Treatment satisfaction of patients with advanced-stage non-small-cell lung cancer receiving platinum-based chemotherapy: results from a prospective cohort study (PERSONAL)

S. Visser,
M. de Mol,
K. Cheung,
J.J. van Toor,
N.C. van Walree,
B.H. Stricker,
B.L. den Oudsten[†],
J.G.J.V. Aerts[†]

[†]*These authors contributed equally to this work.*

Clinical Lung Cancer 2018;19(4):e503-e516

ABSTRACT

Introduction: In patients with advanced-stage non-small-cell lung cancer (NSCLC) treatment benefits and risks need to be constantly weighed. We explored patient reported satisfaction with therapy (SWT) and assessed its added value alongside Quality of Life (QoL) and adverse events (AEs).

Patients and methods: In a prospective multi-center cohort study, patients with stage IIIB/IV NSCLC received platinum-pemetrexed chemotherapy. They completed the World Health Organization Quality of Life-BREF (WHOQOL-BREF) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) before and during chemotherapy. After the last cycle, patients reported on SWT, expectations of therapy (ET) and feelings about side effects (FSE) using the Cancer Therapy Satisfaction Questionnaire (CTSQ). Explained variance (R^2) of QoL after treatment by SWT was calculated. Using (multivariable) linear regression, we examined the association of SWT with patient and treatment-related variables, FSE and AEs.

Results: Eighty-nine patients finished four cycles of chemotherapy, of whom 65 completed the CTSQ. Fifty-six patients (86.2%) would probably/definitely decide to undergo the same treatment again, regardless of a deterioration/improvement of QoL or high/low frequency of AEs during chemotherapy. Explained variance of QoL by SWT was highest for the EORTC QLQ C-30 global Health Status/QoL scale (R^2=0.170). Patients' age (β=0.43; 95%CI 0.05-0.82), FSE (β=0.17; 95%CI 0.06-0.29) and tumor response (β=7.93; 95%CI (1.64-14.22) were independently associated with SWT.

Conclusion: SWT may provide important supplementary information besides QoL and treatment toxicities. Tumor response, higher age and FSE score were associated with better SWT. These insights may impact decision making during palliative chemotherapy.

INTRODUCTION

Chemotherapy has shown to improve overall survival and Quality of Life (QoL) of patients with advanced-stage non-small-cell lung cancer (NSCLC) [1,2]. However, survival gain remains limited and treatment is often accompanied by adverse events (AEs) varying in number and severity depending on the different chemotherapy regimens and patients' individual characteristics [1,3]. Therefore, decisions whether to start or continue with treatment are complex and require that patients' expectations, preferences, and values with regard to benefits and risks are taken into account.

The implementation of patient reported outcomes in clinical practice has shown to improve assessment of and communication about symptoms and QoL [4]. AEs can have a considerable impact on Health-Related (HR)QoL [5]. In turn, change of (HR)QoL provides prognostic information with regard to (lung) cancer survival [6–9]. HRQoL has gained importance in treatment decision making in addition to clinical effectiveness of treatment, since it incorporates the influence of AEs (treatment or cancer-related) and acts as a prognostic factor for survival. However, considering treatment decisions in this manner ignores patients' reflection on treatment harms and benefits.

Another challenge in clinical decision making is the considerable variability in how patients value the importance of survival benefit and symptom relief offered by chemotherapy [10–12]. In general, patients with metastatic lung cancer consider even a small increase in life expectancy as worthwhile, yet 10-25% of patients would not choose chemotherapy if additional survival is less than 12 months [13]. Younger patients tend to accept a much smaller treatment benefit compared to older patients [13,14]. Patients' preferences are also affected by their understanding of prognosis. Many patients receiving chemotherapy for metastatic (lung) cancer overestimate their life expectancy, which might explain the discordance between the treatment decisions they make and their actual preferences [15–17].

To date, there is little insight into which patient or treatment-related factors are associated with treatment satisfaction. Taking into account patients' perceptions of prognosis and treatment satisfaction could offer a patient-centered view on the impact of negative and positive treatment effects and therefore may have added value in decision making.

In this prospective multi-center study from a real-world's perspective, we explored the association between SWT and patient and treatment-related factors and (feelings about) AEs in patients with advanced-stage NSCLC treated with chemotherapy and we aimed to assess the added value of SWT alongside generally accepted clinical outcomes (HR)QoL and AEs.

PATIENTS AND METHODS

Pemetrexed and biomarkers: an observational study (PERSONAL) is a prospective multicenter cohort study of adult patients with locally advanced or metastatic (stage IIIB/IV) non-squamous NSCLC and unresectable mesothelioma receiving platinum-combined pemetrexed as first-line and pemetrexed monotherapy as second-line treatment. Patients were recruited from October 2012 until November 2014 from a university hospital (Erasmus University Medical Center), two large teaching hospitals specialized in lung cancer care (Amphia hospital; Franciscus Gasthuis) and a regional hospital (Bravis hospital) located in the southwestern part of the Netherlands. Patients with unresectable mesothelioma were excluded from analyses in the present study. All patients provided written informed consent. This study was approved by the Institutional Review Board of the Erasmus University Medical Center in Rotterdam, The Netherlands.

Data collection

The validated Cancer Therapy Satisfaction Questionnaire (CTSQ) consists of 16 items covering three domains: satisfaction with therapy (SWT; seven items), feelings about side effects (FSE; four items) and expectations of therapy (ET; 5 items) [18]. Items were scored on a scale from one (worst score) to five (best score). Four items were reverse coded. Each domain score was calculated by linear transformation of the mean of the corresponding item scores, resulting in a domain score range from 0 to 100. A higher score represents a better outcome on each domain, for instance a higher domain score of SWT corresponds with better treatment satisfaction. Items of special interest from the ET and SWT domain were the following: “How often do you think the chemotherapy can cure the disease?” (ET domain) and two items from the SWT domain; “The chemotherapy was worth it, even with side effects?”; “Would you decide to take the chemotherapy again, if given the choice?”.

