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ORIGINAL REPORT

Effect of Adjuvant Chemotherapy on Survival of Patients With Stage III Colon Cancer Diagnosed After Age 75 Years

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See accompanying editorial on page 2576; listen to the podcast by Dr Muss at www.jco.org/podcasts

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ABSTRACT

Purpose
Few patients 75 years of age and older participate in clinical trials, thus whether adjuvant chemotherapy for stage III colon cancer (CC) benefits this group is unknown.

Methods
A total of 5,489 patients ≥ 75 years of age with resected stage III CC, diagnosed between 2004 and 2007, were selected from four data sets containing demographic, stage, treatment, and survival information. These data sets included SEER-Medicare, a linkage between the New York State Cancer Registry (NYSCR) and its Medicare programs, and prospective cohort studies Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) and the National Comprehensive Cancer Network. Data sets were analyzed in parallel using covariate adjusted and propensity score (PS) matched proportional hazards models to evaluate the effect of treatment on survival. PS trimming was used to mitigate the effects of selection bias.

Results
Use of adjuvant therapy declined with age and comorbidity. Chemotherapy receipt was associated with a survival benefit of comparable magnitude to clinical trials results (SEER-Medicare PS-matched mortality, hazard ratio [HR], 0.60; 95% CI, 0.53 to 0.68). The incremental benefit of oxaliplatin over non–oxaliplatin-containing regimens was also of similar magnitude to clinical trial results (SEER-Medicare, HR, 0.84; 95% CI, 0.69 to 1.04; NYSCR-Medicare, HR, 0.82, 95% CI, 0.51 to 1.33) in two of three examined data sources. However, statistical significance was inconsistent. The beneficial effect of chemotherapy and oxaliplatin did not seem solely attributable to confounding.

Conclusion
The noninvestigational experience suggests patients with stage III CC ≥ 75 years of age may anticipate a survival benefit from adjuvant chemotherapy. Oxaliplatin offers no more than a small incremental benefit. Use of adjuvant chemotherapy after the age of 75 years merits consideration in discussions that weigh individual risks and preferences.

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INTRODUCTION

Colorectal cancer is a disease of aging. Of the 141,000 people diagnosed with colorectal cancer in the United States in 2011,[1] 40% will be 75 years of age or older.[2,3] Patients older than 75 years also account for half of colorectal cancer deaths.[1] Despite this disproportionate burden, older patients are underrepresented in clinical trials of colorectal cancer chemotherapy. With scarce efficacy data, elderly patients and their physicians lack clear standards to guide treatment decisions.

For patients with stage III colon cancer, adjuvant chemotherapy after curative intent surgical resection improves the chance of cure. Adjuvant treatment options include fluorouracil with modulating leucovorin (FU), the oral FU prodrug capecitabine, or the combination of FU or capecitabine with oxaliplatin. FU significantly improves disease-free survival (DFS) and overall survival (OS) over surgery alone, with relative risk reductions of 30% and 26% respectively.[4] The MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial demonstrated that the addition of oxaliplatin to this FU backbone further improves DFS by 23% and OS by 20%, leading to a 4.2% absolute improvement

in OS for the FU/oxaliplatin-treated patients with stage III colon cancer.[5,6]

However, the two major trials demonstrating the efficacy of adjuvant oxaliplatin enrolled only 25 (< 1%) and 131 (5%) patients ≥ 75 of age each (D.J. Sargent, personal communication, November 2009).[5,7] In light of the small number of older patients in these trials, investigators have pooled data from multiple trials to increase the statistical power in the elderly subgroup. An analysis of patients older than 70 years treated with adjuvant FU found no evidence of diminishing effect of chemotherapy on cancer recurrences or deaths with increasing age, but this study predates the oxaliplatin era.[8] An analysis of more contemporary trials found that the incremental benefit of oxaliplatin was less for patients older than 70 years than for younger patients.[9] Thus the extent to which patients older than 75 years benefit from postsurgical chemotherapy remains a challenge that is frequently encountered in oncology practice. To shed light on actual practice patterns and outcomes, we evaluated the effectiveness of any adjuvant chemotherapy for patients older than 75 years with stage III colon cancer and whether the addition of oxaliplatin provides additional survival benefit.

METHODS

Data Sources

Four data sources were assembled: (1) the SEER program cancer registry linked to Medicare claims (SEER-Medicare), (2) the New York State Cancer Registry (NYSCR) linked to Medicare claims, (3) the National Comprehensive Cancer Network (NCCN) Outcomes Database, and (4) the Cancer Care Outcomes Research & Surveillance Consortium (CanCORS). The National Cancer Institute's SEER program collects data on incident cancer diagnoses from registries covering 26% of the US population. SEER-Medicare links patients with cancer to their corresponding Medicare claims for investigation of treatment and outcomes.[10,11] The NYSCR-Medicare data allow for similar investigation of treatment outcomes for patients diagnosed in New York State. Since 2005, the NCCN Outcomes Database has prospectively abstracted data on incident colorectal cancers from medical records at eight National Cancer Institute–designated Comprehensive Cancer Centers.[12,13] CanCORS is a population- and health system–based cohort study of patients diagnosed with colorectal cancer between 2004 and 2007 from four geographical regions, five large health maintenance organizations, and 15 Veterans' Administration hospitals.[14,15] In CanCORS, demographics were collected by patient survey. Tumor site, stage, and treatment were ascertained through medical record review.

Case Eligibility

All patients were ≥ 75 years of age at time of diagnosis, had histologically confirmed stage III adenocarcinoma of the colon resected ≤ 90 days from diagnosis, and survived ≥ 30 days after surgery (Fig 1). Exclusions were rectal cancer, prior history of colon cancer, and autopsy diagnoses. Patients in SEER-Medicare and NYSCR-Medicare were excluded if enrolled in a health maintenance organization or not continuously enrolled in both Medicare Parts A and B for 6 months from diagnosis to ensure all claims were available for analysis. Those diagnosed before 2004, the year of oxaliplatin's approval for this indication, were excluded.

Ascertainment of Treatment

This investigation included two main treatment comparisons: chemotherapy versus no chemotherapy and, for the subset treated with chemotherapy, oxaliplatin-containing versus non–oxaliplatin-containing treatment regimens. For the Medicare cohorts, treatment was ascertained based on the presence of billing codes for chemotherapy, including the presence of specific J codes for oxaliplatin. Medical records were the source of treatment information in NCCN and CanCORS.

