Modifiable factors affecting older patients' quality of life and physical function during cancer treatment

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Keywords: physical function, quality of life, geriatric assessment, geriatric oncology

Running head: Older patients with cancer, quality of life, and physical function

•List of where and when the study has been presented in part elsewhere, if applicable.

Parts of the present study were presented as a poster at the European Association of Palliative Care conference in May 2019. Otherwise, this study has not been presented anywhere else, but other results emerging from the same prospective, observational study has been presented as referred in the present paper, and as follows:

- Kirkhus L, Saltyte Benth J, Rostoft S, et al: Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. Br J Cancer 117:470-477, 2017
- Kirkhus L, Saltyte Benth J, Gronberg BH, et al: Frailty identified by geriatric assessment is associated with poor functioning, high symptom burden and increased risk of physical decline in older cancer patients: Prospective observational study. Palliat Med:269216319825972, 2019
- Harneshaug M, Kirkhus L, Benth JŠ, Grønberg BH, Bergh S, Whist JE, Rostoft S, Jordhøy MS: Screening for frailty among older patients with cancer using blood biomarkers of inflammation. J Geriatr Oncol. 2019 Mar;10(2):272-278. doi: 10.1016/j.jgo.2018.07.003. Epub 2018 Jul 23.

Abstract

Background: Maintaining physical function and quality of life (QoL) are prioritized outcomes among older adults. We aimed to identify potentially modifiable factors affecting older patients' physical function and QoL during cancer treatment.

Methods: Prospective, multicenter study of 307 patients with cancer ≥70 years, referred for systemic treatment. Pre-treatment, a modified geriatric assessment (mGA) was performed, including registration of comorbidities, medications, nutritional status, cognitive function, depressive symptoms (Geriatric Depression Scale-15 [GDS]), and mobility (Timed Up and Go [TUG]). Patient-reported physical function (PF) -, global QoL-, and symptom scores were assessed at baseline, two, four, and six months by the EORTC Quality of Life Core Questionnaire-C30. The impact of mGA components and symptoms on patients' PF and global QoL scores during six months was investigated by linear mixed models. To identify groups following distinct PF trajectories, a growth mixture model was estimated.

Results: 288 patients were eligible, mean age was 76.9 years, 68% received palliative treatment. Higher GDS-scores and poorer TUG were independently associated with an overall level of poorer PF and global QoL throughout follow-up, as were more pain, dyspnea, and appetite loss, and sleep disturbance. Three groups with distinct PF trajectories were identified: a poor group exhibiting a non-linear statistically ($p<0.001$) and clinically significant decline (≥10 points), an intermediate group with a statistically ($p=0.003$), but not clinically significant linear decline, and a good group with a stable trajectory. Higher GDS-scores and poorer TUG, more pre-treatment pain and dyspnea were associated with higher odds of belonging to the poor compared to the good PF group.

Conclusion: Depressive symptoms, reduced mobility, and more physical symptoms increased the risk of decrements in older patients' PF and global QoL scores during cancer treatment, and represent potential targets for interventions aiming at improving these outcomes.

Introduction

Older adults often have complex problems, and compared to their younger counterparts, they are more vulnerable, and at higher risk of experiencing a reduction in physical function, and thereby functional decline and dependence, following otherwise successful treatment (1, 2). In older patients receiving cancer treatment, reduced abilities to carry out daily life activities reportedly occur in about 20% to 40% (3-6), and may negatively affect quality of life (QoL) (7, 8). As maintaining independence and QoL are highly prioritized (9-12), decrements come at high costs for the older patients, and may also significantly increase caregivers' burden and health care demands. Precise knowledge on how physical function and QoL may develop during cancer treatment is therefore crucial to make treatment decisions in accordance with patients' wishes and priorities. Moreover, considering the rapidly growing number of older patients with cancer and older cancer survivors (13), it is of uttermost importance to develop targeted interventions that may prevent decline in physical function and QoL during cancer treatment. Thus, precise knowledge on risk factors for such negative outcomes is needed.

Frailty is widely recognized as a syndrome of increased vulnerability to stressors (14). In older patients with other diseases than cancer, frailty is closely related to poor QoL and an established predictor of disability and dependence (14, 15). In oncology settings, a geriatric assessment (GA), which includes frailty indicators such as comorbidity, polypharmacy, physical, mental and nutritional deficits, is known to predict survival and side effects of cancer treatment (16-19). The potential role of GA and individual frailty indicators as predictors of physical function and QoL during and after treatment is scarcely investigated. There are indications that impairments in activities of daily living (ADL), abnormal nutritional status, and depressive symptoms may predict decline in physical function in older

patients with cancer (3, 5), but the results of the few studies available are not consistent (4, 20). Symptom distress may also have a substantial negative impact on physical function and QoL (21-23), but for older patients with cancer, the longitudinal interrelation between symptom burden, physical function and QoL during the course of treatment has not been established.

We have previously demonstrated that frailty identified by a modified GA was independently predictive of survival and associated with poorer physical function and more symptoms in a cohort of older patients with cancer ≥ 70 years, referred for systemic cancer treatment (24, 25). Addressing the same population, the aim of the present study was to identify individual, modifiable factors associated with a poorer physical function and QoL during treatment. We investigated the impact of pre-treatment frailty indicators on patient-reported physical function and global QoL during six months after referral, and the association between these outcomes and patients' symptom reports during the same period.

