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ORIGINAL ARTICLE

Symptoms during chemotherapy in colorectal cancer patients

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Abstract

Purpose Colorectal cancer (CRC) patients experience several physical and psychological co-occurring symptoms, but little is known about symptom variation during chemotherapy cycles. Therefore, the aims were (1) to assess the occurrence and severity of frequently occurring symptoms (worrying, lack of energy, numbness/tingling, nausea, and pain) at multiple time points during chemotherapy, (2) to investigate differences in symptom trajectories between chemotherapy groups, and (3) to determine whether selected patient and clinical characteristics are associated with symptom severity throughout the treatment trajectory.

Methods In total, 120 CRC patients receiving chemotherapy with curative or palliative intent completed the Memorial Symptom Assessment Scale (MSAS), Self-Administered Comorbidity Questionnaire (SCQ-19), and Karnofsky Performance Status (KPS) scale eight times, during two cycles of chemotherapy and 3 and 6 months after enrolment. Data were analyzed using linear mixed models for repeated measures to assess the effects of selected variables on outcomes over time.

Results The patients experienced greatest symptom severity in the days following the administration of chemotherapy; these were *lack of energy*, *numbness/tingling* (oxaliplatin group), and *nausea.* Palliative patients reported significantly higher *pain* scores compared with curative patients over time, whereas the severity of *worrying* decreased over time in both treatment groups. Age, sex, educational level, performance status, treatment intent and type of chemotherapy were significantly associated with symptom severity throughout the chemotherapy trajectory.

Conclusion Clinicians can use these findings to identify and inform patients about risk for more severe symptom burden, in order to offer supportive care at the right time during the chemotherapy treatment.

Keywords Colorectal neoplasm · Chemotherapy · Symptoms · Trajectory · Longitudinal · Memorial Symptom Assessment Scale

Introduction

A significant number of people are living with colorectal cancer (CRC), which accounts for the third most frequent cancer diagnosis worldwide [1]. CRC patients experience a high symptom burden already early in the treatment phase [2, 3] followed by a range of physical and psychological co-occurring symptoms during the chemotherapy trajectory [4]. Co-occurring symptoms are reported to catalyze each other [5], however without systematic symptom assessment with Patient-Reported Outcome Measures (PROMs) during the chemotherapy cycles, symptoms are at risk of not being detected [6, 7]. Previous research has shown that patients report lowest levels of symptoms at the day of chemotherapy [7] whereas chemotherapy triggers the need of unplanned visits to the general practitioners or hospital in the days following chemotherapy [8].

Treatment for CRC includes surgery, which is the mainstay of curative treatment and is often supplemented with radiotherapy or chemotherapy. Patients operated for colon cancer stage III are recommended adjuvant chemotherapy, either 5-fluorouracil (5FU)-based therapy or in combination with oxaliplatin [9, 10]. Patients receiving palliative chemotherapy for stage IV disease usually receive combination regimens with 5FU and oxaliplatin or irinotecan, or 5FU monotherapy,

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often combined with targeted therapy, and often several lines of chemotherapy until disease progression or toxicity [11].

Chemotherapy is commonly given in cycles, which compromises the days of chemotherapy administration (often over 1–3 consecutive days) followed by a period without treatment (at home) before the next cycle. Insight into the self-reported symptoms and their severity are of importance to give the best supportive care during treatment [12, 13]. Knowledge about the symptoms occurrence and severity during and between chemotherapy cycles is almost nonexisting in CRC outpatients.

Each chemotherapy regimen has a distinct toxicity profile. A well-known side effect of oxaliplatin is peripheral neuropathy [10, 14, 15] which increases with cumulative dose [16], is often dose-limiting, and may persist after treatment cessation [15, 16]. Irinotecan and 5FU can cause gastrointestinal toxicity such as diarrhea [10]. Other common side effects of chemotherapy include neutropenia, nausea, difficulty sleeping [2, 17, 18], cognitive impairment of attention and memory [19], and lack of energy [2, 20–22]. The disease itself may also cause pain [3, 21, 23].

