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ORIGINAL ARTICLE

Trajectories of health-related quality of life and symptom burden in patients with advanced cancer towards the end of life: Longitudinal results from the eQuiPe study

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Abstract

Background: Support for health-related quality of life (HRQOL) is an essential part of cancer care in the final stages of life, yet empirical guidance regarding HRQOL and symptom trajectories is lacking.

Aim: To assess the change in HRQOL and symptom burden in the last year of life in patients with advanced cancer and its association with health care–related factors, cancer-specific treatment, and comorbidity.

Methods: A prospective, multicenter, observational study in patients with advanced cancer (eQuiPe). Three monthly questionnaires included European Organization for

Research and Treatment of Cancer Quality of Life-C30 and reported continuity of care. Multivariable mixed-effects analysis was used to assess the association between HRQOL and health care–related factors.

Results: A total of 762 deceased patients were included with a mean age of 66 (SD, 10) years and 52% were male. The most common primary tumors were lung (29%), colorectal (20%), and breast cancer (13%). Mean overall HRQOL decreased in the last 9 months of life, with the greatest decrease in the last 3 months (β −16.2). Fatigue, pain, appetite loss, dyspnea, constipation, and nausea worsened significantly in the last year of life. Multimorbidity (β −7.5) and a better reported continuity of care (β 0.7) were both significantly associated with the trajectory of HRQOL.

Conclusion: Mean overall HRQOL begins to decline 9 months before death, highlighting the need for early identification and (re)assessment of different symptoms as aspects of HRQOL follow different trajectories. Multimorbidity and reported continuity of care may be associated with the trajectory of HRQOL.

KEYWORDS
advanced cancer, continuity of care, longitudinal, palliative care, quality of life

INTRODUCTION

Palliative care has been defined as an approach that improves the quality of life of patients and their family members facing problems associated with a life-threatening illness. Quality of life can be improved through early identification, assessment, and treatment of pain and other physical, psychosocial, and spiritual problems.[1] Health-related quality of life (HRQOL) in patients with cancer is known to be dynamic and can vary throughout the cancer trajectory. A typical cancer trajectory has been described as one of a relatively stable HRQOL followed by a relatively short period of marked decline in the last 2 to 3 months of life.[2–7] However, most evidence is based on small study samples and cross-sectional study designs; longitudinal results are scarce. Moreover, some cross-sectional studies suggest a positive association between satisfaction with care and emotional functioning in patients with advanced cancer.[8] An association between reported continuity of care and global functioning has also been suggested, but longitudinal results are lacking.[9] In addition, the trajectory of HRQOL is influenced by the (cancer-specific) treatment received and comorbidity.[10–12] Therefore, the aim of this study was to assess the change in HRQOL and symptom burden over time in the last year of life in patients with advanced cancer using a longitudinal multicenter population-based study design, and its association with specific health care–related factors, adjusted for the (cancer-specific) treatment received and comorbidity.

METHODS

Study design

A prospective, longitudinal, multicenter, observational (eQuiPe) study on HRQOL and experienced quality of care of patients with advanced cancer was conducted in the Netherlands.[13] From November 2017 to March 2020, patients were invited by their treating physician from one of the 40 participating hospitals or were self-registered. After informed consent, patients completed a questionnaire every 3 months via the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship registry[14] until death or loss to follow-up. The questionnaires were linked to the Netherlands Cancer Registry to obtain clinical data and date of death. The study was exempted from medical ethical review by the Medical Research Ethics Committee of the Antoni van Leeuwenhoek Hospital (METC17.1491) according to the Dutch Medical Research Involving Human Subjects Act. The study is registered in the Netherlands Trial Register as NTR6584. Details of the study protocol have been reported elsewhere.[13]

Study population

All patients with advanced cancer (solid tumor with metastasis) aged older than 18 years were eligible for inclusion. Additional criteria were defined for patients with breast and prostate cancer; patients with breast cancer were eligible if they had metastasis in multiple organ systems and patients with prostate cancer were eligible if their cancer was castrate resistant. All deceased patients (data cutoff June 2022) were selected for this analysis.

