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Course of chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer patients: A longitudinal study

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HIGHLIGHTS

- Sensory neuropathy symptoms were stable over time.
- Motor neuropathy symptoms improved at 1 year.
- A high level of sensory neuropathy was associated with worse functioning.
- A high motor neuropathy level was associated with worse HRQoL.

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ABSTRACT

Objective. Chemotherapy-induced peripheral neuropathy (CIPN) presents itself as sensory peripheral neuropathy (SPN) or motor peripheral neuropathy (MPN). Our aim was to examine the course of SPN and MPN, and their impact on health-related quality of life (HRQoL) among ovarian cancer patients.

Methods. All newly diagnosed ovarian cancer patients from twelve hospitals in the South of the Netherlands were eligible for participation. Patients (N = 174) completed questions on CIPN (EORTC QLQ-OV28) and HRQoL (EORTC QLQ-C30) after initial treatment and at 6, 12, and 24 months (response rates were 70%, 71%, 58%, and 43% respectively).

Results. Generalized linear mixed models showed that among chemotherapy-treated patients (N = 98), SPN levels were stable over time. For MPN, symptoms significantly improved at 12 months. At 2 years, 13% still reported high SPN. Also, 11% still reported high MPN. Regarding HRQoL, patients with high SPN reported a worse physical, role, emotional, social, and cognitive functioning compared to those with low SPN. Moreover, those who changed from low to high SPN over time worsened on physical functioning. For MPN, a worse global quality of life and a worse functioning was reported among patients with high MPN. Also, those who changed from low to high MPN over time worsened on global quality of life and on physical, role, social, and cognitive functioning.

Conclusions. Among chemotherapy-treated ovarian cancer patients, SPN levels were stable over time. In contrast, MPN symptoms significantly improved at 12 months. These symptoms seriously impacted HRQoL. Future studies should examine the impact of different treatment decisions and alterations on CIPN, so recommendations can be made to reduce CIPN (prevalence).

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1. Introduction

Ovarian cancer was one of the first solid tumors for which effective chemotherapy became available with the introduction of cisplatin in 1978. The addition of paclitaxel to the standard chemotherapy regime in 1994 improved survival rates [1–3]. Unfortunately, chemotherapy-induced peripheral neuropathy (CIPN), one of the most life-affecting side effects of chemotherapy, has become a major concern. CIPN interferes with optimal cancer treatment, as it is often needed to reduce chemotherapy doses and delay treatment and it may even lead to premature cessation of treatment. Unfortunately, there is currently no well-accepted treatment or prevention strategy against CIPN [4].

CIPN can present as sensory peripheral neuropathy (SPN) (i.e. numbness, tingling, cramps and pain in the fingers, hands, toes, and feet) and motor peripheral neuropathy (MPN) (i.e. weakness, muscle wasting, cramps or fasciculation) [5]. These symptoms can cause problems with regular daily activities, such as buttoning a shirt or opening a bottle, but also with walking or driving [6,7].

While symptoms of CIPN often reverse or improve in the first few months after treatment, a significant proportion of cancer patients experience chronic CIPN. Also, CIPN symptoms can develop years after completion of chemotherapy treatment [8–11].

Given the serious limitations in daily functioning that accompany CIPN, it could also have a negative impact on health-related quality of life (HRQoL) [8,11–14]. In ovarian cancer, three cross-sectional studies and one longitudinal study have examined the relationship between CIPN and HRQoL, with mixed findings [11,13,15,16]. Also, no longitudinal study has examined the course of CIPN over time and its impact on HRQoL after treatment has ended.

Understanding the impact of CIPN can help inform both clinicians and patients about the possible side effects of cancer treatment. As the symptoms of SPN and MPN are distinctly different from one other, they could have a different course as well as different effects on HRQoL. Therefore, this study aims to prospectively assess the course of SPN and MPN and their relationship with HRQoL among ovarian cancer patients up to 2 years after diagnosis. We hypothesize that both SPN and MPN will show either a stable course or a small decline after 6 months among chemotherapy-treated patients, while we expect both courses to be stable among those treated without chemotherapy. Furthermore, we expect that both SPN and MPN will be related to a worse HRQoL.

2. Methods

2.1. Setting and participants

This study is a secondary analysis of the ROGY Care trial; a longitudinal, pragmatic cluster-randomized trial among patients with gynecological cancer, aimed to gain insight in the effect of an automatically generated Survivorship Care Plan (SCP) on patient- and health care provider-reported outcomes [17]. Twelve hospitals in the South of the Netherlands were randomly assigned to either “usual care” or “SCP care”, in which patients received a SCP. All patients newly diagnosed with ovarian cancer and endometrial cancer as a primary tumor between April 2011 and March 2014 were eligible for participation. Patient exclusion criteria (i.e., borderline ovarian cancer, undergoing palliative care, or unable to complete a Dutch questionnaire) were minimal to maximize generalizability [18]. For this study, we only selected ovarian cancer patients. We included those treated with and without chemotherapy as previous studies have shown that CIPN-like symptoms were already present in those who did not (yet) receive chemotherapy [19,20]. The ROGY Care trial was centrally approved by a Medical Research Ethics Committee, as well as by each participating center.

2.2. Data collection

Shortly after initial treatment, all eligible patients were invited to participate in the study via a letter with informed consent form and the first questionnaire that were send by their own gynecologist [21]. For this analyses we used outcomes assessed at baseline (T1) and at 6 (T2), 12 (T3), and 24 months (T5).

2.3. Sociodemographic and clinical characteristics

Patients' sociodemographic (i.e., age and socioeconomic status) and clinical (e.g., cancer type, FIGO stage, date of diagnosis) data were available from the Netherlands Cancer Registry (NCR), which routinely collects data on newly diagnosed cancer patients in all hospitals in the Netherlands [21]. Other sociodemographic data (e.g., partner status, educational level, and employment status) were assessed with the first questionnaire. Comorbidity was assessed with the adapted Self-administered comorbidity questionnaire (SCQ) [22]. Data on the presence of a recurrence were retrospectively extracted from the medical records two years after completion of inclusion of the trial.

