



## Original research

# Survival and patient-reported outcomes of real-world high-risk stage II and stage III colon cancer patients after reduction of adjuvant CAPOX duration from 6 to 3 months

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## ARTICLE INFO

## Keywords:

Colon cancer  
Adjuvant chemotherapy  
Survival, patient reported outcome measures  
Quality of life  
Real-world data

## ABSTRACT

**Aim:** Adjuvant chemotherapy has been advised for high-risk stage II and III colon cancer since 2004. After the IDEA study showed no clinically relevant difference in outcome, reduction of adjuvant CAPOX duration from 6 to 3 months was rapidly adopted in the Dutch treatment guideline in 2017. This study investigates the real-world impact of the guideline change on overall survival (OS) and patient-reported outcomes (PROs).

**Methods:** Patients with high-risk stage II (pT4+) and III (pN+) colon cancer were selected from the Netherlands Cancer Registry, based on surgical resection and adjuvant CAPOX before (2015–2016) versus after (2018–2019) the guideline change. Both groups were compared on OS, using multivariable Cox regression, and on PROs.

**Results:** Patients treated before (n = 2330) and after (n = 2108) the guideline change showed similar OS (HR 1.02; 95 %CI [0.89–1.16]), also in high-risk stage III (pT4/N2, HR 1.06 [0.89–1.26]). After the guideline change, 90 % of patients were treated for 3 months with no inferior OS to those still receiving 6 months (HR 0.89 [0.66–1.20]). PROs 2 years after CAPOX completion, available for a subset of patients, suggest a lower neuropathy (n = 366; 26.2 [21.3–31.1] to 16.5 [14.4–18.6]) and better quality of life (n = 396; 80.9 [78.6–83.2] to 83.9 [82.8–84.9]), but no significant difference in workability (n = 120; 31.5 [27.9–35.1] to 35.3 [33.8–36.7]), with reduction from 6 to 3 months of CAPOX.

**Conclusion:** This real-world study confirmed that shorter adjuvant CAPOX did not compromise OS and may improve PROs, complementing the IDEA study and supporting 3 months of adjuvant CAPOX in daily clinical practice.

## 1. Introduction

Patients with colon cancer classified as high-risk stage II (pT4 or other risk factors) or stage III (pN+ involvement of local lymph nodes) are at increased risk of disease recurrence [1]. Compared to surgical resection only, systemic adjuvant chemotherapy (ACT) with a fluoropyrimidine (5FU or capecitabine) improved prognosis [1,2], with additional benefit from combination with oxaliplatin (FOLFOX or CAPOX, respectively) [3,4]. This doublet has been standard of care since 2004 [5], although at the expense of oxaliplatin-associated sensory peripheral neuropathy [3,6] and lower workability [7].

The international duration evaluation of adjuvant chemotherapy (IDEA) study found that the reduction of 6 months to 3 months doublet ACT was able to reduce neuropathy [8,9], improve quality of life, and lower costs [10,11]. Moreover, this shorter treatment duration was non-inferior for CAPOX, but non-inferiority was not met for the high-risk stage III subgroup and for FOLFOX [8,12]. Based on these results, international guidelines adhere to 6 months of CAPOX or FOLFOX in high-risk stage III (pT4 and/or pN2), while recommending 6 months of FOLFOX or 3 months of CAPOX in low-risk stage III (pT1–3N1). In stage II colon cancer (pT3–4N0), guidelines differ in risk factors to consider whether benefit outweighs harm of ACT, using fluoropyrimidine

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<https://doi.org/10.1016/j.ejca.2024.114207>

Received 26 April 2024; Received in revised form 14 June 2024; Accepted 30 June 2024

Available online 10 July 2024

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monotherapy (6 months) or also oxaliplatin (6 or 3 months) [13,14].

The Dutch guideline changed in 2017 from 6 to 3 months of CAPOX for both stage III and high risk stage II, redefined as only pT4 combined with proficient mismatch repair status (pMMR) [5]. A previous publication using Dutch population-based data between 2015 and 2019 demonstrated quick implementation of the guideline in clinical practice, with a reduction of mean ACT duration from 18.6 to 9.5 weeks. With the shorter duration, more patients received ACT (stage III 61 % to 69 %), with a larger proportion of doublet ACT (74 % to 83 % CAPOX) [15]. This quick and broad implementation of the guideline change offers the unique opportunity to investigate its effect in daily clinical practice, resembling ‘random’ treatment assignment in a large natural experiment.

