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Research Paper

Geriatric impairments are associated with reduced quality of life and physical function in older patients with cancer receiving radiotherapy - A prospective observational study.

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ABSTRACT

Introduction: Quality of life (QoL) and function are important outcomes for older adults with cancer. We aimed to assess differences in trends in patient-reported outcomes (PROs) during radiotherapy (RT) between (1) groups with curative or palliative treatment intent and (2) groups defined according to the number of geriatric impairments.

Materials and Methods: A prospective observational study including patients aged ≥65 years receiving curative or palliative RT was conducted. Geriatric assessment (GA) was performed before RT, and cut-offs for impairments within each domain were defined. Patients were grouped according to the number of geriatric impairments: 0, 1, 2, 3, and ≥ 4. Our primary outcomes, global QoL and physical function (PF), were assessed by The European Organisation for Research and Treatment of Cancer Quality-of-Life Core Questionnaire (EORTC) (QLQ-C30) at baseline, RT completion, and two, eight, and sixteen weeks later. Differences in trends in outcomes between the groups were assessed by linear mixed models.

Results: 301 patients were enrolled, mean age was 73.6 years, 53.8% received curative RT. Patients receiving palliative RT reported significantly worse global QoL and PF compared to the curative group. The prevalence of 0, 1, 2, 3 and ≥ 4 geriatric impairments was 16.6%, 22.7%, 16.9%, 16.3% and 27.5%, respectively. Global QoL and PF gradually decreased with an increasing number of impairments. These group differences remained stable from baseline throughout follow-up without any clinically significant changes for any of the outcomes.

Discussion: Increasing number of geriatric impairments had a profound negative impact on global QoL and PF, but no further decline was observed for any group or outcome, indicating that RT was mainly well tolerated. Thus, geriatric impairments per se should not be reasons for withholding RT. GA is key to identifying vulnerable patients in need of supportive measures, which may have the potential to improve treatment tolerance.

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Table 1
Geriatric assessment scales and cut-off points for geriatric impairments.

Domain	Assessment	Rated by	Variable name	Scores and range	Interpretation	Cut-off for impairment
Comorbidity	Charlson Comorbidity Index [29,30]	Patient/ Nurse	CCI	0–26 (continuous)	Higher score = more comorbidity	≥2
Medications	Registration of regular medications by ATC[a] system	Nurse	Medications	Number of daily medications		≥5
Nutritional status	Mini Nutritional Assessment Short Form [31]	Nurse	MNA-SF	0–14 (continuous)	Higher score = better nutritional status	≤11
Mobility	Timed Up and Go [32]	Nurse	TUG	Number of seconds (continuous)		≥14
Falls the last six months	Registration of number of falls	Patient	Falls	0–1 or ≥ 2 (dichotomized)		≥2
Basic activities of daily living (ADL)	Barthel Index [33]	Patient	Barthel	0–20 (continuous)	Higher score = better function	<19
Instrumental activities of daily living (IADL)	Nottingham Extended Activities of Daily Living [34]	Patient	NEADL	0–66 (continuous)	Higher score = better function	<44
Cognitive function	Montreal Cognitive Assessment test [35]	Nurse	MoCA	0–30 (continuous)	Higher score = better function	65–75 years ≤23 > 75 years ≤21
Depressive symptoms	Geriatric Depression Scale-15 [36]	Patient	GDS-15	0–15 (continuous)	Higher score = more depressive symptoms	≥5

[a] Anatomical Therapeutic Chemical Classification System.

1. Introduction

The prevalence of older adults with cancer is increasing, and advancing age inherently leads to a gradual decline in functional reserves and reduced life expectancy. This can influence older adult patients' preferences regarding cancer treatment [1–4]. Maintaining functional status and independence are important priorities for many older adults [3,5,6]. As a consequence, patient-centered outcomes such as quality of life (QoL) and function are crucial and should be addressed in clinical trials targeting older adults [7].

Radiotherapy (RT) is a mainstay in cancer treatment, and it is estimated that approximately 50–60% of patients with cancer are offered irradiation at some point [8,9]. Curative RT may involve several weeks of daily treatment, and a transient decline in health status might be acceptable in exchange for longevity [9]. By contrast, the aim of palliative RT is to alleviate symptoms and/or provide local tumour control through a short treatment course, thereby improving QoL at minimal inconvenience [10,11]. However, irrespective of treatment intent, RT can cause severe short- and long-term toxicities that could be localised depending on the radiated site, or generalised, such as fatigue. As shown in other oncologic treatment settings, vulnerable patients with several geriatric-related problems may be more prone to some of these negative consequences [12–15]. To fully consider the pros and cons, it is therefore essential to gain knowledge of how older adult patients undergoing RT perceive their QoL and function during the course of treatment.

Geriatric assessment (GA) is a means to address the diversity in older adult patients' health status and entails a comprehensive appraisal of typical age-related health issues such as comorbidities, and physical- and cognitive functioning [16]. Frailty is a broad term encompassing older adults' gradual loss of organ- and functional reserves leading to increased vulnerability to stressors and increased risk of negative outcomes [17]. For practical reasons, frailty is often defined as the presence of ≥1 or ≥ 2 impaired GA domains [17,18]. There is emerging evidence that both individual GA domains and frailty are related to a decline in patient-reported outcomes (PROs) including QoL, physical function, and a higher symptom burden [2,19–23]. Whether this applies to older patients undergoing RT is hitherto scarcely investigated [23–25]. Furthermore, in real life, frailty represents a continuum of a patient's reduced reserve capacity and can be understood as a syndrome of age-related accumulated deficits [26,27]. Whether the sum of these acquired deficits is reflected in a corresponding gradual decline in QoL and physical function remains uncertain.

We have previously shown that the GA domains nutritional- and functional status were independently predictive of mortality in a cohort of older patients with cancer receiving RT with curative or palliative treatment intent [28]. In the present paper, targeting the same population, we aimed to assess differences in trends in patient-reported QoL and function during the course of RT between (1) groups with different treatment intent and (2) groups defined according to the number of geriatric impairments identified by GA.

2. Material and Methods

2.1. Patients

From February 2017 to July 2018, we conducted a prospective, single-centre observational study at the Radiotherapy Unit, Innlandet Hospital Trust, Norway. The inclusion criteria were referral for RT with curative or palliative treatment intent, age ≥ 65 years, histologically confirmed malignant disease, inhabitant of Innlandet County, fluent in oral and written Norwegian, and capable of answering self-report questionnaires.