Frequent symptom assessments during treatment increase the chance of capturing symptom fluctuations [6, 7, 24]. In a review of multiple co-occurring symptoms in CRC patients receiving chemotherapy, only five studies used a multidimensional symptom assessment instrument [21]. Of these, one studied CRC patients receiving second-line palliative chemotherapy with a longitudinal design and found that moderate to severe fatigue was the most common symptom, whereas pain and nausea improved slightly over time [18]. Symptom burden at enrolment was reported to be a predictor of symptom burden during chemotherapy; however, no specification of assessment times were reported [18]. Other longitudinal studies of CRC patients have assessed few or single symptoms and have reported increasing fatigue and depression [22] and decreasing level of anxiety [15, 25] over the course of chemotherapy, and persisting neuropathy after chemotherapy [15]. Small study samples and assessment of only a single or few symptoms [15, 22, 25] limit the conclusions about symptom experience that may be drawn from these studies. In a recently published longitudinal study of gastrointestinal cancers, the symptoms varied across the course of chemotherapy [4]. However, the time of assessment did not follow the chemotherapy cycle and therefore does not demonstrate possible symptom severity between the chemotherapy cycles [7, 8].

Based on the knowledge gap of multiple symptoms during, and in the days following chemotherapy administration in CRC outpatients, the aims of the present study were (1) to assess prospectively the occurrence and severity of symptoms (worrying, lack of energy, numbness/tingling, nausea, and pain) at multiple time points during two chemotherapy cycles, and at 3 and 6 months; (2) to investigate the differences in symptom trajectories between the chemotherapy groups (patients receiving 5FU, irinotecan/5FU, or oxaliplatin/5FU); and (3) to determine whether selected demographic and clinical characteristics are associated with symptom severity during the chemotherapy trajectory.

Methods

Study procedures

The present study is part of a larger longitudinal study of symptom clusters and quality of life (QoL) in oncology patients ($N = 534$) (Clinicaltrials.gov, NCT00769301) [3, 26]. Patients with CRC who were scheduled to receive outpatient chemotherapy at Oslo University Hospital were included in the present study ($n = 120$). Eligible patients received information about the study from the research nurse, and informed consent was obtained from all participants.

The patients completed the self-assessment questionnaires before chemotherapy (T1), after 3 (T2) and 7 days (T3), and before the second chemotherapy cycle (T4), after 3 (T5) and 7 days (T6), at 3 (T7) and 6 months (T8) (Fig. 1). The enrolment questionnaires were completed before initiation of the first chemotherapy cycle, and questionnaires for the next five measurements were given to the patients. For the last two measurements, the questionnaires were sent to the patients' home address along with an addressed, stamped return envelope. The study nurse telephoned the patients at T2–T6 to remind them to complete the questionnaires.

Patients

Patients were eligible for inclusion if they were ≥ 18 years of age, scheduled to start a new chemotherapy regimen for CRC, and were able to read and write Norwegian. Patients with brain metastases or diseases affecting their cognitive ability were excluded.

Data collection

Demographic and clinical characteristics

The patients completed a questionnaire on demography including age, sex, marital/cohabitation status, care of children, occupation, sick leave, and level of education. Height and weight were measured and body mass index (BMI) calculated. Information of disease, stage, and treatment was obtained from the medical records, and the treatment intent was registered as either curative or palliative. Information about survival was obtained from the medical records.

Multiple symptoms To measure multiple symptoms, the Memorial Symptom Assessment Scale (MSAS) was used.

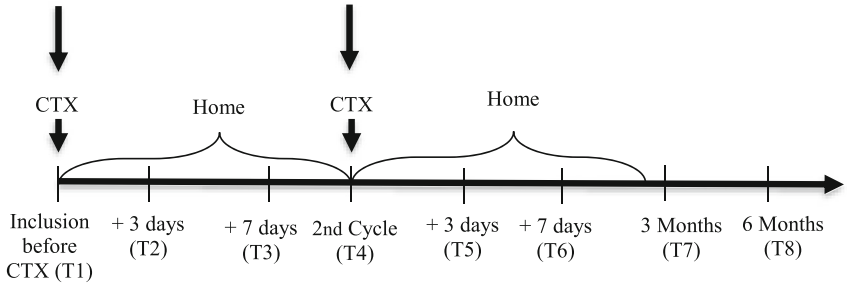


Fig. 1 Timeline of data collection over 6 months' chemotherapy

Abbreviations: CTX= chemotherapy; T1 = at enrolment; T2 and T3 = 3 days and 7 days after initiation of the first chemotherapy cycle; T4 = before chemotherapy administration at the second cycle; T5 and T6 = 3 days and 7 days after initiation of the second chemotherapy cycle; T7 = 3 months after enrolment; T8 = 6 months after enrolment

MSAS contains of 32 physical and psychological cancer or treatment symptoms and three optional symptoms [27]. For each symptom, patients were asked to indicate whether they had the symptom during the past week (i.e., occurrence), and to rate its frequency, severity, and distress. Symptom severity (1 = slight, 2 = moderate, 3 = severe, 4 = very severe) were rated using four-point scales. Only occurrence and severity were used in the present study. The reliability and validity of the MSAS are satisfactory [27], and the MSAS has been used previously in CRC patients [2, 4] and other Norwegian cancer patients [26].