Our study investigates the generalizability of the IDEA results to a real-world population of patients with high-risk stage II and stage III colon cancer, hypothesizing that the reduced adjuvant CAPOX duration from 6 months to 3 months is not associated with an inferior overall survival, while benefitting patient-reported neurotoxicity, quality of life and workability.

2. Material and methods

2.1. Study population

As depicted in the flowchart (Fig. 1), all adult patients diagnosed with pathologically confirmed high-risk stage II (pT4) and stage III (pN+) colon cancer between 2015 and 2019 and treated with surgical resection and adjuvant CAPOX without neoadjuvant treatment were selected from the Netherlands Cancer Registry (NCR). The NCR is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) and has near complete coverage (>99 %) of all newly diagnosed malignancies [16]. Adjuvant CAPOX, the ACT regimen used in circa 80 % in the Netherlands [15], was defined as capecitabine with at least 1 simultaneous cycle of oxaliplatin after surgery. Patients treated in the guideline transition year 2017 or with an unknown number of administered cycles of CAPOX were excluded because of unknown intended treatment duration. Also patients surviving < 3 months after CAPOX initiation were excluded to avoid immortal time bias between 3 and 6 months of CAPOX.

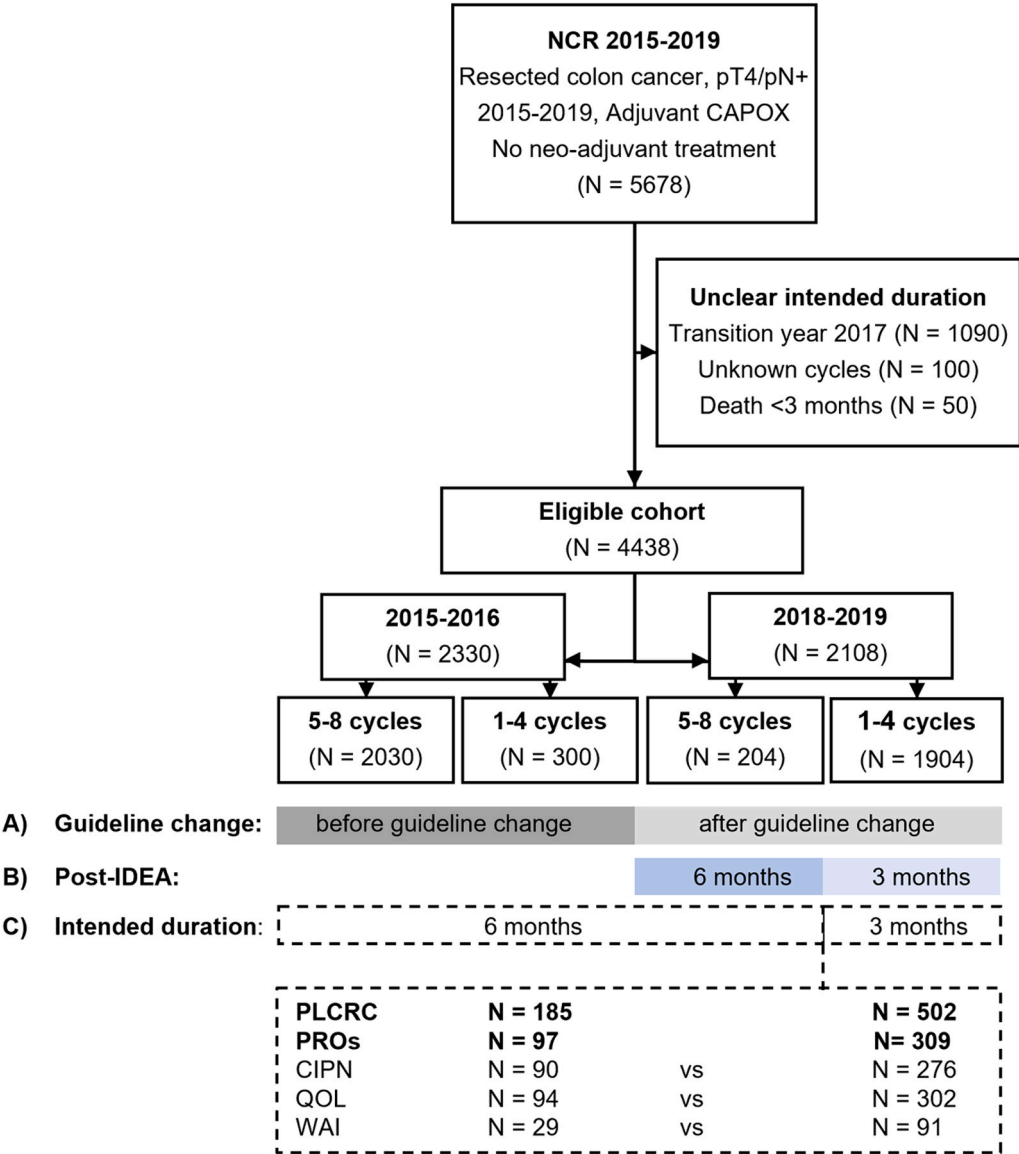


Fig. 1. Flow diagram of the study population, and the 3 approaches of analyzing CAPOX duration.