Patients and methods

Patients ≥70 years, referred for systemic cancer treatment for a histologically confirmed solid tumor (new diagnosis or first relapse after previous curative treatment) were consecutively included into this prospective observational study at eight Norwegian outpatient oncology clinics (two university hospitals and six local hospitals) (24). At inclusion, the patients' oncologists reported cancer type according to the International Classification of Diseases-10th Edition (ICD-10), stage of disease, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and whether patients received palliative or curative treatment. The oncologists were blinded for the study specific assessments, and treatment decisions were based on clinical judgment and Norwegian national guidelines. Data on administered

treatment the two first months after inclusion were retrospectively retrieved from the patients' hospital medical records by checking administered infusions, prescriptions, surgical notes and notes from the radiotherapy clinic. Treatment was thereafter classified as 1) curative i.e. neoadjuvant or adjuvant chemotherapy, 2) palliative chemotherapy, i.e. traditional cytotoxic regimens, 3) other palliative systemic cancer treatment, i.e. hormone therapy and modern targeted treatment, 4) other palliative care (i.e. radiotherapy, surgery, medical symptom treatment). Stage was classified as localized (I-II), locally advanced (III) or metastatic (IV), and PS as 0-1 or 2-4.

Physical function, QoL and symptom assessment

The patients reported their physical function, global QoL and symptoms at inclusion and at two, four, and six months of follow-up on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire-C30 (QLQ-C30) (26). The QLQ-C30 physical function scale (PF) consists of five items: 1) any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase; 2) any trouble taking a long walk; 3) any trouble taking a short walk outside of the house; 4) need to stay in bed or a chair during the day; 5) need of help with eating, dressing, washing yourself or using the toilet. The global QoL scale consists of two items asking the patients to rate their overall health and QoL. Physical symptoms are assessed on three multi-item scales (i.e. fatigue, pain, and nausea/vomiting) and five single item measures (dyspnea, sleep disturbances, appetite loss, constipation, and diarrhea). Fatigue was excluded from our analyses since we primarily aimed at identifying factors that might be modified by targeted interventions, and since treatment of fatigue generally implies identifying and treating contributing factors, including the other symptoms assessed on the QLQ-C30.

All QLQ-C30 items are scored on an ordinal scale ranging from 1 (not at all) to 4 (very much), except for the two items constituting the global QoL score, going from 1 (very poor) to 7 (excellent). Before analyses, raw scores on all scales/items were transformed into scales from 0 to 100 points (27). Higher scores on the PF and global QoL scales indicate better function/QoL, whereas higher scores on the symptom scales/items denote more symptoms. For all scales, a difference in scores of 5 to 10 points has been found to represent "a little" difference for better or for worse for the patients, and a difference by 10 to 20 points as moderate (28). Accordingly, data suggest that a 10-point change in scores represents a change in supportive care needs (29). Thus, a difference of $\geq$ 10 points was defined as clinically significant (28)

Frailty indicators

Frailty indicators were chosen based on a modification of the Balducci frailty criteria (24, 30) and recommendations for the content of a GA (16, 18), and assessed at baseline, partly by trained oncology nurses, partly by patient-report. Details of the assessment tools and procedures have been described elsewhere (24) and are summarized in Table 1. Eight frailty indicators were included: number of comorbidities assessed by a subscale of the Older Americans' Resources and Services Questionnaire (OARS) (31, 32), number of regular medications, nutritional status using the Patient-Generated Subjective Global Assessment (PG-SGA) (33), depressive symptoms using the Geriatric Depression Scale-15 (GDS-15) (34), cognitive function using the Norwegian Revised Mini Mental State Examination (MMSE-NR) (35), number of falls the last six months, and mobility using the Timed Up and Go test (TUG) (36). The patients were asked to perform TUG at a fast pace (37). Basic ADL were assessed from question 5 of the QLQ-C30 PF scale (Table 1).

Statistical analyses

The QLQ-C30 PF and global QoL scales were defined as our primary and secondary endpoints, respectively. The absolute values of the patients' scores at each assessment point from baseline to six months were used in the statistical analyses. The overall course of both PF and global QoL scores during this period was assessed by a linear mixed model with fixed effects for time as second-order polynomial to capture possible non-linear behavior. Random effects for patients nested within cancer clinics were included to account for within-patient correlations due to repeated measurements and possible within-clinic cluster effect.

To investigate if the frailty indicators and symptoms were associated to the patients' overall level of PF and global QoL during six months of follow-up, the linear mixed models were adjusted for the frailty indicators and symptoms by first including them one by one into bivariate models. Next, three multiple linear mixed models (A, B and C) for each outcome were estimated. The independent impact of the frailty indicators was assessed by first including them all into a multiple model (A). Then, model A was adjusted for age, gender, and cancer related factors i.e. PS, type of cancer, stage of disease and treatment (model B). Finally, the impact of symptom occurrence was investigated by adding symptom scores reported simultaneously with PF and global QoL from baseline to six months to the model (C). In each multiple model (A, B, C), all covariates were included simultaneously. As basic ADL was derived from one item of the QLQ-C30 PF scale, which was also the outcome, this frailty indicator was excluded from all models for PF. No co-linearity issues were detected when performing correlation analysis.

The linear mixed model described above assesses the overall course of PF and global QoL during six months for all patients. By means of an exploratory approach, growth mixture

model was estimated to identify possible unobserved groups of patients following distinct trajectories in the main endpoint, PF. The method assesses individual trajectories and attempts to group the patients with similar profiles together. The optimal number of groups was determined by using Akaike's Information Criterion (AIC) and aiming at average within-group probabilities larger than 0.8, non-overlapping 95% CI for each trajectory, and reasonable group size. The model does not include patient characteristics, thus identified groups were next described by bivariate and multiple nominal regression models with group membership as dependent variable and baseline characteristics as covariates. The included covariates were age, gender, cancer related factors as described above, and baseline symptom scores (pain, dyspnea, appetite loss, sleeping disturbances, constipation and nausea/vomiting). AIC was used to reduce the multiple model for excessive variables.

The analyses were performed using SPSS v25 and STATA v14. Results with p-values below 0.05 were considered statistically significant.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway and registered at ClinicalTrials.gov (NCT01742442). All patients provided written informed consent.

