Age-related considerations when providing radiotherapy to older patients with cancer

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Hamar, November 2022.

Summary in Norwegian

Bakgrunn

Verdens befolkning eldes, og alder er en viktig risikofaktor for kreft. Median alder ved diagnosetidspunkt i Norge er omlag 70 år, og antallet eldre med kreft øker raskt. Det er store variasjoner i eldre menneskers generelle helsetilstand, og kronologisk alder er derfor ikke et godt mål på biologisk alder. Mange eldre lever med «skrøpelighet», en tilstand som kjennetegnes av nedsatte fysiologiske og funksjonelle organ reserver som medfører økt sårbarhet for «stressorer». Geriatrisk vurdering (GV) er en systematisk kartlegging av områder hvor eldre ofte har problemer som komorbiditet, polyfarmasi, ernæringsstatus, fysisk funksjon, funksjonsnivå og psykososial funksjon. GV kan brukes til å identifisere pasienters sårbarhet og funksjonelle reserver, og er sterkt anbefalt hos eldre med kreft. Dessverre gjøres ikke dette rutinemessig. Eldre pasienter prioriterer ofte livskvalitet, fysisk funksjon og selvstendighet i dagliglivet høyere enn kortvarig økt levetid, selv om ca. 50% av alle med kreft vil trenge strålebehandling i sykdomsforløpet, har vi lite kunnskap om hvordan strålebehandling påvirker disse utfallene hos eldre kreftpasienter.

Mål

Vi undersøkte forekomsten av aldersrelaterte helseproblemer, og utviklingen i kognitiv funksjon, blant eldre kreftpasienter henvist til kurativ eller palliativ strålebehandling, og undersøkte hvordan aldersrelaterte helseproblemer påvirket overlevelse, livskvalitet og fysisk funksjon i forløpet.

Metode

Vi gjennomførte en prospektiv observasjons-studie og inkluderte pasienter ≥65 år med kreft henvist til kurativ eller palliativt strålebehandling. Før stråling gjorde vi GV, inkludert komorbiditet, medikamenter, ernæringsstatus, personlige -og instrumentelle daglige aktiviteter (IADL), mobilitet, fall, kognitiv funksjon og depressive symptomer ved bruk av anbefalte instrumenter utviklet til dette formålet. GV ble gjentatt ved avslutning av strålebehandlingen, og 2, 8, og 16 uker senere. Samtidig besvarte pasientene European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ-C30) om livskvalitet og fysisk funksjon. «Geriatriske problemer» basert på GV ble definert på bakgrunn av andres forskningsresultaters og anbefalinger. Overlevelse ble presentert med Kaplan Meier kurver for grupper definert ut fra antall geriatriske problemer.

Assosiasjon mellom geriatriske problemer identifisert med GV og overlevelse ble estimert med Cox proportional hazard regresjons analyse. Hvordan geriatriske problemer påvirket livskvalitet og fysisk funksjon ble undersøkt med linear mixed models. Kognitiv funksjon ble vurdert med Montreal Cognitive Assessment (MoCA). Forekomsten av kognitiv svikt ble estimert med å sammenligne med alder, kjønn og utdannings-matchede norske normdata. Utviklingen i kognitiv funksjon ble estimert med growth mixture models.

Resultater

301 pasienter be inkludert, 142 (47.2%) var kvinner, gjennomsnittsalder var 73.6 (SD 6.3) år, og 162 (53.8%) fikk kurativ stråling. De vanligste kreftdiagnosene var bryst (95 [31.6%]), prostata (73 [24.3%]), og lunge (65 [21.6%]), mens 68 (22.6%) hadde andre typer kreft. Forekomsten av henholdsvis 0,1,2,3, og ≥4 geriatriske problemer var 16.3%, 22.3%, 16.6%, 15.9%, and 26.9% (2.0% missing). Desto flere geriatriske problemer, desto kortere overlevelse hadde pasientene. Dårlig ernæringsstatus og avhengighet i IADL predikerte redusert overlevelse. Med økende antall geriatriske problemer rapporterte pasientene gradvis dårligere livskvalitet og fysisk funksjon, men nivåene holdt seg stabile under oppfølgingen. Sammenlignet med norske normdata hadde 37.9% av pasientene tegn på kognitiv svikt. Vi identifiserte fire grupper med ulike MoCA score forløp. Majoriteten hadde stabile verdier, bortsett fra en liten gruppe med veldig dårlige skår.

Konklusjon

En geriatrisk vurdering kan gi viktig prognostisk informasjon om eldre pasienter med kreft. Økende antall geriatriske problemer var assosiert med gradvis dårligere overlevelse, livskvalitet og fysisk funksjon. Våre funn indikerer at «skrøpelighet» er karakterisert av gradvis økende sårbarhet. Dette er viktig fordi det kan forbygges/bremses ved å iverksette målrettede tiltak for å bedre geriatriske problemer, og potensielt bedre utfallet av behandlingen. Majoriteten rapporterte stabil livskvalitet og fysisk funksjon under oppfølgingen, hvilket indikerer at toleransen for strålingen per se var god. Imidlertid hadde pasienter med flere geriatriske problemer og kort forventet levetid vedvarende dårlig livskvalitet og fysisk funksjon. Dette er pasienter som krever tett oppfølging og har et spesielt behov for støttebehandling.

Summary in English

Background

The global population is ageing, and age is an important risk factor for cancer. The median age at diagnosis in Norway is about 70 years, and the number of older patients with cancer is rapidly increasing. The older population exhibit a large variety in general health status, and chronologic age is a poor marker for biologic age. Many older adults live with frailty, a condition characterised by depleted physiological and functional organ reserves leading to increased vulnerability to stressors. Geriatric assessment (GA) is a systematic evaluation of domains where older adults commonly have problems such as comorbidity, polypharmacy, nutritional status, physical function, functional status, and psychosocial function. Performing GA to identify patients' vulnerabilities and reserves is strongly advocated, although seldom applied in oncology practice. Approximately 50% of patients with cancer will need radiotherapy (RT) at some point during the disease trajectory. Older patients may prioritise preserved quality of life (QoL), physical function, and independency over limited survival benefits. However, little is known about how RT influences these outcomes in older patients with cancer.

Aim

We aimed to investigate the prevalence of age-related health problems and the development in cognitive function, in a cohort of older patients with cancer receiving RT with curative or palliative treatment intent and to assess the impact of age-related health problems on overall survival (OS), global QoL and physical function.

Methods

A single centre prospective observational study was conducted including patients ≥65 years referred for curative or palliative RT. Prior to RT, we performed a modified GA (mGA) including comorbidities, medications, nutritional status, basic and instrumental activities of daily living (IADL), mobility, falls, cognition and depressive symptoms using recommended and validated tools. The mGA was repeated at RT completion, and two, eight and sixteen weeks later. At the same time points, patients reported global QoL and physical function (PF) by the European Organisation for Research and Treatment of Cancer Quality of Life Core questionnaire (QLQ-C30). Impairments in each mGA domain were defined based on recommended cut-points. OS was presented by Kaplan Meier plots for groups defined according to number of geriatric impairments and compared using the log-rank test. The

association between individual mGA domains and OS was assessed by Cox proportional hazard regression analysis. We investigated differences in trends in global QoL and PF between groups defined according to the number of geriatric impairments by estimating linear mixed models, and explored groups following distinct trajectories. Cognitive function was evaluated by the Montreal Cognitive Assessment (MoCA). The prevalence of cognitive impairment was estimated by comparison to Norwegian age-, gender- and education-matched normative data. The development in cognitive function was assessed by estimating growth mixture models.

Results

Among 301 patients included, 142 (47.2%) were women, mean age was 73.6 (SD 6.3) years and 162 (53.8%) received RT with curative intent. The most frequent diagnoses were breast (95 [31.6%]), prostate (73 [24.3%]) and lung cancer (65 [21.6%]), while 68 (22.6%) had other types of cancer. The prevalence of 0,1,2,3 and ≥4 geriatric impairments was 16.3%, 22.3%, 16.6%, 15.9% and 26.9%, respectively (2.0% missing). OS gradually decreased with increasing number of geriatric impairments. Poor nutritional status and IADL function were independent predictors of reduced OS. A gradual decline in global QoL and PF for groups with increasing number of impairments was registered, but the levels remained stable during follow-up. There were four groups with distinct global QoL and PF trajectories, and patients with several impairments and unfavourable prognostic traits reported worse scores. Compared to Norwegian normative data, 37.9% had MoCA scores indicating cognitive impairment. We identified four groups following distinct MoCA trajectories. The majority had stable or slightly improved scores, expect for a small group with very poor scores.

Conclusion

We found that mGA holds important prognostic information in older patients undergoing RT. An increasing number of impairments was associated with a gradual decline in OS, global QoL and PF, showing that frailty represents a continuum of increased vulnerability. Interventions aiming to ameliorate impairments may prevent further decline and possibly improve outcomes. The majority had stable global QoL, PF and MoCA trajectories, indicating good RT tolerance. However, patients with several impairments and unfavourable prognostic traits reported overall poor global QoL and PF, and these patients require close follow-up and are in particular need of supportive measures.

List of papers

1

Eriksen GF, Šaltytė Benth J, Grønberg BH, Rostoft S, Kirkhus L, Kirkevold Ø, Hjelstuen A, Slaaen M. Geriatric impairments are prevalent and predictive of survival in older patients with cancer receiving radiotherapy: a prospective observational study. Acta Oncol. 2021:1-10.

2

Eriksen GF, Šaltytė Benth J, Grønberg BH, Rostoft S, Kirkhus L, Kirkevold Ø, Oldervoll LM, Bye A, Hjelstuen A, Slaaen M. Geriatric impairments are associated with reduced quality of life and physical function in older patients with cancer receving radiotherapy - a prospective observational study. J Geriatr Oncol. 2022. (In press 2022 Sep 27;S1879-4068(22)00227-2. doi: 10.1016/j.jgo.2022.09.008.)

3

Eriksen GF, Šaltytė Benth J, Grønberg BH, Rostoft S, Kirkevold Ø, Bergh S, et al. Cognitive trajectories in older patients with cancer undergoing radiotherapy - a prospective observational study. Curr Oncol. 2022;29(7):5164-78.

Abbreviations

ADL	Activities of daily living
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CCI	Charlson Comorbidity Index
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CRCI	Cancer-related cognitive impairment
CT	Computerised tomography
DSM-5	Diagnostic and Statistical Manual of Mental Disorders fifth edition
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy General
FDA	U.S. Food and Drug Administration
G-8	Geratric-8
GA	Geriatric assessment
GAM	Geriatric assessment with management
GDS-15	Geriatric Depression Scale-15
Global QoL	Global quality of life assessed by QLQ-30
Gy	Gray
HR	Hazards ratio
IADL	Instrumental activities of daily living
IMRT	Intensity modulated radiotherapy
KPS	Karnofsky Performance Status
MNA-SF	Mini Nutritional Assessment Ahort Form
MCI	Mild cognitive impairment
MMSE	Mini Mental Status Examination

MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NEADL	Nottingham Extended Activities of Daily Living
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
mGA	Modified geriatric assessment
OARS	Older American's Resource and Services Questionnaire
OS	Overall survival
PF	Physical function assessed by QLQ-C30
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
QLQ-C30	EORTC Quality-of-life Core Questionnaire
QoL	Health related quality of life
RC	Regression coefficient
RCT	Randomised controlled trial
RT	Radiotherapy
SD	Standard deviation
SIOG	International Society of Geriatric Oncology
TUG	Timed Up and Go
VMAT	Volumetric modulated arc therapy
WHO	World Health Organization

Introduction

Ageing

Ageing biology

Ageing is an inherent part of life, but as opposed to chronological ageing, biologic ageing occurs at a highly individual pace. From the beginning of life, there is a constant turnover of cells in the human body, where new daughter cells are born by cell division and old cells die by apoptosis (programmed celled death) or necrosis. Over time, human cells acquire accumulated damage as a consequence of genomic instability, shortening of telomeres, epigenetic changes and cellular senescence (1). These disturbances are caused by a combination of genetic, epigenetic and environmental factors, such as diet, obesity, drugs, chemicals, exercise and stress (1-3). The exact mechanisms involved are complex, multifactorial and not fully understood. However, the result of the cellular damage is poor cellular repair, reduced tissue and organ function, declined physiologic reserves and diminished ability to maintain homeostasis in situations with external stressors (2, 4). Since genetic predispositions and exposure to the aforementioned environmental factors vary considerably, biological ageing is diverse, and chronologic age is a poor marker of biologic age.

Consequences of ageing

Biological ageing affects the whole human organism. There is a gradual loss of functional units and thereby functional reserves within all organs, e.g. loss of cerebral neurons, alveoli in the lungs and cells in the bone marrow (1). However, functional reserves are abundant, thus losses usually becomes noticeable only in situations with unusual demands, or if functional capacity falls to a level of organ failure. There is also a general reduction in tissue elasticity which, for instance, leads to wrinkles in the skin, reduced ventilation in the lungs and stiffness of the artery walls accompanied by increased blood pressure and workload on the heart (1). Moreover, the immune system is affected, leading to poorer response to vaccines and reduced defence against infectious agents (5). Muscle mass is gradually wasted and is replaced by fat and there is a decline in bone mass, hence the overall body composition is altered. For these reasons, as well as the reduction in organ function, pharmacodynamics and pharmacokinetic processes are affected by age and act differently in older compared to younger persons (5).

Overall, age-related changes render the older adult more vulnerable, and although the line between normal and pathologic symptoms of biological ageing are blurry, increasing age is a

risk factor for almost all non-communicable diseases in humans. This include physical and functional impairments, as well as somatic and psychological problems. Geriatric syndromes are clinical conditions triggered in response to, often minor, stressors in vulnerable individuals due to reduced organ reserves and lack of compensatory mechanisms (6). Typical examples of geriatric syndromes are delirium (i.e. acute confusion and attention deficit), falls and incontinence, which often coincide and presumably have common multifactorial explanations (6, 7). Furthermore, a range of conditions, such as cardiovascular disease, obstructive lung disorders, diabetes type 2, and degenerative skeletal and neurocognitive disorders are associated with increased age (5). Consequently, multimorbidity is more frequent in older patients (8). Finally, the social network may diminish due to loss of friends and partners, and as a result of reduced mobility, functional impairments and mental health issues (9).

Frailty

'Frailty is a state of increased vulnerability to poor resolution of homeostasis following a stress, which increases the risk of adverse (health) outcomes' (10). Frail patients often have multimorbidity; however, patients with multimorbidity are not necessarily frail (11, 12). Likewise, frailty is strongly associated with, but not synonymous with, advanced age. There are two commonly applied theories explaining the concept of frailty. According to Fried et al., the *physical frailty phenotype* is characterised by three or more of the following criteria: exhaustion, weight loss, physical inactivity, slow gait speed and weak grip strength (13). In 2013, an international consensus was reached on the definition of the term physical frailty, i.e. 'a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death' (14). The physical frailty phenotype model only considers physical functioning, and may therefore not be sufficiently holistic (15). Another approach suggested by Rockwood et al. is based on the Canadian Study of Health and Aging (16) where accumulated *deficits* are summarised into a *Frailty Index* (15-17). The deficits assessed in the model are multidimensional and include symptoms, signs, disabilities, diseases, nutritional status and a few laboratory measurements (17). Examples of deficits are multimorbidity, physical and cognitive impairment and geriatric syndromes (e.g. falls). According to the Frailty Index, the product, or the sum of all accumulated deficits could be thought of as the degree of frailty.

Frailty is a dynamic process that may evolve to more severe stages over time; it represents a continuum with gradually reduced resilience to stressors (18). This is a key point, since acknowledging frailty at an early or 'pre-frail' stage is essential to implement interventions that may prevent or delay further decline (19). Identifying frailty is also important for therapeutic measures and prognostication (14, 20). The underlying causes are multifactorial and not completely understood, but age-related diminished physiologic reserves seem predispose to the accelerated failure of homeostasis and low grade inflammation that have been associated with frailty (10, 21). Patients who are frail may experience a disproportionate decline in their functional status if exposed to even a minor stressor such as a urinary tract infection, and may not fully recover and regain their habitual functioning (10). Patients living with frailty are at risk of experiencing geriatric syndromes, physical limitations, falls, fractures, dependency, hospitalisations, reduced quality of life, complications to treatment and premature death (20, 22).

A systematic review assessing community dwelling adults age 65 years and older, found that the reported prevalence of frailty varied from 4 to 59% (23). The authors attributed the substantial variation to differences in frailty assessments, and concluded that frailty is common among older adults, and increasingly so with higher age and among women compared to men. Another systematic review found that 40% and 53% of long term nursing home patients over 60 years were pre-frail and frail, respectively (24). Studies assessing the prevalence of frailty in the Norwegian population are lacking, but one small study found that 75% of patients ≥65 years with weekly home health care services lived with moderate or severe frailty (25). Furthermore, over 80% of patients admitted to Norwegian nursing homes have dementia (26), which indicates some degree of frailty (15-17). This is a great concern and challenge for the health care system, and frailty is considered an emerging global health burden (27).

Based on the constructive models of Fried et al. (13) and Rockwood et al. (17), a large number of different instruments to assess frailty have been developed and used in clinical trials (28), but there is still no consensus on how frailty should be identified. There are also several frailty screening tools available, including the Clinical Frailty Scale (CFS) (15), the Vulnerable Elders Survey (29), and the Edmonton Frail Scale (30). However, to fully capture the complexity of frailty, i.e. the underlying causes and their impact on both physical and psychological functions, performing a comprehensive geriatric assessments is considered the gold standard (10).

Geriatric assessment

A geriatric assessment (GA) is a systematic evaluation of areas were older patients commonly have problems. The overarching domains taken into consideration include somatic health (comorbidities, medications), physical function (mobility, basic and instrumental activities of daily living), psychological function (cognitive and emotional) and socio-environmental factors (31). Notably, the GA is an extension of (not a replacement for) the normal history taking, physical examination, laboratory tests, and supplementary investigations (e.g. electrocardiogram), which are routine for all in-patient medical consultations.

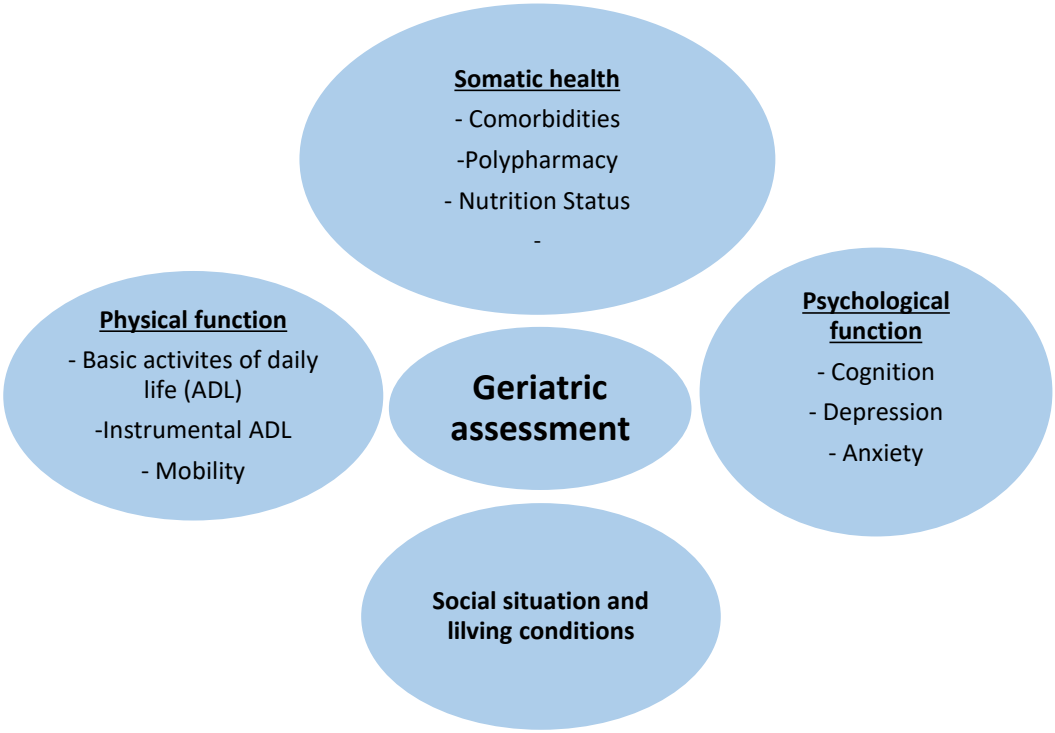


Figure 1. The four overarching domains of a geriatric assessment.

The figure is inspired by the work and ideas presented by Rubenstein (31), and adapted for the purpose of this thesis.

A *comprehensive* GA (CGA) has been defined as 'a multidimensional, interdisciplinary, diagnostic process to identify care needs, plan care, and improve outcomes of frail older people' (31). Thus, a CGA should ideally be performed by a multidisciplinary team consisting of several experts, such as a geriatrician, occupational therapist, nutritionist and a geriatric nurse. In addition to being a tool for identifying age-related health problems and functional reserves, CGA should serve as the basis for the development and implementation of a treatment plan, followed by monitoring of response and revision of the treatment plan if necessary (32, 33). Since the early beginning of CGA in the 1970s, it has been widely

accepted, and it is now an integrated part of geriatric medicine (31). CGA is a core tool in geriatric medicine and forms the basis for this specialty. CGA also predicts the risk of disability, institutionalisation and death among acute ill patients (34-36). However, to identifying patients who are most likely to benefit from CGA remains challenging, both from an individual and a cost-effective point of view (34).

Cancer

Epidemiology

The biochemical process of developing cancer is closely linked to the biochemical process of ageing (3), and age is an important risk factor for developing cancer (37). A higher standard of living and improved health conditions have resulted in a rapidly increasing absolute number and proportion of older adults worldwide. According to the World Health Organization (WHO), the number of people developing cancer aged 60 years and older was 1 billion in 2019, which is expected to rise to 2.1 billion by 2050 (38). Norway has a population of 5.4 million people with approximately 13% aged ≥70 years, estimated to increase to 21% by 2050 (39). As cancer is a disease closely related to ageing and the global population of older adults is growing, so is the incidence of cancer (37). In 2021, the Norwegian Cancer Registry reported 36,998 new cancer cases (registered in 36,017 individuals), 6,000 more than in 2011 (40). Among those diagnosed in 2021, there were 19,684 men and 17,314 women (40). The most common diagnoses were prostate (5,188), female breast (4,023), lung (3,499), and colon cancer (3,204) (40). At the time of diagnosis, 55% of men and 49% of women were ≥70 years.

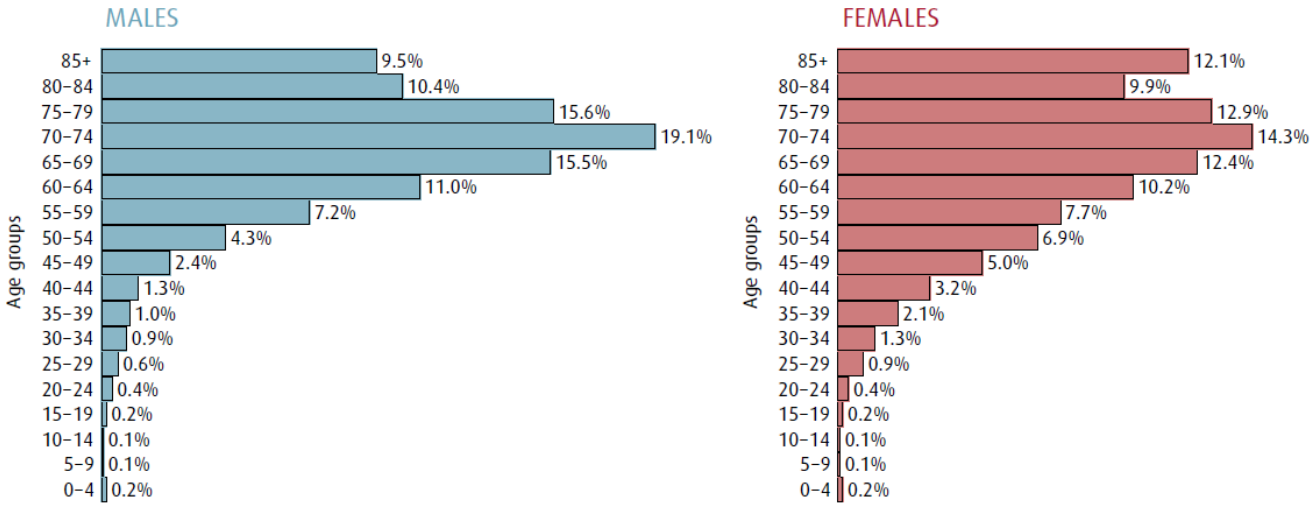


Figure 2. Percentage distribution of cancer incidence by age in males and females in Norway (2017-2021). Figure from The Norwegian Cancer Registry, Cancer in Norway 2021 (40).

Cancer was the most frequent cause of death in Norway in 2021, and has bypassed cardiovascular diseases (41). Cancer accounted for 10,981 deaths in Norway in 2020, and lung (20%), colon (11%), prostate (9%), pancreas (7%) and female breast cancer (5%) had the highest mortality. However, the cancer mortality in Norway is decreasing (40). This positive trend could be attributed to a combination of improved diagnostics, better health status among cancer patients and improved cancer treatment (40). Rising incidences and survival leads to a rapidly increasing prevalence of patients with cancer, also among older adults. It has been estimated that people aged 65 years and older accounted for 64% of patients living with cancer in North America in 2019, and the percentage is expected to increase in the near future (42). Combined, these demographic and epidemiologic changes pose a major challenge for the current and future health care systems, both nationally and globally.