The symptom selection was based on the following: worrying and lack of energy were the two most occurring symptoms previously reported in the current patient group [3], numbness/tingling and nausea are known side effects of chemotherapy, and pain is a common and distressing symptom and often underreported [17, 23]. Symptom severity was only presented for the five abovementioned symptoms.

Comorbidity

The Self-Administered Comorbidity Questionnaire (SCQ-19) comprises 16 common and three optional comorbidities [28]. The total number of comorbidities registered (0–19) was used in the analyses. The SCQ-19 has well-established validity and reliability in patients with cancer [28] and has been used previously to assess comorbidity in Norwegian cancer patients [26].

Performance status

The performance status was self-assessed using the Karnofsky Performance Status (KPS) scale with scores ranging from 40 (i.e., disabled, requires special care and assistance) to 100 (i.e., normal no complaints, no evidence of disease). The KPS scale is used extensively and has well-established validity and reliability in cancer patients [29].

Data analysis

Descriptive statistics are used to present the demographic and clinical characteristics. Continuous variables are described with median and range, and mean and standard deviation (SD) (when normally distributed), and categorical data as proportions and percentages.

To analyze possible differences between treatment groups after adjusting for possible confounders, and using worrying, lack of energy, numbness/tingling, nausea, and pain as outcomes, linear mixed models (LMMs) for repeated measures were fitted. The outcome variable for each of the selected symptoms on MSAS was constructed as follows: If a patient reported not having a symptom, the symptom severity was coded as zero. If the patients rated severity > 0 despite reporting "no" on symptom occurrence, they were coded as having the symptom. When a patient reported having a symptom and a level of severity, this level was used as a category in the new combined occurrence/severity variable. Thus, the new symptom variable score ranged from 0 (no symptom) to 4 (the highest possible level of severity).

An unstructured covariance matrix was used to model dependencies among measurements for the same individual at different time points to accommodate the uneven spacing between measurements when fitting LMM. Individual differences at enrolment were accounted for by a random intercept parameter. To test whether possible confounders affected the results, the LMMs were adjusted for covariates measured at enrolment (sex, age, educational level (primary/secondary school or high school/university), treatment intent (curative or palliative), primary tumor site (colon or rectum cancer), type of chemotherapy (three groups), metastatic sites (0 or ≥ 1), SCQ score (0 or ≥ 1 comorbidities, and KPS)), and status as fixed effects. An interaction term between time (measurement time point) and type of chemotherapy (group 1 = 5FU, group 2 = irinotecan/5FU, and group 3 = oxaliplatin/5FU (reference)) was added to evaluate whether the symptom * time trajectories developed differently among the groups. The covariates were selected based on previous research

and clinical considerations and tested together in the same model for each symptom.

The LMM provides estimates using all available data; thus, no imputation of missing data was considered necessary. The results are presented as *p* values for the overall effects of the variables when taking the time from the inclusion scores and all seven additional time points into consideration. The results are also presented as point estimates of the regression parameter beta with 95% confidence interval (CI). Our analyses were considered exploratory; thus, no correction for multiple testing was made. For all tests, a two-sided *p* value < .05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 23 (Armonk, NY: IBM Corp).

Results

Patient and disease characteristics

A total of 134 patients were approached; 125 provided informed consent and agreed to participate, 120 completed the enrolment questionnaires and were included in the analyses, and 88 completed all eight assessments. Their demographic and clinical characteristics are presented in Table 1. The median age was 65 years, 39% were women, and 44% were retired. The median number of comorbidities (SCQ) was 2.0 (range 0–8), most commonly hypertension (31%). Median BMI was 25 kg/m^2 (range 16–38).

Curative chemotherapy was scheduled for 68 (57%) patients (adjuvant or neoadjuvant) and palliative chemotherapy for 52 (43%) (Table 1). The primary tumor was in the colon for 72% of the patients and in the rectum for 28%, and liver was the predominant metastatic site. Patients received 5FU monotherapy (17%), irinotecan/5FU combination (23%) or oxaliplatin/5FU combination (60%) regimens. Three patients received bevacizumab or cetuximab in combination with irinotecan.

