Supportive Care in Cancer (2019) 27:4753–4762
https://doi.org/10.1007/s00520-019-04771-8

ORIGINAL ARTICLE

Minimal clinically important difference of the EORTC QLQ-CIPN20 for worsening peripheral neuropathy in patients receiving neurotoxic chemotherapy

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Received: 28 January 2019 / Accepted: 21 March 2019 / Published online: 10 April 2019

Abstract

Context/objectives This is the first study to determine the minimal clinically important difference (MCID) of the European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire-CIPN twenty-item scale (EORTC QLQ-CIPN20), a validated instrument designed to elicit cancer patients' experience of symptoms and functional limitations related to chemotherapy-induced peripheral neuropathy.

Methods Cancer patients receiving neurotoxic chemotherapy completed EORTC QLQ-CIPN20 and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity [FACT/GOG-NTX] at baseline, second cycle of chemotherapy (T2, $n = 287$), and 12 months after chemotherapy (T3, $n = 191$). Anchor-based approach used the validated FACT/GOG-NTX neurotoxicity (Ntx) subscale to identify optimal MCID cutoff for deterioration. Distribution-based approach used one-third standard deviation (SD), half SD, and one standard error of measurement of the total EORTC QLQ-CIPN20 score.

Results There was a moderate correlation between the change scores of the Ntx subscale and sensory and motor subscales of QLQ-CIPN20 (T2: $r = -0.722$, $p < 0.001$ and $r = -0.518$, $p < 0.001$, respectively; T3: $r = -0.699$; $p < 0.001$ and $r = -0.523$, $p < 0.001$, respectively). The correlation between the change scores of the Ntx subscale and the QLQ-CIPN20 autonomic subscale was poor (T2: $r = -0.354$, $p < 0.001$; T3: $r = 0.286$, $p < 0.001$). Based on the MCID derived using distribution-based method, the MCID for the QLQ-CIPN20 sensory subscale was 2.5–5.9 (6.9% to 16.4% of the subdomain score) and for motor subscale was 2.6–5.0 (8.1%–15.6% of the subdomain score).

Conclusion The MCID for the EORTC QLQ-CIPN20 established using distribution-based approaches was 2.5–5.9 for the sensory subscale and 2.6–5.0 for the motor subscale. When noted in assessments even with small change in scores, clinicians can be alerted for appropriate intervention.

Keywords Peripheral neuropathy · Minimal clinically important difference · EORTC QLQ-CIPN20 · FACT/GOG-NTX · Cancer

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Introduction

Chemotherapy-induced peripheral neurotoxicity (CIPN) is one of the prevalent non-hematological adverse effects and can greatly impact patients' treatment outcomes [1]. CIPN is also a major cause of significant distress in cancer patients and can be associated with decreased quality of life, reduced functional ability, and increased risk for falls. A number of cytotoxic chemotherapy agents are associated with peripheral neuropathy, and these agents include taxanes, platinums, vinca alkaloids, and bortezomib [2, 3]. Although a number of agents have been investigated for the management of CIPN, effective agents for managing such debilitating toxicity are extremely limited [4].

In order to study the impact of CIPN on quality of life, in clinical studies, a number of assessment tools have been used on oncology patients receiving chemotherapy. Assessments of CIPN include the use of objective measurements (e.g., nerve conduction studies [5, 6]), clinician-assessed outcomes (e.g., NCI-CTCAE [2, 7]), patient-reported outcomes (PRO) scores [8, 9], and even composite scores using a combination of nerve conduction studies and patient-reported outcome scores (e.g., total neuropathy score [TNS] [10]). In the literature, it is recognized that PRO measures of sensory CIPN are preferred over clinician-determined assessments [11]. PRO tools that are commonly used include the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire-CIPN twenty-item scale (EORTC QLQ-CIPN20) and the Functional Assessment of Cancer Therapy/*Gynecologic* Oncology *Group-Neurotoxicity* (FACT/GOG-NTX) tools [12, 13].

Clinicians can utilize PRO tools longitudinally to monitor patients' CIPN symptoms over the course of treatment. However, depending on the statistical tests alone to determine statistically meaningful difference in CIPN scores might be of little clinical relevance to patients and would not be applicable in daily clinical practice. In such situations, the minimal clinically important difference of CIPN scores would be valuable. The MCID is defined as the smallest difference in score that patients perceive as beneficial and that would mandate a change in the patient's management, which also represents the smallest change in score in which symptom worsening is clinically significant [14, 15].

