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Health-related quality of life among cancer patients in their last year of life: results from the PROFILES registry

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Abstract

Purpose The aim of this study was to assess health-related quality of life (HRQoL) in the last year of life of cancer patients stratified by four periods of time before death.

Patients and methods Between 2008 and 2015, cancer patients were invited to participate in PROFILES (Patient Reported Outcomes Following Initial Treatment and Long-term Evaluation of Survivorship) registry studies. Patients were eligible for inclusion in this secondary analysis if they had been invited to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) in their last year of life ($N = 892$). Four hundred fifty-eight patients (51%) responded. Descriptive statistics were used to describe the HRQoL of cancer patients in the last 3 months of life ($N = 61$), the last 3–6 months ($N = 110$), the last 6–9 months ($N = 138$), or the last 9–12 months of their life ($N = 129$).

Results Patients in the last 3 months report a significant lower HRQoL, lower functioning, and higher symptom burden of fatigue and appetite loss compared to patients in different time periods before death ($p < 0.008$). Clinical relevance of the differences for global QoL, cognitive, and social functioning was large. Patients' HRQoL in the last year of life was significantly lower than that of the normative population ($p < 0.001$).

Conclusions All aspects of HRQoL are considerably impaired in patients with advanced cancer, with a marked lower HRQoL in the final months of life. This marked decline of HRQoL in the final months of life may be an indicator of approaching death and serve as an important trigger for end-of-life communication and decision-making about subsequent treatment and supportive care.

Keywords Quality of life · Advanced cancer · Palliative care · Population-based cohort

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Introduction

Treatment of cancer is evolving rapidly and in recent decades cancer survival has improved partly attributed to screening (early detection) and better treatment [1]. Trends in the USA show that 5-year relative survival in adults with solid cancer has increased from 49 to 68% over the last 40 years [2]. Nevertheless, despite these advances, cancer is still the second leading cause of death worldwide and more than 8 million people die of cancer every year [3]. Ergo, a large number of cancer patients experience a phase of their illness in which they might need palliative care. Palliative care aims to improve or maintain the quality of life (QoL) of patients and their relatives facing problems associated with a life-threatening disease, such as cancer. In their landmark paper, Temel et al. showed that early palliative care in fact

leads to significant improvements in both QoL and mood [4], as confirmed by a recent meta-analysis [5].

QoL is the perceived quality of an individual's life, that is, an assessment of their well-being and includes multiple domains, including the physical, psychological, social, and spiritual domain. QoL is subjective and dynamic over time. Lynn and Anderson [6] have distinguished three common illness trajectories in patients potentially in need of palliative care, including the cancer trajectory. The "cancer trajectory" consists of a short period of marked decline of function and a foreseen death. In line with this trajectory, several studies showed that cancer patients experience a steep decline of function and QoL in the last months of life. Giesinger et al. [7] used routinely collected clinical practice data of 85 advanced cancer patients and showed that during the last 3 months of life HRQoL worsened sharply. Hwang et al. [8] reported a fast deterioration in the last 2 months of life of 67 advanced cancer patients admitted to a US tertiary care teaching hospital. Furthermore, Elmqvist et al. [9] combined data of two clinical trials from Norway and Sweden and showed that advanced patients' functioning ($n = 116$) deteriorated and the most marked changes occurred in the last 2 months of life.

Insight in the course of advanced cancer patients' quality of life (QoL) during the final year of life will serve to identify goals for timely interventions to improve patients' QoL at the end-of-life. However, there are few population-based studies reporting the self-reported QoL of large groups of cancer patients in their last months of life. Furthermore, previous studies reported on patients admitted to a single hospital who received medical care with palliative intent or on patients with limited expected survival who were included in a clinical trial regarding advanced palliative care, both potential subject to selection bias. Moreover, clinical trial data does not reflect the daily practice. Population-based information about QoL during the final course of the disease for all cancer patients is lacking. Therefore, this study used data of a large population-based cohort to assess health-related quality of life (HRQoL) in the last year of life of advanced cancer patients stratified by four different periods of time before death.

