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## Patient-Reported (EORTC QLQ-CIPN20) Versus Physician-Reported (CTCAE) Quantification of Oxaliplatin- and Paclitaxel/Carboplatin-Induced Peripheral Neuropathy in NCCTG/Alliance Clinical Trials

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### Abstract

**Purpose**—Clinical practice guidelines on chemotherapy-induced peripheral neuropathy (CIPN) use the NCI Common Terminology Criteria for Adverse Events (CTCAE), while recent clinical trials employ a potentially superior measure, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN twenty-item scale (QLQ-CIPN20), a patient reported outcome (PRO). Practitioners and researchers lack guidance, how QLQ-CIPN20 results relate to the traditional CTCAE during the serial assessment of patients undergoing chemotherapy.

**Methods**—Two large CIPN clinical trial datasets (538 patients) pairing QLQ-CIPN20 and CTCAE outcomes were analyzed using a multivariable linear mixed model with QLQ-CIPN20 score as the outcome variable, CTCAE grade as the main effect, and patient as random effect (accounting for internal correlation of serial measures).

**Results**—The association between QLQ-CIPN20 scores and CTCAE grades was strong ( $p < 0.0001$ ), whereby patients with higher CTCAE grade had worse QLQ-CIPN20 scores. Some variation of QLQ-CIPN20 scores was observed based on drug, treatment, and cycle. While there was a marked difference in the mean QLQ-CIPN20 scores between CTCAE grades, the ranges of

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QLQ-CIPN20 scores within each CTCAE grade were large leading to large overlap in CIPN20 scores across CTCAE grades.

**Conclusions**—A strong positive association of QLQ-CIPN20 scores and CTCAE grade provides evidence of convergent validity as well as practical guidance, how to quantitatively interpret QLQ-CIPN20 scores at the study level in terms of the traditional CTCAE. The present results also highlight an important clinical caveat, specifically, that conversion of QLQ-CIPN20 to a CTCAE may not be reliable at the level of an individual patient.

### Keywords

peripheral neuropathy; CTCAE; EORTC QLQ-CIPN20; patient-reported outcome; physician-reported outcome

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## Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a prominent clinical problem. In clinical trials evaluating the prevention and/or treatment of CIPN, the degree of neuropathy has commonly been measured using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) [1 – 3]. CTCAE was also the primary assessment of CIPN in most studies included in a recent systematic review on CIPN by Mols et al. [4], as well as the recent American Society of Clinical Oncology clinical practice guidelines for the prevention and management of CIPN [5]. However, in recent years, it has been well recognized that the CTCAE method is not an adequate measure to quantify the degree of neuropathy [6 – 11]. The lack of uniformly and clearly defined criteria lead to subjective assignment of CTCAE grades, with an inter-observer agreement of only 46% [6]. Patient reported outcome tools, such as the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-CIPN twenty-item scale (QLQ-CIPN20), have been shown to be better measures of neuropathy than clinician determined CTCAE grading [12, 13]. For example, the QLQ-CIPN tool has undergone validity testing [21, 23], whereby the CTCAE has not. Furthermore, CTCAE collected in large oncology clinical trials such as those analyzed in this study can be from multiple physicians involved in the longitudinal assessment of a patient, which adds inter-observer variability. Pursuant to this, some clinical trials evaluating CIPN have utilized patient reported outcomes (PRO) alone, without concomitant collection of NCI CTCAE data [14 - 17] while a few others collected both patient-reported as well as clinician-assessed outcomes [3, 8, 18 – 20].

When researchers report QLQ-CIPN20 data, clinicians often ask how these reported scores align with CTCAE grades. To date, this question has been difficult to address because few published studies provide a comparison of the scores obtained from the two. Smith et al. [21], in their paper assessing the reliability and validity of the QLQ-CIPN20, reported a low correlation ( $n = 203$ ), though statistically significant, between the baseline QLQ-CIPN20 subscales and sensory neuropathy grading using the CTCAE v3.0. Alberti et al. [22] examined the association between the QLQ-CIPN20 sensory subscale and clinician-assessed sensory grading using the NCI – Common Toxicity Criteria (CTC) v2.0, the clinical Total Neuropathy Score (TNSc<sup>®</sup>), and the modified Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score (mISS), reporting a linear trend between the QLQ-

CIPN20 sensory subscale and the NCI-CTC sensory grade (n = 281). Both studies evaluated the association between patient-reported and clinician-assessed scores at a single time point (baseline [21] or the first evaluation [22]) and included older versions of the NCI CTCAE grading. More importantly, neither of these studies addressed whether or not a direct comparison exists between QLQ-CIPN20 scores and CTCAE neuropathy grades, while other studies that used both instruments [3, 8, 18 – 20] only reported these outcomes separately.

The current project was developed to investigate the relationship between patient-reported QLQ-CIPN20 scores and physician-reported CTCAE v4.0 grading, and to determine whether it is possible to define ranges of QLQ-CIPN 20 scores associated with different CTCAE neuropathy grades. This secondary analysis includes data from all treatment cycles of two clinical trials conducted by the North Central Cancer Treatment Group (NCCTG), N08CB [19] and N08CA [20]. The NCCTG is now part of the Alliance for Clinical Trials in Oncology (Alliance).

## Methods

### Clinical trial cohorts

NCCTG N08CB and N08CA were both randomized phase III, double-blind, placebo-controlled trials for prevention of CIPN in which paired data using the QLQ-CIPN20 and the NCI CTCAE were collected at each study visit. The data for both of these measures was collected prior to a subsequent dose of chemotherapy on the appointed day. N08CB was a study of intravenous calcium (Ca) and magnesium (Mg) to prevent oxaliplatin-induced neurotoxicity, where 353 patients with colon cancer were randomly assigned to one of three arms: Ca/Mg before and after oxaliplatin-containing therapy, Ca/Mg before and placebo after, and placebo before and after [19]. Three randomized patients were later found to be ineligible for the trial and were excluded from our analysis hence the analysis of N08CB included data from 350 patients.

