.1)	1091 (22.2)	
MMR status, *n* (%)			0.0001[a]
Missing	644	1831	
dMMR	139 (15.7)	342 (10.9)	
pMMR	749 (84.3)	2796 (89.1)	
***KRAS* status**, *n* (%)			0.3527[a]
Missing	880	1530	
MT	221 (33.9)	1231 (35.8)	
WT	431 (66.1)	2208 (64.2)	
***BRAF* status**, *n* (%)			0.0159[a]
Missing	581	1478	
MT	123 (12.9)	356 (10.2)	
WT	828 (87.1)	3135 (89.8)	

dMMR, deficient mismatch repair; MMR, mismatch repair; MT, mutant type; pMMR, proficient mismatch repair; WT, wild type.
[a] Chi-square test *P* value.

RESULTS

A total of 6501 patients with stage III colon cancer enrolled in six adjuvant trials and received FOLFOX as their only adjuvant treatment. Two trials [$n = 1532$ (24%) patients] and four trials [$n = 4969$ (76%) patients] were conducted in older (1998–2003) and newer (2004–2009) eras, respectively (Table 1 and supplementary Table S1, available at *Annals of Oncology* online). Overall 1793 patients relapsed, 222 died without recurrence, and 4483 were alive without any recurrence with a median follow-up of 6.6 years.

Patient characteristics

Patient characteristics by newer versus older era are included in Table 1. Patients enrolled in the newer (versus older) era were more likely to have T4, N2 disease, a performance score of 1, higher tumor grade, and left-sided tumors with a moderate increase in proportion (<4.5%, $P < 0.02$). A greater number of patients in the newer era had ≥12 lymph nodes (LNs) examined compared with those

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in the older era (76.1% versus 61.0%, $P < 0.0001$). Among patients with available molecular marker data, fewer patients enrolled in the newer (versus older) era had DNA mismatch repair deficient (dMMR) tumors (10.9% versus 15.7%, $P = 0.0001$) and *BRAF* mutant tumors (10.2% versus 12.9%, $P = 0.0159$).

Outcomes

Figure 1 and Table 2 include detailed comparisons of the outcomes between patients treated in the two eras. A statistically significant improvement of both DFS (adjusted 3-year rate, 74.7% versus 72.3%, $P = 0.0235$) and TTR (adjusted 3-year rate, 76.1% versus 73.0%, $P = 0.0008$) was observed in patients with stage III colon cancer who received adjuvant FOLFOX in the newer versus older era. Furthermore, patients enrolled in 2004 and afterward experienced longer SAR compared with patients enrolled before 2004, with an adjusted median SAR increase from 17.7 to 27.0 months ($P < 0.0001$). The gains in DFS, TTR, and especially SAR translated into OS improvement with a 5.2% absolute increase in the adjusted 5-year OS rate (80.9% versus 75.7%, $P < 0.0001$) compared with patients treated in the older era.