2.2. Assessments

Prior to irradiation, patients underwent GA mainly performed by a trained oncology nurse, not a multi-disciplinary team, henceforth referred to as *modified* GA (mGA). The following nine mGA domains were assessed using validated scales: comorbidities, medications, nutritional status, mobility, falls, basic activities of daily living (ADL), instrumental ADL (IADL), and cognitive and emotional function (Table 1). The treating radiation oncologists were blinded for mGA results. Cut-off points for geriatric impairment within each domain were retrospectively set based on well-established and/or commonly used reference values (Table1), as elaborated in a previous publication [28]. Patients with complete mGA were stratified into five groups according to the number of geriatric impairments present at baseline: 0, 1, 2, 3, or ≥ 4. This excluded three patients with missing Montreal Cognitive Assessment (MoCA) tests. Patients with missing Timed up and Go (TUG) due to the inability to perform the test ($n = 19$), were classified as having an impairment in this domain. Baseline sociodemographic and medical data were attained through patients' interviews supplemented by their electronic medical records. Data collected included Eastern Cooperative Oncology Group performances status (ECOG PS) (dichotomized to 0–1 or 2–4), cancer diagnosis (grouped as breast-, prostate-, lung- or other types of cancer), RT regimen, and treatment intent (curative or palliative).

Table 2
Patient characteristics and mGA scores according to number of geriatric impairments.

Variable	Total $n = 298$[a]	0 geriatric impairment $n = 49$ (16.6%)	1 geriatric impairment $n = 67$ (22.7%)	2 geriatric impairments $n = 50$ (16.9%)	3 geriatric impairments $n = 48$ (16.3%)	≥4 geriatric impairments $n = 81$ (27.5%)
Age, mean (SD)	73.6 (6.3)	71.1 (5.1)	72.2 (5.9)	74.1 (5.7)	73.4 (6.1)	76.2 (7.1)
Sex, female (%)	141 (47.3)	22 (44.9)	35 (52.2)	26 (52.0)	28 (58.3)	29 (35.8)
RT intent, n (%)						
Curative	161 (54.0)	41 (83.7)	49 (73.1)	28 (56.0)	20 (41.7)	23 (28.4)
Palliative	137 (46.0)	8 (16.3)	18 (26.9)	22 (44.0)	28 (58.3)	58 (71.6)
Cancer type, n (%)						
Breast	95 (31.9)	20 (40.9)	32 (47.8)	15 (30.0)	14 (29.2)	14 (17.3)
Prostate	72 (24.2)	18 (36.7)	17 (25.4)	10 (20.0)	9 (18.8)	18 (22.2)
Lung	65 (21.8)	5 (10.2)	8 (11.9)	14 (28.0)	11 (22.9)	25 (30.9)
Other	66 (22.1)	6 (12.2)	10 (14.9)	11 (22.0)	14 (29.2)	24 (29.6)
ECOG PS, n (%)						
0–1	254 (85.2)	49 (100.0)	67 (100.0)	50 (100.0)	47 (97.9)	40 (49.4)
2–4	44 (14.8)	0	0	0	1 (2.1)	41 (50.6)
Stage, n (%)						
I	62 (20.8)	17 (34.8)	21 (31.3)	10 (20.0)	6 (12.5)	8 (9.9)
II	41 (13.8)	8 (16.3)	10 (14.9)	7 (14.0)	7 (14.6)	9 (11.1)
III	78 (26.2)	18 (36.7)	20 (29.9)	12 (24.0)	12 (25.0)	15 (18.5)
IV	117 (39.2)	6 (12.2)	16 (23.9)	21 (42.0)	23 (47.9)	49 (60.5)
Distant metastasis, n (%)						
No	187 (62.8)	43 (87.8)	51 (76.1)	29 (58.0)	28 (58.3)	35 (43.2)
Yes	11 (37.2)	6 (12.2)	16 (23.9)	21 (42.0)	20 (41.7)	46 (56.8)
Total radiation dose (Gy)						
Median (min-max)	40.0 (4.0–78.0)	40.1 (4.0–78.0)	40.0 (20.0–78.0)	40.0 (20.0–78.0)	39.5 (8.0–78.0)	30.0 (8.0–78.0)
Dose per fraction (Gy)						
Median (min-max)	2.7 (1.0–8.0)	2.7 (2.0–4.0)	2.7 (1.5–4.0)	2.8 (1.5–6.0)	3.0(1.5–8.0)	3.5 (1.0–8.0)
No. of fractions						
Median (min-max)	14.8 (1–39)	19 (2–39)	14.8 (5–39)	4.8 (4–39)	13.9 (1–39)	10 (1–39)
mGA domains						
CCI						
Mean (SD)	1.1 (1.3)	0.2 (0.4)	0.4 (0.6)	0.9 (1.1)	1.4 (1.4)	2.0 (1.7)
No (%) with impairment	80 (27.1)	0	4 (6.0)	10 (20.0)	20 (41.7)	46 (56.8)
Medications						
Mean (SD)	5.5 (3.6)	2.0 (1.5)	3.6 (2.4)	5.0 (2.6)	6.2 (2.2)	8.9 (3.3)
No (%) with impairment	161 (54.6)	0	20 (29.9)	29 (58.0)	38 (79.2)	74 (91.4)
MNA-SF						
Mean (SD)	10.6 (2.3)	12.6 (0.9)	11.5 (1.7)	10.7 (2.1)	10.3 (2.4)	8.8 (2.1)
No (%) with impairment	161 (54.6)	0	27 (40.3)	29 (58.0)	31 (64.6)	74 (91.4)
TUG						
missing	19[b]	0	0	2	0	17
Mean (SD)	10.5 (5.6)	7.5 (1.4)	8.2 (1.8)	9.3 (3.2)	10.3 (2.1)	16.3 (8.7)
No (%) with impairment	60 (20.3)	0	0	3 (6.0)	4 (8.3)	53 (65.4)
Falls						
0 or 1, n (%)	264 (88.6)	49 (100)	66 (98.5)	48 (96)	36 (75.0)	62 (76.5)
≥2 = impairment, n (%)	34 (11.4)	0	1 (1.5)	2 (4)	12 (25.0)	19 (23.5)
NEADL						
Mean (SD)	53.2 (14.0)	61.6 (5.4)	61.5 (5.2)	59.4 (6.3)	56.2 (5.5	36.1 (13.6)
No (%) with impairment	61 (20.7)	0	0	0	1 (2.1)	60 (74.1)
Barthel Index						
Mean (SD)	19.0 (2.2)	19.9 (0.2)	19.9 (0.3)	19.7 (0.5)	19.4 (0.8)	17.2 (3.3)
No (%) with impairment	56 (19.0)	0	0	1 (2.0)	8 (16.7)	47 (58.0)
MoCA						
missing	3[a]	0	0	0	0	0
$n = 65$–75 years	196	40	49	33	31	43
$n > 75$ years	99	9	18	17	17	38
Mean (SD)	24.0 (3.7)	26.2 (2.0)	25.6 (2.8)	24.2 (3.2)	24.3 (2.8)	21.1 (4.1)
No (%) with impairment	103 (34.9)	0	13 (19.4)	17 (34.0)	18 (37.5)	55 (67.9)
GDS-15						
Mean (SD)	2.9 (2.6)	1.1 (1.1)	2.0 (1.7)	2.5 (2.3)	3.5 (2.7)	4.7 (2.8)
No (%) with impairment	61 (20.7)	0	2 (3.0)	9 (18.0)	12 (25.0)	38 (46.9)