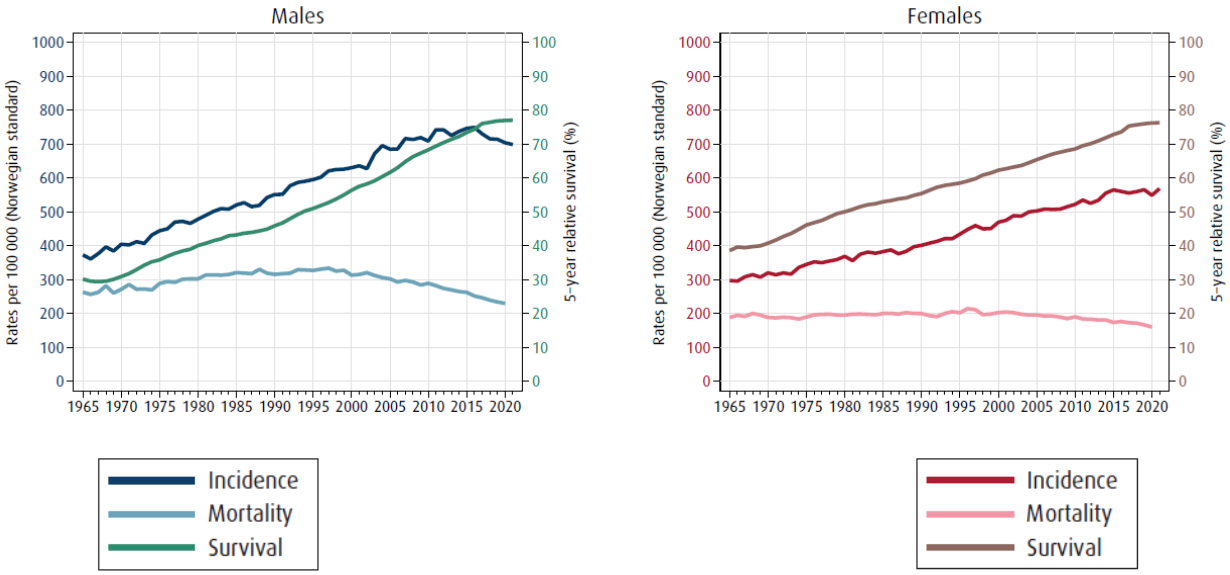


Figure 3. Trends in incidence and mortality rates and five-year relative survival proportions. Figure from the Norwegian Cancer Registry, Cancer in Norway 2021 (40).

Classification of cancer

Neoplasms can be divided into solid tumours, i.e. they form a mass of malignant tissue that does not contain liquids or cysts, or non-solid tumours. The most commonly occurring cancers, i.e. breast, prostate, colorectal and lung cancer are all examples of solid tumours. Leukemia, lymphoma and multiple myeloma are examples of non-solid tumours.

Classification of cancer is usually based on the organ of origin, histological examination and molecular profiling. The molecular profiling is becoming increasingly important, since research focuses on developing therapies targeting specific tumour traits. This represents one

of the major breakthroughs in the last decades (43), so-called ‘personalised’ or ‘precision’ cancer medicine.

Routine workup in oncology

In addition to the type of cancer, the extent of tumour growth (staging) and patients’ health status, are the other two main variables essential for making appropriate treatment decisions. In this respect, assessing patient-related factors that may influence prognosis or interfere with treatment, such as performance status, comorbidities and medications is important. Advanced age is inevitably associated with shorter life expectancy, and for some cancer types the prognosis differs between genders (40, 41). If a person has several comorbidities, the risk of polypharmacy, side-effects and interactions is likely to increase (44). This may again trigger a negative cycle where new medications are prescribed to treat the side-effects of others. A full review of patients’ medications, including whether they are appropriate in relation to the different indications and current situation, is not routinely or systematically applied. In the following section, the main aspects of an oncological workup (besides an appropriate cancer classification) are addressed, i.e. staging, performance status and comorbidity.

Stage of disease

Staging of cancer involves mapping the anatomical extent of the disease at the time of diagnosis, which provides essential information about treatment opportunities, prognostication and evaluation of treatment (45). Solid tumours are staged according to the TNM system (46). ‘T’ denotes tumour size, ‘N’ the spread to and extent of lymph node involvement, and ‘M’ the presence of distant metastasis, as indicated in Table 1. Clinical stage (c-stage) is based on physical examination, imaging and sampling of suspected lesions, whereas the pathological stage (p-stage) is based on the pathology report after surgery.

Table 1. Simplified overview of the TNM classification system.

TNM classification system	
Primary tumour (**T**)	**Tx** Cannot be evaluated **T0** No primary tumour **Tis** Carcinoma in situ **T1-T4** Higher number indicates larger size/extension into surrounding tissue
Regional lymph nodes (**N**)	**Nx** Cannot be evaluated **N0** No regional lymph nodes **N1-3** Higher number indicates more severe lymph node involvement
Distant metastasis (**M**)	**M0** No distant metastasis **M1** Distant metastasis present

Based on the TNM stage, the extent of disease is divided into four stages (I-IV) commonly referred to in clinical practice and used in cancer research in Norway (40). Stage I represents a localised tumour, stages II-III represent locally advanced cancer (local extensive primary tumour growth with or without invasion in local lymph nodes), and stage IV denotes metastatic disease. For non-solid tumours (e.g. myelomas and lymphomas) there are other criteria and procedures for staging, but is not described here since only six patients (two multiple myelomas, four lymphomas) out of 301 in our study had non-solid tumours.

Performance status

The patients' performance status (PS), i.e. functioning level, is routinely evaluated in oncology practice. The most commonly applied assessment tools are the Karnofsky PS (KPS) (47) and the Eastern Cooperative Oncology Group (ECOG) PS (48). KPS is a scale ranging from 0 to 100, where a higher score indicates better ability to perform daily activities. ECOG PS is a cruder measure of functional level based on patient reports and/or the physicians' observations, and is scored from 0 (no functional restrictions) to 5 (dead), as indicated in Table 2. ECOG PS is associated with chemotherapy toxicities (49) and mortality in patients with cancer (50) and is frequently used to guide treatment decisions. However, ECOG PS was validated among younger patients and does not necessarily capture the diversity in older adults' functional status (51-53).

Table 2. ECOG PS

Grade	Definition
0	Fully active, i.e. no performance restrictions.
1	Strenuous physical activity restricted. Fully ambulatory and able to carry out light work.
2	Capable of all self-care, but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable only of limited self-care, confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care. Totally confined to bed or chair.
5	Dead

Based on original version published by Oken et al. 1982 (48).

Comorbidity

Comorbidities are diseases or chronic conditions coinciding with an index disease, i.e. cancer. Comorbidities are common in older adults, and in patients with cancer (54, 55). In a large cross-sectional study, it was found that patients aged 65-84 years on average had 2.6 diseases and 3.6 in those over 85 years (56). The reported prevalence of comorbidity among older patients with cancer varies depending on cancer type (57) and assessment method (58), but it is estimated that more than half of older adults with cancer have a comorbid condition that may interfere with cancer treatment (54). In a study assessing patient reported comorbidities in patients with cancer aged ≥ 65 years, 92% reported ≥1 comorbid condition, with a mean of 2.7 conditions (59).

Comorbidity in patients with cancer is important for several reasons. The presence of comorbidities increases the risk of adverse outcomes such as chemotherapy toxicities, complications after surgery, and poor OS (54, 55). Older adults with comorbidities have a higher risk of febrile neutropenia and death of neutropenic infection (60). The association between comorbidity and increased mortality in patients with cancer is a consistent finding, as demonstrated in a review reporting five-year hazard ratios (HRs) ranging from 1.1 to 5.8 for patients with comorbidity (57). Comorbidity is also associated with poor quality of life, increased health care costs and worsening of the pre-existing diseases secondary to cancer treatment (58). Comorbidity may be a limiting factor for oncological treatment options. For instance, surgery or specific chemotherapies may be contraindicated due to organ failure (e.g. kidney failure) or significantly reduced organ reserves.

Patients with comorbidities are less likely to receive curative cancer treatment (58), more often exempted from chemotherapy and have more dose reductions (53). In older adults, comorbidity can also delay treatment initiation and cause treatment discontinuation as well as dose alterations (59). Comorbidities may represent competing risks of death, but there is little evidence on how to select treatment and treatment intensity in patients with comorbidities, and many patients are probably overtreated, while others do not receive effective therapy (58). Despite the documented impact of comorbidity on treatment outcomes, it is often not reported (54) and inconsistently assessed in clinical trials, as highlighted in a systematic review identifying 21 different approaches (61). Oncologists tend to only assess major comorbidities, and few systematically perform a comprehensive assessment of either the number or the severity of comorbidities. Moreover, patients with comorbidities are often excluded from cancer trials (62), in particular randomised controlled trials (RCTs) (58).

Treatment of cancer

As mentioned, oncological treatment is mainly selected based on the type of cancer and the extent of the disease. As a main rule, curative treatment is offered for early stage disease, whereas most patients with advanced disease are offered palliative therapy. The three cornerstones of cancer treatment are surgery, radiotherapy (RT), and systemic medical treatment. These treatment modalities can be administered alone, in combination or sequentially. Adjuvant therapy (e.g. RT, chemotherapy and endocrine therapy) is given *after* the primary treatment to reduce the risk of recurrence. Neo-adjuvant therapy is given *before* the main treatment, mainly to shrink tumour masses that promote radical surgery. Many cancer treatments are highly toxic. Traditionally, more toxicity is accepted in a curative setting, whereas in a palliative setting, it is more important to balance the benefits and disadvantages of the treatment. In the following section, overarching principles of the main treatment modalities will be discussed, focusing on radiotherapy.

Surgery

Surgery remains the most important curative cancer treatment. The aim is to remove all tumour lesions. Even if all known lesions are removed, other therapies are often needed in order to treat micrometastases, e.g. postoperative adjuvant chemotherapy or neoadjuvant chemotherapy. In recent years, surgery has also been increasingly used to remove oligometastases (63) or to relieve symptoms of obstruction, tumour hemorrhage or fixation of pathological fractures.

Systemic cancer therapy

Systemic cancer therapy is the main treatment for non-solid tumours. In solid tumours treated with curative intent, systemic cancer treatment is often given in addition to surgery or radiotherapy, as explained above.

In palliative settings, systemic cancer treatment is the most important treatment modality. Endocrine therapy is essential in the treatment of hormone sensitive neoplasms, mainly breast and prostate cancer, and acts by blocking or removing hormone-stimulated tumour growth. In traditional hormone therapy, the main side effects are related to changes in hormone levels and include loss of libido, impotence, muscle loss, hot flashes and increased risk of osteoporosis, thromboembolism and cerebrovascular events (64). Cytotoxic chemotherapy comprises a large group of substances that induce apoptosis in dividing cells by a variety of mechanisms, but with poor discrimination between normal and malignant cells (65). Most chemotherapeutics are administered intravenously. Regimens vary with cancer type and setting and usually include combinations of several drugs. Toxicities are frequent and mainly come from normal tissue with a high cellular turnover (many cells in the process of dividing), such as the skin, gastrointestinal mucosa and bone marrow. Some agents affect organs, such as the kidney, heart and the nerve system, resulting in corresponding organ-specific side effects (65).

Targeted therapies specifically target proteins, mainly cellular receptors that due to mutations are distinct in malignant and normal cells, that control how cancer cells grow, divide and spread. This is the foundation of precision medicine (66). Targeted therapies are small molecular drugs or monoclonal antibodies, and are used if the cancer cells contain specific molecular aberrations. Monoclonal antibodies can also be used to deliver radioactive and chemotherapeutics directly to cancer cells (66). Despite the affinity for cancer cells, targeted agents may, however, also bind to normal cells and frequently cause side effects, such as diarrhoea, liver problems, skin rashes, hypertension, fatigue, mouth sores and poor wound healing (65, 67). Immunotherapy activates an immune response in the host that leads to an attack on cancer cells, thereby overcoming their ability to evade destruction by the immune system (68). Immune check point inhibitors have become the backbone of systemic therapy of a wide range of cancers (69, 70). The indications are constantly evolving, and enormous research has been conducted in the field (71). Common side effects are autoimmune conditions, which vary in degree of severity, and includes colitis, hepatitis and endocrineopathies, such as thyroiditis and hypophysitis (72). The most important benefit of

immunotherapy is that some patients achieve excellent disease control five to ten years after initial treatment, possibly suggesting that patients with metastatic disease might be cured (73).

Radiotherapy

External beam radiotherapy, henceforth referred to as RT, is most frequently high energy photons delivered locally at the tumour site by a linear accelerator using various techniques, the most modern being intensity modulated RT (IMRT) and volumetric modulated arc therapy (VMAT) (74). Irradiation can also be performed by implanting a radiation (gamma ray) emitting source within the patient, known as brachytherapy. Proton therapy is not yet available in Norway, but two proton centres are currently under construction.

RT is usually delivered focally at the tumour site in fractions, i.e. in multiple smaller doses, exploiting the differences in radiation sensitivity between tumour and normal tissue with respect to re-oxygenation, repair, redistribution in cell cycle stages and repopulation between doses, to kill cancer cells while limiting normal tissue toxicity (75). However, some energy is inevitably deposited in adjacent normal tissue, which limits the utility and effect of RT (74). Both normal tissue and tumours have different sensitivity to RT, and balancing between delivering high enough doses to kill tumour cells while preserving sufficient normal tissue is the main challenge (75).

Stereotactic body radiation therapy (SBRT) is a relative new technique that enables us to deliver high RT doses with great precision, reducing treatment duration and sparing normal tissue (75). It is mainly used for treatment of inoperable stage I lung cancer (76), but also represents a major improvement in the treatment of brain metastases. SBRT was not available at our hospital during our study period, and eligible patients were referred to the university hospital in Oslo.

Radiotherapy with curative intent

RT has an important place in curative cancer treatment, both as a single modality and in combination with systemic cancer treatment (e.g. lung and head and neck cancer), as adjuvant treatment (e.g. breast cancer), neo-adjuvant treatment (e.g. rectum cancer) and concurrently with other therapies to enhance tumour response. Conventional fractionation regimens for curative RT typically include 2 Gray (Gy) fractions administered once daily five days per week (Monday to Friday), for a total dose of 60-80 Gy (77). Hypofractionated RT (daily dose > 2 Gy) reduces treatment time, and is, for example, the standard treatment for breast cancer in Norway (64). RT is routinely used after breast conserving surgery, and in certain

specifically defined situations where supplements of irradiation have documented prognostic benefits, in the curative treatment of breast cancer (64). Hypofractionated RT with 2.67 Gy in 15 fractions delivered over three weeks is currently the recommended curative treatment regimen in Norway (64).

In addition to radical prostatectomy, RT is an established treatment option in local/locally advanced cancer prostate with or without endocrine therapy, depending on tumour characteristics (78). The standard total dose is 76-78 Gy, or 2.6-3 Gy over four to six weeks (moderate hypofractionation) is considered for patients with localised intermediate risk disease, especially in men with advanced age, a comorbidity that may complicate surgery and locally advanced disease. RT can also be administered after radical prostatectomy, either adjuvant (immediately after surgery) or as salvage (in biochemical recurrence, i.e. relapse of elevated prostate specific antigen in blood) (78).

In patients with stage I-III non-small cell lung cancer (NSCLC), curative RT is an option for those who are technically inoperable, inoperable due to comorbidity and for patients who do not want an operation. In stage III disease, concurrent or sequential chemotherapy is recommended followed by consolidation immunotherapy, which is standard therapy for PD-L1 positive tumours (76). When radiochemotherapy is given concurrently, standard fractionation, according to Norwegian guidelines, is 2 Gy x 30-33 (76). Patients ineligible for chemotherapy are offered RT alone.

RT is also implemented in the curative treatment of other cancer types. However, at the RT unit where the patients in the present study were enrolled, curative treatment offers were limited to breast, prostate, lung and certain skin cancers. All other indications were handled by the nearby university hospital; thus, these will not be further discussed.

Radiotherapy with palliative intent

The aim of RT with palliative intent is to achieve local disease control mainly to alleviate or prevent symptoms, but also prolong survival. In general, palliative RT consists of lower total RT doses and fewer fractions, typically from one to two weeks or only a single fraction for symptom management (79). Common indications include painful bone metastases, tumour obstructions (e.g. airway and oesophageal obstructions), symptomatic brain metastases and tumour haemorrhage (e.g. in bladder cancer) (79). For painful bone metastasis, partial pain control can be obtained for 60-80% of patients, and complete relief is achieved in 30-50% of patients within three to four weeks after RT (80). By providing temporary local tumour

control, palliative RT can prolong life for several months, for example, in glioblastomas and lung cancer (80). Furthermore, RT is indicated in some oncological emergency situations such as if the spinal cord or large veins (vena cava superior syndrome) are compressed.

Radiotherapy toxicities

Radiotoxicity is usually defined as short or long term, local or generalised. Local reactions are caused by an immune response at the irradiated site secondary to cellular destruction (74) and include skin reactions, such as erythema, oedema, calor (heat) and pain, or reactions in internal organs such as pneumonitis, oesophagitis, proctitis and mucositis (74). These acute reactions are usually most prominent two to three weeks following RT and are most frequent in tissue with high cellular turnover. Acute toxicities usually heal within four to six weeks after treatment completion (79). However, in tissues with longer turnover time, such as vascular endothelium and neurons, side effects may not manifest until months or even years after irradiation (74). The toxicity profile depends on the anatomic region, irradiated volume and total radiation dose. Local long-term side effects are caused by fibrosis, such as oesophageal stricture and pulmonary fibrosis, and RT-induced atherosclerosis is accompanied by increased risk of cardiovascular diseases (81). Among generalised toxicities, fatigue is the most common (up to 80% of patients), which can persist for months or years after treatment completion and significantly reduce patient's quality of life (81). A major concern is the risk of inducing secondary cancers, which is estimated to account for 8% of solid tumours (82). Thus, RT is avoided if possible in younger patients with cancer.

Outcome measures in cancer research

Conventional outcome measures in oncology can be divided into patient-centred measures, representing a direct clinical benefit for the patients, and surrogate measures, which are indirect measures of benefits (83). Overall survival (OS) is the major patient-centred measure and considered the gold standard in cancer clinical trials (84). Extended survival is an obvious benefit, and OS is easily and precisely measured, and not subjected to bias (83). The drawback with OS is that it may take time to assess, may need a considerable number of patients, and may be affected by crossover and sequential therapies (83). Thus, with the rapid development of new treatment agents resulting in multiple treatment lines and the need for rapid drug approval, other outcomes have largely replaced OS as the primary outcome in drug trials (85). These outcomes are based on measures of tumour growth and also referred to as tumour-centred endpoints. These include overall response rate (ORR), time to progression (TTP), and progression-free survival (PFS), of which PFS has emerged as the most commonly

used for assessing drug efficacy (86). In addition, patient-centred outcomes, usually patient-reported outcomes, are used to assess clinical benefits from the patients' perspective.

Patient-reported outcome measures

Patient-reported outcome measures (PROMs) are means to measure and quantify different health-related aspects by asking the patient directly, therefore representing their subjective evaluation (87). The use of these measures is highly advocated, including by the U.S. Food and Drug Administration (FDA) (88-91), but their use is also connected with substantial challenges, such as missing data and unknown clinical relevance of smaller changes (83). Quality of life (QoL), which is not suitable for objective assessment, is an important and frequently used PROM in cancer research. WHO defines QoL as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' (92). This is a broad definition involving all aspects of life, underlining that QoL is a multidimensional concept. In medical research, the term 'health related quality of life' (HRQoL) has been defined, narrowing the concept to aspects affected by an illness and /or its treatment (93). For simplicity, QoL will henceforth be used synonymously with HRQoL.

QoL is a multifaceted and complex construct and preferably assessed by multidimensional scales, often including both physical and emotional symptoms (94). Several QoL questionnaires have been developed for oncology settings. Some of these are general and may be used irrespective of cancer type, while others are disease-specific. The most commonly used general questionnaires are the European Organisation for Treatment of Cancer Quality-of-Life Core Questionnaire (EORTC) (QLQ-C30) (95), and the Functional Assessment of Cancer Therapy General (FACT-G) (96). Both questionnaires are multidimensional and include physical, functional, emotional and social aspects (97, 98). The QLQ-C30 also assesses several common symptoms in cancer. The QLQ-C30 is traditionally used in European trials and FACT-G is commonly used in the North America. A study comparing the two questionnaires found no significant differences in psychometric properties (i.e. the validity and reliability) (99).

Cognitive function in ageing and cancer

Normal ageing involves structural changes of the brain that can be observed on neuroimaging, often accompanied by reduction in cognitive abilities, such as memory and processing speed (10, 100, 101). Mild cognitive impairment (MCI) is a condition where reduced cognitive

abilities can be objectively detected, but these do not significantly impact basic daily activities (102). The decline from a state with normal age-related cognitive symptoms to a pathologic condition that affects functional status represents a continuum. MCI can, but does not necessarily, progress to dementia, a group of neurocognitive brain disorders among which Alzheimer's disease is the most frequent. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), dementia is a progressive neurodegenerative disorder characterised by a decline in cognitive abilities to the extent where it interferes with a person's functioning level, accompanied by neuropsychiatric symptoms (103). Dementia is recognised by the World Health Organization as the biggest global health challenge in this century.

The 47 million people who were living with dementia in 2015 is expected to triple by 2050 (104). In a recent large population-based Norwegian study, in which all older adults aged ≥70 years in Trøndelag County were invited to participate, the prevalence of MCI was 35.3% and dementia 14.6%, respectively, judged by clinical experts using the DSM-5 criteria (105). By applying previously published data in people <70 years, it was estimated that 101,118 persons lived with dementia in Norway in 2020, projected to increase to 236, 789 by 2050 (105). This represents a major health problem as it often causes dependency, is associated with a high caregiver burden and increases mortality (104). Moreover, cognitive impairment and dementia are dreaded conditions that significantly reduce quality of life and cause human suffering (106). Lifestyle-related factors, such as smoking, alcohol consumption, and obesity increase the risk of developing dementia. A number of comorbidities, many associated with the same lifestyle factors, can predispose to cognitive impairment, such as systemic atherosclerosis, stroke, hypertension, impaired hearing, depression and diabetes mellitus (107, 108). On the other hand, education/active brain stimulation, physical exercise and social engagement seem to have a preventive effect (108). Most neurocognitive disorders are progressive, and although there is no cure or effective disease-modifying treatment available, early detection of MCI is crucial, as a growing body of evidence suggests that adequate treatment of predisposing factors may slow down its progression and thus improve the disease trajectory (107, 109).

Cancer related cognitive impairment

Over the last decade, there has been an increasing awareness of a condition referred to as 'cancer-related cognitive impairment' (CRCI) (110-112). CRCI is characterised by patient-reported and objectively measured reduction in cognitive abilities presenting in relation to

cancer and/or its treatment (111). Commonly affected cognitive domains are memory, attention, executive function and processing speed (110, 113). The symptoms are often subtle and may persist after completing the oncological treatment (110, 114). CRCI was first acknowledged in women receiving chemotherapy for breast cancer and was initially referred to as 'chemobrain' (115). However, the majority of patients with cancer receive multiple treatment modalities, and research suggests a complex and multifactorial aetiology (111). There are indications that endocrine therapy, immunotherapy, antiangiogenics and general anaesthesia can contribute to CRCI (110, 116).

Data from a large register study showed that among patients with cancer aged ≥65 years, 3.8-7% had pre-existing dementia, with varying prevalence depending on cancer type (117). Cognitive impairment, identified by different cognitive screening tools, was reported in a median of 26% (range 3% - 38%) of older patients with cancer in a systematic review (118). An RCT including patients ≥70 years with various types of advanced cancer, used geriatric screening tools and identified impaired cognition in 36% at baseline (119). Older patients, and in particular patients living with frailty and reduced cognitive reserves (120), seem to be at risk of experiencing deterioration in cognitive function during systemic cancer therapy (121-123). This is concerning knowing that preserved cognitive abilities is a highly prioritised outcome for these patients (106). Moreover, CRCI disproportionally affects older patients who also report complaints, such as fatigue, distress and depression (110). Thus the research on CRCI has developed from focusing on pharmacotoxicology (i.e. chemobrain) to a broader and multidimensional perspective investigating the contribution of multiple cancer treatments, the biology of cancer, and patient characteristics associated with cognitive decline during and after treatment (111). However, studies investigating CRCI in patients treated primarily by RT is lacking (111).

In the treatment of cancer, cognitive impairment can have several important implications. Cognitive impairment can affect patients' preferences, ability to understand prognostic information and shared-decision making (122). Moreover, patients' ability to self-care, treatment compliance, (e.g. intake of oral medications) and reporting of side effects may be inadequate and lead to adverse events. Among older patient with cancer, pre-treatment cognitive impairment is associated with increased chemotherapy toxicity (124, 125) and reduced survival (126, 127). Assessing cognitive function is not part of a routine oncological workup, and cognitive impairment may be overlooked in clinical consultations (128, 129).

Geriatric oncology

Presently, geriatric oncology, is represented by broad research efforts and international collaboration, but as a specific discipline within oncology, it is rather young. The first conference with geriatric oncology as a topic was arranged by the National Institutes of Health (NIH) as early as in 1983, the NIH Conference on Cancer in the Elderly (130), but the progress in the field remained slow until the turn of the millennium. This can briefly be illustrated by a PubMed search from 1983 until today using the pragmatic terms 'older adults AND cancer showing that only approximately 25% (305,556) of all retrieved publications (1,275,418) were published before 1999. In 2000, Yancik et al. published the work 'Aging and Cancer in America', and estimated that over 60% of cancer incidents and 70% of all cancer deaths occurred in adults aged ≥65 years (131). This served as an eye-opener to the challenges imposed by the predicted demographic and epidemiologic changes in the years to come. Later the same year, the International Society of Geriatric Oncology (SIOG) was founded. In the following years, influential organisations, such as the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) became engaged. Many geriatric oncology training and research centres have subsequently been established both in North America and Europe, but so far not in any of the Scandinavian countries (132).

Following this development of geriatric oncology, specific demands related to the management of a growing number of older patients with cancer have become generally acknowledged. Older patients, in particular those living with frailty, were and still are underrepresented in clinical cancer trials (133-135). Results from trials performed in a younger population may not be applicable, and evidence-based guidelines on how to treat patients with age-related problems are lacking. Thus, clinical trials addressing older patients in particular have been highly advocated, leading to a steadily increasing number of studies and progress in the field (136). At present, it is also consistently realised that chronologic age and standard oncological workups provide limited prognostic information due to the heterogeneity in older patients' health status (124).

Specific considerations in geriatric oncology

The main challenges in the treatment of older patients with cancer are related to the bodily consequences of ageing, the highly individual pace of the biologic ageing process and the following variations in health status in the older population. A large proportion of older

patients with cancer can be regarded as fit or robust, but frailty is common. In a systematic review, the estimated median prevalence of pre-frailty and frailty among older patients with cancer was 42% and 43%, respectively (137). Moreover, remaining survival at a given age varies largely according to these differences in health status (138, 139) as does tolerance to treatment (52, 125). In 2000, Lodovico Balducci, recognised as the 'father of geriatric oncology' (140) formulated four questions, which are widely cited and seem to capture the essence of geriatric oncology (141):

1. Is the patient going to die with cancer or of cancer?
2. Is the person going to suffer the complications of cancer during his/her lifetime?
3. Is the patient able to tolerate the treatment safely?
4. Will the treatment provide more benefits than harm?