2.4. Health-related quality of life

The EORTC QLQ-C30 (Version 3.0) was used to assess HRQoL. In this study, only the five functioning scales and the global quality of life scale were used. Items are answered on a 4-point Likert scale ranging from

Table 1
Sociodemographic and clinical characteristics at T1 of ovarian cancer patients who completed at least two questionnaires, stratified by chemotherapy.

	Chemotherapy N = 98 (80%)	No chemotherapy N = 25 (20%)	p-Value
Age (mean, SD)	64.8 (9.7)	59.6 (11.8)	**0.02**
Partner (yes)	75 (77%)	16 (67%)	0.32
Educational level[a]			0.23
Low	15 (16%)	1 (4%)	
Medium	61 (63%)	15 (63%)	
High	21 (22%)	8 (33%)	
Socio-economic status			0.82
Low	15 (17%)	5 (22%)	
Medium	33 (38%)	9 (39%)	
High	40 (46%)	9 (39%)	
Employment (yes)	25 (26%)	11 (46%)	0.05
ROGY Condition			0.55
Care as usual	33 (34%)	15 (60%)	
Intervention	65 (66%)	10 (40%)	
FIGO stage at diagnosis			<**0.001**
1	13 (14%)	24 (96%)	
2	12 (13%)	1 (4%)	
3	51 (53%)	–	
4	20 (21%)	–	
Surgical treatment	91 (93%)	25 (100%)	0.34
Number of comorbidities			0.75
None	25 (26%)	5 (21%)	
One	29 (30%)	9 (38%)	
Two or more	43 (44%)	10 (42%)	
Comorbidities associated with PN[b]			
Osteoarthritis	25 (33%)	8 (44%)	0.36
Rheumatoid arthritis	12 (17%)	4 (24%)	0.51
Diabetes mellitus	19 (26%)	5 (28%)	0.99
CIPN (Mean, SD)[c]	40.3 (30.8)	10.2 (16.0)	<**0.001**
Sensory neuropathy (Mean, SD)	41.3 (37.5)	7.6 (17.0)	<**0.001**
Motor neuropathy (Mean, SD)	38.1 (32.4)	15.3 (21.9)	<**0.001**

Variables may deviate from 100% due to rounding off.
SD standard deviation. Bold p-values indicate statistically significance.
[a] Education: low (no or primary school); medium (lower general secondary education or vocational training); high (pre-university education, high vocational training, university).
[b] Most frequent comorbidities associated with chemotherapy-induced peripheral neuropathy.
[c] Total score of the peripheral neuropathy scale of the EORTC QLQ-OV28.

(1) *not at all* to (4) *very much*, except the global quality of life items which are answered on a seven-point Likert scale ranging from (1) *very poor* to (7) *excellent*. Scores were linearly transformed to a 0–100 scale [23]. Higher scores indicate a better HRQoL.

2.5. Chemotherapy-induced peripheral neuropathy

CIPN was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life, Ovarian cancer module (EORTC QLQ-OV28) [24]. The peripheral neuropathy scale consists of three items: 'Have you had tingling hands or feet?', 'Have you had numbness in your fingers or toes', and 'Have you felt weak in your arms or legs?'. The questions were framed as 'during the past week…'.

Response scales of the items range from (1) *not at all* to (4) *very much*. For this study, two scales were formed: 1) the SPN scale, using the first two items, and 2) the MPN scale, using the last item. Scores were linearly transformed to a 0–100 scale [23]. Higher scores indicate more symptoms.

As we expect that the impact of CIPN on HRQoL will be strongest among those with the most CIPN symptoms, SPN and MPN were dichotomized into: 1) high level of SPN/MPN and 2) low level of SPN/MPN. Patients were allocated to the category 'high level of SPN' if they answered at least one of the two SPN items with *very much*, otherwise they were allocated to the 'low level of SPN' group. A different cut-off was used for MPN, as MPN symptoms were not as prevalent in our sample. Therefore, patients were allocated to the "high level of MPN" group if they answered the MPN item with *quite a bit* or *very much*, while those who answered *not at all* or *a little* were categorized into the 'low level of MPN' group. Finally, to examine SPN levels over time, patients were divided into three groups: 1) never high SPN, 2) fluctuating SPN, and 3) always high SPN. The same was done for MPN.

2.6. Statistical analyses

Sociodemographic and clinical characteristics at T1 of patients who completed only one questionnaire versus those who completed two or more questionnaires were compared with independent samples *t*-tests (or Welch's *t*-test in case of unequal group variances) for continuous and chi-square tests (or Fisher's exact tests in case of sparse contingency tables) for categorical characteristics. All other analyses are based on patients who completed at least two questionnaires. First, sociodemographic and clinical characteristics at T1 of patients treated with or without chemotherapy were compared using *t*-tests and chi-square or Fisher's exact analyses. Second, prevalence rates of high SPN/MPN levels at all time points were compared using chi-square tests. Moreover, differences in HRQoL between patients according to the stability of their SPN or MPN levels (never high SPN/MPN; fluctuating SPN/MPN; always high SPN/MPN) were determined by ANOVAs at each time point, with post-hoc comparisons (Bonferroni correction).

The course of CIPN, for SPN and MPN separately, was examined using generalized linear mixed models (GLMM) with the use of maximum likelihood estimation and an unstructured covariance matrix with a 2-level structure ((i.e., repeated time points [lower level], patients [higher level]). Time was analyzed as a regular categorical predictor with four levels (i.e., four time points). GLMM includes all available data for each participant under the assumption that any missing values are missing at random. Confounding background variables known or expected to impact CIPN were also included: age, diabetes mellitus, osteoarthritis, rheumatoid arthritis, and ROGY condition (SCP care or care as usual). Differences in SPN and MPN symptoms between patients with or without chemotherapy were determined similarly, but without time as a predictor.