N08CA included 185 patients with ovarian, lung, and other cancers receiving a paclitaxel/carboplatin regimen who were randomly assigned to receive glutathione or placebo for prevention of paclitaxel/carboplatin-induced peripheral neuropathy [20]. One hundred and sixty four of these patients were treated every 3 weeks while the remaining patients were treated at either weekly, or every-4-week intervals. To ensure consistency in treatment cycle, the analysis of N08CA was limited to the 164 patients treated every three weeks. Due to differences in diseases, treatment regimens, cycles, and designs between these two studies, CIPN measurement data were analyzed separately. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines.

### CIPN Assessments

Clinician-assessed CIPN was reported as grade 0, 1, 2, 3 or 4 per criteria established in NCI CTCAE v. 4.0 using means that have been established over decades for generating toxicity evaluation by this method. In the N08CB trial, additional standardized questions were used

to quantify neurotoxicity associated with chemotherapy (details provided in that publication). The CTCAE was done by clinicians.

Patient assessment of CIPN was obtained using the QLQ-CIPN20 questionnaire, which was completed prior to any chemotherapy on the appointed day. There was no prescription as to whether it was completed before or after clinician judgment of CTCAE scores, although it is not usual to share these scores with patients. This questionnaire contains 20 items on which patients rate their experience for each symptom during the previous week using scores from 1 (not at all) to 4 (very much). The sum score was obtained by adding the scores of items 1 to 19 resulting in a sum score range of 19 to 76, which was termed CIPN20 sum<sub>1-19</sub>. Item 20 rates male impotence; this is non-informative in female patients and frequently not provided by male patients. As a consequence, this item was excluded in the CIPN20 sum<sub>1-19</sub> score in the main analysis. The association between item 20, where available, and CTCAE grading was explored in a separate analysis. Of note, item 19 rates difficulty using the pedals and is only applicable to patients who drive a car. This item can be excluded from the sum scores where the majority of patients do not drive. Since the response rate for this question is higher than 85% in our data, item 19 was included in the sum score for this analysis. In addition to a sum score, the items in CIPN20 have been divided into three subscales. The sensory subscale consists of items 1, 2, 3, 4, 5, 6, 9, 10, and 18; motor: items 7, 8, 11, 12, 13, 14, 15, and 19; and autonomic: items 16, 17, and 20. Four publications provide information regarding the QLQ-CIPN-20's psychometric properties. [8, 21, 22, 23] The published data provide preliminary evidence of its internal consistency and stability reliability, sensitivity, validity (structural, convergent, discriminant), and responsiveness.

### Statistical analysis

The primary analysis of this study focuses on the association between CIPN20 sum<sub>1-19</sub> score and CTCAE grade. Association among the QLQ-CIPN20 subscale scores and CTCAE grades were also evaluated. The following analyses were conducted separately for data from N08CB and N08CA. In a descriptive analysis, the box and whisker plots of the sum<sub>1-19</sub> score and subscales were constructed by CTCAE grade. The mean and standard error (SE) of QLQ-CIPN20 sum and subscale scores were estimated for each CTCAE grade using data from all occurrences (evaluation cycles) as well as from the first occurrence. Plots of the means and SEs were provided. Data from all occurrences were analyzed using multivariable linear mixed models, with patient as the random effect, to account for potential correlation between multiple observations from the same patient. QLQ-CIPN20 score was the outcome variable. CTCAE grade was included in all models as the main effect. CTCAE is a grading scale with five levels. It is an ordinal variable and was treated as such in this analysis. Note that a correlation coefficient is not an appropriate measure of association between QLQ-CIPN20 (a continuous variable) and CTCAE (an ordinal variable) in this analysis and, hence, was not reported. To adjust for other factors that may impact QLQ-CIPN20 scores and their association with CTCAE, we tested for the effect of cycle and its interaction with CTCAE grade and found that this interaction was not statistically significant. Although, as previously reported, QLQ-CIPN20 scores were not different between treatment arms [19, 20], we tested for an interaction between CTCAE grade and arm to determine whether the association between CTCAE and QLQ-CIPN20 score were different by treatment arm and

found that it was not statistically significant. Hence, treatment arm was not included in the final models. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. All analyses were based on the study database frozen on January 22, 2013.

## Results

### QLQ-CIPN20 sum scores corresponding to CTCAE grades 0, 1, 2, and 3 in oxaliplatin treated patients (N08CB)

For N08CB,  $n=3269$  paired CIPN assessments, QLQ-CIPN20/CTCAE, were obtained over the course of multiple patient visits (in 350 patients). Data pairs with missing QLQ-CIPN20 score or missing CTCAE scores were excluded from the analysis. Complete data were available for  $n=3176$  observations and were used for subsequent analysis.

The box and whisker plots of the QLQ-CIPN20 sum score (Fig. 1A) and sensory subscale score (Fig. 1B), for all occurrences and for first occurrence, of patients in N08CB show that the ranges of QLQ-CIPN20 scores by CTCAE grade were large and there was substantial overlap between CTCAE grades. Even when considering only the middle 50% of the scores (the boxes in Fig. 1A and Fig. 1B), there is no clear separation in QLQ-CIPN20 scores between CTCAE grades.