## 2.2. Study variables

Information on patient and tumor characteristics and treatment was routinely collected from medical records by trained administrators in the year of diagnosis. Key variables such as year, number of CAPOX cycles, pathological stage, age and sex were complete. Other baseline variables include American Society of Anesthesiologists (ASA) physical status, tumor sidedness (proximal versus distal to splenic flexure), prior malignancy, radicality of resection, differentiation grade, number of lymph nodes dissected, lymphatic invasion (all <10 % missing), vascular invasion (17 % missing), and MMR status (34 % missing). Missing data was accounted for by multiple regression-based imputation on all mentioned baseline variables and the auxiliary variable world health organization (WHO) performance status. Survival was derived from the national municipal population registry in January 2024 and calculated from start of adjuvant CAPOX, and was censored at loss to follow-up.

## 2.3. Approaches to classify CAPOX duration

Three complementary approaches were used to classify CAPOX duration for association with OS, all excluding 2017 as guideline transition year (Fig. 1). First, to evaluate the impact of the guideline change, OS was compared between patients treated with adjuvant CAPOX before (2015–2016) versus after (2018–2019) the guideline change. Second, to assess the robustness of the results after the guideline change (2018–2019), a post-IDEA sensitivity analysis was performed between patients still receiving 5–8 cycles versus patients actually adhering to the changed guideline with 1–4 cycles. Third, patients were compared between an intended duration of 6 months (all patients treated in 2015–2016 and patients still receiving 5–8 cycles in 2018–2019) and intended duration of 3 months (1–4 cycles in 2018–2019).

## 2.4. Overall survival

For all three approaches, OS was assessed in Kaplan Meier curves with 5-year survival rates as main outcome (81 % complete follow-up) and 3-year survival rates supplementary (>99 % complete). Hazard ratios (HRs) with 95 % confidence intervals (CIs) were generated using both univariable log-rank analysis and a multivariable Cox regression model including the 12 preselected baseline factors. All OS analyses were performed in the overall population and in prespecified subgroup analyses focusing on high-risk stage III, while pooling low-risk stage III and high-risk stage II. Interactions between CAPOX duration and other variables were assessed. Variables that visibly and statistically based on Schoenfeld residuals did not meet the proportional hazards assumption were modelled as stratification factors.

## 2.5. PROs

For a subset of patients, longitudinal patient-reported outcomes were available through the Prospective Dutch ColoRectal Cancer (PLCRC) cohort (NCT02070146) [17]. To assess the influence of reduction of CAPOX duration on long-term PROs, questionnaires were selected closest to two years after treatment cessation (minimum 1 to maximum 3 years). Chemotherapy-induced polyneuropathy (CIPN20) was based on 9 sensory, 8 motor and 3 autonomic symptoms over the past week [18]. With the exception of driving a car and erection due to their conditional nature [19], all items were combined to (sub)total scores and linearly transformed to a scale from 0 ('not at all') to 100 ('very much'). The EORTC-QLQ-C30's 9 cancer-related symptoms (0–100 'no-maximal') and 5 functional scales (physical, role, emotional, cognitive and social functioning; 0–100 'worst-best') were used to calculate the quality of life summary score [20,21]. For patients aged < 67 years with a paid job, the current workability compared to best ever (rated 1–10), number of comorbidities, work impairment, sick

leave, expected workability in next two years and vitality were used to determine the workability index (WAI score 7–27 'poor', 28–36 'moderate', 37–43 'good', 44–49 'excellent') [7,22].

## 2.6. Statistical methods

After confirming similar baseline characteristics, PROs were compared between patients with an intended CAPOX duration of 6 versus 3 months, using the Mann-Whitney U test for continuous scores and  $\chi^2$  test for categorical items. All statistical tests were performed using R version 3.5.1, with a two-sided p-value of < 0.05 considered statistically significant, without correction for multiple testing. Applied R packages include table1, mice, ggplot2, survival, survminer and ggsurvfit.