Methods

Study design and setting

Data from the PROFILES ("Patient Reported Outcomes Following Initial Treatment and Long-term Evaluation of Survivorship") registry were used for secondary analyses. The PROFILES registry is an ongoing data collection of PROs within the sampling frame of the Netherlands Cancer Registry (NCR) and can be linked with clinical data of all individuals newly diagnosed with cancer in the Netherlands [10].

Study population

The current analysis included patients with cancer between May 2009 and October 2015 who received a questionnaire in their last year of life, using all study samples from the PROFILES registry. In all study samples, participants were included if they were older than 18 years at diagnosis and excluded if they were not able to complete a Dutch questionnaire according to their (ex-)attending specialist (i.e., cognitive impairment, non-native speaker, too ill to participate). Ethical approval was obtained for all study samples separately.

Data collection

A detailed description of the data collection has been published previously [11]. In brief, in each study sample, cancer patients were informed about the study via a letter by their (ex-)attending specialist. This letter contained either an informed consent and a postal questionnaire, or a secured link to a web-based informed consent and online questionnaire. In study samples where the secured link was provided, the patient could return a postcard to request a paper-and-pencil questionnaire, if preferred. Data from the PROFILES registry are available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration [12].

Study measures

Socio-demographic and clinical data

Socio-demographic and clinical data were obtained from the NCR. Socio-demographic variables included date of birth, gender, and socio-economic status (SES). SES was based on postal code of the residence area of the patient, combining aggregated individual fiscal data on the economic value of the home and household incomes, and was categorized into low, medium, or high [13]. Questions on educational level and partnership were added to all questionnaire packages. Clinical data include cancer type, stage, and date of diagnosis. Cancer type was classified according to the third International Classification of Diseases for Oncology (ICDO-3) [14] and disease stage was classified according to TNM [15] or Ann Arbor Code (Hodgkin lymphoma and non-Hodgkin lymphoma). TNM5 was used for patients diagnosed from 2002 to 2003, TNM6 for patients diagnosed from 2003 to 2010, and TNM7 for patients diagnosed from 2010. Comorbidity was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ). Patients were asked to report comorbid conditions present in the past 12 months. The total score was the sum of all positive responses (range 0–14) and categorized into no comorbid condition, one comorbid condition, and at least two comorbid conditions [16]. Vital

status and date of death were obtained from the Dutch municipal personal records database and was last verified on February 1, 2017.

Quality of life

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (version 3.0) was used to assess HRQoL in cancer patients [17, 18]. It contains five functional scales on physical, role, cognitive, emotional, and social functioning; an overall health status/global QoL scale; three symptom scales on fatigue, nausea and vomiting, and pain; and six single items. The scores were linearly transformed into a score between 0 and 100 [19]. A higher score for a functional scale indicates a higher level of functioning, but a higher score for a symptom scale represents a higher level of symptomatology. Furthermore, the recently developed QLQ-C30 summary score has been used, because the sensitivity of the global QoL (ql) in advanced cancer patients seems limited, i.e., it seems not particularly well suited for detecting changes between patient groups [20]. This QLQ-C30 summary score was developed by Giesinger et al. [21], with a higher score indicating a better HRQoL.

Normative population

A reference cohort of 2194 individuals from the general Dutch population (center panel) was used to obtain the normative population. This reference cohort is representative for the Dutch-speaking adult population in the Netherlands [22]. The normative population completed a questionnaire in November 2013 that included the EORTC QLQ-C30, and items on socio-demographics. From this normative population, an age- and gender-matched selection ($N = 288$) was made to compare HRQoL with the patient group.

