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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.

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Complete List of Authors:	Kirkhus, Lene; Sykehuset Innlandet HF Divisjon Psykisk helsevern, The Centre for Old Age Psychiatry Research; Universitetet i Oslo Institutt for klinisk medisin, Faculty of Medicine Šaltytė Benth , Jūratė; Sykehuset Innlandet HF Divisjon Psykisk helsevern, The Centre for Old Age Psychiatry Research; Akershus Universitetssykehus HF, HØKH Research Centre; Universitetet i Oslo Institutt for klinisk medisin, Campus Ahus Gronberg, Bjorn; Sankt Olavs Hospital Universitetssykehuset i Trondheim, The Cancer Clinic; Norwegian University of Science and Technology Department of Clinical and Molecular Medicine Hjermstad, Marianne; European Palliative Care Research Centre (PRC) , Department of Oncology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo Rostoft, Siri; Universitetet i Oslo Institutt for klinisk medisin, Faculty of medicine; Oslo universitetssykehus Ulleval, Department of Geriatric Medicine Harneshaug, Magnus; Sykehuset Innlandet HF Divisjon Psykisk helsevern, The Centre for Old Age Psychiatry Research; Universitetet i Oslo Institutt for klinisk medisin, Faculty of Medicine Selbaek, Geir; Sykehuset Innlandet HF Divisjon Psykisk helsevern, The Centre for Old Age Psychiatry Research; Sykehuset i Vestfold HF, Norwegian Advisory Unit on Ageing and Health; Universitetet i Oslo Institutt for helse og samfunn, Faculty of Medicine Wyller, Torgeir; Universitetet i Oslo Institutt for klinisk medisin, Faculty of medicine; Oslo universitetssykehus Ulleval, Department of Geriatric Medicine Jordhøy, Marit; Universitetet i Oslo Institutt for klinisk medisin, Faculty of Medicine; Sykehuset Innlandet Helseforetaket, The Cancer Unit Hamar
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Abstract:	Background: Maintaining quality of life including physical functioning is highly prioritized among older cancer patients. Geriatric assessment is a recommended approach to identify patients with increased vulnerability to stressors (frailty). How frailty affects quality of life and physical

	functioning in older cancer patients has scarcely been investigated. Aim: Focusing on physical functioning and global quality of life, we investigated if frailty identified by a geriatric assessment was associated with higher risk of quality of life deterioration during cancer treatment and follow-up. Design: Prospective, observational study. Patients were classified as frail or non-frail by a modified geriatric assessment. Quality of life was measured using the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire at inclusion, 2, 4, 6 and 12 months. Setting: Eight Norwegian outpatient cancer clinics. Participants: Patients ≥70 years with solid tumours referred for palliative or curative systemic medical cancer treatment. Results: Among 288 patients included, 140 (49%) were frail and 148 (51%) non-frail. Frail patients consistently reported poorer scores on all functioning and symptom scales. Independent of age, gender and major cancer related factors, frail patients had significantly poorer physical functioning and global quality of life during follow-up, and opposed to non-frail patients they had both a clinically and statistically significant decline in physical functioning from baseline until 12 months. Conclusion: Geriatric assessment identifies frail patients with increased risk of physical decline, poor functioning and high symptom burden during and following cancer treatment. Frail patients should therefore receive early supportive or palliative care.

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.

Lene Kirkhus* 1, 2,
Jūratė Šaltytė Benth 1, 3, 11
Bjørn Henning Grønberg 5, 6,
Marianne J. Hjermstad 7,
Siri Rostoft 2, 4,
Magnus Harneshaug 1, 2,
Geir Selbæk 1, 8, 9,
Torgeir Bruun Wyller 2, 4,
Marit S. Jordhøy 2, 10,

1 The Centre for Old Age Psychiatry Research, Innlandet Hospital Trust, P.O. box 68, 2313 Ottestad, Norway
2 Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, P.O. box 4956 Nydalen, 0424 Oslo, Norway
3 HØKH Research Centre, Akershus University Hospital, P.O. box 1000, 1478 Lørenskog, Norway
4 Department of Geriatric Medicine, Oslo University Hospital, P.O box 4956 Nydalen, 0424 Oslo, Norway
5 The Cancer Clinic, St. Olav's Hospital, Trondheim University Hospital, P.O. box 3250 Sluppen, 7006 Trondheim, Norway
6 Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, P.O. box 8905, 7491 Trondheim, Norway
7 European Palliative Care Research Centre (PRC), Department of Oncology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, P.O. Box 4956 Nydalen, 0424 Oslo, Norway
8 Norwegian Advisory Unit on Ageing and Health, Vestfold Hospital Trust, P.O. box 2136, 3103 Tønsberg, Norway
9 Institute of Health and Society, Faculty of Medicine, University of Oslo, P.O. box 1130 Blindern, 0318 Oslo, Norway
10 The Cancer Unit, Innlandet Hospital Trust, Hamar Hospital, Skolegata 32, 2326 Hamar, Norway
11 Institute of Clinical Medicine, Campus Ahus, University of Oslo, P.O. Box 1171, 0318 Blindern, Norway

*Corresponding author

E-mail	lene.kirkhus@gmail.com
Telephone number	0047 48 13 38 17
Mailing address	The Centre for Old Age Psychiatry Research, Innlandet Hospital Trust, P.O. box 68, 2313 Ottestad, Norway

Abstract

Background: Maintaining quality of life including physical functioning is highly prioritized among older cancer patients. Geriatric assessment is a recommended approach to identify patients with increased vulnerability to stressors (frailty). How frailty affects quality of life and physical functioning in older cancer patients has scarcely been investigated.

Aim: Focusing on physical functioning and global quality of life, we investigated if frailty identified by a geriatric assessment was associated with higher risk of quality of life deterioration during cancer treatment and follow-up.

Design: Prospective, observational study. Patients were classified as frail or non-frail by a modified geriatric assessment. Quality of life was measured using the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire at inclusion, 2, 4, 6 and 12 months.

Setting: Eight Norwegian outpatient cancer clinics.

Participants: Patients ≥70 years with solid tumours referred for palliative or curative systemic medical cancer treatment.

