Received: 25 June 2021 | Revised: 19 August 2021 | Accepted: 30 August 2021

DOI: 10.1002/ijc.33806

CANCER THERAPY AND PREVENTION

IJC International Journal of Cancer

Survival outcomes associated with completion of adjuvant oxaliplatin-based chemotherapy for stage III colon cancer: A national population-based study

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Funding information
This work was supported by a National Institute for Health Research (NIHR) Advanced Fellowship (NIHR300599) to Ajay Aggarwal and by the Medical Research Council (MR/S020470/1) to Thomas E. Cowling. These grant sources had no involvement in the study design; collection, analysis and interpretation of data; in writing of the report or decision to submit the article for publication.

Abstract

The impact of cycle completion rates of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer in real-world practice is unknown. We assessed its impact, and that of treatment modification, on 3-year cancer-specific mortality. Four thousand one hundred and forty-seven patients with pathological stage III colon cancer undergoing major resection from 2014 to 2017 in the English National Health Service were included. Chemotherapy data came from linked national administrative datasets. Competing risk regression analysis for 3-year cancer-specific mortality was performed according to completion of <6, 6-11, or 12 5-fluoropyrimidine and oxaliplatin (FOLFOX) cycles, or <4, 4-7, or 8 capecitabine and oxaliplatin (CAPOX) cycles, adjusted for patient, tumour and hospital-level characteristics. Median age was 64 years. Thirty-two per cent of patients had at least one comorbidity. Forty-two per cent of patients had T4 disease, and 40% had N2 disease. Compared to completion of 12 FOLFOX cycles, cancer-specific mortality was higher in patients completing <6 cycles [subdistribution hazard ratios (sHR) 2.17; 95% CI 1.56-3.03] or 6-11 cycles (sHR 1.40; 95% CI 1.09-1.78) ($P < .001$). Compared to completion of 8 CAPOX cycles, cancer-specific mortality was higher in patients completing <4 cycles (sHR 2.02; 95% CI 1.53-2.67) or 4-7 cycles (sHR 1.63; 95% CI 1.27-2.10) ($P < .001$). Dose reduction and early oxaliplatin discontinuation did not impact mortality in patients completing all cycles. Completion of all cycles of chemotherapy was associated with improved cancer-specific survival in real-world practice. Poor prognostic factors may have affected findings, however, patients completing <50% of cycles had poor outcomes. Clinicians may wish to facilitate completion with treatment modification in those able to tolerate it.

Abbreviations: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FOLFOX, 5-fluoropyrimidine and oxaliplatin; HES-APC, Hospital Episode Statistics Admitted Patient Care; ICD-10, International Classification of Diseases 10th edition; IMD, Index of Multiple Deprivation; IMDQ, Index of Multiple Deprivation Quintile; NBOCA, National Bowel Cancer Audit; NHS, National Health Service; ONS, Office for National Statistics; OPCS-4, Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, fourth revision; RCT, randomised controlled trial; SACT, systemic anticancer therapy; sHR, subdistribution hazard ratios.

Kate Walker, Michael S. Braun and Ajay Aggarwal are joint senior authors.

KEYWORDS
adjuvant chemotherapy, colon cancer, completion of treatment, epidemiology, stage III, survival

What's New

Adjuvant chemotherapy following curative surgical resection is an established treatment for stage III colon cancer. However, many patients do not complete the planned duration of chemotherapy. This is the largest cohort study in real-world practice to evaluate cancer-specific survival according to the cycle completion rate of oxaliplatin-based adjuvant chemotherapy in stage III colon cancer patients, and the first to assess the impact of treatment modification strategies. The results show that patients who do not complete their planned cycles have significantly poorer outcomes. In the absence of demonstrated negative impacts, clinicians could use treatment modifications to facilitate completion of adjuvant chemotherapy.

1 | INTRODUCTION

Adjuvant chemotherapy after a planned curative surgical resection for stage III colon cancer is an established treatment.[1,2] However, many patients do not complete the planned duration of chemotherapy, even in clinical trials, and in real-world practice this proportion is even higher with non-completion rates reported as high as 45%.[3,4] The impact of not completing adjuvant oxaliplatin-based chemotherapy on patient outcomes in real-world practice is unknown.

FOLFOX and CAPOX have been shown in RCTs to improve outcomes compared to fluoropyrimidines alone.[5-7] After publication of this data, standard practice involved 6 months of adjuvant chemotherapy (8 cycles of CAPOX or 12 cycles of FOLFOX). However, long-term morbidity, in particular cumulative neurotoxicity associated with oxaliplatin-based chemotherapy, is concerning.[5]

The recent IDEA collaborative study sought to establish the impact of reducing treatment duration by comparing 6 months treatment to 3 months (4 cycles of CAPOX or 6 cycles of FOLFOX).[8,9] Although the study failed to demonstrate overall noninferiority of a reduced target of 3 months of oxaliplatin-based chemotherapy, subgroup analysis suggested that 3 months of CAPOX, particularly in patients with low-risk disease, may be as effective as 6 months with reduced toxicity. The study found that those prescribed FOLFOX, or with high-risk disease, may still benefit from longer target durations.[8-10]

Evidence comparing the efficacy of different target durations of adjuvant chemotherapy comes from high quality, large RCTs.[5,11,12] RCTs, however, include highly selected patient populations under rigorously controlled conditions, generally underrepresenting elderly, frail and comorbid patients. One study showed that 59% of stage II or III colon cancer patients in a real-world setting would not be eligible for RCT inclusion.[13] Population-based studies, using data such as electronic healthcare records, are needed to assess the effectiveness of actual durations of adjuvant chemotherapy on outcomes in diverse non-selected populations under routine clinical conditions to complement trial findings.[14-18]

To date, observational studies evaluating the impact of cycle completion rates for oxaliplatin-based adjuvant chemotherapy on survival for colon cancer have been limited by a lack of accountability for important confounders, and their small sample size (most have fewer than 500 patients).[19] In addition, previous studies have not evaluated the survival impacts of treatment modifications (eg, dose reductions) which aim to reduce toxicity and support completion of the target duration of therapy.