## 3. Results

### 3.1. Study population

Of the 5678 colon cancer patients identified in the NCR with adjuvant CAPOX in 2015–2019, 4438 were eligible after excluding the guideline transition year 2017 (19 %), an unclear number of CAPOX cycles (2 %) or < 3 months survival (1 %) (Figure 1). Of the 2330 patients treated before the guideline change (2015–2016), 2030 (87 %) completed 5–8 cycles conform the recommended duration. The other 2108 patients received adjuvant CAPOX after the guideline change (2018–2019), of whom 204 (10 %) still received 5–8 cycles, while 1904 (90 %) received 1–4 cycles in accordance with the changed guideline.

The overall study population's mean age was 63 years (SD 8.6), 55 % was male, 87 % ASA1 or ASA2, 56 % harbored a left-sided tumor and 90 % experienced no prior malignancy. Based on pathological TNM, 6 % was high-risk stage II (pT4N0), 53 % low-risk stage III (pT1–3N1) and 41 % high-risk stage III (pT4/N2). The majority of patients had a R0 resection (98 %), good or moderate differentiation (88 %),  $\geq 10$  lymph nodes dissected (96 %), no lymphatic invasion (66 %), no vascular invasion (72 %) and proficient MMR status (86 %). These baseline characteristics were comparable between patients treated before versus after the guideline change (Table 1; more detailed in Supplementary Table 1).

### 3.2. Guideline change: before (2015–2016) versus after (2018–2019) the guideline change

Patients treated with adjuvant CAPOX before (n = 2330 in 2015–2016) and after (n = 2108 in 2018–2019) the guideline change had a median follow-up of 91 months (IQR 8 months) and 57 months (IQR 7 months), respectively. After both 3 years (Supplementary Table 2) and 5 years (Table 2), survival was not significantly different between patients treated before (5-year OS 81 %; 95 %CI [79–82]) and after the guideline change (5-year OS 80 % [78–81], HR 1.02 [0.89–1.16] based on the multivariable Cox model in Supplementary Table 3) (Figure 2A). Also the subgroup with high-risk stage III showed similar OS before (n = 992, 5-year OS 71 % [68–74]) and after (n = 824, 5-year OS 68 % [65–72]) the guideline change (HR 1.06 [0.89–1.26]) (Table 2).

### 3.3. Post-IDEA: 6 months versus 3 months CAPOX after the guideline change (2018–2019)

After the guideline change in 2017, patients could receive the recommended 3 months (n = 1904) or still 6 months of CAPOX (n = 204, 10 %) based on shared decision making. Patients still receiving 6 months tended to be younger (61 versus 63 years), with more stage T4 and/or N2 (67 % versus 26 %) and poor pathological characteristics (Supplementary Table 1). Compared to survival after 6 months of CAPOX (5-year OS 73 % [67–79]), survival after 3 months of CAPOX (5-year OS 80 % [79–82]) was better in univariable analysis (HR 0.68

**Table 1**  
Baseline characteristics before (2015–2016; advice 6 months) versus after (2018–2019; advice 3 months) the guideline change.

	Before change N=2330	After change N=2108	Overall N=4438
<b>pTNM stage</b>			
High-risk stage II	133 (5.7 %)	139 (6.6 %)	272 (6.1 %)
Low-risk stage III	992 (42.6 %)	824 (39.1 %)	2350 (53.0 %)
High-risk stage III	1205 (51.7 %)	1145 (54.3 %)	1816 (40.9 %)
<b>Age</b>			
Mean (SD)	62.9 (8.5)	63.0 (9.7)	62.9 (9.1)
<b>Sex</b>			
Male	1321 (56.7 %)	1101 (52.2 %)	2422 (54.6 %)
Female	1009 (43.3 %)	1007 (47.8 %)	2016 (45.4 %)
<b>ASA physical status</b>			
ASA1	582 (27.0 %)	382 (18.8 %)	964 (23.0 %)
ASA2	1347 (62.4 %)	1280 (63.1 %)	2627 (62.8 %)
ASA3-4	228 (10.6 %)	366 (18.0 %)	594 (14.2 %)
Missing	173	80	253
<b>Sidedness tumor</b>			
Left	1324 (57.4 %)	1141 (54.7 %)	2465 (56.1 %)
Right	984 (42.6 %)	946 (45.3 %)	1930 (43.9 %)
Missing	22	21	43
<b>Prior malignancy</b>			
No	2117 (90.9 %)	1873 (88.9 %)	3990 (89.9 %)
Yes	213 (9.1 %)	235 (11.1 %)	448 (10.1 %)
<b>Radical resection</b>			
R0	2256 (98.0 %)	2035 (98.3 %)	4291 (98.1 %)
R1 or R2	46 (2.0 %)	35 (1.7 %)	81 (1.9 %)
Missing	22	38	66
<b>Differentiation grade</b>			
Good-moderate	1860 (87.4 %)	1751 (88.6 %)	3611 (88.0 %)
Poor	268 (12.6 %)	226 (11.4 %)	494 (12.0 %)
Missing	202	131	333
<b>Lymph nodes</b>			
≥ 10 dissected	2242 (96.2 %)	2027 (96.2 %)	4269 (96.2 %)
<10 dissected	88 (3.8 %)	81 (3.8 %)	169 (3.8 %)
<b>Lymphatic invasion</b>			
No invasion	1530 (68.0 %)	309 (63.4 %)	2839 (65.8 %)
Lymphatic invasion	720 (32.0 %)	756 (36.6 %)	1476 (34.2 %)
Missing	80	43	123
<b>Vascular invasion</b>			
No invasion	1141 (71.3 %)	1487 (71.9 %)	2628 (71.6 %)
Vascular invasion	460 (28.7 %)	580 (28.1 %)	1040 (28.4 %)
Missing	729	41	770
<b>Mismatch repair</b>			
Proficient	1010 (87.1 %)	1499 (85.9 %)	2509 (86.4 %)
Deficient	150 (12.9 %)	246 (14.1 %)	396 (13.6 %)
Missing	1170	363	1533

