Impact of relative dose intensity of oxaliplatin in adjuvant therapy among stage III colon cancer patients on early recurrence: a retrospective cohort study

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Abstract

Background: Oxaliplatin-based therapy with FOLFOX-4 or CAPOX administered over 6 months remains the standard adjuvant treatment for stage III colon cancer (CC) patients. However, many patients experience dose reduction or early termination of chemotherapy due to oxaliplatin toxicity, which may increase the risk of early recurrence. The objective of this study was to analyze the relationship between the relative dose intensity of oxaliplatin (RDI-O) and early recurrence among stage III CC patients.

Methods: The study included 365 patients treated at five oncology centers in Poland between 2000 and 2014. Survival analysis was performed using the Kaplan-Meier method. Univariate analysis was performed using the Cox proportional hazard model; multivariate analysis was performed with the stepwise forward approach. For all analyses the α level of 0.05 was employed.

Results: The median follow-up was 51.8 months (range 8.2-115.1). Early recurrence <36 months after surgery occurred in 130 patients (37.8%). In this group 51 (39.2%) and 87 (66.9%) of patients were low and high-risk, respectively. Receipt <60% of RDI-O was associated with early recurrence within 18 months after surgery (OR=2.05; 95%CI: 1.18-3.51; p=0.010), especially in low-risk group (HR=1.56 (95%CI: 0.96-2.53), p=0.07). In the multivariate analysis early recurrence was correlated with grade (OR=2.47; 95% CI: 1.25-4.8; p=0.008), pN (OR=2.63; 95% CI: 1.55-4.54; p<0.001), the number of lymph nodes harvested (OR=0.51; 95% CI: 0.29-0.86; p=0.013) and RDI-O (OR=1.91; 95%CI: 1.06-3.39; p=0.028). The early vs. late recurrence negatively correlated with OS regardless of the RDI-O (HR=22.9 (95%CI: 13.9-37.6; p<0.001).

Conclusions: RDI-O <60% in adjuvant therapy among stage III CC (especially in low-risk group) increases the risk of early recurrence within 18 months of surgery. Patients with early recurrence showed worse overall survival regardless of the RDI-O.

Background

Significant advances have been made in the study of the colon cancer (CC) over the last few years. In patients with stage III CC, oxaliplatin and fluoropyrimidine-based chemotherapy is currently the standard of therapy in adjuvant setting [1–6]. Three prospective phase 3 trials: MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil, Leucovorin in the Adjuvant Treatment of Colon Cancer), NASBP-C07 (National Surgical Breast and Bowel Project) and NO16968 (XELOXA Trial) showed improvement in prolonged disease-free time (DFS) and overall survival (OS), especially in younger patients under 65 years [1–6]. Similar efficacy, with better tolerability, has been demonstrated for capecitabine in the oxaliplatin regimen (CAPOX) [7]. The intended dose of oxaliplatin is usually reported as part of the design of clinical studies, but administered dose is often reduced due to chemotherapy side effects such as myelotoxicity or peripheral neuropathy, which may increase the risk of early recurrence [1–6]. In colorectal cancer (CRC) patients, 60–80% of recurrences becoming apparent within the first 2 years after curative surgery and 90% within the first 4 years [8–10]. The factors affecting early and late recurrence in CRC may differ among stage and primary tumour site [8, 10, 11]. The objectives of this study were to analyze the

relationship between the relative dose intensity of oxaliplatin (RDI-O) in adjuvant setting and early recurrence in stage III CC patients.

Materials And Methods

Study population

The study group included 365 stage III colon cancer patients of Caucasian race, age 18 or older, who underwent radical surgical treatment followed by adjuvant chemotherapy with fluoropyrimidine and oxaliplatin. The patients were diagnosed and treated between 2000-2014 in five oncology centers in Poland. The exclusion criteria included: rectal tumours (as defined by the presence of the inferior pole of the tumour below the peritoneal reflection (<15 cm from the anal margin), not clear resection margins (residual tumour at the primary site: R1 or R2), inability to start adjuvant chemotherapy, incomplete medical records. This study was approved by the Bioethics Committee, Medical Chamber in Opole (Agreement No. 245/2017). All data were coded to secure full protection of personal information therefore patient consent was not sought. All research was performed in accordance with relevant guidelines and regulations.