Abbreviations: mGA, modified geriatric assessment; SD, standard deviation; RT, radiotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gy, Gray; CCI, Charlson Comorbidity Index; MNA-SF, Mini Nutritional Assessment Short Form; TUG, Timed Up and Go; NEADL, Nottingham Extended Activities of Daily Living; MoCA, Montreal Cognitive Assessment test; GDS-15, Geriatric Depression Scale-15.

[a] 3 patients with missing MoCA test were not grouped according to number of geriatric impairments.

[b] 19 patients with missing TUG were classified as having an impairment in the domain mobility.

Table 3
Results of the linear mixed model assessing the trend in primary and secondary outcomes stratified by treatment intent (palliative vs curative, n = 298).

	Unadjusted		Adjusted[a]	
	RC (SE)	p-value	RC (SE)	p-value
Global quality of life				
Intercept	73.69 (1.72)	<0.001	81.48 (12.10)	<0.001
Time	−1.31 (0.64)	**0.041**	−1.30 (0.64)	**0.042**
Time^2[b]	0.18 (0.09)	**0.039**	0.18 (0.09)	**0.040**
Time^3[c]	−0.006 (0.003)	0.052	−0.006 (0.003)	0.053
Treatment intent, palliative	−15.82 (2.53)	**<0.001**	−9.33 (2.91)	**0.001**
Time x Treatment intent	1.40 (0.98)	0.152	1.35 (0.98)	0.168
Time^2 x Treatment intent	−0.34 (0.14)	**0.016**	−0.34 (0.14)	**0.016**
Time^3 x Treatment intent	0.01 (0.005)	**0.007**	0.01 (0.005)	**0.007**
Physical function				
Intercept	80.89 (1.84)	<0.001	126.69 (12.83)	<0.001
Time	−0.30 (0.40)	0.450	−0.32 (0.40)	0.423
Time^2	0.01 (0.06)	0.809	0.01 (0.06)	0.803
Time^3	−0.00002 (0.002)	0.991	−0.00002 (0.002)	0.993
Treatment intent, palliative	−24.19 (2.57)	**<0.001**	−11.02 (2.70)	**<0.001**
Role function				
Intercept	78.28 (2.32)	<0.001	98.99 (16.61)	<0.001
Time	−0.04 (0.64)	0.947	−0.08 (0.64)	0.895
Time^2	−0.06 (0.09)	0.544	−0.05 (0.09)	0.547
Time^3	0.003 (0.003)	0.428	0.003 (0.003)	0.420
Treatment intent, palliative	−28.13 (3.14)	**<0.001**	−13.97 (3.49)	**<0.001**
Fatigue				
Intercept	30.33 (2.02)	<0.001	2.70 (14.77)	0.855
Time	3.22 (0.70)	**<0.001**	3.22 (0.70)	**<0.001**
Time^2	−0.43 (0.10)	**<0.001**	−0.43 (0.10)	**<0.001**
Time^3	0.01 (0.003)	**<0.001**	0.01 (0.003)	**<0.001**
Treatment intent, palliative	15.43 (2.98)	**<0.001**	10.65 (3.47)	**0.002**
Time x Treatment intent				
Time^2 x Treatment intent Time^3 x Treatment intent	−2.01 (1.07)	0.061	−1.98 (1.07)	0.065
	0.39 (0.15)	**0.011**	0.39 (0.15)	**0.011**
	−0.01 (0.005)	**0.009**	−0.01 (0.005)	**0.009**
Pain				
Intercept	22.24 (2.14)	<0.001	22.35 (16.84)	0.186
Time	−1.36 (0.63)	**0.032**	−1.34 (0.63)	**0.035**
Time^2	0.21 (0.09)	**0.022**	0.21 (0.09)	**0.022**
Time^3	−0.007 (0.003)	**0.023**	−0.007 (0.003)	**0.023**
Treatment intent, palliative	14.98 (2.85)	**<0.001**	12.50 (3.54)	**<0.001**
NEADL				
Intercept	59.06 (1.06)	<0.001	83.12 (6.90)	<0.001
Time	−0.25 (0.22)	0.252	−0.28 (0.22)	0.197
Time^2	0.01 (0.03)	0.682	0.02 (0.03)	0.613
Time^3	−0.0001 (0.001)	0.917	−0.0002 (0.001)	0.856
Treatment intent, palliative	−12.99 (1.50)	**<0.001**	−3.58 (1.45)	**0.014**

Abbreviations: RC, regression coefficient; SE, standard error; NEADL, Nottingham Extended Activities of Daily Living.
[a] Adjusted for age, sex, cancer type, and ECOG PS.
[b] Second-order time component.
[c] Third-order time component.

2.3. Outcome Assessments

The European Organisation for Research and Treatment of Cancer Quality-of-Life Core Questionnaire version 3.0 (EORTC) (QLQ-C30) [37] and the Nottingham Extended Index of Activities of Daily Living (NEADL) [34] were distributed to all patients at five different time points; at baseline (T0), at RT completion (T1) and two (T2), eight (T3) and sixteen (T4) weeks after completing RT. At T1, per protocol exceptions were made for QLQ-C30 for patients receiving a single RT fraction ($n = 12$), and for NEADL for patients receiving <10 fractions ($n = 59$). At T0 and T1, the questionnaires were handed out and collected by the study nurse at the Radiotherapy Unit. Subsequent forms were sent by mail accompanied by a prepaid return envelope. If no answer was received after a week, the patient received a reminder.