The first question points to the necessity of estimating non-cancer based life expectancy. This depends on several factors, such as gender, lifestyle, body mass index (BMI) and physical and cognitive function (124, 138, 139). Comorbidities are also important, representing potential competing risks, in particular in situations where the cancer prognosis per se is good (57, 58). The second and third questions point to the need of having a full picture of the patients' health status and vulnerability, including common age-related conditions that may affect cancer prognosis and treatment tolerance. The fourth question underlines the particular importance of weighing the pros and cons when considering oncology treatment for the older adult, but also implies that it is necessary to understand the patient's priorities and what actually represents a benefit for the older patient. When diagnosed with cancer, older adults may have different priorities than their young counterparts (106). Outcomes such as function in everyday activities, independence and quality of life may be more highly valued, as may the absence of burdensome symptoms and disease trajectories that interfere with their priorities (142-144). Still, the development in physical function and functional status from the time of diagnosis and during and after cancer treatment has been scarcely investigated (145). Measures of functioning and patient-reported outcomes (PROs) are pivotal, and are recommended for use in clinical trials targeting older patients with cancer (84). As a means to meet the challenges addressed by the four questions, Balducci underlined the importance of a proper assessment that could capture the diversity in health status and identify the frail versus the robust patients (141). For this purpose, based on the documented benefits of GA from geriatric medicine, he proposed to adapt this approach for older patients with cancer (141).

Geriatric assessment in oncology

GA was originally introduced in oncology as a means to systematically evaluate the heterogeneity in older patients' health status, i.e. to decide the patient's frailty status (141). Opposed to the 'geriatric' CGA, which also includes implementation of a treatment plan (31, 33), the assessment performed in oncology has traditionally been less extensive and thought of as a tool 'to identify opportunities for intervention', as phrased by Puts et al. (146). Thus, a systematic assessment of age-related health problems performed in an oncology setting will henceforth be referred to as GA.

In 2005, SIOG officially recommended that GA should be performed in all older patients with cancer (147). These recommendations were updated in 2014 with guidelines on which domains to include in GA (148). The National Comprehensive Cancer Network (NCCN) (149), EORTC (150), and ASCO (124) have all published guidelines endorsing the use of GA in geriatric oncology. However, performing GA on all patients can be time and resource consuming and may not be relevant for all. Thus, a geriatric screening aiming to identify patients who may benefit from a complete GA may be a feasible alternative and is recommended for all patients aged ≥70 years (151). Although there are several available screening tools, SIOG promotes Geriatric-8 (G-8) and the Vulnerable Elders Survey (VES-13) due to their psychometric properties and associations with outcomes such as chemotherapy toxicities and survival (151). Ideally, the GA should be followed by pre-planned interventions to ameliorate identified impairments, known as a GA with management (GAM) (33). It has therefore been a priority to develop guidelines for what kind of interventions GA should trigger, resulting in two Delphi consensus papers (152, 153).

On the basis of GA, a patient can be classified as either fit, vulnerable or frail by different methods, but there is no standardised way of defining frailty. According to the Balducci criteria presented in 2000, a patient is considered frail if one or more of the following characteristic are present: age ≥85 years, ≥3 comorbidities, ≥ 1 dependency in ADL, and ≥ 1 geriatric syndrome (154). Several studies have used these criteria or a modified version to identify frailty (155, 156). The result of GA could also be described by an adapted version of the Fraily Index, i.e. a higher number of impaired domains indicate a more severe degree of frailty (10, 157, 158). Although there are some minor variations in guidelines, there is general agreement that GA should include evaluation of comorbidity, medications, nutritional status, physical function, function and falls, cognitive function, depressive symptoms and social support (124, 148, 153).

Geriatric assessment domains

Comorbidity

As discussed, a systematic assessment of comorbidity is advocated in older patients with cancer. There are several recommended tools for this purpose (62). Some of the most commonly applied instruments are the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (159), the Older American's Resource and Services Questionnaire (OARS) (160) and the Charlson Comorbidity Index (CCI) (161). CIRS-G and CCI are rated by health care personnel, whereas OARS may be used for patient reports.

Medications

The term 'polypharmacy' refers to the daily use of several prescribed medications. There is no consensus as to how it should be defined, but the use of five or more regular medications is frequently applied (162). In general, polypharmacy increases the risk of drug interactions and side effects, in particular in older age due to age related pharmacodynamics and pharmacokinetic changes (5). It is most common in older age, and the prevalence is increasing (163). According to a report from the Norwegian Prescription Registry, 58% of adults ≥65 years used more than five drugs during a year, 23% used more than ten drugs, and the latter proportion had increased from 19% during the last decade (164). These numbers reflect that modern pharmacological treatment has a major role in prevention and treatment of health problems that are frequent in older age. When diagnosed with cancer and experiencing cancer-related symptoms requiring drug management (e.g. analgesics), the number of daily medications will inevitable increase. Polypharmacy is thus prevalent in older patients with cancer (54), and in this population, it has been associated with poor outcomes such as increased risk of falling, adverse drug reactions (ADRs), cognitive impairment and hospitalisations (165, 166). To register and evaluate medications is therefore crucial, but most importantly, the appropriateness of the prescribed medications should be assessed (166, 167).There are several tools available for evaluating potentially inappropriate medications (PIMs), such as the Beers Criteria published by the American Geriatrics Society (168) and the STOPP/START criteria, which can be used as an intervention to manage PIMs (169).

Nutritional status

Malnutrition is a multifactorial condition that can be defined as 'a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease' (170). Malnutrition typically involves unintended weight loss, low

body mass index (BMI), reduced muscle mass, reduced food intake, and an index disease that is accompanied by inflammation, such as major infections, trauma, congestive heart failure or cancer (171). However, ageing per se and the consequential physiological changes are recognised risk factors (172), and since cancer is a major cause of inflammation and catabolic dysregulation (173), older patients with cancer are at a particular risk of developing malnutrition. Frequently occurring comorbidity and common cancer-related symptoms, such as pain, nausea and lack of appetite may further aggravate the situation (174). Thus, malnutrition is frequent in this population with a reported prevalence between 30.9% and 66% depending on the setting, assessment method and definition applied (175-177).

In older adults in general, it is well documented that malnutrition has a deleterious impact, carries a higher risk of morbidity and mortality and is associated with frailty (172, 178). A recent systematic review addressing patients age 65 and older with cancer confirmed that malnutrition and risk of malnutrition were significantly associated with increased mortality in this population, a HR of 1.86 compared to normal nutritional status was found (179). Additionally, and in accordance with an earlier review on the predictive value of individual geriatric domains (180), associations between malnutrition and more postoperative complications, more use of health care services and premature secession of chemotherapy were documented (179). Thus, to identify risk of malnutrition and malnutrition is paramount to enable application of targeted, supportive measures that may have the potential to improve outcomes (179). However, malnutrition and risk of malnutrition often go unnoticed in patients with cancer (181), although there are several screening tools available. The most commonly used are the Mini Nutritional Assessment - short form (MNS-SF) (182), the Malnutrition Universal Screening Tool (MUST) (183), and the Patient-generated Subjective Global Assessment (PG-SGA) (184).

Physical function, functional status and falls

Mobility, strength and balance are all prerequisite for normal physical function (185). These basic functions can be compromised due to normal age-related changes such as reduced muscle mass or secondary to diseases affecting the cardiac, pulmonary, neurologic and musculoskeletal systems (186). Declined physical function often leads to reduced functional capacity, i.e. dependency in performing everyday activities, and is a major concern for the affected individual, their next of kin and the health care system (185). Thus, physical function and functional status are highly interconnected. Maintaining functional status and independence are highly prioritised outcomes for older patients with severe diseases such as

cancer (106). The evaluation of physical function typically involves assessment of mobility, gait speed or grip strength.

Functional status is measured by assessing the patient's ability to perform basic activities of daily living (ADL) and instrumental activities of daily living (IADL). Basic ADL involves activities such as dressing, toileting, feeding and transferring, whereas IADL describes more complex tasks, such as cooking, grocery shopping, handling finances and medications. Notably, preserved cognitive function is prerequisite for independency in ADL and IADL (187). ECOG PS, which is routinely used to assess functional status, is less sensitive when applied to older patients (51-53), and assessment of ADL and IADL is therefore important. Available tools for assessing functional status include the Katz Index of Independence in ADL (188), the Barthel Index (189), Lawton's IADL (190) and the Nottingham Extended Activities of Daily Living (NEADL) (191). These may be rated by the patient, by an observer or by a mix of observation and reports from the patient and/or next of kin. Mobility, balance, strength and endurance are assessed by performance tests. Examples are hand grip strength, the Short Physical Performance Battery (SPPB) (192), gait speed test and the Timed Up and Go (TUG) test (193), which are all recommended tools for assessment of physical function. Physical function may also be patient-reported, either by an interview or a questionnaire. According to a relatively recent review, the QLQ-C30 is most commonly used instrument for patient reporting of physical function in cancer research (194). Both physical function and functional status should ideally be assessed by a mix of objective and patient-reported measures, since there may be deviations in patients subjective opinions and actual performance (195).

A wide range of underlying causes may lead to reduced physical function and functional status in older adults, such as comorbidities, malnutrition, cognitive impairment and polypharmacy, and older patients with cancer are at particular risk (145). In patients with cancer, the disease per se and/or its treatment can contribute to reduced functioning secondary to symptoms, such as weight loss, pain, dyspnoea and fatigue (196). Reduced physical function is associated with poor QoL (197), chemotherapy toxicity, postoperative complications and mortality (180). Poor functional status is associated with adverse outcomes for older patients with cancer, including chemotherapy toxicity, decline in QoL, further functional decline and survival (198, 199).

Falls in older adults are in the majority of cases related to reduced physical function, and as such regarded as a geriatric syndrome, commonly included in the GA (148). Approximately

30-40% of persons aged 65 years or older, and 50% over 80 years in the general population experience at least one fall each year (200). Older patients with cancer are at particular risk due to physical and functional deficits often accompanying cancer and its treatment (201-203). For the older patient, falls can be fatal, lead to hospitalisations, fractures and poor quality of life (202). Falls are also a predictor of reduced chemotherapy tolerability and postoperative complications (52). Evaluating the risk of falling and underlying causes is important to prevent falls and their undesirable consequences. This domain may be assessed by asking the patient about the experienced number of falls the last six months (124, 148).

Cognitive function

Evaluating cognitive function is important and highly recommend by multiple stakeholders in geriatric oncology (124, 148, 149). Assessment *before* treatment initiation is prerequisite to detecting changes during follow-up. There is a wide range of recommended tools for assessing cognitive function in geriatric oncology (204). The Mini Mental Status Examination (MMSE) (205) and Mini-Cog (206) are among the most commonly applied instruments. MMSE was developed to detect signs of dementia and consists of 20 questions testing orientation, attention, recall, language, calculation and visuospatial abilities. The Mini Cog includes a clock drawing test and three-word recall, with a standardised scoring. Although less frequently used than the MMSE, the Montreal Cognitive Assessment (MoCA) (207) is a recommended alternative (124) and the chosen instrument for the present study.

Depressive symptoms

It is estimated that depressive symptoms occur in one of three older adults (208). Symptoms tend to be more serious with advancing age (208), and adults with chronic illnesses, cognitive impairment and disabilities are at particular risk (209). Among older patients with cancer, depression is common with a reported prevalence between 14.9% and 44% (210-213). This substantial variation may be attributed to differences in definition and patient population in these studies. Depressive symptoms in older adults with cancer are associated with several negative outcomes and concerns: increased mortality, poor QoL, reduced functional status, more self-reported pain, symptoms of anxiety and distress, cognitive impairment and social isolation (197, 210, 211, 214, 215). As cancer and depression may have overlapping symptoms such as weight loss, fatigue, and sleep disturbances, depression may be difficult to uncover in patients with cancer (210). Several treatment and managing strategies for depression that may improve outcomes are available (6). In geriatric oncology, the Geriatric

Depression Scale-15 (GDS-15) (216) is the most commonly applied screening tool for depression (124).

Social support

The National Cancer Institute (NCI) defines social support as ‘a network of family, friends, neighbours, and community members that is available in times of need to give psychological, physical, and financial help' (217). Deficient social support is associated with reduced QoL and increased chemotherapy toxicity in older adults with cancer (218). Its relation to survival remains uncertain (218). Adequate social support is important for older patients with cancer in several treatment-related aspects, such as transportation, coordination of appointments, management of side-effects and emotional and physical assistance during treatment (141). SIOG suggests assessing social support through history taking during the oncological workup and by questions on the patient’s living situation, marital status, educational level, availability of family support and functionality of the social environment (148). The Medical Outcomes Study (MOS) Social Activity Survey (219) is mentioned in SIOG guidelines as means to systematically assess social support, and considering the caregiver’s burden is also advised (148).

Documented benefits of geriatric assessment

Over the last decades, the number of clinical studies incorporating GA in the assessment of older patients with cancer has substantially increased. The main focus of conducted studies has been to investigate the ability of GA to predict outcomes of cancer treatment, GA’s influence on treatment decisions and the feasibility of performing GA. As a consequence of the rapid development and growing body of knowledge in the field, several systematic reviews and summary papers have been published over the last decade (146, 180, 220-223). However, due to variations in assessed domains, the numerous tools applied (120, 125), the absence of a uniform frailty definition and the lack of standardised cut-points for impairments, there is great heterogeneity in geriatric oncology research. Studies included in these recent reviews exhibit inconsistency in sample size, clinical setting, cancer diagnosis, GA domains evaluated, GA tools applied, definitions of frailty and/or impairments and outcomes assessed. This hampers comparisons between the studies and also makes extrapolation of documented evidence challenging.

Nevertheless, the reviews provide strong evidence that GA can predict outcomes of cancer treatment, lead to changes in treatment plans, and serve as the basis for non-oncological interventions (146, 180, 220-223). For example, multiple studies have shown that GA can

predict adverse outcomes of cancer treatment such as chemotherapy toxicity (52, 125). In addition, frailty (137) and certain GA domains (nutrition, functional level, comorbidity, and mental health) are associated with increased mortality (57, 148, 180, 222). Moreover, GA can identify patients with increased risk of postoperative complications and mortality after colorectal surgery (224, 225). A few studies have investigated the association between impaired individual GA domains and/or frailty and PROMs, and found a negative impact on QoL, physical function and symptom burden (226-229).

Furthermore, there is evidence that GA can alter oncological treatment decisions, and that performing GA in an oncology setting is feasible (221). In a review published by Hamaker et al. in 2022, the authors found that the pre-planned oncological treatment was altered in a median of 31% cases based on the GA, which for the majority (73%) involved less aggressive treatment (223). Interestingly, in some cases the treatment was altered to a more ambitious regimen, indicating that some older patients may be undertreated. GA can also lead to better shared decision-making and improve patient satisfaction (230). Moreover, performing a systematic assessment can uncover age-related conditions that may have remained unrecognised in a routine oncological workup (128). This is important knowledge since several of these conditions may be modifiable, and thus could be treated or optimised to prevent further decline. A systematic review reported that non-oncological interventions were suggested for a median of 72% of patients after GA, most frequently aiming at optimising polypharmacy, comorbidities, nutritional status and social support (223). Having a pre-defined treatment plan for uncovered impairments (GAM), can increase the number of patients receiving non-oncological interventions (231). Moreover, there is emerging evidence from recently published RCTs that GAM may reduce chemotherapy toxicity in older patients without compromising OS, and that problems related to falls and polypharmacy may be prevented (119, 232).

Knowledge gaps relevant for this thesis

Older patients, and in particular patients with age-related health problems such as comorbidities and functional impairments, are often excluded from clinical trials (133-135). Moreover, the majority of studies investigating the potential benefits of GA in oncology have been performed on older patients primarily treated with systemic cancer therapy and cancer surgery (146, 180, 220-223) In 2018, the year after inclusion in our study started, the first systematic review that specifically evaluated the use of GA in patients undergoing RT was published. Due to the paucity of evidence, the authors were unable to draw any coherent conclusion about the benefits of GA in an RT setting (233). There are few studies investigating the prevalence of age-related health problems, and their impact on older patients' tolerance and outcomes of RT. This is disturbing, as an estimated 50-60% of all patients with cancer will require RT at some point during their disease trajectory (234, 235).

RT is a localised treatment that is generally well tolerated compared to other cancer treatment modalities (235), but it is unknown whether this also applies to older and frail patients (236, 237). Does treatment intent or age-related health problems impact patients' perceptions of RT outcomes, i.e. PROMs such as QoL and functioning? In other oncological treatment settings, frailty, defined by various methods, has been associated with adverse outcomes (10, 137). However, in real life frailty represents a continuum with a gradual declined resilience to stressors. Whether an increasing degree of frailty is associated with a corresponding deterioration in PROMs during RT has been scarcely investigated. In the absence of treatment guidelines for older adults, this knowledge is important to avoid both over- and undertreatment.

Finally, older adults are underrepresented in trials investigating CRCI, and most studies in this field exclude patients with pre-existing neurocognitive disorders such as MCI (110). Except for research on patients with childhood cancer and primary CNS tumours, there are few studies investigating the potential impact of undergoing RT on cognitive abilities (238, 239). Existing evidence suggests that older patients with cancer may be at particular risk of experiencing a decline in cognitive function during the disease trajectory (110, 111), but whether this applies to patients treated with RT remains unclear. MMSE is commonly used to assess cognitive function in geriatric oncology, and there is, for instance, robust data for the association between MMSE and chemotherapy toxicity (125). However, MoCA is a recommended (124), although less frequently used, alternative, which may be more sensitive when in identifying patients with MCI (207).

Aims and objectives

The main objective of this thesis was to investigate the prevalence of age-related health problems and the development in cognitive function, in a cohort of older patients with cancer receiving RT with curative or palliative treatment intent, and to assess the impact of age-related health problems on OS, QoL and physical function.

Paper 1

1) Estimate the prevalence of geriatric impairments and investigate if GA results differed between patients receiving RT with curative and palliative intent.
2) Investigate the association between GA domains and OS, and compare OS between patients receiving RT with curative and palliative treatment intent.
3) Explore differences in OS according to the accumulated number of geriatric impairments.

Paper 2

1) Assess differences in trends in patient-reported global QoL and physical function between groups defined according to treatment intent and the number of geriatric impairments.
2) Explore if there were groups of patients following distinct trajectories in global QoL and physical function.

Paper 3

1) Estimate the prevalence of cognitive impairment by comparing patient´s baseline MoCA scores to Norwegian normative data.
2) Investigate the association between baseline MoCA scores and factors assumed to impact cognitive function in older patients with cancer.
3) Describe the development in cognitive function during the course of RT aiming to identify groups with distinct MoCA score trajectories.

Materials and method

Study design

To answer the research aims, we conducted a single-centre prospective observational including older patients with cancer referred to RT with curative or palliative treatment intent. Age-related problems were evaluated, and patients answered self-report questionnaires, at five different time points during the observation period. The study represents a collaboration between the Research Centre for Age-related Functional Decline and Disease and the RT unit at Gjøvik Hospital, Innlandet Hospital Trust, and the municipal health services in Innlandet County. Innlandet County constitutes the RT unit´s catchment area, with approximately 370,000 inhabitants living in 48 different municipalities. Before initiating recruitment, 41 of these municipalities committed to participate in the study and to perform patient follow-up assessments. The RT unit at Gjøvik Hospital offers external beam RT delivered with modern techniques including IMRT (but not VMAT) with curative intent to patients with breast, prostate and lung cancer, in addition to some selected skin cancers, whilst palliative RT is provided for all types of cancer.

Inclusion criteria

Patients were eligible for inclusion if they fulfilled the following criteria:

- Age ≥65 years
- Referred to RT with curative or palliative treatment intent at the RT unit, Gjøvik Hospital, Innlandet Hospital Trust
- Resident of Innlandet county
- Histologically verified cancer diagnosis
- Fluent in oral and written Norwegian
- Able to understand and answer self-report questionnaires
- Provide written, informed consent

Patient recruitment

Together with the summoning letter to the first radiation oncologist consultation, potentially eligible patients received a flyer with brief information about the study. After the first consultation at the RT unit, patients whom the treating radiation oncologist confirmed met the inclusion criteria were approached by a study nurse, i.e. a cancer nurse committed to the study, or a Ph.D. candidate, i.e. the author of this thesis. These patients received oral and written information about the study before they were formally asked to participate. After

providing written informed consent, included patients underwent baseline assessments either the same day or during their next scheduled appointment at the RT unit, usually the first day of irradiation. Potentially eligible patients who were not enrolled, were registered with age, diagnosis, and one of the following reasons for non-inclusion: the patient did not want to participate, did not fulfil the inclusion criteria, was considered too sick or was not included for other reasons (e.g. absent study nurse, change in treatment plan).

Data collection

Sociodemographic and medical data were obtained through patient interviews performed by the study nurse or the Ph.D. candidate at enrollment, supplemented by information from the treating radiation oncologist and the patient's electronic medical record. Cancer diagnosis was registered according to the ICD-10 classification system and categorised as breast, prostate, lung or other type of cancer, and the TNM classification was used for staging. RT treatment intent (curative or palliative) was registered as defined by the treating radiation oncologist, and the RT regimen, including field, dose and fractionation, was noted. ECOG PS was categorised from 0 to 4, and dichotomised 0-1 and 2-4. Previous and concurrent cancer treatments were registered. At inclusion, patients underwent what we refer to as a *modified* GA (mGA), since it was performed by specially trained health care personnel, not a multidisciplinary team. The mGA included the following nine domains: comorbidities, medications, nutritional status, mobility, falls, ADL, IADL, cognitive function and depressive symptoms, assessed by using recommended and validated scales. The baseline (T0) mGA was repeated at RT completion (T1), two (T2), eight (T3) and sixteen (T4) weeks after RT. T0 and T1 assessments were performed by the study nurse or the Ph.D. candidate at the RT unit. Subsequent mGAs were conducted by municipal cancer contact nurses who visited patients in their current residence. At the same five time points, patients filled out the EORTC QLQ-C30 version 3.0 (95), and NEADL (191). At T0 and T1 these questionnaires were distributed to patients at the RT unit, and the follow-up questionnaires were sent by mail together with a prepaid return envelope. Patients received a reminder if no answer was obtained within one week. There were some per-protocol exceptions from the aforementioned assessments. First, patients who received only a single radiation fraction did not undergo any assessments or answer any questionnaires at T1, as we did not expect changes in outcomes in such a short time. Second, exceptions were made for some assessments at T1 for patients receiving less than ten fractions. Third, patients recruited from one of seven municipalities in Innlandet

County/the catchment area that did not commit to participate in the study, did not undergo mGA at T2, T3 and T4. Please see Table 3 for an overview of data collection.

Table 3 Overview of data collection

Sociodemographic and medical data							
Domain		**Baseline (T0)**	**RT completion (T1)***	**RT completion (T1)****	**Weeks after RT**		
					2 (T2)	**8 (T3)**	**16 (T4)**
Sociodemographic data		x					
Medical data, including former cancer treatment and planned RT regimen		x					
Medical data, including actually received RT			x	x			
Medical data, including ongoing cancer treatment, hospital and nursing home admissions.					x	x	x
Height (only baseline) and weight.		x	x	x	x	x	x
Modified geriatric assessment (mGA)							
mGA domains	**Method/tool**						
Comorbidity	Charlson Comorbidity Index (CCI)	x					
Medications	Number of regular medications	x	x	x	x	x	x
Mobility	Timed Up and Go (TUG)	x		x	x	x	x
Falls	Number of falls in the last six months	x			x	x	x
ADL	Barthel Index	x		x	x	x	x
Nutritional status	Mini Nutritional Assessment Short Form (MNA-SF)	x	**only weight**	x	x	x	x
Cognitive function	Montreal Cognitive Assessment (MoCA test)	x		x		x	x
Depressive symptoms	Geriatric Depression Scale-15 (GDS-15)	x		x		x	x
Patient-reported outcomes							
QoL, functions and symptoms	EORTC QLQ-C30	x	x	x	x	x	x
IADL	NEADL	x		x	x	x	x
mGA feasibility							
Time spent, completion rate, benefits and inconvenience (patient/nurse)					x	x	x

Green marking; baseline assessments. Yellow marking; follow-up assessments * Patients receiving ≥2 and <10 radiation fractions (patients receiving only a single fraction had no assessments at T1); ** Patients receiving ≥10 fractions. Abbreviations: RT, radiotherapy; ADL, Activities of daily living; IADL, Instrumental activities of daily living.

Modified table from study protocol published at clinicaltrial.gov (240); reprinted with permission from Marit Slaaen.

Modified geriatric assessment (mGA) tools and definitions of geriatric impairments

Comorbidity

Comorbidity was registered using the Charlson Comorbidity Index (CCI) (161) based on information provided by the patients, and supplemented by their electronic medical records. The CCI was originally developed to predict one-year mortality among hospitalised patients with breast cancer (237). We used the ICD-10 version which includes 17 comorbidities, and each condition was scored according to a weighted scale (241). Cancer was considered the index disease for all patients included, thus no points were given for malignancy or metastasis, unless the patient had a second cancer. CCI scores range from 0 to 26, with higher scores indicating more comorbidities, and were not age-adjusted. We set the cut-point for impairment at ≥2, which is consistent with recommendations when the index disease is grave and carries a high risk or death (161).

Medications

Medications were registered according to the Anatomical Therapeutic Chemical (ATC) Classification System with codes and dosages. The use of five or more regular medications is a common definition of polypharmacy (162, 166), and in line with others, we used this as cut-point for impairment (230).

Nutritional status

We used the Mini Nutritional Assessment Short Form (MNA-SF) to evaluate nutritional status (182). The questionnaire was completed based on information about the patient´s food intake, weight loss, psychological status and mobility, in addition to the objective measure of BMI (weight [kg]/ height² [m]). MNA-SF is a sensitive screening tool for malnutrition, which has been validated in geriatric populations (242). MNA-SF is scored from 0-14, and the summarised score is divided into the following categories: 14-12 (normal nutritional status), 8-11 (at risk of malnutrition) and 7-0 (malnourished). Similar to others (230), we chose to include all patients at risk of malnutrition when defining impairment in this domain and set the cut-point at ≤11.

Physical function, functional status, and falls

Mobility: To assess patients´ mobility we used Timed Up and Go (TUG) (193). TUG has been found to predict falls and mortality among older patients with cancer (243, 244). The test is

simple, does not require any expensive equipment, and has high inter-rater reliability (185). TUG is performed with the patient sitting down in a chair and it evaluates the number of seconds it takes for the patient to get up, walk three meters at a normal pace, walk back and sit down again. The mean number of seconds of two subsequent tests is noted. The cut-point for impairment on TUG was set at ≥14 seconds since the same definition has been used in previous research where patients received similar instructions (230, 245, 246), i.e. to perform the test at a normal walking pace.