The no chemotherapy group included patients with no claim or record for chemotherapy within 120 days of surgery; those with a claim/record within 120 days of surgery comprised the chemotherapy group. This chemotherapy group was divided into an oxaliplatin group—any claim/record of oxaliplatin within 30 days of the first chemotherapy dose—and a nonoxaliplatin group—patients without oxaliplatin claim/record, including those receiving oral, bolus, and infusional FU.[16-19] Because of the small number of oxaliplatin-treated patients, chemotherapy regimens were not compared in CanCORS.

Statistical Methods

Covariates in effectiveness data sets. Variables common to all four data sets included age, race, sex, marital status, year of diagnosis, tumor substage, and tumor grade. Income based on residence zip code or census tract was available for SEER-Medicare, NCCN, and NYSCR; CanCORS contains individual estimates. Comorbidity was measured by the Charlson Comorbidity Index in NCCN, the Deyo modification of the Charlson Comorbidity Index in NYSCR-Medicare, and the Deyo-Klabunde modification in SEER-Medicare.[20-22] Comorbidity in CanCORS was measured using the Adult Comorbidity Evaluation–27 index.[13,23] Given the presumed key contribution of comorbid conditions to treatment and outcomes in older patients, though measured differently in each sample, comorbidity was retained in all analyses.

OS. The primary outcome of interest was OS, measured from 30 days after surgery until death from any cause. This was chosen as the anchor date because it could be reliably ascertained and consistently measured for all cohorts. Because the survival measure began 90 days before the chemotherapy exposure window ended, we explored the potential for immortal person-time bias whereby patients dying during the exposure window have a lower chance of receiving treatment, thus worsening the outcome of the no treatment group.[24] In the no chemotherapy group, 12% of patients in SEER-Medicare and 13% in NYSCR died within 120 days of surgery compared with only 3% of patients in the chemotherapy group. Thus patients dying within 120 days of surgery were excluded from the survival comparison of chemotherapy versus no chemotherapy to minimize bias. Sensitivity analysis showed that anchoring survival at 120 days instead of 30 days had little effect on outcomes, thus 30 days was retained to better approximate clinical trials survival estimates.

Analysis. Because of the heterogeneous methods of data ascertainment and measurement across cohorts as well as stipulations in data use agreements, data sets were not combined. Instead, we applied consistent inclusion criteria and covariate specifications across cohorts in parallel. Within each cohort, univariate and multivariate logistic regressions assessed associations between covariates, chemotherapy use, and oxaliplatin receipt. OS of treatment groups were compared descriptively by Kaplan-Meier survival estimates.

Because treatment effect estimates are likely confounded by factors related to treatment selection, we performed a propensity score (PS) matched analysis to compare the effect of treatment on survival among patients of similar risk profiles as assessed by measured, known confounders.[25,26] To do so, we generated two PSs: one estimated the likelihood of chemotherapy receipt, and the other estimated the likelihood of oxaliplatin receipt in chemotherapy-treated patients. For each comparison, exposed patients (eg, chemotherapy, oxaliplatin) were matched to patients with the same PS from the unexposed treatment group. Patients for whom there was no match were excluded. In this way, we generated a PS-matched cohort balanced across treatment groups for measured confounders. OS survival was then compared in these PS-matched cohorts. PS matching was not performed with NCCN because of small sample and data use agreements. Instead, a Cox proportional hazards model adjusted for confounding.

To estimate the extent to which unmeasured confounding was responsible for the measured treatment effect, we conducted a sensitivity analysis whereby patients treated contrary to their PS prediction were trimmed from the sample.[27] Because patients treated contrary to prediction are most likely to have unmeasured confounders determining their treatment selection (eg, frailty), omitting them increases the validity of the treatment effect estimate.[27] If the observed treatment effect estimate is largely due to unmeasured confounding, with trimming the survival hazard ratio (HR) should more closely approach the null. Trimming was conducted in an asymmetric iterative fashion by percentiles at cut points of 1%/99%, 2.5%/97.5%, and 5%/95%.[27] After