The MCID of EORTC QLQ-CIPN20 has not been established in the literature. There is great clinical utility with establishing the MCID. Patients whose change in clinical neuropathy score exceeds the MCID of the EORTC QLQ-CIPN20 could benefit from active and timely management of their neuropathy symptoms. In addition, the MCID of the EORTC QLQ-CIPN20 can be potentially used to establish adjunctive treatment recommendations for future patients with cancer or to determine sample size estimates of future clinical trials on CIPN management.

In view of the lack of the MCID of EORTC QLQ-CIPN20, we have designed a study to determine the MCID of EORTC QLQ-CIPN20 among patients receiving neurotoxic chemotherapy.

Materials and methods

Study setting and population

This is a secondary analysis of a prospective study conducted at both inpatient and outpatient oncology units of three hospitals located in Hong Kong, Singapore, and United Kingdom [16]. All eligible patients must be (1) ≥ 18 years old, (2) diagnosed with cancer by a medical oncologist, (3) chemotherapy-naïve, (4) planned to receive taxane- and/or platinum-based chemotherapy, (5) have an expected survival of at least 12 months, and (6) able to provide informed consent.

Study procedure

At the point of recruitment, patient's demographic and clinical information such as age, cancer history, and cancer treatment history were collected from existing in-house electronic databases and patients' interview. Two quality of life questionnaires, EORTC QLQ-CIPN20 and FACT/GOG-NTX, were administered at baseline (namely timepoint 1, or T1), at second cycle of chemotherapy (namely timepoint 2, or T2) after chemotherapy initiation and at 12-month follow-up after chemotherapy initiation (namely timepoint 3, or T3). Generally, T2 and T3 occurred 3 weeks and 12 months, respectively, after baseline. These timepoints were chosen to compare the change of neuropathy symptoms after exposure to neurotoxic chemotherapy on baseline.

Instruments

The Functional Assessment of Cancer Therapy/*Gynecologic Oncology Group-Neurotoxicity* [FACT/GOG-NTX] is a 38-item self-reported questionnaire comprising two subscales, the first being a 27-item general assessment of quality of life subscale and the second being an 11-item neurotoxicity (Ntx) subscale that evaluates symptoms associated specifically with chemotherapy-induced neuropathy [17]. All items are linearly converted to a 0–152 scale with higher scores suggestive of a better quality of life.

The European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire-CIPN twenty-item scale [EORTC QLQ-CIPN20] is a 20-item questionnaire that assesses the severity of neuropathy symptoms experienced by patients [18]. It comprises three domains: sensory (nine items), motor (eight items), and autonomic (three items) subscales. With a 4-point Likert scale (1 = not at all, 2 = a little,

3 = quite a bit, and 4 = very much), patients will rate their symptoms during the past week. Sensory scale scores range from 1 to 36, motor scale scores range from 1 to 32, and autonomic scale scores range from 1 to 12 for men and 1–8 for women (erect dysfunction item excluded). All items are linearly converted to a 0–100 scale with higher scores indicative of more symptoms. In the Caucasian population, the EORTC QLQ-CIPN20 is also a validated tool that demonstrated good internal consistency reliability based on Cronbach's alpha coefficients of 0.88, 0.88, and 0.78 for the sensory, motor, and autonomic scales, respectively [19].

Statistical analysis

To compare the EORTC-QLQ-CIPN20 and FACT/GOG-NTX scores across (i) baseline and T2 and (ii) baseline and T3, a paired *t* test was used. The MCID of the EORTC-QLQ-CIPN20 was determined using anchor-based and distribution-based approaches [20, 21]. The SPSS software Version 24.0 for Windows was used for the statistical analysis.

Anchor-based approach

The Ntx-subscale of FACT/GOG-NTX was used as an external criterion against which changes in EORTC QLQ-CIPN20 were anchored and calibrated. Spearman rank correlation coefficient was used to quantify the association between EORTC QLQ-CIPN20 and Ntx subscale. To establish an MCID, it has been recommended that the change scores of the anchor and the instrument being examined have a correlation threshold of $r > 0.30$ [22]. We have previously validated and confirmed the psychometric properties of QLQ-CIPN20 in the Asian population, the research group conducted a separate study that included a cohort of oncology patients from Hong Kong, Singapore, and United Kingdom. In the study, EORTC QLQ-CIPN20 sensory and motor scores were moderately correlated with NCI CTCAE sensory ($r = 0.46$) and motor scores ($r = 0.52$) respectively, suggesting concurrent validity. Good internal consistency reliability was also observed with Cronbach's alpha coefficients of 0.79 and 0.47 for the sensory and motor scales, respectively (unpublished).