Study treatment and procedures

The adjuvant chemotherapy included regimens with oxaliplatin and fluoropyrimidine FOLFOX-4 or CAPOX used for 6 months. For each regimen the number of cycles, the duration of treatment, the cumulative dose (CD) and RDI-O are given. The primary tumour staging was performed in accordance with the seventh version of the TNM classification, developed by the American Joint Committee on Cancer (AJCC) and International Union for the Fight against Cancer (IUCC) [12]. The assessment of the adverse events (AEs) severity was based on the classification developed by the National Cancer Institute (NCI-National Cancer Institute) - Terminology Criteria for Adverse Events (CTCAE), version 4 [13]. All AEs reported in medical records during the treatment period or within 30 days after the last chemotherapy cycle are listed. Safety analyses were done for patients who received at least dose of treatment. Patients may have had more than one AE. The manuscript was prepared according to the STROBE guideline [14]. Follow-up was measured since adjuvant chemotherapy initiation until death or last follow-up information. DFS was defined as the period between chemotherapy initiation and disease recurrence (local or distant), while OS was defined as the period between chemotherapy initiation and death (irrespective of the cause). We used 36 months as the cut off (<36 vs ³36) to define early and late recurrence. RDI represents the ratio of the amount of a drug actually administered to the amount planned for a fixed time period, according to formula: [DDI/SDI]x100%. DDI, delivered dose intensity is delivered total dose (in mg/m^2)/standard time to complete chemotherapy (in days) and SDI is standard total dose (in mg/m^2)/actual time to complete chemotherapy with imputation for missed cycles (in days) [15].

Statistical design

Statistical analysis was performed using R statistical software (version 4.0.0) [16]. The normality of distribution was assessed using the Shapiro-Wilk test. Due to the lack of normally distributed data, the comparison between two groups was performed using the Mann-Whitney U test, while the comparison between multiple groups was performed using the Kruskal-Wallis test and the post-hoc Dunn test with the Benjamini-Hochberg correction for multiple testing [17]. The data were visualized with box-plots. The RDI-O cut-off was selected based on its association with DFS and OS. Survival analysis was performed using the Kaplan-Meier method [18]. Univariate analysis was performed using the Cox' proportional hazard model; multivariate analysis was performed with the stepwise forward approach. Similarly, logistic regression analysis was performed for 12-month, 18-month and 36-month DFS, while the multivariate analysis employed the stepwise forward approach. For all analyses the α level of 0.05 was employed.

Results

Study population

The study group included 365 stage III colon cancer patients – 176 females (48.2%) and 189 males (51.8%) (Table 1). The mean age at diagnosis was 61.2 years (range 25–80 years), 176 (48.2%) patients were 63 years and 15.3% above 70 years. There were 176 patients (48.2%) with high risk (pT4 and/or pN2) and 189 (51.8%) with low risk (pT1-3 and pN1) stage III CC. The mean number of harvested lymph nodes was 13.2 (range 1–50). Left and right-sided, primary tumours was 203 (55.6%) and 161 (44.1%), respectively. Most patients did not have diabetes at the time of diagnosis 325 (89%) and median body mass index (BMI) was 26.4 (range 15.6–44). Other baseline clinical and pathology characteristics are summarized in Table 1.

Table 1
Patient characteristics.

Variables		n 365 (100%)
Age at diagnosis; years		
	Mean	62
	Range	25–80
	< 63	189 (51.8%)
	≥ 63	176 (48.2%)
	> 70	56 (15.3%)
Gender		
	Female	176 (48.2%)
	Male	189 (51.8%)
Body mass index (kg/m^2)		
	Median	26.4
	Range	15.6–44
	≤ 18,5	13 (3.6%)
	18,5–24,9	128 (35.1%)
	≥ 25,0	224 (61.4%)
Diabetes mellitus		
	No	325 (89%)
	Yes	40 (11%)
Histology		
	Adenocarcinoma not otherwise specified (NOS)	304 (83.3%)
	Mucinous adenocarcinoma	54 (14.8%)
	Adenocarcinoma of cylindrical cells	2 (0.5%)
	Signet ring adenocarcinoma	2 (0.5%)
	Adenosquamous carcinoma	1 (0.3%)
	Undifferentiated carcinoma	2 (0.5%)
Histopathology grade (G)		

Variables		n 365 (100%)
	G1 (well differentiated)	33 (9.0%)
	G2 (moderate differentiated)	279 (76.4%)
	G3 (poor differentiated)	52 (14.2%)
	No data	1 (0.3%)
Primary tumor classification (pT)		
	1	3 (0.8%)
	2	47 (12.9%)
	3	249 (68.2%)
	4a	48 (13.2%)
	4b	18 (4.9%)
Regional lymph nodes classification (pN)		
	1a	106 (29.0%)
	1b	119 (32.6%)
	1c	1 (0.3%)
	1	1 (0.3%)
	2a	80 (21.9%)
	2b	58 (15.9%)
Number of harvested lymph nodes		
	< 12	196 (53.7%)
	≥12	165 (45.2%)
	No data	4 (1.1%)
Primary tumor location		

