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ARTICLE

Comparative Effectiveness of Oxaliplatin vs Non–Oxaliplatin-containing Adjuvant Chemotherapy for Stage III Colon Cancer

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Background The addition of oxaliplatin to adjuvant 5-fluorouracil (5-FU) improves survival of patients with stage III colon cancer in randomized clinical trials (RCTs). However, RCT participants are younger, healthier, and less racially diverse than the general cancer population. Thus, the benefit of oxaliplatin outside RCTs is uncertain.

Subjects and Methods Patients younger than 75 years with stage III colon cancer who received chemotherapy within 120 days of surgical resection were identified from five observational data sources—the Surveillance, Epidemiology, and End Results registry linked to Medicare claims (SEER–Medicare), the New York State Cancer Registry (NYSCR) linked to Medicaid and Medicare claims, the National Comprehensive Cancer Network (NCCN) Outcomes Database, and the Cancer Care Outcomes Research & Surveillance Consortium (CanCORS). Overall survival (OS) was compared among patients treated with oxaliplatin vs non–oxaliplatin-containing adjuvant chemotherapy. Overall survival for 4060 patients diagnosed during 2004–2009 was compared with pooled data from five RCTs (the Adjuvant Colon Cancer ENdpoinTs [ACCENT] group, n = 8292). Datasets were juxtaposed but not combined using Kaplan–Meier curves. Covariate and propensity score adjusted proportional hazards models were used to calculate adjusted survival hazard ratios (HR). Stratified analyses examined effect modifiers. All statistical tests were two-sided.

Results The survival advantage associated with the addition of oxaliplatin to adjuvant 5-FU was evident across diverse practice settings (3-year OS: RCTs, 86% [n = 1273]; SEER–Medicare, 80% [n = 1152]; CanCORS, 88% [n = 129]; NYSCR–Medicaid, 82% [n = 54]; NYSCR–Medicare, 79% [n = 180]; and NCCN, 86% [n = 438]). A statistically significant improvement in 3-year overall survival was seen in the largest cohort, SEER–Medicare, and in the NYSCR–Medicare cohort (non–oxaliplatin-containing vs oxaliplatin-containing adjuvant therapy, adjusted HR of death: pooled RCTs: HR = 0.80, 95% CI = 0.70 to 0.92, $P = .002$; SEER–Medicare: HR = 0.70, 95% CI = 0.60 to 0.82, $P < .001$; NYSCR–Medicare patients aged ≥65 years: HR = 0.58, 95% CI = 0.38 to 0.90, $P = .02$). The association between oxaliplatin treatment and better survival was maintained in older and minority group patients, as well as those with higher comorbidity.

Conclusion The addition of oxaliplatin to 5-FU appears to be associated with better survival among patients receiving adjuvant colon cancer treatment in the community.

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Colon cancer is a leading cause of morbidity and mortality worldwide. An anticipated 101 340 Americans will be diagnosed with colon cancer in 2011, about one-third of whom will have stage III, or node-positive, disease (1,2). Surgery is the mainstay of curative therapy for stage III colon cancer. Surgery alone, however, results in an unacceptably low 5-year disease-free survival of 15%–50% depending on substage (3). During 1990–2004, post-surgical adjuvant chemotherapy with leucovorin-modulated fluorouracil (hereafter 5-FU) was the standard of care for stage III colon cancer based on a 26% relative reduction in mortality compared with surgery alone (3,4). In 2004, the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial reported that the addition of oxaliplatin to 5-FU provided 23% further improvement in relative disease-free survival and 4% absolute improvement in 6-year overall survival in stage III colon cancer (5,6). The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial confirmed this finding (7), making adjuvant therapy with 5-FU and oxaliplatin the new standard for patients with resected stage III colon cancer.

CONTEXT AND CAVEATS

Prior knowledge

Randomized controlled trials have demonstrated that oxaliplatin-containing adjuvant therapy improves the survival of patients with stage III colon cancer. However, it is not known whether this therapy improves survival to the same extent in cancer patients in the general population.

Study design

The overall survival of 4060 patients treated with oxaliplatin-containing vs non–oxaliplatin-containing adjuvant chemotherapy was assessed from five observational data sources and compared with pooled data from five randomized controlled trials.

Contribution

The use of oxaliplatin-containing adjuvant therapy was associated with a consistent pattern of improved survival across the diverse practice settings represented by the five cohorts of stage III colon cancer patients, including older and minority group patients and those with higher comorbidity.

Implications

The addition of oxaliplatin to adjuvant therapies for stage III colon cancer shown to confer a survival advantage by randomized controlled trials has proven to be equally beneficial in the more diverse therapeutic settings in the general population.

Limitations

The small sample sizes of racial and ethnic minorities limited the precision of the hazard ratio estimates. Different follow-up times in the different cohorts precluded a unified interpretation across all cohorts. The potential for confounding based on patient selection as a substantial cause of improved survival in oxaliplatin-treated patients could not be eliminated.

From the Editors

The addition of oxaliplatin to 5-FU unequivocally improves outcomes of patients enrolled in RCTs; however, fewer than 2% of patients with incident cancer enroll in National Cancer Institute trials (8). The patient populations in clinical trials, including MOSAIC and C-07, are substantially younger, healthier, and less racially and/or ethnically diverse than the general population of cancer patients. In addition, dosing and follow-up are defined in trials but are at the discretion of the treating physician in routine practice. Because oxaliplatin increases toxicity, specifically nausea, vomiting, neutropenia, and peripheral neuropathy (5), variations in dosing might be expected to alter tolerance and drug delivery and thus attenuate the benefit of adjuvant oxaliplatin in community settings. Given these potential differences, it is critical to understand the community-based effectiveness of adjuvant chemotherapy. We sought to assess the benefit of adding oxaliplatin to 5-FU for stage III colon cancer in patients treated in the community (effectiveness) and to compare that with oxaliplatin benefit in phase III RCTs (efficacy). To that end, we compared overall survival of patients treated with oxaliplatin-containing adjuvant chemotherapy with overall survival of patients treated with non–oxaliplatin-containing regimens in effectiveness samples drawn from five observational cohorts and an efficacy sample drawn from pooled individual patient data from five phase III adjuvant chemotherapy trials.

Methods

Data Sources

Effectiveness samples came from the following sources: Surveillance, Epidemiology, and End Results registry linked to Medicare claims (SEER–Medicare); the New York State Cancer Registry (NYSCR) linked to Medicaid and Medicare claims; the National Comprehensive Cancer Network (NCCN) Outcomes Database; and the Cancer Care Outcomes Research & Surveillance Consortium (CanCORS). The efficacy sample was drawn from the Adjuvant Colon Cancer ENdpoinTs (ACCENT) group. This study was approved by the Institutional Review Boards at the University of North Carolina (IRB 09-0764); the Brigham and Women's Hospital/Dana-Farber Cancer Institute (IRB 08-338); and the Mayo Clinic (IRB 531-04, 120-2005).

Effectiveness Samples. The National Cancer Institute (NCI) SEER program of cancer registries collects data on incident cancer cases from registries covering 26% of the US population. Linkage of case patients to their corresponding Medicare claims allows investigation of treatment and outcomes (9,10). A novel linkage between the NYSCR and Medicaid and Medicare claims captures information on incident cancer case patients diagnosed in New York State. The NCCN Outcomes Database comprises prospectively abstracted information for incident colorectal cancers treated at eight NCI-designated comprehensive cancer centers (11,12). CanCORS is a population-based cohort study of patients with newly diagnosed colorectal cancer in four geographical regions, five large health maintenance organizations, and 15 Veterans Administration hospitals. Minorities were oversampled, and information was gathered through medical records abstraction and patient and provider surveys (13,14). There is potential overlap between effectiveness cohorts in select geographical regions; however, confidentiality restrictions precluded our ability to determine the extent of this potential overlap. Because the Food and Drug Administration approved oxaliplatin for stage III colon cancer in 2004, case patients diagnosed in 2004 or later were included.

Efficacy Sample. ACCENT contains individual patient data from 21 phase III adjuvant colon cancer chemotherapy trials during 1977–2008. For a contemporary comparison, only trials enrolling patients in 1999 and later for which follow-up data were complete were included. Five RCTs with a 5-FU control arm met these criteria. The experimental arms consisted of capecitabine (XACT), 5-FU/irinotecan combinations (PETACC-3, C89803), and oxaliplatin/5-FU combinations (MOSAIC, C-07) (Table 1) (5,7,15–17).