Although there is no MCID established for FACT/GOG-NTX, it is a validated PRO tool and the NTX-subscale correlates highly with both the objective and subjective neuropathy assessments [17, 23]. Therefore, in this study, we define a 3.3–4.4 point change of the subscale score as clinically important change in the 11-item NTX subscale of FACT/GOG-NTX. This is based on current recommendations that the general minimally important difference for Functional Assessment of Chronic Illness Therapy (FACIT) cancer-specific subscales is 0.3 to 0.4 point change per item, and previous studies that have also utilized similar approaches on anchoring with FACIT's questionnaires [20]. To obtain the MCID for deterioration, the mean difference in scores for "no change" was subtracted from the mean difference in scores for "deterioration by at least one category." Likewise, the average difference scores for patients classified as "improvement by at least one category" were compared with those for "no change" to compute the MCID estimate for improvement. The associated effect sizes (ESs) were determined for the respective clinical categories by dividing the mean change in scores by the overall baseline standard deviations (SDs) for the sample. The ES determines the responsiveness of the EORTC QLQ-CIPN20 to changes in neuropathy symptoms. An ES of 0.2, 0.5, and 0.8 is considered to be small, moderate, and large, respectively. A threshold of $ES < 0.2$ was used to exclude MCID estimates too small to be interpreted [24].

Distribution-based approach

The magnitude of MCID for EORTC QLQ-CIPN20 scores was estimated using effect sizes (ES). An ES is a standardized index of change that represents the number of SDs by which the scores have changed from T1-T2 and T1-T3. MCID determinant studies for FACIT and EORTC QLQ instruments show that one-third and half SDs closely approximate the MCID [25, 26]. Thus, one-third and half SDs were calculated at T1, T2, T3, T1-T2 score changes and for T1-T3 score changes. Additionally, the standard error of measurement (SEM) was used to calculate the MCID estimate. A one SEM is considered to likely approximation of the MCID [25–27]. The one-SEM value was computed using the following formula: $SEM = \sigma\sqrt{(1-r)}$, where σ = the SD of the EORTC QLQ-CIPN20 scores and r = the mean test-retest reliability of the instrument. The *r* value taken to calculate one SEM was 0.836, 0.844, and 0.726 for sensory, motor, and autonomic subscales, respectively [28].

Estimation of the overall MCID

Instead of estimating the MCID as an absolute single threshold, Hays et al. [29] suggested to combine a possible range of MCIDs to accommodate for the method- and sample-dependent variations. Therefore, the estimated value range was achieved by combining the MCID values obtained from the aforementioned anchor-based and distribution-based approaches.

Results

Demographics

At T1, 343 patients were recruited, with mean age of 55 years (SD = 9.4) (Table 1). At T2 and T3, 287 (mean age 55 years (SD = 9.2)) and 191 (mean age 56 years (SD = 9.2)) patients,

Table 1 Patients' characteristics and demographics

Demographics	Baseline, T1 ($n = 343$)	3 weeks after baseline, T2 ($n = 287$)	12 months after baseline, T3 ($n = 191$)
Age (year), mean (SD)	55 (9.4)	55 (9.2)	56 (9.2)
Gender, *n* (%)			
Female	256 (74.6)	222 (77.4)	143 (74.9)
Male	87 (25.4)	65 (22.6)	48 (25.1)
Cancer diagnosis, *n* (%)			
Breast	174 (50.7)	159 (55.4)	103 (53.9)
Lung	48 (14.0)	32 (11.2)	18 (9.4)
Ovarian	32 (9.3)	25 (8.7)	18 (9.4)
Others	89 (26.0)	71 (24.7)	52 (27.3)
Cancer stage, *n* (%)			
I	52 (15.2)	45 (15.7)	32 (16.8)
II	99 (28.9)	91 (31.7)	53 (27.7)
III	116 (33.8)	93 (32.4)	59 (30.9)
IV	76 (22.2)	58 (20.2)	47 (24.6)
Treatment intent			
Adjuvant	199 (58.0)	176 (61.3)	105 (55)
Neoadjuvant	51 (14.9)	46 (16)	30 (15.7)
Concurrent	30 (8.7)	17 (6)	16 (8.4)
Palliative	63 (18.4)	48 (16.7)	40 (20.9)
Chemotherapy Regimen, *n* (%)			
Taxane	155 (45.2)	140 (48.8)	93 (48.7)
Platinum	109 (31.8)	80 (27.9)	55 (28.8)
Combined taxane and platinum	79 (23.0)	67 (23.3)	43 (22.5)

respectively, remained in the study. The vast majority were female (T1 = 74.6%, T2 = 77.4%, T3 = 74.9%) and had stages I–III cancer (T1 = 77.9%, T2 = 79.8%, T3 = 75.4%). At T1, T2, and T3, 174 (50.7%), 159 (55.4%), and 103 (53.9%) patients, respectively, were diagnosed with breast cancer, received adjuvant chemotherapy (T1 = 58%, T2 = 61.3%, T3 = 55%). Taxane-based chemotherapy (T1 = 45.2%, T2 = 48.8%, T3 = 48.7%) was the most commonly used chemotherapeutic protocol among patients.