Basic activities of daily living (ADL): Patients filled out the Barthel ADL-index (189) which assesses basic self-care abilities, such as eating, showering, getting dressed and fecal-and urinary continence. To obtain a full score on each of its ten items, the patient would have to be totally independent in performing the activities. Scores range from 0 to 20, and higher scores indicate a higher level of independence. As any ADL dependency is considered an impairment according to ASCO guidelines and is highly associated with frailty (124), the cut-point for impairment was set at <19.

Instrumental activities of daily living (IADL): Patients' functional ability in IADL was assessed by self-report on NEADL (191). NEADL comprises 22 items and covers mobility in kitchen, domestic and leisure activities. Each item is scored from 0-3 according to the patient's capacity to perform the activity (0 = not able to, 1 = with help, 2 = independently with difficulties, 3 = independently). Item scores are summarised in a scale ranging from 0 to 66, and higher scores denote better function. The estimated minimal important difference in NEDAL score is crude, and varies from 2.4 to 6.1 (247). We therefore chose to define the most conservative estimate of 6 points as clinically significant. Similar to others, we considered NEADL score <44 as an impairment, which would correspond to a patient responding by managing all activities independently with difficulties (224).

Falls: Patients were asked to state the number of falls experienced during the last six months. It is estimated that 30-40% of the population aged 65 years or older will experience at least one fall annually (200). Similar to others, we therefore defined having experienced ≥2 falls over the past six months as an impairment (245, 246).

Cognitive function

Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA), which was developed to screen patients with mild cognitive complaints (207). MoCA assesses the following cognitive domains: visuospatial abilities (2 points), naming of objects (3 points),

attention and concentration (6 points), language (3 points), abstraction (2 points), working memory (5 points) and orientation to time and place (6 points). Scores are summarised ranging from 0 to 30, with higher scores indicating better function. Patients with educational level ≤12 years were assigned one extra point up to maximum score of 30 (207). To define a cut-point for impairment, we chose to use normative data from a cognitive healthy Swedish population aged 65-85 years, showing that scores were highly dependent on age and education (no extra points for education ≤ 12 years were assigned) (248). We divided our cohort into two age groups, and determined the cut-point for each group by applying the mean Swedish population score minus 2 SD for people in the corresponding age groups who completed secondary school:

For those 65-75 years: mean MoCA 26.7 minus 2 SD (26.7- (2 x 2.1) ≈23): Cut-point ≤ 23; and for those >75 years: mean MoCA 26.0 minus 2 SD (26- (2 x 2.6) ≈ 21): Cut-point ≤ 21. These cut-points were used for the analyses in Papers 1 and 2, whereas for Paper 3, we used age-, gender- and education-matched normative data from a Norwegian population that had just been published (109). In Paper 3, impairment in cognitive function was defined as MoCA scores 1SD below the normative mean, as recommended (109, 113, 249).

Depressive symptoms

Patients reported depressive symptoms on the Geriatric Depression Scale-15 (GDS-15) (216), which has been validated in geriatric populations (250). Scores range from 0 to 15, and higher scores indicate more symptoms. To identify impairment according to GDS-15, it should be noted that various cut-points have previously been applied (214). As our purpose was to capture patients with depressive symptoms, indicating vulnerability within this domain, we chose a relatively low cut-point at ≥5, in accordance with previous studies (124, 251).

Table 4. Overview of mGA tools and cut-points for geriatric impairments

mGA domains	Assessment tool	Rated by	Scores and range	Interpretation	Cut-points for impairment
Comorbidity	CCI	Patient/ Nurse	0-26	Higher score = more comorbidities	≥2
Medications	Registration of regular medications by ATC[a] system	Nurse	Number of daily medications		≥5
Nutritional status	MNA-SF	Nurse	0-14	Higher score = better nutritional status	≤11
Mobility	TUG	Nurse	Number of seconds		≥14
Falls	Registration of number of falls last six months	Patient	0-1 or ≥2 (dichotomised)		≥2
ADL	Barthel Index	Patient	0-20	Higher score = better function	<19
IADL	NEADL	Patient	0-66	Higher score = better function	<44
Cognitive function	MoCA	Nurse	0-30	Higher score = better function	65-75 years ≤23 >75 years ≤21
Depressive symptoms	GDS-15	Patient	0-15	Higher score = more depressive symptoms	≥5

[a] Anatomical Therapeutic Chemical Classification System. Abbreviations: CCI, Charlson Comorbidity Index; MNA-SF, Mini Nutritional Assessment short-form; TUG, Timed Up and Go; ADL, Activities of daily living; IADL Instrumental activities of daily living; NEADL, Nottingham Extended Activities of Daily Living, MoCA Montreal Cognitive Assessment; GDS-15, Geriatric Depression Scale-15.

QLQ-C30

The QLQ C-30 questionnaire was specifically developed for self-reporting of outcomes in patients with cancer. It is widely used in clinical research, and the Norwegian translation has been validated (93, 252). Moreover, QLQ-C30 has documented responsiveness on repeated assessments (93). The QLQ-C30 includes a total of 30 items and is composed of scales assessing global QoL (2 items), physical (five items), emotional (four items) role (two items), cognitive (two items), and social (two items) functioning. Higher scores on these scales imply better global QoL and functioning. There are also three symptom scales assessing fatigue (three items), nausea and vomiting (two items) and pain (two items), and six single items assessing dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties. Higher scores on these symptom scales/items represent more symptoms. All items are scored from 1 (not at all) to 4 (very much), except for the global QoL items, which are scored from 1 (very poor) to 7 (excellent). Before statistical analyses, scale/item scores are linearly transformed to scores ranging from 0 to 100. Missing QLQ C-30 items were handled and imputed according to instructions provided in the official manual (253). A clinical significant change in any scale/item, was defined as a difference ≥10 points (254).

Predefined outcomes

The primary outcome in Paper 1 was overall survival (OS) defined as the time from inclusion to death, or to the last observation date maximum two years after RT completion. In Paper 2, the primary outcomes were global QoL and physical function (PF), patient-reported using the QLQ-C30. Secondary outcomes were IADL function reported by NEADL, role function (RF), fatigue and pain assessed by QLQ-C30. Paper 3 has an explorative approach where MoCA scores and the prevalence of cognitive impairment identified by MoCA were the outcomes.

Statistics

In all papers, categorical data were described with frequencies and percentages and continuous data with means and standard deviations (SD). Mean scores for mGA domains were presented and compared between groups by independent sample t-test, χ^{2-} test, or ANOVA, as appropriate. All tests were two-sided, and p-values below 0.05 were considered statistically significant. The statistical analyses were pre-planned and published at clinicaltrials.gov (Papers 1 and 2) (240). Analyses were performed in IBM SPSS Statistics 26 (IBM Corp. Armonk, NY), SAS v9.4 (SAS Institute, Cary NC) and STATA v16 (Stata Corp. College Station, Texas).

Missing single values in MoCA (n=1), the Barthel Index (n=6), and NEADL (n=20) were imputed if at least half the scale had been answered. The imputation was performed by generating an empirical distribution for each item based on non-missing values, and a random number drawn from it was used to replace the missing value. There were 19 patients with missing TUG due to inability to perform the test. In the regression analyses, where TUG was used as a continuous variable, TUG was inverted and patients were assigned the value 0, i.e. they used indefinite time. To estimate the prevalence of geriatric impairments, patients who were unable to perform TUG were classified as having an impairment in the mobility domain.

In the first paper, unadjusted and adjusted Cox proportional hazard regression models were estimated to investigate the association between OS and individual GA domains (CCI, medications, MNA-SF, TUG, falls, NEADL, MoCA and GDS-15). Factors selected for adjustment were age, gender, diagnosis group (categorised into breast, prostate, lung, and other type of cancer) and treatment intent (curative or palliative). Correlation analyses between mGA domains, the aforementioned adjustment variables and ECOG PS, were performed prior to the regression analyses. Because a high correlation between TUG, NEADL, Barthel Index and ECOG PS was identified, Barthel Index and ECOG PS were

excluded from the adjusted model. Since ECOG PS is an established mortality predictor in oncology, we wished to investigate if mGA could add prognostic information to ECOG PS. For this purpose we estimated an explorative Cox regression model where ECOG PS substituted all mGA domains in the model described above. The predictive abilities of the two adjusted Cox regression models were compared with a C-index. OS was presented using Kaplan-Meier curves, and compared between patients with different RT treatment intent and groups defined according to number of geriatric impairments using the log-rank test.

In the second paper, we assessed differences in trends in PROs between groups defined according to 1) treatment intent and 2) number of geriatric impairments by estimating two linear mixed models. All questionnaires completed at T0, T1, T2, T3, and T4 were used, and due to repeated assessments, random effects for patients were included to control for within-patient correlations. Both models included fixed effects for (non-linear) time, and the first model for treatment intent and interaction between time and treatment intent. The second model included fixed effects for groups defined according to the number of impairments, and interactions between time and the groups being compared. Both models were adjusted for age, gender, diagnosis group, and ECOG PS. In addition, adjustment for treatment intent was done in the model comparing groups defined according to number of impairments. Results from unadjusted linear mixed models were illustrated as estimated mean values with corresponding 95% confidence intervals (CIs) at each assessment point.

In the third paper, a publicly available MoCA score calculator (249) was used to compare patients´ baseline MoCA scores to recently published Norwegian normative data (109). The MoCA calculator estimates the person´s Z-score, i.e. the number of SD from the mean normative score, based on age-, gender- and education-matched controls. MoCA scores more than 1 SD below the normative mean were defined as cognitive impairment (249). Unadjusted and adjusted linear regression models were estimated to assess the association between baseline MoCA scores and predefined factors of potential influence on cognitive function among older patients with cancer. These predefined factors were carefully chosen based on review of relevant literature, and included previous cancer treatment, RT treatment intent, brain cancer/brain metastases, fatigue (reported on QLQ C-30) and number of physical impairments (Barthel Index, NEADL, falls, TUG and MNA-SF). We adjusted for the following factors known to affect cognition: age, gender, educational level, comorbidity, medications and depression. Spearman´s roh identified no multicollinearity issues among variables included in the models.

For explorative purposes, we investigated if there were unobserved groups of patients following distinct trajectories in global QoL and PF (Paper 2) and MoCA scores (Paper 3) by estimating growth mixture models. This was done to identify patients with distinct outcome trajectories, if present. For these analyses, a difference in MoCA score ≥3 (10%) points was considered clinically significant (255). The optimal number of groups was determined using Bayes information criterion where a smaller value indicates a better model. Reasonable group size, average within-group probabilities larger than 0.8 and non-overlapping 95% CI for trajectories had to be present. For the MoCA trajectories, two identical growth mixture models were estimated for sensitivity analyses. The first model excluded patients who died during the 16 weeks follow-up, and the second only included patients who completed MoCA at all time points.

Ethical considerations

This study was conducted in accordance with ethical guidelines in the Helsinki Declaration, and approved by the Regional Committee for Medical Research Ethics South East Norway. The study was registered and the protocol was published at clinicaltrials.gov (NCT03071640) (240). Before consenting to study participation, all patients were informed that they at any time could withdraw from the study without giving a reason and without consequences for their further treatment and follow-up. At inclusion, all patients provided written informed consent.

Competence to consent is an important concern in medical research when targeting a vulnerable group, i.e. older patients with a severe condition such as cancer. Since it is possible to have cognitive impairment and still have competence to consent (256-258), cognitive impairment was not an exclusion criterion in this study. Eligibility was initially evaluated by the treating oncologist before any study assessments were performed. Later, if the result of the baseline MoCA test raised serious concerns about the patient's competence to consent (total MoCA score ≤18), the treating radiation oncologist was specifically asked to re-evaluate this. Due to the observational study design, the treating radiation oncologist was otherwise blinded regarding the mGA results. Exceptions were made only if assessments revealed previously unrecognised severe health problems. In such cases, a pre-prepared manual with advice for further actions was followed if the patient agreed. All study assessments at the hospital were conducted during otherwise scheduled appointments at the RT unit to minimise the additional burden of participating in the study. For the same reason, study registrations after RT

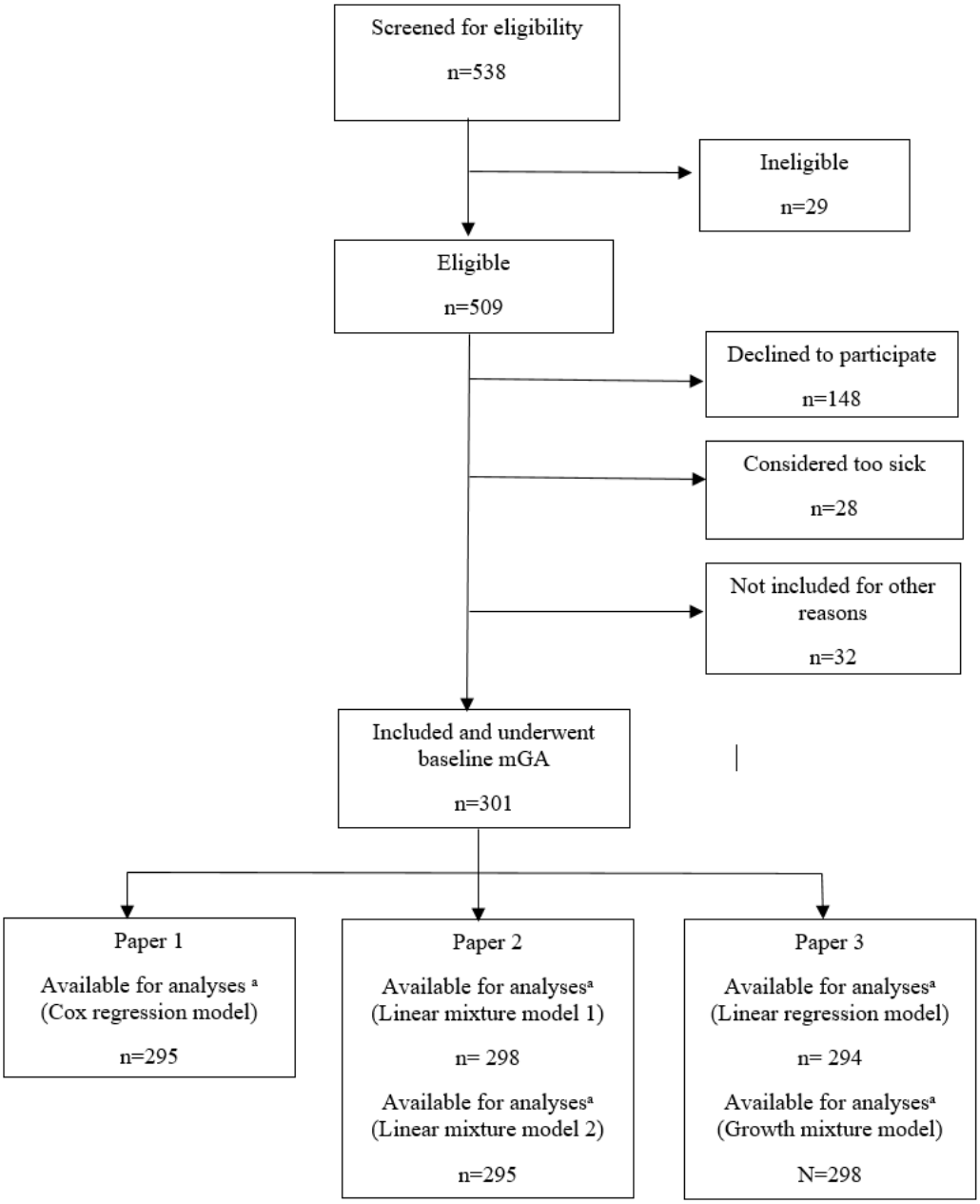
completion were performed in the patient's current residence. Importantly, participating in the study did not involve any intervention or specific risks of harm.

The study was funded by Innlandet Hospital Trust, and received no external funding.

Main results

Study recruitment

From February 2017 to July 2018, 509 patients ≥65 years referred to RT with curative or palliative treatment intent were found potentially eligible, and 301 (59.1%) were consecutively recruited (Figure 4). Among the 40.9% non-included patients, 148 (29.1%) declined to participate, 28 (5.5%) were considered too sick, and 32 (6.3%) were not included for other reasons (e.g. absent study nurse or change in treatment plan).



[a] Patients with complete questionnaires and medical data included in the analyses. For further details, please see each individual paper (Appendixes Paper 1, Paper 2 and Paper 3).

Figure 4. Patient recruitment

Patient characteristics

Among included patients, 142 (47.2%) were women, the mean age was 73.6 (SD 6.3) years and the majority, 256 (85.0%), had ECOG PS 0-1 (Table 5). The most common diagnoses were breast (95 [31.6%]), prostate (73 [24.3%]) and lung cancer (65 [21.6%]), while 68 (22.6%) had other types of cancer (Table 6). RT with curative intent was given to 162 (53.8%) patients, while 139 (46.2%) were treated for palliative purposes. Only 58 (19.3%) patients had not received any pervious cancer treatment, while 173 (57.5%) been through cancer surgery, 80 (26.6%), had been treated with chemotherapy, 57 (18.9%) had received endocrine therapy and 39 (13.0%) had underwent RT. Moreover, 114 (37.9%) received concurrent systemic cancer therapy.

Table 5. Baseline patient characteristics

	Total N=301 (100%)	**Curative RT** N=162 (53.8%)	**Palliative RT** N=139(46.2%)
Age, mean (SD)	73.6 (6.3)	72.5 (6.1)	74.9 (6.4)
Gender, female, n (%)	142 (47.2)	92 (56.8)	50 (36.0)
Cancer type, n (%)			
Breast	95 (31.6)	82 (50.6)	13 (9.4)
Prostate	73 (24.3)	51 (31.5)	22 (15.8)
Lung	65 (21.6)	15 (9.3)	50 (36.0)
Other	68 (22.6)	14 (8.6)	54 (38.8)
ECOG PS, n (%)			
0-1	256 (85.0)	155 (95.7)	101 (72.7)
2-4	45 (15.0)	7 (4.3)	38 (27.3)
Stage, n (%)			
I	62 (20.6)	62 (38.3)	0
II	42 (14.0)	39 (24.1)	3 (2.2)
III	78 (25.9)	61 (37.7)	17 (12.2)
IV	119 (39.5)	0	119 (85.6)[a]
Distant metastasis, n (%)			
No	188 (62.5)	162 (100%)	26 (18.7)
Yes	113 (37.5)	0	113 (81.3)
Total radiation dose (Gy)			
Median (min-max)	40.0 (4.0-78.0)	45.5 (4.0-78)	30.0 (8.0-60.0)
Number of fractions			
Median (min-max)	14.8 (1-39)	17.8 (2-39)	10 (1-30)
Single fraction, n (%)	13 (4.3)	0	13 (9.4)
<10 fractions, n (%)	60 (19.9)	2 (1.2)	58 (41.7)
Previous treatment, n (%)			
Radiotherapy	39 (13.0)	2 (1.2)	37 (26.6)
Surgery	173 (57.5)	108 (66.7)	65 (46.8)
Chemotherapy	80 (26.6)	26 (16.0)	54 (38.8)
Endocrine	57 (18.9)	28 (17.3)	29 (20.9)
Other systemic treatment	28 (9.3)	2 (1.2)	26 (18.7)
None	58 (19.3)	27 (16.7)	31 (22.3)
Concurrent systemic treatment, n (%)			
No	187 (62.1)	105 (64.8)	82 (59.0)
Yes	114 (37.9)	57 (35.2)	57 (41.0)
Type of concurrent systemic treatment			
Chemotherapy	29 (9.6)	9 (5.6)	20 (14.1)
Endocrine	74 (24.6)	48 (29.6)	26 (18.7)
Other systemic treatment	30 (10.0)	8 (4.9)	22 (15.8)

[a]Six patients receiving palliative treatment were classified as having stage IV disease without the presence of distant metastasis, among whom four had glioblastoma and two had lymphoma. Abbreviations: RT, radiotherapy; SD, standard deviations; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gy, Gray.

Table 6. Diagnoses included in the category 'other types of cancer'

Cancer type	Frequency (n) Total n=68	Percent (%)
Oesophageal cancer	2	2.9
Gastric cancer	1	1.5
Colon cancer	7	10.3
Rectal cancer	5	7.4
Pancreatic cancer	1	1.5
Thymoma	1	1.5
Malignant melanoma	3	4.4
Other malignancies of the skin	10	14.7
Mesothelioma	2	2.9
Peritoneal cancer	1	1.5
Malignancy in soft tissue	1	1.5
Cervical cancer	1	1.5
Other female genital cancer	1	1.5
Kidney cancer	12	17.6
Bladder cancer	9	13.2
Brain cancer	4	5.9
Unspecified cancer in lymph nodes	1	1.5
Follicular lymphoma	1	1.5
Non-follicular lymphoma	3	4.4
Multiple myeloma	2	4.4

Survival

Median follow-up with respect to OS was 24.2 months, during which period 123 (40.9%) patients died. Among these, 13 (8.0%) and 110 (79.1%) received RT with curative and palliative intent, respectively. No patients died during RT, but within T2, T3 and T4, a total number of 13, 26, and 41 patients had died, respectively. For the entire cohort, the cumulative survival probability was 93.7% at one month, 88.7% at three months, 70.1% at one year, and 59.1% two years after RT.

QLQ-C30 and NEADL completion rates

At baseline, 298 patients answered both QLQ-C30 and NEADL, and were thus available for analyses (Paper 2). Accounting for deaths and per protocol exceptions (259), the QLQ-C30 completion rates at T0, T1, T2, T3 and T4 were 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) and 89.9% (231/257).

MoCA completion rates

The MoCA completion rates, when accounting for per-protocol exceptions and deaths, were 100% (298/298), 81.3% (195/240), 72.7% (186/256) and 69.0% (167/242) at T0, T1, T3 and

T4, respectively. Per protocol, MoCA was omitted from the mGA two weeks after RT (T2) (Table 3). To avoid confusion, the reader should note that in the published paper (260), the naming of the four assessment time points is slightly different from what is used in this thesis, because MoCA was per protocol not performed at T2 (two weeks after RT).

Paper 1.

Estimating the prevalence of geriatric impairments and investigating the association between mGA domains and OS.

The majority, 246 (81.7%) patients, had at least one or more geriatric impairments, while 49 (16.3%) had no impairments (Table 7). Geriatric impairments were more frequent among patients receiving RT with palliative intent compared to patients treated curatively, with the mean number of impairments 3.0 (0-9) vs 1.0 (0-9), respectively.

Table 7. Groups defined according to the accumulated number of geriatric impairments, and distribution of impairments according to treatment intent.

No. of geriatric impairments	**Total** N=301 (100%)	**Curative RT** N=162 (53.8%)	**Palliative RT** N=139 (46.2%)
Median (min-max)	2.0 (0-9)	1.0 (0-9)	3 (0-9)
0, n (%)	49 (16.3)	41 (25.3)	8 (5.4)
1, n (%)	67 (22.3)	49 (30.2)	18 (12.9)
2, n (%)	50 (16.6)	28 (17.3)	22 (15.8)
3, n (%)	48 (15.9)	20 (12.3)	28 (20.1)
≥4, n (%)	81 (26.9)	23 (14.2)	58 (41.7)
Missing, n (%)	6 (2.0)	1 (0.7)	5 (3.6)

Due to the relative high correlation between several covariates, ECOG PS and Barthel Index were excluded from the main model (Table 8).

Table 8. A priori correlation analysis of mGA domains, adjustment variables, and ECOG PS.

Correlations		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Death	**1**	-0.25	-0.25	-0.41	0.09	0.56	0.26	0.36	-0.43	-0.44	0.20	-0.19	0.50	0.26
MoCA	**2**		0.41	0.47	-0.13	-0.29	-0.21	-0.35	0.24	0.50	-0.37	0.10	-0.21	-0.47
Bathel	**3**			**0.62**	-0.27	-0.31	-0.30	-0.45	0.36	**0.72**	-0.21	-0.01	-0.14	**-0.66**
TUG	**4**				-0.22	-0.42	-0.45	-0.55	0.43	**0.75**	-0.33	0.02	-0.26	**-0.63**
Falls	**5**					0.10	0.15	0.19	-0.10	-0.27	0.04	0.00	0.18	0.22
CCI	**6**						0.26	0.49	-0.31	-0.46	0.14	-0.25	0.40	0.34
GDS-15	**7**							0.35	-0.31	-0.50	0.13	0.03	0.16	0.37
Medications	**8**								-0.33	-0.58	0.19	-0.05	0.16	0.43
MNA-SF	**9**									-0.46	0.10	0.02	0.19	0.45
NEADL	**10**										-0.29	0.12	-0.33	**-0.73**
Age	**11**											-0.09	0.26	0.16
Gender	**12**												-0.44	-0.06
Canser type	**13**													0.16
ECOG PS	**14**													

Bold numbers indicate high degree of correlation.
Abbreviations: MoCA, Montreal Cognitive Assessment; TUG, Timed Up and Go; CCI, Charlson Comorbidity Index; GDS-15, Geriatric Depression Scale-15, MNA-SF, Mini Nutritional Assessment-Short Form; NEADL, Nottingham Extended Activities of Daily Livig; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

According to the unadjusted Cox regression model, all included mGA domains, except falls, had a statistically significant impact on OS. After adjustments, the domains nutritional status (MNA-SF) (HR 0.90, 95% CI [0.81; 0.99], p=0.038) and IADL (NEADL) (HR 0.98, 95% CI [0.95; 1.00], p=0.027) remained independently associated with OS. There was a significant interaction between treatment intent and cancer diagnosis. In the curative intent group, patients with lung and other types of cancer had significantly higher mortality risk than patients with breast and prostate cancer.

According to both the adjusted and unadjusted explorative Cox regression models where ECOG PS replaced all mGA domains, having ECOG PS 2-4 was significantly associated with reduced OS. The C-index for the adjusted explorative model was 0.843 (95% CI [0.812; 0.874] compared to 0.867 (95% CI [0.80; 0.893], p=0.33) for the main adjusted model including all mGA domains.

The OS was significantly different between curative (mean 24.8 months, 95% CI [24.2; 25.4]) and palliative patients (11.0 months, 95% CI [9.5; 12.5], p=0.001). There was also a significant difference in OS between patients with 0, 1, 2, 3, and ≥4 geriatric impairments (p<0.001), and an increasing number of impairments was associated with reduced survival

Paper 2.

Global QoL and PF in relation to the accumulated number of geriatric impairments

Results of unadjusted and adjusted linear mixed models assessing the trends in PROs stratified by treatment intent, showed that patients treated with curative intent reported statistically and clinically significant better overall mean scores for global QoL, PF, NEADL, RF, fatigue and pain compared to palliative patients (all $p<0.001$). We identified a statistically significant non-linear trend in several outcomes when comparing curative and palliative patients, but none represented a *clinically* significant change.