Statistical analysis

Descriptive statistics were used to assess socio-demographic and clinical data and to determine the HRQoL in the last year of life of cancer patients. Respondents and non-respondents were compared using t test (age) and chi-square test (gender, partnership, SES). Four groups were created: patients who completed a questionnaire in their last 3 months of life ($N = 61$), last 3–6 months ($N = 110$), last 6–9 months ($N = 138$), and last 9–12 months ($N = 129$). Differences between the four groups in HRQoL were analyzed with a one-way ANOVA, followed by a Bonferroni post hoc test. A Bonferroni correction was applied ($p < 0.008$) to account for multiple testing. Additionally, clinical relevance of the differences was assessed using the meta-analysis of Cocks et al. [23], who published a guideline to aid interpretation of differences in EORTC QLQ-C30 scores defining thresholds for trivial, small, medium, and large differences per subscale. A

multivariable regression model was used to determine the associations between the EORTC QoL summary score and moment of completing the questionnaire (time before death in months as continuous variable), adjusted for gender, age, cancer type, and initial treatment.

Results

A total of 892 patients received a questionnaire in their last year of life and 458 patients (51%) completed the questionnaire (mean age 72, standard deviation [SD] 9) (Table 1). Most common diagnoses were colorectal cancer (58%), lymphoma (22%), and gynecological cancer (12%). Non-respondents ($n = 434$) were more often female and were more often in the last 3 months of life compared to respondents ($p < 0.05$).

HRQoL in patients at the end of life

Overall, the mean QLQ-C30 summary score of all patients in their last year of life was 73(SD 19), while in the last 3 months of life the mean QLQ-C30 summary score was 62(SD 22) (Table 2). Most severe symptom burden in the last year of life was found for fatigue (44 (SD 30)) and dyspnea (30 (SD 34)), while in the last 3 months, fatigue 57 (SD 29) and pain 39 (SD 35) were most burdensome.

HRQoL trajectory towards the end of life

Significant differences of the QLQ-C30 summary score between different time periods before death were found (F (3, 234) = 9.57, $p = 0.000$). HRQoL was statistically significantly lower in the last 3 months of life compared to the last 3–6 months ($p = 0.0001$), the last 6–9 months ($p = 0.000$), and the last 9–12 months of life ($p = 0.000$) (Table 2 and Fig. 1). All functioning subscales were significantly lower in the last 3 months of life, compared to patients in the previous time periods ($p < 0.008$). Subscales global QoL and cognitive and social functioning showed a large clinically relevant mean lower score in patients in their last 3 months compared to patients in their last 9–12 months, respectively 17, 14, and 18 points. Physical and role functioning showed a medium clinically relevant lower score, respectively 19 and 23 points. Differences of the symptoms fatigue and appetite loss between the last 3 months and the last 9–12 months were also statistically significant. Fatigue, appetite loss, pain, insomnia, dyspnea, and nausea and vomiting showed medium clinically relevant differences between the last 3 months and the last 9–12 months of life (range 11–19 points).

HRQoL steeply declined in the last 6 months towards death; the QLQ-C30 summary score and the moment of completing the questionnaire (time before death in months) were