Results: Among 288 patients included, 140 (49%) were frail and 148 (51%) non-frail. Frail patients consistently reported poorer scores on all functioning and symptom scales. Independent of age, gender and major cancer related factors, frail patients had significantly poorer physical functioning and global quality of life during follow-up, and opposed to non-frail patients they had both a clinically and statistically significant decline in physical functioning from baseline until 12 months.

Conclusion: Geriatric assessment identifies frail patients with increased risk of physical decline, poor functioning and high symptom burden during and following cancer treatment. Frail patients should therefore receive early supportive or palliative care.

Keywords: geriatric assessment, frailty, quality of life, cancer, observational study, EORTC QLQ-C30.

What is already known on the topic?

Frailty identified by geriatric assessment is associated with increased risk of death and treatment complications in older cancer patients.

Although geriatric assessment is recommended for older cancer patients it is rarely implemented into clinical practice.

Studies investigating the impact of frailty on highly relevant outcomes like physical functioning and quality of life are scarce.

What this paper adds? (outcome)

Frailty identified by geriatric assessment independently predicts a clinically significant decline in physical functioning.

Frailty is associated with worse global quality of life, poorer functioning and a higher symptom burden throughout the cancer trajectory

Implication for practice, theory, or policy

Including routine geriatric assessment for older cancer patients undergoing systemic medical cancer treatment will aid oncologists in identifying frail patients who need early supportive and palliative care.

Introduction

Prolonging survival is usually considered the main goal of cancer care. However, maintaining or improving quality of life can be equally important. This applies especially to older patients, who have poorer survival in comparison with their younger counterparts and may be less willing to exchange current quality of life for smaller survival benefits[1, 2]. The quality of life concept embraces multiple dimensions: emotional, social, existential as well as physical, the latter including aspects such as patient reported somatic symptoms and physical functioning. Physical functioning is strongly associated with independent living, which is highly prioritized among older patients [3, 4], and is also a key driver for how they perceive their overall quality of life [5, 6]. Thus, making appropriate treatment decisions for older cancer patients requires knowledge on how quality of life may be affected and ability to identify patients at risk of deterioration. Particular attention to physical functioning seems essential.

Frailty is defined as increased vulnerability to adverse changes in health status [7], and is associated with increased mortality, postoperative complications and intolerance to cancer treatment [8, 9]. Frail patients have been found to have poorer quality of life than non-frail patients[10-12], but longitudinal studies investigating the impact of frailty on quality of life during and after cancer treatment are scarce. Results from those available are not consistent, having shown both similar changes in quality of life trajectories of frail and non-frail patients [10, 11] as well as accelerated decline of some dimensions among frail patients [13].

A challenge to all frailty research is the lack of universally accepted operational criteria. Over 70 different methods for measuring frailty have been developed, most of which are linked to the two dominating pathophysiological theories of frailty; the physical frailty phenotype and the cumulative deficit model[14, 15]. In the oncology literature, geriatric assessment is the

recommended approach to identifying frailty [14] and to guide treatment decisions for older patients [16]. This approach includes a systematic assessment of areas such as functional status, mobility, cognitive function, comorbidity and geriatric syndromes [8, 16]. Still, geriatric assessment remains to be widely implemented into oncology practice, perhaps hampered by its comprehensiveness. Simpler frailty screening tools are more time-efficient and might be easier to implement into clinical practice, but their lower sensitivity and specificity is a challenge [17]. Thus, geriatric assessment is considered the gold standard,[14] although screening tools may be used to select patients for a complete geriatric assessment[18]. There is, however, no general agreement on how frailty should be defined based on a geriatric assessment. Varying domains and thresholds have been applied in different studies[8], but the criteria as proposed by Balducci et al [19] have commonly been used [20, 21].

We have formerly demonstrated that frailty identified by a modified geriatric assessment and a modification of the Balducci criteria [22, 23], was independently predictive of survival in cancer patients ≥ 70 years of age [24]. In the present study, targeting the same population, we aimed at investigating if frailty was associated with higher risk of quality of life deterioration during treatment and follow-up. Our main hypothesis was that patients classified as frail upon start of treatment would experience a steeper decline in both physical functioning and global quality of life than non-frail patients.

Materials and methods

Patients

Patients were consecutively recruited from January 2013 until April 2015 at eight Norwegian outpatient oncology clinics (two university hospitals and six local hospitals). Eligible patients were ≥70 years and referred for systemic medical cancer treatment (chemotherapy, hormonal

or targeted therapy) with a histologically confirmed solid tumour (newly diagnosed or first relapse after previous curative treatment). Patients provided written, informed consent.

Assessments

Oncologists reported cancer type (ICD-10), stage of disease, planned treatment and ECOG performance status. Data on administered treatment were retrieved from the patients' medical records.

Physical functioning and global quality of life was assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ-C30) [25] at inclusion, and after 2, 4, 6, and 12 months. QLQ-C30 consists of 30 questions comprising five functioning scales, nine symptom scales/items and a global quality of life scale. The functioning scales include physical, role, social, cognitive and emotional functioning. Symptoms include fatigue, pain, nausea/vomiting, sleep disturbances (insomnia), appetite loss, diarrhoea, dyspnoea and constipation, and financial impact. The raw scores are transformed into scales from 0 to 100 points [26]. Higher scores on the functioning and global quality of life scales represent better functioning, whereas higher scores on symptom scales/items indicate a higher symptom burden.

Frailty was identified by a geriatric assessment which we have referred to as modified since it was not performed by an interdisciplinary team, but by trained oncology nurses and patients' self-report, [24] using well-known and validated instruments for each included domain [27-31] (Table 1). Our frailty definition was predefined and following the Balducci criteria, patients were categorized as frail if they fulfilled at least one of the following; dependencies in activities of daily living, significant comorbidity or one or more geriatric syndromes (cognitive function, depression, malnutrition, falls). Similar to Kristjansson et al [22], we

included polypharmacy as a criterion, and added impairment according to Timed Up and Go [27], a sensitive and specific measure of frailty [32]. Cut-off values for each domain were chosen in line with former reports and practice (Table 1) [23, 33-40]. A detailed explanation is found in a previous paper [24]. To screen for deficits in activities of daily living a question from the QLQ-C30 physical functioning scale ("Do you need help with eating, dressing, washing yourself or using the toilet?") were used.

Statistical analyses

Medical and sociodemographic factors were compared between frail and non-frail patients by independent samples t-tests or χ^2-test.