The means QLQ-CIPN20  $\text{sum}_{1-19}$  scores using all occurrences by CTCAE grade 0, 1, 2, and 3 were 21.6 (SE = 0.12), 24.3 (0.13), 29.9 (0.41), and 33.6 (1.90), respectively. The same result can be expressed on a scale of 0 to 100 (lower scores correspond to worse symptoms, Supplementary Table 1), which represents a simple linear conversion and is provided throughout this report. Expressed on that scale, the results were: 94.9 (0.20), 90.1 (0.24), 79.8 (0.74), and 71.8 (3.67), respectively (Fig. 2A).

Results from the linear mixed model indicate a significant association between QLQ-CIPN20 and CTCAE (p-value < .0001) as well as an association with treatment cycle (p-value < .0001). As expected, after adjusting for cycle, patients with CTCAE grade 3 had the worst QLQ-CIPN20 scores (the highest symptom burden). The mean QLQ-CIPN20 sum score was 8.2 percentage points (95% confidence interval (CI): 7.4– 9.0,  $p < 0.01$ ) lower in patients with grade 3 compared to those with grade 2, 9.3 (95% CI: 8.1– 10.4,  $p < 0.01$ ) lower in grade 2 compared to grade 1, and 3.6 (95% CI: 2.8– 4.4,  $p < 0.01$ ) lower in grade 1 compared to grade 0 (Supplementary Table 2).

Given the same CTCAE grade, QLQ-CIPN20 scores in later cycles tend to be worse than in earlier cycles. This explains the lower (better) mean QLQ-CIPN20  $\text{sum}_{1-19}$  score for CTCAE grade 1 when only the first evaluation for each patient was considered (Fig. 2B) compared to the mean when all occurrences were included (Fig. 2A). Fig 2C shows the sum score for each CTCAE grade by treatment cycle. Specifically for grade 1, a marked correlation of the QLQ-CIPN20  $\text{sum}_{1-19}$  with cycle was seen ( $R^2 = 0.75$ ,  $p = 1.8 \times 10^{-4}$ ), which suggests that the QLQ-CIPN20  $\text{sum}_{1-19}$  was a finer-grained assessment method showing gradual symptom worsening over a period, when physicians could not differentiate early or more advanced symptoms within grade 1. Patients in N08CB received one of three

treatments. Results did not differ when broken down by treatment arm. Item 20 of the CIPN20, a rating of male impotence that was omitted from the QLQ-CIPN20 sum<sub>1-19</sub> score revealed no notable correlation with CTCAE grade at the whole-cohort level.

### **QLQ-CIPN20 sum scores corresponding to CTCAE grades 0, 1, 2, and 3 in paclitaxel/ carboplatin treated patients (N08CA)**

For N08CA, n=746 paired CIPN assessments, QLQ-CIPN20/CTCAE, were obtained over the course of multiple patient visits (in 164 patients). Complete data were available for n=709 observations (used for subsequent analysis). Similar to the trend observed in N08CB, the ranges of QLQ-CIPN20 scores by CTCAE grade in N08CA were large and there was substantial overlap between CTCAE grades (Fig. 3A and Fig. 3B). Only two paired assessments with grade 3 were observed. The mean CIPN20 sum<sub>1-19</sub> scores in patients with CTCAE grade 0, 1, 2 and 3 were 22.8 (SE = 0.28), 29.4 (0.55), 36.9 (1.08) and 38.0 (13.00), respectively, which on the alternate scale corresponded to 92.8 (0.52), 80.9 (1.00), 66.8 (1.95) and 62.9 (24.07) (Fig. 4A, Supplementary Table 1).

The association between CTCAE and QLQ-CIPN20 from this analysis is consistent with the results shown for N08CB, with a p-value <0.0001. The association with treatment cycle was also significant (p=0.005). Again, patients with grade 3 CTCAE had the worst QLQ-CIPN20 scores. On average, QLQ-CIPN20 sum scores were 3.8 (95% CI: -15.2 – 22.8, p = 0.7) percentage points lower in patients with grade 3 compared to those with grade 2, 13.9 (95% CI: 9.9– 17.8, p <0. 01) lower in grade 2 compared to grade 1, and 10.8 (95% CI: 8.6– 13.0, p = <0. 01) lower in grade 1 compared to grade 0.

Plots of QLQ-CIPN20 sum<sub>1-19</sub> score including only the first occurrence (Fig 3A and 4B) show similar pattern as all occurrences for CTCAE grades 0. However, QLQ-CIPN20 sum<sub>1-19</sub> for CTCAE grades 1 and 2 appears to be lower (better) when only the first occurrence of grade 1 was considered which is consistent with the pattern observed in N08CB. A further depiction of the QLQ-CIPN20 sum<sub>1-19</sub> by CTCAE grade by cycle again suggests a correlation between QLQ-CIPN20 scores and treatment cycle for CTCAE grades 1 and 2 (Fig. 4C). This is consistent with the multivariable results indicating an association between cycle and QLQ-CIPN20 scores in this study after adjusting for CTCAE grade. The results did not differ by treatment arm. QLQ-CIPN20 item 20 data were available in too few patients in N08CA to be meaningfully assessed, particularly because many patients in this protocol were women.

### **Sensory-, motor-, and autonomic EORTC CIPN20 “subscales”**

The subscales of the EORTC QLQ-CIPN20, especially the sensory subscale, are often used instead of the QLQ-CIPN20 sum<sub>1-19</sub> score [3, 16, 20 – 21]. Slightly larger differences between grade 1 vs. 0 and between grade 2 vs. 1 were observed in models assessing association between sensory subscale and CTCAE than was observed in analysis of motor and autonomic subscales (Fig 5A and 5B). This confirms the higher responsiveness of the sensory subscale [8, 21]. However, the overall patterns of association between CTCAE and the subscales of QLQ-CIPN20 were consistent with the results shown for the QLQ-CIPN20 sum<sub>1-19</sub> score.