Variables		n 365 (100%)
	Ceacum	64 (17.5%)
	Ascending colon	49 (13.4%)
	Hepatic flexure	28 (7.7%)
	Transverse colon	20 (5.5%)
	Splenic flexure	22 (6.0%)
	Descending colon	14 (3.8%)
	Sigmoid colon	168 (46.1%)
Primary tumor location		
	Right colon	161 (44.1%)
	Left colon	203 (55.6%)
	No data	1 (0.3%)
Surgery		
	Right hemicolectomy	116 (31.8%)
	Right hemicolectomy extended	36 (9.9%)
	Left hemicolectomy	45 (12.3%)
	Sigmoidectomy	167 (45.8%)
	Transversectomy	1 (0.3%)
Adjuvant chemotherapy		
	FOLFOX-4	336 (92%)
	CAPOX (XELOX)	29 (8%)
CEA concentration before surgery; ng/ml		
	< 5	96 (26.3%)
	≥5	28 (7.7%)
	No data	241 (66.0%)
CEA concentration after surgery; ng/ml		
	< 5	292 (80.0%)
	≥5	33 (9.0%)
	No data	40 (11.0%)

Treatment Duration And Safety

The median follow-up was 51.8 months (range 8.2-115.1). The majority of patients received FOLFOX-4 (336 patients; 92%) and 29 patients (8%) CAPOX. The mean number of chemotherapy cycles was 10.2 (standard deviation 2.76). Two hundred and nine (57.3%), forty- five (12.3%) and 31 (10%) received 12 and 6 and < 6 cycles, respectively. The distribution of chemotherapy cycles was well balanced between clinical stages IIIA ($pT_{1-2}N_{1a-c}/pT_1N_{2a}$), IIIB ($pT_{3-4a}N_{1a-c}/pT_{2-3}N_{2a}/pT_{1-2}N_{2b}$), IIIC ($pT_{4a}N_{2a}/pT_{3-4a}N_{2b}/pT_{4b}N_{1-2}$), p = 0.47.

The number of chemotherapy cycles was correlated with toxicity (Kruskal-Wallis-test p = 10^{-10}). Seventy-one patients (19.5%) discontinued oxaliplatin-based chemotherapy due to adverse events. The median cumulative dose (CD) and RDI-O were 936.86 mg/m^2 (range 84.03-1042.70; interquartile range, IQR: 763.78-1016.94 [mg/m^2]) and 82.32% (range 6.02-196.42, IQR: 61.37–94.27), respectively. In the group of patients, who completed 12 chemotherapy cycles, CD was 1012.33 mg/m^2 (range 632.50-1042.70; IQR: 961.50-961.50 [mg/m^2]) and RDI-O was 91.58% (range 30.16-196.42, IQR: 83.01–98.94). There was no difference between median CD, RDI-O and pT (p = 0.46; p = 0.07), pN (p = 0.85; p = 0.66), pTNM stage (p = 0.92; p = 0.90) (Fig. 1). The CD and RDI-O were correlated with therapy toxicity (0 = 0.03 and p < 0.01). Oxaliplatin-induced peripheral neuropathy (OXIPN): sensory and motor occurred in 212 (58.1%), and 35 (9.6%) patients, respectively. Severe (grade 3) and life-threatening (grade 4) OXIPN were diagnosed in 54 (14.8%) and 9 (2.5%) patients. There was no relationship between diabetes and the risk of OXIPN (p = 0.31).

Figure 1. Relative dose intensity for oxaliplatin and pT, pN, TNM and maximal toxicity grade.

Activity And Efficacy

At last follow-up 228 (62.5%) were alive and 137 (37.5%) died. Median DFS was 43.86 months (range 0.79- 113.42) and OS was 51.8 months (range 8.2-115.1). The number of cycles ≥ 6 vs. <6 was not correlated with DFS and OS (HR = 0.68 (95% CI: 0.43–1.07) p = 0.09 and HR = 0.72 (95% CI: 0.43–1.18); p = 0.19, respectively.

The early recurrence within 36 months after surgery occurred in 130 patients (36.6%). The most common type of early relapse was distant metastases (100 patients; 76.9%), rarely local recurrence (8 patients; 6.2%) or both distant metastases and local recurrence (22 patients; 16.9%). The most common recurrence site was liver (74 patients; 60.7%), followed by the lung (41 patients; 33.6%), lymph nodes (27 patients; 22.1%), other organs (16 patients; 13.1%) and peritoneum (20 patients; 16.4%). Bone and brain metastases were diagnosed in 6 (4.9%) and 3 (2.5%) cases.

The RDI-O < 60% was related with recurrence within 12 and 18 months (OR = 2.04; 95%CI: 1.08–3.78; p = 0.024 and OR = 2.05; 95%CI: 1.18–3.51; p = 0.010) but not within 36 months (OR = 1.50; 95%CI: 0.90–

2.48; p = 0.117) (Table 2), HR = 1.39 (95%CI: 0.96-2.0, p = 0.08 (Fig. 2).