Our predefined main endpoints were changes in physical functioning during the two first months of follow-up (primary), and changes in physical functioning and global quality of life during 12 months (secondary). Changes during 12 months for the remaining QLQ-C30 scales and items were assessed by exploratory analyses using the same approach as for the main endpoints.

Differences between frail and non-frail patients in changes over time were assessed by linear mixed models. All models included random intercepts for cancer clinics and for patients nested within cancer clinics to account for intra-patient correlations due to repeated measurements and possible within-clinic cluster effect. The models also included fixed effects for frailty group, time (as second-order polynomial to account for non-linear trends in models assessing data on 12 months follow-up) and the interaction term between frailty group and time (frail*time). A significant interaction term would imply that there were differences in change between frail and non-frail patients. Models adjusting for age, sex, cancer type, performance status, stage and treatment were also estimated. Treatment was classified as; 1)

Curative treatment, i.e. patients referred for neoadjuvant chemotherapy treatment, adjuvant chemotherapy and/or endocrine treatment after curative surgery or curative radiotherapy, 2) palliative chemotherapy, 3) other palliative systemic cancer treatment, 4) non-systemic palliative treatment the first two months after inclusion (i.e. radiotherapy, surgery or palliative care). Performance status was classified as 0-1 or 2-4, and stage as local, locally advanced or metastatic. The results were tabulated as regression coefficients with standard errors (SE) and p-values for the primary and secondary analyses of physical functioning and global quality of life. The results from unadjusted models were also presented graphically as estimated mean values with 95% confidence intervals (CI) for all QLQ-C30 scales/items. Within- and between-group differences with the corresponding 95% CI and p-values were calculated from the models. Significance level was set at 5%. A difference of ≥10 points on the functional and symptom scales/items was considered a clinically significant change [41].

Missing values in QLQ-C30 multi-item scales were imputed according to the official manual if at least half of the scale had been answered [26].

The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway 09.02.2012 (Reference number 2012/104) and registered at clinicaltrials.gov (NCT01742442).

Results

Patients

From January 2013 to April 2015 a total of 307 patients were included. One patient withdrew consent and 18 had missing baseline questionnaires and therefore incomplete geriatric assessments. Thus, 288 (94%) patients were eligible for the present frailty study. A total of 140 patients (49%) fulfilled one or more of the predefined criteria and were categorized as

frail. The most frequent deficits were comorbidity (n = 82, 28%), malnutrition (n = 43, 15%), polypharmacy (n = 37, 13%) and depressive symptoms (n = 35, 12%). Forty patients (14%) had deficits in physical functional aspects: activities of daily living (12 patients), Timed Up and Go (18 patients) and number of falls (10 patients). Nine patients (3%) had cognitive impairment. Of the 140 patients categorized as frail, 67 (48%) patients had two or more registered deficits. Only one patient was classified frail based on the activities of daily living criterion alone, which was screened for by using question 5 from the physical functioning scale of QLQ-C30.

The patients' baseline characteristics are shown in Table 2. Mean age was 76.9 (5.1) years, 56% were male, the most common cancer types were colorectal (29%), lung (21%) and prostate cancer (19%). The majority of patients had distant metastases (56%), and overall, 68% received palliative treatment. A higher percentage of frail compared to non-frail patients had lung cancer, distant metastases, performance status 2-4 and received palliative chemotherapy.

At 2, 4, 6 and 12 months of follow-up, 13 (5%), 27 (9%), 52 (18%) and 93 (32%) patients of the overall cohort had died. Median overall survival was shorter among frail than non-frail patients (15 vs 29 months) [24]. The first 12 months, 83 (59%) of frail and 112 (76%) of non-frail patients were alive, resulting in relative risk of death of 1.7 (95% CI 1.2; 2.4) for frail compared to non-frail patients. The proportion of completed questionnaires ranged between 89% and 95% for those alive at the various assessment points (Figure 1). The mean proportion of missing items ranged from 0.51% to 0.96%.

Quality of life-analyses

At baseline, frail patients reported poorer functioning and more symptoms than non-frail patients on all scales/items (Table 2).

Both frail and non-frail patients reported a statistically, but not clinically significant decline in physical functioning from baseline to two months. The decline was not significantly different between frail and non-frail patients (unadjusted model: p = 0.181, adjusted model: p = 0.218). According to the unadjusted linear mixed model, there were, however, statistically significant differences in physical functioning scores between the two groups in disfavour of frail patients, mean 18.2 (CI 13.3; 23.1) points at baseline and 15.0 (CI 9.9; 20.0) points at two months (p<0.001) (Figure 2, Table 3a). The differences remained statistically significant when adjusting for age, gender, cancer type, stage, performance status and treatment (12.2 (CI 7.5; 16.9) points at baseline, 9.2 (CI 4.4; 14.1) at two months) (p<0.001) (Figure 2, Table 3a).

For our secondary endpoint, physical functioning during 12 months of follow-up, a statistically significant decline was found for non-frail patients from baseline to 6 months, and for frail patients from baseline to both 6 and 12 months. Only frail patients had a clinically significant (≥10 points) decline. In unadjusted models the decline in physical functioning for frail and non-frail patients was not significantly different (p=0.089) (Table 3b, Figure 2). However, when adjusting for age, gender, cancer type, stage, performance status and treatment, the decline was found to be significantly steeper for frail patients (p=0.022) (Table 3b). Thus, the observed difference in scores in disfavour of frail patients during the two first months increased throughout the follow-up period and remained statistically and clinically significant, both according to unadjusted (Figure 2, Table 3b) and adjusted models (Table 3b) (p < 0.001).

For global quality of life during 12 months of follow-up, there was no significant difference between frail and non-frail patients in the course of changes ($p = 0.369$ in unadjusted models; $p = 0.273$ in adjusted models) (Table 3c). Both models demonstrated that frail patients had statistically and clinically significantly worse scores compared to non-frail patients at all assessment points ($p<0.001$) (Figure 2, Table 3c).