## Discussion

NCCTG N08CB and N08CA provide a unique opportunity to evaluate the relationship between patient-reported CIPN symptoms (EORTC QLQ-CIPN20) vs. clinician-assessed neuropathy grading (NCI CTCAE). Both were phase III trials with hundreds of patients where QLQ-CIPN20 scores and CTCAE grades were collected concurrently at each of many cycles of treatment, resulting in two large sets of data with paired measures. Data from both studies showed very strong correlation between CIPN20 and CTCAE, suggesting strong convergent validity because both assessment tools, in principle, measure the same symptoms. While this finding is not unexpected, it is, nevertheless, reassuring.

The patient populations from these studies differed in disease, chemotherapy regimens, and CIPN treatments. While the principal findings are similar in both studies, certain specific differences were noted. Specifically, QLQ-CIPN20 scores in paclitaxel/carboplatin-treated patients appeared to be worse (showing more neuropathy burden) for each CTCAE grade than in oxaliplatin-treated patients. Data from both trials showed a consistently strong association between QLQ-CIPN20 score and CTCAE neuropathy grade. While this association has been previously reported by Smith et al. [21] and Alberti et al. [22] with a single observation per patient (i.e., a single time point), the present study extends these findings showing that this association holds over time when data from multiple treatment cycles per patient are available and that this association is independent of treatment cycle.

Our study was based on the largest dataset,  $n = 3176$  and  $709$  for N08CB and N08CA, respectively, available to date among reports assessing the relationship between patient-reported versus clinician-assessed grading of neuropathy ( $n = 230$  [21] and  $n = 281$  [22]). We found a large range in QLQ-CIPN20 scores within each CTCAE grade, when considering inter-patient variation. Accordingly, we conclude that it is not possible to assign ranges of QLQ-CIPN20 scores that correspond to CTCAE grading levels. This result was not surprising because perfect agreement in each patient would render the QLQ-CIPN-20 redundant. It is more about sensitivity and responsiveness. While both measures are valid (they measure what they are intended to measure – CIPN), the QLQ-CIPN20 questionnaire provides more detailed information, distinguishes more subtle degrees of neuropathy, and is more responsive to change over time. In studies of preventative agents, detection of subtle changes is important. Thus, important information would have been missed, if only the CTCAE - previously the standard - had been recorded in the two trials. An alternative view would be that the overlap in the CIPN20 across CTCAE grades likely reflects the inaccuracy of the CTCAE and the CIPN20 may be more likely to be accurate and sensitive than CTCAE.

QLQ-CIPN20 and CTCAE were very highly correlated at the cohort level (that is the means of QLQ-CIPN20 scores were different across CTCAE grades), a relationship that the present study could describe quantitatively with high precision thanks to the large size of the available cohorts. The data provided may also serve as a critical reference in the planning of future research, supporting that a patient-reported instrument, such as the QLQ-CIPN20, should be used to most accurately measure CIPN in clinical trials designed to do such. The NCI Patient-reported outcome version of the CTCAE, called the PRO-CTCAE, has recently