Table 1 Socio-demographic and clinical characteristics

	Respondents (N = 458)	Non-respondents (N = 434)	p value	Normative population[a] (N = 288)
Age (mean (SD); range min–max)	72 (9); 40–96	73 (11); 21–99	0.1985	71 (11); 24–90
Gender (% male)	59%	49%	0.005*	54%
Cancer type			0.000*	n.a.
Colon/rectum	58% (n = 264)	48% (n = 208)		
Lymphoma	22% (n = 100)	15% (n = 66)		
Gynecological	12% (n = 54)	20% (n = 88)		
Prostate	6.1% (n = 28)	9.5% (n = 41)		
Other	2.6% (n = 12)	7.1% (n = 31)		
Metastasis at diagnosis			0.254	n.a.
Yes	25% (n = 114)	22% (n = 94)		
No	75% (n = 344)	78% (n = 340)		
Time since diagnosis (years) (mean (SD))	3.6 (2.6)	3.6 (2.8)	0.7915	n.a.
Up to 2 years	27% (n = 125)	33% (n = 141)		
2–4 years	40% (n = 185)	34% (n = 147)		
More than 4 years	32% (n = 148)	34% (n = 146)		
Moment of receiving questionnaire			0.000*	n.a.
Last 3 months of life	14% (n = 65)	27% (n = 118)		
3–12 months before death	86% (n = 393)	73% (n = 316)		
Comorbidity				
No comorbid condition	30% (n = 126)	–		23% (n = 66)
One comorbid condition	24% (n = 110)	–		26% (n = 76)
More than one comorbid conditions	48% (n = 222)	–		51% (n = 146)
Most frequent conditions				
Hypertension	34% (n = 138)	–		37% (n = 107)
Back pain	30% (n = 116)	–		35% (n = 101)
Arthritis	29% (n = 113)	–		33% (n = 96)
Heart disease	27% (n = 109)	–		24% (n = 69)
Diabetes mellitus	20% (n = 80)	–		11% (n = 32)
Pulmonary disease	17% (n = 66)	–		12% (n = 35)
Partnership[b]				
Yes	74% (n = 338)	–		69% (n = 199)
No	24% (n = 110)	–		31% (n = 89)
Social economic status[b]				
High	23.6% (n = 102)	23% (n = 100)		–
Intermediate	41.6% (n = 180)	41.5% (n = 180)		–
Low	34.9% (n = 151)	27.4% (n = 119)		–

Due to rounding off, percentages can exceed 100% and an asterisk indicated statistically significance at p < 0.01

[a] Matched normative population on age and gender

[b] Due to missings, it does not add up to 458 (missings did not exceed 5%)

statistically significantly associated ($\beta = 2.3$, 95% CI 0.23–4.33, $p = 0.029$).

Normative population

The QLQ-C30 summary score of advanced cancer patients was significantly lower in patients in their last year compared to the normative population, respectively 73 (SD 19) vs. 87 (SD 13), $p < 0.000$ (Table 2). Overall, patients in their last year of life reported a lower functioning and a higher symptom burden on all subscales compared to the normative population.

Discussion

Advanced cancer patients experience a significantly impaired HRQoL in their last year of life, especially in the last 3 months of life. Patients also experience a high symptom burden, in

particular regarding fatigue, dyspnea, and pain. HRQoL of cancer patients in their last year of life is worse compared to the normative population, particularly in the final phase of life.

The marked lower QoL in the last 3 months of life is in line with the theoretical disease trajectory as described by Lynn and Adamson [6] and is in accordance with previous smaller studies [7–9]. A short period of evident decline is typical for cancer, as most patients with malignancies maintain a high level of functioning for a substantial period. However, once the cancer advances, the patient's QoL sharply declines in the final weeks preceding death.

Our analyses demonstrate that QoL measurement using patient-reported outcomes (PROs) is feasible in cancer patients in their last year of life. A response rate in the last year of life of 51% can be considered reasonable compared to the overall response rate of cancer patients in the PROFILES registry (73–75%) [24–26]. As expected, we see a lower response

Table 2 Health-related quality of life of cancer patients in their last months of life ($n = 458$)