In this national population-based study using linked administrative datasets, we assessed the impact of the cycle completion rate of oxaliplatin-based adjuvant chemotherapy on cancer-specific survival for stage III colon cancer patients treated in the English NHS, accounting for important confounders in the largest observational study to date. In addition, the effects of treatment modification on cancer-specific survival, namely dose reduction and early discontinuation of oxaliplatin, were analysed.

2 | METHODS

2.1 | Study population

Our study used NBOCA data,[20] HES-APC[21] and SACT data[22] linked at patient-level.

2.1.1 | National Bowel Cancer Audit

NBOCA is a prospective mandatory database for all newly diagnosed colorectal cancer patients in the English NHS. Patients aged 18 years and above with a primary diagnosis of colon cancer, according to ICD-10 code C18, undergoing major resection between June 1, 2014 and April 30, 2017 with pathological stage III colon cancer were identified in the NBOCA database. Cancers of the appendix were excluded.

2.1.2 | Hospital episode statistics admitted patient care

HES-APC is an administrative dataset of all admissions to English NHS hospitals. Inpatient and day case chemotherapy use is captured via clinical coding, primarily through dedicated OPCS-4 codes,[23] with chemotherapy-related ICD-10 codes also available.[24]

2.1.3 | Systemic anticancer therapy database

SACT is a dedicated chemotherapy dataset held by the National Cancer Registry and Analysis Service.[25] Data collection is largely done via electronic prescribing systems. It includes the capture of detailed drug-level information such as administration date, drug name, dose, and administration route for each cycle of chemotherapy. SACT records chemotherapy administered in any inpatient, day case, outpatient, or community setting.[22]

SACT and HES-APC data from June 30, 2014 until April 30, 2018 were used because not all English NHS chemotherapy providers were submitting SACT data before that period.[22] This ensured that all patients had a minimum of 12 months SACT and HES-APC follow-up data from the NBOCA date of surgery to allow adequate time for adjuvant chemotherapy completion, accounting for potential delays.

Previously established methods were used to ascertain adjuvant chemotherapy receipt, regimen, and number of recorded cycles making use of the information in both SACT and HES-APC.[26] Patients receiving oxaliplatin-based adjuvant chemotherapy according to either SACT or HES-APC were included in the analysis (Figure 1).

2.2 | Study outcome and comparison groups

The primary outcome was colorectal cancer-specific death within 3 years from the date of the first cycle of adjuvant chemotherapy. Date and underlying cause of death were obtained from linkage to official death records provided by the ONS.[27] The date of the latest available death record was 10th February 2020, at which point follow-up times were censored.

Levels of completion of chemotherapy cycles were compared, separately for each regimen. Completion was compared in the groups <50%, 50%-92%, and 100% (<6 cycles, 6-11 cycles, 12 cycles FOLFOX and <4 cycles, 4-7 cycles, 8 cycles CAPOX).

Separate subanalyses were undertaken to evaluate two common treatment modification strategies: dose reduction and early discontinuation of oxaliplatin, both stratified by regimen. For these analyses, only patients completing 12 cycles of FOLFOX or 8 cycles of CAPOX, and with linked SACT records were included (3375 patients). Dose reduction is a binary (yes/no) variable within SACT which refers to dose reduction of "any anti-cancer drug administered at any point in the regimen after commencement of the regimen".[22] Discontinuation of oxaliplatin was derived from drug-level information.