Measurements

Health-related quality of life

HRQOL was measured using the European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30).[15,16] The EORTC QLQ-C30 consists of five functioning subscales (physical, emotional, role, cognitive, and social), three symptom subscales (fatigue, nausea/vomiting, and pain), five single-symptom items (insomnia, dyspnea, constipation, diarrhea, and appetite loss), and one item on perceived financial impact. A recently developed QLQ-C30 summary score, validated by Giesinger et al.,[17] was used as a measure of overall HRQOL. All scores were transformed to a 0 to 100 scale, with higher scores indicating better functioning, higher symptom burden, or better overall HRQOL.

Reported continuity of care and satisfaction with care

Continuity of care, as reported by the patient, was measured by the Consumer Quality Index Palliative Care,[18] using a single item "Does the care you received from different health care providers match each other?" A 4-point Likert scale was used, ranging from "never" to "always," and responses were linearly transformed into a score of 0 to 100, with higher scores indicating greater reported continuity of care.

Overall satisfaction with care was measured using the validated Satisfaction with In-Patient Cancer Care questionnaire.[19] The single item of the overall satisfaction with care scale ("How would you rate the quality of care you received in the past month?") on a 5-point Likert scale ranging from "poor" to "excellent" was used. Responses were linearly transformed to a score of 0 to 100, with higher scores indicating greater satisfaction with care.

Sociodemographic and clinical characteristics

Age, gender, education, marital status, and ethnicity were self-reported in the baseline questionnaire. Comorbidity at the time of completing the questionnaire was measured using the Self-administered Comorbidity Questionnaire in both the baseline and follow-up questionnaires.[20] Cancer-specific treatments received were self-reported during follow-up, and primary tumor type, date of primary cancer diagnosis, and date of death were obtained from the Netherlands Cancer Registry.

Statistical analysis

Descriptive analyses were used to describe the sociodemographic and clinical characteristics. Time to death was categorized into groups of 3 months: >12 months before death (T4, baseline), 10 to 12 months (T3), 7 to 9 months (T2), 4 to 6 months (T1), and 0 to 3 months before death (T0). The thresholds for clinical relevance of Giesinger et al.[21] were used to calculate the percentage of patients with a clinically relevant problem regarding the subscales and items. The crude association between time to death and overall HRQOL was examined using a mixed-effects model. We then adjusted the association for age and gender (adjusted model) and additionally for reported continuity of care, satisfaction with care, number of cancer-specific treatments received, and comorbidity (multivariable model) to explore which factors were associated with the association between HRQOL and time to death. These three models were then used to analyze the association between all separate functioning scores and symptom burden scores included in the EORTC QLQ-C30 and time to death. Statistical significance was achieved at $p < .01$. All statistical analyses were performed using STATA 17.0.

RESULTS

A total of 1108 patients participated in the eQuiPe study. Of these, 762 (69%) had died before the data cutoff (June 2022), had quality of life data available, and were included for analysis (Figure 1). At inclusion (baseline assessment), the deceased patients had a mean age of 66 years (SD, 10) and were predominantly male (52%) (Table 1). The most common primary tumor types were lung (29%), colorectal (20%), and breast cancer (13%). More than half of the patients died within 5 years of the initial cancer diagnosis.

Health-related quality of life

Mean overall HRQOL decreased significantly over time toward death, with a steeper decline in the last 3 months; namely from 79

