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# Motor disorders related to oxaliplatin-induced peripheral neuropathy: long-term severity and impact on quality of life

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## Abstract

**Purpose:** Sensory chemotherapy-induced peripheral neuropathy (CIPN) is well-recognized, but motor CIPN remains understudied. This secondary analysis focused on the long-term severity and impact of motor disorders, their relation to sensory CIPN, neuropathic pain, psychological distress, and health-related quality of life (HRQoL) after oxaliplatin-based chemotherapy in colorectal cancer (CRC) survivors.

**Methods:** Data from a multicenter, cross-sectional study were re-analyzed to explore motor CIPN among CRC survivors up to 5 years post-chemotherapy, with no longitudinal follow-up. Questionnaires assessed sensory and motor CIPN (QLQ-CIPN20), neuropathic pain (DN4), anxiety and depression (HADS), and HRQoL (QLQ-C30).

**Results:** Among 405 CRC survivors, 31.1% had sensory CIPN as previously described. When categorizing the 405 CRC survivors based on the years since their last oxaliplatin-based chemotherapy, the motor scores derived from the QLQ-CIPN20 showed no significant difference between years ( $p = 0.08$ ). Motor CIPN scores correlated with female gender, higher oxaliplatin dose intensity, sensory CIPN, and neuropathic pain. Motor CIPN also linked to decreased HRQoL and increased psychological distress.

**Conclusion:** The study underscores the detrimental impact of motor disorders on CRC survivors post-oxaliplatin-based chemotherapy. Oncologists should prioritize assessing and managing motor manifestations alongside sensory symptoms to enhance post-cancer quality of life.

**Trial registration:** NCT02970526 (2016-11-18)

**Keywords:** oxaliplatin; colorectal cancer; chemotherapy-induced peripheral neuropathy; motor disorders; cancer survivors

**Author Contributions:** Conceptualization, D.P., D.B., V.M.; methodology, S.T., V.P., D.P., D.B. and V.M.; software, D.B.; validation, B.P. and D.B.; formal analysis, M.S., B.P., and D.B.; investigation, D.B., N.K., M.S., C.G., C.P., A.V.-B., S.M., S.K., M.H., O.B., F.S., V.B., V.L.-L., F.T., T.M., D.T., K.E.B., B.M., M.R., D.P.-V., F.H.-P., A.B., F.G., C.L., D.P., and V.M.; resources, D.B.; data curation, D.B. and V.M.; writing—original draft preparation, D.B., M.S., B.P., N.K., D.P., and V.M.; writing—review and editing, D.B., M.S., B.P., N.K., D.P., and V.M.; visualization, D.B., B.P., and V.M.; supervision, D.B., D.P., and V.M.; project administration, D.B. and V.M.; funding acquisition, D.B. All authors have read and agreed to the published version of the manuscript.

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00008526, No. 2016/CE16, 26/02/2016) and was carried out anonymously. The study was approved by the Advisory Committee on the Treatment of Research Information (No. 15.645, 13/05/2015).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Data will be made available upon request to the corresponding author.

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# 1. Introduction

Oxaliplatin stands as a cornerstone in advanced colorectal cancer (CRC) therapy, frequently combined with agents like 5-fluorouracil, folinic acid, or irinotecan. However, its clinical utility is hindered by chemotherapy-induced peripheral neuropathy (CIPN), a debilitating complication shared with other neurotoxic agents such as cisplatin, taxanes, and vinca alkaloids [1, 2]. CIPN presents as a dose-limiting adverse effect characterized by symmetric distal paresthesia and dysesthesia, significantly diminishing patients' health-related quality of life (HRQoL) both during and after treatment. Despite its gravity, preventive strategies remain elusive, with duloxetine being the sole agent demonstrating modest efficacy in managing associated neuropathic pain, as endorsed by major oncology societies [3, 4]. Consequently, clinicians are often confronted with the challenge of balancing treatment efficacy against the risk of neurotoxicity-related dose adjustments, potentially compromising disease control and progression-free survival [5].

Oxaliplatin, in particular, is notorious for its pronounced incidence of acute and transient neuropathy, affecting over 90% of patients during treatment, with a considerable subset progressing to chronic CIPN [6]. Our multicenter cross-sectional study in France unveiled that a notable proportion of CRC survivors encountered sensory CIPN within five years post-adjuvant FOLFOX chemotherapy, with prevalence rates demonstrating relative stability over time [7]. Importantly, sensory CIPN was associated with decreased HRQoL and psychological distress, emphasizing its enduring impact on survivorship [7].

While sensory symptoms dominate the clinical landscape of CIPN, recognition of motor manifestations is gaining prominence [8]. Motor CIPN encompasses a spectrum of impairments, including muscle weakness, atrophy, and functional limitations, often masked by overlapping symptoms of fatigue and generalized weakness [8, 9]. However, studies delving into the motor aspects of CIPN are scant, warranting further exploration of its prevalence, evolution, and impact on functional outcomes.