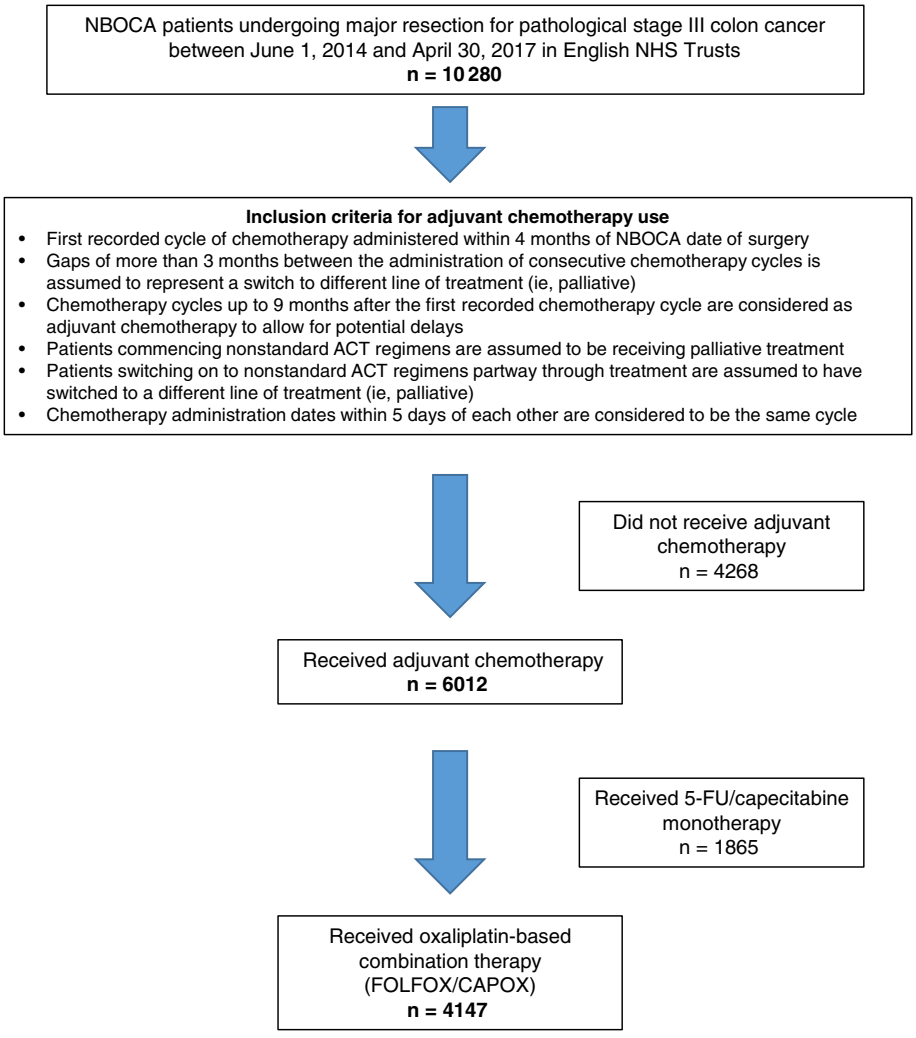

FIGURE 1 Flow chart showing inclusion of patients [Color figure can be viewed at wileyonlinelibrary.com]

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TABLE 1 Patient, tumour, and hospital-level characteristics according to level of completion of adjuvant chemotherapy (n = 4147)

	FOLFOX (n = 1776)					CAPOX (n = 2371)				
	<50% (n = 236)	50%-92% (n = 659)	100% (n = 881)	Total		<50% (n=381)	50%-92% (n = 824)	100% (n = 1166)	Total	
	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)
Sex					**<.001**					.125
Male	110 (46.6)	318 (48.3)	503 (57.1)	931 (52.4)		191 (50.1)	446 (54.1)	654 (56.1)	1291 (54.4)	
Female	126 (53.4)	341 (51.7)	378 (42.9)	845 (47.6)		190 (49.9)	378 (45.9)	512 (43.9)	1080 (45.6)	
Age, years					.318					**<.001**
<60	72 (30.5)	218 (33.1)	320 (36.3)	610 (34.3)		100 (26.2)	284 (34.5)	430 (36.9)	814 (34.3)	
60-69	86 (36.4)	264 (40.1)	336 (38.1)	686 (38.6)		162 (42.5)	321 (39.0)	493 (42.3)	976 (41.2)	
70-79	72 (30.5)	165 (25.0)	210 (23.8)	447 (25.2)		114 (29.9)	208 (25.2)	231 (19.8)	553 (23.3)	
≥80	6 (2.5)	12 (1.8)	15 (1.7)	33 (1.9)		5 (1.3)	11 (1.3)	12 (1.0)	28 (1.2)	
IMDQ					.073					.693
1 (most deprived)	31 (13.1)	96 (14.6)	112 (12.7)	239 (13.5)		56 (14.7)	110 (13.4)	140 (12.0)	306 (12.9)	
2	35 (14.8)	114 (17.4)	158 (18.0)	307 (17.3)		68 (17.8)	137 (16.6)	203 (17.4)	408 (17.2)	
3	55 (23.3)	105 (16.0)	168 (19.1)	328 (18.5)		85 (22.3)	200 (24.3)	280 (24.0)	565 (23.8)	
4	62 (26.3)	172 (26.2)	190 (21.6)	424 (23.9)		87 (22.8)	165 (20.0)	264 (22.7)	516 (21.8)	
5 (least deprived)	53 (22.5)	170 (25.9)	252 (28.6)	475 (26.7)		85 (22.3)	211 (25.6)	278 (23.9)	574 (24.2)	
Missing	0	2 (0.3)	1 (0.1)	3 (0.2)		0	1 (0.1)	1 (0.1)	2 (<0.1)	
RCS Charlson Score					.179					.226
0	147 (62.3)	441 (66.9)	605 (68.7)	1193 (67.2)		248 (65.1)	549 (66.6)	819 (70.2)	1616 (68.2)	
1	65 (27.5)	177 (26.9)	218 (24.7)	460 (25.9)		106 (27.8)	227 (27.5)	288 (24.7)	621 (26.2)	
≥2	24 (10.2)	41 (6.2)	58 (6.6)	123 (6.9)		27 (7.1)	48 (5.8)	59 (5.1)	134 (5.7)	
Cardiac history					**.012**					.493
Yes	19 (8.1)	27 (4.1)	32 (3.6)	78 (4.4)		16 (4.2)	24 (2.9)	37 (3.2)	77 (3.2)	
No	217 (91.9)	632 (95.9)	849 (96.4)	1698 (95.6)		365 (95.8)	800 (97.1)	1129 (96.8)	2294 (96.8)	
Liver disease					.826					.076
Yes	10 (4.2)	25 (3.8)	39 (4.4)	74 (4.2)		19 (5.0)	25 (3.0)	31 (2.7)	75 (3.2)	
No	226 (95.8)	634 (96.2)	842 (95.6)	1702 (95.8)		362 (95.0)	799 (97.0)	1135 (97.3)	2296 (96.8)	
Renal disease					**.042**					.300
Yes	12 (5.1)	24 (3.6)	19 (2.2)	55 (3.1)		14 (3.7)	23 (2.8)	26 (2.2)	63 (2.7)	
No	224 (94.9)	635 (96.4)	862 (97.8)	1721 (96.9)		367 (96.3)	801 (97.2)	1140 (97.8)	2308 (97.3)	