Table 2
Uni- and multivariate logistic regression for disease recurrence within 12, 18, and 36 months.

DFS	Variable	Grade 3 vs 2 vs 1	pT 4 vs 3 vs 2 vs 1	pN 2 vs 1	N° harvested ≥ vs < 12	RDI-O < 60 vs≥60%
		OR (95% CI); p				
12 months	Univariate analysis	2.82 (1.39–5.53) 0.003	3.03 (1.58–5.70) 0.001	1.78 (0.99–3.20) 0.051	0.59 (0.32–1.06) 0.078	2.04 (1.08–3.78) 0.024
	Multivariate analysis	2.36 (1.09–4.93) 0.025	2.84 (1.40–5.65) 0.003	1.93 (1.03–3.63) 0.041	0.49 (0.25–0.92) 0.028	2.06 (1.03–4.01) 0.036
18 months	Univariate analysis	2.45 (1.30–4.55) 0.005	1.93 (1.07–3.68) 0.027	2.23 (1.36–3.68) 0.002	0.61 (0.37-1.00) 0.051	2.05 (1.18–3.51) 0.010
	Multivariate analysis	2.47 (1.25–4.80) 0.008	-	2.63 (1.55–4.54) < 0.001	0.51 (0.29–0.86) 0.013	1.91 (1.06–3.39) 0.028
36 months	Univariate analysis	2.09 (1.15–3.80) 0.015	2.80 (1.62–4.88) < 0.001	2.17 (1.39–3.39) 0.001	0.62 (0.40–0.96) 0.034	1.50 (0.90–2.48) 0.117
	Multivariate analysis	1.93 (1.02–3.65) 0.043	2.66 (1.49–4.79) 0.001	2.46 (1.53–4.01) < 0.001	0.46 (0.28–0.74) 0.001	-

DFS: disease free survival; CI: confidence interval; OR: odds ratio; p: pathological; N°: number; RDI-O: relative dose intensity of oxaliplatin

Figure 2. The relative dose intensity of oxaliplatin (RDI-O) ≥60 vs < 60% and early recurrence in the whole group: within 12, 18 and 36 months.

The low-risk group recurrence within 12 and 18 months (OR = 3.31; 95%CI: 1.21–9.04; p = 0.018 and OR = 2.73; 95%CI: 1.16–6.37; p = 0.020) and high-risk group (OR = 1.72; 95%CI: 0.71–3.96; p = 0.209 and OR = 2.06; 95%CI: 0.96–4.42; p = 0.062) (Table 2); HR = 1.56 (95%CI: 0.96–2.53), p = 0.07 (Fig. 3A) and HR = 1.39 (95%CI: 0.79–2.44; p = 0.25) (Fig. 3B).

Figure 3. The relative dose intensity of oxaliplatin (RDI-O) ≥60 vs < 60% and early recurrence in low-risk (A) and high-risk (B) subgroups: within 12, 18 and 36 months.

In the univariate analysis, other factors correlated with recurrence within 12 and 18 months were tumor grade (OR = 2.82; 95%CI: 1.39–5.53; p = 0.003 and OR = 2.45; 95%CI: 1.30–4.55; p = 0.005), pT (OR = 3.03; 95% CI: 1.58–5.70; p = 0.001 and OR = 1.93; 95% CI: 1.07–3.68; p = 0.027), pN (OR = 1.78; 95% CI: 0.99–3.20; p = 0.051 and OR = 2.23; 95% CI: 1.36–3.68; p = 0.002) (Table 2). In the multivarite analysis, recurrence within 12 and 18 months correlated with grade (OR = 2.36; 95%CI: 1.09–4.9; p = 0.025 and OR = 2.47; 95% CI: 1.25–4.8; p = 0.008), pT (OR = 2.84; 95% CI: 1.4–5.65; p = 0.003), pN (OR = 1.93; 95% CI: 1.03–3.63; p = 0.041 and OR = 2.63; 95% CI: 1.55–4.54; p < 0.001), the number of lymph nodes harvested (OR = 0.49; 95% CI: 0.25–0.92; p = 0.028 and OR = 0.51; 95% CI: 0.29–0.86; p = 0.013) and RDI-O (OR = 2.06; 95%CI: 1.03–4.01; p = 0.036 and OR = 1.91; 95%CI: 1.06–3.39; p = 0.028) (Table 2).

In the multivariate analysis, recurrence within 36 months correlated with grade (OR = 1.93; 95%CI: 1.02–3.65; p = 0.043), pT (OR = 2.66; 95%CI: 1.49–4.79; p = 0.001), pN (OR; 95% CI: 1.53–4.01; p < 0.001), and the number of lymph nodes harvested (OR = 0.46; 95%CI: 0.28–0.74; p = 0.001) (Table 2). The early vs. late recurrence negatively correlated with OS regardless of the RDI-O (HR = 22.9 (95%CI: 13.9–37.6; p < 0.001).