[0.51–0.91]), but not when correcting for the baseline differences (HR 0.89 [0.66–1.20]) or when stratifying for high-risk stage III (HR 0.87 [0.63–1.19]) (Fig. 2B, Table 2).

**Table 2**  
5-year survival after 6 months (ref) versus 3 months of CAPOX, according to 3 approaches.

	6 months CAPOX			3 months CAPOX			Univariable		Multivariable	
	N	OS%	[95 %CI]	N	OS%	[95 %CI]	HR	[95 %CI]	HR	[95 %CI]
<b>A) Guideline change: before (2015-2016) versus after (2018-2019)</b>										
all patients	2330	81 %	[79–82]	2108	80 %	[78–81]	1.07	[0.93-1.22]	1.02	[0.89-1.16]
high-risk stage III	992	71 %	[68–74]	824	68 %	[65–71]	1.14	[0.96-1.36]	1.06	[0.89-1.26]
low-risk stage III / II	1338	88 %	[86–90]	1284	87 %	[85–89]	1.06	[0.85-1.32]	0.95	[0.76-1.19]
<b>B) Post-IDEA: 6 months (2018-2019) versus 3 months (2018-2019)</b>										
all patients	204	73 %	[67–80]	1904	80 %	[79–82]	0.68	[0.51-0.91]	0.89	[0.66-1.20]
high-risk stage III	136	65 %	[58–74]	688	69 %	[65–72]	0.86	[0.63-1.18]	0.87	[0.63-1.19]
low-risk stage III / II	68	89 %	[81–97]	1216	87 %	[85–89]	1.21	[0.57-2.58]	1.23	[0.57-2.66]
<b>C) Intended duration: 6 months (2015-2019) versus 3 months (2018-2019)</b>										
all patients	2534	80 %	[79–82]	1904	80 %	[79–82]	0.98	[0.86-1.13]	0.99	[0.86-1.13]
high-risk stage III	1128	70 %	[68-73]	688	69 %	[65–72]	1.08	[0.90-1.28]	1.01	[0.85-1.21]
low-risk stage III / II	1406	88 %	[86–90]	1216	87 %	[85–89]	1.08	[0.86-1.34]	0.98	[0.78-1.23]

Abbreviation: OS, Overall Survival after 5 years (%). HR, Hazard Rate. CI, Confidence Interval (lower–upper bound)

3.4. Intended duration: 6 months (2015–2019) versus 3 months (2018–2019)

Lastly, patients still receiving 5–8 cycles after the guideline change (n = 204) were combined with all patients treated before the guideline change (n = 2330) as group with intended CAPOX duration of 6 months. In comparison, patients receiving 1–4 cycles after the guideline change (n = 1904) with an intended duration of 3 months did not show clinically relevant differences in baseline characteristics (Supplementary Table 1) or survival (5-year OS 80 % [79–82] in both groups, HR 0.99 [0.86–1.13]) (Figure 2C, Table 2).