The World Health Organization Quality of Life-BREF (WHOQOL-BREF) is a generic QoL instrument developed to use in a wide range of disorders and health problems, including oncological diseases [19]. The questionnaire comprises 26 items covering four domains (physical health, psychological health, social relationships, and environment) and one facet, including one item to assess overall QoL and one item to measure general health. The domain scores range between 4 to 20 and the facet is scored on a 2 to 10 scale, with a higher score indicating a better QoL.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) is a HRQoL questionnaire, which is internationally used in clinical studies [20]. The questionnaire consists of 30 items and incorporates a global Health Status/QoL scale and five functional scales. Each of the QLQ-C30 scales is scored on a 0 to 100 scale, with a higher score being representative of a better HRQoL.

Patients completed (HR)QoL questionnaires before the start of chemotherapy (baseline). Follow-up assessments were performed during the 2nd cycle (day 7-14) and during the 4th cycle (day 14-21) of chemotherapy. At the latter moment, patients were also requested to complete the CTSQ. We collected sociodemographic information (age, sex, ethnicity), Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, disease stage and treatment. After the start of chemotherapy, all clinical and laboratory AEs (cancer or therapy-related) were weekly registered according to Common Terminology Criteria for Adverse Events (CTCAE 4.0). Tumor response measurements were obtained according to RECIST 1.1 after the 2nd and 4th cycle of chemotherapy.

Statistical analysis

Sociodemographic and clinical variables were compared between patients who completed the CTSQ questionnaires and patients who did not. We used the independent-samples *t*-test and the χ^2-test or Fisher's exact test for continuous and categorical variables respectively.

Patients were categorized into two groups using the median number of all grades clinical AEs and into three groups with regard to alteration of QoL during treatment, based on known minimal clinically important differences (MCID) of the EORTC QLQ-C30 and WHO-QOL-BREF [21,22] [de Mol M, Visser S, Aerts JG et al. Satisfactory results of a psychometric analysis and calculation of minimal clinically important differences of the WHOQoL-BREF questionnaire in lung cancer patients. *Submitted for publication*]: deterioration, no change or improvement (Supplemental Appendix A1).

Using the Mann-Whitney U and Kruskal-Wallis test, differences in response distributions to individual items of the SWT domain were examined across mentioned groups according to alteration of QoL and frequency of AEs. Differences in mean SWT domain scores were described for the three groups based on alteration of QoL. The Pearson's correlation coefficients (ρ) were used to calculate the explained variance (R^2) of QoL after four cycles of chemotherapy by SWT.

Patient and treatment-related variables and (feelings about) AEs associated with SWT ($P < 0.05$) in univariable analyses, were analyzed with the use of multivariable linear regression (method: Enter). These regression analyses were restricted to patients treated with first-line platinum-based treatment to ensure a more homogeneous population.

All statistical analyses were performed with the use of SPSS, version 22.0 (IBM Corporation, Armonk, NY).

RESULTS

In total, 165 patients with advanced-stage NSCLC were enrolled in this study (Figure 1). All patients included for analyses received pemetrexed-based chemotherapy as first or second-line treatment. Of these patients, 85.5% completed the (HR)QoL questionnaires at baseline. Eighty-nine (53.9%) patients finished four cycles of chemotherapy, of whom 73.0% completed the CTSQ and (HR)QoL questionnaires. Reasons for non-completion of the questionnaires are reported in Supplemental Table A1. Seventy-six patients stopped chemotherapy preliminary due to intolerable toxicities (42.1%), progressive disease (38.2%) or preplanned sequential radiotherapy or surgery (19.7%).

Patient characteristics

Patient characteristics are outlined in Table 1. The mean age in this population was 63.3±9.2 years and slightly more than half of the patients were male (50.9%). The majority of patients had metastatic NSCLC (87.3%) and received pemetrexed as first-line treatment (90.3%), mostly combined with cisplatin (61.8%) or carboplatin (36.4%). The patients who completed the CTSQ questionnaires after four cycles of chemotherapy had a significantly lower ECOG performance score at baseline ($P = 0.001$), a better tumor response ($P < 0.001$), and a higher frequency of treatment- or cancer-related AEs ($P < 0.001$) than patients who did not complete the CTSQ.