Sample Eligibility

RCTs have included too few patients older than 75 years to make robust conclusions about oxaliplatin's efficacy in older patients. Therefore, this analysis is restricted to patients younger than 75 years

Table 1. Characteristics of clinical trials included as the efficacy sample from the adjuvant colon cancer ENdpoinTs database*

Characteristic	No. (%)						
				C07		MOSAIC‡	
	X-ACT, N = 1982†	PETACC3, N = 2264†	C89803, N = 1238†	5-FU, N = 871†	FLOX, N = 862	5-FU, N = 675†	FOLFOX, N = 672
Age, y							
<50	270 (14)	476 (22)	237 (19)	185 (21)	194 (23)	118 (17)	109 (16)
50–64	893 (45)	1090 (48)	515 (42)	393 (45)	395 (46)	330 (49)	327 (49)
65–69	422 (21)	421 (19)	193 (16)	142 (16)	130 (15)	133 (20)	140 (21)
70–74	353 (18)	265 (12)	188 (15)	98 (11)	97 (11)	90 (13)	88 (13)
75–79	41 (2)	12 (1)	83 (7)	42 (5)	43 (5)	4 (1)	8 (1)
80–84	2 (<1)	0 (0)	19 (2)	10 (1)	3 (<1)	0 (0)	0 (0)
≥85	0 (0)	0 (0)	3 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Sex							
Women	910 (46)	1029 (45)	550 (44)	384 (44)	381 (44)	322 (48)	299 (44)
Men	1072 (54)	1235 (55)	688 (56)	487 (56)	481 (56)	353 (52)	373 (56)
Race							
White	Imputed	Imputed	1098 (89)	761 (87)	731 (85)	662 (98)	647 (96)
Black	—	—	85 (7)	54 (6)	61 (7)	3 (<1)	7 (1)
Asian	—	—	14 (1)	26 (3)	30 (3)	8 (1)	14 (2)
Other	—	—	41 (3)	30 (3)	40 (5)	2 (<1)	4 (1)
Performance status							
0	Imputed	Imputed	923 (75)	730 (84)	724 (84)	583 (86)	570 (85)
1	—	—	304 (25)	140 (16)	136 (16)	89 (13)	100 (15)
2	—	—	7 (1)	1 (<1)	2 (<1)	3 (<1)	2 (<1)
AJCC T stage							
T1	18 (1)	44 (2)	43 (3)	37 (4)	30 (3)	8 (1)	6 (1)
T2	182 (9)	149 (7)	114 (9)	122 (14)	104 (12)	54 (8)	51 (8)
T3	1506 (76)	1720 (76)	971 (79)	647 (75)	672 (78)	491 (73)	486 (72)
T4	276 (14)	349 (15)	103 (8)	61 (7)	54 (6)	121 (18)	129 (19)
AJCC N stage							
N1	1389 (70)	1469 (65)	789 (64)	559 (64)	550 (64)	443 (66)	443 (66)
N2	593 (30)	795 (35)	449 (36)	312 (36)	312 (36)	232 (34)	229 (34)
Year of diagnosis							
1998	14 (1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	4 (1)
1999	528 (27)	5 (<1)	136 (11)	0 (0)	0 (0)	276 (41)	275 (41)
2000	831 (42)	302 (13)	653 (53)	225 (26)	211 (24)	377 (56)	374 (56)
2001	609 (31)	1436 (63)	449 (36)	294 (34)	299 (35)	19 (3)	19 (3)
2002	0 (0)	521 (23)	0 (0)	352 (40)	352 (41)	0 (0)	0 (0)

* This table includes all patients enrolled on these trials. Only patients younger than 75 years were included as the Efficacy cohort of this study. AJCC = American Joint Committee on Cancer; FLOX = 5-FU, leucovorin, oxaliplatin with 5-FU given as a bolus; FOLFOX = 5-FU, leucovorin, oxaliplatin with 5-FU given as both a bolus and continuous infusion; MOSAIC = Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer; N = Node; PETACC3 = Pan-European Trial Adjuvant Colon Cancer-3; T = Tumor; X-ACT = Xeloda in Adjuvant Colon Cancer Therapy; 5-FU = 5-Fluorouracil.

† Non-oxaliplatin arms.

‡ Performance status is estimated by Eastern Cooperative Oncology Group except MOSAIC, which used Karnofsky performance status. In MOSAIC, the Karnofsky performance status was converted to Eastern Cooperative Oncology Group using the following: performance status 0 = 80–100; 1 = 60–70; 2 = <60.

for whom RCTs compellingly demonstrate oxaliplatin benefit. All patients in all samples had histologically confirmed stage III adenocarcinoma of the colon (not rectum) resected within 90 days of diagnosis and received adjuvant chemotherapy within 120 days of resection (Figure 1). To assure complete claims information, 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 in the 6 months following diagnosis. To facilitate interpretation of the NYSCR with regard to dual Medicare/Medicaid eligibility, the cohort was divided into Medicaid patients younger than 65 years (32% of whom were also enrolled in Medicare) and Medicare patients who were at least 65 years of age (28% of whom were also enrolled in Medicaid).

Treatment Ascertainment

Two treatment groups were compared—those receiving oxaliplatin-containing chemotherapy and those receiving non–oxaliplatin-containing chemotherapy. In the effectiveness sample, the oxaliplatin group included patients with any claim/record of oxaliplatin within 30 days of their first chemotherapy dose. The non-oxaliplatin group comprised all other patients, including those who received capecitabine (16–20). In the efficacy sample the oxaliplatin group comprised the oxaliplatin/5-FU arms of C-07

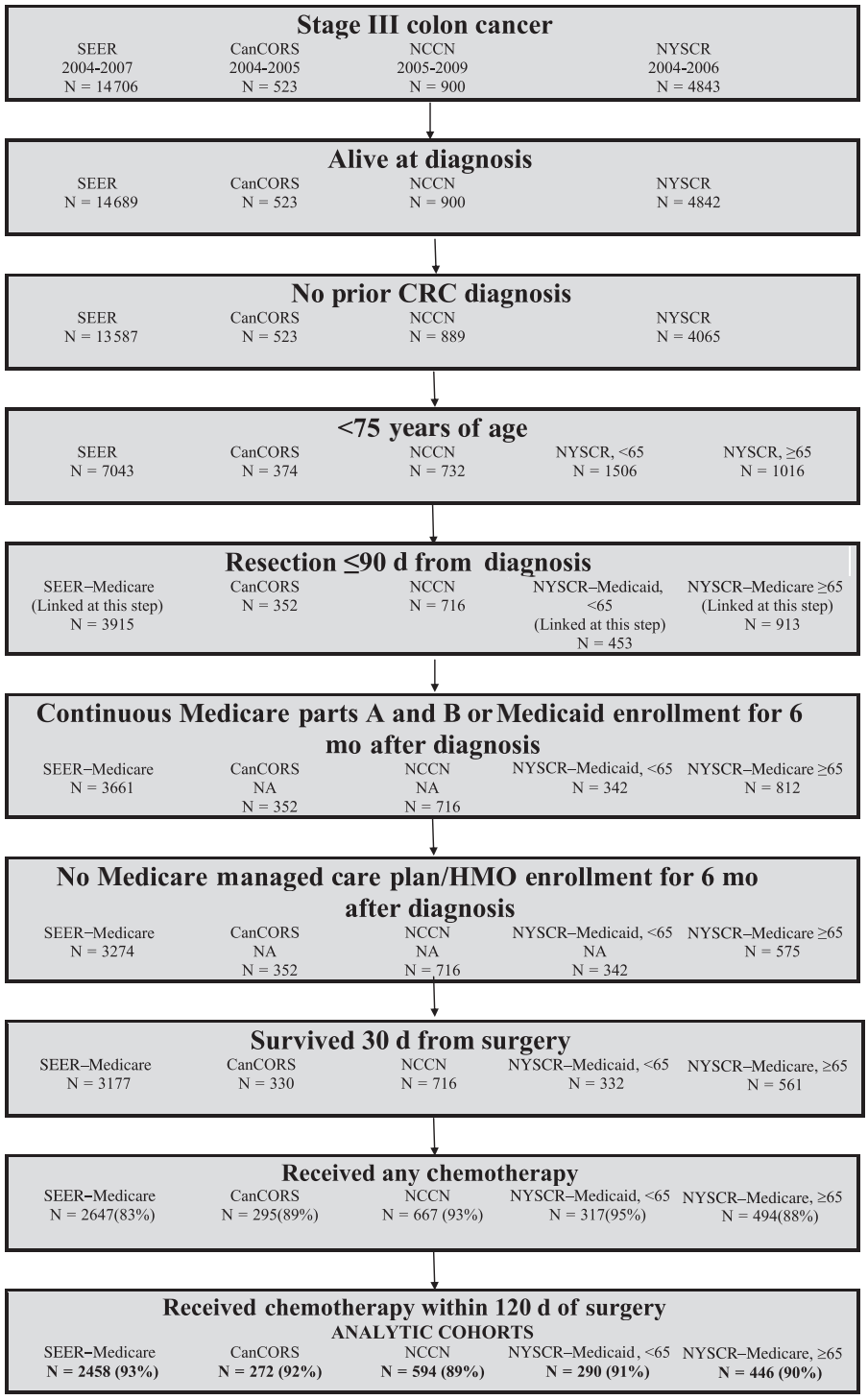


Figure 1. Effectiveness cohort assembly. CanCORS = Cancer Care Outcomes Research & Surveillance Consortium; NCCN = National Comprehensive Cancer Network Outcomes Database; NYSCR = New York State Cancer Registry; SEER = Surveillance, Epidemiology, and End Results Registry.

(n = 862) and MOSAIC (n = 672). The 5-FU arms of C-07 and MOSAIC and all arms of the other studies comprised the non-oxaliplatin group.