been validated<sup>24</sup>. The PRO-CTCAE includes two items asking patients to rate the severity and interference associated with numbness and tingling in their hands and feet. We recommend evaluating the association between QLQ-CIPN20 and PRO-CTCAE in future research.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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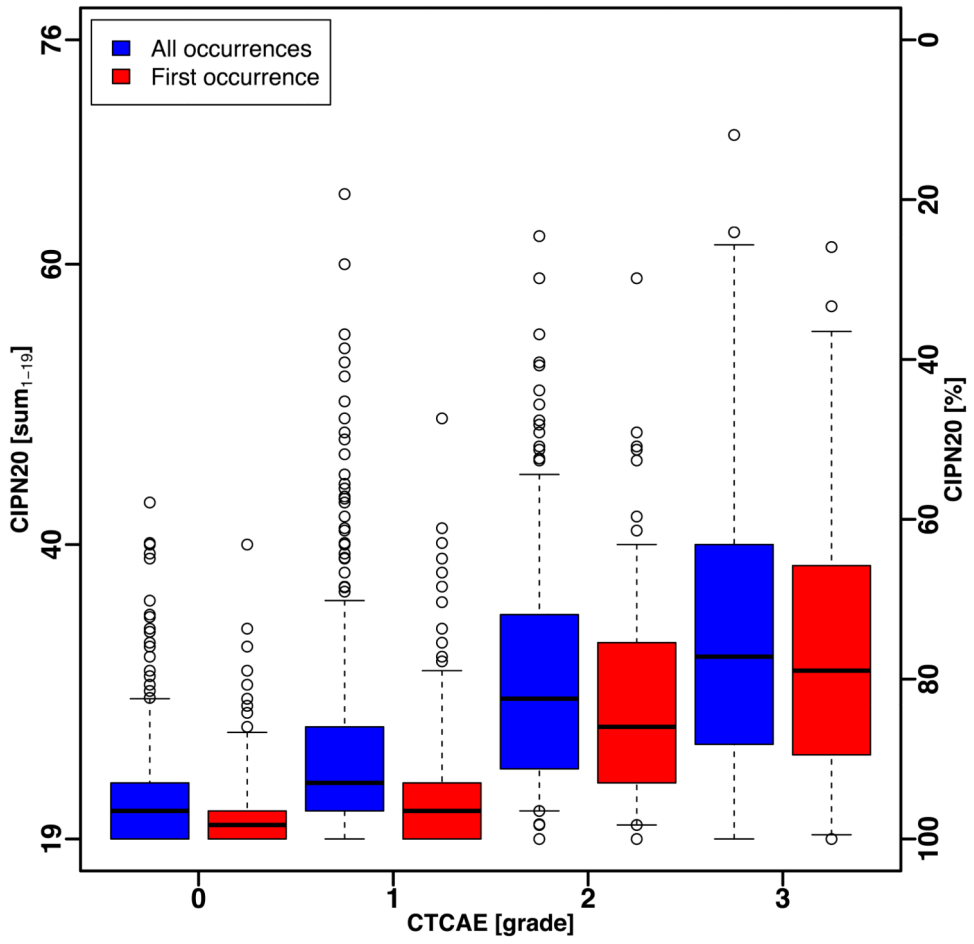
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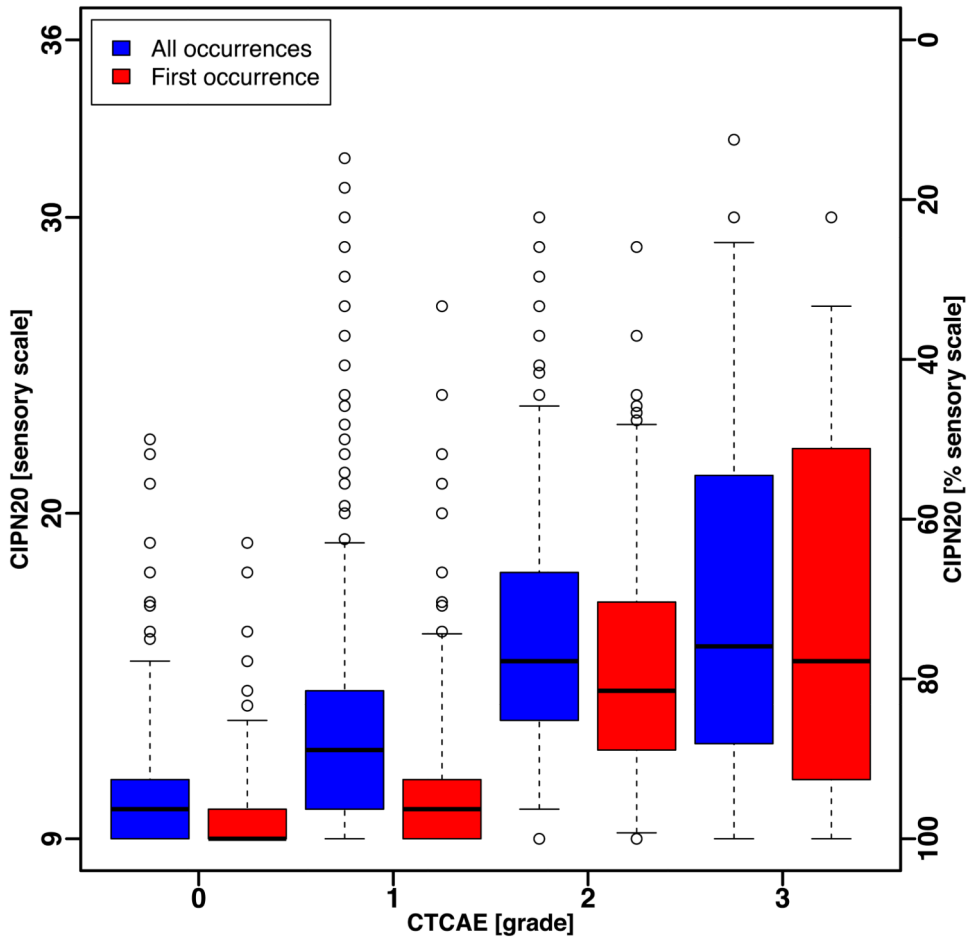
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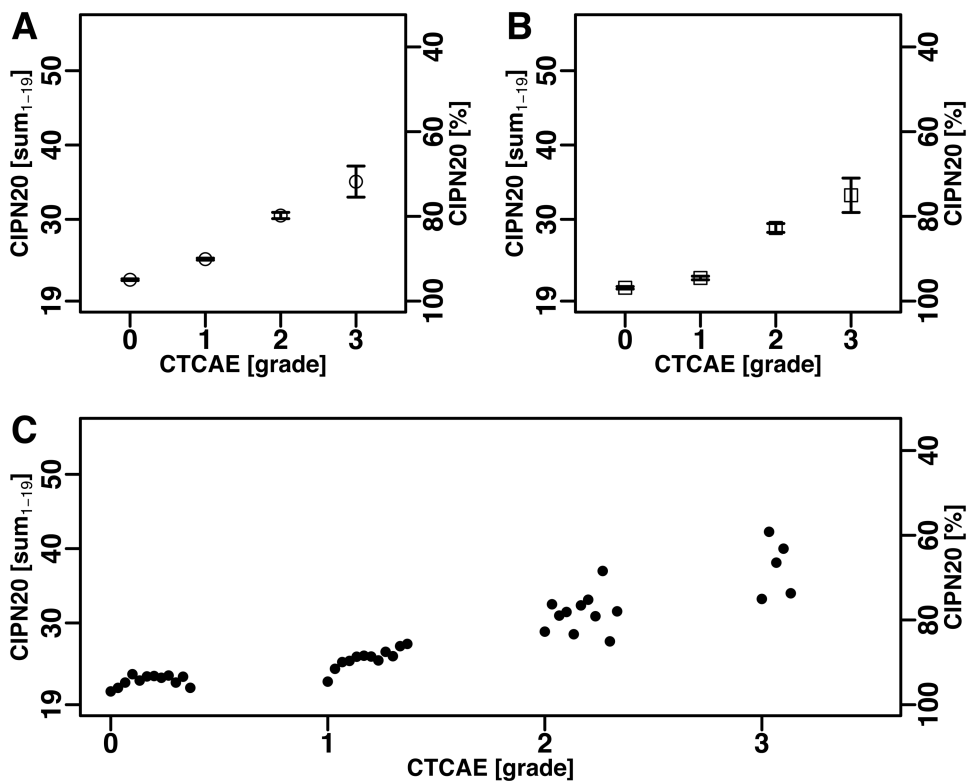
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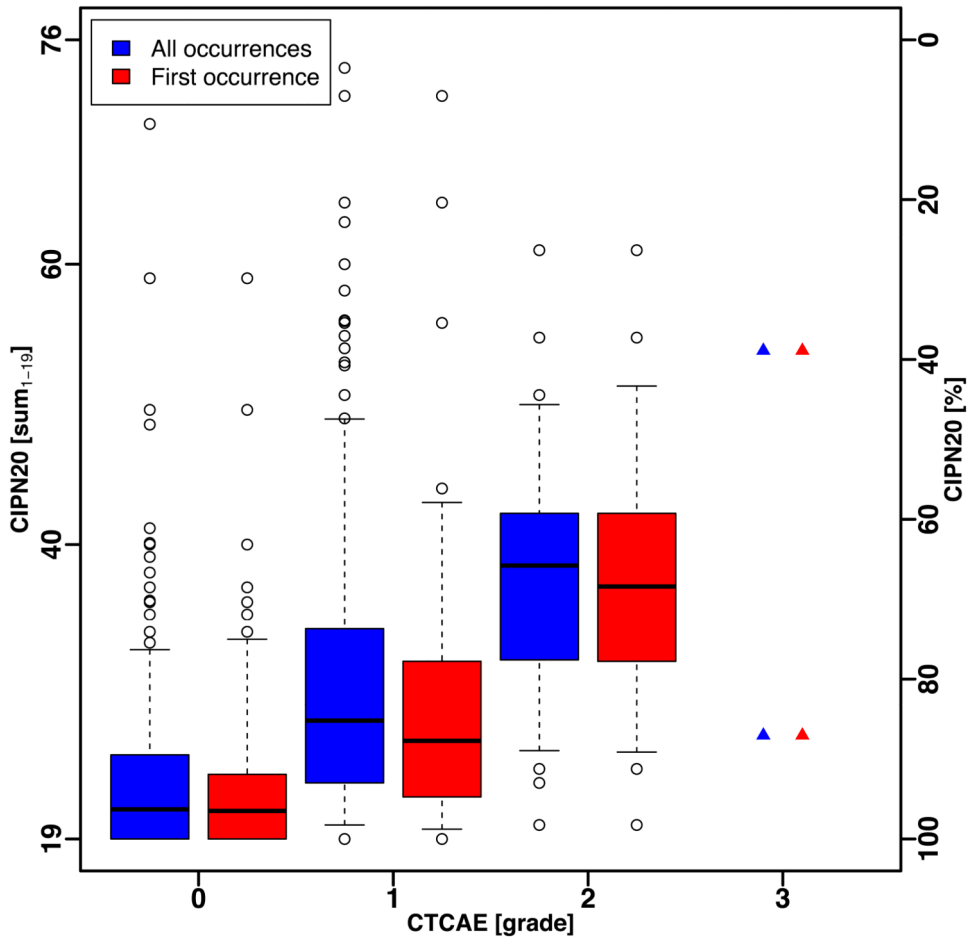