3.5. Effect of 6 months (2015–2019) versus 3 months (2018–2019) CAPOX on PROs

Of patients with an intended duration of 6 and 3 months, respectively 7 % and 26 % participated in PLCRC, through which 4 % and 16 % had available prospective questionnaires two years after ACT. Baseline characteristics were comparable between the subgroup with PROs and the total cohort with OS data, as well as between patients with an intended duration of 6 and 3 months (Supplementary Table 4). Patient reports (supplementary) were used to generate summary scores (Table 3). Compared to an intended duration of 6 months of CAPOX (n = 90, mean 26.2 [21.3–31.1]), the CIPN total score was lower after 3 months of CAPOX (n = 276, mean 16.5 [14.4–18.6]) (p < 0.001), with the largest difference in the sensory subscore (especially tingling, burning pain or numbness in hands or feet) (Supplementary Table 5).

The quality of life summary score two years after CAPOX improved with reduction from 6 months (n = 94, mean 80.9 [78.6–83.2]) to 3 months (n = 302, mean 83.9 [82.8–84.9]) (p = 0.013, Table 3). Especially role functioning, social functioning and cancer related symptoms (Supplementary Table 6). Among the small group of patients with income from work, the WAI score did not differ significantly between 6 months (n = 29, mean 31.5 [27.9–35.1]) versus 3 months (n = 91, mean 35.3 [33.8–36.7], p = 0.12), except for self-assessed current workability (6.6 [5.6–7.7] versus 7.6 [7.2–8.1], with 10 ‘best ever’, p = 0.042) (Supplementary Table 7).

4. Discussion

This large real-world population-based cohort of patients with high-risk stage II and III colon cancer confirmed that the IDEA-based guideline change from 6 to 3 months of adjuvant CAPOX was not associated with inferior OS. This was confirmed in a sensitivity analysis, comparing patients with 6 versus 3 months post-IDEA and in TNM-based subgroup analyses. The high-risk stage III subgroup was of special interest, because of the international ongoing debate after the IDEA study failed to show non-inferiority (5-year OS 72.4 % to 71.4 %, HR 1.03