Building upon our preceding investigation focusing on sensory CIPN in CRC survivors [7], this secondary analysis endeavors to comprehensively evaluate the long-term severity and impact of motor disorders, alongside neuropathic pain, psychological distress, and HRQoL following adjuvant FOLFOX chemotherapy. By elucidating the multifaceted nature of CIPN, we aspire to guide tailored interventions aimed at alleviating its burden on cancer survivors' quality of life and long-term outcomes.

## 2. Materials and Methods

### 2.1. Design

This multicenter, cross-sectional study aimed to assess the extent of motor CIPN among CRC survivors for a period of 5 years following the conclusion of oxaliplatin-based chemotherapy. This assessment was based on self-administered questionnaires. The secondary objectives of the study included investigating the correlation between the severity of motor CIPN and sensory CIPN, as well as analyzing patient characteristics, details of oxaliplatin-based chemotherapy, levels of anxiety, depression, and HRQoL. The assessments were conducted once, and no longitudinal tracking of CRC survivors was undertaken.

The study results are presented according to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [10], and the study protocol was registered on ClinicalTrials.gov (NCT02970526). Ethical approval was granted by a local ethics committee (Comité de

Protection des Personnes sud-est 6, IRB: 00008526, No. 2016/CE16, 26/02/2016), and the research was carried out with full anonymity. Additionally, the Advisory Committee on the Treatment of Research Information approved the study (No. 15.645, 13/05/2015). All participants provided their informed consent via telephone.

## **2.2. Setting**

The University Hospital of Clermont-Ferrand (CHU Clermont-Ferrand, France) served as the coordinating institution for this study. Patient recruitment took place across 16 French centers, which included University Hospitals such as CHU Clermont-Ferrand, CHU Limoges, CHU Reims, CHRU Lille, and Institut du Cancer Montpellier, as well as General Hospitals like CH Saint-Flour, CH Moulins, CH Boulogne-sur-Mer, CH Béziers, CH Puy en Velay, Infirmierie Protestante de Lyon, CH Saint-Joseph Saint Luc Lyon, CH Alpes Leman, CHI Les Hôpitaux du Léman, CH Vichy, and GHM Grenoble. The patient recruitment period spanned from June 21, 2016, to August 29, 2019

## **2.3. Participants**

The study's inclusion criteria were as follows: (1) receipt of adjuvant oxaliplatin-based chemotherapy (FOLFOX-4) for CRC, (2) completion of the survey within  $\leq 5$  years from the cessation of chemotherapy, and (3) absence of cancer relapse during the subsequent 5-year period (cancer survivor). Exclusion criteria encompassed individuals under 18 years of age and patients diagnosed with neurological disorders such as stroke, Parkinson's disease, and Alzheimer's disease.

CRC survivors were identified through the chemotherapy prescription software database of each participating center. Subsequently, in accordance with the established inclusion and exclusion criteria, each center contacted their respective patients to inquire about their interest in participating in the study. Upon obtaining patient informed consent, a paper questionnaire along with a pre-stamped envelope for response submission was dispatched to the patient. Completed questionnaires were anonymous and returned by the CRC survivors to the coordinating center, where the collected data were documented and subjected to analysis.

## **2.4. Variables**

The primary endpoint was the motor score of the EORTC QLQ-CIPN20, which assesses the severity of motor CIPN on a scale from 0 (least severe) to 100 (most severe) over the past week [11]. For scoring details, please refer to: <https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf>.

Sensory CIPN was evaluated as a quantitative variable using sensory scores from the EORTC QLQ-CIPN20 [11], and as a qualitative variable with sensory CIPN defined by a QLQ-CIPN20 score of  $\geq 30/100$ , based on a study by Alberti et al. (2014) [12]. Ongoing neuropathic pain was identified by a visual analogue scale (VAS) score  $\geq 4/10$  and a DN4 interview questionnaire score  $\geq 3/7$  [13]. Anxiety and depression levels were measured using the Hospital Anxiety and Depression Scale (HADS) questionnaire, with scores categorized as follows: normal ( $\leq 7/21$ ), borderline or suggestive of anxiety/depression (8–10/21), and indicative of anxiety/depression ( $\geq 11/21$ ) [14]. The assessment of patient HRQoL at the time of response utilized the EORTC QLQ-C30, encompassing global health status (ranging from 0 to 100, where higher scores indicate better status), functioning dimensions (ranging from 0 to 100, where higher scores indicate better functioning), and symptoms (ranging from 0 to 100, where higher scores indicate greater symptom severity) [15].