Entailing 30 items, QLQ-C30 includes a global QoL scale, five functioning scales (physical-, role-, emotional-, cognitive- and social function), and nine symptom scales/items (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). All items are scored from 1 (not at all) to 4 (very much), except for global QoL which is scored from 1 (very poor) to 7 (excellent). Before analyses, the raw scores were converted to scales ranging from 0 to 100. Higher scores on the global QoL- and functioning scales indicate better function, whereas higher scores on the symptom scales/items denote more symptoms. Missing items were imputed in accordance with the official manual [38]. A difference of ≥10 points on any scale was considered clinically significant [39]. NEADL assesses IADL function by the subscales mobility, kitchen-, domestic-, and leisure activities. Each of the 22 items is scored from 0 to 3, and item scores are summarized into a total score ranging from 0 to 66, where higher scores indicate better function. Based on the estimated minimal clinically important difference in NEADL score of 2.4–6.1 [40], we chose to use the most conservative value of 6 points as clinically significant. Missing single NEADL items were imputed for cases where at least half of the scale had been answered by generating an empirical distribution for each item based on non-missing values, and drawing a random number from it to replace the missing value. Pre-defined primary outcomes were global

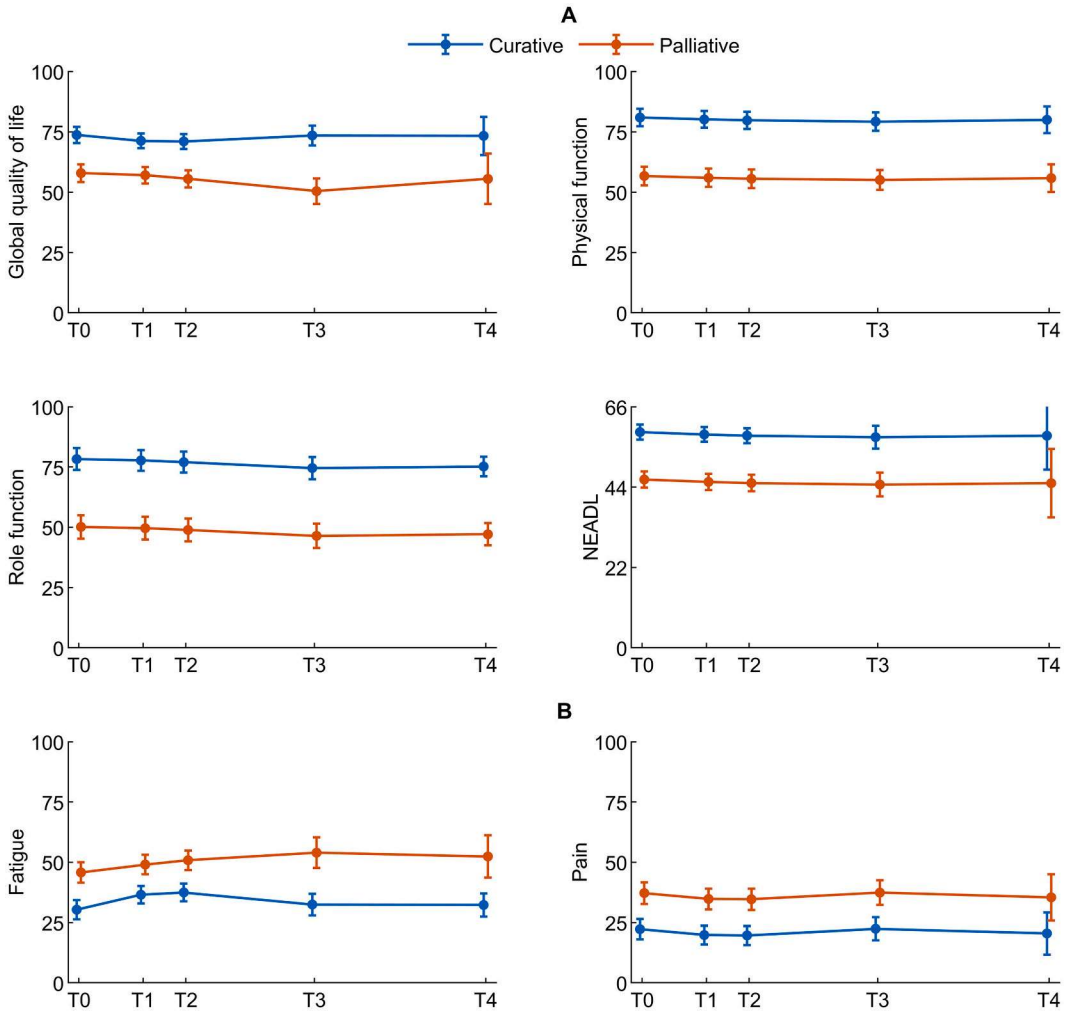

Fig. 1. Trends in primary and secondary outcomes for patients receiving curative and palliative radiotherapy (RT), unadjusted results of the linear mixed model. Abbreviations: NEADL, Nottingham extended activates of daily living. T0 = baseline, T1 = at RT completion, T2 = two, T3 = eight, T4 = sixteen weeks after completing RT.
Mean values with 95% CIs for primary and secondary outcomes assessed by QLQ-C30 (scale range 0–100), and NEADL (scale range 0–66). Fig. A: For quality of life and all functioning scales, higher scores indicate better function. Fig. B: For all symptom scales, higher scores indicate more symptoms.

QoL and physical function (PF) assessed by QLQ-C30. Secondary outcomes were IADL function assessed by NEADL, role function (RF), fatigue, and pain reported on QLQ-C30.

2.4. Statistical Analyses

Baseline patient characteristics and mGA scores were presented for the total cohort and stratified according to the number of geriatric impairments. Categorical data were described with frequencies and percentages, and continuous data with means and standard deviations (SDs), or median and min-max values. Baseline mean scores for QLQ-C30 and NEADL were tabulated for groups defined according to the number of impairments. To assess differences in trends in primary and secondary outcomes between patients receiving curative and palliative treatment, we estimated a linear mixed model with fixed effects for (non-linear) time, treatment group, and interaction between the time and treatment group. Random effects for patients were included to control for within-patient correlations due to repeated measurements. Further, the results were adjusted for age, sex, ECOG PS, and cancer diagnosis by estimating bivariate and multiple linear mixed models. To assess differences in trends in outcomes between groups defined according to the number of impairments, we estimated the same model as above with fixed effect for treatment group substituted with the number of impairments. In addition to the aforementioned adjustment variables, treatment intent (curative/palliative) was included in the latter model. Significant interaction terms in the models would imply a significant difference in trend in outcomes between the groups being compared. Non-significant interactions were excluded from the models. For explorative purposes, similar models were estimated for the remaining QLQ-C30 symptom scales (except for financial difficulties). Results from unadjusted linear mixed models were presented graphically as estimated mean values with corresponding 95% confidence intervals (CIs) at each assessment point. Finally, as an explorative approach, growth mixture models were estimated to identify possible unobserved groups of patients following distinct trajectories in global QoL and PF. This approach assesses individual trajectories and attempts to group patients with similar profiles together. To determine the optimal number of groups, Bayes Information Criterion, where the smaller value means a better model, was applied. In addition, it was required that average within-group probabilities were larger than 0.8, 95% CIs for trajectories non-overlapping, and groups had reasonable size. The identified groups were compared according to baseline characteristics. All tests were two-sided and results with *p*-values below 0.05 were considered statistically significant. The analyses were performed in SAS v9.4 and STATA v16.