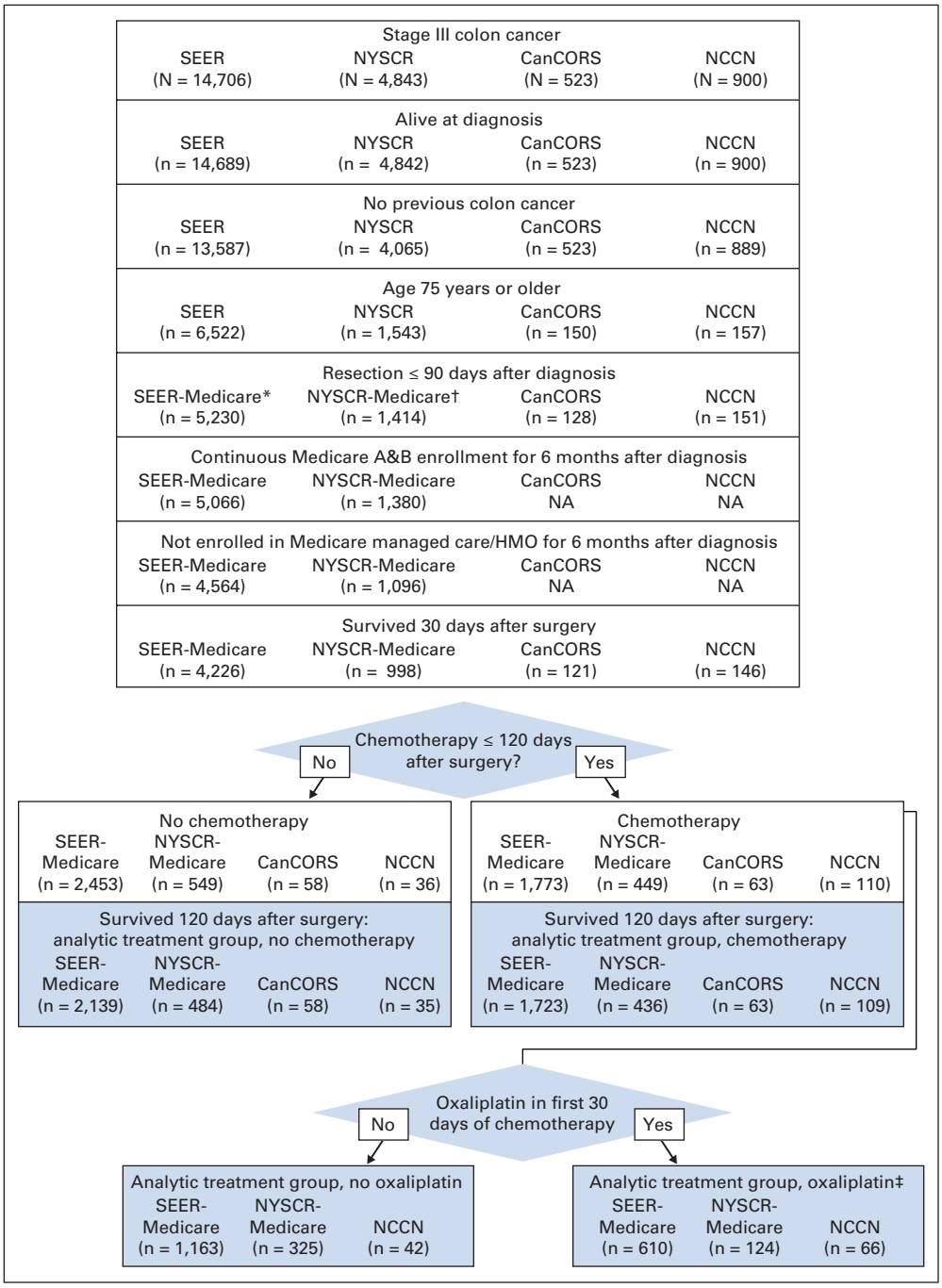

Fig 1. Cohort assembly CONSORT diagram. (*) SEER cases and Medicare claims were linked at this step. (†) New York State Cancer Registry (NYSCR) cases and Medicare claims were linked at this step. (‡) Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) cases were not included in the oxaliplatin versus nonoxaliplatin comparison because of small numbers of oxaliplatin-treated patients. In National Comprehensive Cancer Network (NCCN), two patients were dropped because the chemotherapy regimen could not be determined. NA, not applicable.

each iteration, PS matching was again performed and a survival HR calculated for the trimmed, matched group.

RESULTS

A total of 5,489 patients ≥ 75 years of age with resected stage III colon cancer were included: 4,226 from SEER-Medicare, 998 from the NYSCR-Medicare, 121 from CanCORS, and 144 from NCCN (Table 1). Because of differences in cohort assembly, there were substantial differences in the distribution of important covariates, such as sex, race, and income, across cohorts.

Three hundred sixty-four (9%) patients in SEER-Medicare and 78 patients (8%) in NYSCR-Medicare died within 120 days of colon resection. These patients who died within 120 days of surgery were substantially older than the surviving patients. Only 50 patients in SEER-Medicare and 13 patients in NYSCR-Medicare received any chemotherapy before dying 120 days after surgery, which is 3% of chemotherapy-treated patients in each cohort. Only one NCCN and no CanCORS chemotherapy-treated patients died within 120 days of surgery.

The use of any chemotherapy after resection of stage III cancer differed across cohorts: 42% in SEER-Medicare, 45% in NYSCR-Medicare, 52% in CanCORS, and 75% in NCCN. Among those receiving

Table 1. Characteristics of Elderly Patients With Resected Stage III Colon Cancer