At the last assessment (T8), 47 patients (39%) were alive with no evidence of disease, 41 (34%) with stable disease, and 21 (18%) with progression of disease. Five (4%) patients had died. Six patients withdrew consent before the last assessment (T8).

Symptom occurrence during chemotherapy

The occurrence rates at all assessment times for worrying, lack of energy, numbness/tingling, pain, and nausea are presented in Table 2. Worrying was the most occurring symptom at enrolment, and lack of energy at 6 months. Lack of energy, numbness/tingling, and nausea showed a peak in occurrence in the days and week after each chemotherapy administration and lower prevalence before start of the next chemotherapy. Worrying and pain declined in occurrence during the 6-month treatment. The occurrence rates for all 32 MSAS symptoms at all eight assessments are shown in Appendix Table 4.

Symptom severity during chemotherapy

When adjusted for selected covariates, the patients reported the greatest severity of *worrying* at enrolment and decreased with time (Table 3; Fig. 2). *Lack of energy* increased in severity 3–7 days after each chemotherapy cycle (Table 3, Fig. 2). *Numbness/tingling* increased in severity 3–7 days after each cycle; however, this symptom also increased markedly with time for oxaliplatin-based chemotherapy (Table 3; Fig. 2). *Nausea* was markedly worst on day 3 of each cycle among the chemotherapy groups (Table 3; Fig. 2). There were no significant changes in severity scores for *pain* with time (Table 3; Fig. 2).

Worrying

In the adjusted analyses, the severity score for *worrying* did not differ significantly between the chemotherapy groups, treatments groups, or according to educational level (Table 3). Women scored higher on *worrying* than men ($B = 0.35$, 95% CI [0.02–0.68], $p = .04$). Age was significantly associated with *worrying*, with the highest score among the youngest ($B = -0.02$, 95% CI [− 0.04 to– 0.01], $p = .04$). The patients scored 0.2 points higher on *worrying* for each 10-point decrease in KPS score ($B = 0.24$, 95% CI [0.12–0.34], $p < .01$).

Lack of energy

In the adjusted analyses, *lack of energy* did not differ between the chemotherapy groups (Table 3). Women scored higher on *lack of energy* than men ($B = 0.30$, 95% CI [0.02–0.58], $p = .04$). Age was significantly associated with *lack of energy*, with the highest score among the youngest ($B = -0.02$, 95% CI [− 0.03 to – 0.01], $p = .03$). Palliative patients scored significantly higher on *lack of energy* ($B = 0.33$, 95% CI [0.01–0.66], $p = .05$) compared with curative patients. The patients scored 0.04 points higher on *lack of energy* for each 10-point decrease in KPS score ($B = .43$, 95% CI [0.03–0.05], $p < .01$).

Numbness/tingling

In the adjusted analyses, patients receiving oxaliplatin scored significantly higher on *numbness/tingling* compared with those receiving 5FU ($B = 0.55$, 95% CI [0.19–0.90], $p < .01$) or irinotecan ($B = 0.76$, 95% CI [0.43–1.10], $p < .01$) (Table 3; Fig. 2). Men scored higher on *numbness/tingling* compared with women ($B = 0.22$, 95% CI [− 0.01–0.44], $p = .05$). *Numbness/tingling* was scored significantly higher in patients with low educational level ($B = 0.26$, 95% CI [0.03–0.49], $p = .03$).

Table 1 Patient and clinical characteristics at enrolment in colorectal cancer patients ($n = 120$) scheduled to receive chemotherapy

	Number	Percent	Median (range)	Mean (SD)
Age, years			64.7 (33–80)	62.8 (10.2)
Sex				
Male	73	60.8		
Female	47	39.2		
Cohabitation				
Living alone	38	31.9		
Living with someone	81	68.1		
Educational level				
Primary/secondary	68	58.0		
College/university	50	42.0		
Occupation				
Part-/full-time work	9	8.3		
On sick leave	51	47.2		
Retired	48	44.4		
Treatment intent				
Curative	68	56.7		
Palliative	52	43.3		
Primary tumor site				
Colon	86	72.3		
Rectum	33	27.7		
Previous treatment				
Surgery	93	77.5		
Chemotherapy	34	28.3		
Radiotherapy	18	15.0		
Metastasis at enrolment	69	57.5		
Metastatic sites[a]				
Liver	54	45.0		
Lung	25	20.8		
Lymph nodes	25	20.8		
Peritoneum	10	8.3		
Other	10	8.3		
Type of chemotherapy				
5FU[b] monotherapy	20	16.7		
Irinotecan/ 5FU	28	23.3		
Oxaliplatin/5FU	72	60.0		
Karnofsky Performance Status[b]			90 (60–100)	