To examine the between-patients and within-patients effects of SPN or MPN on HRQoL, GLMM with random intercepts were conducted

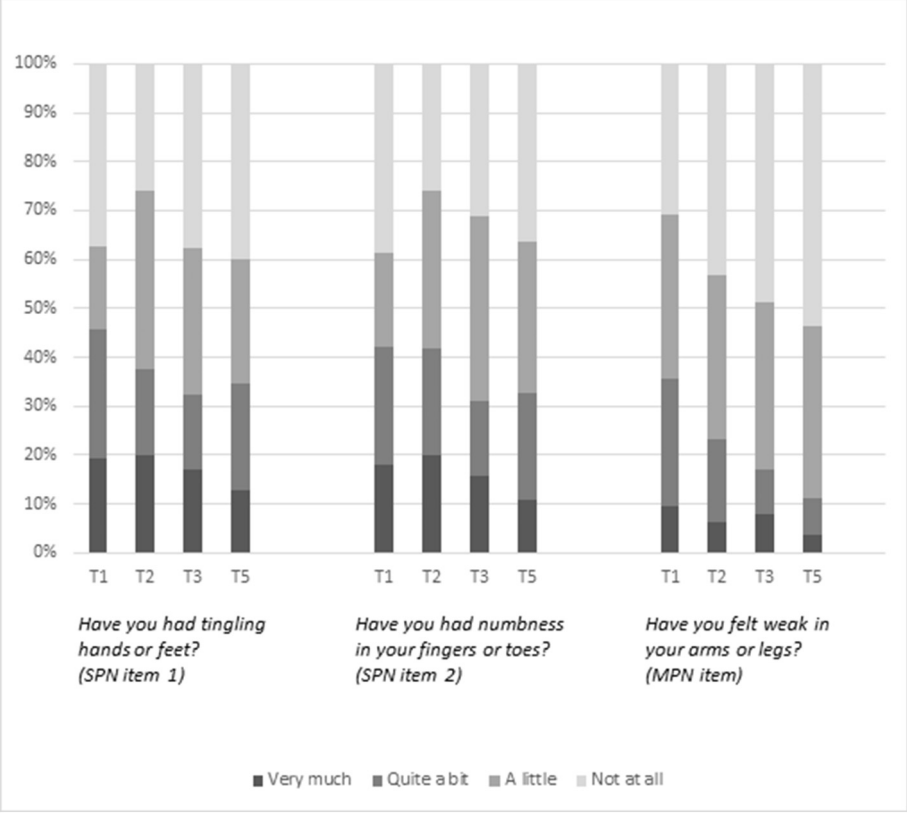

Fig. 1. Responses (%) on the sensory and motor peripheral neuropathy items that were reported during the past week among patients who were treated with chemotherapy and who completed at least two questionnaires (N = 98). The percentages reflect patients who answered: "not at all", "a little", "quite a bit" or "very much" on the particular item. *SPN* sensory peripheral neuropathy; *MPN* motor peripheral neuropathy T1, baseline; T2, 6 months; T3, 12 months; T5, 24 months

among chemotherapy-treated patients. To examine these two effects, either the two SPN or MPN variables (i.e., between-patients variable and within-patients variable) were included in the models. The between-patients effect is based on the difference between a patients' average SPN/MPN score, and the average of the total group, while the within-patients effect is based on the difference between a patients' SPN/MPN level at one time point and that patients' average SPN/MPN level across all time points. In the analyses, SPN and MPN were included as a dichotomous variable (high level vs. low level of SPN/MPN). Both models were adjusted for age, FIGO stage, education, ROGY condition, diabetes mellitus, osteoarthritis, and rheumatoid arthritis.

For all GLMM analyses, sociodemographic and clinical characteristics were analyzed as time-invariant predictors (i.e., baseline characteristics were used) and continuous variables were grand-mean centered for correct interpretation of all model parameters. A p value <0.05 was regarded as statistically significant. All analyses were performed using SPSS 22 (IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corps USA). Finally, clinically relevant differences were determined using guidelines by Cocks et al. [25].

3. Results

3.1. Sociodemographic and clinical characteristics

In total, 248 ovarian cancer patients were invited to the study. The questionnaire was completed by 70% (n = 174) at T1, followed by 71% (n = 124) at T2, 58% (n = 101) at T3, and 43% (n = 75) at T5. Of the non-respondents, 8 (16%) had died at T2, 13 (57%) had died at T3, and 16 (62%) had died at T3. More details on patient enrollment can be found in a previously published flow-chart [26]. Previous research found no differences between respondents and all non-respondents [26]. However, patients that were lost to follow-up did have a higher FIGO stage (p = 0.03). After selecting those with complete chemotherapy data, 166 participants were included in the analyses. Among chemotherapy-treated patients (n = 127), those who completed only one questionnaire were older compared to patients who completed two or more questionnaires. Among patients without chemotherapy treatment (n = 39), there were no differences between respondents who completed one questionnaire and those who completed two or more questionnaires. Finally, among respondents who completed at least two questionnaires, chemotherapy-treated patients were older and more often had a higher FIGO stage at diagnosis, compared to those not treated with chemotherapy (Table 1). As expected, they also had higher CIPN, SPN, and MPN scores.

Among chemotherapy-treated patients, 21% (*n* = 17) reported high levels (i.e., answered *very much*) of SPN at T1, 24% (n = 23) at T2, 18% (n = 14) at T3, and 13% (n = 7) at T5 (Fig. 1). For patients not treated with chemotherapy, 4% (n = 1) reported high SPN levels at T1, 4% (n = 1) at T2, 0% (n = 0) at T3, and 5% (n = 1) at T5. However, only the differences at T2 and T3 were significantly different compared to chemotherapy-treated patients (both p < 0.05). Regarding MPN, 36% (n = 30) of chemotherapy-treated patients reported high levels (i.e., *quite a bit* or *very much*) of MPN at T1 and this was 23% (n = 22) at T2, 17% (n = 13) at T3, and 11% (n = 6) at T5. At T1, 8% (n = 2) of patients without chemotherapy reported a high level of MPN, which is significantly less often compared to chemotherapy-treated patients (p = 0.002). Also, 8% (n = 2) reported a high level of MPN at T2, 14% (n = 3) at T3, and 15% (n = 3) at T5. However, this was not significantly different from chemotherapy-treated patients.

