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Velzen, M.J.M. van; Pape, M.; Sprangers, M.A.G.; Kleef, J.J. van; Mostert, B.; Beerepoot, L.; ... ; Laarhoven, H.W.M. van

Chemotherapy-Induced Peripheral Neuropathy in Patients With Gastroesophageal Cancer

Merel J.M. van Velzen, MD[1,2]; Marieke Pape, MSc, PhD[1–3]; Mirjam A.G. Sprangers, MSc, PhD[2,4]; Jessy Joy van Kleef, MSc[1,4]; Bianca Mostert, MD, PhD[5]; Laurens V. Beerepoot, MD, PhD[6]; Marije Slingerland, MD, PhD[7]; Elske C. Gootjes, MD, PhD[8]; Ronald Hoekstra, MD, PhD[9]; Lonneke V. van de Poll-Franse, MSc, PhD[3,10,11]; Nadia Haj Mohammad, MD, PhD[12]; and Hanneke W.M. van Laarhoven, MD, PhD, PhD[1,2]

Abstract

Background: Chemotherapy for various stages of gastroesophageal cancer (GEC) is often neurotoxic. Chemotherapy-induced peripheral neuropathy (CIPN) impairs health-related quality of life (HRQoL). This study investigates the incidence and severity of CIPN and its association with HRQoL in patients with GEC. **Patients and Methods:** Patients who received chemoradiotherapy or chemotherapy for GEC were identified from the Netherlands Cancer Registry. Patient-reported data (measured using the EORTC QLQ-CIPN20 and EORTC QLQ-C30) were collected through the Prospective Observational Cohort Study of Esophageal-Gastric Cancer Patients (POCOP) at baseline and at 3, 6, 9, 12, 18, and 24 months after treatment initiation. Linear mixed effects models were constructed to assess CIPN and the correlation between CIPN and HRQoL was analyzed using Spearman's correlation. **Results:** A total of 2,135 patients were included (chemoradiotherapy: 1,593; chemotherapy with curative intent: 295; palliative chemotherapy: 247). In all 3 treatment groups, CIPN significantly increased during treatment (adjusted mean score of CIPN at 6 months: chemoradiotherapy, 8.3 [baseline: 5.5]; chemotherapy with curative intent, 16.0 [baseline: 5.6]; palliative therapy, 25.4 [baseline: 10.7]). For chemoradiotherapy, the adjusted mean score continued to increase after treatment (24 months: 11.2). For chemotherapy with curative intent and palliative therapy, the adjusted mean score of CIPN decreased after treatment but did not return to baseline values. CIPN was negatively correlated with HRQoL in all treatment groups, although significance and strength of the correlation differed over time. **Conclusions:** Because of the poor prognosis of GEC, it is essential to consider side effects of (neurotoxic) treatment. The high prevalence and association with HRQoL indicate the need for early recognition of CIPN.

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Background

In gastroesophageal cancer (GEC), systemic therapy is one of the main treatment modalities for both curative and palliative treatment.[1–3] Chemotherapy regimens almost always include platinum compounds and/or taxanes, which are known to cause acute and chronic peripheral neuropathy.[4,5] The incidence and severity of chemotherapy-induced peripheral neuropathy (CIPN) mostly depends on the cytotoxic agents used, their dose intensity, and cumulative dose.[6] The incidence of CIPN differs among chemotherapy types, varying between 10% to 20% for taxanes, 10% to 40% for carboplatin and cisplatin, and up to 80% for oxaliplatin, as reported in randomized trials.[7]

CIPN burden is most often expressed by sensory symptoms and problems (eg, tingling, numbness, and pain) but may also present as motor symptoms, such as cramping and distal weakness, or autonomic symptoms. These problems may persist or sometimes even worsen after end of treatment in up to 60% of patients.[8] Previous research in other cancer types has shown a negative association between CIPN burden and health-related quality of life (HRQoL) in both cancer survivors and patients with advanced cancer.[9] Therefore, close monitoring of CIPN is crucial to direct toward dose reductions and/or treatment discontinuation if deemed necessary by medical professionals or at patient request.