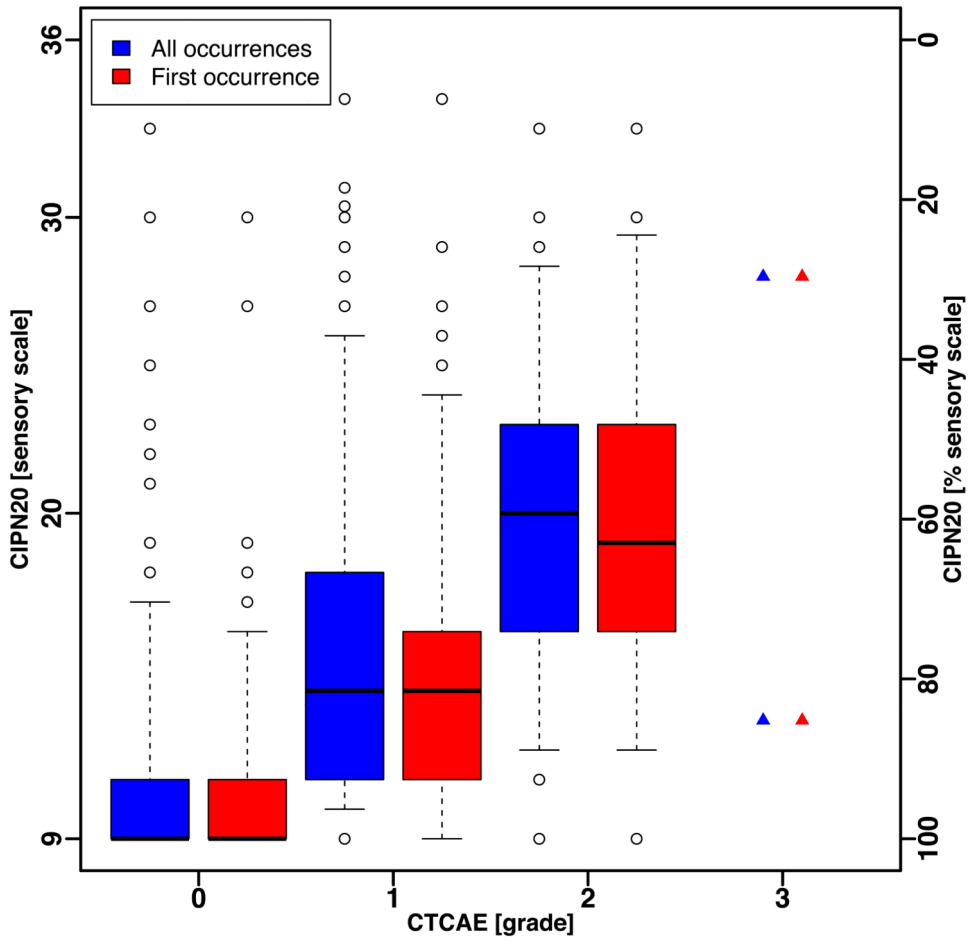


**Figure 1.** Box and whisker plot of CIPN20 scores by CTCAE grade for all occurrences and first occurrence in patients treated with oxaliplatin (N08CB). Whiskers show the 5<sup>th</sup> and 95<sup>th</sup> percentile of scores.  
 (A) Sum<sub>1-19</sub> score.  
 (B) Sensory subscale.

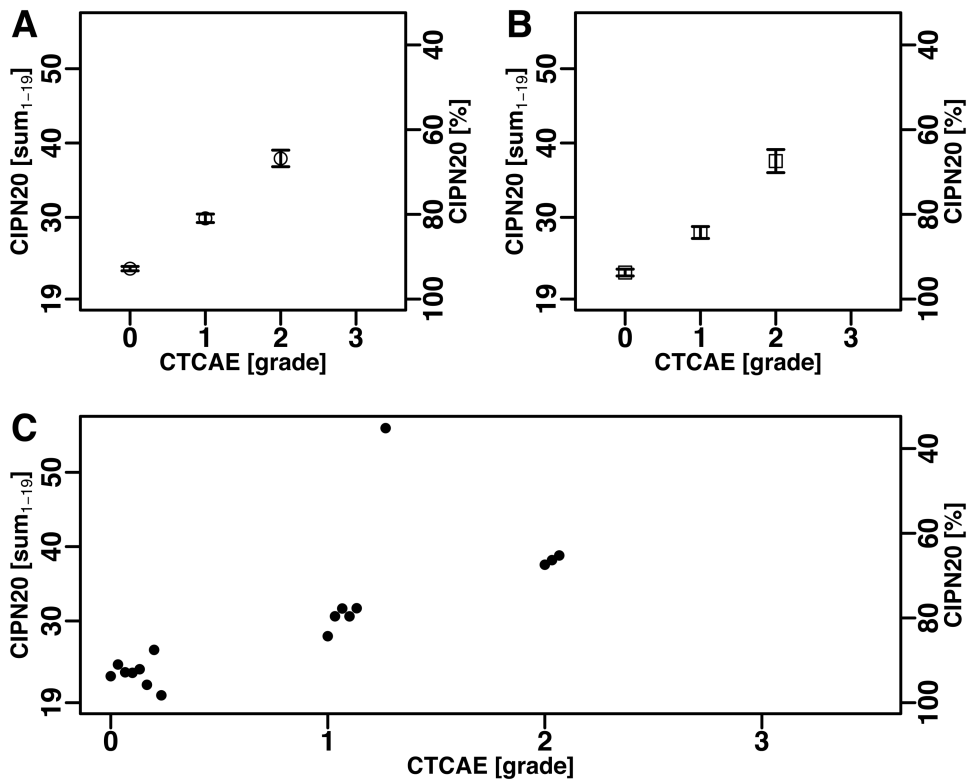


**Figure 2.**  
 Mean and mean ± SEM of CIPN20 scores by CTCAE grade in patients treated with oxaliplatin (N08CB).  
 (A) The CIPN20 sum<sub>1-19</sub> for all occurrences.  
 (B) The CIPN20 sum<sub>1-19</sub> at the first occurrence.  
 (C) The CIPN20 sum<sub>1-19</sub> for each CTCAE grade at the first and subsequent occurrences (mean) showing a time dependent trend for grade 1. The time dependent trend observed within grade 1 was significant as discussed in the main text.