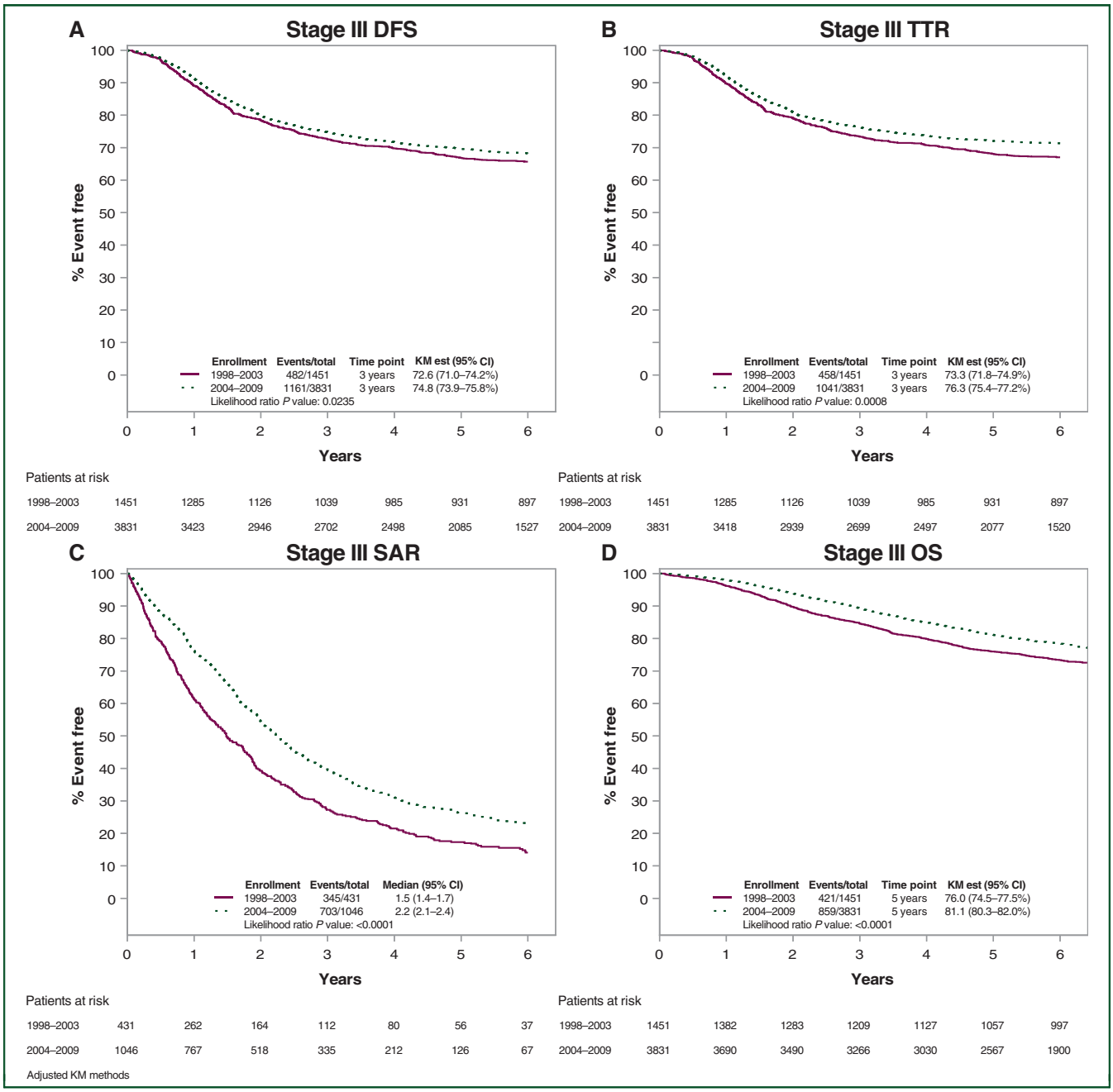

Figure 1. Comparing clinical outcomes between newer and old era trials.
DFS, disease-free survival; KM, Kaplan–Meier; OS, overall survival; SAR, survival after recurrence; TTR, time to recurrence.