	SEER-Medicare (n = 4,226)						NYSCR-Medicare (n = 998)						CanCORS (n = 121)				NCCN (n = 144)					
			Chemo (n = 1,773; 42%)						Chemo (n = 449; 45%)									Chemo (n = 108; 75%)				
	No chemo (n = 2,453)		FU (n = 1,163; 66%)		Oxaliplatin (n = 610; 42%)		No Chemo (n = 549)		FU (n = 325; 72%)		Oxaliplatin (n = 124; 28%)		No Chemo (n = 58; 48%)		Chemo[a] (n = 63; 52%)		No Chemo (n = 36; 25%)		FU (n = 42; 39%)		Oxaliplatin (n = 66; 61%)	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years													[b]									
Median	84		80		78		83		80		78						79		80		78	
Range	75-105		75-95		75-89		75-101		75-94		75-90						75-92		75-88		75-109	
75-79	565	23	530	46	445	73	93	17	120	37	68	55	[c]		31	49	18	50	18	43	51	77
80-84 (CanCORS 80-81)	823	34	466	40	152	25	190	35	140	43	41	33	23	40	13	21	18	50	24	57	15	23
85+ (CanCORS ≥ 82)	1,065	43	167	14	13	2	266	48	65	20	15	12	35	60	19	30	[c]		[c]		[c]	
Sex																						
Female	1,631	66	693	60	330	54	361	66	190	58	67	54	31	53	28	44	22	61	16	38	35	53
Male	822	34	470	40	280	46	188	34	135	42	57	46	27	47	35	56	14	39	26	62	31	47
Race																						
White	2,081	85	979	84	524	86	494	90	287	88	117	94	43	74	46	73	30	83	34	81	58	88
Black	211	9	64	6	39	6	42	8	20	6	[d]		[d]		[d]		[d]		[d]		[d]	
Asian	87	4	62	5	27	4	13	2	18	6	[d]		[d]		[d]		[d]		[d]		[d]	
Other	74	3	58	5	20	3	[c]		[c]		0	0	[d]		[d]		[d]		[d]		[d]	
Latino																						
Yes	111	5	70	6	35	6	32	6	17	5	[d]		[e]		—		[d]		[d]		[d]	
No	2,342	95	1,093	94	575	94	517	94	308	95	> 90[f]		—		—		32	89	37	88	58	88
Unknown																	[d]		[d]		[d]	
Charlson[g]																						
0	1,196	49	650	56	381	62	349	64	229	70	93	75	NA		NA		17	47	18	43	34	52
1	670	27	319	27	159	26	103	19	54	17	31	25					19	53	24	57	31	48
≥ 2	587	24	194	17	70	11	97	18	13	42	[c]						[c]		[c]		[c]	
ACE-27																						
None	NA		NA		NA		NA		NA		NA		[c]		[c]		NA		NA		NA	
Mild													34	59	41	65						
Moderate													24	41	22	35						
Severe													[c]		[c]							
Marital status																						
Married	865	35	591	51	351	58	154	28	146	45	54	44	24	41	35	56	NA		NA		NA	
Single	191	8	65	6	33	5	77	14	46	14	16	13	[e]		[e]							
Widow/divorce	1,302	53	471	40	196	36	318	58	133	41	54	44	33	56	28	44						
Other	95	4	36	3	30	5	[c]		[c]		[c]		[c]		[c]							
AJCC stage																						
IIIa	232	9	119	10	47	8	56	10	40	12	[c]		[c]		13	21	[d]		[c]		[d]	
IIIb	1,499	61	672	58	314	51	326	59	176	54	76	61	43	74	31	49	26	72	27	65	39	59
IIIc	722	29	372	32	249	41	167	30	109	34	48	39	15	26	19	30	[d]		15	35	17	26
IIINOS							[c]		[c]		0	[c]		[c]		0	0	0	0		[d]	
Tumor grade																						
Well differentiated	121	5	51	4	40	7	357	65	189	58	68	55	[d]		[d]		0	0	[d]		[c]	
Moderately differentiated	1,491	61	690	59	357	59	192	35	121	37	55	45	38	66	46	73	21	58	32	76	40	61
Un/poorly differentiated	790	32	399	34	199	33	[c]		15	5	[c]		16	28	[d]		15	42	[c]		26	39
Unknown	51	2	23	2	14	2							[d]		[d]		[c]		0	0	0	0
Median income																						
Top quantile	200,008		159,521		151,970		134,325		131,402		200,000		[h]		—		87,638		99,076		111,492	
3rd quantile	45,665		46,214		51,199		58,803		62,569		63,379		—		—		54,677		64,787		67,226	
2nd quantile	35,064		35,317		38,478		43,035		46,291		51,565		—		—		41,455		47,456		48,744	
1st quantile	27,195		27,526		28,892		33,990		33,573		35,425		—		—		33,656		37,996		38,487	
Bottom quantile	7,344		8,544		10,076		14,896		14,271		20,582		—		—		17,529		18,968		20,334	
Missing																						
Year of diagnosis																						
2004	624	25	390	34	82	13	190	35	144	44	28	23	58	100	51	81	—		—		—	
2005	647	26	336	29	165	27	189	34	101	31	38	31	[c]		12	19	16 (2005-2006)	45	16 (2005-2006)	38	24 (2005-2006)	37
2006	591	24	208	18	167	27	170	31	80	25	58	47	—		—		[c]		[c]		[c]	
2007	591	24	229	20	196	32	—		—		—		—		—		20 (2007-2009)	55	26 (2007-2009)	62	15	23
2008	—		—		—		—		—		—		—		—		[c]		[c]		27 (2008-2009)	40
2009	—		—		—		—		—		—		—		—		[c]		[c]		[c]	
Time from surgery to first chemo, days	NA						NA						NA				NA					
Median			47		47				48		46				43				51		51	
Range			0-119		10-120				5-120		17-115				20-116				25-116		22-117	

(continued on following page)

Table 1. Characteristics of Elderly Patients With Resected Stage III Colon Cancer (continued)

	SEER-Medicare (n = 4,226)			NYSCR-Medicare (n = 998)			CanCORS (n = 121)		NCCN (n = 144)		
		Chemo (n = 1,773; 42%)			Chemo (n = 449; 45%)					Chemo (n = 108; 75%)	
	No chemo (n = 2,453)	FU (n = 1,163; 66%)	Oxaliplatin (n = 610; 42%)	No Chemo (n = 549)	FU (n = 325; 72%)	Oxaliplatin (n = 124; 28%)	No Chemo (n = 58; 48%)	Chemo[a] (n = 63; 52%)	No Chemo (n = 36; 25%)	FU (n = 42; 39%)	Oxaliplatin (n = 66; 61%)
Characteristic	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
F/U time, days											
Median	740	1,109	1,053	552	772	601	1,260	1,260	780	984	823
Range	0-2,153	17-2,154	29-2,133	0-1,422	30-1,430	39-1,397	131-1,260	147-1,260	38-1,930	275-1,874	100-1,872

Abbreviations: ACE-27, Adult Comorbidity Evaluation–27; AJCC, American Joint Committee on Cancer; CanCORS, Cancer Care Outcomes Research and Surveillance Consortium; CCI, Charlson Comorbidity Index; Chemo, chemotherapy; F/U, follow-up; FU, fluorouracil with modulating leucovorin; NA, not applicable; NCCN, National Comprehensive Cancer Network; NOS, not otherwise specified; NYSCR, New York State Cancer Registry.

[a]Only 10 patients in CanCORS received oxaliplatin; therefore, the chemo group is not subdivided to preserve patient confidentiality and because of the limitation of analysis of such a small sample.

[b]Age was measured categorically in CanCORS, median is not available. Catergories are 75-79, 80-81, ≥ 82.

[c]Collapsed with category above/below because of small numbers to preserve confidentiality.

[d]Eleven or fewer patients; number omitted to preserve confidentiality.

[e]Latino patients in CanCORS are combined with "Other" because of small numbers. Single patients were combined with "Other" because of small numbers.

[f]The majority of oxaliplatin-treated patients in NYSCR-Medicare were non-Latino. The exact number is masked to preserve confidentiality of the Latino patients.

[g]Comorbidity is measured with the CCI in NCCN, the Deyo-Klabunde modification in SEER-Medicare, and the Deyo modification in NYSCR-Medicare. Comorbidity is measured by the ACE-27 in CanCORS.