TABLE 1 (Continued)

	FOLFOX (n = 1776)					CAPOX (n = 2371)				
	<50% (n = 236)	50%-92% (n = 659)	100% (n = 881)	Total		<50% (n=381)	50%-92% (n = 824)	100% (n = 1166)	Total	
	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)
Performance status					.172					.320
0	123 (61.8)	371 (65.5)	515 (64.9)	1009 (56.8)		218 (66.3)	465 (65.9)	695 (68.3)	1378 (58.1)	
1	59 (29.6)	151 (26.7)	237 (29.9)	447 (25.2)		88 (26.7)	184 (26.1)	266 (26.2)	538 (22.7)	
≥2	17 (8.5)	44 (7.8)	41 (5.2)	102 (5.7)		23 (7.0)	57 (8.1)	56 (5.5)	136 (5.7)	
Missing	37 (15.7)	93 (14.1)	88 (10.0)	218 (12.3)		52 (13.6)	118 (14.3)	149 (12.8)	319 (13.5)	
Pathological T-stage					.972					.887
T1/T2	16 (6.8)	45 (6.8)	63 (7.2)	124 (7.0)		34 (8.9)	87 (10.6)	111 (9.5)	232 (9.8)	
T3	118 (50.0)	343 (52.0)	445 (50.6)	906 (51.0)		187 (49.1)	404 (49.1)	570 (48.9)	1161 (49.0)	
T4	102 (43.2)	271 (41.1)	372 (42.3)	745 (41.9)		160 (42.0)	332 (40.3)	485 (41.6)	977 (41.2)	
Missing	0	0	1 (0.1)	1 (<0.1)		0	1 (0.1)	0	1 (<0.1)	
Pathological N-stage					.778					**.027**
N1	143 (60.6)	382 (58.0)	515 (58.5)	1040 (58.6)		254 (66.7)	492 (59.7)	689 (59.1)	1435 (60.5)	
N2	93 (39.4)	277 (42.0)	366 (41.5)	736 (41.4)		127 (33.3)	332 (40.3)	477 (40.9)	936 (39.5)	
Surgical urgency					**.035**					.203
Elective/scheduled	166 (70.3)	517 (78.7)	673 (76.5)	1356 (76.4)		317 (83.2)	677 (82.3)	930 (79.8)	1924 (81.1)	
Emergency/urgent	70 (29.7)	140 (21.3)	207 (23.5)	417 (23.5)		64 (16.8)	146 (17.7)	236 (20.2)	446 (18.8)	
Missing	0	2 (0.3)	1 (0.1)	3 (0.2)		0	1 (0.1)	0	1 (<0.1)	
Unplanned readmission					.314					.821
Yes	22 (9.3)	44 (6.7)	74 (8.4)	140 (7.9)		28 (7.3)	65 (7.9)	97 (8.3)	190 (8.0)	
No	214 (90.7)	615 (93.3)	807 (91.6)	1636 (92.1)		353 (92.7)	759 (92.1)	1069 (91.7)	2181 (92.0)	
Surgical access					.191					.270
Open	95 (40.4)	242 (36.9)	333 (37.9)	670 (37.7)		115 (30.2)	264 (32.2)	393 (33.9)	772 (32.6)	
Laparoscopic converted	28 (11.9)	50 (7.6)	79 (9.0)	157 (8.8)		33 (8.7)	75 (9.1)	79 (6.8)	187 (7.9)	
Laparoscopic	112 (47.7)	363 (55.4)	467 (53.1)	942 (53.0)		233 (61.2)	482 (58.7)	689 (59.3)	1404 (59.2)	
Missing	1 (0.4)	4 (0.6)	2 (0.2)	7 (0.4)		0	3 (0.4)	5 (0.4)	8 (0.3)	
Time from surgery					**.025**					.123
<8 weeks	124 (52.5)	299 (45.4)	376 (42.7)	799 (45.0)		166 (43.6)	355 (43.1)	456 (39.1)	977 (41.2)	
≥8 weeks	112 (47.5)	360 (54.6)	505 (57.3)	977 (55.0)		215 (56.4)	469 (56.9)	710 (60.9)	1394 (58.8)	

(Continues)

TABLE 1 (Continued)

	FOLFOX (n = 1776)					CAPOX (n = 2371)				
	<50% (n = 236)	50%-92% (n = 659)	100% (n = 881)	Total		<50% (n=381)	50%-92% (n = 824)	100% (n = 1166)	Total	
	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)
Chemotherapy on-site					**.039**					**.047**
Yes	219 (92.8)	571 (86.6)	781 (88.6)	1571 (88.5)		336 (88.2)	723 (87.7)	1061 (91.0)	2120 (89.4)	
No	17 (7.2)	88 (13.4)	100 (11.4)	205 (11.5)		45 (11.8)	101 (12.3)	105 (9.0)	251 (10.6)	
University hospital					.529					**.004**
Yes	53 (22.5)	170 (25.8)	211 (24.0)	434 (24.4)		117 (30.7)	229 (27.8)	269 (23.1)	615 (25.9)	
No	183 (77.5)	489 (74.2)	670 (76.0)	1342 (75.6)		264 (69.3)	595 (72.2)	897 (76.9)	1756 (74.1)	

Note: Bold values denote *P* values <.05 and deemed statistically significant.