Table 2. Multivariate model results

	DFS (*N* = 5282, events = 1643)		TTR (*N* = 5282, events = 1499)		SAR (*N* = 1477, events = 1048)		OS (*N* = 5282, events = 1280)	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Enrollment		0.0235[a]		0.0008[a]		<0.0001[a]		<0.0001[a]
1998–2003	Reference		Reference		Reference		Reference	
2004–2009	0.88 (0.79–0.98)	0.0223[b]	0.83 (0.74–0.92)	0.0007[b]	0.65 (0.57–0.74)	<0.0001[b]	0.78 (0.69–0.88)	<0.0001[b]
Sex		0.0011[a]		0.0274[a]		0.2046[a]		<0.0001[a]
Female	Reference		Reference		Reference		Reference	
Male	1.18 (1.07–1.30)	0.0011[b]	1.12 (1.01–1.24)	0.0277[b]	1.08 (0.96–1.22)	0.2052[b]	1.25 (1.12–1.40)	<0.0001[b]
Performance score		0.0030[a]		0.0399[a]		0.0133[a]		<0.0001[a]
0	Reference		Reference		Reference		Reference	
1	1.20 (1.07–1.35)	0.0025[b]	1.14 (1.01–1.30)	0.0373[b]	1.21 (1.04–1.40)	0.0118[b]	1.35 (1.18–1.54)	<0.0001[b]
T stage (grouped)		<0.0001[a]		<0.0001[a]		0.0008[a]		<0.0001[a]
T1/2	0.26 (0.21–0.32)	<0.0001[b]	0.22 (0.17–0.28)	<0.0001[b]	0.61 (0.44–0.84)	0.0027[b]	0.28 (0.21–0.36)	<0.0001[b]
T3	0.53 (0.47–0.60)	<0.0001[b]	0.50 (0.44–0.56)	<0.0001[b]	0.79 (0.68–0.91)	0.0014[b]	0.54 (0.48–0.62)	<0.0001[b]
T4	Reference		Reference		Reference		Reference	
N stage		<0.0001[a]		<0.0001[a]		0.0001[a]		<0.0001[a]
N1	Reference		Reference		Reference		Reference	
N2	2.08 (1.88–2.29)	<0.0001[b]	2.24 (2.02–2.48)	<0.0001[b]	1.28 (1.13–1.45)	0.0001[b]	2.09 (1.87–2.34)	<0.0001[b]
Age (years)		0.0062[a]		0.4743[a]		0.0066[a]		<0.0001[a]
<45	0.81 (0.68–0.96)	0.0152[b]	0.91 (0.76–1.09)	0.3028[b]	0.78 (0.62–0.97)	0.0246[b]	0.63 (0.52–0.77)	<0.0001[b]
45–65	0.85 (0.76–0.95)	0.0035[b]	0.94 (0.84–1.06)	0.2941[b]	0.81 (0.71–0.93)	0.0024[b]	0.72 (0.64–0.81)	<0.0001[b]
>65	Reference		Reference		Reference		Reference	
Tumor sidedness		0.0461[a]		0.1582[a]		<0.0001[a]		<0.0001[a]
Left colon	Reference		Reference		Reference		Reference	
Right colon	1.14 (1.03–1.27)	0.0130[b]	1.11 (1.00–1.24)	0.0544[b]	1.61 (1.41–1.83)	<0.0001[b]	1.35 (1.20–1.52)	<0.0001[b]
Transverse	1.07 (0.90–1.29)	0.4439[b]	1.05 (0.87–1.27)	0.6368[b]	1.35 (1.08–1.70)	0.0093[b]	1.19 (0.97–1.46)	0.0974[b]
Differentiation grade		0.0200[a]		0.0297[a]		<0.0001[a]		0.0034[a]
Low (grade 1–2)	Reference		Reference		Reference		Reference	
High (grade 3/4/anaplastic)	1.15 (1.02–1.29)	0.0188[b]	1.14 (1.01–1.29)	0.0281[b]	1.35 (1.17–1.55)	<0.0001[b]	1.21 (1.07–1.38)	0.0030[b]

DFS, disease free survival; OS, overall survival; SAR, survival after recurrence; TTR, time to recurrence.
[a] Type 3 likelihood ratio *P* value.
[b] Covariate Wald test *P* value.

Analysis by patient risk defined by T and N stage

There were significant interaction effects between the risk groups (low: T1–3 N1 versus high: T4 and/or N2) and eras for DFS ($P_{interaction} = 0.042$), TTR ($P_{interaction} = 0.022$), and OS ($P_{interaction} = 0.033$), except SAR ($P_{interaction} = 0.51$). Among the low-risk patients with stage III colon cancer treated with FOLFOX, an improvement in DFS, TTR, and SAR was observed in the newer era when compared with the older era (adjusted 3-year DFS rate = 85.8% versus 81.1%; adjusted 3-year recurrence rate, 87.0% versus 82.0%; adjusted median SAR = 36.3 versus 22.6 months, $P \leq 0.01$). Finally, gains among the low-risk group in DFS, TTR, and SAR translated into an increased OS (adjusted 5-year rate = 89.3% versus 83.9%; $P = 0.0005$). Among the high-risk patients with stage III colon cancer, only SAR showed significant improvement for those enrolled in the newer era compared with the older era (adjusted median time: 24.4 versus 14.8 months; $P < 0.0001$).