Table 4
Baseline EORTC QLQ-C30 and NEADL mean scores stratified by number of geriatric impairments.

	Total n	0 geriatric impairment n (%)	1 geriatric impairment n (%)	2 geriatric impairments n (%)	3 geriatric impairments n (%)	≥4 geriatric impairments n (%)
	298[a]	49 (16.6)	67 (22.7)	50 (16.9)	48 (16.3)	81 (27.5)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD
Global quality of life	66.9 (23.0)	81.6 (19.0)	74.9 (16.3)	68.8 (21.0)	60.6 (20.5)	51.5 (22.4)
Functional scales						
Physical function	69.8 (26.2)	90.7 (14.7)	84.2 (18.0)	75.1 (18.6)	70.2 (20.3)	43.4 (21.6)
Role function	65.0 (34.0)	90.1 (22.8)	80.6 (23.1)	71.7 (24.1)	65.6 (26.0)	34.8 (33.4)
Emotional function	82.0 (18.4)	86.8 (15.1)	84.3 (14.8)	86.3 (16.3)	78.5 (21.9)	76.6 (20.4)
Cognitive function	83.6 (17.7)	89.6 (13.1)	90.5 (14.3)	86.3 (13.3)	83.0 (15.6)	73.5 (20.9)
Social function	75.6 (24.8)	86.1 (20.7)	82.1 (19.0)	75.7 (20.5)	72.9 (20.8)	66.5 (31.2)
Symptom scales/items						
Fatigue	37.5 (25.4)	18.5 (18.2)	29.0 (22.4)	36.9 (18.9)	43.1 (23.9)	52.6 (25.0)
Nausea/vomiting	6.7 (13.3)	1.7 (5.1)	2.2 (6.4)	6.7 (13.5)	12.5 (16.3)	10.1 (16.6)
Pain	29.4 (32.0)	11.2 (18.1)	15.4 (22.7)	30.0 (28.6)	33.0 (31.0)	48.1 (36.4)
Dyspnoea	29.2 (32.6)	12.5 (24.4)	21.9 (26.9)	28.0 (28.1)	31.3 (32.5)	42.0 (36.0)
Insomnia	27.3 (28.0)	19.7 (21.4)	21.2 (25.2)	27.3 (24.9)	34.0 (30.4)	32.5 (32.0)
Appetite loss	17.9 (29.0)	1.4 (9.5)	11.4 (22.1)	12.0 (25.0)	28.5 (34.4)	30.9 (33.2)
Constipation	22.6 (29.5)	7.6 (15.7)	13.4 (23.3)	24.0 (28.6)	25.0 (30.4)	37.5 (33.7)
Diarrhoea	15.5 (24.8)	11.8 (23.3)	15.9 (20.4)	12.0 (23.1)	20.1 (29.0)	16.3 (27.0)
Financial difficulties	4.1 (13.4)	0.7 (4.8)	4.5 (11.5)	1.3 (6.6)	8.3 (17.5)	4.9 (17.6)
NEADL	53.2 (14.0)	61.3 (5.4)	61.5 (5.2)	59.4 (6.3)	56.2 (5.5)	36.1 (13.6)

Abbreviations: The European Organisation for Research and Treatment of Cancer Quality-of-Life Core Questionnaire; NEADL, Nottingham Extended Activities of Daily Living; SD, standard deviation.

[a] Among the 298 patients with complete QLQ-30 and NEADL, 3 patients had incomplete mGA (missing MoCA) and therefore 295 patients were grouped according to number of geriatric impairments.

2.5. Ethics

All enrolled patients provided written informed consent. Guidelines with advice for actions in case mGA revealed previously unrecognized severe health problems were prepared before recruitment started. The study protocol was approved by the Regional Committee for Medical Research Ethics South East Norway and was registered at clinicaltrials.gov (NCT03071640).

3. Results

3.1. Patients

During the recruitment period, 301 (59.1% of eligible) patients were enrolled, 298 patients completed the baseline self-report questionnaires, and were included in the present study. Reasons for non-inclusion were refusal to participate (148 [29.1%]), considered too sick (28 [5.5%]), and practical constraints (e.g., absent study nurse) (32 [6.3%]). Further details were not collected due to ethical regulations. The mean age among participants was 73.6 years (SD 6.3), 141 (47.3%) were female, 161 (54.0%) received RT with curative intent, and 254 (85.2%) had ECOG PS 0–1 (Table 2). Breast (31.9%), prostate (24.2%), and lung cancer (21.8%) were the most common diagnoses, and 22.1% had other types of cancer.

3.2. Survival and PROs Completion Rate

During a median observation period of 24.2 months, 123 (41.3%) patients died. No patients died during RT, but 13, 26, and 41 patients died within two, eight, and sixteen weeks after completion of RT, respectively. Of the 41 patients who were dead by sixteen weeks, 39 (95.1%) received RT with palliative intent, 22 (53.7%) had lung cancer, and 24 (58.5%) had ≥4 impairments. During follow-up, seven patients declined to answer further questionnaires, but did not withdraw consent for analyses of the data already provided. Accounting for deaths and per protocol exceptions [41], the completion rate of QLQ-C30 at T0, T1, T2, T3 and T4 was 100% (298/298), 96.5% (276/286), 91.2% (260/285), 93.0% (253/272) and 89.1% (229/257), respectively. For NEADL the corresponding completion rates were 100% (298/298), 83.6% (200/239), 90.5% (258/285), 93.0% (253/272), 89.9% (231/257).