Patient-specific oncological treatment characteristics were recorded, including cumulative dose (mg/m<sup>2</sup>), dose intensity (mg/m<sup>2</sup>/week), number of oxaliplatin cycles, and dates of the first and last oxaliplatin cycles. Socio-demographic information captured at the time of response included sex, age, daily cigarette usage, occasional alcohol consumption, and hazardous alcohol use (males:  $\geq 21$  alcohol units/week and females:  $\geq 14$  alcohol units/week). Additionally, height, weight, body mass index (BMI), and body surface area during oxaliplatin treatment were extracted from chemotherapy prescription software.

## 2.5. Data sources and measurements

Clinical data pertaining to CIPN, anxiety, depression, and HRQoL were derived from the completed questionnaire. Oncological information and patient characteristics were extracted from the chemotherapy prescription software employed by each center. The entire dataset was meticulously recorded and organized using REDCap electronic data capture tool, which was hosted at CHU Clermont-Ferrand.

## 2.6. Statistical considerations

Categorical data were presented using number of CRC survivors, percentage, and appropriate 95% CIs. Continuous data were expressed as means and standard deviations. The assumption of normality was analyzed using the Shapiro-Wilk test.

Continuous data, such as sensory QLQ-CIPN20 scores, were compared between independent groups (such as year 1 until year 5 after the end of chemotherapy or normal vs. suggestive vs. indicative scores for anxiety and depression disorders) using analysis of variance or Kruskal-Wallis test. The assumption of homoscedasticity was assessed using the Bartlett test. To analyze the relationships between continuous parameters (i.e., between QLQ-C30 scores and QLQ-CIPN20 motor scores), Pearson and Spearman correlation coefficients were estimated according to the statistical distribution of variables, and by applying Sidak's type I error correction.

To determine factors associated with the QLQ-CIPN20 sensory score (dependent variable), multivariable analyses were performed, including patient characteristics (sex, age, tobacco, alcohol, and weight variation) and characteristics of chemotherapy (chemotherapy date, cumulative dose and dose intensity of oxaliplatin, and center). More precisely, a random-effects multiple linear model was used to take into account between and within center variability (center as random effect). The normality of residuals from these models was analyzed. Particular attention was paid to the study of multicollinearity between covariates (1) studying the relationships between the covariables and (2) evaluating the impact to add or delete variables on multivariable model. Results are expressed as regression coefficients and 95% CIs, and forest-plot was used to present the results.

In addition, the categorical data were compared between groups using the chi-squared test or Fisher's exact test, for example in order to evaluate the severity of the motor items of QLQ-CIPN20 based on sensory CIPN (yes/no).

Statistical analyses were performed using Stata software (version 15, StataCorp, College Station, United States). All tests were two-sided, with a type I error set at 5%. As less than 5% of data were missing, no handling of missing data was applied. As reported in the literature [16], we reported all individual p-values without applying systematically a mathematical correction. Specific attention was given to the magnitude of differences (i.e., ESs) and clinical relevance. When appropriate, the results were expressed using Hedge's effect-sizes (ESs) and 95%

CI) and were interpreted according to the recommendations of Cohen, who defined the ES bounds as small (ES = 0.2), medium (ES = 0.5), and large (ES = 0.8).

### 3. Results

#### 3.1. Population

As previously described [7], the study initially included 406 CRC survivors for assessing the prevalence of sensory CIPN. However, in the current analysis, one patient was excluded due to insufficient data availability regarding the primary endpoint (motor score of the QLQ-CIPN20). Consequently, a total of 405 CRC survivors were subjected to analysis (Flow chart, see supplements Figure S1), and their individual characteristics are described in Table 1. Within this patient cohort, 31.1% (95% CI [26.6% to 35.9%]) exhibited sensory CIPN (as indicated by sensory scores of the QLQ-CIPN20  $\geq$  30/100), while 15.3% (95% CI [11.9% to 19.2%]) experienced neuropathic pain (based on VAS pain scores  $\geq$  4/10 and DN4 interview questionnaire score  $\geq$  3/7) (Table 1).

#### 3.2. Motor CIPN

The motor scale of the QLQ-CIPN20, encompassing eight items, demonstrated a robust internal consistency (Cronbach's  $\alpha = 0.83$ ), and the sensory scale, consisting of nine items, exhibited a similarly strong internal consistency (Cronbach's  $\alpha = 0.83$ ), as previously described [7].