Some frequencies do not account up to full sample size of $n = 120$ due to missing numbers

5FU fluorouracil, *SD* standard deviation

[a] Metastasis could be present at more than one site

[b] Karnofsky Performance Status range 60 (requires occasional assistance, but able to care for most of his needs)–100 (normal no complaints)

Nausea

In the adjusted analyses, the severity of *nausea* did not differ significantly between the chemotherapy groups. There was a peak in severity scores on day 3 after each chemotherapy cycle (Fig. 2). Women scored significantly higher on *nausea* compared with men ($B = 0.27$, 95% CI [0.05–0.49], $p = .02$). The patients scored significantly 0.2 points higher on *nausea* for each 10-point decrease in KPS score ($B = 0.02$, 95% CI [0.01–0.03], $p = .01$).

Pain

In the adjusted analyses, pain did not differ significantly between the chemotherapy groups with time (Table 3).

Table 2 Occurrence rates for the five selected symptoms at each assessment point

Assessment time Study population (*n*)	T1 120	T2 116	T3 112	T4 110	T5 108	T6 103	T7 98	T8 88
Symptoms	%	%	%	%	%	%	%	%
Worrying	65.0	55.8	52.5	47.5	49.2	48.3	35.8	35.8
Lack of energy	59.2	71.7	65.8	60.8	65.0	63.3	64.2	53.3
Numbness/tingling	22.5	40.8	35.0	30.8	45.8	46.7	43.3	48.3
Nausea	28.3	61.7	52.5	35.8	51.7	54.2	43.3	29.2
Pain	50.8	49.2	45.0	37.5	35.8	35.0	34.2	33.3

T1 = at enrolment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at second cycle before chemotherapy; T5 = 3 days after 2nd chemotherapy; T6 = 7 days after 2nd chemotherapy; T7 = 3 months after enrolment; T8 = 6 months after enrolment

Palliative patients scored significantly higher on *pain* ($B = 0.45$, 95% CI [0.11–0.79], $p = .01$) compared with curative patients. The patients scored 0.3 points significantly higher on *pain* for each 10-point decrease in KPS score ($B = 0.03$, 95% CI [0.23–0.45], $p < .01$).

Clinical characteristics with no significant effect on symptom trajectories

Cohabitation, marital status, care of children, tumor site (colon or rectum), number of metastatic sites, and the presence of comorbidities (SCQ) had no significant effect ($p > .05$) on the symptom trajectory for any of the analyzed symptoms *worrying*, *lack of energy*, *numbness/tingling*, *nausea*, or *pain* (data not shown).

Discussion

This study reports the occurrence and severity of self-reported physical and psychological co-occurring symptoms at defined time points during chemotherapy for CRC. The patients reported the highest symptom severity scores for *lack of energy*, *numbness/tingling* (oxaliplatin group), and *nausea* in the days following chemotherapy. Palliative patients reported higher *pain* scores than the curative patients with time, whereas the severity of *worrying* was reduced with time in all patient groups. Lower performance status was associated with increased symptom burden.

Symptoms during chemotherapy

Lack of energy, *numbness/tingling*, and *nausea* showed increased symptom severity in the days and week after each

Table 3 The effect of the covariates on five selected symptoms ($n = 120$) measured at enrolment

Source/covariates	Dependent variables									
	Worrying		Lack of energy		Numbness/tingling		Nausea		Pain	
	F	*p* value	F	*p* value	F	*p* value	F	*p* value	F	*p* value
Time	2.32	*.03*	3.83	*<.01*	7.22	*< .01*	3.74	*< .01*	1.30	.26
Chemotherapy group [a]	0.06	.94	1.54	.22	12.60	*< .01*	0.71	.49	1.71	.19
Treatment intent [b]	1.43	.24	4.06	*< .05**	0.29	.59	3.01	.09	6.84	*.01*
Age	4.36	*.04*	4.60	*.03*	1.18	.28	0.98	.33	0.11	.74
Sex [c]	4.53	*.04*	4.55	*.04*	3.93	*.05*	5.99	*.02*	0.27	.61
Performance status (KPS)	14.97	*< .01*	67.79	*< .01*	1.71	.19	17.84	*< .01*	37.49	*< .01*
Education group [d]	0.01	.95	0.33	.57	5.14	*.03*	0.61	.44	0.37	.55
Time × chemotherapy group	0.65	.81	1.61	.09	3.90	*< .01*	1.18	.31	1.17	.31