	I: Last 3 months of life N = 65 Mean (SD)	II: Last 3–6 months of life N = 118 Mean (SD)	III: Last 6–9 months of life N = 142 Mean (SD)	IV: Last 9–12 months of life N = 133 Mean (SD)	p value[a]	Clinical relevance of mean difference between I and IV[b]	Normative population N = 288 Mean (SD)
Summary score QoL	62 (22)	73 (19)	75 (18)	77 (17)	0.0000*		87 (13)
Quality of life							
Physical functioning	48 (28)	63 (24)	62 (25)	67 (25)	0.0000*	Medium	83 (19)
Role functioning	39 (37)	59 (35)	57 (34)	62 (32)	0.0001*	Medium	83 (25)
Emotional functioning	64 (26)	75 (25)	78 (23)	83 (20)	0.0000*	–	87 (18)
Cognitive functioning	68 (28)	80 (29)	76 (28)	82 (20)	0.0004*	Large	88 (17)
Social functioning	60 (29)	74 (31)	72 (30)	78 (24)	0.0007*	Large	92 (18)
Global quality of life	50 (27)	61 (24)	60 (24)	67 (20)	0.0000*	Large	75 (19)
Symptoms							
Fatigue	57 (29)	44 (30)	42 (29)	38 (28)	0.0006*	Medium	23 (24)
Nausea/vomiting	18 (24)	15 (25)	11 (22)	9.8 (20)	0.0536	Medium	3 (11)
Pain	39 (35)	28 (29)	27 (32)	25 (29)	0.0322	Medium	22 (27)
Dyspnea	37 (38)	33 (34)	28 (34)	26 (32)	0.0758	Medium	12 (22)
Insomnia	37 (36)	30 (32)	26 (31)	22 (31)	0.0214	Medium	19 (26)
Appetite loss	36 (34)	25 (35)	18 (27)	17 (30)	0.0002*	Medium	5 (16)
Constipation	21 (31)	12 (25)	14 (24)	12 (24)	0.0893	Small	9 (18)
Diarrhea	22 (33)	11 (20)	13 (24)	19 (28)	0.0081	Small	6 (14)

[a] A one-way ANOVA was conducted to determine if QoL differed for patients in different number of months before death, followed by post hoc Bonferroni test (not shown)

[b] Indication of clinical relevance of mean differences, as reported by Cocks et al. 2010

*Statistically significant; a Bonferroni correction was applied ($p < 0.008$) to account for multiple testing

rate among patients who participated in their last 3 months of life (36%). Completing a questionnaire in the final phase of life is obviously more difficult, possibly due to deterioration and higher symptom burden (as shown in this study). Using PROs in (early and late) palliative oncological care is important, as it provides valuable information about the QoL that would support end-of-life decision-making about subsequent treatment and supportive care. Furthermore, monitoring QoL and symptoms increases awareness among health care professionals to better anticipate on patients' changing needs [27, 28] and improves clinical outcomes (i.e., fewer ER visits, fewer hospitalizations, and better survival) [28].

Strengths and limitations

An important strength of the current analysis is the large population-based sample of cancer patients in their last year of life, including different primary cancer sites. Another strength is that, through linkage with cancer registry data

and the Dutch municipal personal records database, we had access to complete and comprehensive data on socio-demographic and clinical characteristics, for the full population of respondents and non-respondents. Furthermore, in our analysis, we have used the EORTC QLQ-C30, a widely used instrument to measure HRQoL within oncology. However, many instruments to assess HRQoL of patients with advanced cancer are available [29]. The EORTC QLQ-C30 seems suitable for patients with advanced cancer, although for patients in their final weeks of life, the shortened version of this questionnaire, the EORTC QLQ-C15-PAL, might be more appropriate [30]. A limitation of our study is its design, a cross-sectional analyses, based on a collection of separate study samples, with different inclusion criteria.