3.2. Course of CIPN

The mean SPN scores of chemotherapy-treated ovarian cancer patients showed a stable course, with mean scores of 41 (SD = 38) at T1, 44 (SD = 33) at 6 months follow-up (T2), 38 (SD = 34) at 1-year follow-up (T3), and 36 (SD = 32) at 2-year follow-up (T5) (Fig. 2).

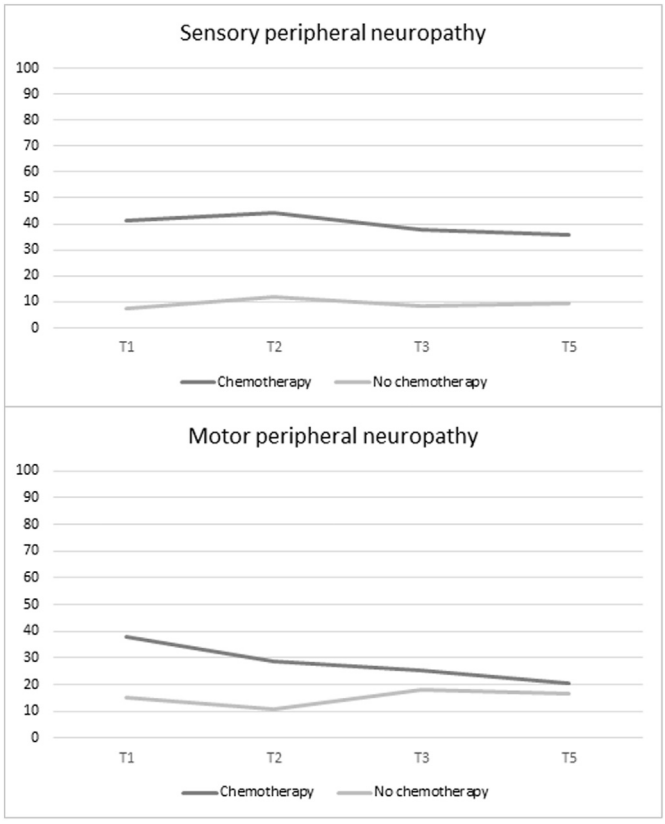

Fig. 2. Course of sensory and motor neuropathy among ovarian cancer patients, stratified by chemotherapy. A higher score on both the sensory and motor peripheral neuropathy scale indicates more neuropathy symptoms. T1, baseline; T2, 6 months; T3, 12 months; T5, 24 months.

For MPN, the mean score at baseline was 38 (SD = 32), and this dropped to 29 (SD = 31) at 6 months follow-up, to 25 (SD = 31) at 1-year follow-up, and finally to 20 (SD = 26) at 2-year follow-up (Fig. 2). GLMM showed that while the decline at 6 months follow-up was not statistically significant (p = 0.07), the decline at 1-year follow-up and 2-year follow-up (p = 0.03 and p = 0.001, respectively) were.

To examine the course of SPN/MPN among patients without chemotherapy, only ROGY condition and age were added as confounding variables since diabetes mellitus, osteoarthritis, and rheumatoid arthritis were highly correlated. To be able to compare the course of SPN/MPN between chemotherapy-treated patients and patients without chemotherapy, we re-ran the analyses for chemotherapy-treated patients without correcting for diabetes mellitus, osteoarthritis, and rheumatoid arthritis. This showed that for chemotherapy-treated patients, the SPN course was still stable. Regarding MPN, the decline at T2 (p = 0.02), T3 (p = 0.003), and T5 (p <0.001) were now all statistically significant. For patients without chemotherapy, the SPN course was also stable. However, compared to chemotherapy-treated patients, they did report less SPN symptoms across all time points (p < 0.001), with mean SPN scores of 8 (SD = 17) at T1, 12 (SD = 22) at T2, 8 (SD = 17) at T3, and 9 (SD = 19) at T5. For MPN, mean scores at T1 (M = 15, SD = 22), T2 (M = 11, SD = 21), T3 (M = 18, SD = 25), and T5 (M = 17, SD = 25) showed a stable course. Also, compared to chemotherapy-treated patients, they reported less MPN at T1 and T2 (both p < 0.05), but not at T3 and T5.

Finally, as 25% (n = 23) of chemotherapy-treated patients had experienced a recurrence during the study, post-hoc analyses were conducted to determine differences between patients without chemotherapy, chemotherapy-treated patients who did not experience a recurrence (n = 69), and chemotherapy-treated patients who did

experience a recurrence, for which they were treated with additional chemotherapy (n = 23). Results showed that patients without chemotherapy reported less SPN symptoms across time compared to both chemotherapy-treated groups (both $p < 0.001$), but no differences were found between the two chemotherapy-treated groups ($p = 0.87$). Similar results were found for MPN; patients without chemotherapy reported less MPN symptoms across time compared to chemotherapy-treated patients who did not experience a recurrence ($p = 0.02$) and those who did ($p = 0.03$), but there were no differences between the two chemotherapy-treated groups ($p = 0.72$).

3.3. CIPN and HRQoL

For the HRQoL analyses, only chemotherapy-treated patients who completed at least two questionnaires were included (n = 98). The HRQoL scales of patients at the four time points according to the stability of their SPN levels are presented in Fig. 3. At T1, patients in the 'always high SPN' group had a worse emotional functioning compared to patients who never had high SPN scores or those with fluctuating SPN scores. At T2, patients in the 'always high SPN' group also reported worse global quality of life scores and worse physical, role, and emotional functioning compared to the other two groups. Finally, they also reported worse social functioning at T2, but only compared to those with fluctuating SPN scores. All significant differences were of large clinical relevance.