Statistical Analysis

Covariates. Data on age (measured continuously in all cohorts except CanCORS where categories were ages 21–49, 50–64, 65–69, and 70–74 years), sex, race (white, black, Asian, Latino, other) tumor substage (IIIA, IIIB, IIIC, III not otherwise specified), tumor grade (well or moderately differentiated, poorly or undifferentiated, differentiation unknown), and year of diagnosis (2004–2009) were available in all effectiveness samples. Income (quantiles) based on zip code or census tract residence was available for SEER–Medicare, NCCN, and NYSCR; CanCORS contains individual estimates (>$60 000; $40 000–$60 000; $20 000–$40 000; <$20 000). Comorbidity was measured using the Charlson Comorbidity Index (CCI) in NCCN, its Deyo modification in NYSCR, and its Deyo-Klabunde modification in SEER–Medicare (21–23). Comorbidity

in CanCORS was measured using the Adult Comorbidity Evaluation (ACE)-27 index (24,25). Income and comorbidity, important covariates estimated differently in each sample, were retained in statistical analyses.

For ACCENT, age, sex, substage, and year of trial enrollment were available on all patients. Individual patient performance status and race were not available on all patients; missing data were imputed based on available clinical variables as previously reported (n = 4246) (3,26,27). Because 97% of patients enrolled in XACT and the overwhelming majority in PETACC-3 were white, all XACT and PETACC-3 patients were assumed to be white.

Overall Survival. Overall survival in the effectiveness cohorts was measured from 30 days after surgery. This anchor date was selected because it could be reliably ascertained in the effectiveness datasets and is a comparable start point to clinical trial randomization date. Overall survival in the efficacy cohort was measured from time of random assignment to death from any cause. Because of short follow-up in most cohorts, 3-year rather than 5-year overall survival is reported.

In SEER–Medicare, NYSCR, and NCCN, vital status was ascertained through the National Death Index. For CanCORS, each participating site updated vital status with censoring at the time of each update.

Given their heterogeneity, effectiveness data were not combined but juxtaposed after applying consistent inclusion criteria and covariate specifications. Within each effectiveness cohort, univariate and multivariable logistic regression were used to assess the associations among covariates and oxaliplatin receipt. Next, overall survival of treatment groups was compared descriptively with Kaplan–Meier survival estimates. Cox proportional hazards models were used to calculate unadjusted and adjusted hazard ratios of survival. The assumption of proportionality was tested using the ASSESS option of PHREG in SAS (SAS v9.2; SAS Institute, Cary, NC). Survival in each treatment group was compared within subgroups to examine whether key covariates modified the effect of oxaliplatin. Sample size constraints precluded formal interaction testing. Adjusted proportional hazards models were also performed for the efficacy cohorts. Analyses were conducted with SAS version 9.2 (SAS Institute).

A propensity score analysis compared survival of treatment groups within a common range of risk factors for outcome in effectiveness cohorts. Using the same covariates as the proportional hazards model, we estimated the likelihood of oxaliplatin receipt (the propensity score) for each patient (28). Patients with the highest and lowest propensity for oxaliplatin without an overlapping patient of similar propensity in the other treatment group were omitted to create cohorts with overlapping propensity score distributions. Overall survival of treatment groups was compared within propensity score quintiles. Because there was no clear trend of differential treatment effect by quintile, a propensity score–adjusted proportional hazards model was used to calculate the survival hazard ratio. Disease-free survival was not evaluated because it could not be measured in all observational cohorts. All statistical tests were two-sided.

Results

Sample Characteristics

A total of 4060 patients were in the effectiveness sample and 8292 patients in the efficacy sample. As expected from the differences in sample acquisition, there were differences in the distribution of age and race among cohorts (Table 2). Similar proportions of patients across practice settings in the effectiveness sample had serious comorbidity as defined by CCI (≥2) or ACE-27 (severe) comorbid disease (Table 2), categories shown to have comparable hazards of death (29).

Oxaliplatin Receipt in the Community

The proportion of patients treated with oxaliplatin varied considerably: 59% in SEER–Medicare; 54% in CanCORS; 23% in NYSCR–Medicaid; 51% in NYSCR–Medicare; and 94% in NCCN. Except in NCCN where the overwhelming majority of patients received oxaliplatin, year of diagnosis was strongly associated with oxaliplatin use, which increased substantially between 2004 and 2007 (Table 3).

The use of oxaliplatin decreased with advancing age. Among patients aged 70–74 years, 53% in SEER–Medicare, 37% in CanCORS, and 48% in NYSCR–Medicare received oxaliplatin; these rates were lower than for patients aged 65–69 years (eg, SEER–Medicare adjusted OR = 0.67, 95% CI = 0.56 to 0.81). Although 82% of 70- to 74-year-old patients treated at NCCN centers received oxaliplatin, this was still lower than the rate for 65- to 69-year-old patients (96%). Oxaliplatin use was similarly low in patients with extensive comorbidity.

The association between race and oxaliplatin receipt was not uniform. In CanCORS and NYSCR–Medicaid, there was minimal difference in likelihood of oxaliplatin use between blacks and whites, whereas in NCCN, SEER–Medicare, and NYSCR–Medicare, black patients received less oxaliplatin than whites, a difference that was substantial in both Medicare populations (eg, NYSCR–Medicare 36% vs 54%, OR = 0.44, 95% CI = 0.23 to 0.83).

Effect of Oxaliplatin on Survival

Three-year survival was superior for patients treated with oxaliplatin-containing chemotherapy across all cohorts (Figure 2, A–G and Table 4). In the efficacy sample, 3-year overall survival of oxaliplatin-treated patients was 86% (1273 patients), a 4% absolute and a 20% relative improvement in survival compared with non–oxaliplatin-treated patients (adjusted HR of death = 0.80, 95% CI = 0.70 to 0.92, P = .002; Tables 4 and 5). Three-year overall survival of oxaliplatin-treated patients was remarkably similar in the effectiveness cohorts: 80% (1152) SEER–Medicare, 88% (129) CanCORS, 82% (54) NYSCR–Medicaid, 79% (180) NYSCR–Medicare, and 86% (438) NCCN.

Adjusting for differences in patient and tumor characteristics between treatment arms, the survival HR point estimates of all effectiveness cohorts showed at least as much reduction in the rate of death from oxaliplatin treatment as the efficacy cohort (Table 4), although the 95% confidence interval crossed 1.0 in all but SEER–Medicare (HR of death = 0.70, 95% CI = 0.60 to 0.82, P < .001) and NYSCR–Medicare (HR of death = 0.58, 95% CI = 0.38 to 0.90,

Table 2. Characteristics of stage III colon cancer patients treated with adjuvant chemotherapy, by cohort*

	Efficacy	Effectiveness				
Characteristic	**ACCENT, N = 8292**	**SEER–Medicare, N = 2458**	**CanCORS, N = 272**	**NYSCR–Medicaid, <65 y†, N = 290**	**NYSCR–Medicare, ≥65 y†, N = 446**	**NCCN, N = 594**
Non-oxaliplatin, n (%)	6812 (82)	1013(41)	125 (46)	224 (77)	218 (49)	33 (6)
Oxaliplatin, n (%)	1480 (18)	1445(59)	147 (54)	66 (23)	228 (51)	561 (94)
Age, y						
Median years (range)	60 (17–74)	69(27–74)	‡	54 (25–64)	69 (65–74)	56 (19–74)
<50	1589 (19)	47(2)	37 (14)	101 (35)	—	171 (29)
50–64	3943 (48)	252(10)	138 (51)	189 (65)	—	281 (47)
65–69	1581 (19)	1136(46)	51 (19)	—	225 (50)	80 (13)
70–74	1179 (14)	1023(42)	46 (17)	—	221 (50)	62 (10)
Sex, n (%)						
Women	3751 (45)	1279(52)	97 (36)	139 (48)	237 (53)	311 (52)
Men	4541 (55)	1179(48)	175 (64)	151 (52)	209 (47)	283 (48)
Race, n (%)§						
White	3697 (90)	1992(81)	191 (70)	165 (57)	364 (82)	456 (77)
Black	201 (5)	275(11)	47 (17)	90 (31)	59 (13)	71 (12)
Asian	90 (2)	76(3)	12 (4)	31 (11)	19 (4)	48 (8)
Other	114 (3)	115(5)	22 (8)	‖	‖	19 (3)
Latino						
Yes	NA	155(6)	26 (10)	74 (26)	26 (6)	38 (6)
No	—	2303(94)	246 (90)	216 (74)	420 (94)	512 (86)
Unknown	—		—			44 (7)
CCI, n (%)¶						
0	NA	2065(84)	NA	199 (69)	336 (75)	447 (75)
1	—	245(10)	—	41 (14)	67 (15)	87 (15)
≥2	—	148(6)	—	28 (10)	43 (10)	60 (10)
Unknown	—		—	22 (8)		—
ACE-27, n (%)						
None	NA	NA	89 (33)	NA	NA	NA
Mild	—	—	104 (38)	—	—	—
Moderate	—	—	43 (16)	—	—	—
Severe	—	—	36 (13)	—	—	—
Performance status, n (%)						
0	3373 (82)	NA	NA	NA	NA	NA
1	711 (17)	—	—	—	—	—
2	14 (<1)	—	—	—	—	—
Marital status, n (%)						
Married	NA	1487(60)	188 (69)	101 (35)	249 (56)	NA
Single	—	274(11)	27 (10)	127 (44)	66 (15)	—
Widowed/divorced	—	606(25)	54 (20)	59 (20)	120 (27)	—
Other	—	91(4)	‖	‖	‖	—
AJCC stage, n (%)						
IIIA	772 (9)	320(13)	35 (13)	20 (7)	54 (12)	73 (12)
IIIB	4687 (57)	1330(54)	136 (50)	169 (58)	232 (52)	306 (52)
IIIC	2820 (34)	806(33)	87 (32)	100 (34)	160 (36)	212 (36)
III NOS	13 (<1)	‖	14 (5)	‖		‖
Differentiation, n (%)						
Well/Moderate	NA	1705(69)	199 (73)	196 (68)	293 (66)	412 (69)
Un/Poor	—	686(28)	67 (25)	85 (29)	139 (31)	156 (26)
Unknown	—	67(3)	‖	‖	14 (3)	26 (4)
Median income, US dollars#						
Top quantile	NA	$185394	—	$106973	$134325	$153918
Third quantile	—	$52828	83 (31%)	$47266	$61986	$65367
Second quantile	—	$40203	43 (16%)	$35637	$43636	$49958
First quantile	—	$29922	45 (17%)	$24167	$34663	$36315
Bottom quantile	—	$8,366	49 (18%)	$14,271	$14271	$14642
Missing	—		52 (19%)			—

(Table continues)

Table 2 (Continued).