[h]Income was measured categorically in CanCORS: > $60,000, $40,000-60,000, $20,000-40,000; < $20,000.

chemotherapy, a smaller proportion of patients received oxaliplatin as a component of their adjuvant therapy in SEER-Medicare (42%), and NYSCR-Medicare (28%), than at NCCN centers (61%). As expected, the use of both any chemotherapy and oxaliplatin-containing regimens dropped off quickly with advancing age. In multivariate models, age was the factor most strongly associated with both chemotherapy and oxaliplatin receipt (Fig 2; Appendix Tables A3 and A4, online only). Compared with 63% of patients 75 to 79 years of age, only 43% of patients 80 to 84 years of age (odds ratio [OR], 0.44; 95% CI, 0.38 to 0.51) and 14% of patients 85 years of age and older (OR, 0.10; 95% CI, 0.08 to 0.12) in SEER-Medicare received postoperative adjuvant chemotherapy. Of patients treated with chemotherapy, 46% of patients 75 to 79 years of age compared with 25% of patients 80 to 84 years of age (OR, 0.37; 95% CI, 0.29 to 0.46) and 7% of patients 85 years of age and older (OR, 0.08; 95% CI, 0.05 to 0.15) in SEER-Medicare received oxaliplatin. Black elderly patients seemed to be less likely to receive chemotherapy, and Asian patients seemed to be more likely to receive chemotherapy. Small sample sizes, however, limit interpretation about care patterns in these subgroups.

Survival of chemotherapy-treated patients was substantially better than survival of patients not receiving chemotherapy after resection of stage III colon cancer (Table 2; Fig 3). Chemotherapy use was

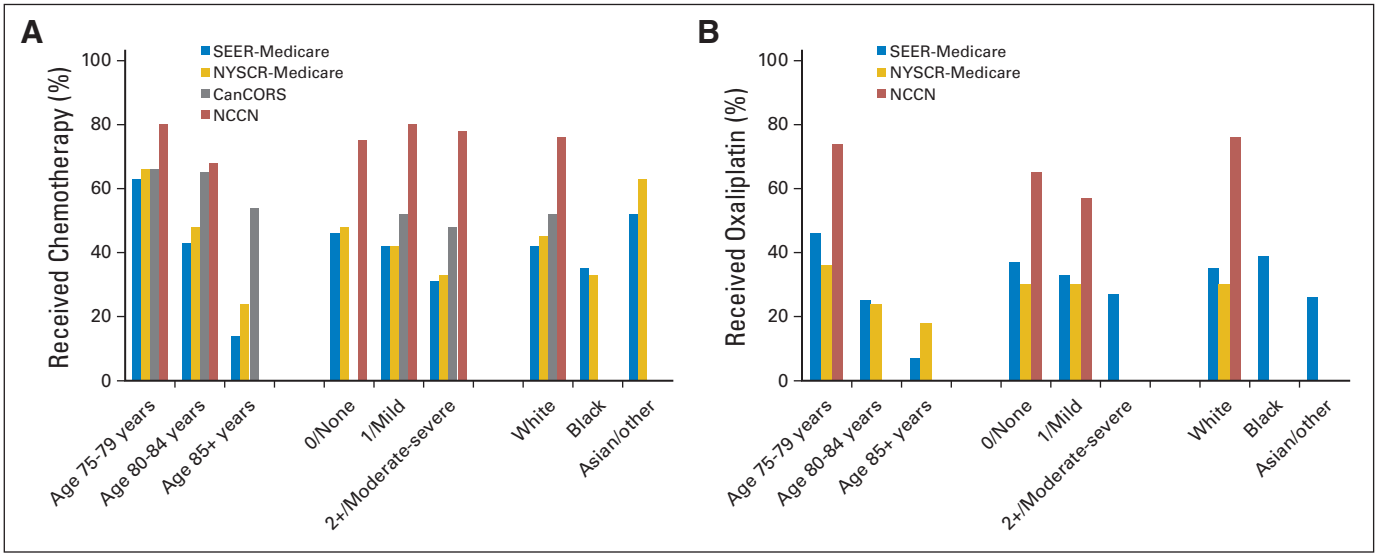

Fig 2. Percentage of elderly patients with stage III colon cancer treated with chemotherapy. The percentage of patients treated with chemotherapy (A) or oxaliplatin (B) is shown broken down by strata of clinically relevant covariates. Bars representing 11 or fewer patients were omitted to preserve patient confidentiality. Comorbidity is measured with the Charlson Comorbidity Index in National Comprehensive Cancer Network (NCCN), the Deyo-Klabunde modification in SEER-Medicare, the Deyo modification in New York State Cancer Registry (NYSCR) –Medicare, and the Adult Comorbidity Evaluation–27 in Cancer Care Outcomes Research and Surveillance Consortium (CanCORS).

Table 2. Benefit of Adjuvant Chemotherapy Among Elderly Patients With Stage III Colon Cancer

	Chemotherapy *v* No Chemotherapy							
	SEER-Medicare		NYSCR-Medicare		CanCORS		NCCN	
Patient Group and Survival	No Chemotherapy	Chemotherapy	No Chemotherapy	Chemotherapy	No Chemotherapy	Chemotherapy	No Chemotherapy	Chemotherapy
Entire cohort	2,453	1,773	549	449	58	63	36	110
Restricted to patients surviving 120 days from surgery	2,139	1,723	484	436	58 (100%)	63 (100%)	35 (97%)	109 (99%)
PS-matched cohort	1,174	1,174	277	277	33	33	NA	NA
3-year OS, unmatched cohort (120-day survivors only), %	50	70	53	63	60	78	59	87
3-year OS, PS-matched cohort (120-day survivors only), %	53	68	53	60	50	71	NA	NA
Crude mortality unmatched								
HR	1	0.51	1	0.72	1	0.49	1	0.35
95% CI		0.46 to 0.56		0.58 to 0.90		0.25 to 0.95		0.16 to 0.77
PS matched mortality								*
HR	1	0.60	1	0.76	1	0.48	1	0.42
95% CI		0.53 to 0.68		0.58 to 1.01		0.19 to 1.21		0.17 to 1.03
Trimmed, PS matched mortality							NA	NA
HR	1	0.62	1	0.72	1	0.31		
95% CI		0.54 to 0.71		0.53 to 0.97		0.10 to 0.96		

NOTE. Three-year OS and HR with 95% CI from an unadjusted Cox proportional hazards model and a PS-matched and trimmed analysis are shown according to the type of postoperative therapy delivered in patients surviving 120 days from surgical resection.

Abbreviations: CanCORS, Cancer Care Outcomes Research and Surveillance Consortium; HR, hazard ratio; NA, not applicable; NCCN, National Comprehensive Cancer Network; NYSCR, New York State Cancer Registry; OS, overall survival; PS, propensity score.