Regarding MPN, patients with always high MPN scores reported lower HRQoL scores on almost all time points for global quality of life and all functioning scales (Fig. 4). Differences in global quality of life, and role and emotional functioning were of medium to large clinical relevance, while the differences in physical, social, and cognitive functioning were of large clinical relevance.

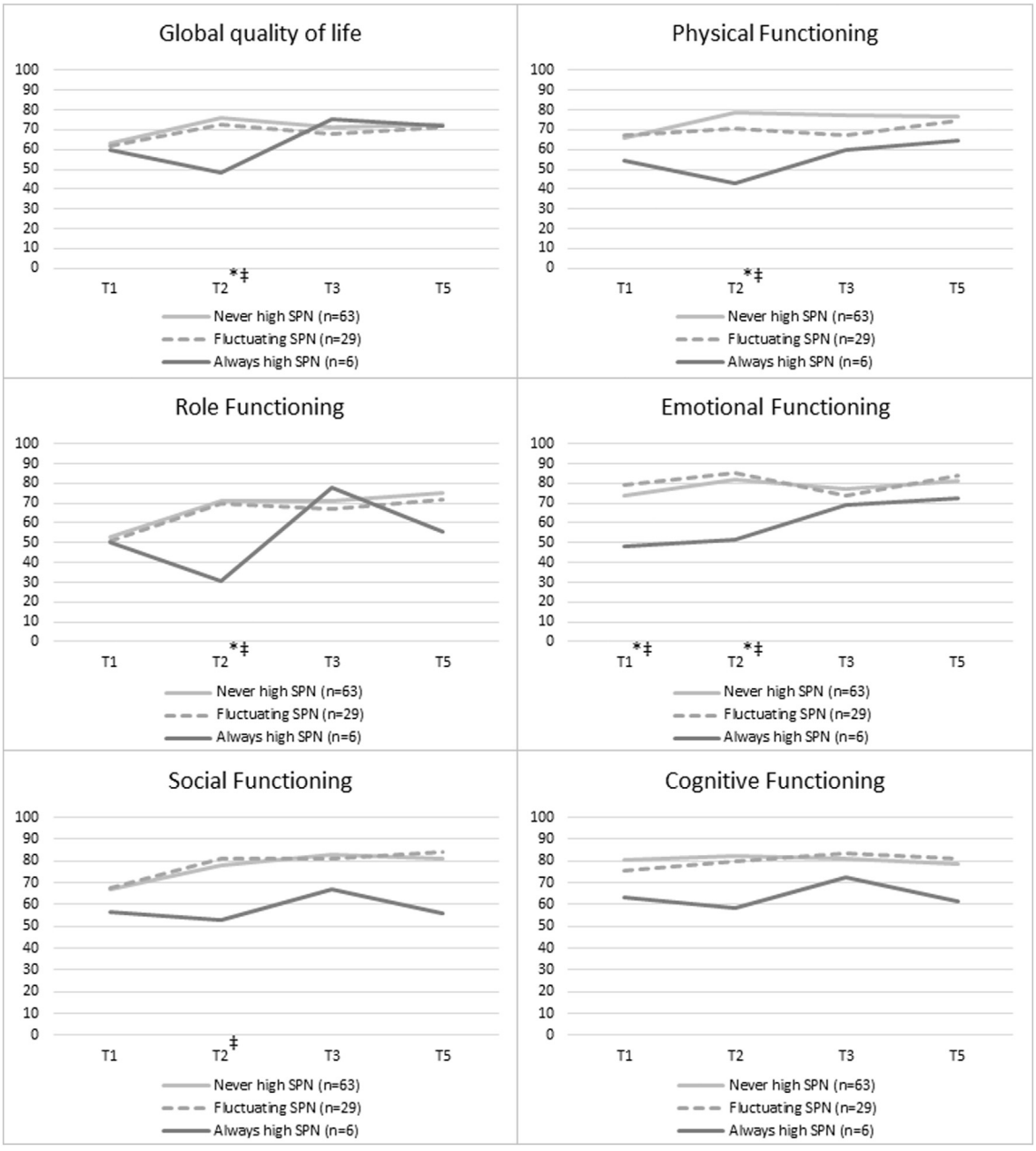

Fig. 3. Course of HRQoL for ovarian cancer patients according to the stability of their sensory peripheral neuropathy level. T1, baseline; T2, 6 months; T3, 12 months; T5, 24 months. *SPN* Sensory peripheral neuropathy A higher score on the global quality of life and functioning scales and implies a better HRQoL. * Significant difference between patients with "always high" and "never high" SPN scores. ‡ Significant difference between patients with "always high" and "fluctuating" SPN scores. † Significant difference between patients with "fluctuating" and "never high" SPN scores.