Characteristic	Efficacy	Effectiveness				
	ACCENT, N = 8292	SEER–Medicare, N = 2458	CanCORS, N = 272	NYSCR–Medicaid, <65 y†, N = 290	NYSCR–Medicare, ≥65 y†, N = 446	NCCN, N = 594
Diagnosis year, n (%)						
1998	20 (<1)	—	—	—	—	—
1999	1195 (14)	—	—	—	—	—
2000	2854 (34)	—	—	—	—	—
2001	3034 (37)	—	—	—	—	—
2002	1189 (14)	—	—	—	—	—
2003	—	—	—	—	—	—
2004	—	690(28)	220 (81)	97 (33)	163 (37)	—
2005	—	612(25)	52 (19)	100 (34)	161 (36)	72 (12)
2006	—	576(23)	—	93 (32)	122 (27)	143 (24)
2007	—	580(24)	—	—	—	133 (22)
2008	—	—	—	—	—	159 (26)
2009	—	—	—	—	—	87 (15)
Median time from surgery to first chemo, d (range)	NA	44 (0–120)	43 (0–115)	39 (0–118)	47 (9–120)	46 (20–116)
Median FU time, d (range)	**	1218 (14–2157)	1479 (90–2305)	773 (35–1418)	782 (1–1418)	608 (120–1588)

* ACCENT = Adjuvant Colon Cancer End Points Group; ACE-27 = Adult Comorbidity Evaluation-27; AJCC = American Joint Committee on Cancer; CCI = Charlson Comorbidity Index; CanCORS = Cancer Care Outcomes Research & Surveillance Consortium; N = Node; NA = not available; NCCN = National Comprehensive Cancer Network Outcomes Database; NYSCR–Medicaid = New York State Cancer Registry linked to Medicaid claims; NYSCR–Medicare = New York State Cancer Registry linked to Medicare claims; SEER–Medicare = Surveillance Epidemiology and End Results registry linked to Medicare claims; T = Tumor.

† Patients included in the column titled "NYSCR–Medicaid <65 y, N = 290" are all patients less than 65 years of age who have continuous Medicaid enrollment for 6 months from diagnosis. Thirty-two percent of the patients included here are less than 65 years of age with enrollment in Medicaid and Medicare. Patients included in the column titled "NYSCR–Medicare ≥65 y, N = 446" are all patients 65 years of age and older that have continuous Medicare enrollment for 6 months from diagnosis. Twenty-eight percent of the patients included here are 65 years of age or older with enrollment in Medicare and Medicaid.

‡ Only categorical data for age are available for CanCORS, and no median can be reported.

§ Race and ethnicity: In NYSCR, Asian patients are included with "other" because of small numbers. Latino ethnicity is not separately available in ACCENT.

‖ Comorbidity: CanCORS reports comorbidity using the ACE-27, NCCN, the CCI, NYSCR, the Deyo modification of the CCI, and SEER–Medicare, Deyo-Klabunde modification of the CCI. ACCENT contains performance status only which was imputed for 4246 patients using multiple imputation based on age, sex, race, treatment, and substage.

¶ N < 11. Value omitted to ensure patient confidentiality.

Income was measured categorically in CanCORS: >$60 000; $40 000–$60 000; $20 000–$40 000; <$20 000.

** Median follow-up for all studies was greater than 5 years.

P = .02). The propensity score–adjusted hazard ratios confirmed the survival benefit from oxaliplatin seen in the covariate-adjusted models (Table 4).

The benefit of oxaliplatin was largely maintained across all clinically relevant subgroups examined, although small sample size limited the precision of hazard ratio estimates. Oxaliplatin-treated patients aged 70–74 years had improved survival in SEER–Medicare (HR of death = 0.66, 95% CI = 0.52 to 0.84) and NYSCR–Medicare (HR of death = 0.62, 95% CI = 0.36 to 1.07), but not in CanCORS (Table 4). Oxaliplatin benefit was also seen in patients with CCI of at least 2 in SEER–Medicare. In three effectiveness cohorts, black patients derived similar or greater benefit from oxaliplatin than whites, although analysis of all racial/ethnic minorities was limited by small sample size.

Discussion

In this study, we found that the use of oxaliplatin-containing adjuvant therapy was associated with a consistent pattern of improved survival across the diverse practice settings represented by the effectiveness cohorts of stage III colon cancer patients, with a statistically significant improvement in the largest cohort, SEER–Medicare, and the NYSCR–Medicare cohort. The survival advantage was maintained in older, sicker, and minority group patients.

In 1990, in the wake of multiple positive RCTs, adjuvant 5-FU became the standard of care for patients with resected stage III colon cancer (4). In 2004, the addition of oxaliplatin was shown to further improve disease-free survival and subsequently overall survival (5–7). The oxaliplatin/5-FU combination, however, has a greater risk of severe cytopenias, nausea and vomiting, diarrhea, and peripheral neuropathy than 5-FU alone (5,7). In light of these toxic effects, which confer greater risk to oxaliplatin-treated patients, should the effectiveness of oxaliplatin be attenuated in the community, routine use of adjuvant oxaliplatin for very small reductions in mortality might not be warranted. To investigate the community effectiveness of oxaliplatin in stage III colon cancer, we assembled five observational datasets from diverse treatment settings to compare oxaliplatin's effectiveness to the efficacy demonstrated in randomized phase III trials. To mirror the trial cohorts, we restricted our analyses to patients diagnosed before age 75 years.

The use of oxaliplatin-containing chemotherapy did improve survival in these effectiveness cohorts notable for their diversity, including patients cared for across the spectrum of treatment venues in the United States: at specialty cancer centers, academic

Table 3. Likelihood of oxaliplatin receipt in stage III colon cancer patients treated with adjuvant chemotherapy*