Questionnaire scoring

The score distributions for the FACT/GOG-NTX for T1-T2 and T1-T3 are summarized in Table 2. The mean (±SD) total FACT/GOG-NTX scores at T1 and T2 were 126.9 ± 18.4 and 123.9 ± 20.8, respectively, with an average change of − 3.04 ± 19.4 ($p = 0.008$). The mean (±SD) total FACT/GOG-NTX scores at T1 and T3 were 129.5 ± 16.6 and 134.2 ± 16.9, respectively, with an average change of 4.8 ± 16.7 ($p < 0.001$).

The score distributions for the EORTC QLQ-CIPN20 for T1-T2 and T1-T3 are summarized in Table 3. For the sensory domain, the mean (±SD) scores at baseline and cycle 2 were 2.9 ± 7.4 and 7.8 ± 13.5, respectively, with an average change of 4.8 ± 14.2 ($p < 0.001$). For the motor domain, the mean (±SD) scores at baseline and cycle 2 were 3.4 ± 6.7 and 5.9 ± 11.4, respectively, with an average change of 2.5 ± 11.7 ($p < 0.001$). For the autonomic domain, the mean (±SD) autonomic domain scores at baseline and cycle 2 were 7 ± 13.4 and 9.2 ± 15.4, respectively, with an average change of 2.2 ± 15.8 ($p = 0.019$). For the sensory domain, the mean (±SD) scores at baseline and T3 were 2.3 ± 5.0 and 6.4 ± 10.1, respectively, with an average change of 4.0 ± 9.4 ($p < 0.001$). For the motor domain, the mean (±SD) scores at baseline and T3 were 2.9 ± 6.0 and 5.3 ± 10.2, respectively, with an average change of 2.4 ± 10.0 ($p = 0.001$). For the autonomic domain, the average change of mean (±SD) scores was found to be statistically insignificant ($p = 0.943$).

Anchor-based analysis

At T2, there was a moderate correlation between the change scores of the FACT/GOG-NTX Ntx subscale and sensory scale and motor scale of EORTC QLQ-CIPN20 ($r = -0.722$, $p < 0.001$ and $r = -0.518$, $p < 0.001$, respectively). However, the correlation between the change scores of the FACT/GOG-NTX Ntx subscale and the autonomic scale of EORTC QLQ-CIPN20 was poor ($r = -0.354$, $p < 0.001$). A decrease of 4.9 points (95% CI: 1.3–8.5; ES = 0.66) of the sensory scale

Table 2 FACT/GOG-NTX scores at (i) baseline (T1) and T2 (3 weeks after baseline, $n = 287$) and (ii) T1 and T3 (12 months after baseline, $n = 191$)

Domains	Baseline (T1) (mean [SD])	T2 or T3 (mean [SD])	Average change (mean [SD]), p value
T1 and T2			
Physical well-being (score 0–28)	24.3 [4.4]	23.3 [5.9]	− 1.06 [6.2], 0.004
Social/Family well-being (score 0–28)	23.7 [5.8]	22.8 [6.3]	− 0.95 [5.9], 0.007
Emotional well-being (score 0–24)	18.2 [4.3]	19.6 [3.8]	1.4 [3.9], < 0.001
Functional well-being (score 0–28)	18.4 [7.5]	18 [7.2]	− 0.49 [7.5], 0.269
Neurotoxicity (Ntx) subscale (score 0–44)	42.2 [3.5]	40.3 [5.7]	− 1.93 [5.9], < 0.001
FACT/GOG-NTX total score (score 0–152)	126.9 [18.4]	123.9 [20.8]	− 3.04 [19.4], 0.008
T1 and T3			
Physical well-being (score 0–28)	24.7 [4.0]	25.7 [3.9]	1.0 [3.9], < 0.001
Social/Family well-being (score 0–28)	24.6 [5.1]	23.6 [5.5]	− 1.0 [5.3], 0.011
Emotional well-being (score 0–24)	18.6 [4.4]	21.2 [3.4]	2.6 [4.5], < 0.001
Functional well-being (score 0–28)	19.1 [6.9]	23.1 [5.4]	4.0 [7.5], < 0.001
Neurotoxicity (Ntx) subscale (score 0–44)	42.5 [2.9]	40.7 [4.9]	− 1.9 [4.5], < 0.001
FACT/GOG-NTX total score (score 0–152)	129.5 [16.6]	134.2 [16.9]	4.8 [16.7], < 0.001