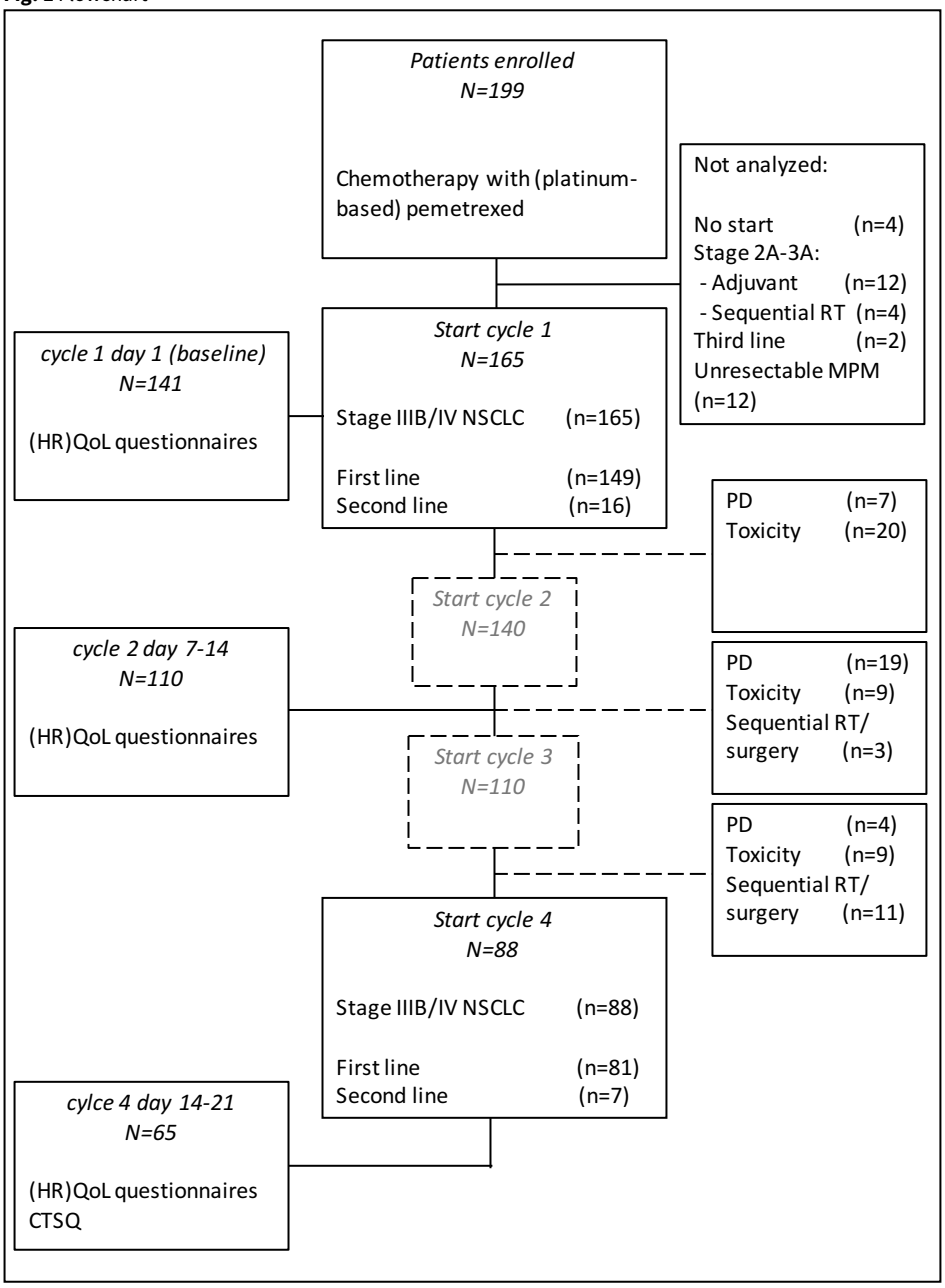
Treatment satisfaction

The median domain scores of SWT, FSE and ET were 82.1 (Interquartile range [IQR]: 71.4-89.3), 56.3 (IQR: 37.5-75.0), and 55.0 (IQR: 40.0-78.8), respectively. Of the patients who completed the CTSQ, 26.1% often or always expected chemotherapy could cure their disease. During treatment, patients experienced 20.5 ± 5.0 all grades AEs, 13.5 ± 3.7 all grades clinical AEs, and 1.8 ± 1.7 grade ≥ 3 AEs, both treatment and cancer-related. Detailed information about treatment-related clinical and laboratory AEs is provided in Table 2.

Responses to individual items within the SWT domain are shown in Figure 2. Of the patients who completed the item whether chemotherapy was worth taking even with side effects (*N*=64), 81.3% answered positively. Twelve patients responded negatively (*N*=3, 4.7%) or were in doubt (*N*=9, 14.1%). Fifty-six of the 65 patients (86.2%) would probably or definitely decide to undergo the same treatment again. Distributions of the answers of both items were not significantly different for patients with a deterioration in QoL compared to patients with no change or improvement of QoL and between patients with a high (≥14) or low (<14) frequency of clinical AEs (both treatment and cancer-related).

Table 3 shows the distribution of SWT scores across different groups based on alteration of QoL during treatment. Patients with an improved WHOQOL-BREF facet score had a statistically higher (p=0.008) SWT domain score (84.1±10.5) than patients without change

Fig. 1 Flowchart



Abbreviations: (HR)QoL, (health-related) quality of life; NSCLC, non-small cell lung cancer; MPM, malignant pleural mesothelioma; CTSQ, Cancer Therapy Satisfaction Questionnaire; PD, progressive disease; RT, radiotherapy.

Table 1. Characteristics of patients who started treatment with pemetrexed

Characteristic	Total (N=165)	Completion CTSQ questionnaire (N=65)	No completion CTSQ questionnaire (N=100)	P-value
Age, mean (SD)	63.3 (9.2)	62.1 (7.9)	64.1 (9.8)	0.174
Gender, male	84 (50.9)	34 (52.3)	50 (50.0)	0.874
Ethnicity, Caucasian	155 (93.9)	60 (92.3)	95 (95.0)	0.814
ECOG performance score				0.001
0 or 1	145 (87.8)	64 (98.5)	81 (81.0)	
≥ 2	20 (12.2)	1 (1.5)	19 (19.0)	
Type of tumor				0.577
Adenocarcinoma	160 (97.0)	63 (96.9)	97 (97.0)	
Large cell carcinoma	5 (3.0)	2 (3.1)	3 (3.0)	
Cancer stage				0.153
Locally advanced (IIIB)	21 (12.7)	5 (7.7)	16 (16.0)	
Metastatic (IV)	144 (87.3)	60 (92.3)	84 (84.0)	
Combination therapy				0.665
Cisplatin	102 (61.8)	39 (60.0)	63 (63.0)	
Carboplatin	60 (36.4)	24 (36.9)	36 (36.0)	
Monotherapy	3 (1.8)	2 (3.1)	1 (1.0)	
Line of therapy				0.595
1st line	149 (90.3)	60 (92.3)	89 (89.0)	
2nd line	16 (9.7)	5 (7.7)	11 (11.0)	
Best tumor response				<0.001
PR	44 (26.7)	24 (36.9)	20 (20.0)	
SD	76 (46.1)	40 (61.5)	36 (36.0)	
PD	17 (10.3)	0 (0.0)	17 (17.0)	
not evaluable*	28 (16.9)	1 (1.5)	27 (27.0)	
Mean number of adverse events per cycle (SD)†				
All grades	7.4 (4.1)	5.1 (1.2)	8.7 (4.6)	<0.001
Grade 1 and 2	6.3 (3.2)	4.7 (1.2)	7.2 (3.5)	<0.001
Grade 3 and 4	1.0 (1.4)	0.5 (0.4)	1.4 (1.7)	<0.001
Comorbidity				
Cardiovascular disease	71 (43.0)	25 (38.5)	46 (46.0)	0.421
COPD	25 (15.2)	7 (10.8)	19 (18.0)	0.268
Diabetes	22 (13.3)	5 (7.7)	17 (17.0)	0.217

Data are expressed as numbers (%) unless stated otherwise.

*Not evaluable due to early progression/death or systemic deterioration.

† Distinct treatment or cancer-related adverse events according to CTCAE 4.0.