Subgroup analysis by other factors

In addition to analysis by patient risk, Figure 2 shows comparisons of DFS, TTR, SAR, and OS in newer versus older trials in subpopulations defined by age group, tumor sidedness, and mutation status with interaction *P* values. An improved SAR in patients in newer versus older era trials was consistently observed among all subgroups by age, tumor sidedness, and *KRAS* and *BRAF* mutation status except for dMMR tumors (likely due to small sample size) (Figure 2).

For DFS and TTR, only the interaction effect between the age and era reached statistical significance ($P_{interaction}$ = 0.031 and 0.015, respectively). The increased 3-year DFS, TTR, and 5-year OS rates in the newer versus older era remained among patients who were 45 years of age or older and not among patients less than 45 years of age (Figure 2). Although the interaction effects did not reach a statistically significant level, the improvements in DFS, TTR, and OS remained in left-colon cancer, mismatch repair proficient (pMMR) tumors, and *BRAF* and *KRAS* wild-type tumors. It is worth noting that among patients with an adequate number of LNs examined (12+), only SAR showed significant improvement (27.1 versus 19.0 months of median SAR) when comparing patients treated in the newer with the older era. The differences in 3-year DFS (0%, 95% CI, −4.1% to 4.1%) and the difference in 3-year TTR (0.5%, 95% CI, −3.6% to 4.6%) rates were small comparing those in patients treated in the newer versus older era.

DISCUSSION

In the present study we examine the potential change in long-term outcomes over time among patients with stage III colon cancer who received adjuvant 5-fluorouracil,