When categorizing the 405 CRC survivors based on the years since their last oxaliplatin-based chemotherapy (see Table 1), the motor scores derived from the QLQ-CIPN20 showed no significant difference between years ( $p = 0.08$ ) (Figure 1). Among the participating centers, mean motor QLQ-CIPN20 scores did not display significant variation ( $p = 0.61$ ), while mean cumulative oxaliplatin doses exhibited significant differences ( $p < 0.001$ ). Notably, the motor scores were not correlated with cumulative oxaliplatin dose, oxaliplatin dose intensity, or the number of oxaliplatin cycles. Moreover, motor scores were notably higher in females compared to males ( $21.6 \pm 20.9$  vs.  $15.7 \pm 18.2$ ,  $p < 0.001$ , effect size: 0.30, 95% CI [0.11 to 0.50]). Motor scores demonstrated no significant correlation with patient age, height, weight (first and last cycles of oxaliplatin), body surface area (first and last cycles of oxaliplatin), or BMI (first and last cycles of oxaliplatin). However, a very weak correlation was observed between motor scores and the duration since the last oxaliplatin administration, percentage variance in weight, body surface area, and BMI between the first and last cycles of oxaliplatin (coefficients: -0.10, -0.14, -0.12, and -0.14, respectively,  $p < 0.05$  in all cases). Motor scores were higher among tobacco smokers compared to non-smokers ( $24.0 \pm 22.6$  vs.  $17.5 \pm 19.1$ ,  $p = 0.045$ , effect size: 0.33, 95% CI [0.04 to 0.63]). Conversely, motor scores were lower among alcohol consumers compared to non-consumers ( $16.9 \pm 19.5$  vs.  $21.2 \pm 19.9$ ,  $p = 0.007$ , effect size: -0.22, 95% CI [-0.42 to -0.01]).

Motor scores were elevated in CRC survivors with sensory CIPN compared to those without ( $36.4 \pm 21.6$  vs.  $10.2 \pm 11.8$ ,  $p < 0.001$ , effect size: 1.68, 95% CI [1.44 to 1.92]). Similarly, all motor items within the QLQ-CIPN20 were more severe in CRC survivors with sensory CIPN than those without (Figure 2).

Among the motor items of the QLQ-CIPN20 that explored symptoms in both hands and feet, motor disorders were more pronounced in the feet than in the hands (Figure 3). Moreover, motor scores were higher in CRC survivors experiencing neuropathic pain compared to those without ( $37.5 \pm 21.9$  vs.  $14.7 \pm 16.8$ ,  $p < 0.001$ , effect size: 1.29, 95% CI [1.00 to 1.57]).



In the multivariable analysis of QLQ-CIPN20 motor scores, it was found that factors such as female gender, oxaliplatin dose intensity, presence of sensory CIPN, and neuropathic pain were significantly associated with elevated motor scores of the QLQ-CIPN20 (Figure 4).

### **3.3. Impact of the motor CIPN on anxiety, depression, and HRQoL**

The motor scores of the QLQ-CIPN20 exhibited higher values among CRC survivors with anxiety or depression disorders (for anxiety: normal vs. suggestive vs. indicative scores:  $14.0 \pm 16.6$  vs.  $22.7 \pm 18.0$  vs.  $32.4 \pm 25.9$ ,  $p < 0.001$ ; for depression: normal vs. suggestive vs. indicative scores:  $14.9 \pm 16.7$  vs.  $23.4 \pm 21.1$  vs.  $38.7 \pm 25.7$ ,  $p < 0.001$ ).

Furthermore, the motor scores of the QLQ-CIPN20 displayed a weak to moderate negative correlation with HRQoL scores (QLQ-C30), indicating a deterioration in HRQoL. Notably, the most notable correlations were observed with role functioning (Spearman coefficient: -0.41) and physical functioning (Spearman coefficient: -0.47) (Table 2). Similarly, the motor scores were weakly to moderately correlated with all symptom dimensions of the QLQ-C30, reflecting increased symptom severity. The most prominent correlations were found with fatigue (Spearman coefficient: 0.43) and pain (Spearman coefficient: 0.47) (Table 2).

## **4. Discussion**

In this ancillary analysis of our previous cross-sectional study [7], the focus is on motor disorders associated with oxaliplatin-induced peripheral neuropathy, their long-term evolution, and their relationship with psychological distress and HRQoL.

In CRC survivors treated with oxaliplatin, motor disorders were clearly associated with the presence and severity of sensory CIPN and neuropathic pain. The severity of motor disorders remained unchanged in the years following chemotherapy completion. Motor CIPN severity was associated with female sex and oxaliplatin dose intensity. As previously described for sensory disorders [7], motor disorders were more pronounced in the feet than in the hands. Additionally, motor disorders were associated with a decrease in HRQoL and psychological distress (anxiety and depression). Importantly, this deterioration in HRQoL was previously reported in patients with sensory CIPN [7] and was recently highlighted in a cohort of CRC survivors [17].

Motor disorders resulting from oxaliplatin treatment may not strictly align with the definition of pure motor neuropathy, but rather encompass mixed sensory and/or motor symptoms. Wang et al. [18] suggested, through the use of the QLQ-CIPN20 questionnaire, that patients can be categorized into three distinct symptom clusters: sensory neuropathy, mixed motor-sensory neuropathy (with predominant motor symptoms), and mixed sensorimotor neuropathy (with predominant sensory symptoms) [18]. For instance, this assertion finds support in the prevalence of individuals experiencing sensory CIPN who report difficulties in manipulating small objects (item 42 of the QLQ-CIPN20 used for assessing motor disorders), a characteristic feature of motor-sensory neuropathy as defined by Wang et al. [18]. However, it's essential to note that this classification was established from a diverse population exposed to various neurotoxic anticancer drugs, including platinum derivatives, taxanes, and vinca alkaloids [18]. Moreover, it is crucial to acknowledge the variability in CIPN symptoms across different neurotoxic anticancer drugs. For instance, oxaliplatin-induced CIPN is characterized by cold and heat nociceptive hypersensitivity, with no alterations in thermal detection thresholds [6], whereas bortezomib-induced CIPN is linked to warm and heat hyposensitivity [19].