*The PS analysis could not be performed in NCCN because of small sample size and data use agreements. An adjusted Cox proportional HR is shown for NCCN including age, sex, ethnicity, race, comorbidity, tumor substage, tumor grade, and income.

associated with significantly lower mortality in the PS-matched SEER-Medicare cohort (HR, 0.60; 95% CI, 0.53 to 0.68), with a comparable effect in the PS-matched NYSCR-Medicare (HR, 0.76; 95% CI, 0.58 to 1.01) and CanCORS (HR, 0.48; 95% CI, 0.19 to 1.21) cohorts. The Cox proportional hazards–adjusted NCCN analysis also showed a reduction in mortality in chemotherapy-treated patients (HR, 0.42; 95% CI, 0.17 to 1.03). Sensitivity analysis showed no evidence of decreasing treatment effect with PS trimming, suggesting that the observed reduction in mortality stemmed from treatment and not simply from unmeasured confounding.[27]

Oxaliplatin use was associated with a trend toward lower mortality among chemotherapy-treated elderly patients in SEER-Medicare (PS-matched HR, 0.84; 95% CI, 0.69 to 01.04) and in NYSCR-Medicare (PS-matched HR, 0.82; 95% CI, 0.51 to 1.33), both corresponding to a 5% absolute improvement in survival at 3 years in the PS-matched cohorts (Table 3; Fig 4). In sensitivity analysis, the effect of oxaliplatin was slightly attenuated by PS trimming in SEER-Medicare with a trimmed HR of 0.87 compared with 0.84, and in NYSCR with a trimmed HR of 0.88 compared with 0.82. Among the 108 chemotherapy-treated patients with age ≥ 75 years in NCCN, there was no apparent benefit associated with oxaliplatin receipt, with exceptionally high 3-year survival of 88% in non–oxaliplatin-treated and 84% in oxaliplatin-treated patients.

DISCUSSION

People ≥ 75 years of age comprise 40% of the colorectal cancer population.[3] Although oxaliplatin increases cure rates for resectable stage III cancer in clinical trials, only 5% of patients enrolled to National Surgical Adjuvant Breast and Bowel Project Trial C07 and fewer than 1% of MOSAIC participants were 75 years of age or older, so the benefit demonstrated by those trials has not been established in the older population. Perhaps as a result of the lack of data in elderly patients, chemotherapy use decreases rapidly with age.[15,28] Facing this gap in the clinical trials evidence, we sought to examine the use and comparative effectiveness of adjuvant chemotherapy, and more specifically adjuvant oxaliplatin, in patients 75 years of age and older with stage III colon cancer.

We found that among patients 75 years of age and older surviving 120 days from resection, those treated with adjuvant chemotherapy had a markedly lower risk of death than those who did not. Using effectiveness cohorts reflecting heterogeneous patient populations, the survival advantage associated with adjuvant chemotherapy was comparable to that demonstrated in clinical trials. In fact, the survival advantage was more substantial than has previously been measured in pooled trials data, where adjuvant FU resulted in a 24% reduction in the risk of death.[8] Two SEER-Medicare analyses of patients treated for stage III colon cancer in the mid-1990s suggested similar treatment effect sizes (27% and 35% relative risk reductions).[29,30] That we found greater association between adjuvant treatment and survival with the inclusion of more recent data may be attributable to the fact that 34% of patients received oxaliplatin. In sensitivity analysis, excluding oxaliplatin-treated patients decreased 3-year survival from 70% to 67% in SEER-Medicare, although this had little effect on the survival HR. If over time, given the emphasis on adjuvant treatment for stage III colon cancer as a quality metric, clinicians have become more comfortable treating older patients with adjuvant therapy, we would anticipate that patients in the no chemotherapy group would become