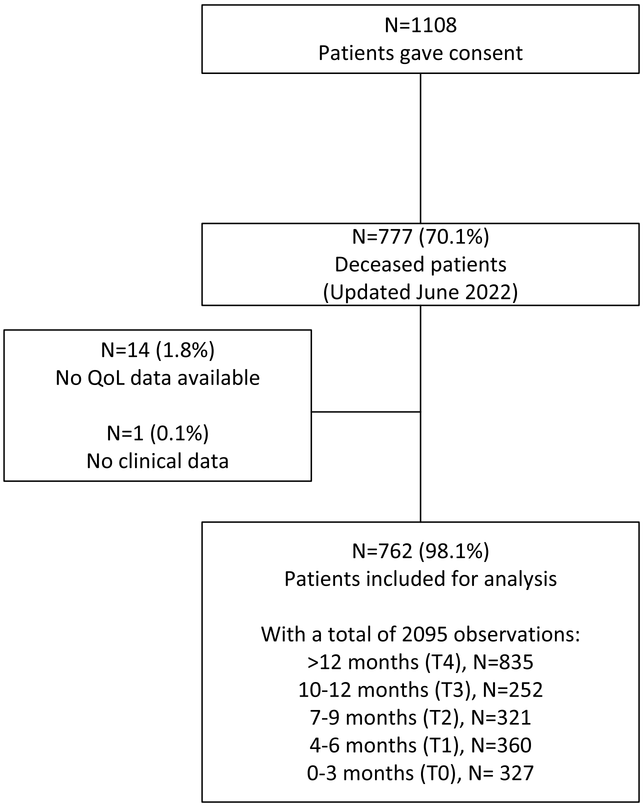


FIGURE 1 Flowchart of the inclusion and distribution of number of patients and number of observations.

TABLE 1 Baseline sociodemographic and clinical characteristics of deceased patients with advanced cancer ($n = 758$).

	No. (%)
Age, mean (SD); range (min-max)	66 (10); 29-93
Gender	
Male	396 (52)
Female	362 (48)
Education[a]	
Low	243 (32)
Medium	312 (41)
High	198 (26)
Ethnic background	
Dutch	686 (91)
Other	19 (3)
Missing	53 (7)
Partner	
Yes	639 (84)
No	118 (16)
Primary tumor type	
Lung	218 (29)
Colorectal	151 (20)
Breast	98 (13)
Prostate	79 (10)
Other	210 (28)
Time between primary cancer diagnosis and death	
<1 year	201 (27)
1–5 years	304 (40)
>5 years	251 (33)
No. of cancer treatments received in the last 3 months	
None	40 (5)
One	515 (68)
More than one simultaneously	203 (27)
Comorbidity	
None	223 (29)
One	249 (33)
Multi	239 (31)
Missing	47 (6)

Note: $N = 758/777$ patients had available baseline data. Number of missing values did not exceed 5% unless stated otherwise. Percentages may not equal 100 because of rounding.

[a] Education was defined according to the International Standard Classification of Educational guidelines. Low: LBO, VBO, LTS, LHNO, VMBO, or MBO1; medium: MAVO, VMBO-t, MBO-kort, MBO, MTS, MEAO, HAVO, or VWO; and high: HBO or WO.

(SD, 14) >12 months before death to 74 (SD, 15) in the last 4 to 6 months of life and reaching 66 (SD, 18) in the last 3 months (Figure 2). The percentage of patients with clinically relevant problems regarding physical functioning increased during the last year of life from 66% (T4) to 73% on T1 and reaching 85% in the last 3 months (T0). Similarly, the percentage of patients with clinically relevant problems regarding cognitive, emotional, and role and social functioning increased between T4 and T0, with the greatest increase between T1 and T0 (Figure 3A).

According to the multivariable mixed effect model, the mean overall HRQOL decreased significantly over time; T3 (β −2.4, $p = .014$), T2 (β −5.4, $p < .001$), T1 (β −6.8, $p < .001$), and T0 (β −16.2, $p < .001$) (Table 2). Patients with multimorbidity showed a steeper decline in mean overall HRQOL during the last year of life compared with patients without comorbidity (β −7.5, $p < .001$). A 10-point increase in continuity of care was associated with a 0.7 increase in the mean overall HRQOL ($p < .001$). Satisfaction with care and the number of cancer-specific treatments received were not significantly associated with changes in overall HRQOL in patients with advanced cancer in the last year of life.