Results

Between January 2013 and April 2015, 307 patients were included (24). One patient withdrew consent and 18 had missing baseline questionnaires. Thus, 288 (94%) patients were eligible for this study. Mean age was 76.9 years, 56% were male, the majority had distant metastases

(56%) and received palliative treatment (68%) (Table 2). The patients reported a mean of 2.7 comorbidities and 4.1 daily medications, 15% were diagnosed as severely malnourished, 3% had experienced more than one fall during the last six months, and the median (min-max) GDS and MMSE scores were 2.0 (0-13) and 29 (19-30), respectively. At two, four, and six months of follow-up, 13 (5%), 27 (9%), and 52 (18%) patients had died. The proportion of completed QLQ-C30 questionnaires ranged from 89% to 95% of those alive at these time points. Mean baseline PF, global QoL and symptom scores are shown in Table 2.

Impact of frailty indicators and symptoms on the overall level of PF and global QoL

According to unadjusted linear mixed models, assessing the overall course during follow-up, PF declined non-linearly and statistically significantly (max 8.9 points at four months, $p<0.001$), whereas the global QoL declined linearly (max 3.9 points at six months, $p=0.008$). However, neither decline was clinically significant (Figure 1A and 1B).

Bivariate linear mixed models showed that all frailty indicators were significantly associated with the patients' overall level of PF during follow-up, as were also age, PS, type of cancer, stage of disease, treatment, and all symptom scores measured simultaneously with PF (Table 3). In the multiple model including all frailty indicators, higher GDS-scores, poorer TUG, and malnutrition were significantly associated with a poorer PF level within the study period (Table 3, model A). In addition to PS, these factors were also the only significant covariates when controlling for age, gender and the cancer-related factors (Table 3, model B). In the final model (C), GDS-scores and TUG remained independent, significant covariates. Higher scores on pain, dyspnea, appetite loss, and sleep disturbance throughout follow-up were also significantly and independently associated with a poorer overall level of PF (Table 3, model C).

Results of the corresponding analyses for global QoL are displayed in Table 4. In bivariate linear mixed models, all frailty indicators except for basic ADL, number of falls, and MMSE, were associated with the patients' global QoL level during follow-up ($p<0.01$). According to the multiple model A, malnutrition ($p=0.004$), higher GDS-score ($p<0.001$), poorer TUG ($p=0.013$), and no ADL deficits ($p=0.048$) were independently associated with a poorer global QoL level. When controlling for age, gender and cancer-related factors (model B), malnutrition ($p=0.013$), GDS score ($p<0.001$), and TUG ($p=0.041$) remained the only significant covariates. In model C, including patients' symptom reports during follow-up, higher GDS-scores ($p<0.001$), poorer TUG ($p=0.029$), more pain, dyspnea, appetite loss, sleeping disturbances (all $p<0.001$), and diarrhea ($p=0.018$) were significantly associated with poorer overall global QoL level throughout the study period (Table 4).

Trajectory analyses to identify distinct subgroups of PF development

Growth mixture model identified three groups of patients with distinct PF trajectories i.e. poor (n=69, 24%), intermediate (n=103, 36%), and good (n=112, 40%) with high mean within-group probabilities (Table 5) and non-overlapping 95% CI (Figure 1C). The poor group had a significantly poorer mean PF score at baseline (mean 51.6 SD 20.8) compared to the intermediate (68.3, SD 13.7) and good (91.5, SD 9.5) groups, and exhibited a non-linear statistically and clinically significant decline by 20.2 points over four months ($p<0.001$). The good group remained stable throughout the follow-up period, and the intermediate group experienced a statistically, though not clinically significant linear decrease ($p=0.003$) (Table 5, Figure 1C).

For all frailty indicators and baseline symptom scores, more deficits and higher symptom intensity were registered for the poor PF group in comparison to the intermediate group, which in turn had more deficits and reported more symptoms than the good PF group (Table 2). According to bivariate nominal regression models, the poor and good PF groups differed significantly on all the considered covariates except for number of falls, gender, and diarrhea (data not shown). In the AIC-reduced multiple model, higher GDS-scores, poorer TUG, and more pain and dyspnea were significantly and independently associated with higher odds of belonging to the poor PF group as compared to good group (OR 1.3 (1.1; 1.5), p=0.008; OR 1.8 (1.5; 2.2), p<0.001; OR 1.0 (1.0; 1.1); p<0.001, and OR 1.0 (1.0; 11.1), p<0.001, respectively).

Within six months, there were also differences in survival between the groups. Whereas 62% of the patients in the poor group survived for six months, the corresponding percentages in the intermediate and good groups were 84% and 92%, respectively (p<0.001).

Discussion

In the present study of older patients referred for systemic cancer treatment, we showed that pre-treatment higher GDS and poorer TUG scores were independently associated to poorer overall levels of patient-reported PF and global QoL during six months of follow-up. Furthermore, more pain, dyspnea, appetite loss, and sleep disturbances within the same period had a profoundly negative impact on both outcomes. Pre-treatment malnutrition was also associated with poorer PF and global QoL scores, although not independently of symptom scores. Exploratory analyses identified three groups of patients with distinct PF trajectories. The poor PF group, comprising 24% of the patients, had the poorest PF at baseline and

reported a clinically significant decline during the study period. In line with our main findings, belonging to this group was independently associated with higher GDS and poorer TUG scores, more pain, and dyspnea at baseline.

We are not aware of any former studies reporting how individual frailty indicators may be associated with global QoL in older patients during systemic cancer treatment, or investigating the longitudinal relationship between symptoms, physical function, and QoL in such patient cohorts. The negative effect of symptom distress found in our study is, however, in line with several cross-sectional studies describing correlations between symptom severity, impairments in physical function, and QoL (21-23). Three recent studies have investigated if pre-treatment GA elements may be associated with functional decline in terms of reduced ability to carry out daily life activities. Decoster et al. reported no independent impact of any of these frailty indicators in newly diagnosed patients with lung cancer (4). Hoppe et al (5) and Kenis et al (3), both studying patients with various cancer types receiving chemotherapy, found that impairments in instrumental ADL (IADL), higher GDS-scores and malnutrition predicted declining ADL. Their results may not be directly comparable to ours due to differences in assessment tool and methods. Whereas we used patient-report, their assessments were made by a geriatrician or a trained nurse, and these measures may only be moderately correlated. Jointly, however, the studies strongly indicate a substantial negative impact of pre-treatment physical impairments, depressive symptoms, and malnutrition on older patients' physical function during cancer treatment. According to our findings, the same factors are of major importance for global QoL.