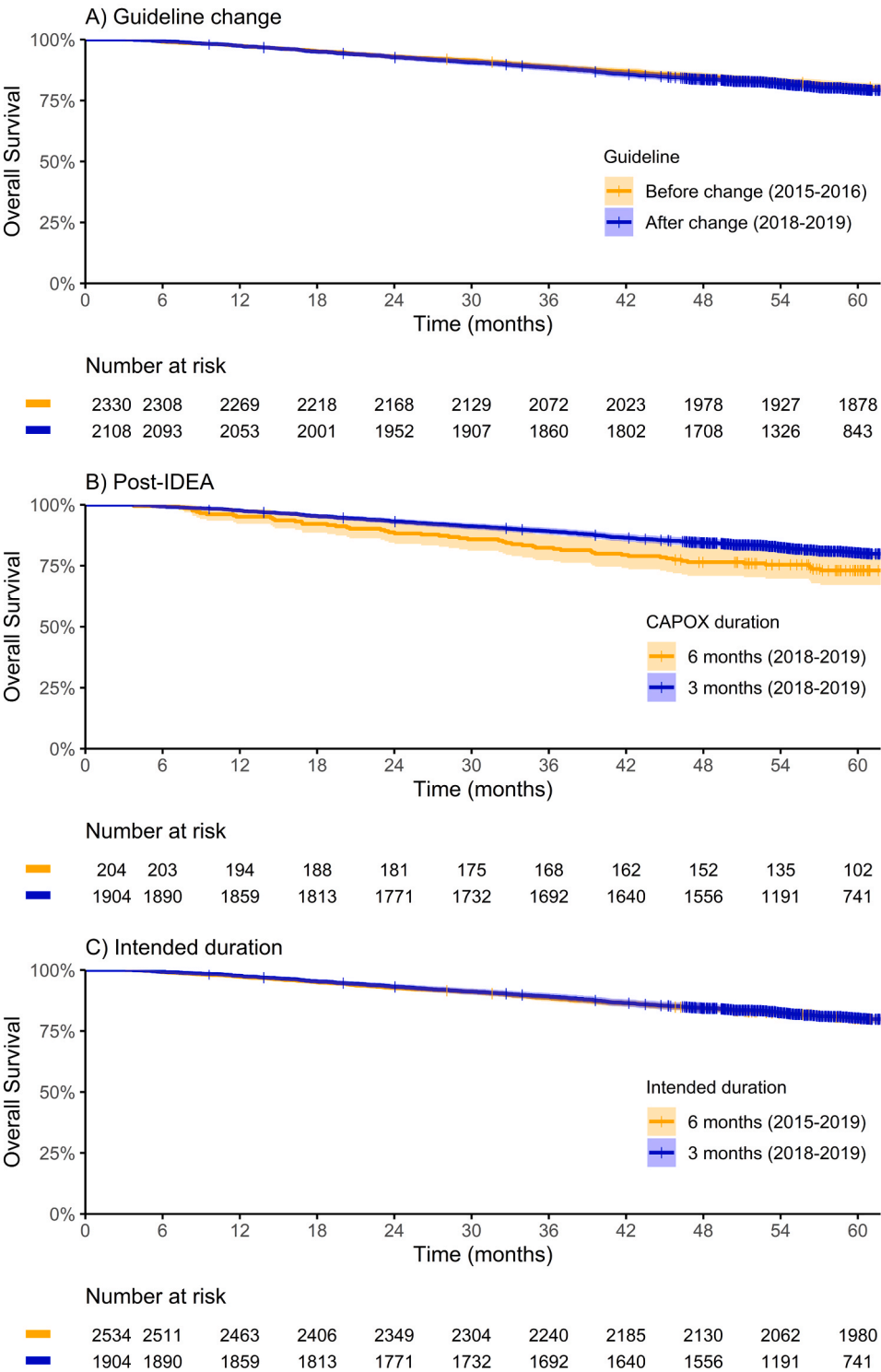


Fig. 2. Kaplan Meier of overall survival based on the 3 approaches of analyzing CAPOX duration.

[0.89–1.02]) [23,24]. In the Netherlands, 3 months was adopted also for high-risk stage III [15,25], allowing us to be the first to robustly show that 3 months of CAPOX was not associated with inferior OS in the real-world population.

Another core finding supporting shorter CAPOX duration is the improved long-term patient-reported outcome. First, we confirmed the lower CIPN following reduced doublet ACT duration observed in the IDEA study [26]. Additionally, we found that shorter CAPOX duration was associated with better quality of life, especially role and social

functioning, even after two years when recovery to baseline is expected [27]. Lastly, workability was regained slightly better in some subscales. This should be interpreted cautiously, considering the limited number of available PROs. However, we expect participation bias [28] to be limited because of the comparable baseline characteristics.

The main limitation of this observational study is the vulnerability to potential bias, which was mitigated through various analysis steps. First, the guideline change resembled ‘random’ treatment assignment between two groups with otherwise comparable characteristics, assumably



**Table 3**  
PROs two years after completion of 6 months (2015-2019) versus 3 months (2018-2019) of intended CAPOX duration.

	6 months CAPOX			3 months CAPOX			Difference	
	N	Mean	[95 %CI]	N	Mean	[95 %CI]	Mean	[95 %CI]
<b>CIPN total score (0-100)</b>	90	26.2	[21.3-31.1]	276	16.5	[14.4-18.6]	-9.7	[-15.0 – -4.4]
Sensory sub score (0-100)		27.5	[22.4 32.7]		17.3	[15.0-19.7]	-10.2	[-15.8 – -4.6]
Motor sub score (0-100)		17.6	[13.4 21.8]		11.4	[9.6-13.2]	-6.2	[-10.9 – -1.9]
Autonomic sub score (0-100)		14.4	[9.6 19.3]		8.8	[7.0-10.6]	-5.6	[-10.7 – -0.5]
<b>QoL-summary score (0-100)</b>	94	80.9	[78.6 83.2]	302	83.9	[82.8-84.9]	+3.0	[+0.5 – +5.5]
Global health status (0-100)		73.3	[69.2 77.5]		79.1	[77.2-81.1]	+7.8	[+1.2 – +10.3]
<b>WAI score (7-49)</b>	29	31.5	[27.9 35.1]	91	35.3	[33.8-36.7]	+3.8	[-0.6 – +7.6]
Compared to best ever (1-10)		6.6	[ 4.6–7.7]		7.6	[7.2-8.1]	+ 1.0	[-0.1 – +2.0]

Abbreviation: CIPN, chemotherapy-induced neuropathy. QoL, quality of life. WAI, workability index

rendering CAPOX duration the only varying independent variable and limiting confounding by indication [29]. To address the confounding characteristics of the 10 % of patients still receiving 5–8 cycles post-IDEA, namely advanced tumor stage (T4 and/or N2) potentially resulting in an underestimation, a separate sensitivity analysis was performed. Multivariable analyses adjusted for known relevant confounders (including stage, age and sex) [30], although residual confounding cannot be ruled out [31,32].