Similar trends were found for the mean scores of each subscale (Supporting Information S1). Global and role functioning declined significantly in the last 12 months of life, with a steeper decline in the last 3 months of life, namely β −20.3 ($p < .001$) and β −27.9 ($p < .001$), respectively. Emotional, physical, and social functioning declined significantly from 7 to 9 months before death (T2), whereas cognitive functioning declined significantly only in the last 3 months of life (T0). A significantly steeper decline in physical functioning was found in female patients and with increasing age. Satisfaction with care was only associated with emotional functioning, whereas reported continuity of care was associated with global, physical, emotional, and social and role functioning. Multimorbidity was associated with a steeper decline in the mean score of all functioning subscales.

Symptom burden

Fatigue, dyspnea, pain, appetite loss, constipation, and nausea increased in the last 12 months of life, with a greater increase in the last 3 months (Figure 4). The symptoms of diarrhea and insomnia and perceived financial burden did not change significantly over time.

Consequently, the proportion of patients experiencing clinically relevant problems regarding the symptom burden also increased over time toward death (Figure 3B). Between >12 months before death and 0 to 3 months before death, the number of patients with a clinically relevant problem increased the most for the symptoms fatigue (+32%), appetite loss (+24%), and pain (+23%).

The multivariable mixed-effects model showed a significant increase in symptom burden starting from 7 to 9 months before death (T2) for appetite loss, fatigue, pain and nausea with the greatest increase in the last 3 months of life, namely β 25.4 ($p < .001$), β 22.3 (<.001), β 21.0 ($p < .001$), and β 12.2 ($p < .001$), respectively (Appendix

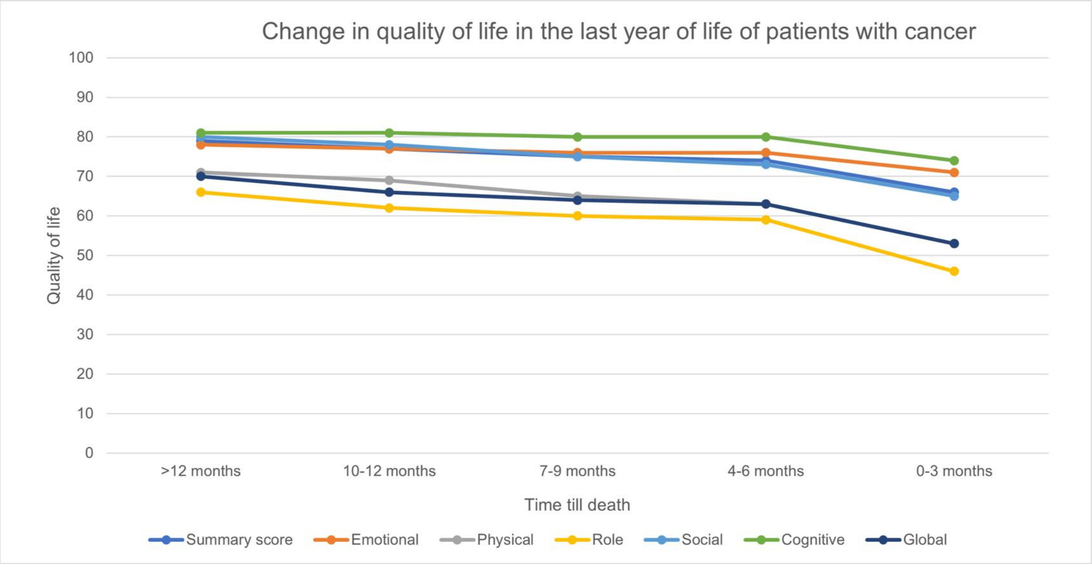


FIGURE 2 Trajectory of the mean overall health-related quality of life until death in patients with advanced cancer.

2). Dyspnea increased significantly at 4 to 6 months before death (β 6.4, $p < .001$) and in the last 3 months (β 16.9, $p < .001$). Constipation increased significantly only in the last 3 months of life (β 7.3, $p < .001$).

Patients with multimorbidity showed a steeper increase in fatigue, pain, insomnia, and perceived financial burden compared with patients without comorbidity. Patients receiving multiple cancer-specific treatments simultaneously had a steeper increase in fatigue than patients not receiving any treatment. Finally, a 10-point increase in reported continuity of care was associated with a smaller increase in pain, insomnia, and perceived financial burden.