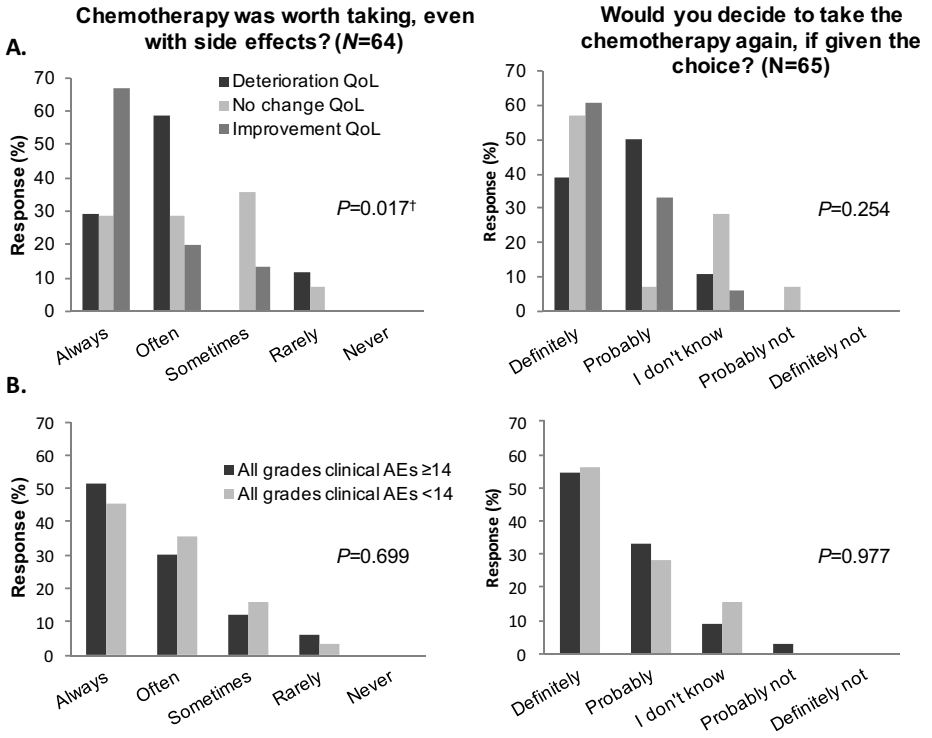
Abbreviations: CTSQ, Cancer Therapy Satisfaction Questionnaire; PR, partial response; SD, stable disease; PD, progressive disease; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; N, number of patients.

Table 2. Adverse events in patients who completed the CTSQ (N=65)

	Frequency (%)	
Adverse event	All grades	Grade ≥ 3
Treatment-related*		
Any	69 (100)	32 (49)
Clinical		
Fatigue	61 (94)	7 (11)
Anemia	57 (88)	8 (12)
Nausea	46 (71)	3 (5)
Decreased appetite	44 (68)	2 (3)
Taste alteration	37 (57)	0
Oral mucositis	33 (51)	1 (2)
Dry eyes/watering eyes	31 (48)	0
Dry skin	29 (45)	0
Constipation	26 (40)	1 (2)
Rash	19 (29)	0
Diarrhea	15 (23)	1 (2)
Vomiting	13 (20)	0
Dizziness	13 (20)	0
Alopecia	13 (20)	0
Dysphagia	12 (18)	0
Dyspepsia	10 (15)	0
Pruritus	10 (15)	0
Abdominal bloating	9 (14)	0
Weight loss	8 (12)	0
Laboratory		
Decreased white cell count	43 (66)	9 (14)
Decreased neutrophil count	42 (65)	18 (28)
Decreased thrombocyte count	33 (51)	6 (9)
Alanine aminotransferase elevation	32 (49)	0
Aspartate aminotransferase elevation	25 (38)	0
Alkaline phosphatase elevation	22 (34)	0
Blood creatinine level elevation	15 (23)	0

Listed are adverse events that are reported in at least 10% of the patients.
*Adverse events were scored as treatment-related if investigator defined relatedness as probably or definitely.

Fig.2 A. Distribution of responses to two items of the SWT domain across patients with a deterioration, no change and improvement of the facet score (global QoL/general health) of the WHOQOL-BREF using minimal clinical important differences. B. Distribution of responses to two items of the SWT domain across patients with more (≥ 14) or less (< 14) clinical adverse events.



†Distribution of answers to this item was significantly different between patients with no change and an improvement of QoL (*P = 0.010*).
Abbreviations: AE, adverse event; QoL, Quality of Life.

(71.2±17.1) or a deterioration (75.8±9.5). The SWT domain scores did not differ between groups across the WHOQOL-BREF domains. No significantly different SWT domain scores were found between groups based on EORTC QLQ C-30 global Health Status/QoL scale and the other scales (Supplemental Table A2). Likewise, the SWT scores did not differ across QoL groups between the 2nd and 4th chemotherapy cycle assessed with the WHOQOL-BREF and EORTC QLQ-C30 respectively (Supplemental Table A3 and A4). The explained variance of (HR)QoL after chemotherapy by SWT ranged from 0.002 (Cognitive scale) to 0.170 (global Health Status/QoL scale) using the EORTC QLQ C-30 and from 0.009 (social relationships) to 0.125 (psychological health) assessed with the WHOQOL-BREF (Table 4).

If we restricted all above mentioned analyses to patients with first-line treatment, no significantly different results were found (data not shown).

Table 3. Mean SWT domain scores across groups regarding change in WHOQOL-BREF facet and domain scores between baseline and after 4th cycle of pemetrexed treatment (N=62)

WHOQOL-BREF facet/ domains	Δ QoL group	N (%)	Mean change in facet/ domain scores†	Domain score SWT	P-value*
Overall QoL/general health	Deterioration	17 (27)	-2.1 (1.1)	75.8 (9.5)	
	No change	14 (23)	0.0 (0.0)	71.2 (17.1)	*0.008*
	Improvement	31 (50)	1.7 (0.9)	84.1 (10.5)	
Physical health	Deterioration	16 (26)	-4.2 (2.6)	76.3 (15.9)	
	No change	24 (39)	0.0 (0.7)	78.1 (13.1)	0.455
	Improvement	20 (32)	3.7 (2.1)	82.0 (10.9)	
	Missing	2 (3)			
Psychological health	Deterioration	26 (42)	-3.0 (1.6)	78.0 (12.7)	
	No change	25 (40)	0.0 (0.5)	79.2 (14.5)	0.853
	Improvement	10 (16)	2.7 (1.3)	80.0 (11.8)	
	Missing	1 (2)			
Social relationships	Deterioration	29 (47)	-3.2 (2.3)	78.6 (13.0)	
	No change	17 (27)	0.0 (0.2)	75.6 (15.1)	0.309
	Improvement	15 (24)	2.2 (1.8)	82.9 (10.6)	
	Missing	1 (2)			
Environment	Deterioration	18 (29)	-2.4 (1.2)	81.3 (9.8)	
	No change	28 (45)	-0.1 (0.8)	76.0 (15.4)	0.428
	Improvement	14 (23)	2.8 (1.3)	82.1 (11.2)	
	Missing	2 (3)			