Baseline QLQ-C30 and NEADL scores showed a gradual worsening from the group with no geriatric impairment having the best global QoL and functioning and most symptoms, as compared to the group with four or more geriatric impairments having the worst scores on all scales. Unadjusted and adjusted linear mixed models showed that these differences persisted during the course of RT, and none of the groups with 0, 1, 2, 3 or ≥4 impairments experienced a clinically significant change.

The growth mixture model analysis identified four groups, i.e. a poor, fair, good, and excellent group, of patients following distinct trajectories for both global QoL and PF with non-overlapping 95% CIs and clinically significant differences in mean baseline scores. For both global QL and PF, the poor group had the overall worst scores, the excellent group had the overall best scores, and the fair and good group had scores in between the two. We observed that for both global QoL and PF, all four groups had relatively stable trajectories with no clinically significant change over time. For both outcomes, the proportion of patients having ECOG PS 2-4 and receiving RT with palliative intent was highest in the poor group, and decreased to the fair and good groups to the lowest proportion in the excellent group. In addition, the proportion of patients with several accumulated impairments decreased from the poor group to the excellent group.

Paper 3.

Estimating the prevalence of cognitive impairment by comparison to normative data and factors associated with cognitive function and its trajectory during the course of RT

Among the 298 patients available for analyses, baseline mean MoCA score was 24.0 (SD 3.7). Compared to age-, gender-, and education-matched cognitive healthy Norwegians, 113 (37.9%) patients had MoCA scores more than 1 SD below the normative mean indicating

cognitive impairment. Among these 113 patients, 61 (20.5% of the total cohort) had scores more than 2 SD below the normative mean.

Age, education level, comorbidity, number of daily medications, depression, the number of physical impairments, fatigue and RT treatment intent were significantly associated with baseline MoCA scores according to the unadjusted linear regression model. After adjustments, higher number of physical impairments (RC -0.82, 95% CI [-1.16; -0.48]) and increasing age (RC -0.13, 95% CI [-0.19; -0.07]) remained independently associated with lower MoCA scores, whereas college/university as compared to compulsory education was associated with higher MoCA scores (RC 2.41, 95% CI [1.50; 3.33]).

The growth mixture model identified four groups of patients following distinct MoCA score trajectories, i.e. very poor (n=19, 6.4%), poor (n=24, 8.1%), fair (n=113, 37.9%) and good (n=142, 47.7%) with high average group probabilities and non-overlapping 95% CIs. The poor and the good group had relatively stable trajectories. In the fair group, we registered a clinically significant (≥3 points) improvement in MoCA scores from baseline (T0) to 16 weeks after RT. A transient decline in MoCA scores from baseline to eight weeks after RT was registered in the very poor group, followed by an improvement 16 weeks after RT. In the very poor group, the proportion of patients with advanced age, higher number of physical impairments, comorbidities and daily medications was highest and gradually decreased to the poor, fair and good group.

The first sensitivity analysis excluding all patients who died within 16 weeks follow-up reproduced the results of the main growth mixture model. The second sensitivity analysis, including only patients who completed MoCA at all time points (n=113), also identified four groups with distinct trajectories; however, the very poor group only consisted of n=2 patients. This demonstrates that the improvement observed at T4 in the very poor group in both the main model and the first sensitivity analysis, could be attributed to these two patients only. Patients who did not complete MoCA at the last assessment had characteristics indicating generally poorer health status compared to completers, e.g. they received palliative RT, had more physical impairments and more fatigue.

Discussion

Methodological considerations

In order to critically review the methods of the current study, the following questions will be addressed: Was the study design suitable to answer the research questions? Were the appropriate patients included, and are they representative, in this case for older patients with cancer undergoing RT in general, or did any selection bias occur (external validity)? Furthermore, were the assessments and choice of outcomes appropriate, i.e. did we measure what we intended to or were there any bias or limitations that threaten the validity of our results (internal validity).

Study design

In collaboration with municipalities in Innlandet County, we conducted a single-centre, prospective observational study including a cohort of older patients with cancer receiving RT. The chosen design can be referred to as a cohort study, which per definition follows participants over time to study the relation between exposure and an observed event (261). In contrast to the RCT, an observational cohort study cannot provide definite evidence of causality, but merely describes ***associations*** between exposure and the observed event. A randomised design allows for a stringent control of confounding factors, i.e. factors that are associated with both the exposure and the outcome (262), whereas the observational design does not. Our aim, however, was to *observe* and *describe* the natural development of age-related problems and global QoL, including patient-reported functioning and symptoms, during exposure to curative or palliative RT.

Furthermore, we aimed to investigate *associations* between predefined (independent) variables and observed changes in outcomes (dependent variables). Based on the present evidence, one might argue that a randomised trial investigating the effect of GAM would have been more relevant. However, at the time the study begun in 2017, the documented benefits of GA in oncology were not as convincing as today (146, 220, 222). In particular, studies implementing GA in an RT setting at the time were, and still are, scarce, as highlighted in a systematic review by Szumacher et al. published in 2018 (233). We therefore concluded that a study describing the use and impact of GA in an RT setting was warranted, and consistent with the discussion above, we determined that a prospective observational study would be the appropriate design.

However, one might question whether our study was strictly observational. Although performing GA is not routine in Norwegian RT units and the treating radiation oncologists were blinded for the mGA results, they were all aware of the study objectives and contributed by screening patients for eligibility. This may subconsciously have increased the oncologists' focus on typical geriatric problems in patient consultations. Moreover, the municipal cancer contact nurses who performed the follow-up mGA assessments, all received a pre-prepared manual with advice for actions if previously unknown severe health conditions were uncovered during the patient assessment. This was necessary for ethical reasons, and although we believe that the impact on study results was negligible, we cannot rule out that this, as well as the contact with the cancer nurse per se may have influenced patients' trajectories, in particular outcomes such as global QoL and symptoms.

Applying a design that included involvement of municipal cancer contact nurses outside of their normal routines, may thus represent a study limitation. We do, however, regard this as a strength and a potential source of future benefits. By delegating the follow-up testing to the municipal cancer contact nurses, the patients did not have to travel to the hospital for the study assessments. This clearly diminished patients' burden and distress, and may have prevented dropouts. Moreover, cancer contact nurses in a range of municipalities were trained in performing a GA, skills that may be useful in the management of patients in the future, both in patients with cancer and other older patients. Collaboration in research may also strengthen the associations between specialists and primary health services in other areas directly related to the care of individual patients, which has been defined as a political goal by Norwegian authorities (263).

Study cohort

Study cohort, limitations, and representativeness

Our objective was to include a non-selected cohort of older patients with cancer referred to curative or palliative RT, i.e. real life patients. Therefore, the inclusion criteria were broad and there was no defined exclusion criteria.

We chose to include patients aged ≥65 years, and this cut-point can be disputed for two reasons. First, setting a strict age-limit may seem somewhat contradictive, since the whole point of implementing GA is that chronologic age is a poor marker for biologic age and functional reserves. For a research project, however, strict and easily applicable criteria are needed to evaluate eligibility. Second, it may be argued that our age-limit was too low. The question is whether being 65 years or older coincides with the age at which most patients are

likely to benefit from a thorough assessment of typical age-related health problems. The EORTC (150) and a consensus paper on GA in oncology (153) operate with a recommended cut-point of 70 years. SIOG did not include a specific age limit in their original guidelines (148), but in the updated recommendations for a geriatric screening for all patients with cancer ≥ 70 years is encouraged (151). However, this age limit has been debated, arguing that those younger than 70 years with age-related concerns should also be referred to GA (153). Moreover, our cut-point is in line with several studies addressing GA using 65 years as an inclusion criterion (222). There are robust data for GA in patients aged ≥ 65 with regard to predicting outcomes. Additionally, this age limit is recommended in ASCO guidelines (124), and in several countries, including Norway, age 65 years is a common for retiring and denotes a transition in life (131). Adding that RT is regarded as a good treatment alternative for older patients who due to general health conditions cannot undergo cancer surgery or systemic cancer treatment (235), we find that our age limit was appropriate.

Our decision to include patients receiving RT with both curative and palliative intent is also debatable. As generally acknowledged and demonstrated in our cohort, the majority of patients in a palliative setting have distinctively different health statuses from those who receive potentially curative treatment. We found that the latter group on average were younger, had better ECOG PS, better global QoL, fewer symptoms, and better survival (Papers 1 and 2). Still, when embarking on the study, we considered that our aims were equally relevant for both groups.

The distinction between what can be characterised as curative and palliative treatment has become increasingly blurry as a result of treatment advances (80). Potentially curative treatment may now be offered in situations that previously were regarded as definite palliative (264). For aggressive cancers, such as lung and pancreatic cancer, however, potentially curative treatment is often followed by rapid recurrence with short survival as a consequence (80). On the other hand, modern treatment has led to improved survival, and patients in some palliative situations may live for several years (73). Assessment, management and impact of geriatric impairments may therefore be just as important for these patients as for those receiving treatment with curative intent. Our study seemed to confirm this by showing that potentially remediable impairments were prevalent among patients receiving both curative and palliative RT, and that geriatric impairments influenced survival and patient-reported outcomes irrespective of treatment intent (Papers 1 and 2). Both groups may thus benefit from

GAM. Considering this, and adding that we appropriately adjusted for treatment intent whenever relevant, we find that the inclusion of both groups represented a study advantage.

Still, the inclusion of patients with a very short life expectancy, representing the majority of those receiving only one RT fraction, may be questioned. This subgroup primarily needs palliative care and the potential benefits of GA are likely to be small. Moreover, the burden of a single RT fraction is generally minor, and co-existing impairments are probably of little importance for prognosis. Consequently, pre-planned single fraction RT and survival expectancy less than three months were exclusion criteria in a subsequent RCT by our study group, evaluating the effect of GAM in an RT setting (265).

Although considered appropriate, the decision to include patients receiving palliative and curative treatment, clearly added to the heterogeneity of our study cohort, which consisted of patients with large variations in diagnoses, RT regimens and foregoing cancer treatment. Overall, this can be seen as a study limitation. Together with a restricted, although reasonably large study sample, our investigated outcomes might have been influenced by factors not accounted for in the analyses, and potential differences in outcomes between smaller subgroups could not be detected. To precisely assess the association between geriatric impairments, survival, global QoL, functions and symptoms in defined subgroups, inclusion criteria that are diagnosis, stage, and RT regimen-specific would have been necessary. However, we aimed at providing new knowledge of older patients routinely seen at an RT unit, which we considered a strength.

The question is whether we actually achieved a non-selected study sample. Overall, 40.9% of potentially eligible patients were not included. For a minority (6.3%) this was due to practical constraints occurring at random such as absence of the study nurse and represented no bias. The majority declined to participate (29.1%). Due to ethical restrictions by the Regional Committee for Medical Research Ethics South East Norway, we could not register their reasons for this. Consequently, we cannot rule out that the frailest patients were those most inclined to opt out. In addition, 5.5% were excluded as they were considered too sick; therefore, it is possible that we retained a cohort representing the fitter part of the eligible population. What we observed, however, was that several seemingly robust patients did not want to participate presumably due to lack of time or interest, or because participation was considered an additional burden in an otherwise distressing situation. We thus do not believe that selection bias seriously challenged the external validity of the study.

There is, however, another issue presenting a limitation to the generalisability of our results to other RT units, although it was not a selection bias. The group receiving curative treatment mainly consisted of patients with breast and prostate cancer (82%), a fair proportion of lung cancer (9.3%) and a remaining minor proportion of other cancers. This distribution reflects the curative irradiation regimens offered at the RT unit. Thus, we cannot extrapolate our results regarding the curative group to other cancer types.

In summary, we believe our broad inclusion criteria were appropriate for our aims and that the results from this study may be applicable to similar populations of older adults receiving RT in other treatment centres, with the limitations and reservations as discussed above.

Content of the mGA

Choice of mGA domain

Our mGA was based on a SIOG consensus paper from 2014 (148), and incorporated nine domains which were considered essential for GA in older patients with cancer. According to the same paper, social support should also be addressed, as it is obviously important for patient care. It was, however, not included in our mGA. Evidence supporting the use of specific screening questions or measures for this domain is lacking and social support is also not included as a domain in present ASCO guidelines (124). Furthermore, social support is connected to social frailty (266), a complex concept for which there is no general agreement on its position in frailty models, which criteria should be used or how these should be operationalised (267). Consequently, choosing a valid method to identify and define impairment within the social domain was hampered by insufficient knowledge.

Fatigue is another domain that was not included in our mGA despite being identified as a key component in physical frailty (13) and recommended by the SIOG consensus paper (148). A brief patient-reported measure of fatigue was available for our patients from the QLQ-C30, but due to the lack of an established cut-point, we chose to omit this from our identification of geriatric impairments. Moreover, fatigue is not included as a domain in other geriatric oncology guidelines (124, 150, 153). Instead, fatigue was treated as an outcome in Paper 2, demonstrating a relationship between an increasing number of impairments and increasing levels of fatigue. In addition, we included fatigue as an independent variable in the predictive model for baseline MoCA scores (Paper 3). Finally, we assessed only one of several suggested geriatric syndromes, i.e. falls (148). We chose falls because of the well-documented association with outcomes in older patients with cancer (6, 52, 202), and because it is

advocated in NCCN guidelines (149). Moreover, falls is incorporated in the Frailty Index, whereas other geriatric syndromes, such as delirium and incontinence are not (15-17). Furthermore, an important aspect of GA is that patients should be evaluated in their steady state (150), and a fall tendency is often a multifactorial and chronic problem that may reflect patients' habitual condition (202). Overall, however, the domains chosen for our mGA correspond to those suggested by Mohile et al. as part of a minimum dataset for GA (152), and are largely in line with other guidelines (124, 150).

Choice of assessment tools

According to the SIOG consensus paper cited above, several instruments and methods can be used to assess each GA domain, and none were endorsed above the other (148). Except for cognitive function, we chose instruments among the recommended alternatives that were familiar, relevant and convenient for the study. The instruments have been validated and tested, and are commonly used for similar purposes. Moreover, our chosen methods for assessment of comorbidity (CCI), mobility (TUG), nutritional risk (MNS-SF), depression (GDS-15) and medications (counting of regular medications) are identical to those stated as the tools of choice by Mohile et al. (152). As done in the present study, assessment of both ADL and IADL was recommended, but no specific instruments for this purpose was stated.

Despite being in line with recommendations, using CCI for comorbidity assessment may be discussed. Some common comorbid conditions such as hypertension, osteoporosis, atrial fibrillation and atherosclerotic and valvular heart disease are not part of CCI (161), but all (except osteoporosis) are part of the Frailty Index (15-17). It is possible that more comorbidities would have been captured if the comprehensive CIRS-G had been chosen (161). This highlights the importance of considering the method of assessment when interpreting prevalence of impairments and other results of GA. Moreover, it should be noted that our CCI scores were not age-adjusted. In the CCI validation study, the authors found that with time (ten-year follow-up), age became a significant mortality predictor. Thus, for studies with long observation times, it is suggested to add one point to the CCI score for each decade after 40 years (e.g. three points for a patient aged 70 years) (161, 268). Our study had a relative short follow-up, and in multivariable analyses, treating age as an independent variable is a preferable approach (161, 268). Therefore, we chose not to age-adjust the CCI scores.
To evaluate cognitive function, we used MoCA instead of MMSE, which has been the most frequently used tools in geriatric oncology (204). The primary reason for this, was that MoCA reportedly is more sensitive in identifying MCI in non-cancer settings such as in patients with

cerebrovascular disease (207, 269). This was considered an advantage, in particular as the study included repeated assessments. MoCA may detect changes over time (270), and in a study published in 2018, the superior sensitivity in capturing cognitive impairment was also demonstrated for older patients with cancer (255). Secondly, MoCA covers executive functions, whereas MMSE does not (271). Difficulties with executive functions are common complaints in patients with cognitive deficits in relation to cancer (111), and assessment of this domain was therefore highly relevant for our study population. Since our study started, MoCA has become an increasingly relevant tool, and is currently endorsed by several stakeholders in updated guidelines for geriatric oncology, including ASCO (124), NCCN (149), and it is recommended in a Young SIOG position paper (272).

Defined cut-points for geriatric impairments

To define geriatric impairments in each mGA domain, we used recommended cut-points if available, and otherwise leaned on commonly applied and previously used definitions as elaborated in the method section. However, some additional points should be considered.

To screen for malnutrition we used MNA-SF (182), which is an abbreviated version of MNA (273). The cut-point for impairment was set at ≤11, thereby including patients classified as malnourished and 'at risk'. MNA-SF is recommended for use in a two-step process where patients classified as 'at risk' should undergo the more comprehensive MNA to discriminate between the two entities and to confirm the diagnosis. In a mixed cohort of hospitalised and community-dwelling older adults classified as 'at risk' by MNA-SF, approximately 20% were likely to be false positives and 80% would be confirmed by the full MNA (182). Thus, it is possible that we may have overestimated the prevalence of malnutrition. However, since malnutrition is associated with poor outcomes in older patients with cancer and can be a progressive condition, early identification and management is essential (179). The significance of malnutrition was confirmed by our Cox regression analyses, where MNA-SF was used as a continuous variable and predicted OS. Hence, we find our chosen cut-point appropriate.

For the analyses in Papers 1 and 2, we defined cognitive impairment according to MoCA scores for two distinct age groups (65-75 years, and >75 years) from a Swedish normative population (248). These points oppose the originally suggested cut-point at <26 points for MCI (207). However, this limit has been widely disputed, as several studies have indicated that it is too high and that scores in addition to education may be dependent on cultural

aspects, age and gender (248, 271, 274-277). To identify cognitive impairment, the use of normative data from populations that are similar in this respect has therefore been advocated (113). To our knowledge, there were no available normative data for the Norwegian older adult (≥ 65 years) population when the analyses for Papers 1 and 2 were planned. Thus, we chose to use normative data from a population with cultural similarities. Unlike in our study, no extra points for education ≤12 years were assigned in the Swedish dataset, hence we chose to use mean values for those who had completed secondary school within the two predefined age groups. Gender was not taken into account as this affected the Swedish scores to a lesser extent than age and education. By applying these cut-points the estimated prevalence of cognitive impairment was 34.9% in the overall cohort.

When embarking on the analyses for Paper 3, a recent publication from 2022 (109) gave us the opportunity to use age-, gender- and education-matched Norwegian normative data for comparison. Using this approach, 37.9% of our cohort met the criterion for cognitive impairment, which is very similar to the results obtained by comparison to the Swedish dataset. In light of this, we believe our originally chosen cut-points in Papers 1 and 2 were appropriate. It could be argued that using two different methods to identifying cognitive impairment might be problematic; however, we do not think the small deviation in estimated prevalence (3.0%) significantly changes the results or the interpretations presented in Papers 1 and 2.

Summary remarks for mGA

We deliberately chose to abstain from using mGA to define frailty, for two main reasons. Firstly, a general principle in statistical analyses is that by combining several scales, and also converting continuous scales to categorical data, information is 'lost'. Reducing all the information entailed in the nine mGA domains to a threefold frailty category such as 'frail', 'vulnerable' and 'fit', or even dichotomising to 'frail' or 'non-frail', therefore seems counterintuitive. Secondly, in real life frailty represents a continuum with gradual decreased level in functional capacity, organ reserves and resilience to stressors. Therefore, we wanted to examine if the accumulated number of geriatric impairments was associated with the predefined outcomes.

Given the lack of a standard GA with respect to domains, instruments and cut-points, we believe our choices overall were appropriate. Nonetheless, we acknowledge that our approach is debatable, and that several domains could have been included. It is also possible that other

instruments might have been more suitable, and it could be discussed whether our cut-points truly captured the 'correct' patients. Thus, bearing the chosen methods in mind is essential when interpreting our results. Notably, none of the tests in our mGA are diagnostic per se, and in clinical practice the need for further investigations should always be considered.

Choice of outcomes and outcome assessments

In Paper 1 we defined OS as our primary outcome. It could be argued that we also should have reported disease-specific (i.e. cancer) survival. However, our study targeted older adults and aimed to assess how age-related vulnerabilities affected prognosis, not the cancer per se. We therefore believe OS was an appropriate survival measure. Nonetheless, it could be questioned whether survival is the most meaningful outcome for our study population. It is well known that older patients with severe illnesses may value preserved QoL, cognitive abilities and independency over small survival benefits (106, 226). Acknowledging this, we included outcomes that may be equally, if not more important from the patient's' perspective.

We used patient reports from the QoL construct QLQ-C30 to measure pre-defined outcomes in Paper 2. The use of PROMs gives direct insight into patients' experiences and provides a comprehensive perspective that could not be captured other than by asking the patient (278). QoL measures are highly relevant in clinical trials and in the care for patients with cancer, particularly when the survival benefit of a treatment is expected to be small (83, 86). In such cases, it is crucial to evaluate if the treatment positively or negatively influences patients' experiences of well-being, function and symptom burden. In our study, this applies to the patients treated with palliative intent for whom many had limited life-expectancy. It is also important to monitor experienced toxicity and overall well-being in patients treated curatively (90). There can be significant discrepancy between toxicities registered by health care personnel and patients' perceptions, and implementing self-reported measures of side-effects may prevent adverse events (279). Taken into account that QoL is a highly prioritised outcome for older patients and that QLQ-30 is a validated instrument, we believe the use of PROM and QLQ-C30 was appropriate.

We aimed to assess patients overall QoL, and therefore defined *global* QoL as a primary outcome. Another option might have been to use the QLQ-C30 summary score. The novel QLQ-C30 summary score was first presented around the time our study was planned, but was otherwise scarcely tested (280). Recent publications indicate, however, that the summary score holds more prognostic information than global QoL and any other scale of the QLQ-C30, and may therefore be relevant for future studies (281).

Patient-reported physical function by QLQ-C30 (i.e. PF) and IADL function by NEADL, were also primary and secondary outcomes, respectively, in Paper 2. Using self-reports for these outcomes may be questioned, since it has been reported that they may deviate from patients' objective performance (282), which could be a particular problem in patients with cognitive impairment. However, our aim was not to measure physical function and functional status per se, but to assess patients' perceived functioning. Performance tests typically evaluate only a single function (e.g. gait speed) and represent a 'picture of the moment'. By contrast, QLQ-C30 and NEADL ask the patient to contemplate the last week, and as a result, they can capture impairments occurring in the patients' habitual environment that are not necessarily present in a test situation (145). Thus, patient reports may be more appropriate in some cases, and patient-reported limitations in physical function is strongly correlated with reduced gait-speed (283). Moreover, self-reported physical limitations/reduced functioning is associated with survival (283), and can be equally as predictive as ECOG PS (284). Finally, patient-reported measures of physical functioning have similar psychometric properties, including validity, sensitivity to change and responsiveness as performance measures. Thus, both assessment methods are recommended in clinical trials (285, 286).

It could be argued that ideally IADL function should be observer-rated. However, NEADL was originally developed as a self-reported questionnaire (287), is referred to as such (145) (288) and is frequently used this way in clinical trials for practical purposes (282). Moreover, NEADL has documented responsiveness when patient-reported in non-cancer settings (289). Overall, we believe patient-reported PF and NEADL were adequate outcome measures given our study aims.

There are some additional aspects that should be considered when using PROMs in clinical trials. With repeated assessments, a response shift, i.e. a change in the meaning of a person's self-evaluation reflecting an adaption to the disease trajectory (290), can occur. In our material, however, this is likely to be of minor importance because of the short follow-up period, and the stability in PRO trajectories for all groups speak against this.

We did not assess specific RT toxicities, such as mucositis or oesophagitis. However, we believe the most important toxicities would have been captured by the QLQ-C30 global QoL and/or symptom scales/items. The National Cancer Institute has emphasised the importance of implementing PROMs in toxicity assessment for all patients with cancer, since such measures are useful in identifying needs for supportive measures and can improve symptom management, communication and patients' satisfaction (90, 291). Consequently, a PRO

version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (292, 293) was developed. The PRO-CTCAE covers the frequency, severity, interference and presence/absence of common symptomatic toxicities, such as nausea, pain and fatigue. Although there are six overlapping symptoms with good correspondence (294), PRO-CTCAE can, by no means, replace QLQ-30 which provides a more holistic perspective as a multidimensional construct for QoL assessment.

Cognitive function

Based on dismal consequences of cognitive impairment and the current paucity of knowledge on its prevalence and impact on older patients treated with RT, we wanted to explore patients' cognitive trajectories during RT and investigate if we could identify patients at risk of experiencing cognitive decline. We chose objective assessment of cognitive function, and not self-reports, which was available from QLQ-C30. A measure of self-reported cognitive function could have been relevant for Paper 3, as CRCI is characterised by a subtle decline in both subjective and objective cognitive function (110, 111). Patient-reported prevalence of cognitive decline during cancer treatment is often significantly higher than objective measures and is a topic of debate (116). However, this may be more relevant in younger populations, and cognition is not recommended for self-reporting based on SIOG guidelines (148). Since older adults with cognitive impairment and dementia may lack self-awareness, we concluded that an objective assessment would be the best approach. MoCA was chosen as the preferred instruments, because it is sensitive, responsive and assesses executive functions.

Repeated measures of MoCA were performed, and as a result of the study design only two different people (the study nurse and Ph.D. candidate) were responsible for assessments at baseline and at RT completion. The two remaining assessments were performed by allocated cancer contact nurses in the 41 participating municipalities. All test personnel received the same specific training in performing mGA in advance, including watching videos on how to conduct MoCA, and were also provided with written instructions. However, we cannot rule out that this relatively high number of test personnel may have influenced the interrater-reliability (94).

While performing MoCA, we noticed that some patients struggled on the trail making test, for instance, because they had left their reading glasses at home. Similarly, patients with impaired hearing had difficulties taking instructions. Interestingly, hearing loss was relative recently acknowledged as a risk factor for dementia in a Lancet Commission report (107), although the mechanisms behind this is still poorly understood (108). Moreover, it has been shown that

impaired hearing and vision may negatively affect MoCA scores (295). We tried to reduce this problem by providing glasses and hearing aid equipment.

Attrition

Attrition indicates a loss to follow-up, which can introduce bias as those who discontinue a study are often different from those who remain (295). Patients may die or drop out for other reasons, such as lack of motivation or time, intercurrent disease and change of residence. Attrition is relevant to discuss for Papers 2 and 3.