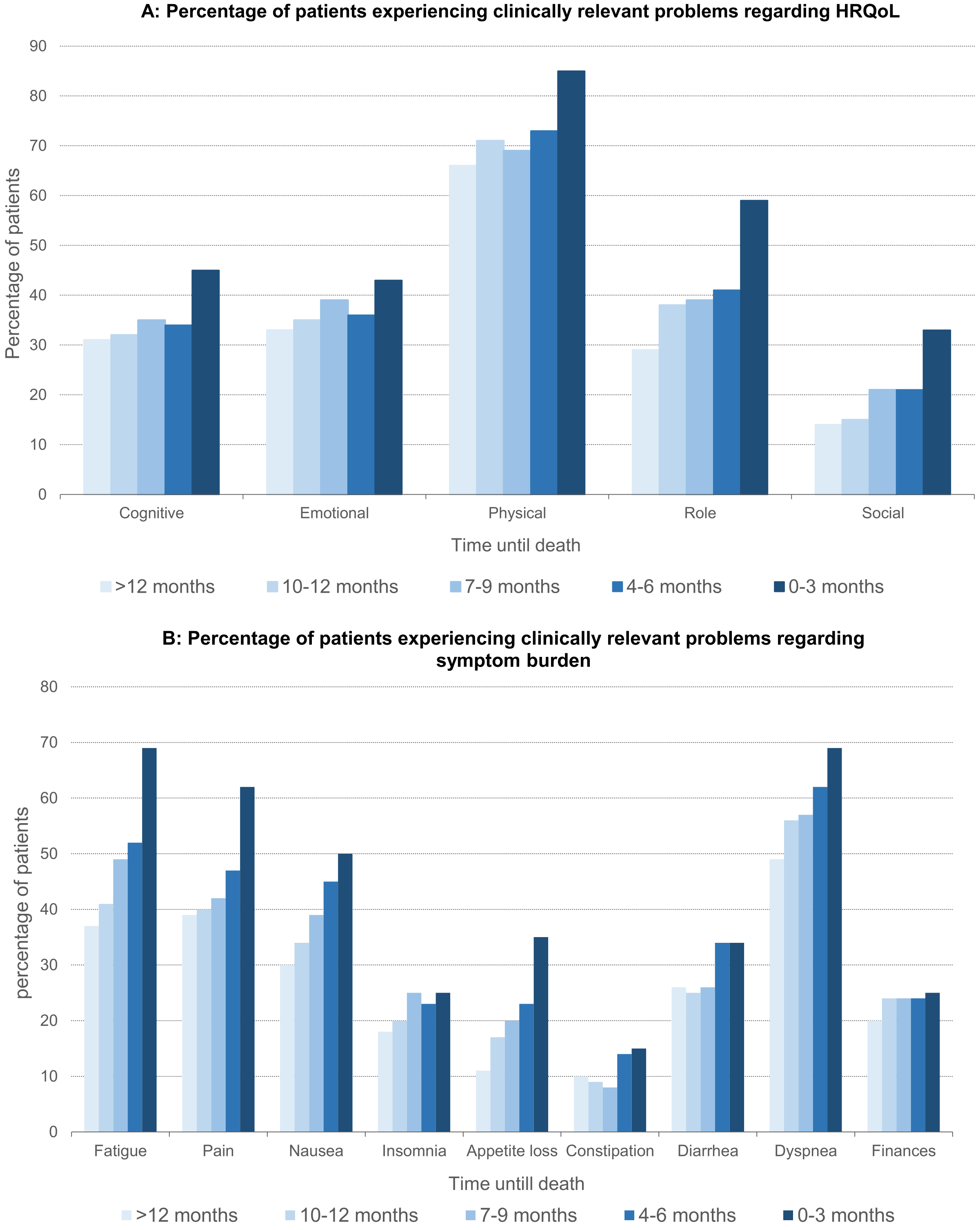
DISCUSSION

In this longitudinal study of 762 patients with advanced cancer, HRQOL began to decline 9 months before death, with a steeper decline in the last 3 months. In the last 3 months, most patients experienced clinically relevant problems related to physical, emotional, cognitive, and social and role functioning, as well as fatigue, pain, and dyspnea. In contrast to the expected greater decline of HRQOL in patients with multimorbidity, patients who experienced a greater continuity of care had a milder decline. Higher reported continuity of care was also associated with a lower increase in fatigue, pain, insomnia, and perceived financial burden.