Data are expressed as means (SD).
†Minimal clinical important differences were used to determine deterioration, no change and improvement of QoL per domain/facet.
*Distributions of SWT scores across change in QoL groups were compared using the Kruskal-Wallis test.
Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF; SWT, satisfaction with therapy; SD, standard deviation; N, number of patients.

Factors associated with satisfaction with therapy

Results of the regression analyses performed in patients treated with first-line platinum-based pemetrexed treatment (*N*=60) with the SWT domain score as dependent variable and patient and treatment-related factors as independent variables are shown in Table 5. In the univariable analyses patients' age (*P* = 0.042), tumor response (*P* = 0.014), sex (*P = 0.048)* and the domain score FSE (*P* = 0.004) were significantly related to SWT. In the multivariable analysis (R^2 = 32.6%), only age (β = 0.43; 95% CI 0.05-0.82), FSE (β = 0.17;

95% CI 0.06-0.29) and tumor response (β = 7.93; 95% CI 1.64-14.22) showed independent relations with SWT. No associations were found between SWT and the frequency of grade 1/2 or grade 3/4 AEs. Similarly, recent AEs (within four weeks before completion of CTSQ) and clinical AEs were not related with SWT (data not shown).

Table 4. QoL scores after 4 cycles of chemotherapy and its explained variance by SWT domain score of the CTSQ

WHOQOL-BREF					EORTC QLQ-C30				
Facet/domains	N	Mean (SD)	ρ	R^2	Scales	N	Mean (SD)	ρ	R^2
Overall QoL/ general health	65	6.3 (1.6)	0.203	0.041	Global Health Status/QoL	63	58.6 (23.8)	0.412	0.170
Physical health	63	13.7 (3.0)	0.240	0.058	Physical functioning	65	65.7 (21.8)	0.279	0.078
Psychological health	64	14.2 (2.2)	0.354	0.125	Role functioning	65	54.9 (33.6)	0.155	0.024
Social relationships	64	15.5 (2.5)	0.094	0.009	Emotional functioning	64	76.0 (21.5)	0.191	0.036
Environment	63	16.2 (2.1)	0.179	0.032	Cognitive functioning	64	78.1 (23.9)	-0.042	0.002
					Social functioning	63	75.4 (26.8)	0.128	0.016

ρ is the Pearson's correlation coefficient between the SWT domain score and the QoL score.
Abbreviations: SWT, satisfaction with therapy; WHOQOL-BREF, World Health Organization Quality of Life-BREF; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QoL, Quality of Life; SD, standard deviation; N, number of patients; R^2, explained variance

Table 5. Linear regression analyses of factors associated with satisfaction with therapy (N=60)

	Univariable analysis		Multivariable analysis	
	β coefficient (95% CI)	P-value	β coefficient* (95% CI)	P-value
Age	0.51 (0.10, 0.93)	*0.042*	0.43 (0.05, 0.82)	*0.028*
Sex				
female vs. male	-6.74 (-13.42, -0.06)	*0.048*	-3.90 (-9.98, 2.17)	0.203
ECOG performance score				
0 vs. ≥1	-1.61 (-9.14, 5.92)	0.670		
Tumor response (4th cycle)				
PR vs. SD or PD	-8.94 (-15.99, -1.90)	*0.014*	7.93 (1.64, 14.22)	*0.014*
No. of grade 1/2 AEs†	-0.13 (-0.86, 0.60)	0.731		
No. of grade 3/4 AEs†	1.27 (-0.77, 3.30)	0.217		
FSE domain score	0.19 (0.06, 0.32)	*0.004*	0.17 (0.06, 0.29)	*0.005*

*Adjusted for all factors statistically significant $p < 0.05$ in the univariable model.
†Cancer or treatment related adverse events during total treatment period.
Abbreviations: β, standardized beta; ECOG, Eastern Cooperative Oncology Group; N, number of patients; PR, partial response; SD, stable disease; PD, progressive disease; QoL, quality of life; AE, adverse event; FSE, feelings about side effects.

DISCUSSION

As shared decision making becomes increasingly important nowadays, the need for clinically useful patient reported outcomes increases likewise. It has been recently demonstrated that shared decisions were positively associated with a higher patient-reported quality of care [23], which may be particularly important in cancer patients with poor prognosis. Therefore, our objective was to assess the value of patient reported SWT alongside widely accepted clinical outcomes of therapy. To our knowledge, this is the first study to have extensively assessed and characterized patients' satisfaction with chemotherapy.

Our results propose that SWT covers different aspects of patient-centered and reported impact of treatment effects than QoL and adverse events and therefore SWT could be useful in decision making, as it offers important supplementary information from a patients' perspective. SWT described < 10% of the variance of the functional scales and domains from both (HR)QoL questionnaires, except for global Health Status/QoL (17%) and the psychological domain (13%). Accordingly, our group [18] already suggested the additional informative value of patients' SWT as the different aspects of (HR)QoL showed a low correlation (<0.3) to items of the CTSQ. Although symptomatic adverse events may substantially contribute to QoL in NSCLC [5], the frequency of (severe) treatment and cancer-related adverse events was not associated with treatment satisfaction. However, patients with better feelings about these side effects appeared to be more content with therapy. Therefore, patients' education about and management of adverse events may have added value in maintaining patients' well-being during chemotherapy, ultimately resulting in higher treatment satisfaction.