Several clinical studies reported chronic motor disorders in patients exposed to oxaliplatin-based chemotherapies, including motor neuropathy grade 1+ observed in 22.1% to 68.9% of oxaliplatin-treated-patients [20, 21], and grade 3+ in 1.2% [21], as assessed using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE). Additionally, various muscular signs have been documented in up to 62% [22], including muscle weakness (51.5%) [23], foot cramps (29.4%) [8], and stiffness (12.1%) [23]. More generally, muscular disorders associated to CIPN can lead to functional motor impairments, such as gait and balance abnormalities [24], impaired fine motor skilled [25], falls [9], and limitations in activities of daily living (such as shopping, walking, performing light housework, and bathing) [9]. Electrophysiological investigations have also revealed motor disorders, such as decrease of superexcitability of motor axons [26], reduced amplitude of the compound motor action potential (CMAP) [27], increased refractoriness of motor axons [26, 28], decreased motor conduction velocities [29], and decreased motor nerve amplitude without affecting conduction velocity [30]. Notably, acute electromyogram abnormalities have shown strong correlation with the acute and transient neurotoxicity of oxaliplatin [31]. However, some studies have reported no alterations in electrophysiological nerve studies [32, 33], no incidence of weakness or muscle atrophy [27], and no modification of CMAP amplitudes and F-wave parameters [29].

Importantly, as reported by Molassiotis and colleagues, there is a need to focus more concretely on the assessment of motor symptoms in the future, as they are also linked with significant impact in daily activities, and to define CIPN more broadly as a motor and sensory impairment [8]. The authors underline that motor CIPN is underassessed and often obscured by sensory symptoms (e.g., numbness and tingling), which are more frequently evaluated during clinical follow-ups. Furthermore, general symptoms such as fatigue or weakness may be misinterpreted as tiredness rather than motor disorders [8]. However, the authors report difficulties in assessing motor CIPN using scales such as the NCI-CTCAE or WHO scales, or through electrophysiology of motor nerves (e.g., the CTCAE motor item overestimates its occurrence, possibly due to confounding factors) [8].

Interestingly, increasing evidence supports the implementation of exercise promotion in cancer care. Systematic reviews and meta-analyses have provided evidence supporting that exercise is a suitable and effective intervention to improve CIPN severity. However, most of the studies explored sensory or sensorimotor outcomes rather than motor ones [34, 35]. In a study exploring basal physical activities in CRC survivors who had received chemotherapy, lower proportions of motor symptoms (e.g., cramps in hands, trouble opening jar/bottle due to loss of strength in hands, and trouble walking stairs or standing up from a chair due to weakness in legs, from the QLQ-CIPN20) were identified in survivors reporting at least 150 minutes of physical activity per week compared to individuals reporting less than 150 minutes of physical activity per week [36]. Moreover, in this study, CRC survivors with CIPN who reported at least 150 minutes of physical activity per week had higher scores of global health status and functioning scales (QLQ-C30) and lower scores of fatigue than those who reported less than 150 minutes of physical activity per week [36].

#### *Limitations of the study*

The cross-sectional design of the study did not allow for exploration of the evolution of motor CIPN throughout the years following chemotherapy completion, as CRC survivors responded to the questionnaire only once. Although the QLQ-CIPN20 is one of the most commonly used questionnaires to assess CIPN severity [37], its

structural validity, along with that of its subscales (i.e., sensory and motor), may be unstable [38, 39], and should therefore be interpreted cautiously. It was not possible to differentiate between CRC survivors with motor CIPN and those without solely based on the motor scores of the QLQ-CIPN20, unlike what can be done for sensory CIPN, due to the lack of comparison between motor scores of the QLQ-CIPN20 and motor CIPN grades in the literature. Another limitation is the absence of a control group (individuals naive to oxaliplatin), as motor disorders tend to increase with age in individuals (sarcopenia and loss of motor neurons) [40]. This suggests that background noise related to motor disorders is likely present in this sample of CRC survivors. Interestingly, the motor scores of the QLQ-CIPN20 in the present study ( $18.4 \pm 19.7$ ) are very close to those reported by another study ( $17.2 \pm 16.8$ ), and the latter were higher than in patients only treated with fluoropyrimidine ( $10.7 \pm 12.7$ ,  $p = 0.009$ ) [41]. Finally, due to the limited number of participants, interpretation of the secondary objectives must be approached cautiously.