The proportion of patients experiencing a decline in physical function in our study was consistent with several other reports on older patients with cancer (3-6). A recent study also

identified three patient groups with distinct trajectories of patient-reported physical function, i.e. poor, intermediate, and good (38), though these were all stable. Supporting our finding, depression, and lower physical activity were among the main characteristics within the poor group. Moreover, it is worth noting that PF scores in our good PF group were higher than reported in a Norwegian reference population, 70 - 79 years of age (female scores 74.9, male scores 84.2) (39). Baseline scores for the poor PF group were comparable to those found in a cancer population with expected survival of three months (scores 46-48) (40), indicating that the observed decline of 20 points may have serious implications for the patients.

The dismal consequences of physical impairment, depression, and malnutrition for cancer survival and treatment complications are well known (41-46). Our findings extend this knowledge, indicating that such problems should also be properly addressed in order to maintain older patients' physical function and QoL throughout systemic cancer treatment. Pre-habilitation and rehabilitation programs including physical exercise and/or nutritional interventions have proven successful in other settings, also among palliative patients (47, 48). Exploring the reasons for depression might be equally important. Motivational and neuro-hormonal mechanisms may for example underlie the association between depression and decline in physical function, and pharmacotherapy and cognitive-behavioral interventions might be helpful (49).

The significant, negative associations between symptom distress during the disease course and patients' PF and global QoL scores reinforce the need to follow patients with systematic and repeated symptom assessment. Despite being highly recommended, this is seldom routinely applied, and is cited as a major reason for inadequate symptom management (50). Consistent with this, evidence is emerging suggesting that systematic symptom monitoring

using patient-reported outcome measures followed by targeted interventions may improve cancer patients' outcomes, including QoL and survival (51, 52). The present study provides no information on treatment response and one might therefore argue that the associations between poorer PF and global QoL scores and more symptoms may reflect cancer progression. It should, however, be noted that even in the group with the poorest trajectory of PF scores, the majority lived for more than six months. Thus, early decline in physical function, poor QoL and a high symptom burden should not be seen as inevitable, but acted upon. For older patients, however, physical symptoms as well as physical impairment, depression, and malnutrition are most likely multifactorial due to co-existing problems. Hence, interventions aiming at maintaining physical function and QoL should be individualized and based on GA in accordance with current recommendations (53).

Our study has several limitations. Firstly, we included a heterogeneous sample of patients with several different cancer diagnoses, stages and treatment. Secondly, the choice of assessment tools may have impacted our results. This particularly applies to our comorbidity assessment, since comorbidity has been found to affect older patients' physical function and QoL in other studies using more comprehensive assessments than the OARS (38, 54).Thirdly, the multitude of factors included in our analyses may introduce uncertainties, and the exploratory analysis related to PF trajectories should be interpreted with caution. Fourthly, it may be argued that fatigue, which is a symptom that may seriously affect patients' physical function and QoL, should have been taken into account. However, fatigue has no uniform, established treatment, and most treatment strategies include treatment of possibly contributing factors, such as malnutrition, depression, pain, and sleep disturbances (55, 56). Consequently, we defined that including the fatigue scores in our analyses would be of little benefit since our analyses comprised a wide range of factors that may contribute to fatigue and be efficiently

treated if properly assessed and detected. Thus, systematically targeting the problems found to affect PF and global QoL in our study may also improve fatigue (56), which would be an important additional outcome in studies aiming to evaluate such an approach.

Strengths of our study are the relatively large sample size, and that factors taken into account were predefined based on former studies and clinical judgement. Our frailty indicators covered recommended domains (16, 18), and were assessed by validated instruments. The QLQ-C30, used for outcome and symptom assessment, provides high completion rates, is widely applied and validated, sensitive to change, and is a recommended measure of physical function (57). Compared to performance measures, patient-reported physical function has been found to have similar psychometric properties, and as patient-report reflects patients' experience from routine life, such measures may also more appropriately capture factors that affect their day to day function (58). In a longitudinal study, however, one can never rule out that a potential response shift, i.e. a psychological adaptation to changing health status, may have occurred. From an observational point of view, declines in physical function and QoL may therefore have been more profound than what was reflected by the patients' scores.

In conclusion, pre-treatment physical impairments, nutritional deficits, depressive and somatic symptoms are associated with poor physical function and global QoL during the course of disease in older patients with cancer, as is also unrelieved symptom distress within the same period. Systematic symptom assessments and interventions targeted to these specific areas might improve these outcomes. Further research is urgently needed to evaluate the effect and feasibility of such interventions, and to provide more information on the course of physical function and QoL during cancer therapy that may be used to facilitate treatment decisions.

Preferably, these studies should include homogeneous cohorts in terms of diagnosis, stage, and treatment, and appropriately assess treatment response and side effects.

Individual authors' contribution

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Acknowledgement

This study was funded by Innlandet Hospital Trust and registered at ClinicalTrials.gov (NCT01742442). We want to thank the cancer clinics at Innlandet Hospital Trust, Oslo University Hospital (OUH) and Akershus University Hospital (AHUS) for their participation in the study. A special thanks to the study nurses at all locations who participated in the inclusion and assessment of patients, and to the local principal investigators at OUH and AHUS: Morten Brændengen and Olav Yri.