In our study, >80% of the patients valued pemetrexed and platinum-based chemotherapy as worth taking and would probably or definitely decide to take the chemotherapy again regardless of the presence of chemotherapy-related adverse events or deterioration in QoL. As ~75% of the patients correctly expected no or unlikely cancer cure, expressed satisfaction with therapy in our study is not solely a reflection of inaccurate expectations. Previous studies evaluating treatment preferences in a variety of oncological populations have reported that patients value even small benefits greatly and judge toxicity as less important [10,24]. More recently, Peeters et al. [12] and Pacchiana et al. [25] assessed patients' perceptions on future maintenance treatment for advanced NSCLC and they showed a generally favorable attitude towards treatment continuation at foresight, even if the expected gain of overall survival would be minimal. In agreement with our findings, mild-to-moderate side effects would be accepted by most patients [12]. Blinman et al [10] noticed that smaller benefits were judged sufficient for metastatic compared to locally advanced NSCLC. Furthermore, pemetrexed has been shown to be associated with relatively mild toxicity profiles and is generally well tolerated [3,26]. In our study population, these

considerations may have contributed to the highly valued merits of treatment despite side effects and the large willingness to undergo treatment again at hindsight.

Older patients showed a higher treatment satisfaction than younger patients, which offers no support to restrained prescription of pemetrexed and platinum-based chemotherapy in the elderly. Although recent studies have shown that palliative platinum-based doublet treatments result in improved survival rates comparable to younger patients, they often receive no chemotherapy or only single-agent regimens resulting in risk of undertreatment [27–29]. However, adequate information about other important treatment outcomes as toxicity, symptom relief and costs are scarce. In general, younger patients are more socially active compared to elderly. Moreover, it is commonly accepted that senescence is associated with an increased risk of morbidity and mortality. Therefore, higher hopes and demands of chemotherapy and worse coping with a shorter life expectancy may explain the finding in our study that younger patients are less easily satisfied with treatment.

Importantly, patients in our study represent a real-life study population, which significantly differs from populations generally included in clinical trials. Many patients in our population had (multiple) comorbidities, which occurs more frequently in unselected cancer populations [30]. However, this is in contrast to earlier clinical trials where patients with significant comorbidities or organ dysfunction were excluded from enrolment [3,31]. Additionally, higher median age and the inclusion of patients with a high (≥ 2) ECOG performance score compared to previous clinical trials could have led to lower tolerability of treatment and higher number of (severe) adverse events. Grutters et al. already showed that (even mild) adverse events might negatively influence QoL outcomes [5].

A major limitation of our study is imposed by the study design, which prevented us to evaluate treatment satisfaction (and its relation with change of QoL) in patients who did not complete the full treatment of four cycles chemotherapy. Therefore, our results were obtained in a group of patients who had a good performance score and who mainly established disease stabilization. These factors could have led to an overestimation of the level of treatment satisfaction and underestimation of the associations between SWT with QoL and (feelings about) adverse events and between treatment response and SWT. In future research, we would recommend to assess SWT earlier during therapy to increase knowledge with respect to treatment satisfaction in patients with clinically important toxicities, poor treatment response and worse QoL. Finally, we cannot exclude the possibility of unmeasured false hope and social desirability bias in our results. Since patients completed the questionnaires by self-report and the questionnaires were collected by their care providers, it is possible patients responded with greater optimism than they actually felt.

CONCLUSION

In conclusion, the CTSQ is a useful tool to extensively assess SWT in research as well as in daily clinical decision making. The results of this study justify further exploration of SWT in patients with advanced NSCLC treated with chemotherapy. In shared decision making on palliative treatment, knowledge about patients' treatment satisfaction may provide important supplementary information besides patients' QoL and treatment toxicities.

ACKNOWLEDGEMENTS

We thank Hans in 't Veen (Franciscus Gasthuis) and Ton van Boxem (Bravis hospital) for providing data.

REFERENCES

1. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. Cochrane database Syst Rev. 2010;(5):CD007309. doi:10.1002/14651858.CD007309.pub2.
2. Mannion E, Gilmartin JJ, Donnellan P, Keane M, Waldron D. Effect of chemotherapy on quality of life in patients with non-small cell lung cancer. Support Care Cancer. 2014;22(5):1417-1428. doi:10.1007/s00520-014-2148-9.
3. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543-3551. doi:10.1200/JCO.2007.15.0375.
4. Howell D, Molloy S, Wilkinson K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. Ann Oncol. 2015;26(9):1846-1858. doi:10.1093/annonc/mdv181.
5. Grutters JPC, Joore MA, Wiegman EM, et al. Health-related quality of life in patients surviving non-small cell lung cancer. Thorax. 2010;65(10):903-907. doi:10.1136/thx.2010.136390.
6. Movsas B, Moughan J, Sarna L, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. J Clin Oncol. 2009;27(34):5816-5822. doi:10.1200/JCO.2009.23.7420.
7. Staren ED, Gupta D, Braun DP. The prognostic role of quality of life assessment in breast cancer. Breast J. 17(6):571-578. doi:10.1111/j.1524-4741.2011.01151.x.
8. Ediebah DE, Coens C, Zikos E, et al. Does change in health-related quality of life score predict survival? Analysis of EORTC 08975 lung cancer trial. Br J Cancer. 2014;110(10):2427-2433. doi:10.1038/bjc.2014.208.
9. Qi Y, Schild SE, Mandrekar SJ, et al. Pretreatment quality of life is an independent prognostic factor for overall survival in patients with advanced stage non-small cell lung cancer. J Thorac Oncol. 2009;4(9):1075-1082. doi:10.1097/JTO.0b013e3181ae27f5.
10. Blinman P, Alam M, Duric V, McLachlan S-A, Stockler MR. Patients' preferences for chemotherapy in non-small-cell lung cancer: a systematic review. Lung Cancer. 2010;69(2):141-147. doi:10.1016/j.lungcan.2010.05.001.
11. Bridges JFP, Mohamed AF, Finnern HW, Woehl A, Hauber AB. Patients' preferences for treatment outcomes for advanced non-small cell lung cancer: a conjoint analysis. Lung Cancer. 2012;77(1):224-231. doi:10.1016/j.lungcan.2012.01.016.
12. Peeters L, Sibille A, Anrys B, et al. Maintenance Therapy for Advanced Non–Small-Cell Lung Cancer: A Pilot Study on Patients' Perceptions. J Thorac Oncol. 2012;7(8):1291-1295. doi:10.1097/JTO.0b013e31825879ea.
13. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. BMJ. 1998;317(7161):771-775. http://www.ncbi.nlm.nih.gov/pubmed/9740561. Accessed June 24, 2016.
14. Brundage MD, Feldman-Stewart D, Cosby R, et al. Cancer patients' attitudes toward treatment options for advanced non-small cell lung cancer: implications for patient education and decision support. Patient Educ Couns. 2001;45(2):149-157. http://www.ncbi.nlm.nih.gov/pubmed/11687329. Accessed June 24, 2016.
15. Weeks JC, Cook EF, O'Day SJ, et al. Relationship Between Cancer Patients' Predictions of Prognosis and Their Treatment Preferences. JAMA. 1998;279(21):1709. doi:10.1001/jama.279.21.1709.