	Effectiveness: adjusted OR for oxaliplatin receipt within strata									
	SEER–Medicare (1445/2458)†		CanCORS (147/272)†		NYSCR–Medicaid, <65 y (66/290)†		NYSCR–Medicare, ≥65 y (228/446)†		NCCN (561/594)†	
Patient and clinical characteristics	Ox, N (%)	Adjusted OR (95% CI)	Ox, N (%)	Adjusted OR (95% CI)	Ox, N (%)	Adjusted OR (95% CI)	Ox, N (%)	Adjusted OR (95% CI)	Ox, N (%)	Adjusted OR (95% CI)
Age, y										
<50	28 (60)	1.04 (054 to 2.03)	24 (65)	2.79 (1.09 to 7.19)	28 (27)	1 (referent)	—	—	167 (97)	0.98 (0.18 to 5.22)
50–64	154 (61)	0.87 (0.64 to1.18)	84 (61)	2.09 (1.06 to 4.12)	38 (21)	0.64 (0.34 to 1.19)	—	—	266 (95)	0.65 (0.16 to 2.61)
65–69	717 (63)	1 (referent)	22 (43)	1	—	—	119 (54)	1 (referent)	77 (96)	1 (referent)
70–74	543 (53)	0.67 (0.56 to 0.81)	17 (37)	0.92 (0.38 to 2.23)	—	—	109 (48)	0.76 (0.51 to 1.14)	51 (82)	0.09 (0.02 to 0.43)
Sex										
Women	753 (59)	1 (referent)	53 (55)	1 (referent)	35 (24)	1 (referent)	123 (51)	1 (referent)	293 (94)	1 (referent)
Men	692 (59)	0.88 (0.74 to1.05)	94 (54)	1.14 (0.66 to1.96)	31 (21)	0.81 (0.43 to1.51)	105 (51)	0.93 (0.61 to 1.41)	268 (95)	1.30 (0.57 to 3.02)
Race‡										
White	1220 (60)	1 (referent)	105 (55)	1 (referent)	38 (24)	1 (referent)	199 (54)	1 (referent)	432 (95)	1 (referent)
Black	129 (48)	0.73 (0.55 to0.97)	29 (62)	1.12 (0.56 to 2.24)	20 (21)	1.05 (0.51 to2.11)	21 (36)	0.44 (0.23 to 0.83)	63 (89)	0.55 (0.19 to 1.55)
Asian	—		§	0.27 (0.07 to 0.97)	§	0.88 (0.31 to 2.33)	§	0.36 (0.13 to 0.91)	—	—
Other	96 (59)	0.88 (0.62 to1.24)	§	0.51 (0.20 to 1.31)					66 (99)	6.77 (0.68 to 67.63)
Latino										
Yes	93 (60)	1.04 (0.73 to1.50)	NA	NA	20 (27)	1.15 (0.54 to2.37)	13 (51)	1.19 (0.48 to 3.02)	34 (89)	0.30 (0.08 to 1.10)
No	1352 (59)	1 (referent)	—	—	46 (21)	1 (referent)	215 (51)	1 (referent)	486 (95)	1 (referent)
Performance status/comorbidity‖										
0/None	1287 (62)	1 (referent)	55 (62)	1 (referent)	48 (24)	1 (referent)	178 (54)	1 (referent)	433 (97)	1 (referent)
1/Mild	106 (43)	0.75 (0.56 to1.02)	58 (56)	0.85 (0.45 to 1.58)	§	1.37 (0.54 to 3.31)	36 (54)	1.02 (0.57 to 1.81)	77 (89)	0.37 (0.14 to 0.97)
≥2/Moderate	52 (35)	0.54 (0.37 to0.79)	22 (51)	0.82 (0.37 to1.84)	§	0.66 (0.18 to1.94)	14 (33)	0.51 (0.24 to 1.06)	51 (85)	0.22 (0.08 to 0.63)
Severe	—	—	12 (33)	0.35 (0.14 to 0.84)	—	—	—	—	—	—
Unknown	—	—	—	—	§	1.47 (0.42 to 4.55)	—	—	—	—
Marital status										
Married	919 (62)	1 (referent)	NA	NA	26 (27)	1	130 (51)	1 (referent)	NA	NA
Single	151 (55)	0.74 (0.56 to 1.00)	—	—	25 (21)	0.57 (0.28 to1.15)	27 (42)	0.60 (0.32 to 1.12)	—	—
Widowed/divorced	322 (53)	0.68 (0.55 to 0.84)	—	—	15 (24)	0.98 (0.41 to 2.28)	66 (54)	1.12 (0.68 to 1.83)	—	—
Other	53 (58)	0.76 (0.48 to 1.21)	—	—	0 (0)	0.00 (– to 3.78)	§	0.54 (0.13 to 2.13)	—	—
AJCC stage										
IIIA	177 (55)	1 (referent)	17 (49)	1 (referent)	§ (15)	1 (referent)	21 (39)	1 (referent)	66 (90)	1 (referent)
IIIB	748 (56)	1.15 (0.89 to1.50)	69 (51)	1.17 (0.53 to 2.58)	36 (21)	1.62 (0.48 to 7.47)	110 (48)	1.16 (0.60 to 2.25)	291 (95)	1.18 (0.34 to 4.06)
IIIC	518 (64)	1.54 (1.16 to 2.05)	53 (61)	1.57 (0.67 to 3.71)	27 (27)	2.08 (0.59 to 9.93)	94 (60)	2.00 (1.01 to 4.01)	201 (95)	1.08 (0.29 to 4.06)
III NOS	—		§	1.09 (0.26 to 4.50)	0 (0)				—	—
Differentiation										
Well/Moderate	996 (58)	1 (referent)	110 (55)	1 (referent)	44 (21)	1 (referent)	148 (51)	1 (referent)	392 (95)	1 (referent)
Un/Poor	407 (59)	0.97 (0.79 to1.18)	33 (49)	0.79 (0.42 to1.47)	21 (24)	1.13 (0.58 to 2.16)	69 (51)	0.94 (0.60 to 1.47)	148 (95)	0.90 (0.35 to 2.30)
Unknown	42 (63)	1.15 (0.67 to 1.97)	§	2.11 (0.30 to 4.98)	§	0.47 (0.02 to 3.17)	§ (57)	1.27 (0.39 to 4.35)	21 (81)	0.11 (0.02 to 0.48)
Median Income¶										
>$65000	227 (70)	2.13 (1.59 to 2.86)	NA	NA	§ (30)	1.21 (0.37 to 3.64)	52 (60)	0.96 (0.51 to 1.81)	144 (98)	3.83 (0.87 to16.77)
$50000–$65000	262 (63)	1.55 (1.20 to 1.99)	—	—	§	0.44 (0.15 to1.11)	42 (42)	0.55 (0.30 to 1.00)	132 (94)	1.21 (0.40 to 3.62)
$35000–$50000	466 (61)	1.35 (1.10 to 1.66)	—	—	20 (24)	0.88 (0.44 to1.75)	70 (51)	0.70 (0.40 to 1.22)	149 (93)	0.73 (0.27 to 2.01)
<$35000	491 (52)	1 (referent)	—	—	33 (24)	1 (referent)	61 (54)	1 (referent)	136 (93)	1 (referent)

(Table continues)

Table 3 (Continued).

Patient and clinical characteristics	Effectiveness: adjusted OR for oxaliplatin receipt within strata									
	SEER–Medicare (1445/2458)†		CanCORS (147/272)†		NYSCR–Medicaid, <65 y (66/290)†		NYSCR–Medicare, ≥65 y (228/446)†		NCCN (561/594)†	
	Ox, N (%)	Adjusted OR (95% CI)	Ox, N (%)	Adjusted OR (95% CI)	Ox, N (%)	Adjusted OR (95% CI)	Ox, N (%)	Adjusted OR (95% CI)	Ox, N (%)	Adjusted OR (95% CI)
Diagnosis year										
2004	255 (37)	1 (referent)	116 (53)	1 (referent)	§	1 (referent)	64 (42)	1 (referent)	—	—
2005	372 (61)	2.82 (2.23 to 3.55)	31 (60)	1.35 (0.70 to 2.63)	26 (27)	3.76 (1.68 to 9.01)	85 (54)	1.76 (1.10 to 2.84)	66 (92)	1 (referent)
2006	404 (70)	3.62 (2.81 to 4.66)	—	—	30 (33)	4.99 (2.22 to12.07)	76 (63)	2.55 (1.53 to 4.29)	137 (96)	1.86 (0.49 to7.01)
2007	414 (71)	3.87 (3.00 to 4.99)	—	—	—	—	—	—	124 (93)	0.99 (0.29 to 3.48)
2008	—	—	—	—	—	—	—	—	150 (94)	0.84 (0.24 to 2.90)
2009	—	—	—	—	—	—	—	—	84 (97)	1.78 (0.37 to 8.71)

* Percent of patients within each stratum treated with oxaliplatin and multivariable logistic regression of factors associated with receipt of oxaliplatin-containing compared with non–oxaliplatin-containing chemotherapy. ACE-27 = Adult Comorbidity Evaluation-27; AJCC = American Joint Committee on Cancer; CanCORS = Cancer Care Outcomes Research & Surveillance Consortium; CCI = Charlson Comorbidity Index; NCCN = National Comprehensive Cancer Network Outcomes Database; NYSCR–Medicaid = New York State Cancer Registry linked to Medicaid claims; NYSCR–Medicare = New York State Cancer Registry linked to Medicare claims; N = Node; NA = not available; OR = odds ratio; Ox = oxaliplatin; SEER–Medicare = Surveillance, Epidemiology, and End Results registry linked to Medicare claims; T = tumor.

† Patients receiving oxaliplatin/total No. of patients.

‡ Race: In SEER–Medicare, NYSCR–Medicaid, NYSCR–Medicare, and NCCN, Asian patients are included with "other" because of small numbers. In NCCN, the "unknown" patients are most likely non-Latinos, but they did not specifically state that.

§ N < 11. Value omitted to ensure patient confidentiality.

‖ Comorbidity: CanCORS reports comorbidity using the ACE-27, NCCN, the CCI, NYSCR, the Deyo modification of the CCI, and SEER–Medicare, the Deyo-Klabunde modification of the CCI.

¶ Income was measured categorically in CanCORS: >$60000; $40000–60000; $20000–40000; <$20000. Income is measured by census tract in SEER–Medicare and NYSCR cohorts. Because of missing values, income was not retained in the final model for CanCORS; however, when included in the full case, model estimates were not affected by inclusion of income.

oncology groups, community oncology practices, and Veterans Administration hospitals. Despite including patients from a wide array of treatment settings, 3-year survival was very similar in oxaliplatin-treated patients in all effectiveness cohorts and the efficacy cohort trial patients. After adjusting for key factors related to treatment selection and survival, the relative reduction in death rates from the addition of oxaliplatin in all effectiveness cohorts was comparable with the 20% relative reduction seen in the efficacy data and the MOSAIC trial and the 13% relative reduction in death from capecitabine/oxaliplatin compared with 5-FU recently reported by the XELOXA trial (6,30). The relative reductions in mortality were more profound in most effectiveness cohorts than the efficacy cohort, likely related to unmeasured confounding such as frailty that led patients treated in the community to forego oxaliplatin and thereby made the non-oxaliplatin group a more frail population.

Oxaliplatin use was associated with statistically significantly improved survival in the oldest age group investigated, 70–74 years, in the SEER–Medicare cohort, with a trend toward improved survival in NYSCR–Medicare. Older CanCORS patients did not benefit from oxaliplatin, although there was no suggestion of harm. Although adjuvant 5-FU clearly improves survival among older patients, the role of combination chemotherapy has been an area of concern (14,31–35). In the case of oxaliplatin/5-FU combinations, two publications (36,37) have suggested that older patients benefit from the addition of oxaliplatin, although a recent pooled analysis suggested oxaliplatin use might be harmful in patients older than 70 years (HR of death = 1.18, 95% CI = 0.90 to 1.57) (38). Although our findings do not support the notion of harm, only about half of this age group received oxaliplatin; thus, it is uncertain from this analysis whether expanding the use of oxaliplatin to the entire group of chemotherapy-treated patients aged 65–74 years would be safe or effective.