Declaration of conflicting interests

Dr. Gronberg reports grants from MSD, Roche, AstraZeneca, BMS, Pfizer, personal fees from Takeda, MSD, Roche, AstraZeneca, BMS, Pfizer, Eli Lilly, Bayer, Pierre Fabre, Novartis, Boehringer Ingelheim, grants from Roche, outside the submitted work; . Dr. Saltvedt reports research collaboration with Boehringer Ingelheim, outside the submitted

work. The rest of the authors declare no potential conflicts of interest with respect to the research, authorship or publications of this article.

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Table 1 Overview of frailty indicators (as a part of the modified geriatric assessment) performed at patient inclusion

Domain	Assessment	Rated by	Variable name	Scores and ranges	Interpretation
Comorbidity	The Physical Health Section of the Older Americans' Resources and Services comorbidity scale (OARS)	Patient	Number of comorbidities	0-15 (continuous)	
Medication		Nurse	Number of medications	(continuous)	
Nutritional status	Patient-generated Subjective Global Assessment (PG-SGA)	Nurse/patient	Malnutrition	Yes=Considered severely malnourished by nurse or self-reported weight loss of ≥10% the last 6 months No=None of the above	
Depressive symptoms	15-item Geriatric depression scale (GDS-15)	Patient	GDS	0-15 (continuous)	Higher scores = more symptoms
Cognitive function	Norwegian Revised Mini Mental State Examination (NR-MMSE)	Nurse	MMSE	0-30 (continuous)	Higher scores = better function
Falls the last six months		Nurse	Number of falls	0-1 or ≥ 2	
Mobility	Timed Up and Go test (TUG) (fast pace)	Nurse	TUG	number of seconds (continuous)	
Activities of daily living (ADL)	Question no. 5 from the physical functioning scale on the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire-C30	Patient	ADL: "Do you need help with eating, dressing, washing yourself or using the toilet?" (dichotomized)	Yes ="A little", "some" or "very much" or No ="Not at all"	

Table 2. Baseline characteristics of the entire cohort (N = 288) and of three patient groups with distinct trajectories of physical function (N=284)

Characteristics	Physical function trajectory			
	All patients (n=288)	**Poor (n=69)**	**Intermediate (n=103)**	**Good (n=112)**
Age, mean (SD)	76.9 (5.1)	78.1 (5.5)	76.9 (5.2)	76.0 (4.7)
Female gender, n (%)	126 (44)	33 (48)	46 (45)	44 (39)
Cancer type, n (%)				
Colorectal	83 (29)	15 (22)	27 (26)	38 (34)
Lung	59 (21)	25 (36)	21 (20)	13 (12)
Prostate	56 (19)	10 (14)	24 (23)	22 (20)
Other gastrointestinal	34 (12)	6 (9)	14 (14)	14 (12)
Breast	30 (10)	4 (6)	6 (6)	19 (17)
Other	26 (9)	9 (13)	11 (11)	6 (5)
Stage, n (%)				
Localized	73 (25)	11 (16)	25 (24)	35 (32)
Locally advanced	55 (19)	10 (14)	21 (20)	24 (21)
Metastatic	160 (56)	48 (70)	57 (56)	53 (47)
Treatment, n (%)				
Curative	91 (32)	10 (14)	31 (30)	48 (43)
Palliative chemotherapy	126 (44)	40 (58)	45 (44)	39 (35)
Other palliative systemic cancer treatment	51 (18)	8 (12)	24 (23)	19 (17)
Other palliative care	20 (7)	11 (16)	3 (3)	6 (5)
ECOG PS[a] 2-4, n (%)	43 (15)	25 (36)	13 (13)	5 (5)
Number of comorbidities, mean (SD)	2.7 (1.7)	3.2 (2.0)	3.1 (1.7)	2.2 (1.4)
Number of medications, mean (SD)	4.1 (2.9)	4.9 (3.2)	4.8 (2.9)	3.1 (2.4)
Malnutrition, n (%)	43 (15)	19 (28)	16 (16)	7 (6)
GDS[b] score, mean (SD)	2.9 (2.8)	4.5 (3.1)	3.3 (2.8)	1.6 (2.0)
≥ 2 falls last six months, n (%)	10 (3)	5 (7)	4 (4)	1 (1)
MMSE[c] score, mean (SD)	28.5 (1.9)	27.9 (2.1)	28.5 (2.1)	28.9 (1.5)
TUG[d] seconds, mean (SD)	8.7 (3.5)	11.2 (4.5)	9.3 (3.3)	6.9 (1.7)
EORTC QLQ C30[e] scores, mean (SD)				
Physical function	72.9 (21.4)	51.6 (20.8)	68.3 (13.7)	91.5 (9.5)
Global QoL	64.1 (23.1)	51.0 (22.6)	56.9 (19.8)	79.0 (17.3)
Pain	24.8 (29.4)	42.5 (34.1)	301 (28.2)	9.4 (17.6)
Dyspnoea	25.7 (31.4)	41.1 (36.7)	29.1 (32.7)	13.4 (20.2)
Appetite loss	21.4 (31.4)	35.7 (37.2)	24.9 (32.2)	9.8 (21.3)
Constipation	24.0 (29.3)	36.7 (35.8)	28.5 (28.9)	12.5 (20.1)
Sleeping disturbance	26.2 (28.5)	38.2 (31.5)	26.8 (27.0)	18.2 (25.3)
Diarrhea	15.2 (22.4)	16.4 (23.3)	14.6 (22.2)	14.5 (21.9)

[a] Eastern Cooperative Oncology Group Performance status [b] 15-item Geriatric depression scale
[c] Norwegian Revised Mini Mental State Examination [d]Timed Up and Go test [e]European Organization for Research and Treatment of Cancer Core Quality of_Life Questionnaire

Table 3. Results of linear mixed models for patient-reported physical function (PF); n=264 (at baseline), n=237 (at 2 months), n=226 (at 4 months), and n=200 (at 6 months).