16. Temel JS, Greer JA, Admane S, et al. Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of early palliative care. J Clin Oncol. 2011;29(17):2319-2326. doi:10.1200/JCO.2010.32.4459.
17. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012;367(17):1616-1625. doi:10.1056/NEJMoa1204410.
18. Cheung K, de Mol M, Visser S, Den Oudsten BL, Stricker BH, Aerts JGJ V. Reliability and validity of the Cancer Therapy Satisfaction Questionnaire in lung cancer. Qual Life Res. 2016;25(1):71-80. doi:10.1007/s11136-015-1062-z.
19. Skevington SM, Lotfy M, O'Connell KA, WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res. 2004;13(2):299-310. http://www.ncbi.nlm.nih.gov/pubmed/15085902. Accessed June 24, 2016.
20. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-376. http://www.ncbi.nlm.nih.gov/pubmed/8433390. Accessed June 26, 2016.
21. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of- life scores. J Clin Oncol. 1998;16(1):139-144. doi:10.1200/jco.1998.16.1.139.
22. Maringwa JT, Quinten C, King M, et al. Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials. Support Care Cancer. 2011;19(11):1753-1760. doi:10.1007/s00520-010-1016-5.
23. Kehl KL, Landrum MB, Arora NK, et al. Association of Actual and Preferred Decision Roles With Patient-Reported Quality of Care: Shared Decision Making in Cancer Care. JAMA Oncol. 2015;1(1):50-58. doi:10.1001/jamaoncol.2014.112.
24. Duric VM, Stockler MR, Heritier S, et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now? Ann Oncol. 2005;16(11):1786-1794. doi:10.1093/annonc/mdi370.
25. Pacchiana MV, Capelletto E, Carnio S, et al. Patients' Attitudes and Physicians' Perceptions Toward Maintenance Therapy for Advanced Non–Small-cell Lung Cancer: A Multicenter Italian Survey. Clin Lung Cancer. 2016. doi:10.1016/j.cllc.2016.10.002.
26. Pujol J-L, Paz-Ares L, de Marinis F, et al. Long-Term and Low-Grade Safety Results of a Phase III Study (PARAMOUNT): Maintenance Pemetrexed Plus Best Supportive Care Versus Placebo Plus Best Supportive Care Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamou. Clin Lung Cancer. 2014;15(6):418-425. doi:10.1016/j.cllc.2014.06.007.
27. Quoix E, Zalcman G, Oster J-P, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet (London, England). 2011;378(9796):1079-1088. doi:10.1016/S0140-6736(11)60780-0.
28. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2191-2197. doi:10.1200/JCO.2009.25.4052.
29. Paz-Ares LG, Zimmermann A, Ciuleanu T, et al. Meta-analysis examining impact of age on overall survival with pemetrexed for the treatment of advanced non-squamous non-small cell lung cancer. Lung Cancer. 2017;104:45-51. doi:10.1016/j.lungcan.2016.12.007.

30. Aarts MJ, Aerts JG, Van Den Borne BE, Biesma B, Lemmens VEPP, Kloover JS. Comorbidity in patients with small-cell lung cancer: Trends and prognostic impact. Clin Lung Cancer. 2015;16(4):282-291. doi:10.1016/j.cllc.2014.12.003.
31. Paz-ares L, Marinis F De, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind , phase 3 , randomised controlled trial. Lancet Oncol. 2012;13(3):247-255. doi:10.1016/S1470-2045(12)70063-3.

SUPPLEMENTAL TABLES

Table A1. Reasons for non-completion of questionnaires by patients who started chemotherapy

	baseline ***N*=165**	**2nd cycle (day 7-14)** ***N*=141**	**4th cycle (day 14-21)** ***N*=89**
	EORTC QLQ-C30 WHOQOL-BREF	*EORTC QLQ-C30 WHOQOL-BREF*	*EORTC QLQ-C30 WHOQOL-BREF CTSQ*
Non-completion, total	24 (14.5)	31 (21.9)	24 (27.0)
Not able to read Dutch	1 (0.6)	1 (0.7)	1 (1.1)
Physical disabilities	3 (1.8)	1 (0.7)	1 (1.1)
Poor condition	8 (4.2)	6 (4.3)	2 (2.2)
Mental burden	7 (4.2)	4 (2.8)	4 (4.5)
Stop study, death	N/A	3 (2.1)	1 (1.1)
Stop study, PD	N/A	3 (2.1)	1 (1.1)
Stop study, toxicity	N/A	1 (0.7)	0
Logistic failure	5 (3.0)	10 (7.1)	10 (11.2)
Unknown	1 (0.6)	2 (1.4)	4 (4.5)

Data are expressed as frequencies (percentage). Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; WHOQOL-BREF, World Health Organization Quality of Life-BREF; CTSQ, Cancer Therapy Satisfaction Questionnaire; PD, progressive disease; N/A, not applicable

Table A2. CTSQ domains in relation with change in EORTC QLQ C-30 QoL and functional scale scores between before and after treatment with pemetrexed (N=63)