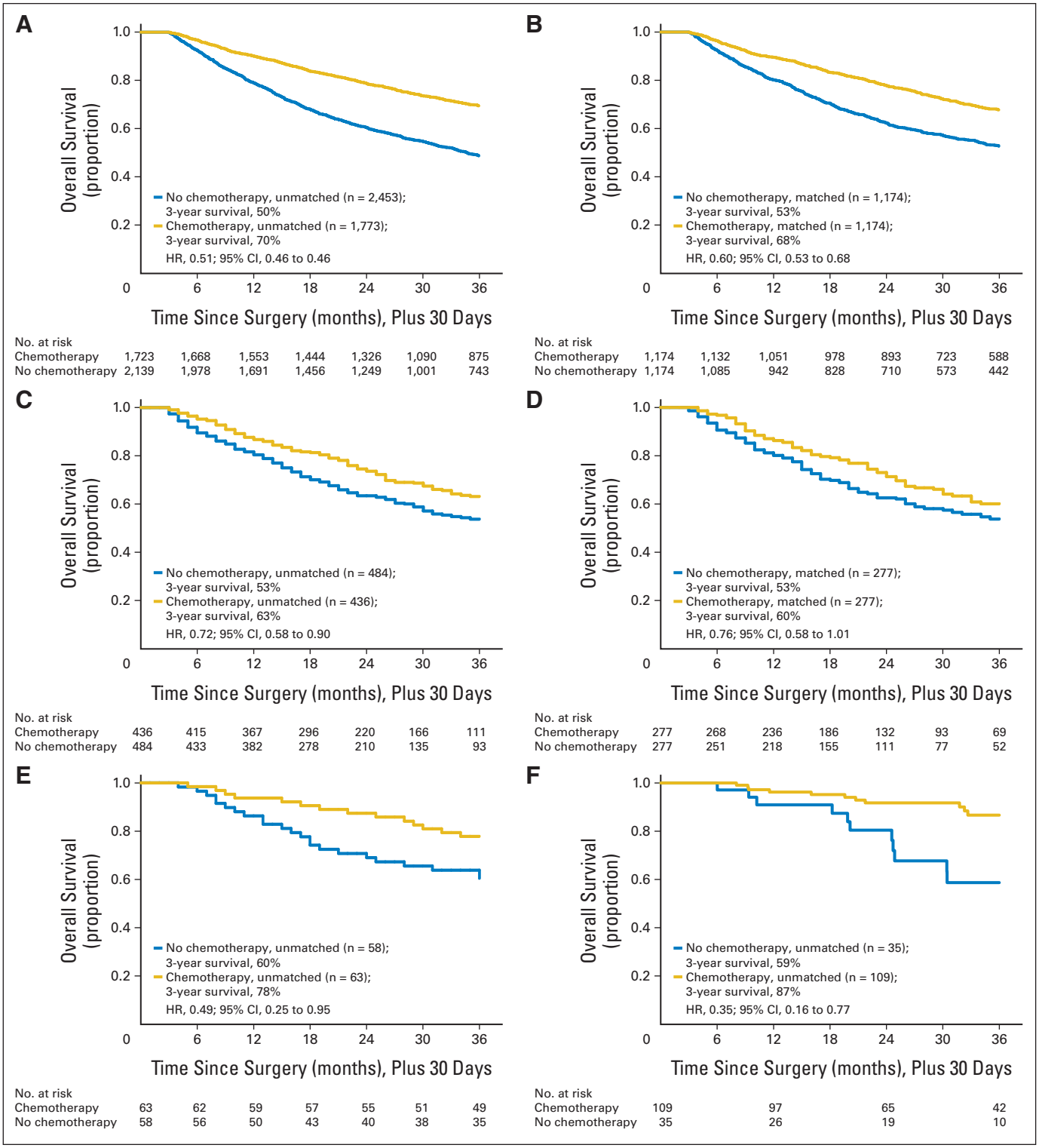

Fig 3. Unadjusted and propensity score–matched Kaplan-Meier survival comparisons of chemotherapy versus no chemotherapy in elderly patients with stage III colon cancer surviving 120 days from surgery. (A) SEER-Medicare unmatched; (B) SEER-Medicare matched; (C) New York State Cancer Registry (NYSCR) –Medicare unmatched; (D) NYSCR-Medicare matched; (E) Cancer Care Outcomes Research and Surveillance Consortium unmatched; (F) National Comprehensive Cancer Network unmatched. HR, hazard ratio.

Table 3. Benefit of Adjuvant Oxaliplatin Among Elderly Patients With Stage III Colon Cancer

	Oxaliplatin *v* Nonoxaliplatin Adjuvant Chemotherapy					
	SEER-Medicare		NYSCR-Medicare		NCCN*	
Patient Group and Survival	Nonoxaliplatin (n = 1,163)	Oxaliplatin (n = 610)	Nonoxaliplatin (n = 325)	Oxaliplatin (n = 124)	Nonoxaliplatin (n = 42)	Oxaliplatin (n = 66)
PS matched	512	512	110	110	NA	NA
3-year OS, unmatched cohort, %	65	74	59	66	88	84
3-year OS, PS-matched cohort, %	68	73	61	66	NA	NA
Crude mortality unmatched						
HR	1	0.71	1	0.83	1	1.25
95% CI		0.60 to 0.85		0.56 to 1.22		0.43 to 3.68
PS matched mortality						*
HR	1	0.84	1	0.82	1	1.84
95% CI		0.69 to 1.04		0.51 to 1.33		0.48 to 7.05
Trimmed, PS matched mortality					NA	NA
HR	1	0.87	1	0.88		
95% CI		0.69 to 1.10		0.51 to 1.53		

NOTE. Three-year OS and HR with 95% CI from an unadjusted Cox proportional hazards model and a PS-matched and trimmed analysis are shown according to the type of postoperative chemotherapy delivered.

Abbreviations: HR, hazard ratio; NA, not applicable; NCCN, National Comprehensive Cancer Network; NYSCR, New York State Cancer Registry; OS, overall survival; PS, propensity score.

*The PS analysis could not be performed in NCCN because of small sample size and data use agreements. An adjusted Cox proportional HR is shown for NCCN including age, sex, ethnicity, race, comorbidity, tumor substage, tumor grade, and income.

more frail over time. The association between adjuvant treatment and survival could be increasing if such selection bias is operational. This bias likely underlies the large effect of chemotherapy measured in NCCN, where patients were more the most likely to get both chemotherapy and oxaliplatin. Although we used available methods to mitigate such selection, including PS-trimmed sensitivity analysis,[27] no method can overcome all such bias in observational data.

The incremental decrease in mortality seen with the addition of oxaliplatin in elderly patients in the community was of comparable size as seen in the MOSAIC and the XELOX in Adjuvant Colon Cancer Treatment (XELOXA) trials, which reported 20% and 13% relative mortality reductions from oxaliplatin, respectively.[6,31] In our effectiveness cohorts, relatively small sample sizes limited our ability to evaluate the association between oxaliplatin-containing adjuvant therapy and survival. With the oxaliplatin results considered in parallel, the consistency of the point estimates in the two Medicare cohorts is reassuring. However, with the modest attenuation of oxaliplatin effect in the PS-trimmed sensitivity analysis and the lack of benefit at the NCCN centers, the incremental survival associated with oxaliplatin in this oldest group of treated colon cancer patients seems to be very modest.

Reports of the effect of FU/oxaliplatin combination chemotherapy in patients older than 70 years in clinical trials do not clearly support its benefit over FU. In an analysis of infusional fluorouracil, leucovorin, and oxaliplatin using pooled data from three trials of metastatic colon cancer and one adjuvant trial (MOSIAC), improvements in progression-free survival, disease-free survival (DFS), and OS were similar among older patients compared with younger ones.[32] However, the subgroup analysis of patients ≥ 65 years of age in MOSAIC found no survival benefit from oxaliplatin.[6] In the XELOXA trial, oxaliplatin's effect on DFS in patients older than 70 years was less robust than in younger patients: DFS HR in patients younger than 70 years, 0.79; 95% CI, 0.66 to 0.94; DFS HR in patients ≥ age 70 years, 0.87; 95% CI, 0.63 to 1.18.[33] No DFS or OS benefit was gained in National Surgical Adjuvant Breast and Bowel Project Trial C07 by adding oxaliplatin in patients older than 70 years.[34] In addition, in a recent analysis of trials in which novel adjuvant chemotherapies (capecitabine, FU/irinotecan, and FU/oxaliplatin) were compared with an FU control, patients older than 70 years did not benefit from any newer regimen, even when younger patients did. In the case of oxaliplatin-based therapies, there was no survival benefit from oxaliplatin in patients older than 70 years (OS HR, 1.13; 95% CI, 0.96 to 1.32; DFS HR, 1.11; 95% CI, 0.97 to 1.28).[9]

It seems implausible that oxaliplatin is truly more effective in patients older than 75 years in the community than in patients older than 70 years in randomized trials. Therefore, although the general consistency of findings, including the PS-trimmed models, strengthens our confidence that both chemotherapy in general and oxaliplatin in particular improves outcomes of elderly patients with colon cancer, it seems likely that despite attempts to control for unmeasured confounding, the inherent differences between FU and oxaliplatin patients were not fully accounted for in our analyses. Ideally, clinical trials would recruit subjects whose characteristics mirror those of the affected population thereby strengthening our certainty with regard to the utility of oxaliplatin in the oldest patients with colon cancer. However, given that drug development studies must ask "How well can this treatment work?" trial populations will likely continue to under-represent the elderly. As such, efforts to examine effectiveness by leveraging best available data sources and most careful analytic techniques remain a priority.