We also examined the comparative treatment effect within clinically relevant patient subgroups. Many of these subgroups were too small to yield precise estimates of oxaliplatin's effect; however, the benefit of oxaliplatin appeared to extend to patients with at least two comorbid conditions as defined by CCI in SEER–Medicare and by "moderate" comorbidity as defined by the ACE-27. The small group of oxaliplatin-treated patients with "severe" comorbidity in CanCORS had inferior survival; however, because we limited this investigation to patients who survived 30 days from resection and received their first dose of chemotherapy within 120 days, most patients with major comorbidity were excluded from the analysis.

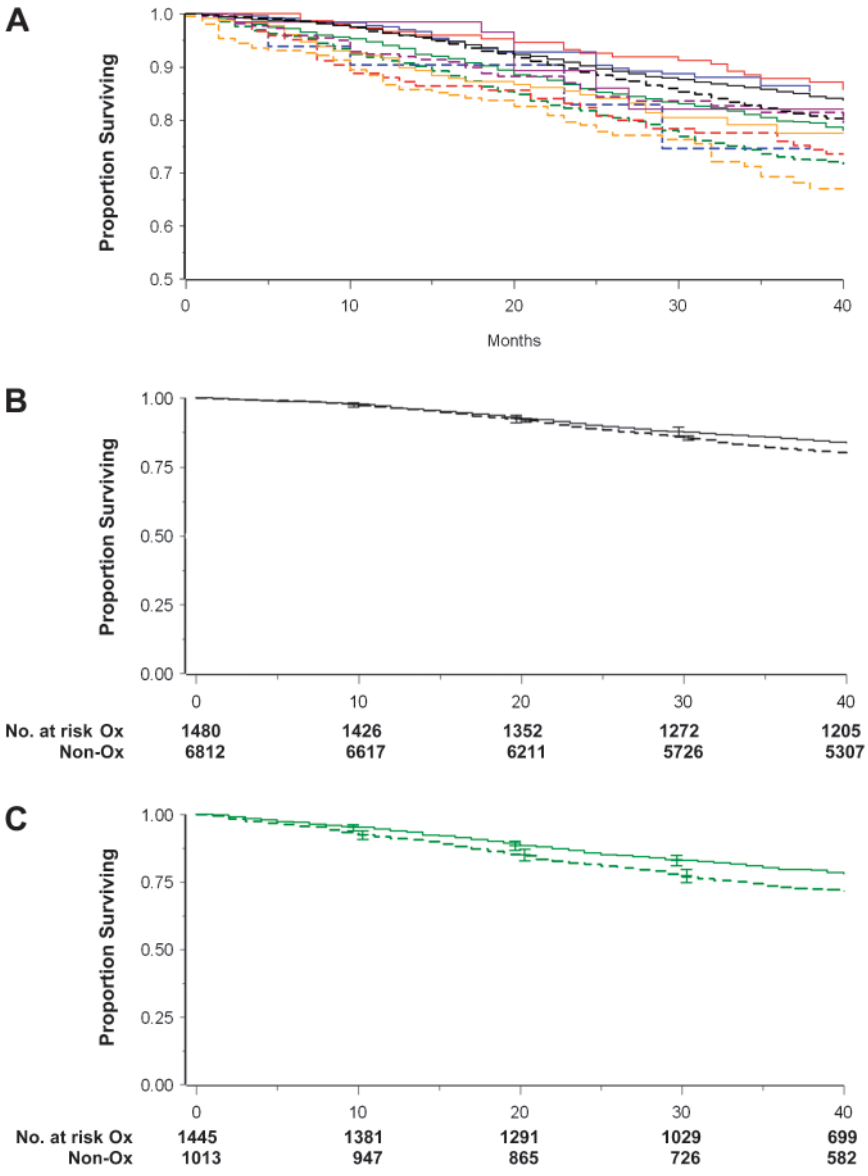
Subgroup analysis also found that oxaliplatin is associated with a similar reduction in death rates in blacks and whites in most cohorts, although variation among cohorts merits a more extensive examination. The small sample size of all racial and ethnic minorities even in this large multi-cohort investigation suggests that efforts specifically designed to study the outcomes of minority patients with colon cancer are warranted.

This study also had some other limitations besides small sample size of racial and ethnic minorities. A multicenter, multi-cohort comparative effectiveness project presents a number of challenges in the examination and interpretation of observational data from multiple sources. For example, different follow-up times among cohorts challenged a unified interpretation. In CanCORS, the effectiveness cohort with the longest follow-up, survival curves

converge around 45 months after which there appears to be no survival benefit from oxaliplatin (not shown); this was not the case in any other dataset. This convergence at a follow-up time point beyond that available in the other cohorts raises the possibility that the effect of oxaliplatin over time may not be as robust in the community as it was in the MOSAIC trial. Unfortunately, the short follow-up for most cohorts currently prevents investigation into whether oxaliplatin effect attenuates with time.

Our analysis was subject to the limitations of each data source. We limited our analyses to overall survival because it was reliably and consistently collected for each cohort; however, disease-free survival is a more direct indicator of colon cancer recurrence and thus failure of adjuvant treatment. Quality of life is another crucial metric that likely varies by the type of chemotherapy given. Neither disease-free survival nor quality of life could be reliably determined across the effectiveness cohorts.

Most importantly, notwithstanding our efforts to assemble comparable cohorts and our multivariable models, we could not eliminate the potential for confounding based on patient selection as a substantial cause of improved survival in oxaliplatin-treated patients. We used a traditional proportional hazards model to account for known relevant confounders rather than propensity score techniques because we found no evidence that subgroups of patients received only one of the compared treatments or nonuniform treatment effects over the propensity score (39,40). We performed a propensity score analysis to compare treatments among patients of similar risk profiles and found minimal differences between covariate-adjusted and propensity score–adjusted hazard ratios. However, both traditional proportional hazards models and propensity score techniques can only account for known measured confounders (41,42). Neither can overcome the inability to measure critical confounders that influence survival such as functional status. Nevertheless, whereas unmeasured confounding related to treatment selection is a potential problem in all effectiveness cohorts, and the confidence intervals crossed 1.0 in three of five cohorts, the consistency of our findings across diverse cohorts with



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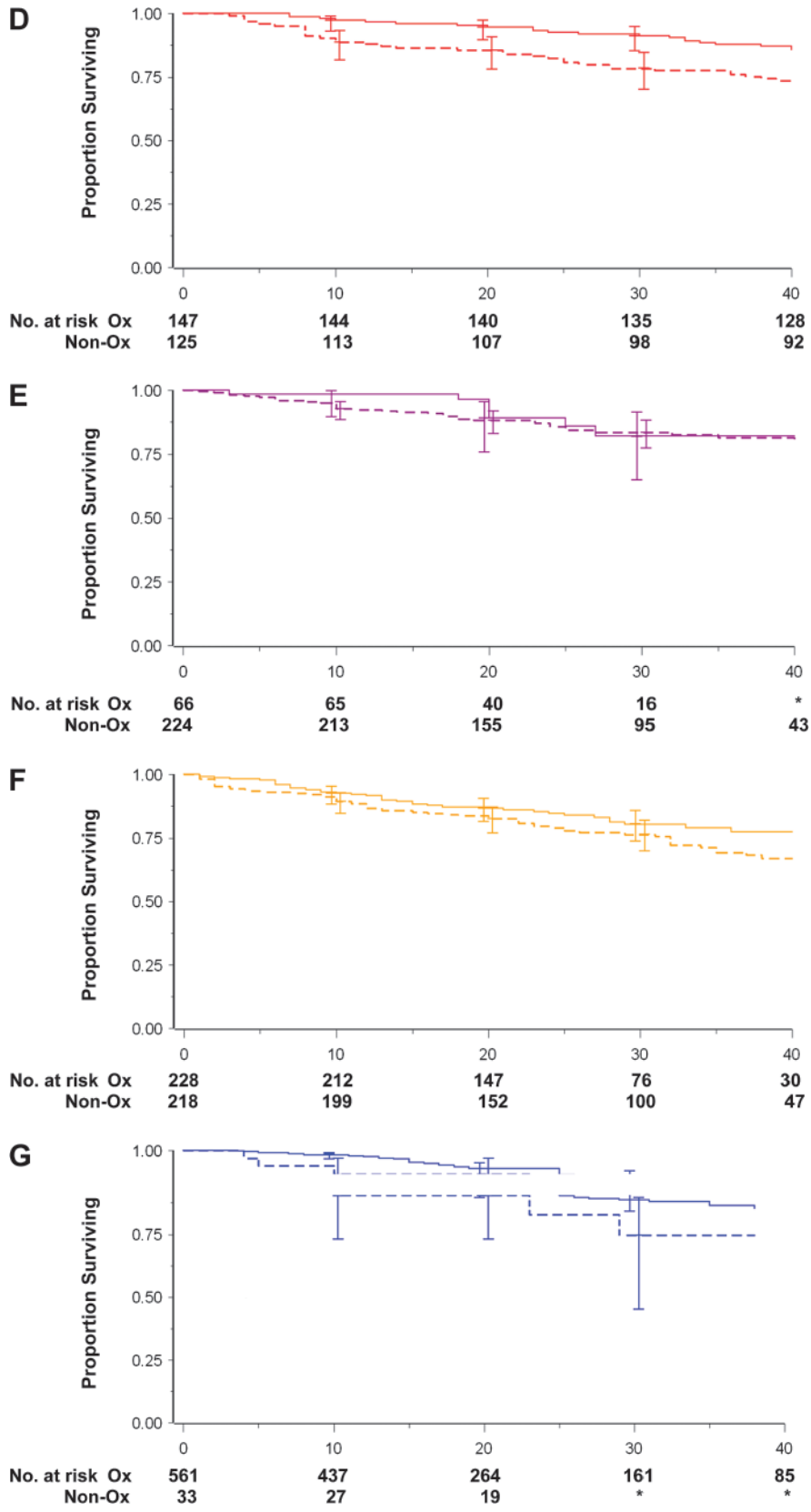