Unadjusted trajectories for frail and non-frail patients for the remaining functioning and symptom scales are shown in Figure 2 and 3. Differences that were both statistically and clinically significant according to unadjusted and adjusted analyses are indicated. In the adjusted model, frail patients had a clinically and statistically significant decline in role functioning from baseline to six months ($p<0.001$). None of the other scales showed any clinically significant changes from baseline in the adjusted models, neither in frail nor non-frail groups. Except for diarrhoea (adjusted model, $p = 0.023$), with a statistically but not clinically significant increase in symptoms from baseline to 6 months for frail patients, the course of the trajectories was not significantly different between the groups. However, adjusted models showed that frail patients had statistically and clinically significantly more constipation ($p < 0.01$), and worse role - ($p<0.001$), social ($p<0.01$), and emotional functioning ($p<0.01$) at all assessments. Accordingly, significant differences between the frailty groups were found at some but not all assessment points for dyspnoea, insomnia, appetite loss and fatigue (Figure 3).

Discussion

In this longitudinal study, older cancer patients were assessed by a modified geriatric assessment, and we identified a group of frail patients who in comparison to non-frail patients

had substantially poorer functioning and more symptoms. Independent of age, gender and major cancer related prognostic factors, they reported significantly worse global quality of life, physical-, role-, social, - and emotional functioning, and more constipation during treatment and follow-up. They also reported a long-term decline in physical functioning that was clinically significant, and significantly steeper than for non-frail patients.

To the best of our knowledge, the present study is the first to report a longitudinal comparison of self-reported physical functioning between frail and non-frail older patients mainly receiving systemic cancer therapy, and the first to suggest a more profound deterioration in this quality of life dimension among frail patients after adjusting for other relevant confounders. Our finding is supported by two former studies reporting frailty indicators to be predictive of observer rated physical decline in older cancer patients receiving chemotherapy or neoadjuvant/adjuvant treatment [42, 43]. No such impact of frailty was found in studies of patients receiving surgery and radiochemotherapy, respectively [10, 11]. In the latter, however, specific assessments of physical functioning were reported only at four weeks after start of therapy, and as indicated by our results, a significant decline may take longer to develop. It is also likely that a protracted course of chemotherapy, which was the treatment received by most of our patients, may have a larger impact on frail patients' physical functioning than surgery.

The results of the few previous studies that have investigated how frail older cancer patients perceive their quality of life are largely consistent with our remaining findings. Frail patients seem to be at a considerable disadvantage throughout the disease trajectory, reporting a substantial symptom burden and poor functioning compared to non-frail patients [10, 11, 44]. In line with the findings for most quality of life aspects in our cohort, others have also found that

although quality of life is poorer, changes mainly follow a similar course in frail and non-frail cancer patients. Increased risks of long-term deterioration has, however, been suggested [13, 44]. How an observed similarity of changes in quality of life trajectories of frail and non-frail patients should be interpreted is not obvious. One might argue that this indicates that frail patients tolerate cancer therapy equally to non-frail patients. However, as frail patients are worse off from the start, changes of the same magnitude may affect these patients more profoundly than those who are non-frail.

Our study has several strengths, i.e. a fairly large patient cohort, 12 months follow-up, use of a well-validated quality of life-questionnaire, high completion rate, and statistics controlling for major factors that may affect quality of life. Still, the results should be interpreted with some caution. Firstly, the population was heterogeneous, details of the chemotherapy regimens were not accounted for, and we cannot rule out that frail patients received modified or less aggressive regimens than those who were non-frail. This is, however, unlikely as the physicians were blinded for the results of the modified geriatric assessment. Also, as formerly reported, there was only a fair agreement between the frailty classification based on this assessment and physician-rated frailty[24]. Secondly, we were not able to accurately register the number of potentially eligible patients who were not included at the various participating clinics. According to the project nurses, however, non-inclusion mainly occurred by random due to lack of time to identify and include patients among their routine clinical tasks. Still, there is some risk that the frailest patients with the poorest overall health more often declined participation or were less frequently invited to participate due to concerns of the additional burden the study tests represented. Thirdly, due to a higher death rate among frail patients, attrition bias may have resulted in underestimation of differences between frail and non-frail patients [45]. Fourthly, physical function, as assessed by Timed Up and Go, number of falls and

one item from the physical functioning scale of the EORTC QLQ-C30, is a key component of a geriatric assessment and frailty definition and can probably explain some of the baseline difference we found in functioning between frail and non-frail patients. However, it is not inherent in our frailty definition that frail patients experience a steeper decline in physical functioning compared to non-frail. Moreover, only a minority of the patients fulfilled these criteria, and the main point to be noted is the overall burden of problems among these frail patients. An additional point of consideration is that we used one question from the QLQ-C30 physical functioning scale, which was also our main endpoint, to identify frailty. Only one patient was classified as frail based on this criterion alone, hence we believe that this did not affect our results. Finally, as there is no consensus on how frailty should be identified, it may be discussed if our frailty definition captures the true concept. One may argue that it was too broad as only one criterion was needed to be classified as frail. A stricter definition might have resulted in larger discrepancies between frail and non-frail patients. However, our approach was adapted from the Balducci criteria, and a similar definition was found superior to the physical frailty phenotype in identifying postoperative complications in cancer patients[46]. There is a need for standardisations of cut-off-values for frailty[8], nevertheless the consistency of findings across studies indicates that geriatric assessment can identify patients who need particular attention.

Our study shows that frailty as identified by a modified geriatric assessment has a severe impact on the patients' quality of life throughout the disease trajectory, independent of cancer related factors. Thus, by introducing geriatric assessment into clinical work, a more correct individualisation of treatment can be achieved [47]. Furthermore, targeted interventions to improve quality of life and maintain functioning may be initiated. Early introduction of palliative care has been shown to improve quality of life, reduce aggressiveness of treatment

and improve survival [48]. Similar studies in frail old cancer patients are needed to examine whether improvement of quality of life can be obtained. Ideally these studies should include interventions on geriatric deficits and measure their effect on quality of life. Particular attention should be paid on avoiding physical decline, which may considerably increase the risk of dependency, a predominant fear among older patients [4, 49]. As indicated by the findings in our study, frail patients report significantly poorer physical functioning than those who are non-frail, meaning that any decline is likely to have more serious consequences.

In conclusion, introducing geriatric assessment into routine clinical practice may help oncologists identify patients with significantly worse quality of life, and enable better individualisation of treatment. This may also facilitate early and correctly targeted interventions. Future research is, however, needed to explore whether intervening on frailty domains can improve functional status, global quality of life, symptom burden or tolerance to cancer therapy.