All data presented as mean [SD]

Higher scores in the FACT/GOG-NTX indicative of better quality of life

corresponded to a minimal important change, and the value was statistically significant (Table 4). Conversely, a decrease of 1.6 (95% CI: − 1.7–4.8) and 6.7 points (95% CI: − 1.0–14.3) of the motor and autonomic scales, respectively, corresponded to a minimal importance change, but both the values were statistically insignificant. Hence, a minimal importance change could not be established with the motor and autonomic scales at T2.

At T3, there was a moderate correlation between the change scores of the FACT/GOG-NTX Ntx subscale and sensory scale and motor scale of EORTC QLQ-CIPN20 ($r = -0.699$, $p < 0.001$ and $r = -0.523$, $p < 0.001$, respectively). In contrast, the correlation between the change scores of the FACT/GOG-NTX Ntx subscale and the autonomic scale of EORTC QLQ-CIPN20 was poor ($r = 0.286$, $p < 0.001$). A decrease of 13.6 points (95% CI: 3.2–24; ES = 2.72) of the sensory subscale and a decrease of 4.2 points (95% CI: 1.4–7.0; ES = 0.70) of the motor corresponded to a minimal important change, and both values were statistically significant (Table 4). In contrast, a decrease of 5.6 points (95% CI: − 5.5–16.7) of the autonomic scale corresponded to a minimal importance change, but the mean change was not statistically significant. Therefore, a minimal importance change could not be established with the autonomic subscale.

Although the 95% CI range for sensory subscale overlapped between T2 (1.3–8.5) and T3 (3.2–24), the mean change scores were found to vary at these timepoints (4.9 points versus 13.6 points). For motor subscale, there was an overlapping of 95% CI range between T2 (− 1.7–4.8) and T3 (1.4–7.0) with similar mean change scores (1.6 points versus 4.2 points). However, the mean score change of motor subscale at T2 was found to be not statistically significant. Therefore, similar to the autonomic subscale, the MCID for

Table 3 EORTC QLQ-CIPN20 scores at (i) baseline (T1) and T2 (3 weeks after baseline, $n = 287$) and (ii) T1 and T3 (12 months after baseline, $n = 191$)

Domain	Baseline (T1) (mean [SD])	T2 or T3 (mean [SD])	Average change (mean [SD]), p value
T1 and T2			
Sensory	2.9 [7.4]	7.8 [13.5]	4.8 [14.2], < 0.001
Motor	3.4 [6.7]	5.9 [11.4]	2.5 [11.7], < 0.001
Autonomic	7 [13.4]	9.2 [15.4]	2.2 [15.8], 0.019
T1 and T3			
Sensory	2.3 [5.0]	6.4 [10.1]	4.0 [9.4], < 0.001
Motor	2.9 [6.0]	5.3 [10.2]	2.4 [10.0], 0.001
Autonomic	7.4 [13.6]	7.3 [13.8]	− 0.1 [16.8], 0.943

All data presented as mean [SD]; all items are linearly converted to a 0–100 scale with higher scores indicative of more symptoms

both sensory and motor subscales could not be established using the anchor-based approach.

Distribution-based analysis

At T2, the calculated means for one-third of the SD and half of the SD produced MCID estimates for the sensory, motor, and autonomic subscales that ranged from 3.5 to 5.9, 3.0 to 5.0, and 4.5 to 7.5, respectively (Table 5). The MCID derived from the value of one SEM was 4.8 for the sensory subscale, 3.9 for the motor subscale, and 7.8 for the autonomic subscale.

At T3, the calculated means for one-third of the SD and half of the SD produced MCID estimates for the sensory, motor, and autonomic subscales that ranged from 2.5 to 4.1, 2.6 to 4.4, and 4.4 to 7.4, respectively. The MCID derived from the value of one SEM was 3.3 for the sensory subscale, 3.5 for the motor subscale, and 7.7 for the autonomic subscale (Table 5).

Altogether, the calculated MCID ranges for the sensory, motor, and autonomic subscales were found to overlap between T2 and T3. The acceptable range for sensory subscale and motor subscale was 2.5–5.9 and 2.6–5.0, respectively. As the mean change score for autonomic subscale between T1 and T3 was not statistically significant (Table 3), the MCID for this subscale could not be established from the distribution-based approach.