2.3 | Patient, tumour and hospital-level characteristics

Data regarding sex, age, pathological staging (TNM staging), operative date, surgical urgency, performance status,[28] and surgical access were obtained from NBOCA. Comorbidities, socioeconomic status, and 30-day unplanned readmission data were obtained from HES-APC.

The Royal College of Surgeons' Charlson comorbidity score was derived from ICD-10 codes recorded in the HES-APC dataset in any hospital admissions in the year preceding colon cancer diagnosis. Individual records for liver, renal, or cardiac disease were obtained for the same timeframe.[29] Patients were recorded as having an unplanned 30-day readmission if HES-APC showed an emergency admission within 30 days of surgery.

Socioeconomic status was derived from the IMD which ranks 32 482 geographical areas of England according to their level of deprivation across seven domains.[30] Patients were allocated to an IMDQ based on the national ranking of the area corresponding to their postcode.

Hospital-level characteristics were derived from the hospital performing the surgery according to NBOCA. University teaching hospitals were identified from the Association of United Kingdom University Hospitals.[31] Onsite chemotherapy presence was collected in an annual national NBOCA survey of colorectal cancer services.[32]

2.4 | Statistical analysis

Patient, tumour and hospital-level characteristics were compared using X^2 tests stratified by chemotherapy regimen alone, and then by regimen and level of completion. The proportion of patients with a dose reduction and the proportion of patients discontinuing oxaliplatin early were reported according to regimen type and level of completion.

As our study evaluates survival outcomes in relation to the completion of chemotherapy, starting the analysis from initiation of chemotherapy may introduce bias as patients who die are unable to receive further cycles of chemotherapy. To account for this, a landmark analysis was undertaken.[33] This involved the designation of a period of time, a priori, from a baseline date (initiation of chemotherapy) to the study start date (the landmark date) known as the exposure period. Patients who died during the exposure period (6 months after chemotherapy initiation) were excluded from the analysis. A sensitivity analysis was undertaken to include those who died within this 6-month period.

The crude 3-year cumulative incidence of cancer-specific death was calculated for each regimen, according to the level of completion, using a competing risks analysis in which other-cause death was the competing event.[34] Fine and Gray[35] competing risk regression models were used to estimate adjusted subdistribution hazard ratios (sHRs) between levels of completion for each regimen, adjusting for all patient, tumour, and hospital-level characteristics.

The same methodology was used to calculate unadjusted and adjusted sHRs for the risk of 3-year cancer-specific death in just those patients completing 100% of cycles, according to whether or not dose reduction occurred. This was then repeated for early discontinuation of oxaliplatin.

Missing values for risk-adjustment variables were imputed with multiple imputation using chained equations, creating 10 datasets and using Rubin's rules to combine the sHRs across the datasets.[36] Wald tests were used to calculate *P* values with the significance level set at .05.

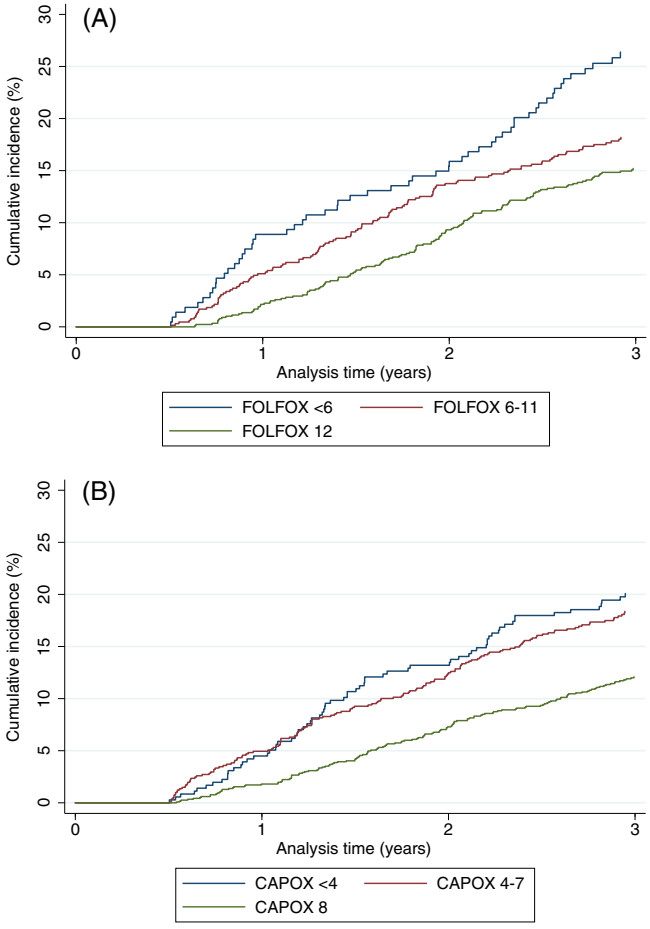

FIGURE 2 Cumulative incidence curves for colon cancer-specific death with competing risk of other-cause death according to level of completion of (A) FOLFOX (n = 1741) and (B) CAPOX (n = 2331) [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

Of the 10 280 patients undergoing major resection with pathological stage III colon cancer between June 1, 2014 and April 30, 2017, 6012 (58%) went on to receive adjuvant chemotherapy (Figure 1). Of these, 4147 patients received an oxaliplatin-based regimen. The remaining 1865 patients received 5-FU/capecitabine monotherapy and were excluded from further analyses.