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Declaration of conflicting interests

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Table 1. The modified Geriatric assessment[a]

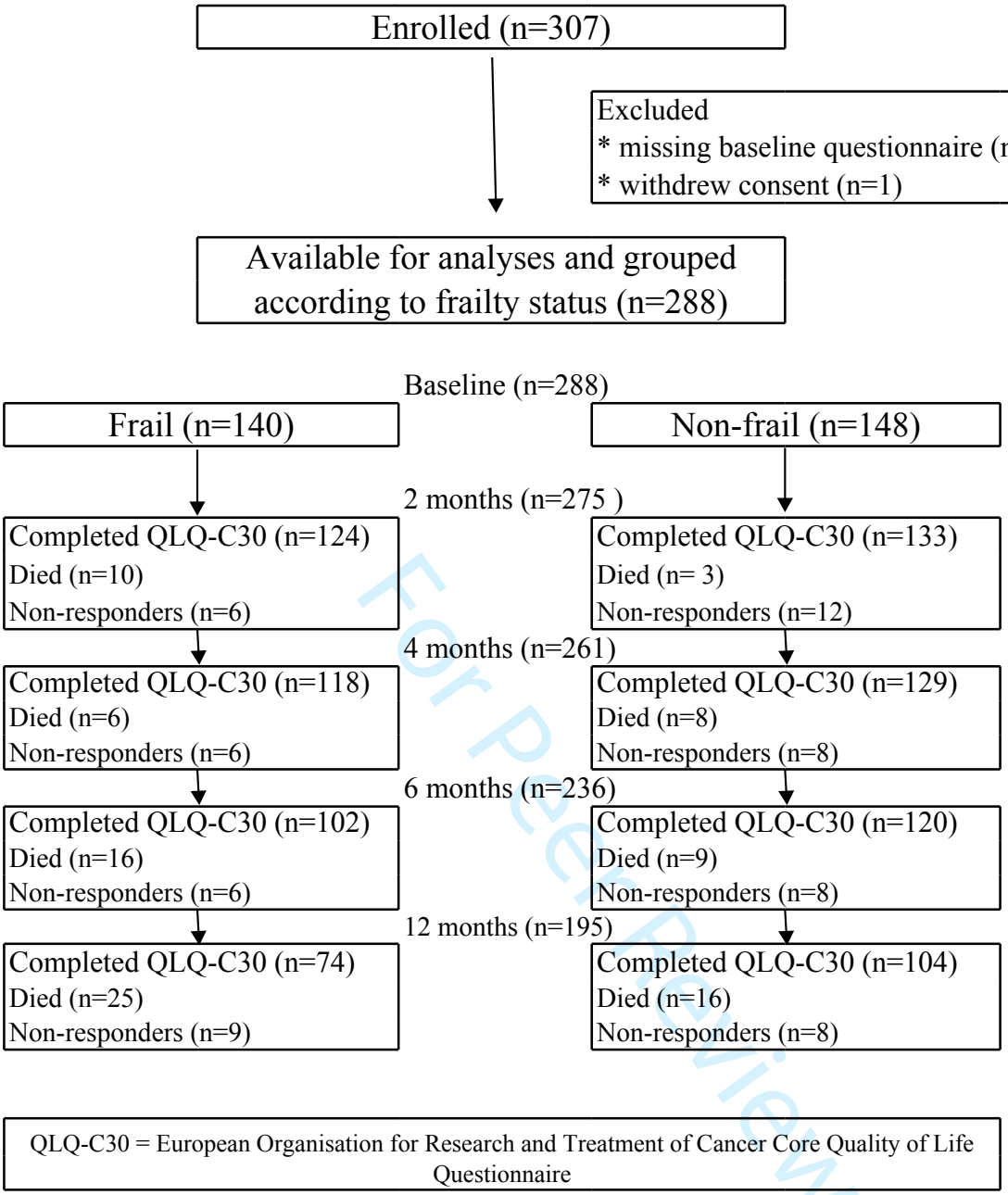
Area	Assessment method	Scores	Performer	Cut off value above which patients were defined as frail
Activities of daily living	EORTC QLQ-C30 Q5[b]		Patient	If reported yes a little/quite a bit/very much on the question "Do you need help with eating, dressing, washing yourself or using the toilet"
Comorbidity	OARS[c]	0-15 (Higher score indicates more comorbidities)	Patient	>3 points
Medications, polypharmacy	ATC[d]	0-13	Nurse/ physician	>7 regular medications (ointments & common vitamins excluded)
Cognitive function	MMSE[e]	0-30 (Higher score indicates better function)	Nurse	<24 points
Depressive symptoms	GDS-15[f]	0-15 (Higher score indicates more symptoms)	Patient	≥7 points
Nutritional status	PG-SGA[g]		Nurse/ Patient	Considered severely malnourished by nurse or self-reported weight loss ≥10% the last 6 months.
Falls			Nurse	Patient reports ≥2 falls the last 6 months
Physical function	TUG[h]		Nurse	>14 seconds

[a]Patients were classified as frail if having ≥ 1 of the criteria listed in the table, [b]The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire, [c]The Physical Health Section of the Older Americans' Resources and Services Questionnaire, [d]Anatomical Therapeutic Chemical Classification System, [e]Norwegian Revised Mini Mental State Examination, [f]Geriatric depression scale, [g]Patient-generated Subjective Global Assessment, [h]Timed up and Go test.