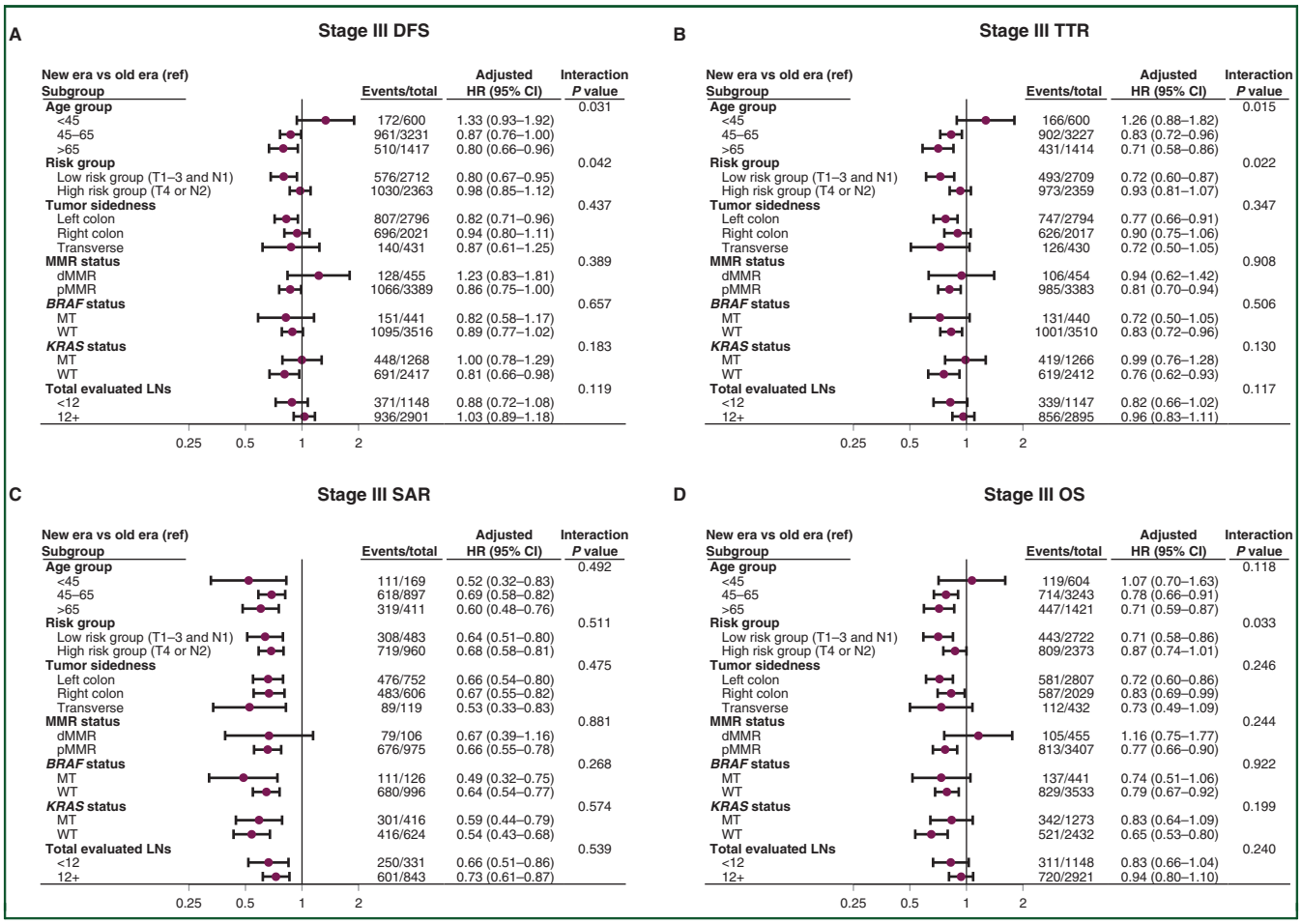

Figure 2. Comparing outcomes between eras (newer versus old) by subpopulations.
DFS, disease-free survival; HR, hazard ratio; MT, mutant type; OS, overall survival; SAR, survival after recurrence; TTR, time to recurrence; WT, wild type.

leucovorin, and oxaliplatin chemotherapy after curative surgical resection. The use of a 5-FU plus oxaliplatin regimen is not only the current standard of care but also serves as the control treatment of testing novel regimens in adjuvant clinical trials. Hence updated estimates of outcomes are critical to facilitate better communication with patients regarding treatment benefits, given potential toxicity in treatment decision making, as well as assist the optimal design for ongoing and future adjuvant trials (e.g. sample size/power and follow-up duration considerations). Overall we observed significant improvement in outcomes. These findings remained after adjusting for key biologic and clinical prognostic factors suggesting a shift in biology may not drive this difference.

The 3-year DFS rate was updated to 74.7% (95% CI, 73.4% to 76.1%) comparing the post-2004 and pre-2004 era. This rate is consistent with contemporary findings reported by the IDEA collaboration, 75.5% (95% CI, 74.4% to 76.7%) in 6 months of the FOLFOX arm.[8] The subgroup analyses show that the improvements in DFS (TTR) were more profound in elderly (65+ years of age) patients, low-risk (T1–3 N1), left-colon, and *KRAS* and *BRAF* wild-type tumors ($HR_{adjusted} < 0.85$, $P < 0.05$). Although only four of six studies supplied data on the LNs examined, we noticed that more patients in the older era had <12 LNs examined compared with those in the post-2004 era (39% versus 24%, respectively). This may suggest a higher risk of under-staging N2 disease and/or residual nodal disease in the older rather than the newer era. The prognosis of patients with <12 (versus ≥12) LNs examined was inferior (3-year DFS rate = 70.9% versus 74.6%; $P = 0.0025$). This may partially contribute to the greater recurrence in the older era in the overall population. Furthermore, the improved DFS (and TTR) remained in the low-risk group (T1—3 N1) but diminished in the high-risk group (T4 or N2), potentially supporting the under-staging phenomenon. When the multivariable model included LNs examined as an additional covariate, the $HR_{adjusted}$ was attenuated for all outcomes (see supplementary Table S2, available at *Annals of Oncology* online). Furthermore, the complete mesocolic excision has been considered as the standard of care in many European countries, as well as the enhanced surgical support, which may contribute to improved outcomes.