Data reported thus far have been derived from clinical trials and real-world studies, the latter mainly being performed in colorectal cancer.[10,11] Population-based data investigating CIPN in GEC are limited.[12–14] Because of the specific treatment regimens of GEC, real-world data on CIPN in this population specifically are needed to inform physicians and patients about CIPN and aid them in decision-making regarding therapy. A high prevalence of CIPN in this population can be expected, because the most often used treatment regimens in GEC contain either paclitaxel, docetaxel, carboplatin, and/or oxaliplatin.[3,15] Additionally, due to the poor prognosis of GEC, it is essential to consider side effects of treatment and their impact on HRQoL.

The aim of this study was to investigate the incidence of CIPN, its severity over time, and its association with HRQoL in a cohort of patients receiving taxane- and/or platinum-based chemoradiotherapy, chemotherapy with curative intent, or with palliative intent for GEC in a real-world setting.

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[1]Department of Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [2]Cancer Centre Amsterdam, Cancer Treatment and Quality of Life, Amsterdam, the Netherlands; [3]Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands; [4]Department of Medical Psychology, Amsterdam Public Health, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [5]Department of Medical Oncology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands; [6]Department of Medical Oncology, Elisabeth-Tweesteden Hospital, Tilburg, the Netherlands; [7]Department of Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands; [8]Department of Medical Oncology, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, the Netherlands; [9]Department of Medical Oncology, Ziekenhuisgroep Twente, Hengelo, the Netherlands; [10]Department of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, the Netherlands; [11]Department of Medical and Clinical Psychology, Center of Research on Psychological and Somatic Disorders (CoRPS), Tilburg University, Tilburg, the Netherlands; and [12]Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands.

Patients and Methods

Patients and Data Sources

Patients diagnosed with esophageal (C15.0–C15.9), gastroesophageal junction (cardia) (C16.0), or gastric cancer (C16.1–C16.9) between 2016 and 2020 who received chemotherapy were selected from the Netherlands Cancer Registry (NCR) irrespective of tumor stage, and included if they were also enrolled in the Prospective Observational Cohort Study of Esophageal-Gastric Cancer Patients (POCOP).[16] Data regarding patient characteristics, diagnosis, and (initial) treatment were routinely extracted from patients' electronic health records by data managers of the Netherlands Comprehensive Cancer Organization (IKNL). Patient-reported outcome measures (PROMs) were sent to POCOP through mail (paper) or email (electronic questionnaires), depending on patient preference. Written informed consent for POCOP was obtained for all patients, and for this specific study, approval was given by the scientific committee of the Dutch Upper GI Cancer Group.

Questionnaires were categorized based on the time between start of treatment and completion of the questionnaire. Baseline questionnaires were completed after initial diagnosis and no more than 7 days after start of treatment. All other questionnaires were categorized into 3 months (±30 days), 6 months (±30 days), 9 months (±30 days), 12 months (±30 days), 18 months (±30 days), and 24 months (±30 days) after start of treatment. Patients were excluded if they did not have at least one questionnaire in any of these timeframes, if they underwent surgical resection of the primary tumor despite having locally advanced disease (T_{4b}) or metastatic disease (M_1), or when type of systemic therapy was unknown (see Figure S1 in the supplementary materials, available online with this article). All missing questionnaires were considered missing at random.

Patients were divided into 3 groups based on type of treatment and clinical stage: (1) patients with nonmetastatic disease or only supraclavicular metastases ($cT_{all}cN_{all}cM_{0-1}$) receiving systemic therapy with concurrent radiotherapy with surgical resection (neoadjuvant chemoradiotherapy) or without resection (definitive chemoradiotherapy); (2) patients with nonmetastatic disease ($cT_{1-4a,x}cN_{all}cM_0$) receiving systemic treatment without concurrent radiotherapy irrespective of surgical resection (chemotherapy with curative intent); and (3) patients with unresectable advanced (cT4b) or synchronous metastatic disease (cM1) receiving palliative chemotherapy (palliative chemotherapy).

Patient-Reported Outcome Measures

CIPN and HRQoL were measured using the EORTC Quality of Life–Chemotherapy-Induced Peripheral Neuropathy (EORTC QLQ-CIPN20) and Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), respectively. The EORTC QLQ-CIPN20 is a 20-item validated questionnaire regarding CIPN symptoms.[17] It contains 8 items on motor symptoms (mCIPN), 9 items on sensory symptoms (sCIPN), and 3 items regarding autonomic functions (aCIPN). The EORTC QLQ-C30 is a 30-item validated questionnaire developed to assess the HRQoL of patients with cancer.[18] For association between CIPN and HRQoL, the global QoL scale was used.