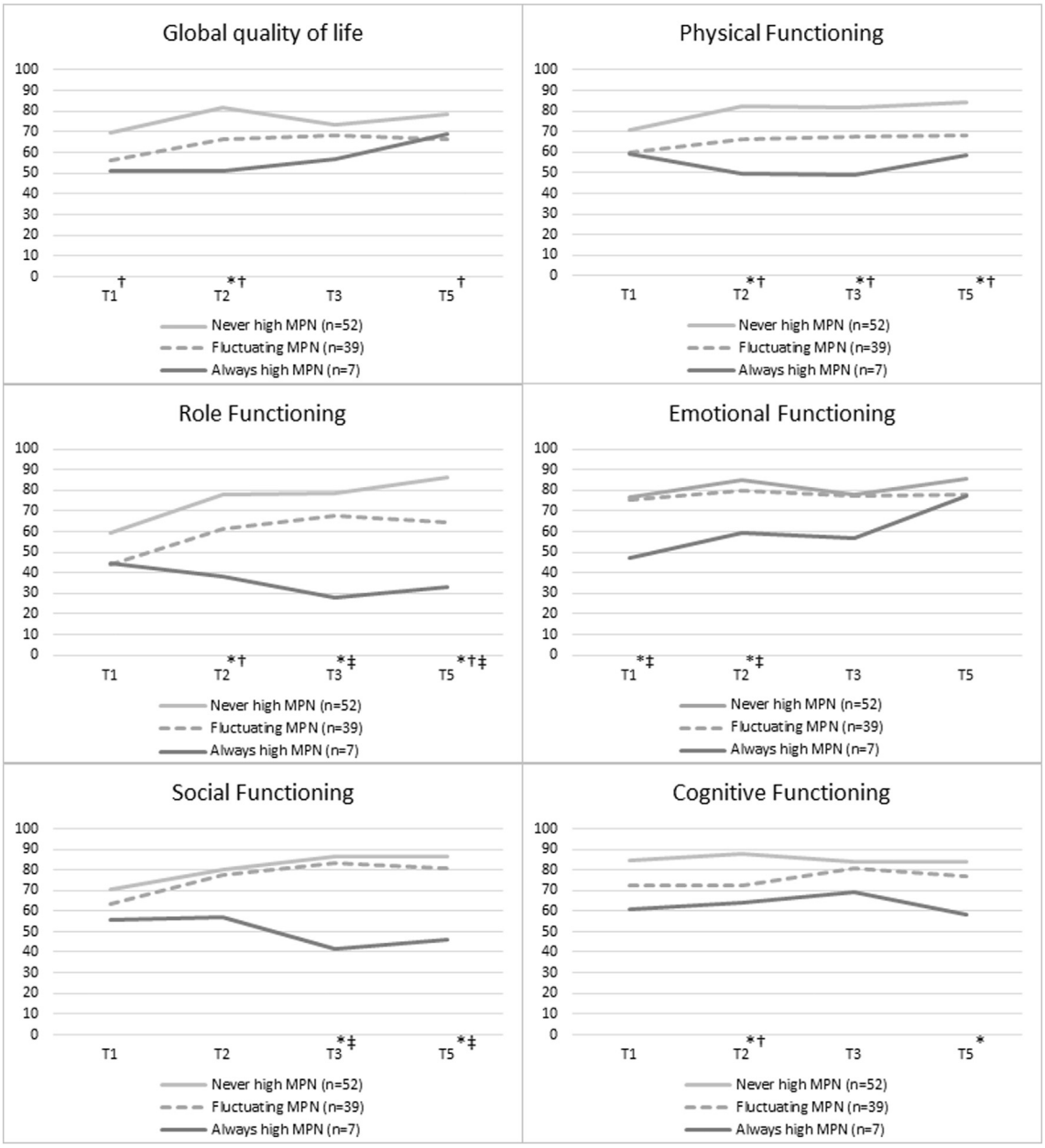

Fig. 4. Course of HRQoL for ovarian cancer patients according to the stability of their motor peripheral neuropathy level. T1, baseline; T2, 6 months; T3, 12vmonths; T5, 24 months. *MPN* Motor peripheral neuropathy A higher score on the global quality of life and functioning scales and implies a better HRQoL. * Significant difference between patients with "always high" and "never high" MPN scores. ‡ Significant difference between patients with "always high" and "fluctuating" MPN scores. † Significant difference between patients with "fluctuating" and "never high" MPN scores.

3.4. Between-patients and within-patients effects of CIPN on HRQoL

Patients with a high SPN level reported a worse physical, role, emotional, social, and cognitive functioning (13.8 to 26.0 points, all $p < 0.05$) compared to those with a low SPN level (between-patients effects) (Table 2). No effect was found on global quality of life. Also, a within-patients effect was found for physical functioning (9.4 points, $p = 0.005$), indicating that patients who changed from a low to a high SPN level over time showed a decrease in physical functioning, while patients who changed from a high to a low SPN level over time showed improvements in physical functioning.

With regard to MPN, patients with a high level scored, on average, 15.9 to 36.2 lower on all HRQoL scales compared to those with a low MPN level (all $p < 0.01$) (Table 2). Also, patients who changed from a low to a high MPN level over time showed a decrease in global quality of life and physical, role, social, and cognitive functioning, while those who changed from a high to a low MPN level over time improved on these scales (10.7 to 25.2 points, all $p < 0.01$).

4. Discussion

In this secondary analyses of a longitudinal study among ovarian cancer patients, we showed that the course of SPN among chemotherapy-treated patients remained stable over the course of 2 years. For MPN, a decline in scores was found at 12 months. Furthermore, at 2 years, 13% still reported high levels of SPN. Regarding MPN, 11% still reported high levels at 2 years. For patients not treated with chemotherapy, both SPN and MPN remained stable. Also, 5% still reported high SPN levels, while for MPN, 15% still reported high levels at 2 years. Our study also showed that among chemotherapy-treated

Table 2
Generalized linear mixed model of between-patients and within-patients effects of sensory and motor peripheral neuropathy on HRQoL.