Figure 2. Comparison of Kaplan–Meier survival in months by treatment in stage III colon cancer patients treated with adjuvant chemotherapy by cohort. **Error bars** indicate 95% confidence intervals at 10-month intervals. Cox proportional hazards models were used to calculate the unadjusted hazard ratios (HRs) of death and 95% confidence intervals (CIs). Unadjusted hazard ratios were not calculated for ACCENT. All statistical tests were two-sided. **A**) All cohorts. **Solid line** = oxaliplatin; **Dotted line** = non-oxaliplatin. ACCENT shown in **black**; SEER–Medicare, **green**; CanCORS, **red**; NYSCR–Medicare, **yellow**; NYSCR–Medicaid, **purple**; NCCN, **blue**. **B**) ACCENT. **C**) SEER–Medicare (HR of death = 0.74, 95% CI = 0.63 to 0.86, $P < .001$). **D**) **CanCORS** (HR of death = 0.68, 95% CI = 0.44 to 1.04, $P = .07$). **E**) NYSCR–Medicaid (HR of death = 0.76, 95% CI = 0.34 to 1.72, $P = .51$). **F**) NYSCR–Medicare (HR of death = 0.70, 95% CI = 0.46 to 1.05, $P = .08$). **G**) NCCN (HR of death = 0.47, 95% CI = 0.18 to 1.20, $P = .11$). ACCENT = Adjuvant Colon Cancer End Points Group; CanCORS = Cancer Care Outcomes Research & Surveillance Consortium; NYSCR–Medicaid = New York State Cancer Registry linked to Medicaid claims; NYSCR–Medicare = New York State Cancer Registry linked to Medicare claims; NCCN = National Comprehensive Cancer Network Outcomes Database; SEER–Medicare = Surveillance Epidemiology and End Results registry linked to Medicare claims. *N < 11. Value omitted to ensure patient confidentiality.

different potential for bias suggests that oxaliplatin is not only efficacious in the clinical trial setting but also effective.

In summary, our analyses suggest that the benefit of oxaliplatin evident in clinical trials appears to manifest in day-to-day practice. Physicians and patients should be reassured from our findings that oxaliplatin is associated with marginally but consistently superior survival for patients diagnosed before age 75 years in community settings. Future research should examine the comparative effec-

Table 4. Effect of oxaliplatin treatment on overall survival of stage III colon cancer patients treated with chemotherapy*

Model estimates and patient and clinical characteristics	Efficacy†	Effectiveness				
	ACCENT, N = 8292	SEER–Medicare, N = 2458	CanCORS, N = 272	NYSCR–Medicaid, <65 y, N = 290	NYSCR-Medicare, ≥65 y, N = 446	NCCN‡, N = 594
Crude 3-year OS, N (%)						
Non-oxaliplatin	5586 (82)	746 (74)	98 (78)	181 (81)	150 (69)	25 (75)
Oxaliplatin	1273 (86)	1152 (80)	129 (88)	54 (82)	180 (79)	438 (86)
Cox model crude HR (95% CI), *P*	§	0.74 (0.63 to 0.86), <.001	0.68 (0.44 to 1.04), .07	0.76 (0.34 to 1.72), .51	0.70 (0.46 to 1.05), .08	0.47 (0.18 to 1.2), .11
Cox model adjusted HR (95% CI), *P*	0.80 (0.70 to 0.92), .002	0.70 (0.60 to 0.82), <.001	0.82 (0.50 to 1.32), .41	0.68(0.28 to 1.63), .38	0.58 (0.38 to 0.90), .02	0.35 (0.12 to 1.04), .06
Propensity score adjusted HR (95% CI), *P*	NA	0.70 (0.59 to 0.82), <.001	0.65 (0.38 to 1.12), .17	0.37(0.12 to 1.07), .07	0.55(0.35 to 0.86), .01	Not performed
		Adjusted HR for death for oxaliplatin compared with non-oxaliplatin chemotherapy within strata				
	Ox, N (%)	HR (95% CI)	Ox, N (%)	HR (95% CI)	Ox, N (%)	HR (95% CI)	Ox, N (%)	HR (95% CI)
Age, y								
<50	28 (60)	1.21 (0.42 to 3.49)	24 (65)	0.10 (0.01 to 1.17)	28 (27)	0.55 (0.12 to 2.43)	—	—
50–64	154 (61)	0.60 (0.37 to 0.97)	84 (61)	0.88 (0.37 to 2.12)	38 (21)	0.75 (0.27 to 2.06)	—	—
65–69	717 (63)	0.75 (0.59 to 0.95)	22 (43)	0.20 (0.05 to 0.84)	—	—	119 (54)	0.56 (0.33 to 0.95)
70–74	543 (53)	0.66 (0.52 to 0.84)	17 (37)	0.98 (0.28 to 3.40)	—	—	109 (48)	0.62 (0.36 to 1.07)
Sex								
Women	753 (59)	0.72 (0.58 to 0.90)	53 (55)	1.02 (0.28 to 3.69)	35 (24)	0.37 (0.08 to 1.67)	123 (51)	0.60 (0.36 to 0.98)
Men	692 (59)	0.68 (0.54 to 0.85)	94 (54)	0.70 (0.40 to 1.23)	31 (21)	1.04 (0.36 to 3.01)	105 (51)	0.57 (0.31 to 1.05)
Race‖								
White	1220 (60)	0.75 (0.62 to 0.89)	105 (55)	0.82 (0.45 to 1.49)	38 (24)	0.18 (0.02 to 1.43)	199 (54)	0.61 (0.39 to 0.94)
Black	129 (48)	0.48 (0.23 to 1.01)	29 (62)	0.39 (0.07 to 2.18)	20 (21)	1.67 (0.65 to 4.31)	21 (36)	0.71 (0.25 to 2.04)
Asian	—		¶	#	¶		¶	
Other	96 (59)	0.52 (0.33 to 0.84)	¶	#				
Performance status /comorbidity**								
0/None	1287 (62)	0.75 (0.62 to 0.89)	55 (62)	0.39 (0.12 to 1.32)	48 (24)	0.51 (0.17 to 1.53)	178 (54)	0.46 (0.28 to 0.74)
1/Mild	106 (43)	0.54 (0.34 to 0.88)	58 (56)	0.71 (0.30 to 1.67)	¶	1.54 (0.34 to 6.98)	36 (54)	0.85 (0.39 to 1.87)
≥2/Moderate	52 (35)	0.54 (0.31 to 0.95)	22 (51)	0.43 (0.10 to 1.82)	¶	††	14 (33)	1.20 (0.42 to 3.44)
Severe			12 (33)	6.70 (0.52 to 86.1)				
AJCC stage								
IIIA	177 (55)	0.64 (0.35 to 1.33)	17 (49)	#	¶	‡‡	21 (39)	‡‡
IIIB	748 (56)	0.65 (0.47 to 0.81)	69 (51)	0.86 (0.44 to 1.70)	36 (21)	0.84 (0.28 to 2.56)	110 (48)	0.34 (0.18 to 0.65)
IIIC	518 (64)	0.76 (0.61 to 0.96)	53 (61)	0.59 (0.27 to 1.32)	27 (27)	0.64 (0.18 to 2.25)	94 (60)	1.31 (0.80 to 2.13)
III NOS			¶	#	0 (0)	#		

(Table continues)

Table 4 (Continued).

Model estimates and patient and clinical characteristics	Efficacy†	Effectiveness							
	ACCENT, N = 8292	SEER–Medicare, N = 2458		CanCORS, N = 272		NYSCR–Medicaid, <65 y, N = 290	NYSCR-Medicare, ≥65 y, N = 446	NCCN‡, N = 594	
Diagnosis year									
2004		255 (37)	0.80 (0.61 to 1.04)	116 (53)	0.82 (0.48 to 1.40)	¶	0.34 (0.04 to 2.71)	64 (42)	0.48 (0.26 to 0.90)
2005		372 (61)	0.61 (0.45 to 0.84)	31 (60)	1.55 (0.29 to 8.34)	26 (27)	1.24 (0.46 to 3.37)	85 (54)	0.65 (0.35 to 1.20)
2006		404 (70)	0.84 (0.58 to 1.21)			30 (33)	0.30 (0.04 to 2.32)	76 (63)	0.77 (0.39 to 1.52)
2007		414 (71)	0.55 (0.39 to 0.79)	—	—				

* Crude 3-year overall survival is shown for each cohort. A multivariable Cox proportional hazards model of survival according to patient and tumor characteristics for each cohort is shown. The number and percent of patients within each of the reported strata who received oxaliplatin is shown. A propensity score–adjusted proportional hazards model for survival is also shown for all effectiveness cohorts except NCCN. For SEER–Medicare, CanCORS, NYSCR–Medicaid and Medicare populations, a separate Cox proportional hazards model comparing the effect of oxaliplatin with non-oxaliplatin treatment was run within each stratum for key covariates. Stratified and propensity score analysis were not completed for NCCN because of the small number of non–oxaliplatin-treated patients. All statistical tests were two-sided. ACCENT = Adjuvant Colon Cancer End Points Group; ACE-27 = Adult Comorbidity Evaluation-27; AJCC = American Joint Committee on Cancer; CanCORS = Cancer Care Outcomes Research & Surveillance Consortium; CCI = Charlson Comorbidity Index; HR = hazard ratio; NA = not available; NCCN = National Comprehensive Cancer Network Outcomes Database; NYSCR–Medicaid = New York State Cancer Registry linked to Medicaid claims; NYSCR–Medicare = New York State Cancer Registry linked to Medicare claims; OS = overall survival; SEER–Medicare = Surveillance Epidemiology and End Results registry linked to Medicare claims.