Scores of the QLQ-CIPN20 and QLQ-C30 were linearly transformed to a score between 0 and 100 and missing data were imputed according to the EORTC scoring manual.[19] Higher symptom scores on the EORTC QLQ-CIPN20 and QLQ-C30 indicate a higher level of symptoms, whereas higher scores for functional scales on the QLQ-C30 (including global health status and QoL) indicate better functioning or QoL.

Statistical Analyses

Baseline characteristics were displayed in counts and percentages for patients within each treatment group. Linear mixed effect models were constructed and least square means were calculated for total CIPN, each CIPN subscale separately, and global health status/QoL to analyze and visualize neuropathy and HRQoL over time. All mixed effect models were adjusted for age, sex, number of comorbidities, diabetes, and performance status, as these are expected to be clinically associated with either CIPN or QoL. The correlation between total CIPN and global health status/QoL was assessed via nonparametric Spearman's correlation (ρ).

To investigate the course of CIPN before and after completion or discontinuation of systemic treatment, an exploratory analysis was performed for each group. A spline function was used for visual representation of the CIPN scores before and after treatment discontinuation (t=0) to allow for nonlinear fitting of the correlated data. For chemoradiotherapy and curative chemotherapy, we only looked into the first 6 months after completion of systemic treatment to minimize bias caused by patients receiving consecutive palliative treatment for metachronously metastasized disease.

All analyses were conducted using SAS 9.4 (SAS Institute Inc.).

Results

Patient Characteristics

In total, 2,135 patients were included, of whom 1,593 received chemoradiotherapy, 295 received chemotherapy with curative intent, and 247 received palliative chemotherapy (Supplementary Figure S1). Most patients in all groups had an adenocarcinoma (78%–98%; Table 1). In the chemoradiotherapy group, most patients had a primary tumor located in the esophagus (87%) and the most frequently used systemic treatment was carboplatin and paclitaxel (94%). In the systemic therapy with curative intent group, 52% of patients had a primary tumor located in the stomach and the most frequently used treatment consisted of any fluoropyrimidine (5-fluorouracil with leucovorin or capecitabine) and oxaliplatin combined with either epirubicin (EOX/EOF, 22%) or docetaxel (FLOT/DOC, 63%). In the palliative chemotherapy group, 59% of patients had a primary tumor located in the esophagus and the most frequent palliative chemotherapy was capecitabine or 5-fluorouracil plus oxaliplatin (78%). Other regimens included carboplatin plus paclitaxel (3%) and FLOT.

CIPN Over Time

Supplementary Table S1 shows the number of questionnaires available for analyses of each patient group at each time point.

In the chemoradiotherapy group, the adjusted mean score for total CIPN significantly increased over time from 5.5 at baseline to 8.3 at 6 months and further to 11.2 at 24 months ($P<.0001$; Table 2, Figure 1, Supplementary Table S2a). Similar results were seen for sCIPN, mCIPN, and aCIPN (Table 2, Figure 1). The adjusted mean score for global health status/QoL was recorded lowest at 6 months and increased again afterward.

In the chemotherapy with curative intent group, the adjusted mean score for total CIPN increased from 5.6 at baseline to 16.0 at