EORTC QLQ C-30 scales	Δ QoL group	N (%)	Mean change in scale score†	Domain score SWT	P-value*
Global Health Status/QoL	Deterioration	21 (33)	-24.6 (24.4)	78.4 (13.2)	0.801
	No change	11 (17)	-0.76 (24.6)	77.3 (14.8)	
	Improvement	31 (49)	13.9 (22.5)	80.0 (12.5)	
Physical functioning	Deterioration	36 (57)	-23.3 (17.0)	76.6 (14.5)	0.346
	No change	6 (10)	0.0 (0.0)	83.8 (8.6)	
	Improvement	21 (33)	20.3 (17.8)	81.8 (10.5)	
Role functioning	Deterioration	33 (52)	-38.9 (120.2)	78.7 (12.4)	0.965
	No change	9 (14)	0.0 (0.0)	77.0 (20.0)	
	Improvement	21 (33)	41.3 (22.7)	80.4 (10.6)	
Emotional functioning	Deterioration	21 (33)	-22.4 (18.2)	77.9 (14.5)	0.818
	No change	8 (13)	0.0 (0.0)	79.9 (19.6)	
	Improvement	32 (51)	22.4 (18.3)	79.2 (10.6)	
	Missing	2 (3)			
Cognitive functioning	Deterioration	21 (33)	-29.4 (22.3)	76.0 (13.9)	0.441
	No change	28 (45)	0.0 (0.0)	80.4 (11.6)	
	Improvement	12 (19)	25.0 (16.7)	80.1 (15.4)	
	Missing	2 (3)			
Social functioning	Deterioration	21 (33)	-30.2 (25.6)	78.5 (13.1)	0.904
	No change	19 (31)	0.0 (0.0)	78.2 (15.0)	
	Improvement	20 (32)	33.3 (18.7)	80.0 (12.1)	
	Missing	3 (5)			

Data are expressed as means (SD).

†Minimal clinical important difference=5, > 5 in positive or negative direction were considered as having an improvement or deterioration in QoL respectively

*Distributions of data across groups were compared using the Kruskal-Wallis test.

Abbreviations: EORTC QLQ-C30; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD, standard deviation; N, number of patients; QoL, Quality of Life; SWT, satisfaction with therapy.

Table A3. CTSQ domains in relation with change in WHOQOL-BREF QoL and domain scores between 2nd and 4thcycle of chemotherapy (after treatment) with pemetrexed (N=55)

WHOQOL-BREF facet/domains	Δ QoL group	N (%)	Mean change in overall QoL/ domain score†	Domain score SWT	P-value*
Overall QoL/ general health	Deterioration	15 (27)	-2.2 (1.2)	78.1 (15.0)	0.230
	No change	16 (29)	0.0 (0.0)	76.1 (12.4)	
	Improvement	24 (44)	1.8 (0.9)	83.2 (9.8)	
Physical health	Deterioration	15 (27)	-3.6 (1.8)	78.5 (15.3)	0.883
	No change	22 (40)	0.0 (0.7)	79.2 (11.3)	
	Improvement	16 (29)	3.0 (1.1)	81.7 (11.7)	
	Missing	2 (4)			
Psychological health	Deterioration	20 (36)	-2.4 (1.2)	75.0 (12.1)	0.132
	No change	20 (36)	0.1 (0.6)	81.8 (13.8)	
	Improvement	14 (25)	2.3 (0.7)	83.2 (9.0)	
	Missing	1 (2)			
Social relationships	Deterioration	22 (40)	-2.6 (2.2)	81.1 (11.0)	0.404
	No change	15 (27)	0.0 (0.2)	75.7 (12.5)	
	Improvement	17 (31)	2.1 (0.9)	81.1 (14.0)	
	Missing	1 (2)			
Environment	Deterioration	13 (24)	-2.8 (1.1)	81.8 (10.2)	0.847
	No change	31 (56)	0.0 (0.6)	79.6 (13.1)	
	Improvement	9 (16)	1.9 (0.6)	78.2 (13.5)	
	Missing	2 (4)			

Data are expressed as means (SD).

†Minimal clinical important differences were used to determine deterioration, no change and improvement of QoL per domain/facet.

*Distributions of data across groups were compared using the Kruskal-Wallis test.

Abbreviations: WHOQOL-BREF, World Health Organization Quality of Life-BREF; QoL, Quality of Life; SD, standard deviation; N, number of patients; SWT, satisfaction with therapy.

Table A4. CTSQ domains in relation with change in EORTC QLQ C-30 QoL and functional domain scores between 2nd and 4thcycle of chemotherapy (after treatment) with pemetrexed (N=60)

EORTC QLQ C-30 scales	Δ QoL group	N (%)	Mean change in scale score†	Domain score SWT	P-value*
Global Health Status/QoL	Deterioration	21 (35)	-26.2 (15.0)	78.2 (11.9)	
	No change	11 (18)	0.0 (0.0)	86.0 (11.8)	0.191
	Improvement	21 (35)	18.3 (13.3)	78.1 (12.9)	
	Missing	7 (12)			
Physical functioning	Deterioration	29 (48)	-20.2 (16.2)	76.9 (15.7)	
	No change	12 (20)	0.0 (0.0)	81.3 (7.2)	0.855
	Improvement	20 (33)	21.0 (11.9)	81.4 (11.6)	
Role functioning	Deterioration	26 (43)	-32.7 (16.0)	78.9 (12.8)	
	No change	19 (32)	0.0 (0.0)	89.1 (13.4)	0.980
	Improvement	15 (25)	36.7 (16.9)	80.2 (14.1)	
Emotional functioning	Deterioration	21 (35)	-22.2 (14.8)	77.9 (14.8)	
	No change	15 (25)	0.0 (0.0)	78.3 (10.0)	0.699
	Improvement	18 (30)	15.7 (7.5)	82.7 (11.2)	
	Missing	6 (10)			
Cognitive functioning	Deterioration	19 (32)	-26.3 (12.8)	77.6 (14.4)	
	No change	21 (35)	0.0 (0.0)	79.6 (10.8)	0.670
	Improvement	14 (23)	26.2 (12.6)	82.4 (12.2)	
	Missing	6 (10)			
Social functioning	Deterioration	20 (33)	-30.0 (23.3)	77.3 (14.3)	
	No change	17 (28)	0.0 (0.0)	80.2 (11.7)	0.807
	Improvement	16 (27)	34.4 (15.5)	82.4 (10.9)	
	Missing	7 (12)			

Data are expressed as means (SD).

†Minimum clinical important difference = 5, > 5 in positive or negative direction was considered as having an improvement or deterioration in QoL, respectively.

*Distributions of data across groups were compared using the Kruskal-Wallis test.

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD, standard deviation; N, number of patients; QoL, Quality of Life; SWT, satisfaction with therapy.