Discussion

The postoperative, oxaliplatin-based adjuvant chemotherapy for stage III CC patients demonstrated an improvement in patient outcome and became the standard of care. In clinical trials, FOLFOX/CAPOX in adjuvant setting has been shown to cause a statistically significant improvement in DFS and OS over fluorouracil-based chemotherapy (4–7% and 2–6%, respectively) [1–6]. Further, in the MOSAIC and NO16968 study an improvement in OS was detected after a longer, approximately seven-year follow-up [2, 6].

Unfortunately, adverse events caused by oxaliplatin often lead to premature termination of therapy and thus a reduction in the number of cycles or dose, and consequently the CD and RDI [2–6]. In the MOSAIC, NASBP-C07 and NO16968 trials approximately 30% of patients receiving oxaliplatin did not complete the planned treatment due to adverse events, mainly burdensome OXIPN [1–3]. Similarly, in our study about twenty percent of patients discontinued treatment due to mainly OXIPN, which occurred in various grades, in 212 patients (58.1%). Therefore, how many adjuvant oxaliplatin-based chemotherapy cycles maybe

enough in this group of patients is still an open question. Tsai et al. have shown that at least eight FOLFOX cycles are needed to have OS benefit, and seven to ensure DFS [19]. Moreover, in the International Duration Evaluation of Adjuvant Therapy (IDEA) project in stage III CC patients, the non-inferiority of FOLFOX/CAPOX regimens used for 3 vs. 6 months was not demonstrated [20–22]. Although in the lower risk group (pT1-3/N1), the 3-month (4 cycles) CAPOX was as effective as the 6-month (8 cycles) treatment and the 3-year rate of DFS was 74.6% and 75.5%, respectively [20–22]. Importantly, the shorter treatment was associated with a lower risk of adverse events, including OXIPN.

To the best of our knowledge, the impact of RDI-O in adjuvant therapy among stage III colon cancer patients on early recurrence has not been systematically addressed, neither in a prospective nor retrospective fashion. The correlation between RDI of systemic therapy and clinical outcomes have demonstrated mainly for diffuse lymphoma [23–25] and metastatic solid tumours that are relatively sensitive to anti-tumour drugs [26–28]. In stage III CC, the retrospective study of 367 patients treated fluoropyrimidine-based chemotherapy mainly without oxaliplatin between 2003 and 2008 at 19 VA medical centers in the USA showed that RDI of chemotherapy above 70% improving 5-year OS [29]. It should be noted that, in this study RDI was calculated for each drug within each regimen i.e. 5-fluorouracil, capecitabine and leucovorin [29]. The one study directly evaluated the prognostic impact of oxaliplatin dose reduction in adjuvant setting but in stage II and III colorectal cancer [30]. In this study, in South Korea patients observed that more than 60% of standard dose of oxaliplatin should be administered to achieve no difference in 5-year DFS and OS [30].

In our study, in homogenous Caucasian race stage III CC patients treated mainly with FOLFOX-4 (N = 336, 92%), no relationship was found between numbers of cycles: ≤6 vs. > 6 cycles and DFS or OS. However, it should be observed that the majority of patients received more than 6 cycles of chemotherapy (N = 320, 88%). Due to the oxaliplatin dose reduction in subsequent chemotherapy cycles, the median CD-O was 936.86 mg/m^2, and in the group of patients who completed 12 cycles, 1012.33 mg/m^2. However, the CD-O in our group treated in clinical practice was higher compared to the doses in the MOSAIC and NASBP-C07 studies (respectively 810 and 677 mg/m^2) but the clinical outcomes were slightly worse, with a 3-year DFS 61.64% and median DFS 43,86 months [1–3]. The results in patients participating in clinical trials are generally better than in patients treated in everyday practice for a variety of reasons. However in our study, half of patients met the criteria of low-risk of relapse – 189 (51.8%) but only 165 patients (45.2%) in whole cohort had at least twelve lymph nodes removed during surgery. The small number of examined nodes may be “under staged” and affect the prognosis. Although some reports suggest that the total number of lymph nodes analyzed in stage III CC is not a prognostic indicator of cancer-specific and DFS [31, 32].

Among CRC patients, 60–80% of recurrences becoming apparent within the first 2 years after curative surgery [8–10]. Previous studies showed that stage III CC patients were more prevalent in the early compared to late-recurrence group and have worse clinical outcome [8, 10, 11, 33]. In the our study, the factors associated with early recurrence (within 18 months) were tumour grade, the number of positive and harvested lymph nodes and also RDI-O < 60%. Interestingly, the risk of early recurrence in patients

with RDI-O < 60% concerned especially low-risk group. These results should be referred to the above-mentioned IDEA project and CAPOX efficacy in low-risk group [20–22]. It seems, that RDI-O may be a more accurate reflection of the true patient-relevant benefit of adjuvant chemotherapy among stage III CC. However, patients with early recurrence showed worse overall survival regardless of the RDI-O.