italics = $p < .05$

F *F*-test

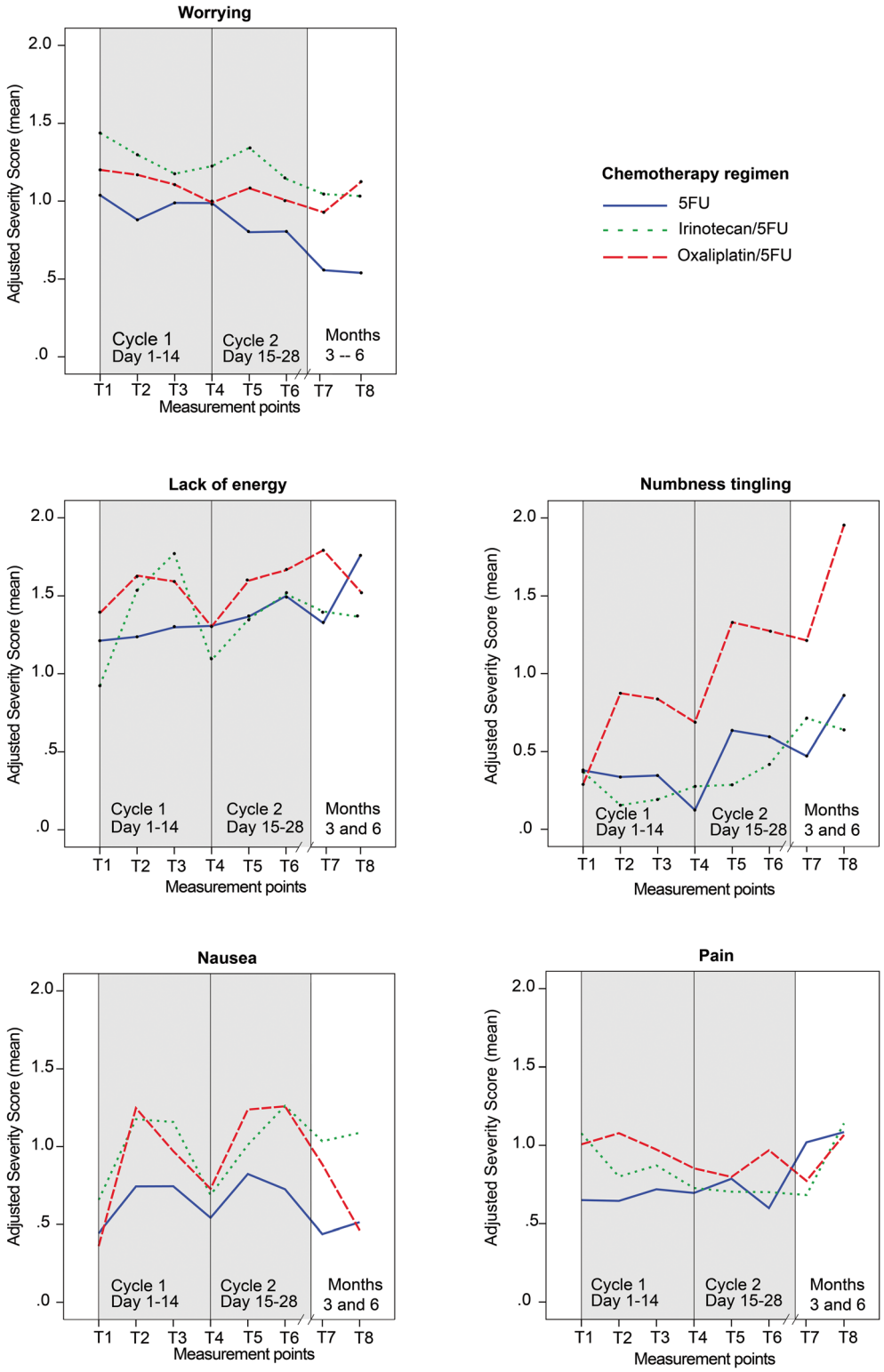
*p value = .04

[a] Chemotherapy group = fluorouracil (5FU) monotherapy, irinotecan/5FU, oxaliplatin/5FU (reference)

[b] Treatment intent = curative or palliative (reference)

[c] Men as reference; education group

[d] Primary/secondary (reference) and college/university



Abbreviations: T1 = at enrollment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at second cycle, chemotherapy given after assessment; T5 = 3 days after 2nd chemotherapy; T6 = 7 days after 2nd chemotherapy; T7 = 3 months after enrollment; T8 = 6 months after enrollment

Fig. 2 Graphs presented for each symptom: Worrying, lack of energy, numbness/tingling, nausea, and pain (adjusted for time, chemotherapy groups, treatment intent, age, sex, KPS, educational groups)

chemotherapy administration, followed by a decrease in severity toward the start of the next cycle (Fig. 2).