Practical implications

Our results clearly show a progressive deterioration in QoL towards the end of life. This marked decline of QoL may be an
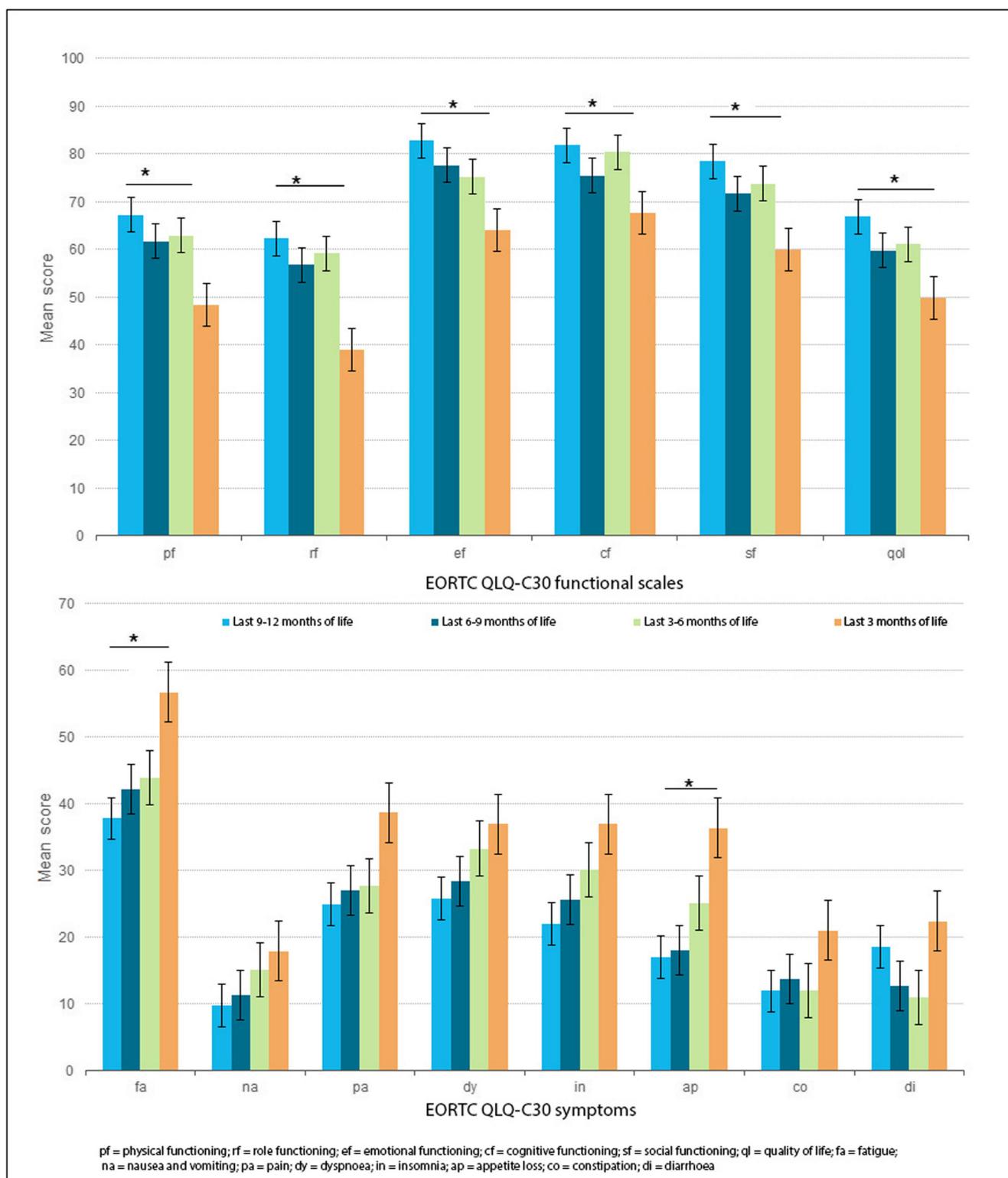
Fig. 1 Differences in HRQoL and its subscales in cancer patients in their last year of life (*n* = 458)

indicator of approaching death and therefore should be an important trigger for end-of-life communication and decision-making about subsequent treatment and care.

Ideally, this should start earlier. However, timing of these end-of-life discussions remain challenging, "it always seems too early, until it's too late." Therefore, in current practice, a

change in QoL or symptom burden can serve as a welcome starting point for these discussions to help professional caregivers to overcome the experienced barriers [31, 32]. The routine assessment of patient-reported outcomes (PROs) in advanced cancer patients helps to provide information on QoL and symptom burden and are widely recommended for clinical oncology practice [33] and for palliative care [34] .

Conclusion

Cancer patients experience a significantly impaired QoL and high symptom burden in their last year of life, especially in the last 3 months of life. This considerable decline of function and increase of symptom burden in the final months of life might serve as an indicator for end-of-life communication and supportive care.

Compliance with ethical standards

Ethical approval was obtained for all study samples separately.

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

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