† The efficacy model is adjusted for age, sex, race, performance status, tumor substage, year of diagnosis. Effectiveness models are adjusted for age, sex, race/ethnicity, comorbidity, marital status, tumor substage, tumor grade, income, year of diagnosis. Because of missing values, income was not retained in the final model for CanCORS; however, when included in the full case model, estimates were not affected by inclusion of income.

‡ Stratified hazard models not performed for NCCN given small number of non-oxaliplatin patients.

§ Crude HR not reported. Among stage III patients in the MOSAIC trial, the crude HR was 0.80, 95% CI = 0.65 to 0.97 [reported in Andre et al. (6)].

‖ Race: In SEER–Medicare, NCCN, and NYSCR, Asian patients are included with "other" because of small numbers.

¶ N < 11. Value omitted to ensure patient confidentiality.

Hazards inestimable because of too small sample size.

** Comorbidity: CanCORS reports comorbidity using the ACE-27, NCCN, the CCI, NYSCR, the Deyo modification of the CCI, and SEER–Medicare reports the Deyo-Klabunde modification of the CCI.

†† In NYSCR–Medicaid cohort, CCI 1 and ≥2 collapsed because of small numbers.

‡‡ In NYSCR–Medicaid and NYSCR–Medicare cohorts, stage IIIA and IIIB collapsed because of small numbers.

Table 5. Adjusted overall survival of stage III colon cancer patients treated with chemotherapy*

Patient and clinical characteristics	Efficacy	Effectiveness				
	ACCENT, N = 8292	SEER–Medicare, N = 2458	CanCORS, N = 272		NYSCR–Medicaid, <65 y, N = 290	NYSCR–Medicare, ≥65 y, N = 446	NCCN, N = 594
	Adjusted HR for death (95% CI)						
Non-oxaliplatin	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)	1 (referent)
Oxaliplatin	0.80 (0.70 to 0.92)	0.70 (0.60 to 0.82)	0.82 (0.50 to 1.32)		0.68 (0.28 to 1.62)	0.58 (0.38 to 0.90)	0.35 (0.12 to 1.04)
Age, y							
<50	0.74 (0.65 to 0.85)	1.47 (0.88 to 2.45)	0.91 (0.41 to 1.99)		1 (referent)		0.37 (0.15 to 0.95)
50–64	0.84 (0.75 to 0.93)	1.03 (0.78 to 1.35)	0.55 (0.29 to 1.02)		0.98 (0.50 to 1.90)		0.32 (0.14 to 0.74)
65–69	1 (referent)	1 (referent)	1 (referent)		—	1 (referent)	1 (referent)
70–74	1.11 (0.97 to 1.26)	1.20 (1.02 to 1.42)	1.21 (0.63 to 2.34)		—	1.41 (0.92 to 2.17)	0.22 (0.07 to 0.69)
Sex							
Women	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)	1 (referent)
Men	1.14 (1.05 to 1.23)	1.20 (1.03 to 1.41)	2.08 (1.20 to 3.70)		0.73 (0.36 to 1.49)	1.09 (0.70 to 1.69)	0.94 (0.50 to 1.78)
Race†							
White	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)	1 (referent)
Black	1.28 (0.99 to 1.67)	1.05 (0.82 to 1.35)	1.59 (0.83 to 3.03)		1.54 (0.76 to 3.10)	1.69 (1.00 to 2.85)	0.65 (0.23 to 1.86)
Asian	—	—	0.77 (0.17 to 3.36)			‡	—
Other	0.87 (0.65 to 1.16)	0.65 (0.44 to 0.94)	0.63 (0.28 to 1.44)				1.08 (0.33 to 3.61)
Latino							
Yes	NA	1.08 (0.80 to 1.46)	NA		0.30 (0.12 to 0.76)	1.86 (0.92 to 3.75)	1 (referent)
No	—	1 (referent)	—		1 (referent)	1 (referent)	1.09 (0.30 to 3.96)
Performance status/comorbidity§							
0/None	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)	1 (referent)
1/Mild	1.09 (0.94 to 1.28)	1.11 (0.86 to 1.43)	0.99 (0.51 to 1.90)		0.86 (0.34 to 2.18)	1.06 (0.57 to 1.97)	2.11 (0.85 to 5.24)
≥2/Moderate	‖	1.59 (1.21 to 2.09)	2.16 (1.04 to 4.45)		1.05 (0.36 to 3.07)	2.86 (1.61 to 5.06)	5.49 (2.53 to 11.90)
Severe	—		3.17 (1.50 to 6.70)				—
AJCC stage							
IIIA	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	
IIIB	2.14 (1.74 to 2.64)	2.82 (1.94 to 4.10)	2.86 (1.01 to 8.15)	1 (referent)¶	2.44 (0.85 to 7.00)	1 (referent)¶	
IIIC	4.12 (3.35 to 5.08)	5.36 (3.68 to 7.81)	3.37 (1.16 to 9.82)	2.56 (1.28 to 5.13)	6.36 (2.24 to 18.1)	5.79 (2.86 to 11.69)	
Diagnosis year							
1998	1.14 (0.57 to 2.30)						
1999	1 (referent)						
2000	0.91 (0.80 to 1.03)	—	—	—	—	—	
2001	0.89 (0.77 to 1.03)	—	—	—	—	—	
2002	0.93 (0.77 to 1.12)	—	—	—	—	—	
2003	—	—	—	—	—	—	

(Table continues)

Table 5 (Continued).

Patient and clinical characteristics	Efficacy	Effectiveness					
	ACCENT, N = 8292	SEER–Medicare, N = 2458	CanCORS, N = 272		NYSCR–Medicaid, <65 y, N = 290	NYSCR–Medicare, ≥65 y, N = 446	NCCN, N = 594
	Adjusted HR for death (95% CI)						
2004	—	1 (referent)	1 (referent)	1 (referent)	1 (referent)		
2005	—	0.88 (0.72 to 1.09)	0.82 (0.44 to 1.56)	1.04 (0.47 to 2.28)	1.34 (0.82 to 2.21)	1 (referent)	
2006	—	1.06 (0.83 to 1.34)	—	0.69 (0.25 to 1.91)	1.27 (0.68 to 2.37)	0.53 (0.24 to 1.18)	
2007	—	1.40 (1.09 to 1.79)	—	—	—	0.50 (0.18 to 1.39)	
2008	—	—	—	—	—	0.70 (0.22 to 2.24)	
2009	—	—	—	—	—	4.0 (0.99 to 16.17)	

* A multivariable Cox proportional hazards model of death according to patient and tumor characteristics for each cohort is shown. All statistical tests were two-sided. The efficacy model is adjusted for age, sex, race, performance status, tumor substage, year of diagnosis. Effectiveness models are adjusted for age, sex, race/ethnicity, comorbidity, marital status, tumor substage, tumor grade, income, year of diagnosis. Because of missing values, income was not retained in the final model for CanCORS, however when included in the full case model, estimates were not affected by inclusion of income. ACE = Adult Comorbidity Evaluation; ACCENT = Adjuvant Colon Cancer End Points Group; AJCC = American Joint Committee on Cancer; CanCORS = Cancer Care Outcomes Research & Surveillance Consortium; CCI = Charlson Comorbidity Index; HR = hazard ratio; NA = not available; NCCN = National Comprehensive Cancer Network Outcomes Database; NYSCR–Medicaid = New York State Cancer Registry linked to Medicaid claims; NYSCR–Medicare = New York State Cancer Registry linked to Medicare claims; OS = overall survival; SEER–Medicare = Surveillance Epidemiology and End Results registry linked to Medicare claims.

† Race: In SEER–Medicare, NCCN, and NYSCR, Asian patients are included with "other" because of small numbers.

‡ HR inestimable, no events in Asian patients.

§ Comorbidity: CanCORS reports comorbidity using the ACE-27, NCCN, the CCI, NYSCR, the Deyo modification of the CCI, and SEER–Medicare, the Deyo-Klabunde modification of the CCI.

‖ In ACCENT, performance status 1 and 2 collapsed because of small numbers.

¶ In NCCN and NYSCR–Medicaid, stage IIIA and IIIB collapsed because of small numbers.

tiveness and safety of oxaliplatin in high-risk subgroups including patients older than 75 years, patients with severe comorbidity, and racial and ethnic minorities. Systematic methods for the study of these groups must be implemented for comparative effectiveness research to successfully address their outcomes.

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