Estimation of the overall MCID

Based on the study, the MCID derived using distribution-based method for the QLQ-CIPN20 sensory subscale was 2.5–5.9 and for motor subscale was 2.6–5.0. The MCIDs derived from the anchor-based analysis for sensory, motor, and autonomic subscales at T2 and T3 were excluded as they were found to be either inconsistent or not statistically significant.

Discussion

To our knowledge, this is the first study to establish the MCID of EORTC QLQ-CIPN20. We determine the MCID based on the neuropathic symptoms that occur at second cycle of chemotherapy as well as 12-month follow-up after chemotherapy initiation. Based on the distribution-based approach, the severity of symptoms at both timepoints was found to be similar. This finding may indicate that the clinically relevant changes can be captured at the early stage of chemotherapy (second cycle) for calculation of the MCID so that appropriate interventions can be made based on clinically relevant neurotoxicity, which include dose modification or therapy alteration. Through our findings, we ascertain that an increase between 2.5 and 5.9 points on the QLQ-CIPN20 sensory subscale and 2.6 to 5.0 points on the QLQ-CIPN20 motor subscale are considered to be the smallest clinically important change. This is important as this would also suggest that increase of such scores may require active interventions by clinicians to manage the neuropathy. The outcome of the study was within our expectations as taxane- and platinum-based chemotherapy received by the cancer patients (Table 1) are known to cause peripheral neuropathy [30, 31]. Unfortunately, using the anchor-based analysis, we were unable to establish the MCID for the autonomic subscale as the mean change at T2 and T3 was not statistically significant (Table 4) to merit consideration. In addition, the mean change between T1 and T3 for the autonomic subscale was found to be statistically insignificant (Table 3). Therefore, the MCID for this subscale could not be established using distribution-based approach.

For PRO tools, there is a rule of thumb that a change of approximately 10% of the total score can be considered as clinically significant [32]. In this study, we observed that a change of sensory subscale by 6.9% to 16.4% of the total score and a change of the motor subscale by 8.1% to 15.6% of the total score of QLQ-CIPN20 are being considered as clinically important. It can be interpreted that patients are more sensitive with the onset of their sensory symptoms, which as a result, a smaller percentage change of the total score was classified as clinically significant as compared to the percentage change of the motor subscale. Recently, PRO tools have been increasingly incorporated in clinical setting as they are inferred to influence the treatment process and improve outcome of care [33, 34]. Participants recruited in our study are a representation of the patients that are encountered in our clinical practice based on the treatment and dose received for their chemotherapy. Therefore, the established MCID for sensory and motor subscales of QLQ-CIPN 20 in this study can be of a useful tool in both research and clinical settings to assist with clinical care.

Using QLQ-CIPN20, it is also recognized that patients experienced more sensory CIPN symptoms as compared to motor CIPN symptoms. When we examine carefully on the symptoms that are assessed under the sensory subscales of QLQ-CIPN20, it examines how neuropathic symptoms impact physical activity of daily living, which include whether one is having (1) tingling, numbness, or burning pain in hands or feet; (2) problem standing or walking; (3) difficulty distinguishing hot and cold water; and (4) difficulty hearing [19]. As these symptoms could create a lot of negative impact to patients when they occur, this would rationalize why patients experiencing any slight bit of these sensory symptoms would consider those symptoms as clinically important. However, it is important to note that definitions of sensory neuropathy have not been consistent across the literature. For example, the National Institute of Neurological Diseases provides a definition on peripheral neuropathy that is distinctly different from QLQ-CIPN20 [35], and they identify sensory nerve damage as poor coordination of complex movements including walking or fastening

Table 4 Anchor-based approach to estimate the MCID of EORTC QLQ-CIPN20 at (i) T2 and (ii) T3