## 5. Conclusions

This real-life study demonstrates the detrimental impact of motor disorders associated to the sensory CIPN in CRC survivors treated by oxaliplatin-based chemotherapy. These motor disorders are strongly correlated with sensory symptoms and neuropathic pain. In addition to addressing sensory symptoms, oncologists and physicians should pay close attention to motor disorders in post cancer management.

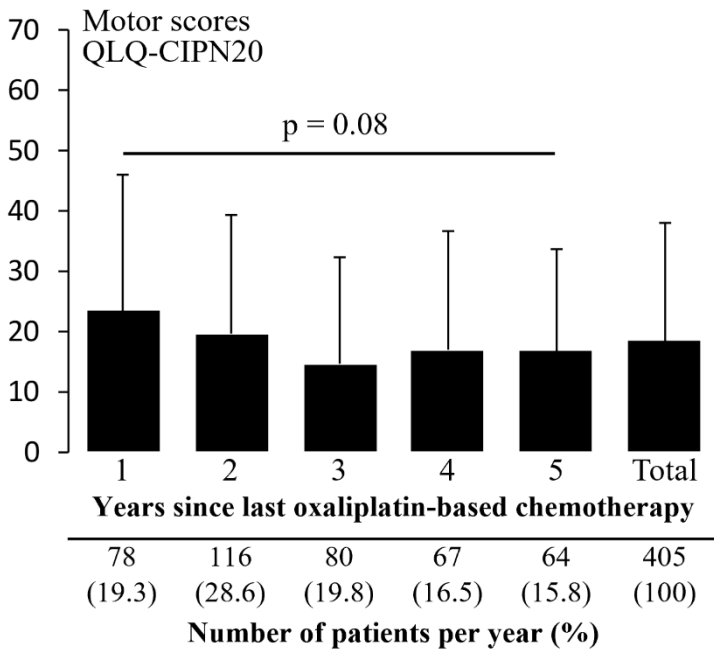
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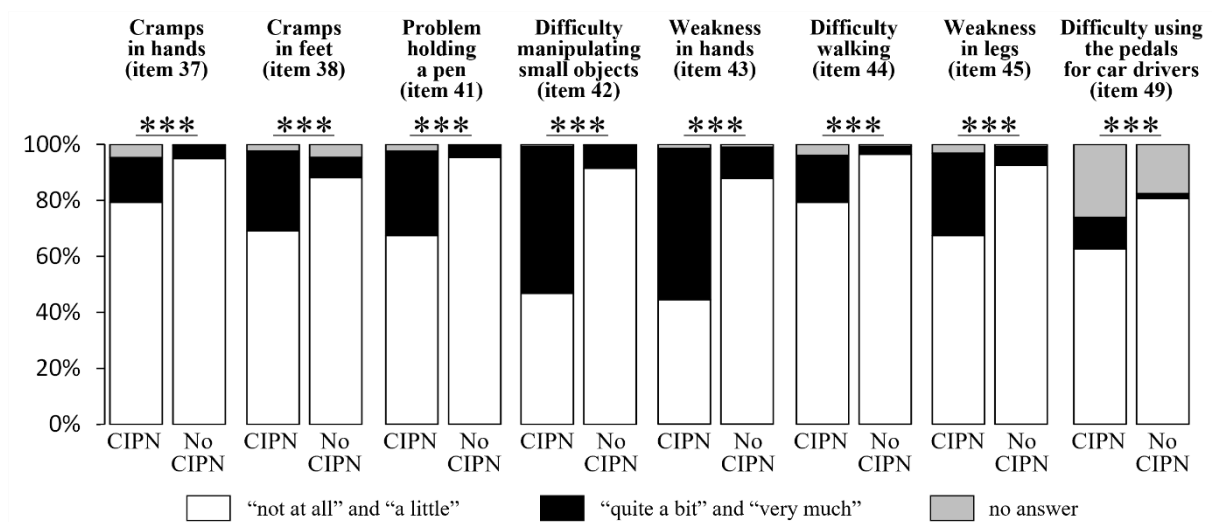
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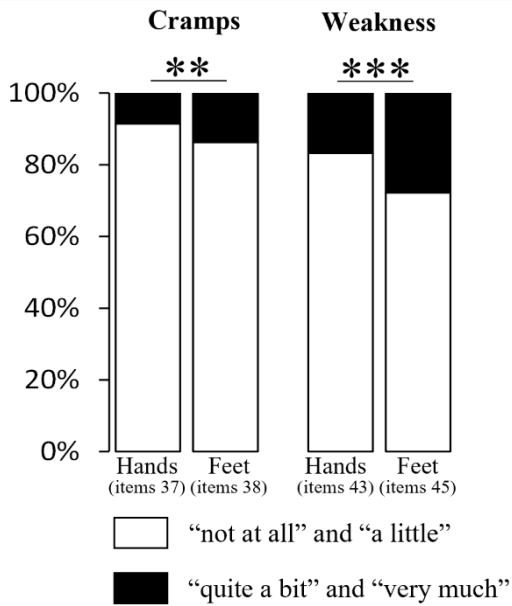
**Figure 1** Motor scores of the QLQ-CIPN20 from year 1 until year 5 after chemotherapy end.