Table 2. Baseline patient characteristics according to frailty status

	All		Frail		Non-frail		
	N (288)	%	N (140)	%	N(148)	%	P-value
Age, mean (SD)	76.9(5.1)		77.5(5.2)		76.2(5.0)		0.032*
Gender							
Female	126	44	64	46	62	42	0.513**
Cancer type							
Colorectal	83	29	39	28	44	30	
Lung	59	21	35	25	24	16	0.045**
Prostate	56	19	22	16	34	23	
Other gastrointestinal	34	12	19	14	15	10	
Breast	30	10	9	6	21	14	
Other	26	9	16	11	10	7	
Stage							
Localized	73	25	30	21	43	29	0.091**
Locally advanced	55	19	23	16	32	22	
Distant metastasis	160	56	87	62	73	49	
ECOG Performance status							
0-1	244	85	106	76	138	93	
2-4	43	15	33	24	10	7	<0.001**
Missing	1		1				
Treatment							
Curative***	91	32	31	22	60	41	
Palliative chemotherapy	126	44	75	54	51	35	0.002**
Other palliative systemic cancer treatment	51	18	22	16	29	20	
Non-systemic palliative treatment****	20	7	12	9	8	5	
	mean	SD	mean	SD	mean	SD	
Functioning scales and global health status							
Physical functioning	72.9	21.4	63.5	21.3	81.7	17.4	
Global quality of life	64.1	23.1	54.5	22.1	73.4	20.1	
Role functioning	65.5	32.1	52.0	31.7	78.4	26.8	
Emotional functioning	83.9	18.1	77.7	21.1	89.8	12.2	
Cognitive functioning	87.6	16.0	83.6	18.1	91.4	12.7	
Social functioning	76.0	25.9	68.3	28.5	83.2	20.9	
Symptom scales/items							
Fatigue	38.8	24.2	48.7	25.6	29.4	18.5	
Nausea and vomiting	6.8	14.8	10.6	18.7	3.3	8.6	
Pain	24.8	29.4	32.9	31.7	17.1	24.9	
Dyspnea	25.7	31.4	33.3	34.1	18.5	26.8	
Insomnia	26.2	28.5	32.1	30.9	20.5	24.8	
Appetite loss	21.4	31.4	30.7	36.0	12.6	23.2	
Constipation	24.0	29.3	30.5	32.4	17.9	24.8	

Diarrhoea	15.2	22.4	17.1	24.2	13.2	20.5	
*Independent samples t-test **Pearson chi-square ***referred for neoadjuvant treatment, adjuvant treatment after curative surgery or curative radiotherapy ****i.e. radiotherapy, palliative surgery or palliative care								



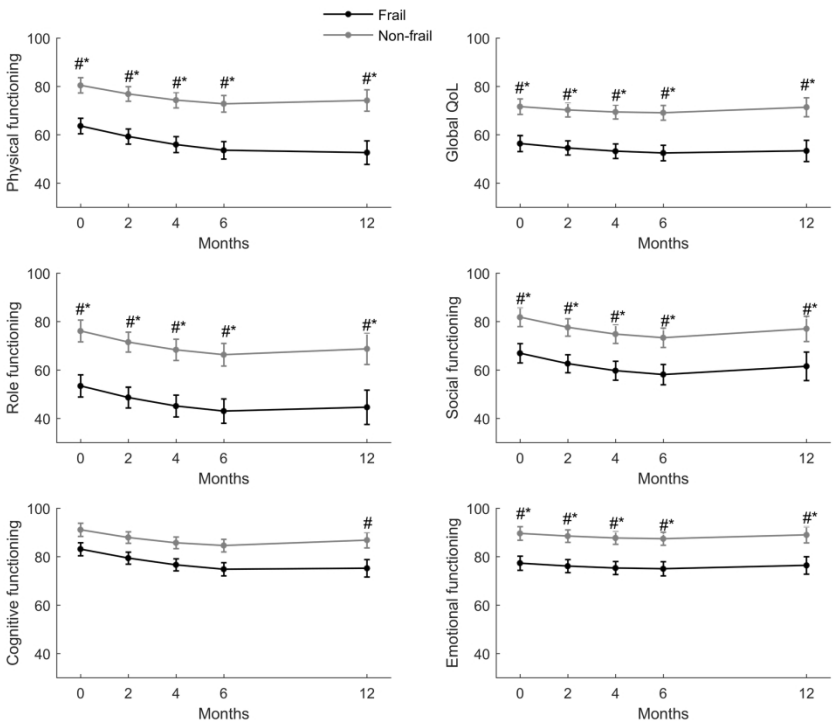


Figure 2. Global quality of life and function scores for frail and non-frail patients, at baseline and at two, four, six and twelve months of follow-up, according to unadjusted mixed linear models. # indicates clinically and statistically significant differences in unadjusted models*indicates clinically and statistically significant differences in adjusted models For these QLQ-C30 functioning scales, higher scores indicate better functioning

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Table 3. Linear mixed models of the trajectories of physical functioning in frail versus non-frail patients during two months of follow up, and of physical functioning and global quality of life during the first 12 months of follow-up

Variable	Unadjusted model			Adjusted model**		
	Coefficient	*SE*	*P-value*	*Coefficient*	*SE*	*P-value*
a) Physical functioning* the first two months.						
Intercept	81.86	1.73	**<0.001**	117.90	18.11	**<0.001**
Frailty (ref.non-frail) †	-18.20	2.48	**<0.001**	-12.21	2.40	**<0.001**
Time 2 months (ref. baseline)	-7.02	1.69	**<0.001**	-7.36	1.67	**<0.001**
Frail*Time††	3.25	2.43	0.181	2.98	2.41	0.218
b)Physical functioning* the first 12 months						
Intercept	80.41	1.61	**<0.001**	124.74	18.52	**<0.001**
Frailty (ref.non-frail) †	-16.80	2.23	**<0.001**	-10.44	2.31	**<0.001**
Time	-2.03	0.35	**<0.001**	-2.13	0.35	**<0.001**
Time^2	0.13	0.03	**<0.001**	0.14	0.03	**<0.001**
Frail*Time††	-0.40	0.23	0.089	-0.49	0.21	**0.022**
c) Global quality of life* the first 12 months						
Intercept	71.62	1.65	**<0.001**	87.78	18.62	**<0.001**
Frailty (ref.non-frail) †	-15.27	2.24	**<0.001**	-12.59	2.37	**<0.001**
Time	-0.83	0.41	**0.046**	-0.91	0.41	**0.029**
Time^2	0.07	0.03	**0.034**	0.07	0.03	**0.025**
Frail*Time††	-0.23	0.25	0.369	-0.28	0.25	0.273

* Physical functioning and global quality of life from the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire **Adjusted for age, gender, cancer type, stage, performance status and treatment

† (Frailty (ref non-frail) refers to estimates of the difference in score between frail and non-frail patients

†† Frail*Time refers to the interaction term between the frail group and time. A significant interaction term implies significant differences in changes over time between frail and non-frail patients