We are aware that the retrospective nature of the study may have influenced our findings. Moreover, in our study we focused only on RDI-O not each drug within regimen and the risk of early recurrence. Further, we did not collect data on molecular abnormalities in primary tumour e.g. the presence of activating mutations in the *KRAS, NRAS* and *BRAF*, or microsatellite instability and defective DNA mismatch repair (dMMR). However, based on previous research only dMMR seems to be important but only among stage II patients being considered for single-agent, fluoropyrimidine-based therapy [34]. Further research should focus on better biomarkers to assess the likelihood of chemotherapy response, based on molecular biology and pharmacokinetic analyses to reduce toxicity and improve treatment outcomes.

Conclusions

We demonstrated that RDI-O under 60% in adjuvant setting among stage III CC patients apparently increase the likelihood of early recurrence especially in low-risk group. It should be noted that research into the optimal dose of oxaliplatin in adjuvant treatment is important due to the lack of effective methods of prevention and therapy of long-term OXIPN, which negatively affects patients' quality of life [35].

Abbreviations

AEs
Adverse events
AJCC
American Joint Committee on Cancer
BMI
Body mass index
BRAF
Proto-oncogene, serine/threonine kinase
CAPOX/XELOX
Chemotherapy schedule (oxaliplatin, capecitabin, leucovorin)
CC
Colon cancer
CD
Cumulative dose
CEA
Carcinoembryonic antigen
CRC

Colorectal cancer

CTCAE

Common Terminology Criteria for Adverse Events

DDI

Delivered dose intensity

DFS

Disease-free survival

dMMR

Defective DNA mismatch repair

FOLFOX

Chemotherapy schedule (oxaliplatin, 5-fluorouracil, leucovorin)

HR

Hazard ratio

IDEA

International Duration Evaluation of Adjuvant Chemotherapy collaboration

IQR

Interquartile range

IUCC

International Union for the Fight against Cancer

KRAS

Kristen rat sarcoma viral oncogene homolog

MOSAIC

Multicenter International Study of oxaliplatin/5-fluorocil, Leucovorin in Adjuvant Treatment of Colon Cancer

NASBP-C07

National surgical Breast and Bowel Project

NCI

National Cancer Institute

NRAS

Neuroblastoma RAS viral oncogene homolog

OS

Overall survival

OXIPN

Oxaliplatin-induced peripheral neuropathy

R1

Microscopic tumour infiltrations

R2

Macroscopic tumour infiltrations

RDI

Relative dose intensity

RDI-O
Relative dose intensity of oxaliplatin
SDI
Standard dose intensity
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TNM
TNM classification of Malignant Tumours

Declarations

Ethics approval and consent to participate:

Bioethics Committee, Medical Chamber in Opole (Agreement No. 245/2017).

Consent for publication:

not applicable

Availability of data and materials:

The dataset used and analyzed in this study are not publicly available due to the data generated for the reporting but available only to the research members on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' Contributions:

Study concepts - J.Ż., R.D.; Study design - J.Ż., R.D., M.B.; Data acquisition - J.Ż., R.D., B.R., M.B., J.K., K.A.; Quality control of data and algorithms - J.Ż., R.D., B.R., M.B., J.K., K.A.; Data analysis and interpretation - J.Ż., R.D., B.R., M.B., J.K., K.A.; Manuscript preparation - J.Ż., M.B., R.D.; Manuscript review - J.Ż., R.D., B.R., M.B., J.K., K.A.