There was a 5.2% (95% CI, 2.2% to 8.2%) absolute increase in the 5-year OS and an approximately 22% reduction in the risk of death. This improvement could be largely driven by the prolongation of the SAR. The updated median SAR of 27.0 months in the post-2004 era is similar to the OS

noted in patients with an initial diagnosis of metastatic disease.[9] Further exploration of the relative mortality rate after recurrence over time showed a delay in the time to reach the mortality rate peak after recurrence (supplementary Figure S1, available at *Annals of Oncology* online). More importantly, this finding is consistent regardless of patient clinical, pathological, and molecular marker status. This could be a strong indication of an increase in recurrence after hepatic resection,[10] especially the access to palliative therapy involving biologic (e.g. bevacizumab and cetuximab) or immune agents after recurrence. The prolonged SAR and OS can have two implications regarding adjuvant trial design and conduct. First, an extended follow-up is needed to obtain a sufficient number of deaths (i.e. statistical power) to demonstrate a treatment effect on OS. This can be shown by a hypothetical trial design considering OS as the primary endpoint with a similar sample size using newer versus older era benchmark OS estimates (supplementary Table S3, available at *Annals of Oncology* online).

Second, the prolonged SAR in patients treated with a standard of care regimen (which will be the control arm in future trials testing novel agents) may reduce the correlation between DFS and OS endpoints, as suggested by de Gramont et al.[11] This raises the question whether 3-year DFS remains a validated surrogate endpoint of 5-year OS with the shifts in the choice of control arm as well as the baseline estimates in these endpoints.

Another interesting finding is that of the impact of age on outcomes. Although the benefits from fluoropyrimidine are well established in elderly patients,[12] treatment using a combination of fluoropyrimidine with oxaliplatin showed mixed results for benefits in different meta-analyses.[13,14] The OS improvements in patients over 65 years of age in the newer compared with the older era trials may reflect the advances we have made in the supportive care of these patients (e.g. increased medical and surgical support), permitting them to benefit more from doublet chemotherapy. Similar to the high-risk (T4 or N2) patients, the outcomes did not show improvement comparing newer versus older eras in patients with early-onset cancer (age $<$45 years). This might give hints of a different risk for patients with early-onset cancer.

We acknowledge that there are several limitations. The dose and delivery schedule of the FOLFOX regimen and its variations in the included trials have evolved over time, especially with increased dose of 5-FU, comparing mFOLFOX6 (newer era) with FOLFOX4 (both eras) and FLOX (older era) (supplementary Table S4, available at *Annals of Oncology* online). By examining the dose intensity data reported in the original publications of included trials (see supplementary Table S1, available at *Annals of Oncology* online), there was a trend that the treatment completeness, especially for 5-FU, was higher in the post-2004 trials. This may indicate the greater experience with the regimen and better toxicity management despite the increased dose. Restricted to FOLFOX4 only, the results are consistent with the overall population (supplementary Figure S2, available at *Annals of Oncology* online). Additional analysis with the regimen included as a covariate did not find differences in outcomes between the variations of FOLFOX treatment (supplementary Table S5, available at *Annals of Oncology* online). Therefore, the heterogeneity in dose and delivery schedule of the therapy may not bias the results.

There are imbalances in several clinical and pathological characteristics between older and newer era patient cohorts. Nevertheless, after adjusting for these factors, the improvements in outcomes remained. Two of the newer era trials (N0147 and PETACC8; both testing the efficacy of cetuximab) amended their design to restrict the randomization to patients with *KRAS* wild-type tumors only. In the N0147 study, post-amendment patients with a mutant *KRAS* tumor were still followed up for outcomes and included in the current analyses. Further sensitivity analyses were conducted among patients with *KRAS* wild-type tumors and the results showed consistent findings in outcomes over time (Figure 1).

In conclusion, we observed improved DFS, TTR, SAR, and OS in patients with stage III colon cancer treated with oxaliplatin and 5-FU/LV adjuvant therapy in the newer versus older trial era. Adherence to sufficient LNs examinations is continuously recommended for accurate diagnosis that provides better treatment decision making. Prolonged SAR calls for revalidation of 3-year DFS as the surrogate endpoint of OS in adjuvant clinical trials and reevaluation of optimal follow-up of OS to confirm trial findings based on DFS endpoints.

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DISCLOSURE

The authors have declared no conflicts of interest.

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