Core variables contained no missing values and were determined before patients started CAPOX, hence restricting post-baseline confounding [33]. The chosen endpoint 5-year OS is the optimal endpoint in trials investigating ACT aimed at curation. It should be noted that immaturity of 5-year OS for patients treated in 2019 may cause an underestimation of the effect of the guideline change, although the trend observed in the Kaplan Meier was constant and consistent with mature 3-year OS. Disease-free survival was not available and would be of interest in the future, although 3-year DFS has been shown to correlate with 5-year OS [34].

The main strength of this study is the population-wide sample size, minimizing selection bias and optimizing generalizability. Since randomized controlled trials often select young patients with less comorbidities, treatment benefit and toxicity may be inferior when applied to a broader population [35,36]. This gap between trial efficacy and real-world effectiveness has been reported in metastatic colorectal cancer [37], but was limited in real-world concerning the addition of ACT to surgery in stage II [38] or stage III [39] colon cancer. Also in our population-based cohort, patient characteristics and survival were comparable to the IDEA study (5-year OS 81.2 % to 82.1 %, HR 0.96 [0.85–1.08]) [8,12], likely thanks to the trial’s broad selection criteria. These findings support pragmatic trial designs that better approximate clinical practice and generalize to real-world effectiveness [29,40].

In conclusion, reduced adjuvant CAPOX duration from 6 to 3 months was not associated with worse OS, also in high-risk stage III. Importantly, long-term PROs in a small subset of patients suggested less neurotoxicity and higher quality of life. This study thereby confirms and complements the findings of the pivotal IDEA study in a real-world population, supporting 3 months of adjuvant CAPOX in daily clinical practice.

**Ethics**

This registry-based study does not require formal approval from an ethics committee, conform the Central Committee on Research involving Human Subjects. The study was approved by the scientific council and the Privacy Review Board of the Netherlands Comprehensive Cancer Organisation (IKNL), which collects and monitors pseudonymized data for the Netherlands Cancer Registry (NCR), using opt-out consent. The Prospective Dutch Colorectal Cancer (PLCRC) cohort was approved by the independent Medical Research Ethics Committee of Utrecht (METC 12–510) and obtained signed informed consent for each patient for the PROs.

**Data sharing statement**

The data supporting the findings of this study are available from the NCR. Restrictions apply to the availability of these data, which were used under license for this study.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The Prospective Dutch Colorectal Cancer (PLCRC) cohort is supported by the Dutch Cancer Society (DCCG); Stand Up to Cancer; ZonMw; Health Holland; Maag Lever Darm Stichting; Merck (unrestricted grant); Bristol-Myers Squibb (unrestricted grant); Bayer (unrestricted grant); and Servier (unrestricted grant).

**CRedit authorship contribution statement**

**Ingrid A. Franken:** Conceptualization, Data curation, Formal analysis, Investigation, Resources, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Frederieke H. van der Baan:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Geraldine R. Vink:** Conceptualization, Writing – review & editing. **Anne M. May:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Wilhelmina M.U. van Grevenstein:** Writing – review & editing. **Miriam Koopman:** Writing – review & editing. **Jeanine M.L. Roodhart:** Conceptualization, Investigation, Supervision, Writing – review & editing.

**Declaration of Competing Interest**

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: I. A.F: Grant to institution: DoMore Diagnostics. F.H.B: Payment to institution from Personal Genome Diagnostics. G.R.V: Grants to institution and/or nonfinancial support: BMS, Merck, Servier, Personal Genome Diagnostics, Bayer, Sirtex, Pierre Fabre, Lilly, Delfi Diagnostics, Nordic all financial supports transferred to the institute. A.M.M and W.M.U.G: declare no potential conflicts of interests. M.K: advisory role: Eisai, Nordic Farma, Merck-Serono, Pierre Fabre, Servier. Institutional scientific grants: Bayer, Bristol Myers Squibb, Merck, Personal Genome Diagnostics (PGDx), Pierre Fabre, Roche, Sirtex, Servier. Non-financial interests: chair of the ESMO RWD-DH working group, co- chair: DCCG, PI PLCRC (national observational cohort study), involved in several clinical trials as PI or co-investigator in CRC. J.M.L.R: institutional financial interests: Bayer, BMS, Merck-Serono, Pierre Fabre, Servier, HUB 4 organoids, Cleara Biotech.

**Acknowledgements**

The authors extend their gratitude to the team of the Netherlands Comprehensive Cancer Organization (IKNL) for data collection for the

Netherlands Cancer Registry (NCR) and scientific advice. PROs were collected through the Prospective Dutch Colorectal Cancer (PLCRC) cohort, which is an initiative of the Dutch Colorectal Cancer Group (DCCG).

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2024.114207](https://doi.org/10.1016/j.ejca.2024.114207).

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