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Figures

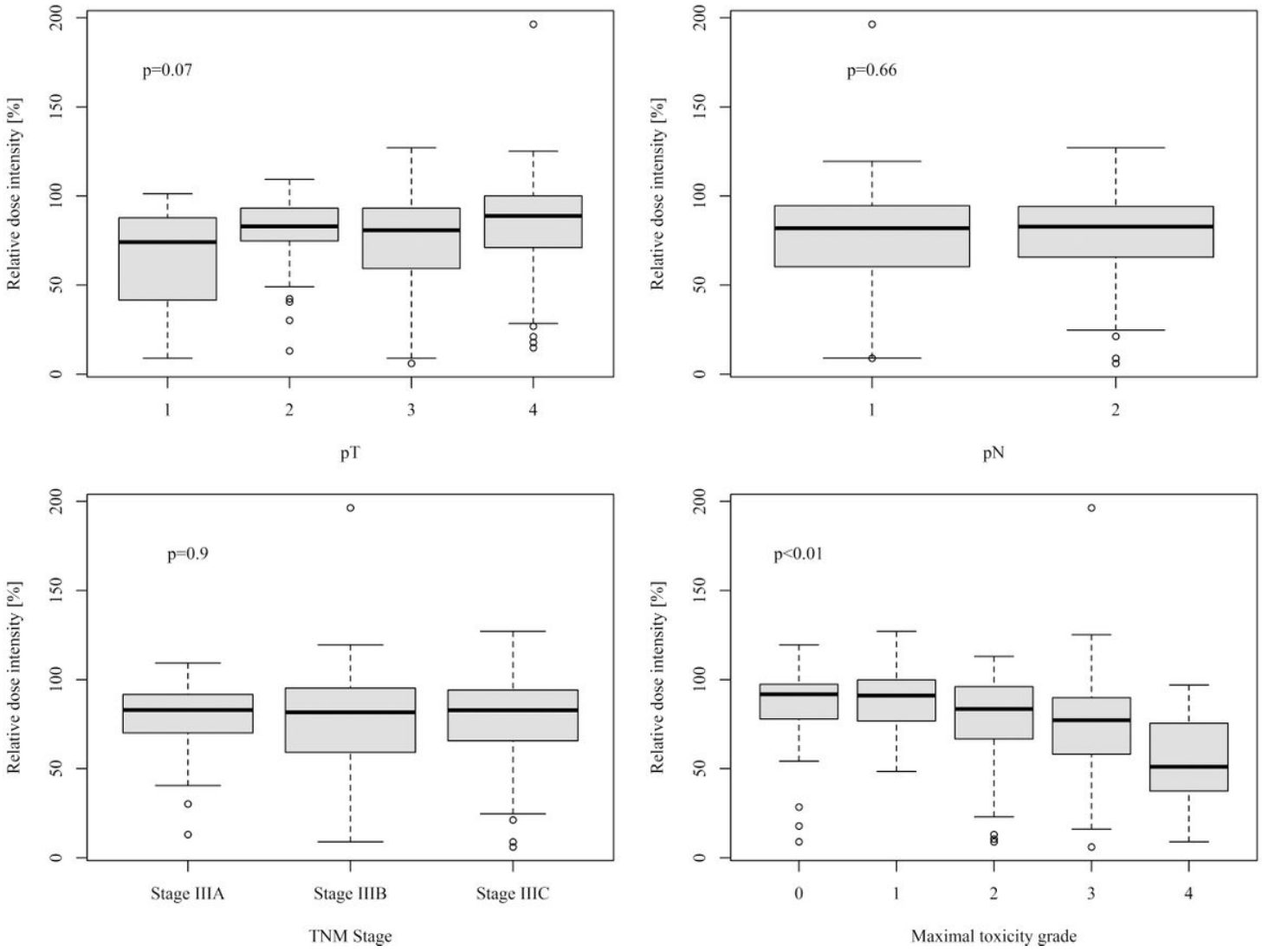

Figure 1

Relative dose intensity for oxaliplatin and pT, pN, TNM and maximal toxicity grade.