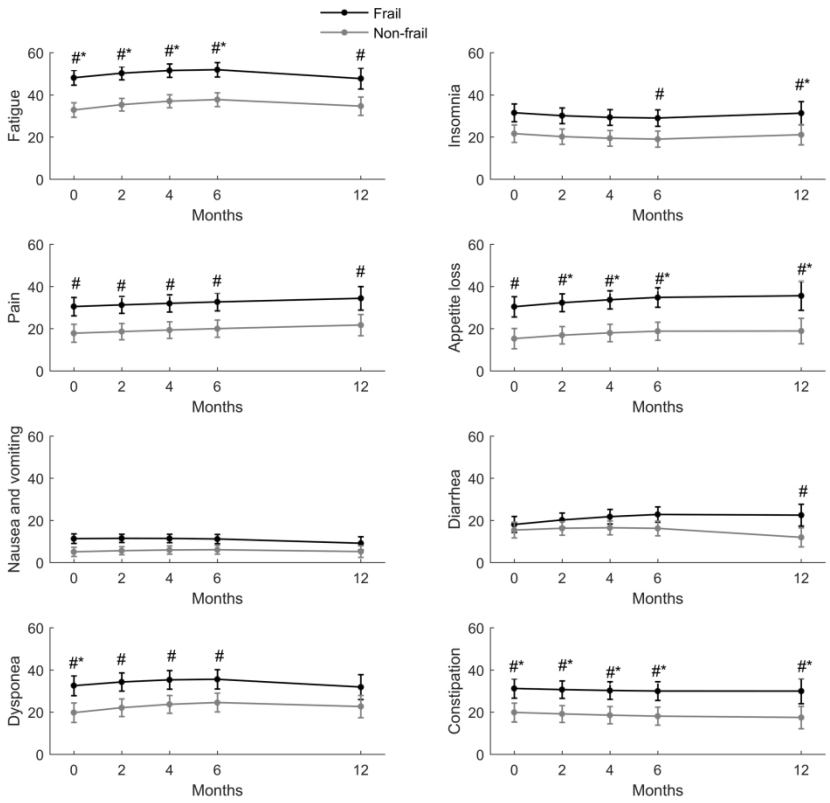

Figure 3. Symtom scores for frail and non-frail patients, at baseline and at two, four, six and twelve months of follow-up, according to unadjusted mixed linear models# indicates clinically and statistically significant differences in unadjusted models*indicates clinically and statistically significant differences in adjusted models For these QLQ-C30 symptom scales/items, higher scores indicate more symptoms

221x193mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Reported in the design section of the abstract.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found A balanced summary are written in abstract
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported The background/rationale has been given in the first three paragraphs in the introduction
Objectives	3	State specific objectives, including any prespecified hypotheses Our objective and hypothesis are included in the fourth paragraph of the introduction.
Methods		
Study design	4	Present key elements of study design early in the paper Included in the design section in abstract and in materials and methods.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Described in Patients and Assessments in materials and methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Eligibility criteria are given in the "Patient section" of materials and methods, the assessment performed and who performed the assessment are registered in the section "Assessment" in materials and methods. In this section we also refer to our previously published paper that give further detailed information about our assessments and follow-up. *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed Not relevant for this study *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Defined in the section "Statistical analyses" of materials and methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group

		In materials and methods in the section "Assessment" details of methods of assessment are described. We also refer to a previously published paper that in more detail describe our frailty assessment.
Bias	9	Describe any efforts to address potential sources of bias Attrition bias have been addressed in the discussion section in the fourth paragraph
Study size	10	Explain how the study size was arrived at This study was planned with a heterogeneous patient sample and with unknown prevalence, distribution, and effect size of variables planned to include in analyses. An exact sample size estimate could therefore not be presented in the protocol, and only estimates were performed. This has not been included to be able to keep the allowed word count of the manuscript.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why' This has been explained in "Statistical analyses" in methods section
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Statistical methods explained in Statistical analyses in methods section
		(*b*) Describe any methods used to examine subgroups and interactions This is described in Statistical analyses in methods section
		(*c*) Explain how missing data were addressed This is explained in statistical analyses in methods section.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed Missing items were imputed statistically, a description of how many loss to follow-up we had at each time were presented in results and attrition bias discussed in the discussion section. *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses -

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Paragraph one of the Result section describes how many patients were included, and how many of these patients were available for analyses. Figure 1 summarize how many that completed follow-up questionnaires at each follow-up time.
		(b) Give reasons for non-participation at each stage Number of patients alive at each follow-up point are presented in figure 1, as well as how many patients that responded on the follow-up questionnaire. At inclusion we have missing information about eligible patients that were not included and this has been discussed as a limitation in the discussion section of this manuscript.
		(c) Consider use of a flow diagram Figure 1 in the revised manuscript gives an overview of patient enrolment and follow-up.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Table 2 and result section "Patients"
		(b) Indicate number of participants with missing data for each variable of interest Patients with missing quality of life questionnaires are reported in figure 1. In our previously publication referred to in this manuscript detailed information about missing in frailty assessment is provided.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) In paragraph 2 of «Patients» in the result section follow-up time are presented.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Figure 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Given in Table 4, figure 2 and 3 as well as in text in "Qol analyses" in result section.
		(*b*) Report category boundaries when continuous variables were categorized We used continuous variables as appropriate.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Exploratory analyses are presented in "Qol-analyses" in result section.
Discussion		
Key results	18	Summarise key results with reference to study objectives The first paragraph of the Discussion section summarizes key results.

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Discussed in fourth paragraph of result section.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Included in the interpretation of the results in the discussion section
Generalisability	21	Discuss the generalisability (external validity) of the study results Briefly discussed in the discussion as well as in previous publication.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Given in "Funding" at the end of the manuscript.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

PALLIATIVE MEDICINE AUTHOR SUBMISSION CHECKLIST

Please complete this checklist for all papers submitted. Please indicate, very briefly, how this has been addressed. This checklist is a mandatory upload on submission.