Table 1. Baseline Characteristics at Primary Diagnosis

	Chemoradiotherapy n (%)	Chemotherapy With Curative Intent n (%)	Palliative Chemotherapy n (%)
Total	1,593	295	247
Sex			
Male	1,261 (79)	200 (68)	190 (77)
Female	332 (21)	95 (32)	57 (23)
Age, median (IQR), y	67 (61–72)	67 (60–72)	65 (59–71)
Number of comorbidities			
0	837 (53)	150 (51)	142 (57)
1	449 (28)	95 (32)	72 (29)
≥2	231 (15)	35 (12)	22 (9)
Unknown	76 (5)	15 (5)	11 (4)
Diabetes			
No	1,352 (85)	249 (84)	216 (87)
Yes	241 (15)	46 (16)	31 (13)
WHO performance score			
0	826 (52)	158 (54)	116 (47)
1	591 (37)	97 (33)	91 (37)
≥2	47 (3)	7 (2)	16 (6)
Unknown	129 (8)	33 (11)	24 (10)
Primary tumor site			
Esophagus	1,381 (87)	31 (11)	146 (59)
Gastroesophageal junction	150 (9)	111 (38)	46 (19)
Stomach	62 (4)	153 (52)	55 (22)
Histology			
Adenocarcinoma	1,243 (78)	288 (98)	235 (95)
Squamous cell carcinoma	350 (22)	7 (2)	12 (5)
Differentiation grade			
Well/Moderate	728 (46)	92 (31)	68 (28)
Poorly/Undifferentiated	532 (33)	153 (52)	86 (35)
Unknown	333 (21)	50 (17)	93 (38)
Clinical T stage			
cT1	16 (1)	1 (0)	1 (0)
cT2	449 (28)	64 (22)	47 (19)
cT3	1,028 (65)	198 (67)	137 (55)
cT4	45 (3)	13 (4)	20 (8)
cTX	55 (3)	19 (6)	42 (17)
Clinical N stage			
cN0	662 (42)	128 (43)	41 (17)
cN1	589 (37)	96 (33)	65 (26)
cN2	298 (19)	52 (18)	103 (42)
cN3	26 (2)	16 (5)	30 (12)
cNX	18 (1)	3 (1)	8 (3)
Clinical M stage			
0	1,541 (97)	295 (100)	4 (2)
1	52 (3)	0 (0)	243 (98)
Surgery			
No	477 (30)	31 (11)	247 (100)
Yes	1,116 (70)	264 (89)	0 (0)

(*continued on next page*)

6 months and decreased to 12.4 at 24 months, remaining significantly elevated compared with baseline ($P<.001$; Table 2, Figure 1, Supplementary Table S2b). For sCIPN, mCIPN, and aCIPN, the highest scores were also reported at 6 months and remained elevated from baseline. Adjusted mean score for QoL was lowest at 6 months, increasing to higher than baseline at 9 months until the end of follow up at 24 months (Table 2, Figure 1).

For the palliative chemotherapy group, the adjusted mean score for total CIPN was 10.7 at baseline and increased to a maximum of 26.5 at 9 months, and remained elevated compared with baseline at 12 months (23.5) ($P<.0001$; Table 2, Figure 1, Supplementary Table S2c). Adjusted mean score was highest at 9 months for sCIPN (24.8) and mCIPN (31.8) and at 6 months for aCIPN (11.4). Adjusted mean scores for QoL were lower in the palliative chemotherapy group compared with the other 2 groups, with a baseline score of 52.8, which decreased to a minimum of 47.5 at 9 months (Table 2, Figure 1).

Exploratory analysis of CIPN scores before and after discontinuation of treatment showed that CIPN continued to increase for at least 6 months after completion of chemoradiotherapy.

Table 1 (cont.). Baseline Characteristics at Primary Diagnosis

	Chemoradiotherapy n (%)	Chemotherapy With Curative Intent n (%)	Palliative Chemotherapy n (%)
Number of metastatic sites			
0	1,541 (97)	295 (100)	4 (2)
1	47 (3)	0 (0)	153 (62)
2	5 (0)	0 (0)	67 (27)
≥3	0 (0)	0 (0)	23 (9)
Chemotherapy regimen			
Monotherapy or targeted therapy only	7 (0)	2 (1)	12 (5)
Doublet therapy	1,548 (97)	25 (8)	216 (87)
Triplet therapy	38 (2)	268 (91)	19 (8)
FLOT/DOC		186	
ECC/EOX/EOF		82	
Platinum therapy			
No platinum	5 (0)	3 (1)	12 (5)
Oxaliplatin	44 (3)	262 (89)	213 (86)
Cisplatin	8 (1)	18 (6)	11 (4)
Carboplatin	1,536 (96)	12 (4)	11 (4)
Taxane therapy			
No taxanes	25 (2)	95 (32)	225 (91)
Paclitaxel	1,530 (96)	13 (4)	13 (5)
Docetaxel	38 (2)	187 (63)	9 (4)

Abbreviations: DOC, docetaxel/oxaliplatin/capecitabine; ECC, epirubicin/cisplatin/capecitabine; EOF, epirubicin/oxaliplatin/5-fluorouracil; EOX, epirubicin/oxaliplatin/capecitabine; FLOT, 5-fluorouracil/leucovorin/oxaliplatin/docetaxel.