This steep decline in HRQOL in the last 3 months of life is a clinical relevant difference according to a recent study by Musoro et al.[22] and is consistent with the original model constructed by Lynn and Adamson[2] and with other (mostly cross-sectional) studies. A Dutch study with 458 deceased patients with cancer showed a lower HRQOL in the last 3 months of life, compared with the previous months, as well as a higher symptom burden because of fatigue and loss of appetite.[4] Our longitudinal results confirm this decline in HRQOL and increase in symptom burden in the last 3 months of life. This decline may serve as an indicator implying that a patient is approaching death. Whereas systematic symptom monitoring in all domains is primarily needed to optimize symptom management, these findings imply that it can also be used to identify the beginning of the last months of life to have appropriate end-of-life care discussions, allowing patients to adjust to their prognosis and to tailor their care according to their needs and wishes.

Although the studies mentioned here suggest that HRQOL is relatively stable until the last 3 months of life, our longitudinal study shows that HRQOL begins to decline 9 months before death. This early decline has previously been described in some longitudinal studies conducted in smaller or more specific populations[5–7,23] and highlights the importance of integrating advance care planning early in the disease trajectory because it allows health care professionals the ability to anticipate the problems that are likely to occur. Advance care planning may also improve the continuity of care by increasing the clarity between the patients and health care professionals about future care preferences.[24]

To our knowledge, this is the first longitudinal study to assess the association between experienced quality of care (reported continuity of care and satisfaction with care) and the trajectory of HRQOL in patients with advanced cancer. Our results suggest that a better reported continuity of care is associated with a smaller decline in HRQOL and a smaller increase in pain, insomnia, and perceived financial burden. Although this is the first study to examine this association in patients with advanced cancer, its findings are consistent with studies in other patient groups, including patients with breast cancer at different stages of their disease,[9] elderly patients with chronic diseases,[25] patients with diabetes,[26] and patients with hypertension.[27] However, continuity of care is defined differently in these studies. In some studies, it is limited to the physician–patient relationship, whereas in our study it is defined as the compatibility of care between the different care providers involved throughout the patient's cancer journey. The lack of studies conducted in comparable



Results are based on the thresholds for clinical relevance of Giesinger et al; cognitive 75, emotional 71, physical 83, role 58, social 58, fatigue 39, pain 25, nausea 8, insomnia 50, appetite loss 50, constipation 50, diarrhea 17, dyspnea 17, and finances 17. Patients were thoough t to experience clinically relevant problems when their functioning scores were below the thresholds and their symptom scores were above the thresholds [21].

FIGURE 3 Percentage of patients with clinically relevant problems regarding HRQOL (A) and symptom burden (B) in the last year of life of patients with advanced cancer. HRQOL indicates health-related quality of life.

patient groups and the difference in definition make it difficult to compare results. However, all results suggest a positive association between continuity of care and HRQOL. Although more research is needed to assess causality, it is important to improve the collaboration between all care providers involved in a patient's disease trajectory. For example, a single point of contact could be identified for

TABLE 2 Mixed effect analysis for the association of summary HRQOL over time until death (in months).