In Paper 2 we compared repeated measures of PROs between groups according to treatment intent and the number of geriatric impairments. Accounting for deaths and per protocol exceptions (259), the completion rates were good (100%-89.1% and 100%-89.9% for QLQ-C30 and NEADL, respectively). Patients receiving palliative treatment and those having several impairments were more likely to die during follow-up (Paper 1). Moreover, previous research on patients with cancer in a palliative setting indicated that those with poor functional status and QoL were more likely to drop out and not respond to PROMs (296). If this applies to our study, it is possible that we have registered a better level of reported outcomes for the palliative group, thus reducing the gap between the curative and palliative group. Additionally, when comparing groups defined according to number of geriatric impairments, it is possible that patients inclined to report poor scores disproportionally dropped out of the study. Hence, the answers obtained may be slightly skewed reflecting the 'fitter' part of our study population. However, we registered stable levels in outcomes for all groups, and similar results were obtained by the growth mixture model, which aimed to identify unobserved groups following distinct trajectories in QoL and physical function. Overall, we believe the results correctly reflect patients' experiences, however, the curves should be interpreted with caution.

In Paper 3, our trajectory analyses identified a small group (n=19) with overall poor MoCA scores with a seemingly transient decline at T3, before an improvement occurred at T4. We had no plausible explanation for this somewhat peculiar finding. Comparing baseline characteristics of MoCA completers and non-completers at T4 (Table 3, Paper 3), we found that the latter had poorer physical and cognitive health. We decided to investigate this further by performing two sensitivity analyses. Accounting for attrition, the results changed and showed that the improvement could be attributed to only two patients completing MoCA at T4, demonstrating the results for this group should be interpreted with the utmost of caution.

Confounding

Confounding is a type of systematic bias occurring when a third factor that influences both the supposed cause (exposure) and effect (outcome) is not accounted for. This is handled by adjusting for their effect in statistical analyses (262). It is paramount to think about confounding factors before study recruitment to ensure that appropriate data are collected (262).

We adjusted for established prognostic factors for OS (Paper 1) and variables known/presumed to impact QoL measures and physical function (Paper 2), including age, gender, cancer diagnosis, ECOG PS and RT treatment intent (40, 45, 49, 50), as appropriate. Correlation analyses between all variables included in the models were performed a priori. As discussed, ECOG PS was omitted in the predictive model for OS. In our opinion, we adequately addressed this issue by estimating an explorative model where ECOG PS replaced all variables in the Cox regression main model and compared the two models using a C-index.

In Paper 3, we assessed the relation between selected independent variables, including previous cancer treatment, treatment intent, cancer directly affecting the brain, fatigue and the accumulated number of physical impairments, and baseline MoCA scores. We adjusted for age, gender, educational level, comorbidity, medications and depression, which have been associated with cognitive impairment/dementia in previous research (107, 109-111, 116, 239). However, we recognise that important risk factors for cognitive impairment/ dementia, such as smoking status and alcohol consumption, were not accounted for (108). Additionally, relevant comorbidity such as impaired hearing, hypertension, hyperlipidaemia, and atherosclerosis were not captured by CCI (108). Of note, the analyses in Paper 3 were highly explorative as specified by study aims, and should be regarded as hypothesis generating.

Our study population was bound to be heterogeneous, which warranted pragmatic decisions when planning analyses. Furthermore, a limited sample size restricted the number of variables reasonable to include in regression models (297, 298). We therefore decided to use treatment intent as a proxy for cancer stage and to categorise cancer diagnoses. However, we recognise that both cancer stage and type of cancer may influence OS, global OoL and physical function to varying degrees. Moreover, RT regimens differed considerably in duration and total dosage, which may have influenced the outcomes. We believe the essence of this issue was captured by classifying patients according to treatment intent (curative/palliative), which was adjusted whenever relevant. Lastly, we did not register treatment response or disease progression during the follow-up. Due to the limited follow-up period with respect to QoL

and physical function, this is unlikely to have introduced bias. Given the material, and in light of our study aims, we believe our approach was the best option available.

Discussion of main results

Treatment intent and outcomes

Not surprisingly, we found that patients treated with curative intent had better OS compared to the palliative group. Treatment intent is a proxy for cancer stage, which is essential for prognosis in virtually all cancer types. Moreover, our results showed that patients treated with curative intent reported statistically and clinically significant better global QoL, PF and lower symptom burden at baseline. This is also in line with results obtained in other treatment settings (299). Since the main purpose of palliative irradiation is to alleviate symptoms and improve patients' well-being, we anticipated an improvement in PROs for this group, which did not occur. However, we did not register the precise RT indication and treatment goal, which could vary, and the study was not designed to capture effects in subgroups.

Prevalence of geriatric impairments

The most commonly impaired domains in the overall cohort were nutritional status (55.5%), polypharmacy (55.1%), cognitive function (65-75 years 33.3%, ≥75 years 39.0%) and comorbidity (27.2%). This is largely in line with a systematic review by Hamaker et al. across various oncological settings reporting a median prevalence of polypharmacy in 67% (range 48-74%), malnourishment 63% (range 37-80%), comorbidity 36% (range 11-64%) and cognitive impairment 26% (range 3-38%) (118). There are few studies reporting the prevalence of GA-based impairments performed specifically in an RT setting. However, one study by Goineau et al. assessing men ≥75 years receiving RT for localised prostate cancer, reported higher prevalence of comorbidities, depressive symptoms, and IADL and ADL dependency than we found in our curative group (264). A possible explanation for these differences is that patients receiving curative RT in our cohort were significantly younger (mean age 72.5 years, [SD 6.1]), and deficits are likely to increase with age. Direct comparison of percentages is, however, not meaningful since these are likely to depend on patient characteristics, tools and cut-points used.

The prevalence of geriatric impairments was significantly higher in the palliative group, and one may question whether this is due to age-related health problems, i.e. patient's intrinsic vulnerability, or related to advanced cancer and/or its treatment. Many patients had been through extensive previous oncological treatment including surgery, chemotherapy, endocrine therapy, and RT, and some received concurrent systemic treatment. The cancer disease per se and side effects of oncological treatment could have influenced geriatric domains such as

nutritional status (e.g. weight loss and anorexia), dependency in IADL (due to fatigue, pain or treatment burden/deconditioning) and polypharmacy (prescribed drugs for symptom management). However, we found that impairments were also common among patients with early stage cancer, i.e. treated curatively, where 17.3%, 12.3% and 14.2% had 2, 3, and ≥4 impairments, respectively.

Overall, 59.4% of patients in our cohort would have been classified as frail if applying a commonly used criterion for frailty, i.e. having two or more geriatric impairments (137, 141). This is largely in line with reports from studies in older patients with various types of cancer, disease stages and settings, where the overall prevalence of frailty was estimated to 43% (range 13%-79%) (137), but places our cohort among the most affected. The reason may be that some patients who are unfit for surgery and systemic cancer treatment are referred to RT, which is generally considered more tolerable (237). Given the high prevalence of impairments in our study, it is interesting that the radiation oncologists classified 85.2% as having ECOG PS 0-1. The discrepancy between this and the prevalence of impairments, is in accordance with previous work indicating that oncologist may be overly optimistic and overlook frailty in older adults (120).

To the contrary, 38.6% of the overall cohort had <2 impairments. It is therefore questionable whether it is necessary to perform GA for all older patients referred to RT. Performing a geriatric screening may be a better approach, where only patients with a positive screening undergo a full GA. This allows improved patient selection and rational use of resources, and is advocated by SIOG (151). There are several suitable screening tools available, for instance, G-8, specifically designed for use in older adults with cancer (300) and the VES-13 (29). For patients undergoing RT, a screening +/- GA could be performed simultaneously with the routine consultation for planning of RT, which usually occurs some days or even a few weeks before treatment initiation. This would provide a window of opportunity to implement targeted interventions (GAM) before RT, to enhance treatment tolerability. Ideally, GA-based interventions should continue during and after RT in accordance with the latest ASCO guidelines (124).

Cognitive function and associated factors

Applying the original cut-point at <26 for MoCA (207), 62.4% of our cohort met the criterion for MCI at basline. When comparing our material with Norwegian normative data, we found that 37.9% of the overall cohort had MoCA scores more than 1 SD below the age-, gender- and education-matched normative mean, which indicates cognitive impairment (109). Thus,

our results confirm that failure to account for age, gender, and education can lead to an overestimation of cognitive impairment. We consider this comparison to Norwegian normative data a considerable strength.

Comparisons of reported prevalence of cognitive impairment between studies in older patients with cancer are hampered by differences in methods, and as for the RT setting, studies assessing cognitive function are nearly non-existing (116). The estimated prevalence of cognitive impairment (37.9%) by our comparison to Norwegian normative data, is within the upper range reported in the systematic review by Hamaker et al. (118), but similar to the results of Mohile et al. in the GAP70+ study. They targeted older adults with advanced disease referred to systemic cancer therapy, and found that 36% had a positive cognitive screening (119). Moreover, we found that 20.5% of the overall cohort had MoCA scores more than two SDs below the normative mean, which is suspicious for dementia (109). Interestingly, only one patient had a diagnosis of dementia according to baseline CCI. This may indicate that cognitive impairment is an underdiagnosed problem among older patients with cancer (110, 119), and points to the importance of assessing cognitive function, which is not part of a routine oncological workup.

In line with other reports (110, 111, 113), we also found that executive functions, memory and attention were the cognitive domains most frequently impaired. MoCA may therefore be a suitable alternative to the frequently used MMSE, which does not assess executive functions.

We found that age, education level and number of physical impairments were independently associated with baseline MoCA scores. The relation between increasing age and lower education, and poorer MoCA scores has been well documented (109, 248, 275). The accumulation of physical impairments may indicate physical frailty (13), and the association between physical frailty and cognitive impairment has been widely confirmed (301-304). In accordance with previous reports, comorbidity, medications, depression and fatigue were significantly associated to cognitive function in unadjusted models (110, 112, 116, 239). As these associations disappeared in the adjusted model, it might be an indication that the association between MoCA and these factors is weaker than between MoCA and age, education and number of physical impairments.

Unlike two studies in community-dwelling Norwegians (109, 271), we did not find that MoCA scores differed between genders. However, the impact of gender may have been masked by other, more influential factors in our study, and the evidence for a gender

difference is conflicting (277, 305, 306). In contrast to established knowledge (307), we found no association between MoCA scores and cancer affecting the brain (primary tumour or cerebral metastases). This can most likely be explained by the very few patients in this subgroup in our cohort. As opposed to other studies, we did not find that previous systemic treatment or cancer stage (i.e.treatment intent) was associated with cognitive function (308, 309). However, since our cohort exhibited heterogeneity in cancer type and stage there is a corresponding variation in previous cancer treatment. We, like others, conclude that it is not possible to separate the effect of these parameters from each other (238).

Notably, our results do not provide information about the underlying causes for impaired MoCA scores. We cannot say whether the cognitive impairment is part of a progressive underlying neurocognitive disorder (e.g. Alzheimer's disease), reflects the impact of cancer and/or its treatment (i.e. CRCI), other factors not accounted for (e.g. distress) or a combination of all these factors. To capture the impact of cancer and/or its treatment, cognitive function should ideally be evaluated at the time of cancer diagnosis and reassessed during the disease trajectory. Also, it is important to emphasise that MoCA is a screening tool for cognitive impairment, and a positive result requires further diagnostic investigations.

Accumulation of geriatric impairments and impact on outcomes

We found that an increasing number of geriatric impairments was associated with a corresponding decline in survival. Interestingly, there was no obvious cut-point with regard to accumulated impairments where the OS seemed to deteriorate. Rather, we registered a steady and gradual decline. Moreover, patients reported gradually worse scores for global QoL, functioning, and more symptoms with increasing number of impairments, which persisted from baseline throughout follow-up. Notably, adjusting for potential confounders, including treatment intent, did not significantly change the results. Additionally, our explorative trajectory analyses confirmed that patients with several impairments and unfavourable prognostic traits reported worse global QoL and PF.

We are not aware of other studies assessing PROMs in relation to accumulated number of geriatric impairments. However, several studies in older patients with cancer have shown that frailty or geriatric deficits are associated with reduced QoL in terms of self-reported global QoL, functioning and symptoms (197, 228, 229, 310-312) and OS (128, 137, 225, 313). In an RT setting, there are limited studies reporting PROMs in older adults. Pottel et al. assessed older patients receiving curative radio(chemo)therapy for head and neck cancer, and found that patients who were vulnerable according to CGA or G-8 reported poorer QoL and had

poorer survival compared to those who were fit on repeated assessments up to 36 months after treatment (314, 315). Although comparison of QoL measures is challenging due to differences in assessment tools and patient populations, our results are largely in line with previous reports, indicating that specific impairments and frailty are significantly associated with poorer QoL.

Moreover, we believe our results in Papers 1 and 2 show that an increased number of impairments is associated with decreased survival, QoL and functioning, effectively demonstrate that frailty represents a continuum of gradually decreased resilience. This indicates that GA can contribute with highly relevant prognostic information in older patients undergoing RT, which may have several implications. Firstly, categorising patients as either frail, pre-frail or fit may not be an important objective per se. Rather, our results suggest that identifications of vulnerabilities at any stage of the continuous frailty scale may allow for targeted intervention that can prevent further decline, and thereby potentially improve outcomes. Therefore, uncovering specific impairments that can be ameliorated is essential.

Impact of individual geriatric impairments

According to our Cox regression model, where MNA-SF and NEADL scores were entered as continuous variables, nutritional status and IADL function were independent predictors of reduced OS. The association between malnutrition and poorer survival in older patients with cancer has been well documented (178, 179). Moreover, both impaired nutritional status and IADL dependency are strong predictors of reduced OS in patients with haematologic malignancies (316, 317).

Malnutrition, which is a underdiagnosed problem in patients with cancer (181), was the most commonly impaired domain in our study affecting more than 50%. We found that about 20% had IADL impairment, which is in line with some studies (145), whereas a systematic review reported a considerably higher proportion of 46% (range 38 – 65%) (118). The high prevalence and negative impact of compromised nutritional and functional status on OS found in our research and documented by others, points to the importance of recognising these impairments.

Research specifically assessing the impact of malnutrition on OS among older patients undergoing RT are scarce (233). In one retrospective study, where patients aged ≥60 years received RT for oesophageal cancer, the authors showed that high and moderate risk of malnutrition independently predicted poor OS (318). Another study included patients with

head and neck cancer treated with curative radio(chemo)therapy, and found that older patients who according to G-8 were vulnerable (cut-point ≤14), had significantly poorer survival compared to fit patients (314). Similarly, a recent prospective multicentre study by Middelburg et al. found that G-8 score ≤14 predicted survival in older patients with various types of cancer receiving curative irradiation (319). Interestingly, G-8 includes assessment of age in addition to seven questions derived from MNA (273). Thus, the two studies documenting an association between survival and G-8 seem to support our finding regarding the impact of nutritional status. Apart from these studies, however, we are not familiar with studies using GA or geriatric screening to predict OS in the RT setting, thus our study contributes with valuable knowledge. In other oncologic settings, malnutrition has also been associated with postoperative complications, increased use of health care services, and discontinuation of chemotherapy which may negatively influence prognosis and QoL (179, 180).

Malnutrition in older patients with cancer may have several underlying causes. The cancer per se can compromise intake of food due to nausea or oesophageal stricture for instance, and alleviating symptoms and treating the cancer may potentially improve the situation. Older patients have increased risk of mucositis which can compromise the alimentary situation. This is a highly relevant problem for patients undergoing RT (149, 320). Moreover, malnutrition may be related to other conditions occurring in older age, such as cognitive impairment, depression, polypharmacy and poor functional status that may cause inadequate intake of food (179). Intervening in these problems could potentially have a synergistic positive effect on nutritional status. There are indications that optimising nutritional status may improve quality of life, reduce radiotherapy toxicity and decrease post-operative infections in older adults (179). However, there is no evidence that nutritional interventions, such as dietary advice and nutritional supplements, provide a survival benefit for older patients with cancer (179). This may have several explanations including patient's selection (type and stage of cancer), and compliance to and intensity of the intervention. Another explanation may be that applied screening tools are not able to distinguish between 'at risk' and malnutrition, i.e. all patients with a positive screening are malnourished such as the problem is captured in an advanced stage, it may not be amendable (321). If this is the case, it supports our choice of using a sensitive tool such as MNA-SF and including patients 'at risk'.

The association between IADL function and OS is also documented in other oncological settings (198, 199, 322, 323). In our study, the importance of assessing IADL function was

further underlined by the explorative survival analyses showing that a model with mGA was superior to one with only ECOG PS in predicting OS. Thus, our result confirmed that ECOG PS alone provides limited information about functional status in older adults (51-53). IADL function is a multidimensional construct interconnected with physical and cognitive function and may be affected by comorbidities (145, 185, 187). This may explain why NEADL was highly correlated with several mGA domains. Similar to Middelburg at al., we did not find that physical performance (mobility evaluated by TUG) was associated with survival in patients treated with RT (319), although this has been widely confirmed in other oncological settings using various measures (146, 180, 324). Poor functional status is also related to other adverse outcomes including chemotherapy toxicity, poor QoL and further functional decline (52, 125, 198, 199). In radiation oncology, an association between IADL impairment and declining QoL during curative treatment for head and neck cancer was demonstrated in one small study by VanderWalde et al. (325).

As for functional status, the complexity of the IADL construct ideally warrants a multidisciplinary approach (145). Possible interventions include referrals to physical therapy and/or occupational therapy, prehabilitation, exercise programs with strength and balance training, home safety evaluation including fall prevention and considering the need for assistive devices (145, 326). Optimising physical function, comorbidity and polypharmacy may potentially improve IADL function; however, the effects of such interventions in older patients with cancer are scarcely documented (145). One RCT including patients ≥65 years with cancer and at least one functional limitation identified by NEADL were randomised to 'usual care' or individualised rehabilitation with an occupational or physiotherapist (327). The primary endpoint was NEADL scores, and the authors hypothesised that there would be no change in score for the intervention arm (preserved function) and a five-point decline for the control arm at follow-up after two to three months. However, both groups experienced a clinically significant decline, and the authors noted several barriers for implementation of the intervention, and further research is needed.

Comorbidity, which is a strong mortality predictor in older patients with cancer (54, 55), was not associated with OS in our analyses. A possible explanation may be that approximately 80% of all deaths occurred in the palliative group, where the cause of death is likely to be cancer-related, and thus competing risks were less relevant. Follow-up was limited to two years, which might be too short for competing risks of death to significantly impact survival.

Radiotherapy tolerance in relation to treatment intent, geriatric impairments and cognition

We found that groups defined both according to treatment intent and accumulated number of geriatric impairments mainly reported stable levels of global QoL, functioning and symptoms from pre-treatment to 16 weeks after RT completion.

Whereas some studies have documented an improvement in QoL measures among older patients with impairments/frailty during cancer treatment (229, 310, 311), others indicate a deterioration (314), and some reported stable levels (227, 312). In a study by Goineau et al. global QoL was repeatedly assessed by QLQ-30, and despite a high prevalence of geriatric impairments at baseline, more than 70% maintained global QoL two months after RT, and no impairments were predictive of a decline (328). This is largely in line with our findings. One study including 903 patients aged 18-92 years, investigated differences in symptoms and their impact on functional status and overall QoL during RT depending on age (329). Irrespective of age, patients reported a similar symptom burden before and after RT. Nonetheless, patients aged ≥65 years more frequently reported that symptoms interfered with walking, daily function and overall QOL after RT. However, frailty level and treatment intent were not accounted for in this study (329).

As for patient-reported physical function and functional status, we had expected to register a decline during follow-up for those with several geriatric impairments (i.e. frailty), which did not occur. This is in accordance with two studies assessing longitudinal development in patient-reported physical function in relation to frailty among patients treated with radio(chemo)therapy by Pottel et al. (315) and those undergoing cancer surgery by Rønning et al. (310). However, our findings contrast with a study conducted by Kirkhus et al. reporting that older frail patients experienced a significant decline in self-reported physical function during systemic cancer therapy compared to non-frail patients (227). One possible explanation may be that systemic cancer therapy is associated with more toxicity. Our results also differ from the study in patients with lung cancer by Decoster et al., where 98% had at least two impaired geriatric domains, and a significant decline in ADL and IADL was registered in 23% and 45%, respectively (330). Comparison of these studies, however, is hampered by differences in study cohorts and definitions of frailty/impairments. In line with our results, the abovementioned studies assessing frailty consistently reported that patients living with frailty overall had poorer physical function than non-frail patients.

The vast majority had stable MoCA scores during follow-up indicating that cognitive abilities were well preserved. However, in the four groups following distinct trajectories varying from good to very poor, we found a slight improvement in MoCA scores in the good and fair group. This may be related to distress before starting RT, but a potential learning effect cannot be ruled out, as the assessments were performed within relatively short time intervals, and we did not use parallel versions of MoCA. In the very poor group, a decline in MoCA scores followed by an increase was observed. These results must be interpreted with caution as they most likely are due to attrition bias. The proportion of patients receiving palliative treatment, having poor performance status and several impairments increased from the good to the very poor group. Thus, equal to the four groups with distinct QoL and PF trajectories, the groups with distinct MoCA trajectories represented a gradual decline from robust to frail. This finding is supported by research documenting an association between frailty and cognitive decline (302) to which patients with cancer may be particular vulnerable (111).

However, when interpreting our results, it is important to remember that our outcome measures represent mean values on a group level. There may be individuals with scores significantly deviating from the mean that are not captured by this approach (83). We therefore consider it a strength that we performed explorative analyses aiming to identify unobserved groups of patients following distinct trajectories in global QoL, physical and cognitive function. Moreover, we have defined a clinically significant change for the QLQ-C30 scales, NEADL and MoCA scores based on pervious recommendations (247, 254, 255), and for NEADL we chose the most conservative. Thus, it is possible that some patients may have experienced incremental outcomes that are meaningful although not presented as significant.

Overall, our results showed that being exposed to RT did not significantly change patients' perceptions of global QoL, physical function, functional status or their cognitive performance. This implies that geriatric impairments per se should not be a reason for withholding RT. Nonetheless, some of the most vulnerable patients, receiving palliative RT and having several accumulated impairments, had particularly poor outcomes and required special attention. For patients with very limited life expectancy, poor functional status and global QoL, the therapeutic goal of RT, should be considered in relation to the realistic outcomes and hazards involved for the patient. For painful bone metastasis, a single RT fraction of 8 Gy is a quick and easily administered treatment that can provide adequate symptom control within three to four weeks (331). It should probably be more broadly applied in palliative medicine, since it

is locally administered, efficient and cost-effective (80). For other indications requiring multiple fractions, it is questionable whether older patients with poor prognoses will profit from RT. Omitting RT and providing other palliative and supportive measures may be a better option, and early palliative care can improve QoL (332, 333). GA may be a useful tool for shared decision-making, and can improve communication and patient satisfaction (143, 230, 232).

Conclusions

- Compromised nutritional status and IADL function were independent predictors of reduced OS.
- An increasing number of geriatric impairments was associated with a corresponding gradual decline in OS.
- Patients treated with palliative intent reported significantly poorer QoL, functioning and more symptoms compared to curative patients.
- An increasing number of geriatric impairments was associated with a corresponding gradual and persistent reduced level of QoL, functioning and symptoms, indicating that frailty represents a continuum of increased vulnerability.
- Irrespective of treatment intent and number of impairments, the majority reported stable levels of QoL, functioning and symptoms during follow-up, indicating generally good tolerance to treatment.
- Patients treated with palliative intent and having several geriatric impairments reported overall poor levels of QoL, functioning and more symptoms. This group requires close follow-up and are in particular need of supportive measures.
- MoCA is a suitable tool for assessment of cognitive function in older patients with cancer.
- Increasing age, lower education and several physical impairment were associated with with poorer baseline MoCA scores.
- Comparisons to age-, gender- and education-matched Norwegian normative data, suggesting that the prevalence of cognitive impairment can be overestimated by using the originally suggested MoCA cut-point.
- Almost 40% had MoCA scores consistent with cognitive impairment, indicating that this is a common problem that should be addressed in older patients treated with RT.
- The majority had stable or slightly improved MoCA trajectories, except for a small group with very poor scores where attrition was high.

Implications and future perspectives

We have demonstrated that age-related health problems were frequent in older patients undergoing RT, and that GA performed in this setting holds important prognostic information. Our work thereby expands the current evidence for the predictive value of GA, which hitherto mainly has been documented in older patients treated with systemic cancer therapy and cancer surgery (146, 180, 221, 222). Since it is estimated that over 50% of patients with cancer will need RT at some point (234, 235), we believe this work contributes with valuable knowledge that may benefit patients in the future.

Compromised nutritional status and IADL function were independent predictors of survival. Early identification of impairments in these domains is pivotal since they are potentially amendable. Furthermore, almost 40 % had MoCA scores indicating cognitive impairment, which is unlikely to have been detected by a routine workup. Recognising cognitive impairment is essential because these patients may need social support and assistance with administrating medications, IADL and transportation. Moreover, by using GA in combination with PROMs, patients with poor trajectories in physical and cognitive function, functional status, and global QoL can be identified. The use of PROMs during the disease trajectory may facilitate open discussions about further oncologic and non-oncologic treatment strategies, including early palliative and supportive care (230). Summarised, our results indicate several benefits of implementing GA for older patients undergoing RT, in line with SIOG and ASCO guidelines (124, 148). However, a significant proportion of patients in our study were robust, which suggests that the use of a two-step model where only patients with a positive geriatric screening undergo a full GA is reasonable.

Despite great efforts of multiple stakeholders, there is still no standardisation of GA in terms of domains, assessment tool, and cut-points to define impairments/frailty. This hampers comparison across studies. A future consensus on these points is warranted. The significance of social support is an important area for future research in geriatric oncology, and a validated measure for systematic assessment of this domain is lacking. It is crucial that unmet social needs are routinely considered in the care for older patients as several interventions might be applied.

Nonetheless, there is solid evidence that GA is useful to identify needs for targeted non-oncologic interventions in older patients treated with chemotherapy or cancer surgery (146, 220-223). Results from four RCTs demonstrated that GA-based interventions, i.e. GAM, can reduce toxicity, enhance QoL, and prevent hospitalisations (119, 232, 334, 335). The gradual decline in survival, global QoL and physical function with increasing number of impairments observed in our study indicate that interventions at any stage of the frailty continuum may prevent further decline and possibly improve outcomes. However, such effects GAM in the RT setting remains to be shown.

By implementing GA up-front, i.e. at time of diagnoses, age-relate vulnerabilities could be intervened on before, during, and after treatment to enhance tolerability and improve outcomes. As frailty is a dynamic condition that may progress during cancer treatment, GA should ideally be repeated during the disease trajectory, for instance when considering a new treatment modality. However, despite the growing body of evidence documenting benefits of GAM, it has to a limited degree been implemented in oncology practice in many countries (336). There may be several obstacles including lack of time, resources or knowledge, and education in geriatric oncology is one of SIOGs main priorities (337). Several studies have documented that GAM is more likely to be effective if performed by a multidisciplinary team and/or if the interventions are pre-planned (223, 336). Although a geriatrician may not be readily available in all treatment centres, a multidisciplinary approach including a trained nurse, nutritionist, occupational therapist or physiotherapist may be beneficial. Furthermore, using standardised predefined non-oncologic interventions, such as those suggested in ASCO guidelines (124), may be feasible way to begin. Another key point for GAM to be effective is patient's adherence to the suggested interventions. As demonstrated in an RCT by Pergolotti et al. focusing on rehabilitation and IADL function, there may be multiple barriers such as time, costs, travelling distance and failure to see the value of the intervention (327). More research in this field is required, but involving local resources such as municipal cancer nurses and home health services could be a solution to overcoming some of these barriers.