A progressive worsening of *lack of energy* with time is supported in previous studies with cancer patients [7] as well as for CRC patients [22]. *Lack of energy*, a proxy for fatigue on the MSAS [4], is one of the most frequent [2, 3, 14, 17, 20, 22] and severe reported symptoms by CRC patients [2, 3, 14]. *Fatigue* occurs during all treatment phases and is often more prominent as the disease worsens [20] with negative impact on QoL [30]. Reducing symptoms that interact with *fatigue* [14, 20, 22, 31] might help to alleviate *fatigue*. Despite limited evidence supporting the use of pharmacological agents to treat *fatigue*, physical activity has been shown to have a positive effect [20].

Numbness/tingling worsened significantly with time in patients receiving oxaliplatin in the present study. Cumulative neuropathy is a well-known side effect of oxaliplatin [14–16] may cause *pain* [23], chronic neuropathy, and impaired QoL [15]. Awareness of neuropathy is important in order to make the necessary dose reductions. The increased severity levels of *nausea* 3 and 7 days after chemotherapy administration were unexpected and raises the question whether adequate antiemetic regimens were prescribed, in particular for late-onset nausea. Recent guidelines for the prevention of chemotherapy-induced nausea [32] recommend a regimen with serotonin receptor antagonists and corticosteroids for 2–3 days, which was the institutional practice. In a European multicenter study, 45% of the cancer patients were inadequately treated for *nausea* [33]. In another study including metastatic CRC patients, > 10% reported moderate to severe *nausea* [14]. *Nausea* is one of the most distressing chemotherapy side effects [32], and *nausea* occurrence rates > 50% was found at multiple time point during the treatment in the present study (Table 2). Systematic symptom assessment at multiple time points may aid clinicians to offer improved supportive care at the right time to these patients.

Anxiety is suggested to be a proxy for *worrying* [34]. *Worrying* became less severe as the time from enrolment progressed. This is consistent with previous research in CRC patients with the highest anxiety scores found in the early treatment phase [2, 3, 25], with gradual decrease over time [25]. An adaption to the situation or social and psychological support might reduce the anxiety levels [25].

No significant differences were found for *pain* with time. One might speculate that regular chemotherapy administration facilitates adequate analgesic treatment. In addition, the efficacy of chemotherapy in metastatic disease can result in less *pain* from metastatic lesions because of tumor shrinkage [27]. However, the pain occurrence rates were high at enrolment (51%) [35]. The fluctuations in symptom severity highlight the importance of regular self-reported symptom assessment [7, 18, 36] with correct timing and duration of assessments to capture the true symptom burden in outpatients with CRC [6, 8]. Symptoms often occur simultaneously [3, 21, 34] and are likely to catalyze each other resulting in a vicious circle of symptoms [5]. Symptom assessment may even be beneficial in terms of increased survival [36].

Differences in symptoms between chemotherapy groups

Patients receiving 5FU monotherapy reported less severe symptom scores than patients receiving combination chemotherapy regimens. As expected, we found a significant increase in the severity of *numbness/tingling* in patients receiving oxaliplatin. Oxaliplatin are shown to cause peripheral neuropathy shortly after chemotherapy and increases with cumulative doses [10, 14].

Demographic and clinical characteristics associated with symptom severity

Severity scores for *lack of energy* and *pain* was higher in palliative compared with curative patients. More severe disease, higher disease burden, and the presence of metastases [23] among palliative patients might be one explanation. Being younger and female was associated with more severe *worrying*, *lack of energy*, and *nausea*. In addition, lower performance status was associated with higher severity scores in most of the analyzed symptoms and combined with multiple symptoms shown to be a predictor for hospitalization [8].

Limitations and strength

The study has some limitations. There was no “true” baseline because some patients had received previous chemotherapy. Comorbidity was patient-reported. Advanced stratification analyses were not performed due to the limited number of patients, although the number of patients was considered adequate for the exploratory study design. The patient sample was restricted to CRC outpatients, and these results might not be generalizable to other cancer types or treatments.

The strengths of the present study include the use of reliable, validated, and multidimensional PROMs completed at multiple defined time points during the treatment, which enabled a comprehensive symptom severity assessment.