	Crude model ($n = 754$)		Adjusted model ($n = 752$)		Multivariable model ($n = 663$)	
	β	P	β	P	β	P
Time until death						
T4	Reference	Reference	Reference	Reference	Reference	Reference
T3	−2.5	.002*	−2.6	.001*	−2.4	.014
T2	−4.3	.000*	−4.5	.000*	−5.4	.000*
T1	−6.2	.000*	−6.4	.000*	−6.8	.000*
T0	−15.2	.000*	−15.4	.000*	−16.2	.000*
Gender						
Male	-	-	Reference	Reference	Reference	Reference
Female	-	-	−2.3	.028	−2.2	.044
Age	-	-	−0.03	.511	−0.04	.423
No. of treatments						
None	-	-	-	-	Reference	Reference
One	-	-	-	-	−1.0	.343
More than one	-	-	-	-	−2.8	.030
No. of comorbidities						
None	-	-	-	-	Reference	Reference
One	-	-	-	-	−2.7	.035
Multi	-	-	-	-	−7.5	.000*
Continuity of care	-	-	-	-	0.7	.000*
Satisfaction with care	-	-	-	-	−0.01	.943

Note: The multivariable is corrected for gender, age, continuity of care, satisfaction with care, number of treatments received at the same time and for the number of comorbidities.

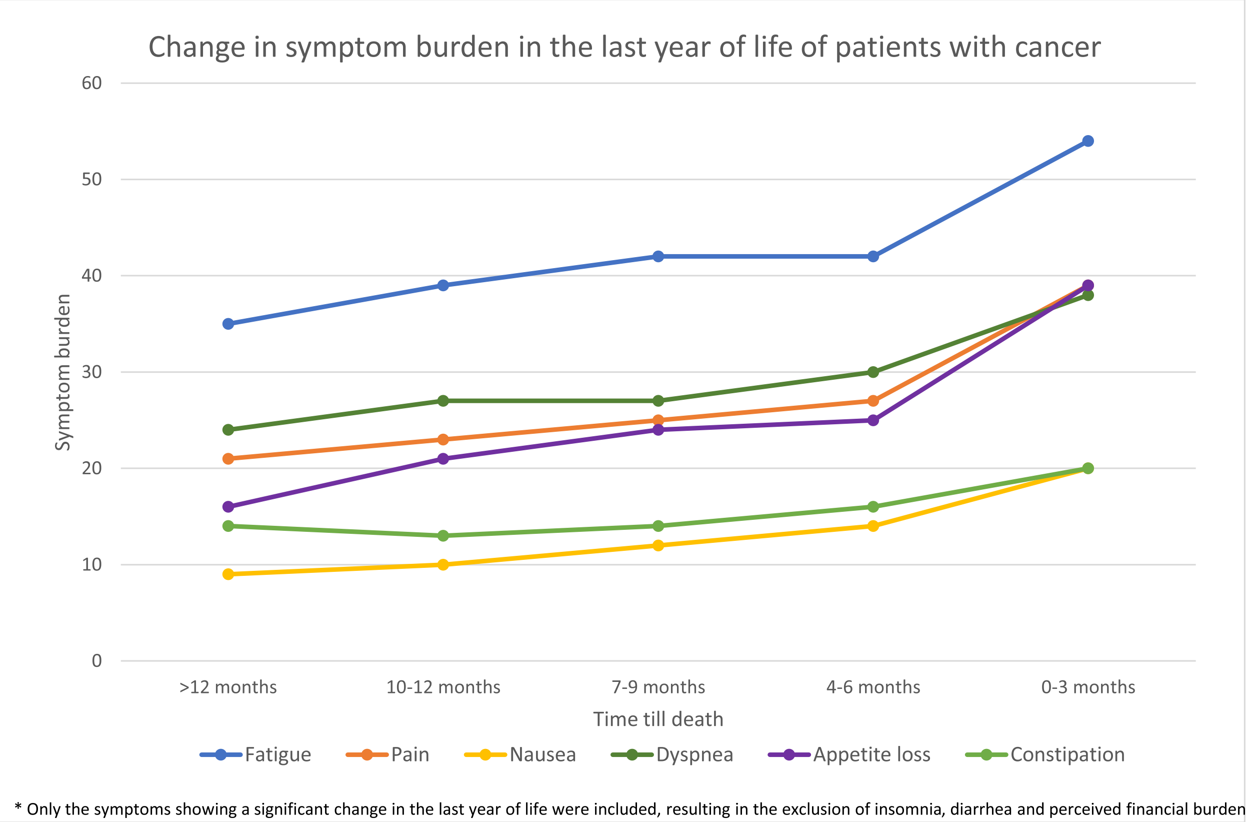
*Significance level reached at $p < .01$.

each patient to ensure that his or her wishes and needs, and those of relatives, are not lost in the transitions and collaborations between different care providers throughout the disease trajectory.