Additionally, GA can guide oncologic treatment decisions and treatment adjustments for older patients with vulnerabilities (221, 223, 338). However, studies documenting a positive effect of such decisions in terms of improved (or non-inferior) survival are scarce. In our study, global QoL, physical and cognitive function were well preserved on group level, indicating that the majority had good RT tolerance. Geriatric impairments or frailty per se should thus not be reasons to withholding RT. Nonetheless, patients with several accumulated

impairments had overall poor survival and global QoL, and benefits vs. the total treatment burden should be carefully considered. Additionally, there are several ways RT could be adjusted to be more tolerable for patients living with frailty (339). Examples are withholding concurrent chemotherapy, using modern treatment techniques such as SBRT or VAMT to reduce toxicity (340), considering hypofractionated regimens for patients with poor functional status and long traveling distances (237, 339, 341), and using single fractions to alleviate pain from bone metastasis (331). Future studies should investigate if GA could be used for selecting patients to modified RT regimens to enhance QoL measures without compromising survival. Similar studies are also warranted for older patients treated with systemic cancer therapy and cancer surgery. One RCT in older patients considered for palliative chemotherapy found that if the oncologists were provided with the GA results and management recommendations before treatment initiation, this led to reduction in chemotherapy doses without compromising survival at 6 months follow-up (119). However, this study included patients with different diagnoses and chemotherapy regimens, and extrapolating these results to specific groups of patients is not possible. Ideally, RCTs including more homogenous study cohorts with similar cancer type and stage, and a longer follow-up is needed. An example is a study by Corre et al. where GA was used to allocate patients with NSCLC to carboplatin-based doublet for fit patients and docetaxel for frail patients, which failed to show an effect on survival (342). However, positive results from such studies in the future may allow for the development of diagnosis-specific guidelines with treatment recommendations according to frailty status. This is also likely to be a strong incentive for a broad implementation of GA in geriatric oncology. Used in combination with PROMs, GA can be a valuable tool for personalising the treatment and care for older patients with cancer.

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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

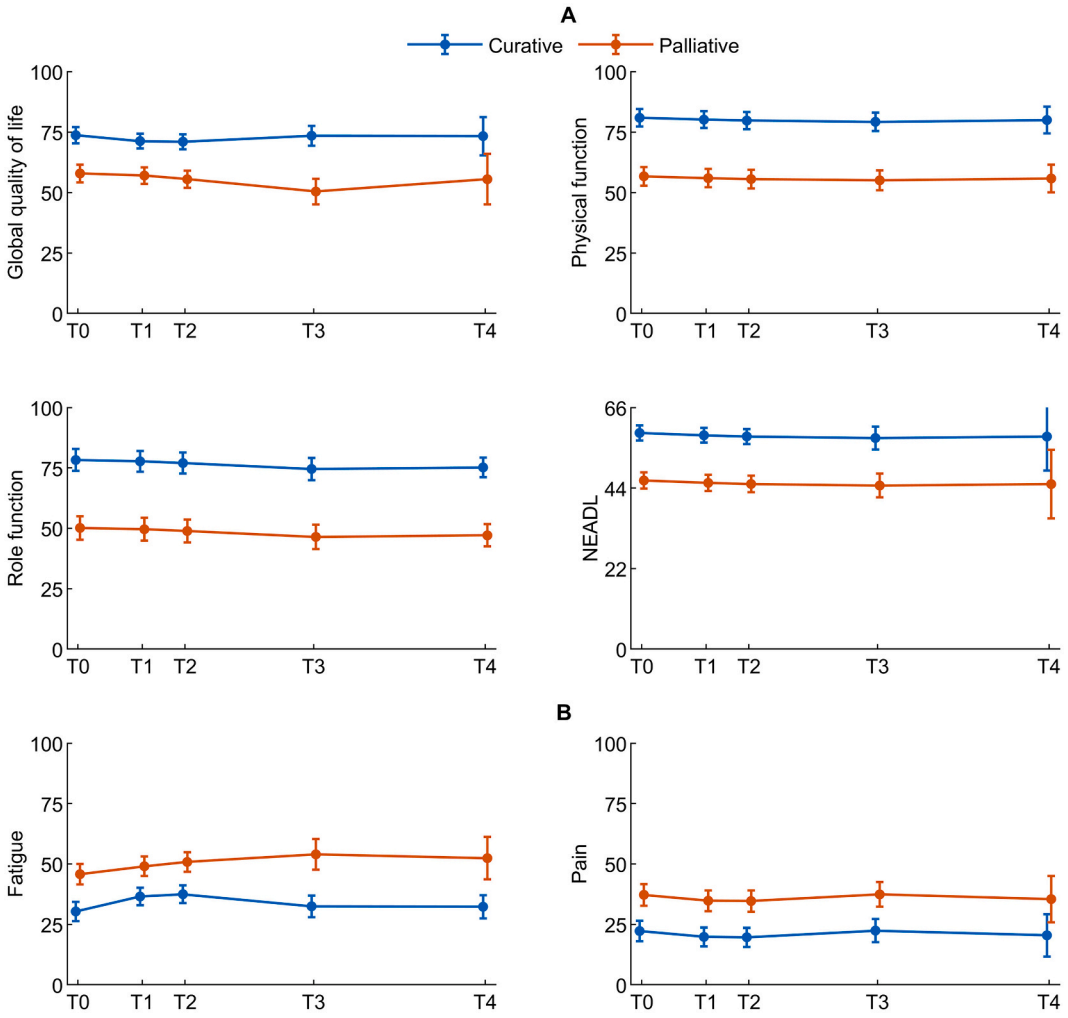

Fig. 1. Trends in primary and secondary outcomes for patients receiving curative and palliative radiotherapy (RT), unadjusted results of the linear mixed model. Abbreviations: NEADL, Nottingham extended activates of daily living. T0 = baseline, T1 = at RT completion, T2 = two, T3 = eight, T4 = sixteen 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.

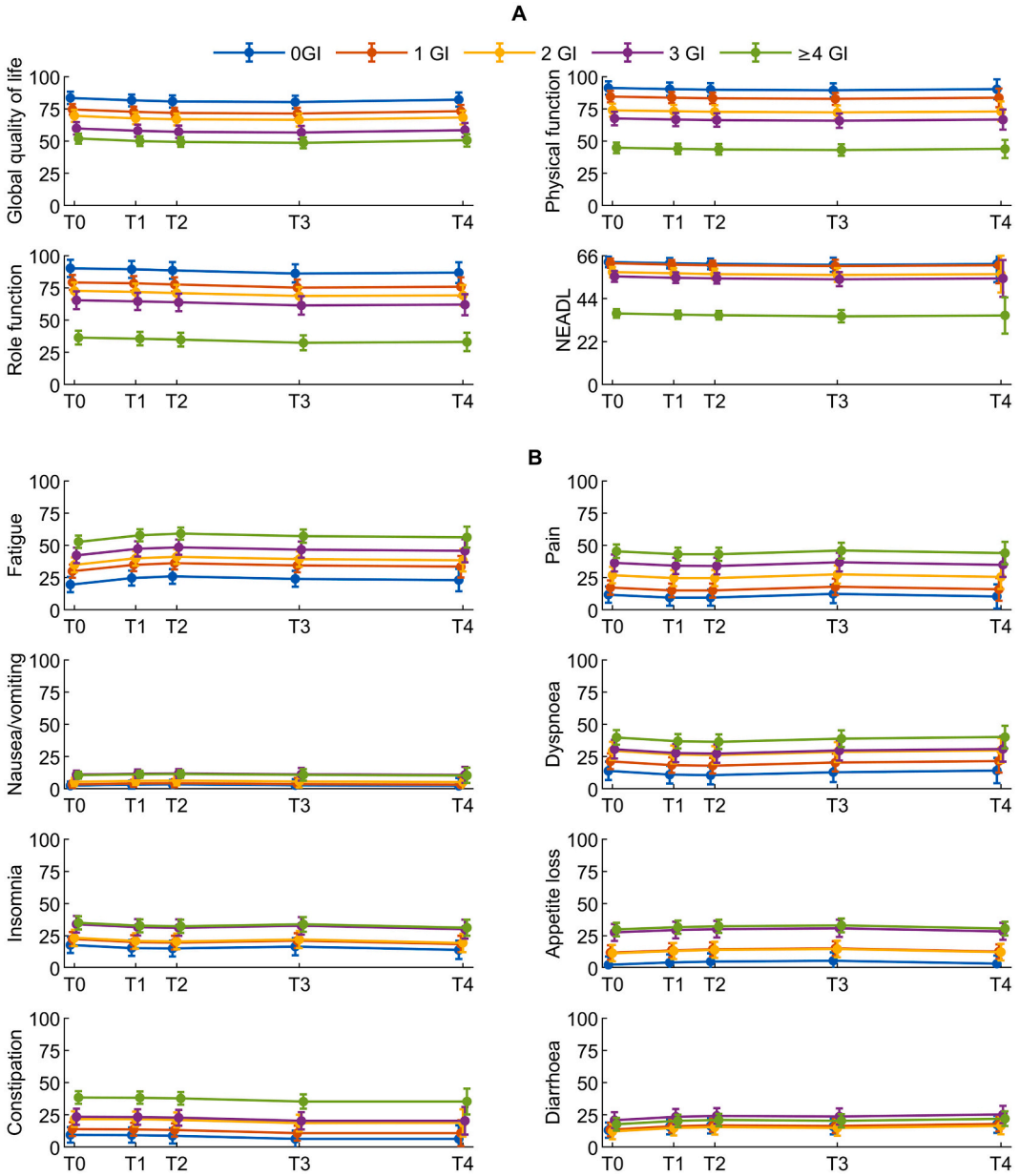

Fig. 2. Trends in primary and secondary outcomes, and symptoms depending on the number of geriatric impairments, unadjusted results of the linear mixed model. Abbreviations: GI, geriatric impairments; NEADL, Nottingham extended activates of daily living. T0 = baseline, T1 = at RT completion, T2 = two, 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 ≥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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III

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Cognitive Trajectories in Older Patients with Cancer Undergoing Radiotherapy—A Prospective Observational Study

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Abstract: Cognitive function can be affected by cancer and/or its treatment, and older patients are at a particular risk. In a prospective observational study including patients ≥65 years referred for radiotherapy (RT), we aimed to investigate the association between patient- and cancer-related factors and cognitive function, as evaluated by the Montreal Cognitive Assessment (MoCA), and sought to identify groups with distinct MoCA trajectories. The MoCA was performed at baseline (T0), RT completion (T1), and 8 (T2) and 16 (T3) weeks later, with scores ranging between 0 and 30 and higher scores indicating better function. Linear regression and growth mixture models were estimated to assess associations and to identify groups with distinct MoCA trajectories, respectively. Among 298 patients with a mean age of 73.6 years (SD 6.3), the baseline mean MoCA score was 24.0 (SD 3.7). Compared to Norwegian norm data, 37.9% had cognitive impairment. Compromised cognition was independently associated with older age, lower education, and physical impairments. Four groups with distinct trajectories were identified: the very poor (6.4%), poor (8.1%), fair (37.9%), and good (47.7%) groups. The MoCA trajectories were mainly stable. We conclude that cognitive impairment was frequent but, for most patients, was not affected by RT. For older patients with cancer, and in particular for those with physical impairments, we recommend an assessment of cognitive function.

Keywords: Montreal Cognitive Assessment; cancer-related cognitive impairment; geriatric oncology; cognitive function; physical impairment; frailty

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1. Introduction

Cognitive impairment is a frequent problem in older age. Among patients with cancer ≥65 years, approximately 3.8–7% have dementia [1], and cognitive impairment is reported in 36% of patients over 70 years with advanced cancer [2]. Over the last decade, there has been an increasing awareness of a condition referred to as cancer-related cognitive

impairment (CRCI) [3–7]. CRCI is characterized by a patient-reported and objectively measured cognitive decline presenting in relation to cancer and/or its treatment [4]. Several studies suggest that older patients with cancer, and especially frail older patients [8], are at particular risk of experiencing a decline in cognitive function during systemic cancer therapy [9–11]. This is concerning, as older patients with severe and life-limiting disease consider preserved cognitive function as one of the most important treatment outcomes [12].

CRCI has mainly been studied in women receiving adjuvant chemotherapy for breast cancer [4], and the phenomenon was for some time referred to as "chemobrain" [13]. More recently, it has been advocated that this term is misleading because the condition probably has a more complex underlying etiology [13]. In addition to issues that are common among patients with cancer and are known to affect cognitive function, such as comorbid conditions, polypharmacy, and depression, frequently occurring symptoms, including fatigue and treatment modalities other than chemotherapy, could also be important influencing factors [3,9,13,14]. There are indications that endocrine therapy can contribute to CRCI in patients with breast and prostate cancer and that immunotherapy and antiangiogenics can have a negative impact [3,7]. Except for research on patients with childhood cancer and tumors involving CNS [15], little is known about how radiotherapy (RT) affects cognitive abilities [6,7].

The assessment of cognitive function is not routinely performed in oncology practice. Hence, cognitive impairment may easily be overlooked [16,17]. Cognitive impairment can have several important implications. It can influence patients' treatment preferences, shared decision making, treatment adherence, the reporting of toxicities, and self-care abilities [18]. Therefore, the evaluation of cognitive function is an important part of a geriatric assessment (GA) and is recommended in all oncology settings [19,20]. The Montreal Cognitive Assessment (MoCA) test was developed as a screening tool to detect the symptoms of mild cognitive impairment (MCI) [21]. The test is sensitive when applied to older adults with cancer [22] and is a recommended by the leading organizations in the field [14,20,23–25].

We previously showed that the age-related health issues identified by GA impact overall survival, quality of life, and physical function in a cohort of older patients with cancer receiving RT [26]. In the present study, addressing the same cohort, our aim was threefold. First, we aimed to describe the prevalence of cognitive impairment by comparing patients' MoCA scores to Norwegian normative data. Second, we explored the associations between MoCA scores and predefined cancer-related factors assumed to have an impact on cognitive function. Third, we intended to study the development of cognitive function during the course of RT, seeking to identify groups with distinct MoCA score trajectories.

2. Materials and Methods

2.1. Patients

From February 2017 to July 2018, we conducted a prospective, single-center, observational study at the radiotherapy unit (RTU) of a Norwegian local hospital serving approximately 370,000 inhabitants [27]. Details about the study design, setting, and conduct have been described [26]. The inclusion criteria were referral for RT with curative or palliative treatment intent, age $\geq$ 65 years, histologically confirmed malignant disease, residence in the hospital catchment area, fluency in oral and written Norwegian, and a capacity to answer self-report questionnaires. The municipal home-care services in 41 of 48 municipalities in the hospital catchment area committed to allocate a designated cancer contact nurse to perform patients' evaluations during follow-up.

2.2. Assessments

Baseline sociodemographic and medical data were attained through patients' interviews, supplemented by their electronic medical records. The collected data included age, gender, educational level, Eastern Cooperative Oncology Group performances status (ECOG PS) (dichotomized 0–1 or 2–4), cancer diagnosis (grouped as breast, prostate,

lung, or other types of cancer), previous cancer treatment, RT regimen, and treatment intent (curative or palliative). Patients answered the European Organisation for Research and Treatment of Cancer Quality-of-Life Core Questionnaire version 3.0 (EORTC) (QLQ-C30) [28], which includes three items assessing fatigue. These items are scored from 1 (not at all) to 4 (very much), and before analyses, raw scores are converted to a fatigue scale ranging from 0–100 [29]. Higher scores indicate more fatigue. At baseline, patients underwent a modified geriatric assessment (mGA) [26], including an evaluation of comorbidities (Charlson Comorbidity Index (CCI) [30]) and polypharmacy (number of daily medications), depression (Geriatric Depression Scale-15 (GDS-15) [31]), and physical domains, i.e., nutritional status (Mini Nutritional Assessment Short Form (MNA-SF), scored 0–14 [32]), mobility (Timed Up and Go (TUG), measured in seconds [33]), falls (number of falls the last six months), basic activities of daily living (ADL) (Barthel Index, scored 0–20 [34]), and instrumental ADL (IADL) (Nottingham Extended Activities of Daily Living (NEADL), scored 0–66 [35]). Based on well-established and/or commonly used reference values, and as elaborated in a previous publication [26], cut points for impairment in physical domains were defined as Barthel Index score <19, NEADL score < 44, $\geq$2 falls the last six months, TUG $\geq$ 14 s, and MNA-SF scores $\leq$ 11 (at risk of malnutrition). For the purpose of the present paper, we summarized the number of physical impairments for individual patients. Cognitive function was assessed by the MoCA test [21], Norwegian version 7.1, as part of an mGA. The test takes about 10 min to complete and assesses cognitive functions with scores for the following items: visuospatial abilities, the naming of objects, attention and concentration, language, abstraction, working memory, and orientation to time and place [36]. All scores are summarized 0–30 points, with higher scores indicating better function. One extra point is added for persons with $\leq$12 years of education up to a max score of 30. A difference in MoCA score of $\geq$3 points (10%) is considered a clinically significant difference [22]. The MoCA test was applied at four time points: at baseline (T0), at RT completion (T1), and eight (T2) and 16 (T3) weeks after completing RT. Per the protocol, the T1 assessment was omitted for patients receiving $\leq$9 RT fractions. For these patients, the interval between T0 and T1 would be less than two weeks, which we considered too short to detect any clinically meaningful change in MoCA scores. The T2 and T3 assessments were not performed for patients residing in non-committing municipalities. A study nurse or a resident physician in oncology performed the tests at T0 and T1 at the RTU. Subsequent tests were performed by a municipal cancer contact nurse at the patients' current residences. All test personnel received the same specific training in addition to a manual with detailed scoring instructions. If the results of the tests at T2 and T3 were not received within a week after the scheduled assessment, the municipal cancer contact nurse received a reminder.

2.3. Statistical Approach

Our statistical approach was descriptive and explorative. Categorical data were described with frequencies and percentages, and continuous data were described with means and SDs or medians and min–max values. To compare characteristics between groups of patients, a Student's *t*-test, ANOVA, or χ^2-test was applied, as appropriate. Using a publicly available MoCA score calculator [37], the baseline MoCA scores were compared to Norwegian normative data from a population of community-dwelling adults aged $\geq$70, excluding those with a history of dementia, mild cognitive impairment, stroke, or depression [38]. The MoCA calculator provides the person's Z-score, i.e., the number of SDs from the mean normative MoCA score, accounting for educational level, age, and gender. MoCA scores more than 1 SD below the age-, education-, and gender-matched Norwegian norm were used to define cognitive impairment [37]. The patients included in the present study aged 65–69 years were, for these specific analyses, assigned the age of 70 years. For descriptive purposes, we also estimated the proportion of patients with MoCA scores below 26, which is the originally suggested cut point for mild cognitive impairment [21]. Unadjusted and adjusted linear regression models were estimated to assess the association between baseline MoCA scores and predefined cancer-related factors

of potential importance. These factors were previous cancer treatment (categorized as endocrine therapy, other systemic therapy (including chemotherapy), cancer surgery, and/or RT), RT treatment intent (curative or palliative, reflecting disease stage, brain cancer, or brain metastases), and fatigue (patient-reported on the QLQ-C30), in addition to a number of physical impairments (continuous 0–5 ADL, IADL, falls, mobility, and nutritional status). The model was adjusted for factors known to influence cognitive function, i.e., age, gender, educational level (categorized as completed compulsory ($\leq$10 years), secondary (11–13 years), or college or university ($\geq$14 years) education), comorbidity (CCI scored 0–26), medications (number of daily mediations), and depression (GDS $\geq$ 5) [3,4,6,7,38]. Only one patient had been diagnosed with dementia according to CCI. Hence, dementia diagnosis was not taken into account. Spearman's rho was calculated among all predefined variables. However, no multicollinearity issues were identified (Supplementary Table S1). A growth mixture model was estimated to identify unobserved groups of patients following distinct MoCA score trajectories. The optimal number of groups was determined using a Bayes information criterion, where a smaller value means a better model, backed by the requirement of reasonably large groups, average within-group probabilities larger than 0.8, and non-overlapping 95% confidence intervals (CIs) for trajectories. For sensitivity analyses, we estimated two growth mixture models identical to the one described above. The first excluded patients who died during the 16-week follow-up, and the second included only patients who completed MoCA at all four time points. 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.

2.4. Ethical Considerations

All patients provided written informed consent. The patients' capacity to consent was evaluated and confirmed by the treating oncologist. If the assessments revealed previously unrecognized severe health problems, test personnel followed pre-defined guidelines for actions. The study protocol was approved by the Regional Committee for Medical Research Ethics South East Norway (protocol code 2016/2031, approved 16 January 2017), and was registered at clinicaltrials.gov (NCT03071640).

3. Results

3.1. Study Recruitment and Patient Characteristics

During the recruitment period, 301 (59.1%) eligible patients were enrolled. Reasons for non-inclusion were refusal to participate (148 (29.1%])), being considered too sick (28 (5.5%)), and other (e.g., absence of a study nurse) (32 (6.3%)). A total of 298 patients completed the baseline MoCA test and were included in the present study. The mean age was 73.6 years (SD 6.3), and 141 (47.3%) were female. Most patients had completed Norwegian compulsory education (age 6–16) (30.3%) or secondary school (age 16–19) (40.4%), 162 (54.4%) received RT with curative intent, and 16 (5.4%) had brain cancer or brain metastases (Table 1). One physical impairment was found for 99 (33.6%) patients, while 86 (29.2%) had two or more. Additional details on previous cancer treatment and mGA results are displayed in Table 1. Furthermore, 255 (85.6%) had ECOG PS 0-1, and the distribution of cancer diagnoses was 95 breast (31.9%), 73 prostate (24.5%), 63 lung (21.1%), and 67 (22.5%) had other types of cancer. The median number of RT fractions was 14.8 (1–39), and the median dose was 40.0 (4.0–78.0) Gray. Only one patient resided in a nursing home, while 286 (96%) lived in their own residence, either alone (102, 34.6%) or with their spouse/children/others (195, 65.4%).

Table 1. Baseline patient characteristics and factors with potential influence on baseline MoCA scores, in total and according to groups with distinct MoCA score trajectories.

	Total *N* = 298	**Very Poor Group** *N* = 19	**Poor Group** *N* = 24	**Fair Group** *N* = 113	**Good Group** *N* = 142	***p*-Value**
Age						
Mean (SD)	73.6 (6.3)	77.7 (7.6)	76.3 (6.4)	74.7 (6.4)	71.8 (5.5)	**<0.001** [2]
Gender, *n* (%)						
Male	157 (52.7)	12 (63.2)	9 (37.5)	73 (64.6)	63 (44.4)	**0.004** [1]
Female	141 (47.3)	7 (36.8)	15 (62.5)	40 (35.4)	79 (55.6)	
Education, *n* (%) (1 missing)						
Compulsory	90 (30.3)	6 (33.3)	17 (70.8)	42 (38.2)	25 (17.6)	**<0.001** [1]
Secondary	120 (40.4)	11 (61.1)	5 (20.8)	44 (40.0)	58 (40.8)	
College or university	87 (29.3)	1 (5.6)	2 (8.3)	24 (21.8)	59 (41.5)	
Comorbidity, CCI						
Mean (SD)	1.1 (1.3)	1.5 (1.4)	1.4 (1.5)	1.3 (1.6)	0.8 (1.0)	**0.003** [2]
Number of daily medications						
Mean (SD)	5.4 (3.6)	8.7 (4.4)	7.2 (4.0)	5.7 (3.7)	4.5 (2.9)	**<0.001** [2]
Geriatric depression scale ≥5, *n* (%)						
No	236 (79.2)	12 (63.2)	17 (70.8)	88 (77.9)	119 (83.8)	0.115 [1]
Yes	62 (20.8)	7 (36.8)	7 (29.2)	25 (22.1)	23 (16.2)	
Number of physical impairments						
Mean (SD) (3 missing)	1.3 (1.4)	3.2 (1.6) [3]	1.9 (1.8)	1.5 (1.5) [4]	0.8 (0.9)	**<0.001** [2]
Fatigue						
Mean (SD) (3 missing)	37.4 (25.3)	45.1 (24.3)	38.9 (27.6)	38.2 (26.7)	35.5 (23.9)	0.449 [2]
RT treatment intent, *n* (%)						
Curative	162 (54.4)	3 (15.8)	13 (54.2)	47 (41.6)	99 (69.7)	**<0.001** [1]
Palliative	136 (45.6)	16 (84.2)	11 (45.8)	66 (58.4)	43 (30.3)	
Previous cancer treatment, *n* (%)						
Endocrine therapy	57 (19.1)	1 (5.3)	7 (29.2)	27 (23.9)	22 (15.5)	0.079 [1]
Other systematic cancer therapy	90 (30.2)	8 (42.1)	5 (20.8)	33 (29.2)	44 (31.0)	0.499 [1]
Cancer surgery/RT	182 (61.1)	10 (52.6)	16 (66.7)	60 (53.1)	96 (67.6)	0.091 [1]
Brain cancer/brain metastases, *n* (%)						
No	282 (94.6)	16 (84.2)	22 (91.7)	108 (95.6)	136 (95.8)	0.169 [1]
Yes	16 (5.4)	3 (15.8)	2 (8.3)	5 (4.4)	6 (4.2)	

Abbreviations: CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Group performance status; Gy, Grey; *p*-value represents comparison of four groups, and *p*-values marked with bold indicate statistically significant differences. [1] χ^2-test, [2] ANOVA, [3] One missing, [4] Two missing.

3.2. MoCA Completion Rates, Scores, and Comparison to Norwegian Normative Data

Within 8 and 16 weeks after RT completion, 23 and 39 patients had died, respectively. Accounting for deaths and per protocol exceptions, the MoCA test completion rates at T1, T2, and T3 were 81.3%, 72.7%, and 69.0%, respectively (Figure 1).

The mean baseline MoCA score was 24.0 (SD 3.7, (min–max 10–30)). At T1, T2, and T3, the mean MoCA scores were 25.6 (SD 3.7), 26.3 (SD 4.4), and 27.1 (SD 3.3), respectively. The most frequently impaired MoCA domains at baseline were working memory (91.9%), abstraction (59.1%), visuospatial abilities (65.1%), and language (68.1%) (Table 2).