Motor scores are presented as mean  $\pm$  standard deviation. The provided P-value indicates the global comparison over time, spanning from year 1 to year 5.



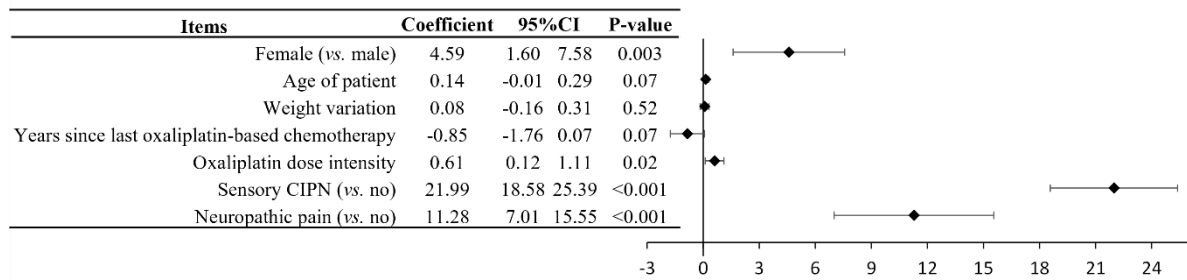
**Figure 2** Severity of the motor items of QLQ-CIPN20 based on sensory CIPN.

Post hoc analyses indicated significant differences ( $p < 0.05$ ) between "not at all" and "a little" vs. "quite a bit" and "very much" for all items. \*\*\*  $p < 0.001$ .



**Figure 3** Severity of motor disorders in hands versus feet for all CRC survivors.

For all the items, post hoc analyses indicated significant differences ( $p < 0.05$ ) between “not at all” and “a little” vs. “quite a bit” and “very much”. \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$ .



**Figure 4** Forest plot of regression coefficients comparing QLQ-CIPN20 motor scores with patient characteristics and oxaliplatin treatments.

Multivariable analysis was conducted, incorporating patient characteristics (sex, age, and weight variation), chemotherapy attributes (years since last chemotherapy cycle, oxaliplatin dose intensity, and center), sensory CIPN (individuals with a sensory score of QLQ-CIPN20  $\geq 30/100$ ), and neuropathic pain



**Table 1** CRC survivors' characteristics.

Categorical variables are expressed as percentages (number). Continuous variables are expressed as mean  $\pm$  standard deviation.

| Items  | CRC survivors (n = 405)                |
|--|--|
| <b>Sex</b>   |  |
| Male   | 54.3 (220)                             |
| Female   | 45.7 (185)                             |
| <b>Age (year)</b>  | 66.3 $\pm$ 9.7<br>Min: 31.1; Max: 89.3 |
| <b>Height (cm)</b>   | 168.1 $\pm$ 9.5                        |
| <b>Weight (kg)</b>   |  |
| 1st chemotherapy cycle                                       | 71.8 $\pm$ 16.3                        |
| Last chemotherapy cycle                                      | 72.1 $\pm$ 16.4                        |
| Mean percentage of variance                                  | 0.7 $\pm$ 6.2                          |
| <b>Body mass index (kg/m<sup>2</sup>)</b>                    |  |
| 1st chemotherapy cycle                                       | 25.3 $\pm$ 5.0                         |
| Last chemotherapy cycle                                      | 25.4 $\pm$ 4.9                         |
| Mean percentage of variance                                  | 0.7 $\pm$ 6.2                          |
| <b>Body surface area (m<sup>2</sup>)</b>                     |  |
| 1st cycle  | 1.8 $\pm$ 0.2                          |
| Last cycle   | 1.8 $\pm$ 0.2                          |
| Mean percentage variance                                     | 0.4 $\pm$ 2.7                          |
| <b>Tobacco use</b>   | 12.4 (50)                              |
| <b>Alcohol use</b>   | 66.4 (269)                             |
| Hazardous alcohol use (males: $\geq$ 21 units/week)          | 14.4 (23)                              |
| Hazardous alcohol use (females: $\geq$ 14 units/week)        | 12.3 (13)                              |
| <b>Time since last oxaliplatin-based chemotherapy (year)</b> | 2.4 $\pm$ 1.6                          |
| Number of individuals: year 1                                | 19.3 (78)                              |
| Number of individuals: year 2                                | 28.6 (116)                             |
| Number of individuals: year 3                                | 19.8 (80)                              |
| Number of individuals: year 4                                | 16.5 (67)                              |
| Number of individuals: year 5                                | 15.8 (64)                              |
| <b>Oxaliplatin chemotherapy</b>                              |  |
| Cumulative dose (mg/m <sup>2</sup> )                         | 1220.3 $\pm$ 457.1                     |
| Number of cycles   | 9.7 $\pm$ 2.7                          |
| Dose intensity (mg/m <sup>2</sup> /weeks)                    | 62.3 $\pm$ 20.9                        |
| <b>CIPN</b>  |  |
| QLQ-CIPN20, motor score                                      | 18.4 $\pm$ 19.7                        |
| QLQ-CIPN20, sensory score                                    | 23.1 $\pm$ 20.6                        |
| QLQ-CIPN20, sensory score $\geq$ 30/100                      | 31.1 (126)                             |
| <b>Neuropathic pain</b>                                      | 15.3 (62)                              |