Our results suggest that there is no association between satisfaction with care and HRQOL or symptom burden, except for emotional functioning. The suggested positive association between satisfaction with care and emotional functioning is consistent with the cross-sectional baseline results of our eQuiPe study indicating the need for physicians to offer psychological support.[8] However, which factors are important when deciding on being less or more satisfied with care are unknown. A recent Swedish study in patients with endocrine gastrointestinal tumors reported that higher satisfaction with nurses' communication skills and physicians' interpersonal skills was associated with several aspects of HRQOL.[28] This suggests that the soft skills of health care workers may play a key role in patients' satisfaction with care and may influence their overall well-being. However, the lack of studies investigating this association in cancer patients, the wide variation in methods used to measure satisfaction with care, and that it is unknown how satisfaction with care is reached call for more research needed on this aspect.

Strengths and limitations

This unique and large prospective longitudinal multicenter study allowed us to detect changes in HRQOL and symptom burden at an individual level. The response rate was high (65%) and almost half of the deceased patients (43%) had also completed a questionnaire in the last 3 months of life. However, there are some limitations. First, patients were recruited by their treating physician, which may introduce selection bias because they tend to recruit relatively healthier patients. This may be reflected in the results as an overestimation of HRQOL and an underestimation of symptom burden, making the need for early identification, continuous assessment, and treatment of symptoms in the last year of life even more urgent. Second, the study period ran from November 2017 to March 2020; therefore, part of the data was collected during the COVID pandemic. Finally, the reported continuity of care was measured using a self-reported item that has not been widely validated. More work is needed to assess continuity of care because its importance will increase with the growth of network-based health care services.



* Only the symptoms showing a significant change in the last year of life were included, resulting in the exclusion of insomnia, diarrhea and perceived financial burden

FIGURE 4 Trajectory of the burden of the individual symptoms until death in patients with advanced cancer.

CONCLUSIONS

The mean overall HRQOL of patients with advanced cancer begins to decline 9 months before death, with a steeper decline in the last 3 months. Different HRQOL aspects and symptoms have different trajectories, emphasizing the importance for clinicians to be alert for screening different symptoms accordingly. Patients with a higher reported continuity of care seem to have a milder decline in HRQOL, highlighting the importance of improving the continuity of care in oncology. Patients who are more satisfied with care seem to have a milder decline in emotional functioning, implying that they may benefit from psychological support from their clinicians to deal with end-of-life decisions. In summary, these findings support the need for early initiation of palliative care to have appropriate end-of-life discussions and calls for the improvement of continuity of care and integration of psychological support in oncology.

AUTHOR CONTRIBUTIONS

Moyke A. J. Versluis: Data curation, formal analysis, investigation, methodology, project administration, resources, software, visualization, and writing - original draft. **Natasja J. H. Raijmakers**: Formal analysis, funding acquisition, methodology, project administration, supervision, and validation. **Yvette M. van der Linden**: Methodology and supervision. **Lonneke V. van de Poll-Franse**: Funding acquisition, methodology, and supervision. All authors contributed to conceptualization and writing - reviewing and editing.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data from the eQuiPe study are available through Questacy (DDI 3.x XML) and can be accessed at the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship registry (www.profilesregistry.nl). To maintain optimal long-term data warehousing and dissemination, the quality guidelines formulated in the “Data Seal of Approval” document developed by Data Archiving and Networked Services (DANS) were followed (www.datasealofapproval.org).

PATIENT CONSENT STATEMENT

All patients gave written informed consent to participate in the eQuiPe study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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