3.3. Geriatric Impairments Identified by mGA

The overall most prevalent geriatric impairments were polypharmacy ($n = 161$ [54.6%]), compromised nutritional status (n = 161 [54.6%]), and cognitive impairment ($n = 103$ [34.9%]) (Table 2). Impairments in TUG ($n = 60$ [20.3%]), GDS-15 ($n = 61$ [20.7%]), NEADL (n = 61 [20.7%]), and Barthel Index ($n = 56$ [19.0%]) were also common. Among patients grouped according to the number of impairments ($n = 295$), 16.6%, 22.7%, 16.9%, 16.3% and 27.5% had 0, 1, 2, 3 and ≥ 4 impairments, respectively (Table 2). The proportion of patients receiving palliative treatment, and having lung or "other types of" cancer, stage IV disease, distant metastasis, and ECOG PS 2–4 successively increased with the increasing number of impairments (Table 2).

3.4. Quality of Life, Physical Function, and Symptoms in Relation to Treatment Intent

Compared to patients treated for palliative purposes, those who received curative RT reported statistically and clinically significantly better overall mean scores for global QoL, PF, NEADL, RF, fatigue, and pain (all $p < 0.001$) (Table 3, Fig. 1). This was also the case for the symptoms of dyspnoea, appetite loss, constipation, and nausea/vomiting, but not for diarrhoea and insomnia (data not shown). There was a significant non-linear trend in global QoL, fatigue, and pain, which for global QoL and fatigue were significantly different between patients receiving curative and palliative treatment (significant interactions) (Table 3). Adjustments did not alter these results. Significant non-linear trends were also found for dyspnoea and insomnia, and for insomnia the trend was significantly different between the two groups (data not shown). None of the observed trends represented a clinically significant change (>10 points).

3.5. Quality of Life, Physical Function, and Symptoms in Relation to the Number of Geriatric Impairments

Baseline scores showed a gradual decrease in global QoL, all QLQ-C30 function scales, and NEADL, and a similar increase in symptoms

Table 5
Results of the linear mixed model assessing the trend in primary and secondary outcomes stratified by the number of geriatric impairments (n = 295).

	Unadjusted		Adjusted[a]	
	RC (SE)	p-verdi	RC (SE)	p-verdi
Global quality of life				
Intercept	83.49 (2.41)	<0.001	76.69 (11.16)	<0.001
Time	−0.80 (0.49)	0.103	−0.83 (0.49)	0.090
Time^2[b]	0.06 (0.07)	0.414	0.06 (0.07)	0.399
Time^3[c]	−0.001 (0.002)	0.699	−0.001 (0.002)	0.684
No.of impairments (0 – ref.)				
1	−8.90 (3.02)	**0.003**	−7.83 (2.90)	**0.007**
2	−13.89 (3.23)	**<0.001**	−10.63 (3.18)	**0.001**
3	−23.58 (3.28)	**<0.001**	−19.15 (3.29)	**<0.001**
≥4	−31.54 (2.95)	**<0.001**	−24.91 (3.46)	**<0.001**
Physical function				
Intercept	91.19 (2.63)	<0.001	117.38 (11.53)	<0.001
Time	−0.32 (0.40)	0.424	−0.34 (0.40)	0.394
Time^2	0.01 (0.06)	0.795	0.02 (0.06)	0.777
Time^3	−0.00003 (0.002)	0.989	−0.00006 (0.002)	0.976
No.of impairments (0 – ref.)				
1	−6.71 (3.37)	**0.047**	−4.87 (3.02)	0.108
2	−17.25 (3.61)	**<0.001**	−11.46 (3.31)	**0.001**
3	−23.63 (3.66)	**<0.001**	−16.57 (3.42)	**<0.001**
≥4	−46.35 (3.27)	**<0.001**	−30.66 (3.59)	**<0.001**
Role function				
Intercept	90.18 (3.41)	<0.001	89.16 (15.36)	<0.001
Time	−0.18 (0.64)	0.778	−0.23 (0.64)	0.721
Time^2	−0.04 (0.09)	0.658	−0.04 (0.09)	0.681
Time^3	0.002 (0.003)	0.515	0.002 (0.003)	0.527
No.of impairments (0 – ref.)				
1	−10.91 (4.30)	**0.011**	−9.24 (4.01)	**0.021**
2	−17.56 (4.60)	**<0.001**	−12.45 (4.39)	**0.005**
3	−24.82 (4.68)	**<0.001**	−18.76 (4.54)	**<0.001**
≥4	−53.76 (4.19)	**<0.001**	−37.67 (4.77)	**<0.001**
Fatigue				
Intercept	19.59 (2.98)	**<0.001**	9.18 (14.13)	0.516
Time	2.43 (0.53)	**<0.001**	2.44 (0.53)	**<0.001**
Time^2	−0.27 (0.08)	**<0.001**	−0.28 (0.08)	**<0.001**
Time^3	0.008 (0.003)	**0.002**	0.008 (0.003)	**0.002**
No.of impairments (0 –ref.)				
1	10.34 (3.77)	**0.006**	8.53 (3.70)	**0.021**
2	15.29 (4.03)	**<0.001**	11.38 (4.05)	**0.005**
3	22.64 (4.10)	**<0.001**	17.59 (4.18)	**<0.001**
≥4	33.18 (3.67)	**<0.001**	26.59 (4.39)	**<0.001**
Pain				
Intercept	11.75 (3.26)	<0.001	33.01 (15.80)	0.038
Time	−1.27 (0.64)	**0.046**	−1.25 (0.64)	0.050
Time^2	0.20 (0.09)	**0.027**	0.20 (0.09)	**0.029**
Time^3	−0.007 (0.003)	**0.026**	−0.007 (0.003)	**0.028**
No.of impairments (0 –ref.)				
1	5.52 (4.10)	0.179	4.76 (4.13)	0.249
2	15.14 (4.39)	**0.001**	14.93 (4.52)	**0.001**
3	24.58 (4.46)	**<0.001**	23.58 (4.67)	**<0.001**
≥4	33.63 (4.00)	**<0.001**	31.10 (4.91)	**<0.001**
NEADL				
Intercept	62.73 (1.38)	<0.001	75.22 (5.95)	<0.001
Time	−0.25 (0.22)	0.253	−0.30 (0.22)	0.173
Time^2	0.01 (0.03)	0.715	0.02 (0.03)	0.580
Time^3	−0.00005 (0.001)	0.962	−0.0003 (0.001)	0.825
No.of impairments (0 – ref.)				
1	−0.67 (1.77)	0.706	0.03 (1.55)	0.985
2	−5.16 (1.89)	**0.007**	−2.53 (1.70)	0.137
3	−7.40 (1.92)	**<0.001**	−4.33 (1.75)	**0.014**
≥4	−26.31 (1.72)	**<0.001**	−16.92 (1.84)	**<0.001**

Abbreviations: RC, regression coefficient; SE, standard error; No. of impairments, number of geriatric impairments; NEADL, Nottingham Extended Activities of Daily Living.