Conclusion

In this study, we explored symptoms at several time points during chemotherapy cycles. We found highest symptom severity in the days following chemotherapy

administration, in particular lack of energy, nausea, and numbness/tingling for patients receiving oxaliplatin. Clinicians can use this knowledge of symptom fluctuations to offer improved symptom management at the right time. Covariates like age, sex, performance status, educational level, and type of chemotherapy were associated with symptom severity. Therefore, we recommend using PROMs in routine oncology practice to capture the changes in symptom burden [12, 13] and to ensure the day-to-day symptom control in outpatients.

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Compliance with ethical standards

The Regional Ethical Committee (2009/1451), the Hospital Privacy Ombudsman, and the institutional review board at Oslo University Hospital approved the study.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix A

Table 4 Occurrence rates of 32 symptoms from the memorial symptom assessment scale (MSAS) in the total study population ($n = 120$) over 6 month treatment trajectory

Assessment time study population (n)	T1 120	T2 116	T3 112	T4 110	T5 108	T6 103	T7 98	T8 88
MSAS symptom								
Worrying	65.0	55.8	52.5	47.5	49.2	48.3	35.8	35.8
Lack of energy	59.2	71.7	65.8	60.8	65.0	63.3	64.2	53.3
Pain	50.8	49.2	45.0	37.5	35.8	35.0	34.2	33.3
Numbness/tingling in hands/feet	22.5	40.8	35.0	30.8	45.8	46.7	43.3	48.3
Nausea	28.3	61.7	52.5	35.8	51.7	54.2	43.3	29.2
Lack of appetite	34.2	49.2	45.8	35.8	40.0	42.5	26.7	25.0
Feeling drowsy	54.2	65.8	58.3	51.7	55.8	56.7	59.2	44.2
Difficulty sleeping	50.0	48.3	47.5	41.7	44.2	40.0	38.3	35.0
Diarrhea	25.0	34.2	37.5	34.2	35.0	36.7	35.0	26.7
Problems with sexual interest	34.2	40.8	35.0	28.3	34.2	31.7	38.3	31.7
Feeling bloated	53.3	55.8	50.0	44.2	49.2	47.5	40.0	39.2
Feeling irritable	20.8	25.8	26.7	21.7	24.2	21.7	18.3	18.3
Sweats	30.8	35.8	26.7	25.0	27.5	20.0	25.8	21.7
Difficulty concentrating	37.5	44.2	45.8	37.5	40.0	41.7	37.5	35.8
Constipation	22.5	38.3	33.3	27.5	35.0	32.5	27.5	24.2
Problems with urination	12.5	17.5	13.3	11.7	12.5	13.3	9.2	10.8
Feeling sad	41.7	49.2	45.0	34.2	40.8	37.5	36.7	25.0
Dry mouth	33.3	41.7	40.8	40.8	38.3	43.3	43.3	35.0
Feeling nervous	42.5	38.3	33.3	30.8	30.0	31.7	20.8	22.5
Cough	23.3	31.7	30.0	30.0	21.7	26.7	22.5	16.7
Itching	19.2	20.8	15.0	19.2	17.5	20.8	11.7	15.0
Shortness of breath	21.7	27.5	27.5	21.7	25.8	26.7	28.3	21.7
Dizziness	20.8	32.5	28.3	23.3	28.3	27.5	27.5	24.2
Weight loss	25.8	30.0	30.0	25.8	26.7	30.0	14.2	18.3
Food tastes different	18.3	32.5	32.5	23.3	35.8	41.7	35.8	29.2
Changes in skin	14.2	16.7	15.8	17.5	21.7	24.2	22.5	22.5
"I do not look like myself"	10.0	15.8	14.2	15.0	21.7	17.5	17.5	14.2
Swelling of arms or legs	8.3	7.5	8.3	5.8	9.2	9.2	9.2	7.5
Mouth sores	4.2	12.5	17.5	16.7	19.2	26.7	15.8	15.8
Vomiting	7.5	12.5	10.0	8.3	19.2	17.5	14.2	6.0
Hair loss	10.0	6.7	8.3	11.7	13.3	16.7	26.7	21.7
Difficulty swallowing	5.0	15.0	12.5	10.0	15.8	14.2	13.3	6.7

T1 = At enrolment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at second cycle before chemotherapy; T5 = 3 days after 2nd chemotherapy; T6 = 7 days after 2nd chemotherapy; T7 = 3 months after enrolment; T8 = 6 months after enrolment

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