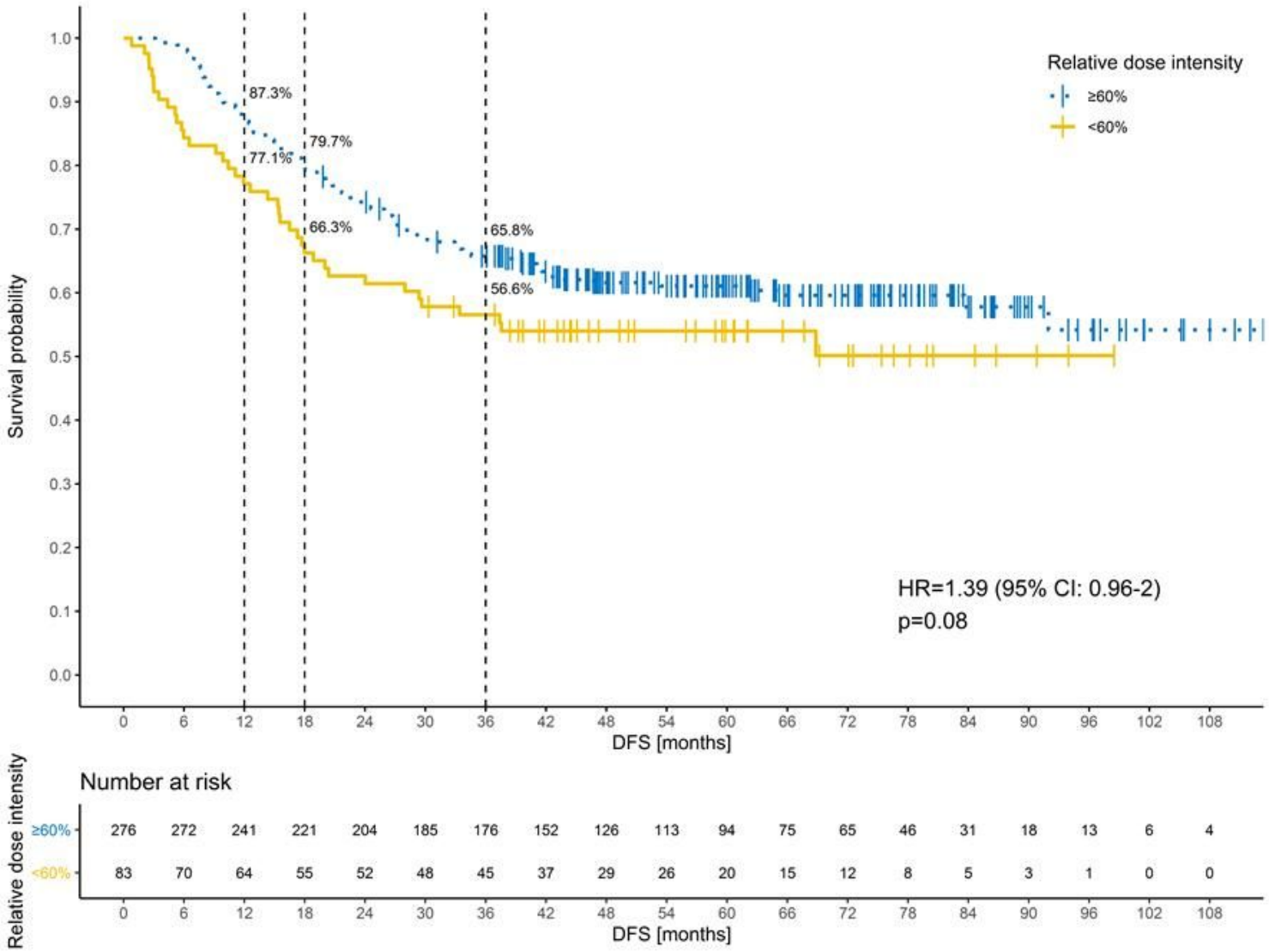

Figure 2

The relative dose intensity of oxaliplatin (RDI-O) ≥60 vs <60% and early recurrence in the whole group: within 12, 18 and 36 months.

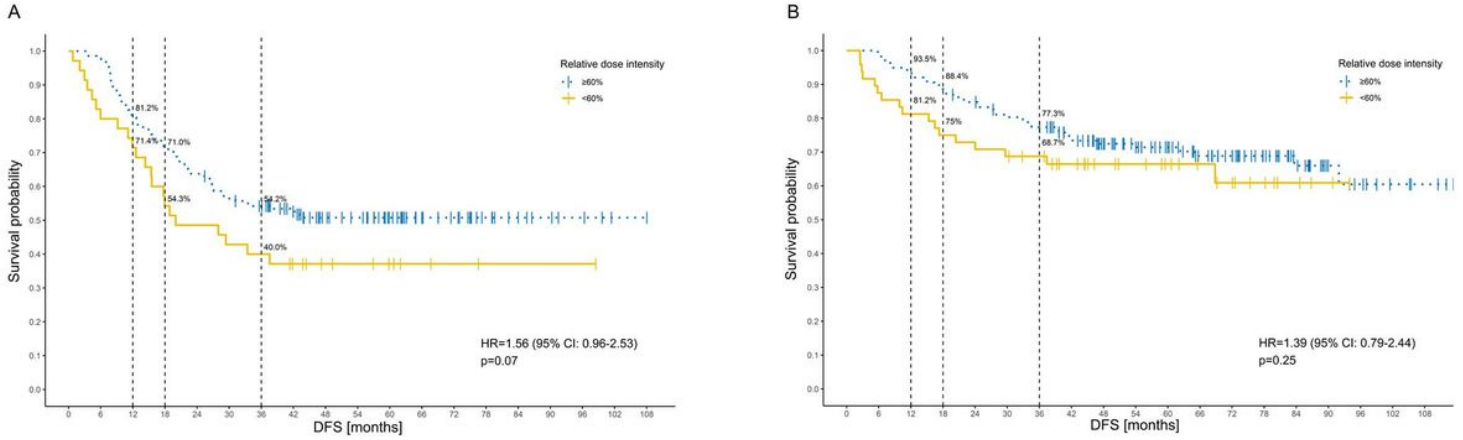

Figure 3

The relative dose intensity of oxaliplatin (RDI-O) ≥60 vs <60% and early recurrence in low-risk and high-risk subgroups: within 12, 18 and 36 months.