For curative chemotherapy, CIPN stabilized after completion of adjuvant chemotherapy for at least 6 months, and for palliative chemotherapy, CIPN stabilized and remained high for the remainder of the time analyzed (21 months after treatment discontinuation; Supplementary Figure 1).

Information on possibly interfering treatment after curative or first-line treatment is shown in Supplementary Table S3. Findings showed that only 12% to 17% of all patients in the chemoradiotherapy and curative chemotherapy groups, respectively, had received possibly neurotoxic treatment (including palliative chemotherapy or chemoradiotherapy) in the case of a recurrence, and for synchronous metastatic disease 47% of patients had received chemotherapy or chemoradiotherapy beyond first line treatment.

CIPN and QoL

CIPN was negatively correlated with QoL in all 3 treatment groups, although significance and strength of the correlation coefficients differed over time (Figure 2). In chemoradiotherapy group, the

Table 2. Adjusted Mean Scores of CIPN and QoL From Linear Mixed Models

	Baseline	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Chemoradiotherapy							
Total CIPN	5.47 (0.63)	7.61 (0.64)***	8.30 (0.65)***	9.06 (0.67)***	9.36 (0.69)***	10.14 (0.70)***	11.21 (0.79)***
sCIPN	4.72 (0.65)	6.42 (0.67)***	7.20 (0.69)***	8.09 (0.71)***	8.66 (0.73)***	9.72 (0.77)***	10.74 (0.85)***
mCIPN	5.73 (0.77)	7.62 (0.79)***	8.39 (0.80)***	9.25 (0.83)***	9.18 (0.83)***	9.66 (0.84)***	10.95 (0.95)***
aCIPN	7.78 (1.07)	12.85 (1.14)***	12.59 (1.13)***	12.73 (1.16)***	12.74 (1.16)***	12.34 (1.16)***	12.87 (1.23)***
QoL	71.10 (1.55)	68.60 (1.58)**	67.58 (1.56)***	70.42 (1.59)	70.25 (1.60)	70.85 (1.60)	70.42 (1.68)
Chemotherapy with curative intent							
Total CIPN	5.59 (1.72)	13.81 (1.85)***	15.97 (1.96)***	14.70 (1.92)***	13.55 (1.97)***	12.94 (1.96)***	12.41 (1.90)**
sCIPN	4.79 (2.18)	14.95 (2.33)***	17.92 (2.52)***	16.86 (2.45)***	14.59 (2.52)***	13.68 (2.48)***	12.78 (2.44)***
mCIPN	5.50 (1.90)	12.24 (2.02)***	13.78 (2.09)***	12.51 (2.07)***	12.04 (2.08)***	11.69 (2.07)***	11.61 (2.10)***
aCIPN	10.51 (3.02)	14.43 (2.90)*	15.62 (3.00)*	12.91 (2.98)	12.63 (3.03)	12.70 (2.98)	11.60 (2.99)
QoL	69.49 (3.78)	67.99 (3.73)	63.66 (3.74)*	71.96 (3.74)	72.51 (3.71)*	73.35 (3.84)*	72.18 (3.91)
Palliative chemotherapy							
Total CIPN	10.72 (1.56)	19.91 (1.78)***	25.35 (1.92)***	26.54 (1.96)***	23.51 (2.07)***		
sCIPN	4.73 (1.80)	16.43 (2.16)***	23.37 (2.27)***	24.83 (2.44)***	22.66 (2.52)***		
mCIPN	20.08 (1.98)	26.88 (2.13)***	31.85 (2.33)***	31.81 (2.29)***	29.62 (2.36)***		
aCIPN	4.86 (2.68)	10.51 (2.99)**	11.37 (2.90)***	9.48 (2.89)**	10.69 (3.22)*		
QoL	52.81 (4.69)	51.24 (4.84)	51.10 (4.84)	47.53 (4.94)*	51.74 (5.04)		

All scores were corrected for age, sex, number of comorbidities, diabetes, and performance status. No adjusted means were calculated for the palliative chemotherapy group at 18 and 24 months due to the low number of questionnaires.
Abbreviations: aCIPN, CIPN autonomic scale; CIPN, chemotherapy-induced peripheral neuropathy; EORTC QLQ-30, EORTC Quality of Life Questionnaire-Core 30; mCIPN, CIPN motor scale; sCIPN, CIPN sensory scale; QoL, global health status/QoL according to EORTC QLQ-C30.
Significant changes compared with baseline: *$P<.05$; **$P<.001$; ***$P<.0001$.