Two thousand three hundred and seventy-one patients (57%) received CAPOX and 1776 patients (43%) received FOLFOX (Table 1). The median age for both regimens was 64 years (interquartile range 56-70 years). The cumulative incidence for 3-year cancer-specific mortality for all patients included in the study was 16.4% (95% CI 15.3%-17.6%).

3.1 | Levels of completion

3.1.1 | FOLFOX

Fifty per cent of patients completed 12 cycles (100%) of FOLFOX, 37% completed 6-11 cycles (50%-92%), and 13% of patients completed <6 cycles (<50%) (Table 1). Patients completing the least FOLFOX chemotherapy were more likely to be female ($P < .001$), have a history of cardiac ($P = .012$) or renal disease ($P = .042$), undergo emergency surgery ($P = .035$), and commence chemotherapy within 8 weeks of surgery ($P = .025$). There was also a suggestion that patients who were from more deprived areas were less likely to complete chemotherapy, although this was not statistically significant ($P = .073$).

The 3-year cumulative incidence of cancer-specific death in patients receiving FOLFOX and completing 12 cycles was 15.1% (95% confidence interval [CI], 12.8%-17.6%), completing 6-11 cycles was 18.2% (95% CI 15.3%-21.3%), and completing <6 cycles was 26.4% (95% CI 20.6%-32.5%) (Figure 2a).

TABLE 2 Three-year cancer-specific death according to level of completion of FOLFOX or CAPOX

Recorded cycles	Number of patients	Cumulative 3-year incidence (%) (95% CI)	Unadjusted sHR (95% CI)	*P* value	Adjusted sHR (95% CI)	*P* value
FOLFOX	**1741**			**<.001**		**<.001**
12 (100%)	880	15.1 (12.8-17.6)	1.0		1.0	
6–11 (50%-92%)	647	18.2 (15.3-21.3)	1.24 (0.99-1.55)		1.40 (1.09-1.78)	
<6 (<50%)	214	26.4 (20.6-32.5)	1.87 (1.38-2.54)		2.18 (1.56-3.03)	
CAPOX	**2331**			**<.001**		**<.001**
8 (100%)	1166	12.0 (10.2-14.0)	1.0		1.0	
4-7 (50%-92%)	809	18.2 (15.6-21.0)	1.60 (1.25-2.06)		1.63 (1.27-2.10)	
<4 (<50%)	356	19.8 (15.8-24.1)	1.77 (1.33-2.34)		2.02 (1.53-2.67)	

Note: Bold values denote *P* values .05 and deemed statistically significant.

TABLE 3 Three-year cancer-specific death according to dose reduction and early discontinuation of oxaliplatin for those completing 100% of FOLFOX (12 cycles) or CAPOX (8 cycles)

Treatment modification	Number of patients	Cumulative 3-year incidence (%) (95% CI)	Unadjusted sHR (95% CI)	*P* value	Adjusted sHR (95% CI)	*P* value
FOLFOX						
Dose reduction				.142		.096
No	396	15.5 (12.1-19.3)	1.0		1.0	
Yes	351	11.8 (8.6-15.5)	0.75 (0.50-1.10)		0.70 (0.46-1.07)	
Oxaliplatin discontinued				.074		.120
No	303	14.0 (10.3-18.3)	1.0		1.0	
Yes	455	11.7 (8.9-15.0)	0.71 (0.48-1.03)		0.72 (0.48-1.09)	
CAPOX						
Dose reduction				.330		.651
No	489	11.1 (8.5-14.1)	1.0		1.0	
Yes	452	10.5 (7.9-13.6)	0.83 (0.57-1.21)		0.92 (0.62-1.34)	
Oxaliplatin discontinued				.248		.414
No	608	11.4 (9.0-14.2)	1.0		1.0	
Yes	364	9.1 (6.4-12.4)	0.79 (0.54-1.17)		0.84 (0.55-1.28)	

The adjusted competing risk regression analysis showed that the risk of 3-year cancer-specific death in patients completing <6 cycles or 6-11 cycles of FOLFOX was up to twice as high ($P < .001$) as those completing 12 cycles (Tables 2 and S1).

3.1.2 | CAPOX

Forty-nine per cent of patients completed 8 cycles (100%) of CAPOX, 35% completed 4-7 cycles (50%-92%), and 16% of patients completed <4 cycles (<50%) (Table 1). Patients completing the least CAPOX chemotherapy were more likely to be older ($P < .001$) and have less advanced N-stage disease ($P = .027$). There was also a suggestion that patients with a history of liver disease were less likely to complete CAPOX chemotherapy, although this was not statistically significant ($P = .073$).