[a] Adjusted for age, sex, cancer type, ECOG PS, and treatment intent (palliative vs curative).

[b] Second-order time component.

[c] Third-order time component.

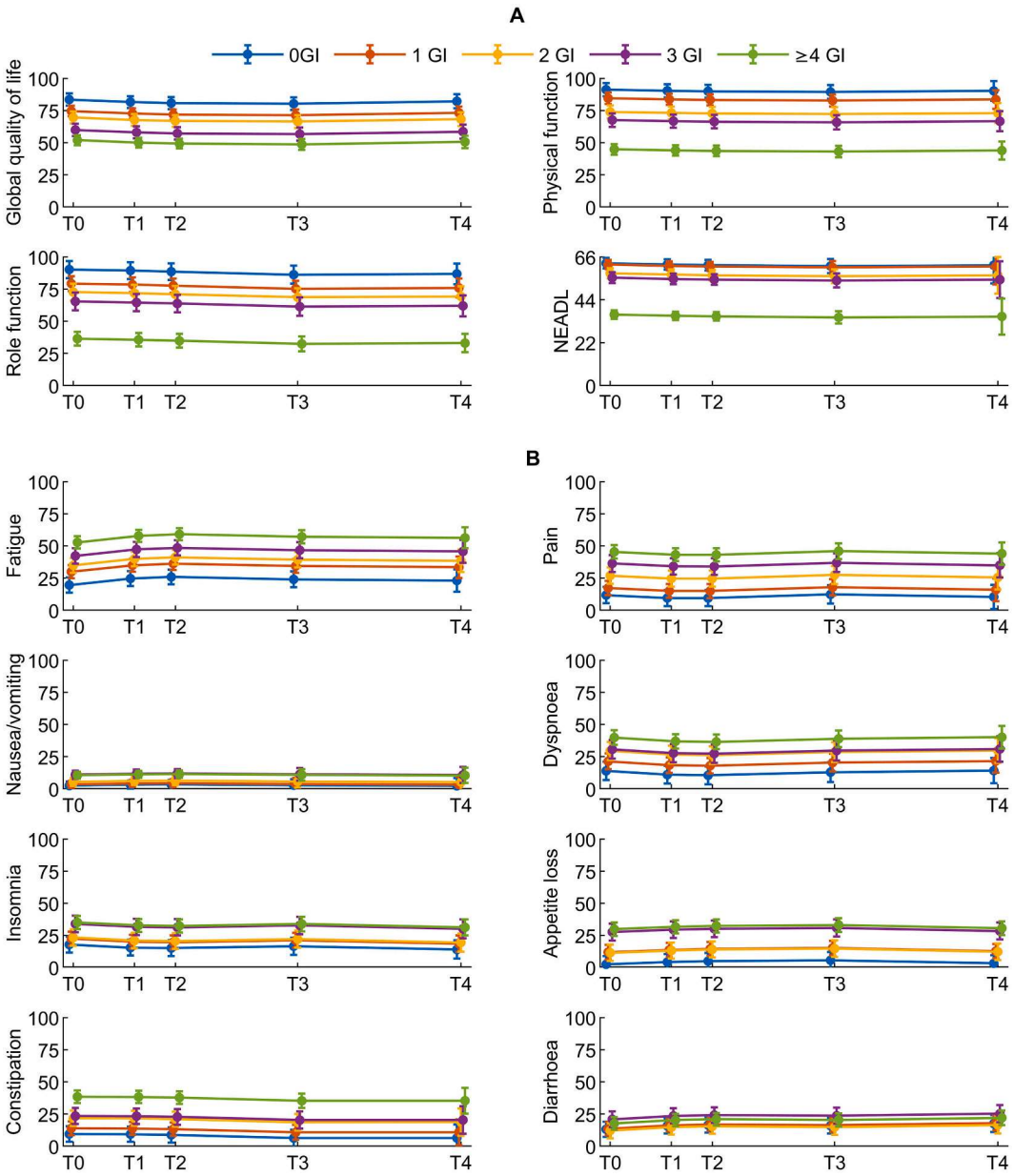

Fig. 2. Trends in primary and secondary outcomes, and symptoms depending on the number of geriatric impairments, unadjusted results of the linear mixed model. Abbreviations: GI, geriatric impairments; NEADL, Nottingham extended activates of daily living. T0 = baseline, T1 = at RT completion, T2 = two, T3 = eight, T4 = sixteen weeks after completing RT.
Mean values with 95% CIs for primary and secondary outcomes assessed by QLQ-C30 (scale range 0–100), and NEADL (scale range 0–66). Fig. A: For quality of life and all functioning scales, higher scores indicate better function. Fig. B: For all symptom scales, higher scores indicate more symptoms.

with the increasing number of geriatric impairments (Table 4). These baseline differences between groups defined according to the number of impairments persisted during follow-up. There were no significant changes in these outcomes over time, except for fatigue and pain, where a statistically significant non-linear trend below clinical significance (<10 points) was present. According to unadjusted linear mixed models, there were also no significant differences in trend between the groups (no significant interaction terms) (Table 5, Fig. 2). For all primary and secondary outcomes, there were overall statistically and clinically significant differences between the group with no impairment and the groups with two or more impairments (0 vs 2, 3, and ≥ 4) (for NEADL only 0 vs 3, and ≥ 4 impairments), between the group with one impairment and the groups with three or more (1 vs 3, and ≥ 4), and between the groups with two impairments and four or more (2 vs ≥4) (Fig. 2). The results were only slightly altered when adjusting for age, sex, ECOG PS, cancer diagnosis, and treatment intent (Table 5). Explorative analyses assessing the remaining QLQ-C30 symptom scores showed no trend that was both statistically and clinically significant, and no differences in trend between groups (Fig. 2). The overall differences between groups with no impairment and two or more impairments were clinically and statistically significant for dyspnoea and constipation. For insomnia and nausea/vomiting and appetite loss, the differences were similarly significant between groups with no impairment and three or more impairments (Fig. 2).