**Table 2** Correlation between QLQ-C30 scores and QLQ-CIPN20 motor scores.

The table displays the correlations between QLQ-C30 scores and QLQ-CIPN20 motor scores, indicating the Spearman correlation coefficient and significance levels. \*  $p < 0.05$ .

| Dimensions             | Number | QLQ-C30 scores | Correlations |
|------------------------|--------|----------------|--------------|
| Global health status   | 397    | 69.1 ± 20.5    | -0.33*       |
| Physical functioning   | 405    | 81.7 ± 19.8    | -0.47*       |
| Role functioning       | 402    | 79.0 ± 28.2    | -0.41*       |
| Emotional functioning  | 401    | 74.5 ± 25.1    | -0.34*       |
| Cognitive functioning  | 400    | 77.5 ± 23.6    | -0.27*       |
| Social functioning     | 401    | 74.2 ± 30.5    | -0.33*       |
| Fatigue                | 404    | 33.8 ± 27.2    | 0.43*        |
| Nausea and vomiting    | 405    | 6.5 ± 15.7     | 0.21*        |
| Pain                   | 404    | 20.5 ± 26.0    | 0.47*        |
| Dyspnea                | 400    | 23.3 ± 28.1    | 0.24*        |
| Insomnia               | 401    | 34.9 ± 35.4    | 0.35*        |
| Appetite loss          | 403    | 11.2 ± 23.6    | 0.31*        |
| Constipation           | 400    | 19.3 ± 28.3    | 0.23*        |
| Diarrhea               | 400    | 24.3 ± 31.9    | 0.17*        |
| Financial difficulties | 398    | 10.0 ± 22.3    | 0.22*        |

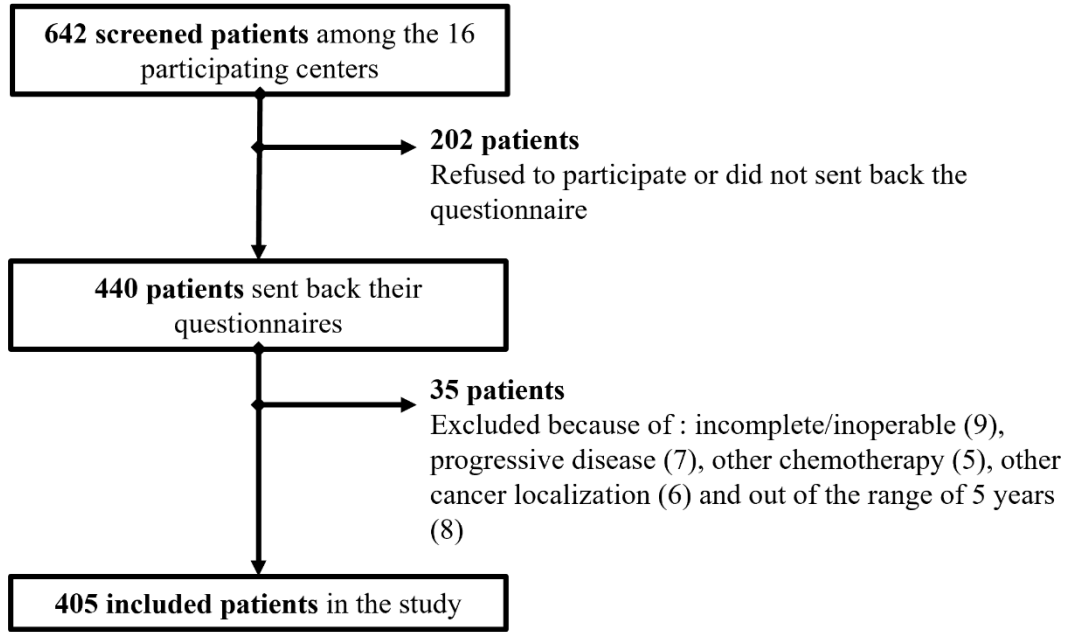


Figure S1: Flow diagram of patient's inclusion