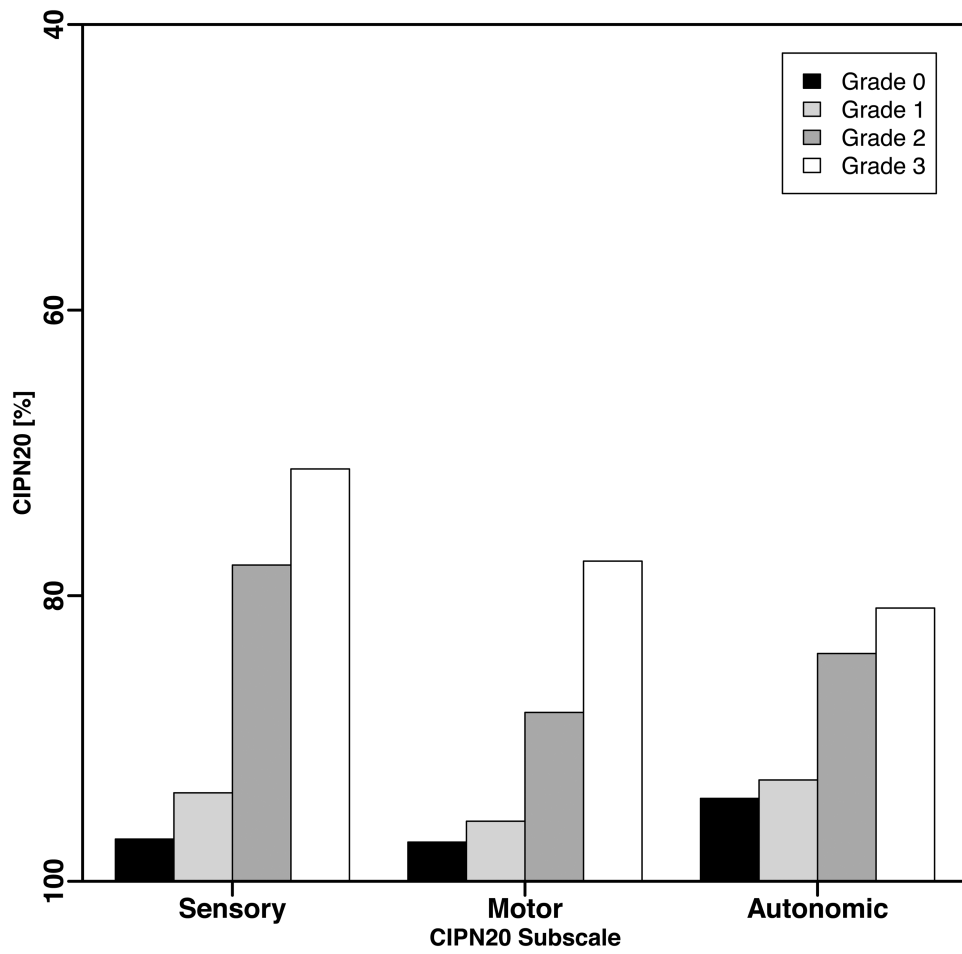


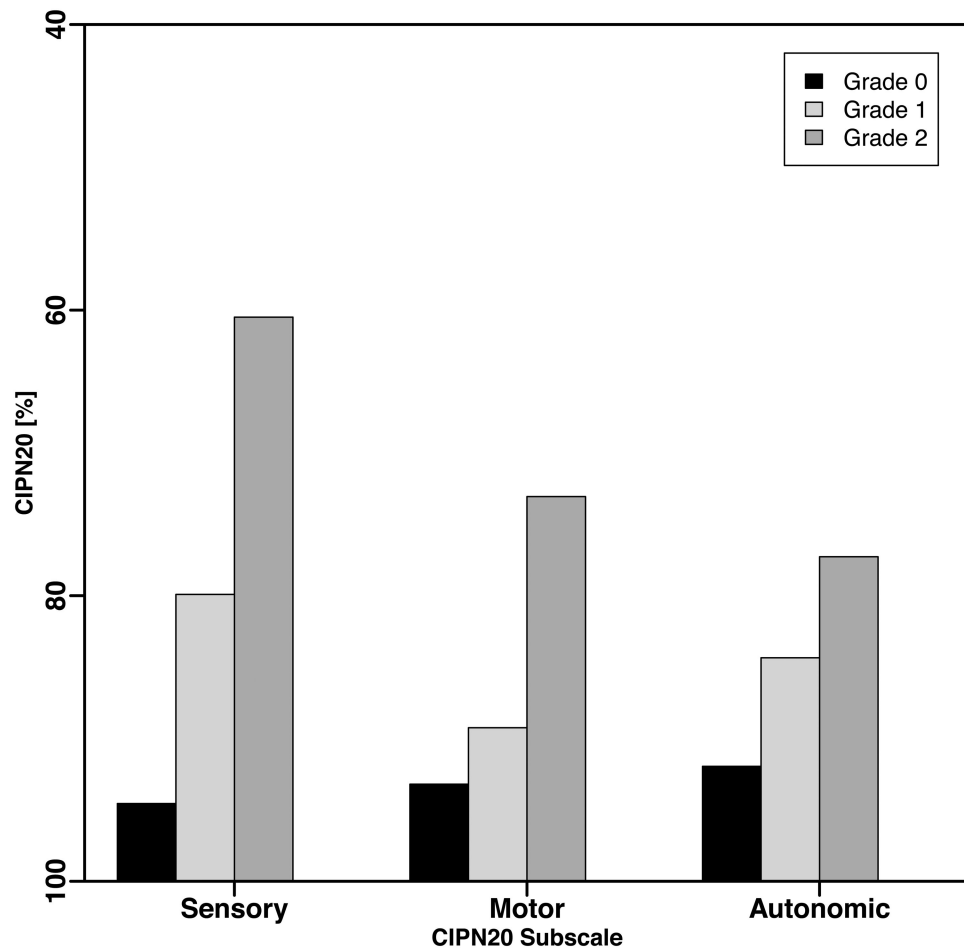
**Figure 3.** Box and whisker plot of CIPN20 scores for all occurrences and first occurrence in patients treated with paclitaxel/carboplatin (N08CA). Whiskers show the 5<sup>th</sup> and 95<sup>th</sup> percentile of scores.  
(A) Sum<sub>1-19</sub> score.  
(B) Sensory subscale.



**Figure 4.**  
 Mean and mean ± SEM of CIPN20 scores by CTCAE grade in patients treated with oxaliplatin (N08CA).  
 (A) The CIPN20 sum<sub>1-19</sub> for all occurrences.  
 (B) The CIPN20 sum<sub>1-19</sub> at the first occurrence.  
 (C) The CIPN20 sum<sub>1-19</sub> for each CTCAE grade at the first and subsequent occurrences (mean) showing a time dependent trend for grade 1.







**Figure 5.** CIPN20 sub-scales. The mean subscale scores were computed for each first occurrence of a CTCAE grade per patient.  
(A) N08CB (oxaliplatin).  
(B) N08CA (paclitaxel/carboplatin).