3.6. *Results of Growth Mixture Model*

The growth mixture model analysis identified four groups of patients with distinct trajectories for both global QoL and PF, named poor, fair, good, and excellent with non-overlapping 95% CIs and clinically

significant differences in mean baseline scores (supplementary table S-A, supplementary fig. S-A). The trajectories were relatively stable for both outcomes in all groups with no clinically significant changes observed during follow-up. Considering both global QoL and PF, the proportion of patients having ECOG PS 2–4 and receiving RT with palliative intent was highest in the poor group, and decreased in the fair and good groups, with the lowest proportion in the excellent group (Supplementary table S—B). Furthermore, the number of impairments decreased from the highest in the poor group to the lowest in the excellent group.

4. Discussion

To the best of our knowledge, this is the first study on older adults with cancer receiving RT where longitudinally retrieved PROs were assessed in relation to treatment intent and the number of geriatric impairments as identified by pre-treatment mGA. We found that patients receiving palliative RT had worse scores on all outcomes compared to those who received potentially curative treatment and that global QoL and PF gradually decreased while symptom burden increased with an increasing number of impairments. These differences persisted from start to sixteen weeks after RT, but no clinically significant change was observed for any groups or outcomes.

The pronounced differences in global QoL, function, and symptoms between patients receiving treatment with palliative and curative intent complies with common knowledge, confirmed in studies from other cancer settings [42]. Previous studies on older adults with cancer have reported frailty or impairments in geriatric domains to have significant negative impact on PROs [2,19,20,43]. Similar studies from RT settings are scarce, but an association between IADL dysfunction and poorer QoL scores was demonstrated in a smaller study ($n = 46$) on older adults with head and neck cancer [13]. Our study substantially expands this knowledge by demonstrating that not only did geriatric impairments negatively affect important aspects of older adults' lives but that an increasing number of impairments was followed by a consistent deterioration in all PROs, independent of treatment intent. These findings were further supported by the results of our exploratory growth mixture model analyses, which were performed to investigate if there were unobserved groups of patients with particularly poor trajectories requiring specific attention and supportive measures. Overall, our findings underline that frailty should be regarded as a continuum of increased vulnerability that has a profound impact on patients' perceptions of QoL and function.

We found that mean scores for all study-specific outcomes were remarkably stable during follow-up. This applied to groups defined according to treatment intent and the number of geriatric impairments, as well as groups with distinct global QoL and PF trajectories. The paucity of age-specific studies addressing PROs in the RT setting hampers comparisons to existing knowledge. One study including 903 patients aged 18–92 years found that participants reported a similar symptom burden before and after RT, regardless of age [14]. However, patients aged $\geq$65 years were more likely to report that symptoms interfered with walking after RT [14], but RT treatment intent or frailty status were not accounted for. We expected that an increasing number of impairments would be associated with a functional decline during follow-up. This was not confirmed, and supported by studies on older patients with prostate cancer reporting that no GA domains were predictive of RT tolerance [44,45]. Our findings for the group receiving curative treatment are largely in line with recent studies in older patients treated for localised breast or prostate cancer [44–46]. We anticipated an improvement in PROs in the palliative group, which did not occur. However, we did not distinguish between specific RT indications, e.g., irradiation for respiratory symptoms or painful bone metastases, and the study was not designed to capture changes in PROs related to this. Thus, the lack of improvement may be due to disease progression, and scores could potentially be worse had it not been for the RT provided.

Overall, our findings indicate that tolerance for the RT regimens was good regardless of treatment intent and number of impairments, i.e., RT did not significantly influence patients' perceived global QoL and functioning. This suggests that existing impairments should not be seen as contraindications for RT per se. However, it is important to note that patients with accumulated impairments reported persistently very poor QoL, functioning, and high symptom burden, and we have previously shown that they also had higher mortality risk [28]. Aimed at preserving function and well-being, these findings emphasize the need for continuous broad evaluations of patients' needs and to apply appropriate interventions before, during, and after RT [47]. Such targeted interventions may also mitigate modifiable geriatric impairments and have the potential to improve overall survival [28]. Preferably, this evaluation should be performed by GA [48,49] supplied by systematic symptom assessment. GA with management (GAM) based on individual needs has been shown to improve outcomes in other oncologic settings [15,50,51], and systematic symptom assessment followed by targeted interventions can ameliorate symptoms and improve QoL [52]. Moreover, as we have demonstrated in this study, patients receiving RT with curative and palliative intent are distinct entities and may have different needs. It may therefore be a favourable approach for future studies to test the effect of GAM for patients referred to curative and palliative RT, or combined modality therapy, separately. Finally, our findings underline the need for careful individual considerations of treatment burden versus benefits. Patients with accumulated impairments, in particular those who have advanced cancer, may profit from modified RT regimens alongside targeted supportive care [53]. In some cases, even omitting RT and providing other palliative measures might be the best option [54,55].

Strengths of this study are the prospective design, relatively large sample size, and the use of reliable and validated scales to assess mGA domains. Moreover, a designated oncology nurse and a resident physician, both specially trained, performed all the mGAs. The PRO completion rate was fairly good during follow-up. Furthermore, the QLQ-C30, including the translated Norwegian version, is validated and its responsiveness well documented in patients with cancer [56]. Assessing an unselected cohort of older adults with cancer, many of whom had advanced cancer and limited life expectancy, our study contributes valuable knowledge about a large group of patients that are often excluded from clinical trials. However, this heterogeneity may also represent a limitation. Previous cancer treatment and other factors not accounted for could have influenced patients' perceptions of the outcomes assessed. Among potentially eligible patients, 40.1% were not included, mainly because the patient declined participation or was considered too sick. Hence, it is possible that the study cohort represent the fittest of older adults referred to RT which may have affected our results. Representing mean values, our results reflect RT tolerance on a group level and should therefore be interpreted with caution. Finally, patients treated for palliative purposes, who also frequently had several accumulated impairments, were more likely to die during follow-up [28], and this may have introduced attrition bias.

In conclusion, our results show that older adults tolerate RT well, and the accumulation of geriatric impairments (i.e., frailty) should not be decisive when considering RT. However, uncovering age-related health issues by GA is key to identifying vulnerable patients so that RT adaptions and/or targeted supportive measures that may improve PROs could be provided. Studies implementing GAM and specifically assessing PROs in the RT setting are warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2022.09.008.

Declaraltion of Competing Interest

The authors have no conflict of interests to declare.

Ethics Approval and Consent to Participate

This study was approved by the Regional Committee for Medical Research Ethics South East Norway and was registered at clinicaltrials.gov (NCT03071640). All patients included provided written informed consent.

Consent for Publication

All authors have approved the final version. Participating patients provided consent to data being used in publications. Confidentiality is guaranteed.

Availability of Data and Materials

According to Norwegian regulations, research data is confidential due to patients' privacy protection. On individual, specific request, anonymised data could be made available.

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