The 3-year cumulative incidence of cancer-specific death in those receiving CAPOX and completing 8 cycles was 12.0% (95% CI 10.2%-14.0%), completing 4-7 cycles was 18.2% (95% CI 15.6%-21.0%), and completing <4 cycles was 19.8% (95% CI 15.8%-24.1%) (Figure 2b).

After adjustment, the risk of 3-year cancer-specific death in those completing <4 cycles or 4-7 cycles was up to twice as high ($P < .001$) as those completing 8 cycles (Tables 2 and S2).

3.2 | Treatment modification

3.2.1 | FOLFOX

In the 747 patients completing all cycles of FOLFOX, 47% had a dose reduction and 60% discontinued oxaliplatin early (Table S3). The adjusted risk of 3-year cancer-specific death in patients with dose reduction showed a trend towards lower mortality rates compared to those receiving the full dose; however, this was not statistically significant (sHR 0.70; 95% CI 0.46-1.07; $P = .096$) (Table 3). Similar findings were observed for the adjusted 3-year cancer-specific death in patients discontinuing oxaliplatin early compared to those completing the oxaliplatin component (sHR 0.72; 95% CI 0.48-1.09; $P = .120$) (Table 3).

3.2.2 | CAPOX

In the 941 patients completing all cycles of CAPOX who had linked SACT data, 48% had a dose reduction and 37% discontinued oxaliplatin early (Table S3). The adjusted risk of 3-year cancer-specific death in those receiving a reduced dose was similar to those receiving the full dose, although the confidence interval was wide (sHR 0.92; 95% CI 0.62-1.34; $P = .651$) (Table 3). The adjusted risk of 3-year cancer-specific death in those discontinuing oxaliplatin early was similar to those completing it although, again, the confidence interval was wide (sHR 0.84; 95% CI 0.55-1.28; $P = .414$) (Table 3).

The sensitivity analyses including those patients who died within 6 months of their first chemotherapy dose did not show any significant differences in results (not presented).

4 | DISCUSSION

This is the largest cohort study of real-world practice to date evaluating cancer-specific survival according to the cycle completion rates of oxaliplatin-based adjuvant chemotherapy in stage III colon cancer patients, and the first to assess the impact of treatment modification strategies.

In real-world practice, patients who completed 100% of adjuvant chemotherapy cycles (12 cycles FOLFOX or 8 cycles CAPOX) had significantly improved cancer-specific survival outcomes compared to those completing fewer cycles. However, in our cohort only half of patients completed 100% of standard cycles for the timeframe studied.

Of those completing all cycles, half had a dose reduction, and a substantial proportion discontinued oxaliplatin early (a third of those completing all CAPOX cycles and two thirds of those completing all FOLFOX cycles). However, cancer-specific survival remained similar in patients completing all cycles, irrespective of any modifications to their chemotherapy regimen. Patients completing <50% of cycles (<6 cycles FOLFOX or <4 cycles CAPOX) had much poorer outcomes. This suggests that completion of adjuvant chemotherapy with treatment modifications rather than early cessation may confer survival advantages.

4.1 | Strengths and limitations

The main limitation of our study is that, although we found that the completion of adjuvant chemotherapy is associated with improved cancer-specific survival, we cannot simply assume a causal relationship. The factors which make patients less likely to complete their chemotherapy, for example, age and comorbidity, can also make them less likely to survive. However, the use of cancer-specific survival reduces the impact that these factors have on survival differences.

Whilst we have adjusted for many confounders (eg, age, comorbidity, performance status), we were unable to account for other causes of chemotherapy discontinuation, for example, patient preference, psychosocial support, and health behaviours. Despite this, the effect sizes seen are large and unlikely to be fully explained by residual confounding.

Second, duration of follow-up was limited by the availability of SACT data from 2014 onwards and cancer recurrence data was not available. The implications of this were that we reported 3-year cancer-specific survival. However, given our early event rate and the survival differences observed within this shorter timeframe, longer follow-up is only expected to accentuate our findings. In addition, approximately 80% of recurrences occur within the first 3 years after major resection.[37]

The strengths of our study include using a large, contemporary and highly representative cohort of patients, which includes all centres providing colon cancer treatment in the English NHS (UK) without exclusions, and 95% of eligible patients.[20] The patient and clinical characteristics of our study are comparable to other observational studies with regards to staging, performance status, surgical urgency, and time from surgery to adjuvant chemotherapy initiation.[38-42] We have also overcome the biases present in previous observational studies by performing extensive risk-adjustment for important confounders.[19]

The study period did not include SCOT trial patients and preceded publication of the IDEA collaborative results, meaning treatment duration reflects toxicity or intolerance, rather than patient or clinician choice informed by these results.[8,43] A landmark analysis was used to exclude patients who died within 6 months of their first chemotherapy dose ($n = 75$, 2%).[44] This was intended to account for immortal time bias; patients who died during the time they should have received chemotherapy would have been unable to complete treatment. Finally, patients within our cohort were analysed by the recorded number of chemotherapy cycles in a validated national curated chemotherapy dataset[26] rather than, for example, insurance or claims data. This has the advantage of using known individual chemotherapy administration dates compared to, for example, estimating completion based on the duration between the first and last claims for chemotherapy without taking account of individual cycles.[45]

4.2 | Completion and survival

Our adjuvant chemotherapy completion rates of approximately 50% for FOLFOX and CAPOX are comparable to those from previous observational studies.[3,4] They are also plausible compared to the completion rates of 59% within the SCOT trial for both regimens, given that adherence rates within trial settings are known to be higher.[43] Of interest, completion of the least FOLFOX was associated with being female. There has been ongoing debate as to whether an underlying difference in toxicities exists with 5-FU due to gender.[46] Clinicians should consider this for their own practice through regimen choice and adequate toxicity prevention measures, for example, antiemetics. Our study predated the widespread use of DPYD testing.