This study suggests that patients older than 75 years of age with surgically resected colon cancer may experience a survival benefit from chemotherapy comparable to that previously demonstrated by younger populations in randomized and observational studies.[4-6,35] From the perspective of a practicing clinician, these results suggest that consideration of adjuvant systemic therapy is absolutely warranted for

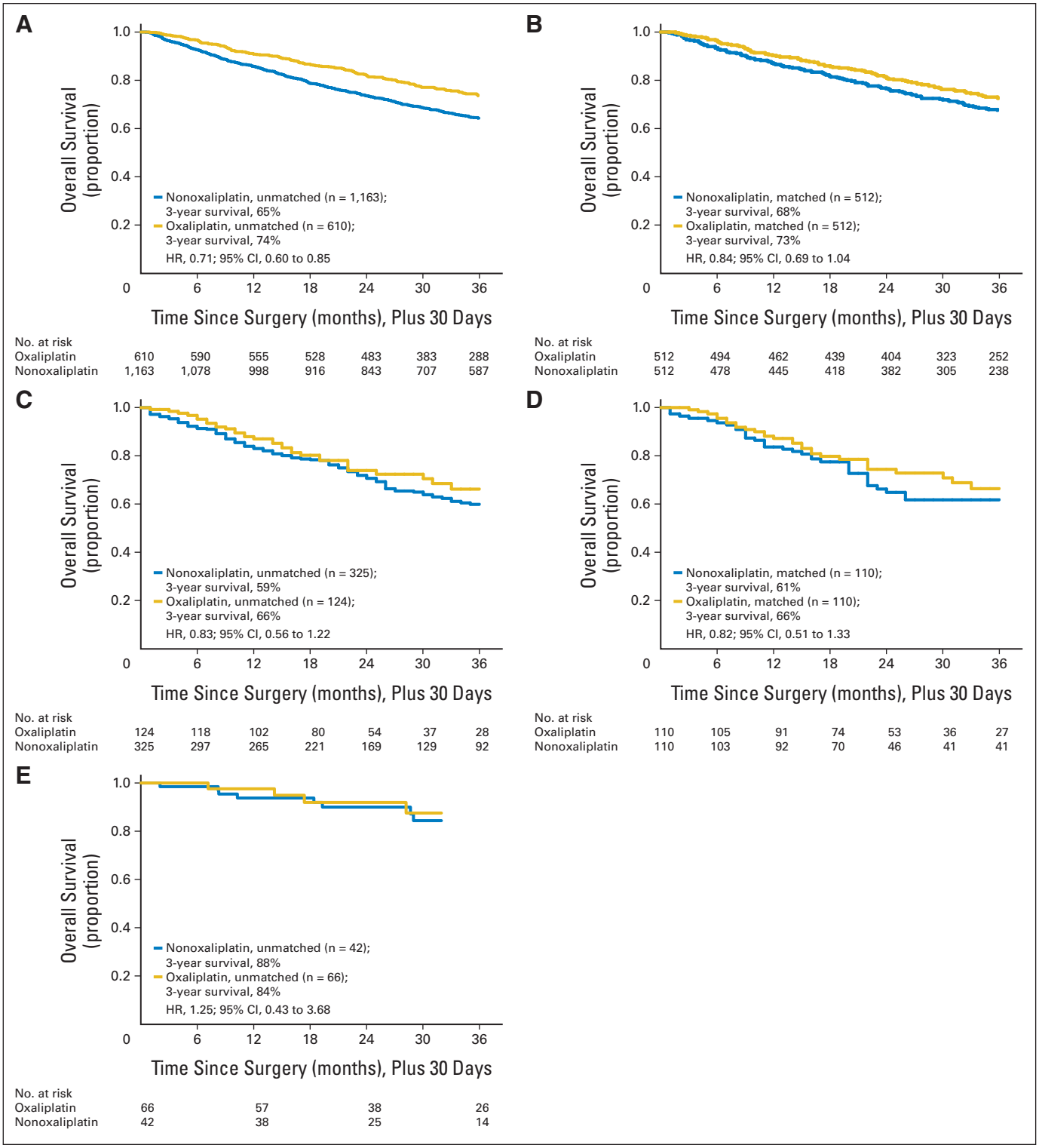

Fig 4. Unadjusted and propensity score–matched Kaplan-Meier survival comparison of oxaliplatin and nonoxaliplatin adjuvant chemotherapy in elderly patients with stage III colon cancer. (A) SEER-Medicare unmatched; (B) SEER-Medicare matched; (C) New York State Cancer Registry (NYSCR) –Medicare unmatched; (D) NYSCR-Medicare matched; (E) National Comprehensive Cancer Network unmatched. HR, hazard ratio.

patients older than 75 years. Because quality of life could not be measured in this analysis, how adjuvant therapy affects the quality of life of older patients with cancer remains a critical, unanswered question. Clearly, treatment decisions need to be made in the context of individual risk profiles and preferences, but the survival estimates from this work provide benchmarks for consideration and may inform discussions about prognosis. Future research examining additional or larger cohorts may further qualify this study's findings, for

example, as they may be modulated by specific patient comorbidities, or as they pertain to a decision to use oxaliplatin versus alternative systemic therapy. In the meantime, this study helps fill the knowledge gap left by clinical trials and inform a prevailing bias away from adjuvant therapy among the oldest patients with colon cancer. The relative consistency of study findings suggests that patients of this age group and their physicians should consider adjuvant chemotherapy as a viable treatment option.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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