	Global quality of life	Physical functioning	Role functioning	Emotional functioning	Social functioning	Cognitive functioning
Sensory peripheral neuropathy (SPN)						
Age[a]	−0.1 (−0.48–0.27)	−0.4 (−0.9–0.02)*	0.1 (−0.5–0.7)	0.4 (−0.1–0.8)	0.2 (−0.3–0.7)	0.6 (0.2–1.1)**
FIGO stage						
Stage I vs. IV	14.8 (2.94–26.7)*	10.5 (−3.0–23.9)	15.2 (−3.5–33.9)	7.7 (−6.9–22.4)	10.3 (−6.5–27.1)	6.0 (−9.2–21.1)
Stage II vs. IV	24.6 (11.7–37.4)***	11.5 (−3.0–26.1)	14.0 (−6.1–34.2)	21.1 (5.3–36.9)**	10.0 (−8.1–28.2)	18.5 (2.2–34.8)*
Stage III vs. IV	9.2 (0.14–18.3)*	0.1 (−10.1–10.4)	3.9 (−10.3–18.2)	9.8 (−1.4–20.9)	1.5 (−11.2–14.3)	2.5 (−8.9–14.0)
Education						
Low vs. High	10.8 (−0.9–22.4)	0.2 (−13.0–13.5)	18.3 (0.1–36.5)*	1.1 (−13.3–15.5)	5.6 (−10.8–22.1)	8.9 (−6.0–23.8)
Middle vs. High	1.9 (−7.1–10.9)	3.5 (−6.8–13.7)	9.6 (−4.6–23.7)	−3.7 (−14.9–7.4)	3.3 (−9.5–16.0)	−0.7 (−12.2–10.8)
ROGY intervention	0.01 (−6.6–6.7)	3.5 (−4.0–11.1)	4.2 (−6.3–14.6)	−6.2 (−14.4–2.1)	3.3 (−6.1–12.7)	4.7 (−3.7–13.2)
Osteoarthritis	−5.2 (−14.4–4.3)	−2.3 (−13.1–8.5)	3.1 (−11.8–18.0)	−1.8 (−13.6–10.0)	4.4 (−9.1–17.9)	−7.1 (−19.3–5.1)
Diabetes mellitus	2.2 (−7.3–11.7)	−6.8 (−17.6–3.9)	−7.4 (−22.5–7.74)	4.4 (−7.3–16.1)	−1.1 (−14.5–12.3)	9.4 (−2.7–21.5)
Rheumatoid arthritis	0.5 (−12.8–13.8)	4.3 (−10.7–19.4)	0.2 (−20.7–21.1)	−0.1 (−16.5–16.3)	−2.5 (−21.3–16.4)	−5.3 (−22.2–11.7)
SPN[b] between	−7.2 (−18.2–3.8)	−13.8 (−26.3–1.4)*	−26.0 (−43.3–8.8)**	−18.0 (−31.6–4.4)*	−20.1 (−35.7–4.5)*	−14.6 (−28.6–0.5)*
SPN[b] within	0.9 (−6.8–8.5)	−9.4 (−16.0–2.9)**	−8.5 (−20.1–3.2)	3.7 (−3.3–10.6)	−1.6 (−10.4–7.3)	−3.2 (−9.9–3.5)
Motor peripheral neuropathy (MPN)						
Age[a]	−0.04 (−0.4–0.3)	−0.4 (−0.7–0.02)	0.1 (−0.4–0.7)	0.4 (−0.1–0.8)	0.2 (−0.3–0.7)	0.7 (0.2–1.1)**
FIGO stage						
Stage I vs. IV	11.7 (−0.02–23.4)	5.1 (−7.5–17.7)	8.0 (−10.3–26.4)	4.8 (−10.1–19.8)	6.0 (−10.7–22.8)	2.1 (−13.0–17.1)
Stage II vs. IV	20.8 (8.4–33.3)**	6.9 (−6.5–20.3)	7.9 (−11.6–27.3)	18.4 (2.5–34.3)*	5.8 (−12.0–23.6)	15.0 (−1.1–31.0)
Stage III vs. IV	5.5 (−3.7–14.6)	−6.2 (−16.1–3.6)	−4.7 (−19.0–9.6)	5.6 (−6.0–17.3)	−4.1 (−17.1–9.0)	−2.3 (−14.1–9.4)
Education						
Low vs. High	8.1 (−3.0–19.2)	−4.2 (−16.3–7.8)	10.0 (−7.4–27.5)	−3.2 (−17.5–11.0)	0.2 (−15.8–16.2)	4.7 (−9.7–19.1)
Middle vs. High	1.4 (−7.2–10.0)	2.5 (−6.8–11.9)	7.6 (−5.9–21.2)	−4.7 (−15.7–6.4)	2.0 (−10.4–14.4)	−1.6 (−12.7–9.6)
ROGY intervention	−0.3 (−6.7–6.0)	3.3 (−3.6–10.2)	3.6 (−6.4–13.6)	−6.7 (−14.9–1.4)	2.6 (−6.5–11.8)	4.4 (−3.9–12.6)
Osteoarthritis	−4.5 (−13.2–4.2)	−2.0 (−11.4–7.5)	1.2 (−12.4–14.7)	−3.7 (−14.9–7.5)	2.8 (−9.7–15.4)	−7.8 (−19.1–3.6)
Diabetes mellitus	3.4 (−5.7–12.5)	−5.0 (−14.7–4.8)	−2.8 (−17.2–11.5)	6.9 (−4.7–18.4)	2.0 (−21.3–15.3)	11.5 (−0.1–23.1)
Rheumatoid arthritis	−0.2 (−13.1–12.6)	−3.8 (−10.0–17.5)	−1.5 (−21.6–18.5)	0.2 (−16.2–16.5)	−3.0 (−21.3–15.3)	−5.8 (−22.2–10.7)
MPN[c] between	−15.9 (−26.8–5.0)**	−26.5 (−38.3–14.7)***	−36.2 (−53.2–19.1)***	−19.5 (−33.5–5.5)**	−25.1 (−40.8–9.4)**	−21.5 (−35.6–7.4)**
MPN[c] within	−10.7 (−17.6–3.8)**	−12.2 (−18.1–6.2)***	−25.2 (−35.3–15.1)***	−0.9 (−7.4–5.6)	−13.7 (−21.7–5.8)**	−9.5 (−15.5–3.5)**

Reported values are Betas (95% CI).
SPN/MPN between = between-patients effect based on the difference between the patients' average amount of SPN/MPN and the average SPN/MPN level of the total group.
SPN/MPN within = within-patients effect based on the difference between a patients' SPN/MPN level at one time point and that patients' average SPN/MPN level across all time points.
SPN sensory peripheral neuropathy; *MPN* motor peripheral neuropathy.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] Continuous variables are grand-mean centered.
[b] SPN: very much vs. not at all/a little/quite a bit.
[c] MPN: very much/quite a bit vs. not at all/a little.

patients, those with a high SPN had a significantly worse functioning compared to those with a low SPN level. Furthermore, those with a high MPN level reported a worse global quality of life, and a worse functioning. Change in SPN over time was negatively associated with changes in HRQoL. This was also the case for MPN.