	Bivariate models		Multiple model A		Multiple model B		Multiple model C	
Variable	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
Time	-4.08 (0.67)	**<0.001**	-4.15 (0.67)	**<0.001**	-4.18 (0.67)	**<0.001**	-3.04 (0.59)	**<0.001**
Time x Time	0.46 (0.11)	**<0.001**	0.47 (0.11)	**<0.001**	0.47 (0.11)	**<0.001**	0.32 (0.10)	**0.001**
Number of comorbidities	-3.82 (-5.22; -2.41)	**<0.001**	-1.16 (-2.55; 0.23)	0.101	-0.93 (-2.35; 0.49)	0.197	0.06 (-1.07; 1.18)	0.923
Number of medications	-2.02 (-2.87; -1.18)	**<0.001**	-0.36 (-1.17; 0.45)	0.384	-0.31 (-1.14; 0.53)	0.471	-0.01 (-0.68; 0.65)	0.971
Malnutrition								
No - ref.	0	-	0	-	0	-	0	-
Yes	-13.06 (-20.22; -5.90)	**<0.001**	-8.54 (-14.41; -2.66)	**0.005**	-8.00 (-14.14; -1.85)	**0.011**	-3.18 (-8.08; 1.71)	0.202
GDS score[a]	-3.29 (-4.10; -2.47)	**<0.001**	-1.83 (-2.62; -1.02)	**<0.001**	-1.60 (-2.40; -0.80)	**<0.001**	-0.71 (-1.36; -0.07)	**0.030**
Falls								
≤ 1 fall - ref.	0	-	0	-	0	-	0	-
≥ 2 fall	-16.30 (-31.24; -1.36)	**0.033**	-1.39 (-13.72; 10.93)	0.824	3.74 (-8.71; 16.19)	0.555	-3.19 (-13.09; 6.72)	0.527
MMSE[b]	1.88 (0.59; 3.17)	**0.004**	-0.01 (-1.11; 1.10)	0.989	-0.10 (-1.20; 1.00)	0.860	-0.25 (-1.12; 0.62)	0.566
TUG[c]	-3.12 (-3.71;-2.53)	**<0.001**	-2.38 (-3.02;-1.74)	**<0.001**	-1.91 (-2.63;-1.18)	**<0.001**	-1.79 (-2.36; -1.21)	**<0.001**
Cancer diagnosis								
Breast – ref.	0	-			0	-	0	-
Prostate	-4.01 (-13.19; 5.17)	0.391			-1.49 (-11.53; 8.56)	0.771	-1.13 (-9.05; 6.79)	0.779
Other gastrointestinal	-5.36 (-15.56; 4.85)	0.302			-0.60 (-10.02; 8.83)	0.901	-2.31 (-9.79; 5.17)	0.544
Lung	-15.99 (-25.33; -6.66)	**0.001**			-7.66 (-16.56; 1.23)	0.091	-3.86 (-10.90; 3.17)	0.281
Colorectal	-4.54 (-13.12; 4.05)	0.299			-2.06 (-9.70; 5.59)	0.597	-2.87 (-8.95; 3.21)	0.353
Other	-16.14 (-27.00; -5.28)	**0.004**			-3.55 (-13.12; 6.02)	0.465	-1.93 (-9.51; 5.65)	0.616
Stage								
Localised – ref.	0	-			0	-	0	-
Locally advanced	-2.16 (-9.49; 5.16)	0.561			0.91 (-5.60; 7.43)	0.783	1.01 (-4.12; 6.14)	0.699
Metastatic	-8.19 (-14.00; -2.37)	**0.006**			-3.76 (-10.58; 3.07)	0.280	-1.06 (-6.44; 4.32)	0.698
Treatment								
Curative – ref.	0	-			0	-	0	-
Palliative chemotherapy	-12.53 (-18.11; -6.95)	**<0.001**			-0.88 (-8.28; 6.51)	0.814	-1.25 (-7.08; 4.58)	0.673
Other pall. sys.cancer treat.	-5.79 (-12.72; 1.14)	0.101			5.74 (-4.26; 15.74)	0.259	2.80 (-5.08; 10.69)	0.484
Other palliative care	-14.80 (-25.21; -4.40)	**0.006**			-2.09 (-11.73; 7.54)	0.669	1.03 (-6.60; 8.66)	0.791
Age	-0.75 (-1.23; -0.28)	**0.002**			-0.37 (-0.81; 0.08)	0.103	-0.25 (-0.60; 0.10)	0.166
Gender								
Man – ref.	0	-			0	-	0	-
Woman	-1.28 (-6.30; 3.73)	0.615			-0.45 (-5.26; 4.37)	0.855	-1.08 (-4.90; 2.75)	0.579
ECOG PS[d]								
ECOG 0-1 – ref.	0				0		0	
ECOG 2-4	-25.03 (-31.80; -18.26)	**<0.001**			-8.59 (-15.67; -1.51)	**0.018**	-6.77 (-12.42; -1.12)	**0.019**
Pain	-0.30 (-0.35; -0.26)	**<0.001**					-0.18 (-0.22; -0.14)	**<0.001**
Dyspnea	-0.26 (-0.30; -0.22)	**<0.001**					-0.16 (-0.20; -0.12)	**<0.001**
Appetite loss	-0.26 (-0.30; -0.22)	**<0.001**					-0.12 (-0.16; -0.09)	**<0.001**
Nausea/vomiting	-0.37 (-0.44; -0.30)	**<0.001**					-0.05 (-0.12; 0.03)	0.224
Constipation	-0.10 (-0.15; -0.06)	**<0.001**					-0.01 (-0.05; 0.03)	0.492
Sleeping disturbance	-0.16 (-0.21; -0.11)	**<0.001**					-0.04 (-0.09; -0.003)	**0.034**
Diarrhea	-0.10 (-0.15; -0.05)	**<0.001**					-0.03 (-0.07; 0.02)	0.224

[a]15-items Geriatric depression scale [b]Norwegian Revised Mini Mental State Examination [c] Timed Up and Go test [d] Eastern Cooperative Oncology Group Performance Status