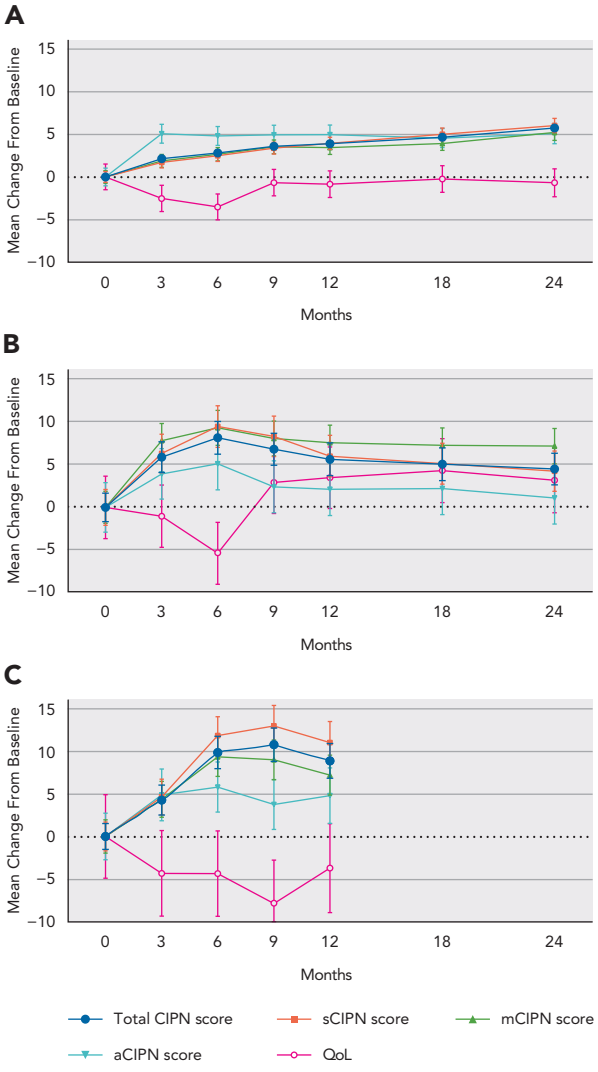

Figure 1. Adjusted mean scores from the linear mixed models for CIPN and QoL compared with baseline for patients treated with **(A)** chemoradiotherapy, **(B)** chemotherapy with curative intent, and **(C)** palliative chemotherapy[a]. Abbreviations: aCIPN, CIPN autonomic scale; CIPN, chemotherapy-induced peripheral neuropathy; EORTC QLQ-30, EORTC Quality of Life Questionnaire-Core 30; HRQoL, health-related quality of life; mCIPN, CIPN motor scale; QoL, global health status/HRQoL according to EORTC QLQ-C30; sCIPN, CIPN sensory scale.
[a]No adjusted means were calculated for 18 and 24 months due to the low number of responses for these time points.