T2 (3 weeks after baseline)			
	Improved by at least one category[a]	No change	Deterioration by at least one category[a]
Ntx-subscale	$n = 3$	$n = 210$	$n = 15$
QLQ-CIPN20-sensory subscale			
Mean change score (95% CI)	− 4.9 (− 15.7 to 5.7)	1.3 (0.7 to 2.0)	4.9 (1.3 to 8.5)
Effect size	0.66	0.18	0.66
QLQ-CIPN20-motor subscale			
Mean change score (95% CI)	− 9.5 (− 40.8 to 21.8)	− 0.0 (− 0.7 to 0.6)	1.6 (− 1.7 to 4.8)
Effect size	1.42	0	0.24
QLQ-CIPN20-autonomic subscale			
Mean change score (95% CI)	− 5.6 (− 29.5 to 18.3)	− 0.2 (− 1.4 to 1.1)	6.7 (− 1.0 to 14.3)
Effect size	0.42	0.01	0.50
T3 (12 months after baseline)			
	Improved by at least one category[a]	No change	Deterioration by at least one category[a]
Ntx subscale	$n = 5$	$n = 132$	$n = 9$
QLQ-CIPN20-sensory subscale			
Mean change score (95% CI)	− 5.2 (− 10.4 to 0.06)	0.8 (0.03 to 1.6)	13.6 (3.2 to 24)
Effect size	1.04	0.16	2.72
QLQ-CIPN20-motor subscale			
Mean change score (95% CI)	− 7.6 (− 16.6 to 1.3)	0.5 (− 0.6 to 1.5)	4.2 (1.4 to 7.0)
Effect size	1.27	0.08	0.70
QLQ-CIPN20 autonomic subscale			
Mean change score (95% CI)	− 13.3 (− 31 to 4.0)	− 1.3 (− 3.2 to 0.7)	5.6 (− 5.5 to 16.7)
Effect size	0.98	0.10	0.41

Timepoint chosen: T2 and T3

[a] One category refers to a 3.3 to 4.4 point change in Ntx subscale scores [20]

Assumption: MCID for Ntx subscale is 3.3 to 4.4

buttons or coordinating balances when eyes are shut. However, muscle weakness is the most commonly associated symptom with motor neuropathy, as well as other symptoms such as painful cramps and fasciculation, muscle atrophy, and decrease reflexes. Yet, these motor symptoms are being classified as sensory neuropathy symptoms using the QLQ-CIPN20. Hence, further evaluation of the appropriateness of the symptom items within the QLQ-CIPN20 scales through psychometric studies would be required.

Our study showed that the MCID ranges derived from the distribution-based approach were consistent across T2 and T3. However, this was not the case using the anchor-based approach (Table 4). In the latter approach, we were unable to establish the MCID for sensory subscale as mean change scores varied between T2 and T3 and that the effect size at T3 was too large (ES = 2.72). In addition, the mean change score for motor subscale at T2 was found to be not statistically significant. In the current study, the defined MCID of 3.3–4.4 point change for the 11-item NTX-subscale of FACT/GOG-NTX is based on the general recommendations of FACIT cancer-specific subscales (Yost and Eton 2005). As a result, this may have generated inconsistencies of the aforementioned results. Additionally, due to the small number of identified patients who experienced a deterioration ($n = 15$ for T2; $n = 9$ for T3) based on the FACT/GOG-NTX NTX-subscale, the width of confidence intervals produced were large, resulting in less precise estimates for the mean change scores of the QLQ-CIPN20 subscales between T2 and T3. The precision of the results could be improved using a larger sample size. Hence, we established the MCID using the distribution-based approach in this study. The MCID derived from the distribution-based approach in the current study is deemed

Table 5 Distribution-based approach to estimate the MCID of EORTC QLQ-CIPN20 at (i) T1 (baseline) and T2 (3 weeks after baseline, $n = 287$) and (ii) T1 (baseline) and T3 (12 months after baseline, $n = 191$)

QLQ-CIPN20-sensory subscale

T1 and T2					T1 and T3				
	SD	0.3 SD	0.5 SD	1 SEM		SD	0.3 SD	0.5 SD	1 SEM
Baseline (T1)	7.37	2.21	3.69	2.98	Baseline (T1)	5	1.50	2.50	2.02
T2	13.56	4.07	6.78	5.49	T3	10.1	3.03	5.05	4.09
Change from T1 to T2	14.23	4.27	7.12	5.76	Change from T1 to T3	9.4	2.82	4.70	3.81
Mean	11.72	3.52	5.86	4.75	Mean	8.17	2.45	4.08	3.31

[a]Reliability value used to calculate 1 SEM was 0.836

QLQ-CIPN20-motor subscale

T1 and T2					T1 and T3				
	SD	0.3 SD	0.5 SD	1 SEM		SD	0.3 SD	0.5 SD	1 SEM
Baseline (T1)	6.68	2.00	3.34	2.64	Baseline (T1)	6	1.80	3.00	2.37
T2	11.44	3.43	5.72	4.52	T3	10.2	3.06	5.10	4.03
Change from T1 to T2	11.71	3.51	5.86	4.63	Change from T1 to T3	10	3.00	5.00	3.95
Mean	9.94	2.98	4.97	3.93	Mean	8.73	2.62	4.37	3.45