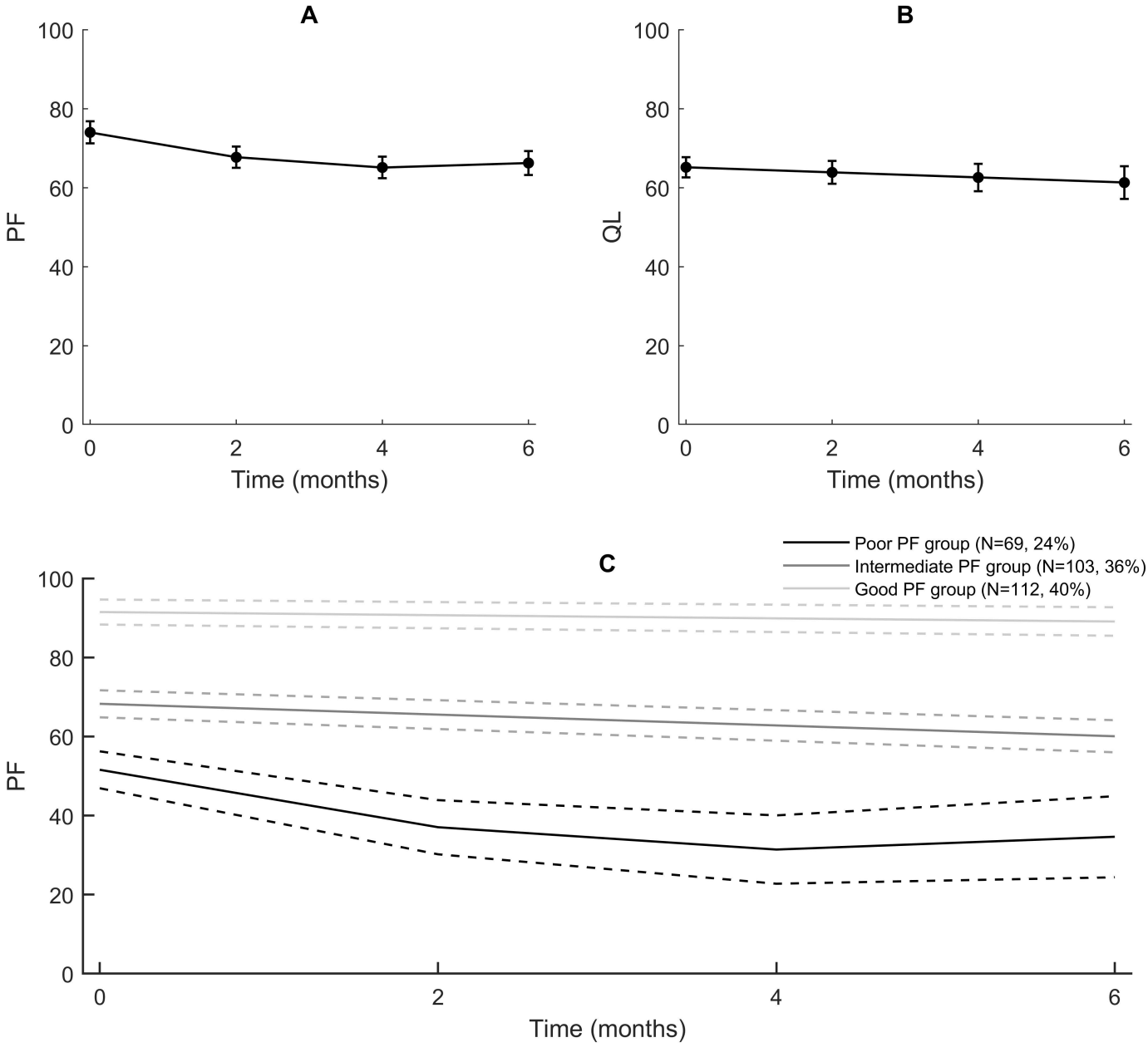
Table 4. Results of linear mixed models for global quality of life (QoL); n=264 (at baseline), n=237 (at 2 months), n=226 (at 4 months), and n=200 (at 6 months).