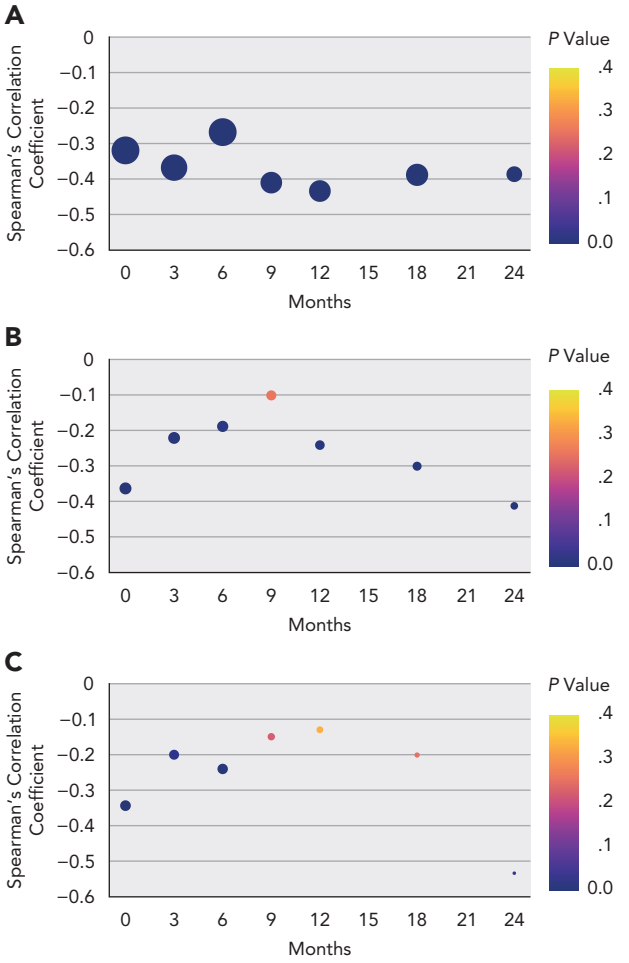

Figure 2. Correlation between total CIPN and global health status/HRQoL as determined with nonparametric Spearman's correlation for patients treated with **(A)** chemoradiotherapy, **(B)** chemotherapy with curative intent, and **(C)** palliative chemotherapy. Size of the circles represent the number of patients used to calculate the correlation coefficient, and the color of the circles represent *P* value. Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; HRQoL, health-related quality of life.

observed correlation coefficient ranged from $\rho = -0.27$ (at 6 months) to $\rho = -0.43$ (at 12 months). In chemotherapy with curative intent, the observed correlation coefficient ranged from $\rho = -0.10$ (at 9 months) to $\rho = -0.41$ (at 24 months). In the palliative chemotherapy group, numbers were small, especially for time points after 6 months and correlation coefficient between CIPN and QoL ranged from $\rho = -0.13$ (at 12 months) to $\rho = -0.53$ (at 24 months).

Discussion

Our results showed that CIPN increased during systemic treatment of GEC and remained higher than pretreatment neuropathy scores in patients receiving chemoradiotherapy, chemotherapy with curative intent, or palliative chemotherapy. Although increase in CIPN per 3-month time period could be subtle, in the perioperative and palliative chemotherapy group the maximum increase compared with baseline is clinically relevant according to the available literature.[20,21] These findings are in line with expectations considering the chemotherapeutic agents used, such as oxaliplatin and other platinum compounds.[7,8,10,11] Interpretation of the clinical relevance of neuropathy in patients receiving chemoradiotherapy varied based on the definition applied. Previously, the clinically relevant thresholds ranged between 2.5 to 5.9 (for the sensory scale), 2.6 to 5.0 (for the motor scale), and 6.2 to 8.4 (for overall CIPN).[20,21]

Nevertheless, the relatively high burden of CIPN in chemoradiotherapy is remarkable. Considering that these patients were treated according to the CROSS regimen, a rather low dose of paclitaxel (50 mg/m^2) and carboplatin (area under the curve [AUC], 2 mg/mL/min) is used, mainly because of the radiosensitizing effect.[3] In the CROSS trial, neurotoxicity of any grade was 15%, and 6 weeks after end of treatment CIPN scores had returned to baseline levels.[3,22] The differences between our study and the data

from the CROSS trial might be the result of differences in study design (ie, real-world vs randomized controlled trial), but can also probably be attributed in part to neurotoxic palliative treatment of patients with recurrent disease in our study.

In our data, the largest changes from baseline CIPN were observed in the palliative chemotherapy group after 9 months, when lowest QoL was also reported. At this time point, the correlation between CIPN and QoL was relatively weak, suggesting that other factors affected the QoL scores, such as potential other side effects of treatment or disease progression. However, despite the low number of patients included in analyses at later time points, the correlation between CIPN and QoL increased at 24 months, indicating that in the long-term, CIPN becomes a more important determinant for QoL. This could also be observed for patients treated with chemoradiotherapy or chemotherapy with curative intent. QoL for these patients was lowest at 6 months after start of treatment, when the correlation between CIPN and QoL was relatively weak. When considering treatment regimens, patients treated with chemoradiotherapy or chemotherapy with curative intent are probably still recovering from surgery or are being treated with postoperative chemotherapy at that time point.[1,3] The observational nature of our study complicates the establishment of definitive conclusions regarding the causality of changes in QoL and CIPN.