The prevalence of SPN and MPN among chemotherapy-treated patients is comparable to the prevalence (6–9%, and 14%, respectively) found in a previous PROFILES study among ovarian cancer survivors 2 to 12 years after treatment [11]. In this cross-sectional study, CIPN symptoms decreased three years after the end of treatment; the present longitudinal study showed an additional significant decline in MPN scores after 1 year. As our follow-up was only up to 24 months after diagnosis, it is possible that the decline in SPN would start after that period of time. Interestingly, post-hoc analyses showed no differences in CIPN symptoms between patients who experienced a recurrence and those that did not, which is in contrast with the findings of the previous PROFILES study among ovarian cancer survivors. These mixed findings could be due to our small sample size. Also, patients with a recurrence might have received either a different chemotherapeutic agent known to cause less neuropathy or weekly chemotherapy. However, while previous studies have shown that weekly chemotherapy might be beneficial for survival while causing less or equal CIPN [27,28], a more recent unpublished finding of the ICON8 trial showed that weekly chemotherapy was associated with worse long-term CIPN [29].

We also found that chemotherapy-treated patients with a high SPN level reported a worse functioning compared to those with a low SPN level. Furthermore, those with a high MPN level reported a worse global quality of life and a worse functioning compared to patients with a low MPN level. These results are in line with two previous cross-sectional studies among ovarian cancer patients and survivors [11,13] and one longitudinal study among ovarian cancer patients [16], which measured the relationship between CIPN and HRQoL during active treatment.

Looking at the impact of both SPN and MPN symptoms on HRQoL, it is very important to try to improve HRQoL by decreasing CIPN, especially for SPN as symptoms remained relatively stable up to 2 years. However, although several agents have been examined for their efficacy in preventing CIPN, none have shown sufficient benefit [4]. For the treatment of established CIPN symptoms, duloxetine seems promising in relieving painful CIPN [30]. In addition, several chemotherapy treatment options and alterations can be taken into account to try to reduce CIPN. First, while the standard chemotherapy treatment for ovarian cancer is a combination of paclitaxel and carboplatin [5], studies have shown that the combination of docetaxel and carboplatin is associated with a lower incidence of CIPN [16,31,32]. Second, while findings on reducing the numbers of cycles from 6 to 3 on recurrence of high-risk ovarian cancer are mixed, it does seem to decrease toxicity [33,34]. More research on these topics is needed to determine whether limiting the cycles or changing chemotherapeutic agent are safe options to reduce toxicity, both in high and lower risk groups. In this research, it is important to follow the time-course of CIPN for a longer duration, because initial reduction in symptoms may not last. Finally, proper staging might be important in reducing neurotoxicity by eliminating unnecessary chemotherapy, as it remains unclear whether patients with low- and intermediate-risk early-stage disease will benefit as much from

adjuvant chemotherapy as women with high-risk disease [35]. Indeed, in the present study it was found that patients not treated with chemotherapy reported less SPN symptoms across all time points. For MPN, less symptoms were found in the first year.

Several limitations of our study must be mentioned. First, we assessed SPN and MPN with the EORTC QLQ-OV28. Autonomic neuropathy, which can be measured with the EORTC-QLQ-CIPN20 [36], might also be present in ovarian cancer patients. Second, CIPN symptoms were only measured with three items, which might have led to certain CIPN symptoms being missed. However, these items were specifically developed to assess CIPN among ovarian cancer patients, so we are confident that the most important symptoms are included. A third limitation might be the item assessing MPN. This item asks respondents about weakness in arms or legs and this may not specifically be caused by MPN, but could be a more general complaint due to the cancer, the effect of SPN, or other comorbidities. Indeed, a previous study [37] found that this item was only weakly associated with the neuropathy scale of the OV28, and another study [11] found that the item was associated with the number of comorbidities. The EORTC QLQ-CIPN20 may be a more suitable instrument, as SPN and MPN are measured with a variety of items, assessing different SPN and MPN symptoms. A fourth limitation is the lost to follow-up, which resulted in a selection of patients who had lower cancer stages. However, the actual health status of those lost to follow-up and the possible effects on the results of this study remain unknown. Furthermore, we do not know if those lost to follow-up stopped completing the questionnaires due to neuropathy symptoms in their hands.

Another limitation is that data on the number of chemotherapy cycles and dose reduction were not available, while it is known that neurotoxicity depends on the cumulative dose and dose reduction is often used to try to decrease CIPN symptoms [4], which could impact HRQoL over time. Therefore, future studies aiming to examine the effect of CIPN on HRQoL should include these data, so recommendations on treatment decisions and treatment alterations can be made. Furthermore, future studies should include a larger sample. Also, it is important to mention that a previous PROFILES study [38] found that patients in the SCP arm reported more symptoms, were more affected emotionally, and were more concerned about their illness. While we do control for ROGY condition in our analyses, this could have impacted the results of our study.

In spite of these limitations, our study is the first (longitudinal) study to measure the course of SPN and MPN separately, and to examine their individual impact on HRQoL among ovarian cancer patients. Furthermore, we also assessed and found within-patient effects for the relationship between CIPN and HRQoL, which is a stronger indication for causality compared to only between-patients effects.

5. Conclusion

Among chemotherapy-treated patients, SPN symptoms remained stable up to 2 years after diagnosis. Regarding MPN, symptoms decreased at 12 months. Moreover, a high SPN level was significantly associated with a worse functioning. For MPN, a high level was significantly associated with a worse global quality of life and a worse functioning. Therefore, it is important that patients are made aware of the impact of CIPN on HRQoL. Furthermore, the results of this study call for future studies to examine the impact of different treatment decisions and treatment alterations on both CIPN and HRQoL. If such information becomes available, treatment recommendations to reduce the prevalence of CIPN should be communicated to both physicians and patients.

Conflict of interest

None to declare.

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