Variable	Bivariate models		Multiple model A		Multiple model B		Multiple model C	
	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
Time	-0.65 (-1.12; -0.17)	**0.008**	-0.67 (-1.15; -0.20)	**0.005**	-0.71 (-1.18; -0.23)	**0.004**	-0.47 (-0.87; -0.08)	**0.020**
Number of comorbidities	-3.14 (-4.44; -1.83)	**<0.001**	-0.80 (-2.17; 0.58)	0.255	-0.76 (-2.21; 0.69)	0.302	0.25 (-0.83; 1.34)	0.640
Number of medications	-1.29 (-2.08; -0.50)	**0.002**	-0.29 (-1.10; 0.52)	0.480	-0.36 (-1.21; 0.50)	0.415	-0.09 (-0.73; 0.55)	0.787
Malnutrition								
No - ref.	0	-	0	-	0	-	0	-
Yes	-11.82 (-18.40; -5.24)	**0.001**	-8.69 (-14.51; -2.86)	**0.004**	-8.02 (-14.31; -1.72)	**0.013**	-3.24 (-7.96; 1.48)	0.178
GDS score[a]	-3.48 (-4.20; -2.76)	**<0.001**	-2.89 (-3.68; -2.10)	**<0.001**	-2.71 (-3.53; -1.89)	**<0.001**	-1.43 (-2.05; -0.81)	**<0.001**
Falls								
≤ 1 fall - ref.	0	-	0	-	0	-	0	-
≥ 2 fall	-4.78 (-18.70; 9.13)	0.499	1.10 (-11.33; 13.53)	0.862	3.05 (-9.91; 16.01)	0.643	-4.71 (-14.47; 5.06)	0.344
MMSE[b]	0.61 (-0.58; 1.81)	0.315	-0.05 (-1.14; 1.05)	0.935	-0.02 (-1.14; 1.11)	0.977	-0.24 (-1.07; 0.60)	0.579
TUG[c]	-1.48 (-2.09;-0.86)	**<0.001**	-0.88 (-1.56;-0.19)	**0.013**	-0.81 (-1.59;-0.03)	**0.041**	-0.65 (-1.23; -0.07)	**0.029**
Impaired ADL[d]								
No – ref.	0		0		0		0	
Yes	-6.05 (-18.19; 6.10)	0.328	12.27 (0.13; 24.42)	**0.048**	8.42 (-4.53; 21.37)	0.202	8.63 (-1.05; 18.32)	0.080
Cancer diagnosis								
Breast – ref.	0	-			0	-	0	-
Prostate	-5.06 (-13.51; 3.39)	0.239			-3.12 (-13.38; 7.15)	0.550	-1.36 (-8.98; 6.25)	0.724
Other gastrointestinal	-9.42 (-18.86; 0.01)	0.050			-3.03 (-12.68; 6.61)	0.536	-4.07 (-11.28; 3.13)	0.267
Lung	-14.99 (-23.61; -6.37)	**0.001**			-6.90 (-16.08; 2.28)	0.140	-3.88 (-10.72; 2.95)	0.264
Colorectal	-5.52 (-13.41; 2.37)	0.170			-2.59 (-10.39; 5.21)	0.514	-3.10 (-8.93; 2.73)	0.295
Other	-13.20 (-23.22; -3.18)	**0.010**			-4.39 (-14.18; 5.40)	0.378	-1.56 (-8.85; 5.73)	0.674
Stage								
Localised – ref.	0	-			0	-	0	-
Locally advanced	-3.38 (-10.12; 3.36)	0.324			0.93 (-5.71; 7.57)	0.783	0.86 (-4.04; 5.77)	0.730
Metastatic	-6.08 (-11.43; -0.72)	**0.026**			-0.85 (-7.87; 6.16)	0.811	2.43 (-2.77; 7.62)	0.358
Treatment								
Curative - ref.	0	-			0	-	0	-
Palliative chemotherapy	-10.07 (-15.23; -4.90)	**<0.001**			-1.70 (-9.26; 5.87)	0.659	-2.34 (-7.93; 3.25)	0.410
Other pall.sys. cancer treat.	-2.38 (-8.79; 4.03)	0.465			3.47 (-6.80; 13.73)	0.506	-1.13 (-8.73; 6.48)	0.770
Other palliative care	-8.38 (-18.11; 1.34)	0.091			-1.14 (-11.04; 8.76)	0.821	2.98 (-4.40; 10.36)	0.427
Age	-0.35 (-0.80; 0.09)	0.101			-0.14 (-0.59; 0.32)	0.552	0.02 (-0.32; 0.36)	0.922
Gender								
Man – ref.	0	-			0	-	0	-
Woman	0.95 (-3.63; 5.54)	0.682			0.90 (-4.04; 5.84)	0.719	1.42 (-2.28; 5.11)	0.451
ECOG PS[e]								
ECOG 0-1 – ref.	0				0		0	
ECOG 2-4	-8.36 (-15.11; -1.61)	**0.015**			1.75 (-5.61; 9.11)	0.639	3.86 (-1.70; 9.43)	0.173
Pain	-0.40 (-0.44; -0.35)	**<0.001**					-0.26 (-0.30; -0.21)	**<0.001**
Dyspnea	-0.24 (-0.29; -0.20)	**<0.001**					-0.09 (-0.13; -0.05)	**<0.001**
Appetite loss	-0.31 (-0.35; -0.27)	**<0.001**					-0.16 (-0.20; -0.12)	**<0.001**
Nausea/vomiting	-0.46 (-0.54; -0.38)	**<0.001**					-0.06 (-0.14; 0.02)	0.143
Constipation	-0.15 (-0.20; -0.10)	**<0.001**					-0.01 (-0.05; 0.03)	0.576
Sleeping disturbance	-0.26 (-0.31; -0.20)	**<0.001**					-0.12 (-0.16; -0.07)	**<0.001**
Diarrhea	-0.14 (-0.20; -0.09)	**<0.001**					-0.06 (-0.10; -0.01)	**0.018**

[a]15-items Geriatric depression scale [b]Norwegian Revised Mini Mental State Examination [c]Timed Up and Go test [d]Activities of daily living [e]Eastern Cooperative Oncology Group Performance Status

Table 5. Results of the growth mixture model for physical function (PF) (N=284)

	Poor group		Intermediate group		Good group	
	Regression coefficient (SE)	p-value	Regression coefficient (SE)	p-value	Regression coefficient (SE)	p-value
Intercept	51.6 (2.4)	**<0.001**	68.3 (1.7)	**<0.001**	91.5 (1.6)	**<0.001**
Linear	-9.5 (1.8)	**<0.001**	-1.4 (0.5)	**0.003**	-0.4 (0.4)	0.266
Quadratic	1.1 (0.3)	**<0.001**	-	-	-	-
N (%)	69 (24)		103 (36)		112 (40)	
Mean within-group probability	0.89		0.86		0.93	
Estimated mean (95% CI) at						
Baseline	51.6 (46.9; 56.2)		68.3 (64.8; 71.7)		91.5 (88.3; 94.6)	
2 months	37.0 (30.2; 43.9)		65.5 (61.9; 69.2)		90.7 (87.4; 94.0)	
4 months	31.4 (22.8; 40.0)		62.8 (58.9; 66.7)		89.9 (86.4; 93.3)	
6 months	34.6 (24.4; 44.9)		60.1 (56.0; 64.1)		89.1 (85.5; 92.7)	


A
PF
Time (months)
B
QL
Time (months)
C
Poor PF group (N=69, 24%)
Intermediate PF group (N=103, 36%)
Good PF group (N=112, 40%)
PF
Time (months)