Item	Explanation	How this has been addressed (briefly, a sentence will suffice)
Article title	***WHY: Because we want readers to find your work.*** Have you followed our guidelines on writing a good title that will be found by search engines? (E.g. with methods in the title, use of common words for the issue addressed, no country names, and possibly indicating findings). If your study has an acronym is it included in the title?	We have use common words for the issue addressed (geriatric assessment, physical decline, old, cancer) and indicate findings from the study.
Abstract	***WHY: Because structured abstracts have more detail for readers and search engines.*** Have you followed our guidelines on writing your structured abstract? Please remember we have separate abstract structures for original research, reviews and case reports. There should be **no** abbreviations in the abstract, EXCEPT a study acronym which should be included if you have one. If a trial (or other design formally registered with a database) have you included your registration details?	We have followed the guidelines and not used abbreviations.
Key statements	***WHY: Because readers want to understand your paper quickly.*** Have you included our key statements within the body of your paper (after abstract and before the main text is a good place!) and followed our guidelines for how these are to be written? There are three main headings required, and each may have 1-3 separate **bullet** points. Please use clear, succinct, single sentence separate bullet points rather than complex or multiple sentences.	Key statements are included with three main headings.
Keywords	***WHY: Because MeSH headings mean it is properly indexed.*** Have you given keywords for your study? We ask that these are current **MeSH** headings unless there is no suitable heading for use (please give explanation in cover letter). https://meshb.nlm.nih.gov/search	Five keywords are included, four are MeSH headings. One word "EORTC QLQ-C30" is not a MeSH heading. This keyword is included as it is the abbreviation of the questionnaire used in our study.
International relevance	***WHY: We have readers from around the world who are interested in your work.*** Have you contextualised your work for an international audience and explained how your work contributes to an international knowledge base? Avoid drawing from policy from one context only, think how your work could be relevant more widely. Do define terms clearly e.g. hospice has a different meaning in many countries.	All tests and questionnaires that are used are internationally known, and the article written to contribute to international knowledge base.

Publishing guidelines	***WHY: Because clear and robust reporting helps people interpret your work accurately*** Have you submitted a completed checklist for a relevant publishing guideline as a supplementary file? http://www.equator-network.org/ These include CONSORT, PRISMA, COREQ checklists, but others may be more relevant for your type of manuscript. If no published checklist exists please create one as a table from the list of requirements in your chosen guideline. If your study design does not have a relevant publishing guideline please review closest matches and use the most appropriate with an explanation.	Yes, STROBE guidelines are included.
Word count	***WHY: Because readers want to find the core information quickly.*** Does your paper adhere to our word count for your article type? Please insert number of words in the box to the right. Remember that tables, figures, qualitative data extracts and references are not included in the word count.	Word count : 3400 (including acknowledgement and funding)
Figures and tables and/or quotations	***WHY: Because readers want to find the core information quickly.*** Have you adhered to our guidelines on the number of tables and figures for your article type? Data (e.g. quotations) for qualitative studies are not included in the word count, and we prefer that they are integrated into the text (e.g. not in a separate table).	Yes, we have included 6 tables/figures.
Study registration	***WHY: Because this means readers understand how you planned your study*** Where appropriate have you included details (including reference number, date of registration and URL) of study registration on a database e.g. trials or review database. If your study has a published protocol, is this referenced within the paper?	We have included information about registration at "clinicaltrials.gov".
Other study publications?	***WHY: So readers can understand the full context of your study*** If there are other publications from this study are these referenced within the body of the paper? Please do not reference papers in preparation or submitted, but in-press publications are acceptable.	One previous publication is referenced within the body of the paper.
Scales, measures or questionnaires	***WHY: So readers can understand your paper in the context of this information*** If your study primarily reports the development or testing of scales/measures or questionnaires have you included a copy of the instrument as a supplementary file?	Not relevant as this is not development of new instrument.
Abbreviations	***WHY: Because abbreviations make a paper hard to read, and are easily misunderstood*** Have you removed **all** abbreviations from the text except for extremely well known, standard abbreviations (e.g. SI units), which should be spelt out in full first? We do not allow abbreviations for core concepts such as palliative or end of life care.	Only the abbreviation QLQ-C30 for the well-known quality of life questionnaire have been spelt out first and then included in the manuscript.
Research ethics and governance approvals for	***WHY: We will only publish ethically conducted research, approved by relevant bodies*** Have you given full details of ethics/governance/data protection approvals with reference numbers, full name of the committee(s) giving approval and the date of approval? If such approvals are not required	Approval for Regional Committee for Medical and Health Research Ethics with reference number is

research involving human subjects	have you made it explicit within the paper why they were not required. Are details of consent procedures clear in the paper?	included and details of consent procedures are clear in the paper.
Date(s) of data collection	***WHY: So readers understand the context within which data were collected*** Have you given the dates of data collection for your study within the body of your text? If your data are over 5 years old you will need to articulate clearly why they are still relevant and important to current practice.	Months of data collection for our study are included in text.
Structured discussion	***WHY: So readers can find key information quickly*** Papers should have a structured discussion, with sub headings, summarising the main findings, addressing strengths and limitations, articulating what this study adds with reference to existing international literature, and presenting the implications for practice.	Our discussion is clearly divided into sections discussing the issues mentioned.
Case reports	***WHY: So that participants are protected, and its importance made clear*** If your study is a case report have you followed our clear structure for a case report, including highlighting what research is needed to address the issue raised? Have you made clear what consent was required or given for the publication of the case report? Have you provided evidence of such consent as a supplementary file to the editor?	Not relevant
Acknowledgements and declarations	***WHY: So readers understand the context of the research*** Have you included a funding declaration according to the SAGE format? Are there acknowledgements to be made? Have you stated where data from the study are deposited and how they may be available to others? Have you conflicts of interest to declare?	Acknowledgements have been made, funding and information about COI have been included. According to Norwegian regulations we are not allowed to transfer data to make them available to others, and this has thus not been included in the manuscript. We have to ask for permission from the regional ethical committee about making our data available for other interested parties, and if permission is given data need to be accessed locally by visiting our institution.
Supplementary	***WHY: So the context is clear, but the main paper succinct for the reader***	No supplementary material

data and materials	Is there any content which could be provided as supplementary data which would appear only in the online version of accepted papers? This could include large tables, full search strategies for reviews, additional data etc.	provided with this paper
References	***WHY: So people can easily find work you have referenced*** Are your references provided in SAGE Vancouver style? You can download this style within Endnote and other referencing software.	Yes, we have use SAGE Vancouver in Endnote
Ownership of work.	Can you assert that you are submitting your original work, that you have the rights in the work, that you are submitting the work for first publication in the Journal and that it is not being considered for publication elsewhere and has not already been published elsewhere, and that you have obtained and can supply all necessary permissions for the reproduction of any copyright works not owned by you.	We are submitting our original research that has not been submitted elsewhere.