According to Beijers et al,[8] the most frequently reported problems relating to CIPN are sensory symptoms in patients treated with oxaliplatin or taxanes. We also observed the highest scores for sensory CIPN in the palliative chemotherapy group, but motor problems were scored higher in the chemotherapy with curative intent group. In the chemoradiotherapy group, autonomic CIPN scores were initially reported highest, possibly because of interference by other autonomic side effects of chemoradiotherapy,[23] but over time differences between the autonomic, motor, and sensory CIPN scores in this group became very small (<2.5). To recognize CIPN, it is important to look for symptoms in all 3 scales to adequately appraise the severity of neurotoxicity.

During treatment, a rapid increase is observed in CIPN scores among patients receiving palliative chemotherapy and the scores do not decrease after discontinuation of treatment. Early recognition of neuropathy and appropriate adjustment of treatment is warranted to reduce CIPN. Careful consideration is necessary when weighing the possible negative impact of CIPN and disease-related symptoms when making choices regarding treatment strategies. This is particularly important considering the poor prognosis of these patients.

Upcoming treatments for GEC, such as targeted therapy and immunotherapy, were found to lead to no or minimal neuropathy.[24–26] However, it is unlikely that the use of conventional (and often neurotoxic) chemotherapy will be abandoned in the near future in this population. Therefore, awareness and prevention of CIPN remain of high importance.

Thus far, treatments to prevent CIPN (eg, calcium/magnesium preparations) have not proven to be useful, and only limiting exposure to neurotoxic agents has been shown to prevent CIPN.[27] Cryotherapy during oxaliplatin infusion might reduce some neuropathy symptoms, but further investigation of this treatment is necessary to determine whether cryotherapy in this population is feasible and truly prevents or reduces CIPN.[28] For treatment of already established CIPN, duloxetine or pregabalin might be useful in reducing CIPN resulting in neuropathic pain, but the magnitude of benefit is modest.[29,30]

A strength of this study is the inclusion of a large number of patients, considering the population-based nature of the study and the difficulty of gathering patient-reported data, especially in a group as vulnerable as patients with GEC. However, analyses at 18 and 24 months since start of initial treatment could not be performed due to limited available data, which reflects the poor prognosis of these patients. Moreover, it is not entirely possible to eliminate sampling bias, because patients with a higher burden of neuropathy may be more inclined to return questionnaires, and those experiencing positive outcomes may stay on treatment longer. In the NCR, information on physical assessment of patients regarding peripheral neuropathy during or after treatment was not available, which was a limitation of this study. However, because of the relatively weak correlation between physical assessment of CIPN and patient-reported impact of CIPN, greater value was placed on patient-reported data.[31]

Our study has several other limitations. Unfortunately, data in the NCR are sometimes limited to initial diagnosis, and information on treatment after recurrence or on further treatment lines was not available for the full population. Only 12% to 17% of patients received systemic therapy for disease recurrence after initial curative treatment and 47% of patients received second-line treatment after experiencing disease progression during first-line palliative treatment. Although the number of patients receiving platinum therapy after initial curative treatment is small (7%–16%), possible interference of neurotoxic treatment after initial treatment could not be completely eliminated. Furthermore, uniform data on doses received by individual patients were not available, and therefore we were unable to explore associations between cumulative dose and CIPN.

Conclusions

Given the high prevalence of CIPN in both curative treatment and palliative treatment in GEC, physicians and patients should be aware of the often long-lasting neurotoxic effects of treatment and should constantly seek the balance between optimal tumor-directed treatment, ensuring the highest chance of cure or minimal disease-specific symptoms and best ability to make early treatment modifications, aiming for minimal side effects (eg, neuropathy).

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Correspondence: Merel J.M. van Velzen, MD, Department of Oncology, Amsterdam UMC, VUmc, De Boelelaan 1118, 1081 HV, Amsterdam ZH 3A44, the Netherlands. Email: m.vanvelzen1@amsterdamumc.nl

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