High early discontinuation rates were observed in older patients with around 15%-20% of patients aged 70-79 years completing <50% of CAPOX or FOLFOX cycles. Based on our study, we are unable to comment as to whether early stoppage reflects greater toxicity in older patients, patient preference, or clinician choice. This is because the completeness of the data item capturing this information in the SACT dataset was very poor (<20% complete). Given the importance of completing the target duration, consideration should be made as to whether monotherapy may be more suitable for elderly patients if this might support improved compliance.

Several observational studies have demonstrated that patients who do not complete fluoropyrimidine adjuvant chemotherapy in real-world practice have less favourable survival outcomes.[3,47-49] A recent systematic review and meta-analysis including 20 observational studies concluded that shortened durations of combination chemotherapy with CAPOX or FOLFOX may not adversely affect survival.[19] However, the findings of this review were limited by the majority of studies failing to address important confounders such as chemotherapy regimen, age, sex, tumour site, and stage. We have systematically addressed these potential confounders in the current study.[19] In addition, many of the studies used outdated data and small sample sizes with the largest study available in abstract format only.[50]

The IDEA collaborative study used intention-to-treat analyses to assess efficacy of two different target durations of adjuvant

chemotherapy, whereas our study sought to evaluate the impact of actual completion rates on survival in real-world practice.[8] Therefore, a direct comparison of the two is not appropriate. There is more relevance to comparing our findings to the per-protocol results in, for example, the SCOT trial which failed to demonstrate equivalence in survival (hazard ratio 1.158; 95% CI 1.018-1.317; $P = .64$) between patients who actually received 3 vs 6 months of FOLFOX or CAPOX.[43] However, even this is not comparable with our findings because the national patient cohort included in our study receiving adjuvant chemotherapy has poorer prognostic factors than those in trials. For example, patients in our national cohort are less fit [one-third have a performance status ≥1 (not fully active) compared to one-fifth within the IDEA study) and have more advanced disease (41.2% have T4 disease compared to 24.6% in the IDEA study, and 39.5% have N2 disease compared to 28.6% in the IDEA study).

Further subanalyses to stratify our findings by low- and high-risk disease were not possible due to small numbers. After the publication of the IDEA/SCOT results, surveys have highlighted the ongoing variation in clinical practice with regards to choice and duration of combination adjuvant chemotherapy with shifts towards the use of 3 months of treatment for high-risk disease, particularly in the UK.[51,52] We recommend that additional research into the outcomes and optimal treatment of patients, particularly those with high-risk disease, is needed.

4.3 | Treatment modification and survival

For patients completing 100% of target cycles, we found that dose reductions or early discontinuation of oxaliplatin was not associated with any difference in cancer-specific survival. This has been observed in other studies, which have demonstrated that reduced dose intensity may not negatively influence survival.[53,54] This may reflect the relative importance of the fluoropyrimdine component of treatment and the uncertain effect in patients aged 70 and above who constitute a quarter of our cohort.[55,56] We found that between 40%-60% of patients discontinued their oxaliplatin (depending on regimen), but continued on a single agent fluoropyrimidine for the rest of their cycles.

Further analysis of the impact of dose reductions or oxaliplatin discontinuation in low- and high-risk prognostic groups was limited by small numbers (reflected in the wide confidence intervals), and an inability to quantify exact dose reductions.

4.4 | Implications for policy and practice

Current recommendations advise 12 cycles of FOLFOX and suggest that 4 cycles of CAPOX can be used dependent on other risk factors, particularly staging.[57] Our findings suggest that in real world practice, once combination chemotherapy has been commenced, completion of at least 4 cycles of CAPOX or 6 cycles of FOLFOX confers a survival advantage over early discontinuation.

Unless toxicities are very severe, our data suggests that patients may benefit from attempting to complete adjuvant chemotherapy with treatment modifications. Improved strategies to support completion of chemotherapy might include prompt identification and management of chemotherapy-related adverse effects, clear clinician-patient communication and education, and provision of adequate support to overcome any physical or psychosocial barriers.

5 | CONCLUSION

Our study demonstrated that in real-world clinical practice only half of stage III colon cancer patients completed all cycles of their adjuvant chemotherapy. Patients who do not complete their cycles were shown to have significantly poorer outcomes. Given that no negative impacts on survival were demonstrated with treatment modifications, clinicians may want to use these to facilitate and encourage completion of adjuvant chemotherapy in those patients able to tolerate it.

ACKNOWLEDGEMENTS

Our study was undertaken alongside the NBOCA. The audit is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme, and funded by NHS England and the Welsh Government (https://www.hqip.org.uk/national-programmes). Neither HQIP nor the funders had any involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The researchers had full independence from HQIP.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request after permission of HQIP.

ETHICS STATEMENT

All patient data used are fully anonymised and are therefore exempt from United Kingdom National Research Ethics Committee approval.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Boyle JM, Kuryba A, Cowling TE, et al. Survival outcomes associated with completion of adjuvant oxaliplatin-based chemotherapy for stage III colon cancer: A national population-based study. *Int. J. Cancer*. 2021;1-12. doi:10.1002/ijc.33806