[a]Reliability value used to calculate 1 SEM was 0.844

QLQ-CIPN20-autonomic subscale

T1 and T2					T1 and T3				
	SD	0.3 SD	0.5 SD	1 SEM		SD	0.3 SD	0.5 SD	1 SEM
Baseline (T1)	13.36	4.01	6.68	6.99	Baseline (T1)	13.6	4.08	6.80	7.12
T2	15.63	4.69	7.82	8.18	T3	13.8	4.14	6.90	7.22
Change from T1 to T2	15.8	4.74	7.90	8.27	Change from T1 to T3	16.8	5.04	8.40	8.79
Mean	14.93	4.48	7.47	7.81	Mean	14.73	4.42	7.37	7.71

[a]Reliability value used to calculate 1 SEM was 0.726

Timepoint chosen: T1 and T2; T1 and T3

[a] Test-retest reliability (r) value taken to calculate 1 SEM was 0.836 for sensory subscale, 0.844 for motor subscale, and 0.726 for autonomic subscale [28]

reliable as similar studies [36, 37] have shown that anchor-based and distribution-based approaches yielded similar MCID range. Currently, there is no consensus on the most appropriate method to calculate the MCID. There is literature that advocates the use of distribution-based approach, as it utilizes statistical property of a data set to establish the appropriate MCID. Both anchor- and distribution-based approaches have both been reported as viable options for computations. Therefore, in our study, we applied the FACT/GOG-NTX Ntx subscale as an external anchor that accounts for the changes in neuropathy symptoms perceived by the patient. On the contrary, the distribution-based methods allow one to examine the precision of the measurement.

We observed a moderate correlation of the Ntx-subscale with sensory and motor scales of QLQ-CIPN20. However, the correlation between the change scores of the Ntx subscale and the autonomic subscale of QLQ-CIPN20 was poor. This could be because there were only three items in the QLQ-CIPN20 instrument assessing autonomic function, and the Ntx subscale does not assess neuropathy symptoms that are presented as dizziness or blurred vision, making it a poor anchor to establish with the autonomic subscale of QLQ-CIPN20. Our finding was found to be consistent to a previous study investigating the relationship between the FACT/GOG-NTx Ntx subscale, and sensory, motor, and autonomic subscales of pin test [17]. Lavoie et al. [19] demonstrated the reliability and validity in the sensory and motor subscales of QLQ-CIPN20. However, the autonomic subscale items were found to be not aligned with symptom severity [38] and showed low item-item correlations ($r < 0.30$) [19]. Future studies would need to utilize a more specific symptom tool (such as Rotterdam Symptom Checklist) that is able to assess autonomic symptoms, which could be a better tool to assess autonomic symptoms. In addition, future prospective studies should examine the correlation between the QLQ-CIPN20/FACT/GOG-NTX score change and dose change/dose delays/regimen change, so that dose change/dose delays/regimen change-based MCID could be established for QLQ-CIPN20/FACT/GOG-NTX. Future studies can examine the impact of dose titration based on recommended MCID for QLQ-CIPN20 as proposed in our study.

There are some limitations with this study. One may also argue whether it is more appropriate to utilize the total score generated from FACT/GOG-NTX, rather than the Ntx subscale, to serve as the anchor in our anchor-based analysis. The items described in other subdomains apart from Ntx subscale possess very little relevance to peripheral neuropathy symptom; hence, it may not have been suitable to utilize the total score. However, we could not establish MCID for QLQ-CIPN20 sensory, motor, and autonomic subscales. Thus, future studies may need to identify another anchor that is more appropriate to determine the MCID of the QLQ-CIPN20 subscales. Lastly, majority of the patients are breast cancer patients receiving taxane-based chemotherapy, which may make one question the generalizability of the data.

In conclusion, this study provided a reasonable range for the MCID of EORTC QLQ-CIPN20, and the estimates can be applied as a measure to assist in the interpretation of clinical relevance in patient-reported neuropathy symptoms and sample size estimates for future studies. An increase of 2.5 to 5.9 points on the sensory subscale and an increase 2.6 to 5.0 points on the motor subscale were established as the smallest meaningful peripheral neuropathy. These established values would allow clinicians and researchers to interpret clinical significance of neuropathy in cancer patients. These current estimates should be further validated and refined by the use of larger data sets and other recommended methodological approaches and on different cancer patient groups.

Acknowledgements The authors would like to thank the participants for their contribution to this study.

Compliance with ethical standards

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

Declaration Herewith I state to have full control of all primary data and that I agree to allow the journal to review our data if requested.

Ethics statement The study was approved by the institutional review boards of each participating institution (National University Health System, Singapore; Queen Elizabeth Hospital, Hong Kong; University of Manchester, UK). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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