Table 2. MoCA domain scores at baseline (*n* = 298).

MoCA Domains	**Maximum Score Possible**	**Mean Score**	**Standard Deviation**	**% with Less than Maximum Score**
Visuospatial abilities	5	3.8	1.3	65.1
Naming of objects	3	2.9	0.4	9.4
Attention and concentration	6	5.2	1.1	46.6
Language	3	2.1	0.8	68.1
Abstraction	2	1.3	0.7	59.1
Working memory	5	2.2	1.6	91.9
Orientation to time and place	6	5.8	0.7	13.8

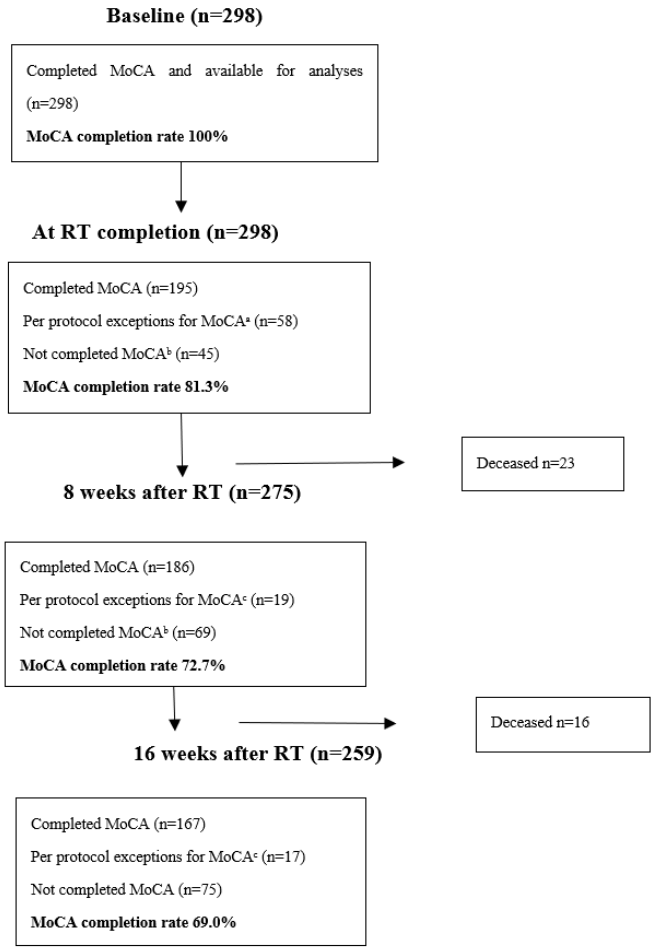

Figure 1. Patient flow chart and MoCA completion rates. [a] Patients receiving ≤9 fractions, per protocol, did not perform the MoCA test at the time of RT completion. [b] Excluding per protocol exceptions and deceased patients. [c] Patients alive at time of assessment and recruited from municipalities that did not participate in performing the mGA during follow-up.

According to the recommended MoCA score cut-off at 26 points, 186 (62.4%) had mild cognitive impairment. Compared to Norwegian normative data, 107 (35.9%) patients had MoCA scores 1–2 SDs above the mean, and 78 (26.2%) had scores <1 SD below the mean. In sum, 185 (62.1%) had scores within what is considered the normal range or better (Figure 2). A total of 113 (37.4%) patients had MoCA scores more than 1 SD below the normative mean, indicating cognitive impairment. Among these, 61 patients (20.5% of the overall cohort) had scores more than 2 SDs below the mean.

Comparing completers and non-completers at T3 (Table 3), we found that, at the time of inclusion, non-completers had poorer MoCA scores, used more daily medications, and had more physical impairments and fatigue.

Moreover, a higher proportion had received systemic therapy (including chemotherapy and excluding endocrine therapy), had cancer affecting the brain, and were treated with palliative intent (Table 3). These differences were larger between completers and non-completers due to death than completers and alive non-completers (analyses not shown). The reasons for non-completion were not registered at T1. For the non-completers still alive at T2 (n = 69) and T3 (n = 75), the reasons for missing the test were related to the home-care services (not enough time and a shortage of nurses at disposal) in 11 and 11 cases, respectively, and to the patients' condition (too ill/admitted to hospital, did not want to perform the test) in 26 and 29 cases, respectively.

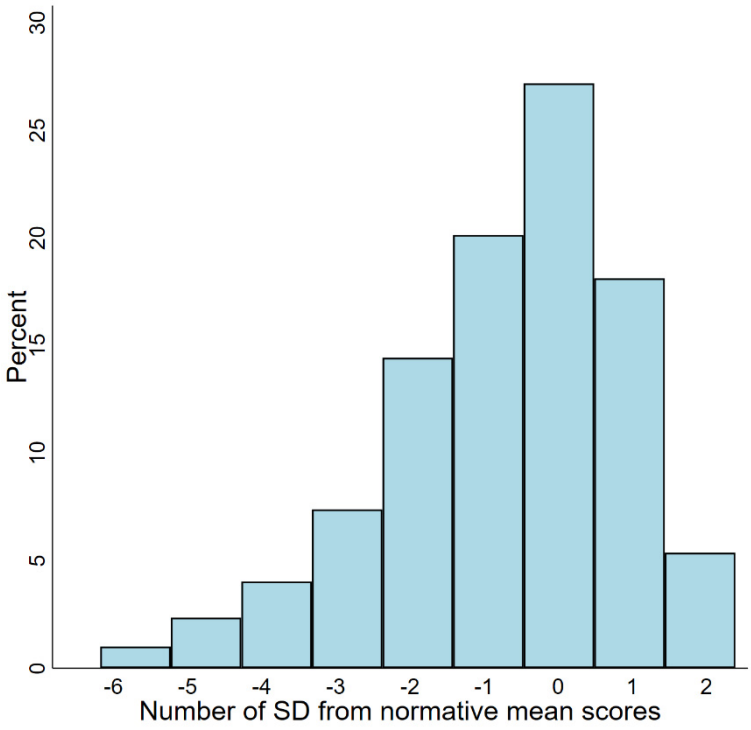

Figure 2. Distribution of MoCA z-scores (SD) based on Norwegian normative data.

Table 3. Characteristics of MoCA test completers and non-completers at 16 weeks after RT.

Total (*n* = 278 [a])	**Completers (*n* = 167)**	**Non-Completers (*n* = 111)**	***p*-Value [b]**	**Non-Completers, Deceased (*n* = 36)**	**Non-Completers, Alive (*n* = 75)**
Baseline MoCA score, mean (SD)	24.7 (3.3)	22.9 (4.1)	**<0.001** [c]	21.9 (4.5)	23.4 (3.8)
Age, mean (SD)	72.9 (5.9)	74.2 (6.7)	0.107 [c]	74.2 (7.1)	74.2 (6.5)
Gender, *n* (%)					
Male	81 (48.5)	63 (56.8)	0.177 [d]	26 (72.2)	37 (49.3)
Female	86 (51.5)	48 (43.2)		10 (27.8)	38 (50.7)
Education, *n* (%) (1 missing)					
Compulsory	48 (28.7)	33 (29.7)	0.843 [d]	12 (33.3)	21 (28.0)
Secondary	68 (40.7)	47 (42.3)		15 (41.7)	32 (42.7)
College or university	51 (30.5)	30 (27.0)		9 (25.0)	21 (28.0)
Comorbidity, CCI, mean (SD)	1.0 (1.3)	1.2 (1.5)	0.246 [c]	1.6 (1.4)	1.0 (1.5)
Number of daily medications, mean (SD)	5.0 (3.5)	6.1 (3.7)	**0.020** [c]	7.6 (3.4)	5.3 (3.7)
Geriatric depression scale ≥5, *n* (%)					
No	136 (81.4)	82 (73.9)	0.133 [d]	26 (72.2)	56 (74.7)
Yes	31 (18.6)	29 (26.1)		10 (27.8)	19 (25.3)
Number of physical impairments, mean (SD), (3 missing)	0.9 (1.1)	1.9 (1.7)	**<0.001** [c]	2.5 (1.6)	1.6 (1.6)
Fatigue, mean (SD) (3 missing)	34.3 (23.9)	43.1 (27.2)	**0.005** [c]	58.7 (22.8)	35.7 (26.0)
RT treatment intent, *n* (%)					
Curative	111 (66.5)	40 (36.0)	<0.001 [d]	2 (5.6)	38 (50.7)
Palliative	56 (33.5)	71 (64.0)		34 (94.4)	37 (49.3)
Previous cancer treatment, *n* (%)					
Endocrine therapy	38 (22.8)	15 (13.5)	0.163 [d]	4 (11.1)	11 (14.7)
Other systematic cancer therapy	42 (25.1)	42 (37.8)	**0.024** [d]	19 (52.8)	23 (30.7)
Cancer surgery/RT	115 (68.9)	56 (50.5)	**0.002** [d]	16 (44.4)	40 (53.3)
Cancer/metastases in the brain, *n* (%)					
No	162 (97.0)	101 (91.0)	**0.030** [d]	28 (77.8)	73 (97.3)
Yes	5 (3.0)	10 (9.0)		8 (22.2)	2 (2.7)

[a] Accounting for protocol exceptions (*n* = 20), i.e., patients recruited from municipalities that did not participate in performing the mGA during follow-up. Of the 39 patients that were deceased by 16 weeks after RT, 3 were recruited from such municipalities. [b] *p*-value represents comparison of MoCA completers and all non-completers, irrespective of cause, 16 weeks after RT. [c] Independent samples *t*-test. [d] χ^2-test. *p*-values marked with bold indicate statistically significant differences.

3.3. Factors Associated with Baseline MoCA Scores

The results of the linear regression models assessing the impact of predefined variables on baseline MoCA scores are presented in Table 4.

Table 4. Results of linear regression analyses investigating factors associated with baseline MoCA scores, (n = 294).

Covariate	Unadjusted Models		Adjusted Model	
	RC (95% CI)	*p*-Value	RC (95% CI)	*p*-Value
Age	−0.22 (−0.28; −0.16)	**<0.001**	−0.13 (−0.19; −0.07)	**<0.001**
Gender, Female	0.72 (−0.12; 1.57)	0.094	0.28 (−0.49; 1.05)	0.479
Education, n				
Compulsory	0		0	
Secondary	1.42 (0.47; 2.37)	**0.004**	0.73 (−0.11; 1.57)	0.089
College or university	3.35 (2.32; 4.38)	**<0.001**	2.41 (1.50; 3.33)	**<0.001**
Comorbidity, CCI	−0.63 (−0.94; −0.33)	**<0.001**	0.02 (−0.30; 0.33)	0.924
Number of daily medications	−0.37 (−0.48; −0.25)	**<0.001**	−0.11 (−0.24; 0.02)	0.107
Geriatric depression scale ≥5	−1.48 (−2.51; −0.45)	**0.005**	−0.26 (−1.25; 0.74)	0.613
Number of physical impairments	−1.23 (−1.49; −0.97)	**<0.001**	−0.82 (−1.16; −0.48)	**<0.001**
Fatigue	−0.02 (−0.04; −0.003)	**0.021**	0.01 (−0.004; 0.03)	0.141
RT treatment intent, Palliative	−1.84 (−2.67; −1.02)	**<0.001**	−0.54 (−1.41; 0.33)	0.223
Previous cancer treatment				
Endocrine therapy	−0.12 (−1.20; 0.96)	0.822	0.14 (−0.81; 1.08)	0.778
Other systematic cancer therapy	0.43 (−0.49; 1.36)	0.360	0.55 (−0.32; 1.42)	0.216
Cancer surgery/RT	0.89 (0.03; 1.76)	**0.043**	0.09 (−0.69; 0.87)	0.817
Cancer/metastases in the brain	−0.98 (−2.85; 0.88)	0.300	−0.06 (−1.70; 1.58)	0.940

Abbreviations: RC, regression coefficient; CI, confidence interval. *p*-values marked with bold indicate statistically significant differences.

According to unadjusted models, all covariates except gender, cancer affecting the brain, and previous systemic cancer treatment were significantly associated with baseline MoCA scores. In the adjusted model, a higher number of physical impairments (regression coefficient (RC) −0.82, 95% CI [−1.16; −0.48]) and increasing age (RC −0.13, 95% CI [−0.19; −0.07]) remained associated with lower MoCA scores, whereas college/university as compared to compulsory education was associated with higher MoCA scores (RC 2.41, 95% CI [1.50; 3.33]).

3.4. MoCA Score Trajectories

A growth mixture model identified four groups of patients following distinct MoCA score trajectories, which we named very poor (n = 19, 6.4%), poor (n = 24, 8.1%), fair (n = 113, 37.9%), and good (n = 142, 47.7%) (Table 5, Figure 3). The average group probabilities varied between 0.79 (fair group) and 0.91 (good group), and the 95% CIs were non-overlapping, indicating homogeneous groups. For the small group with very poor scores, a clinically significant (≥3 points) transient decline in MoCA scores from T0 to T2 was registered, followed by an improvement beyond pre-treatment levels at T3. The fair group experienced a significant improvement in MoCA scores from T0 to T3. The other two groups had relatively stable trajectories. The patient characteristics of these four groups are presented in Table 1. The proportion of patients with advanced age and with a higher number of physical impairments, comorbidities, and daily medications gradually increased from the good group to the very poor group, whereas the proportion with higher education gradually decreased (Table 1). Our first sensitivity analysis, excluding all patients who died within 16 weeks after RT (T3), reproduced the results of the main analysis. The small "very poor" group consisted of 9 patients (10 out of 19 patients in this group died) with a decline from baseline to eight weeks after RT, followed by an improvement (data not shown). The compliance in this small group was poor, even when those who died were excluded, i.e., at T0 all nine patients completed MoCA, at T1 and T2 six patients completed,

whereas at T3 only two patients were completers. In our second sensitivity analysis, only including patients who completed MoCA at all time points (n = 113), we also identified four groups with distinct MoCA trajectories ranging from good to very poor (Supplementary Figure S1 and Supplementary Table S2). Similar to the results of the preceding analyses, the trajectories of the good, fair, and poor group were mainly stable. For the very poor group (n = 2), however, a significant improvement was registered, demonstrating that the improvement observed at T3 in the "very poor" group, identified in both the main analysis and the first sensitivity analysis, could be attributed to these two patients only.

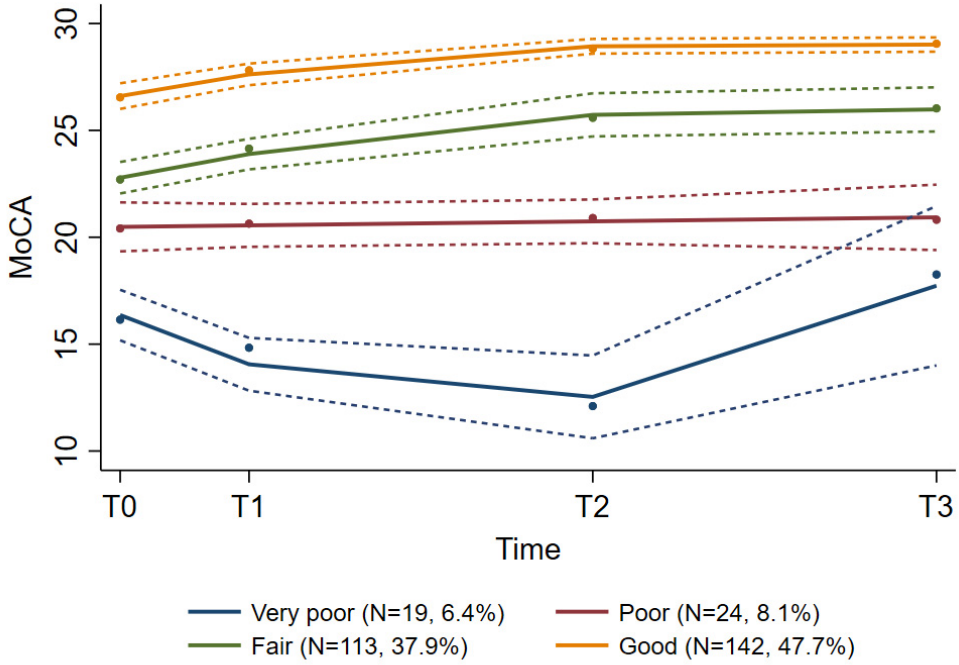

Figure 3. Groups with distinct MoCA score trajectories during the course of radiotherapy.

Table 5. Results of growth mixture model for MoCA scores, n = 298.

	Very Poor *N* = 19 (6.4%)		**Poor** *N* = 24 (8.1%)		**Fair** *N* = 113 (37.9%)		**Good** *N* = 142 (47.7%)	
	RC (SE)	***p*-Value**	**RC (SE)**	***p*-Value**	**RC (SE)**	***p*-Value**	**RC (SE)**	***p*-Value**
Intercept	16.36 (0.60)	<0.001	20.49 (0.58)	<0.001	22.79 (0.37)	<0.001	26.68 (0.23)	<0.001
Linear	−0.93 (0.24)	<0.001	0.02 (0.05)	0.641	0.41 (0.08)	<0.001	0.43 (0.07)	<0.001
Quadratic	0.05 (0.01)	<0.001			−0.01 (0.004)	0.004	−0.01 (0.003)	<0.001
MoCA [a]								
T0	16.4		20.5		22.8		26.6	
T1	14.1		20.6		23.9		27.6	
T2	12.5		20.7		25.7		28.9	
T3	17.7		20.9		26.0		29.0	
Av.prob.	0.84		0.86		0.79		0.91	

Abbreviations: RC, regression coefficient; SE, standard error; T0, baseline; T1, at RT completion; T2, 8 weeks after RT; T3, 16 weeks after RT. Av.prob, average group probability. [a] Predicted mean MoCA values.

4. Discussion

In this study, we have shown that cognitive impairment was frequent in a heterogeneous cohort of older patients undergoing RT. Age, lower education, and physical impairments were independently associated with compromised cognition. We identified four groups of patients with distinct non-overlapping trajectories of MoCA scores. The majority had stable trajectories, but for the group with the poorest overall cognitive function, a declinewas registered.

To our knowledge, this is the first study to longitudinally assess objective cognitive function in older patients with cancer receiving RT and the first to use the MoCA test for this

purpose. According to the original recommended cut-off value at <26 points, assigning one extra point to all with ≤12 years of education [21], the prevalence of cognitive impairment was high (62.4%). However, several studies have indicated that this cut-off may be too high [39–43] and that MoCA scores, in addition to education, could be dependent on age, gender, and cultural aspects. Therefore, we chose the recommended approach [44] and compared patients' scores with recently published Norwegian normative data [38]. According to this, 37.9% of our patients had MoCA scores consistent with cognitive impairment. Thus, our findings support the view that when using a more stringent MoCA score cut-off, the prevalence of cognitive impairment could be overestimated [39–43]. Nevertheless, we find the prevalence of cognitive impairment among older patients with cancer referred to RT alarming, in particular as 20.5% had MoCA scores more than 2 SDs below the normative mean, which indicates dementia [38]. The high prevalence of cognitive impairment among study participants is consistent with studies indicating that CRCI is a common and underdiagnosed problem among older patients [2,3,17]. In line with other reports [3,44], we also found that executive functions, memory, and attention were the cognitive domains that were most frequently impaired.

According to our adjusted regression model, age, educational level, and the number of physical impairments were the only factors independently associated with baseline MoCA scores. That higher age and lower education negatively affect MoCA results is well-known from several studies [38,40,43]. Physical impairments are indicators of physical frailty [45], and the association between physical frailty and cognitive impairment has been widely confirmed [46–49]. Opposed to our expectations and a smaller pilot study on early breast cancer [50], previous treatment with systemic cancer agents was not significantly associated with poorer cognition in the adjusted or unadjusted models. However, in our study, about 50% had advanced cancer (palliative treatment intent), which is found to be associated with reduced cognitive function, even before the initiation of systemic therapy [51]. Furthermore, the majority had previously received several treatment modalities. Thus, as concluded by the authors of a study reporting no difference in cognitive decline between women ≥65 years receiving and not receiving adjuvant chemotherapy [11], the observed decline could be attributed to the joint effect of the cancer and the overall treatment burden, making it impossible to disentangle the impact of one treatment from another. In contrast to the established knowledge [15], we also found no association between MoCA scores and cancer affecting the brain. This is most likely explained by the very small number of patients in this subgroup of our cohort. Gender was another factor that had no association with cognitive function in the adjusted and unadjusted models. Although this is in line with reports from other countries [42], the finding contrasts a study of a Norwegian cognitively healthy population ≥70 years, showing that women aged 70–74 years with education of >13 years had the best MoCA scores [38]. It is possible that the severity of other conditions among our patients masked a potential impact of gender. In line with previous reports, comorbidity, medications, depression, and fatigue were significantly associated with cognitive function in unadjusted models [3,4,6,7]. As these associations disappeared in the adjusted model, it might be an indication that the association between MoCA and these factors is weaker than between MoCA and age, education, and the number of physical impairments.

Four groups with distinct MoCA trajectories were identified, varying from good to very poor. The differences in cognitive function between groups persisted from baseline throughout the follow-up period. Moreover, we observed a higher proportion with poorer health, including more comorbidities, daily medications, and physical impairments, from the good to the very poor group. Thus, the identified groups may be seen as representing a continuum from robust to frail, and this finding is in line with other studies suggesting that frailty may be associated with compromised cognitive function [47,52] that might further be negatively affected by cancer and its treatment in older adults [3,8,9,52–54]. A wide range of mechanisms explaining this phenomenon have been proposed, including DNA damage, inflammation, and oxidative stress [4,6,7,53]. Similarly, systemic inflammation due to RT has been hypothesized to impair cognition, but existing evidence is very limited [6,55]. In

our cohort, the majority had stable or improved cognitive trajectories. This is consistent with previous research in older adults that indicated that RT tolerance is generally good [56,57]. The decline in MoCA scores observed in the small group with the poorest trajectory and poorest health, where only two patients completed MoCA at T3, may be attributed to frailty and reduced cognitive reserves [4]. This assumption is supported by our comparison of the baseline characteristics between completers and non-completers at week 16 after RT, showing that non-completers had poorer cognitive and physical health. The improvement from 8 to 16 weeks after RT reflects the results of two patients, as demonstrated by our sensitivity analysis, and must be interpreted accordingly. However, the overall trajectory of the very poor group should be interpreted with caution due to the small number of patients and substantial attrition. Attrition might also explain the improvement in cognitive function in the fair group, but as this was less pronounced, it is more likely that the transient distress and attention deficits in connection with the start of a new treatment may have affected baseline MoCA scores negatively.

Our results add to the growing evidence showing that multiple factors can contribute to cognitive impairment among older patients with cancer, with age, education, and physical impairments being the most essential. A pre-treatment cognitive assessment is important among older adults, and patients with physical impairments need special attention. As cognitive impairment is associated with negative outcomes such as increased chemotherapy toxicity [20], reduced survival [22], dependency, and reduced quality of life [49], supportive measures before, during, and after RT are necessary.

The strengths of this study are the prospective design, the relatively large sample size, and the mGA performed at baseline. The use of MoCA to assess cognitive function is also a strength in a longitudinal study. In addition to being a sensitive screening tool among older adults in general and older patients with cancer in particular [22], MoCA is reliable in detecting changes in cognitive function over time [58]. Furthermore, the MoCA completion rate was high at all assessment points, and all health care professionals conducting MoCA received the same training. Finally, in the absence of universally accepted and applicable MoCA cut points for cognitive impairment, it is a considerable strength that patients' scores were compared to Norwegian normative data. Besides attrition, as discussed above, this study has some limitations. Representing mean values, our results reflect MoCA scores on group level, and it should be kept in mind that individual trajectories may occur within the groups. The cohort is heterogeneous in terms of cancer diagnoses and disease stages, and the results may not be applicable to specific groups of patients. However, this could also be regarded as a strength since this reflects the heterogeneity among patients seen in routine clinical practice, including patients who, unfortunately, often are excluded from clinical trials. When interpreting the results, it is important to remember that MoCA is a screening tool for cognitive impairment, and the need for further diagnostic inquiries should always be considered. Additionally, it should be noted that we did not use parallel versions of the MoCA test. Thus, a practice effect cannot be ruled out. An objection might be that ECOG PS was not included in the regression model. The number of physical impairments was preferred, as it combines several objective measures of functional status. ECOG PS is observer-dependent and important prognostic information may be lost when applied to older patients [26,59,60]. Furthermore, we did not collect data on psychotropic medications, which might affect cognitive function more than other drugs.

5. Conclusions

Compared to age-, gender-, and education-matched cognitively healthy controls, MoCA revealed cognitive impairment in 37.9% of patients ≥65 years referred to RT, implying that CRCI is a clinically relevant problem. Older age, lower education, and physical impairments were independently associated with reduced cognition prior to RT. Four groups with distinct cognitive trajectories ranging from good to very poor were identified, and their baseline characteristics suggested a corresponding range from fit to frail. Except for the very poor group, where a cognitive decline was registered, the remaining trajec-

tories were mainly stable, indicating good tolerance for RT, irrespective of pre-treatment cognitive function. Assessing cognitive function before RT is a prerequisite, and special attention should be given to the oldest and those with other geriatric problems, especially physical impairments.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/curroncol29070409/s1. Table S1: Spearman's rho correlation for factors included in the linear regression models; Figure S1: Second sensitivity analysis, growth mixture model including only patients who completed MoCA at all time points assessed; Table S2: Results of growth mixture model, second sensitivity analysis only including patients who completed MoCA at all time points assessed.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Regional Committee for Medical Research Ethics South East Norway (protocol code 2016/2031, approved 16 January 2017). The study was registered at clinicaltrials.gov (NCT03071640) 7 March 2017.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: According to Norwegian regulations, research data are confidential due to patient privacy protection. On individual, specific request, anonymized data could be made available.

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Conflicts of Interest: The authors declare no conflict of interest.

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Supplementary table S-A. Results of the growth mixture model for global quality of life and physical function assessed by EORTC QLQ-C30.

Global quality of life (N=297)								
	Poor (N=32, 10.8%)		Fair (N=140, 47.1%)		Good (N=93, 31.3%)		Excellent (N=32, 10.8%)	
	RC (SE)	p-value	RC (SE)	p-value	RC (SE)	p-value	RC (SE)	p-value
Intercept	34.2 (2.3)	<0.001	57.8 (1.6)	<0.001	79.8 (1.4)	<0.001	105.1 (0.4)	<0.001
Linear			-1.1 (0.4)	0.010				
Quadratic			0.06 (0.02)	0.009				
Av.prob.	0.85		0.87		0.89		0.93	
Physical function (N = 298)								
	Poor (N=81, 27.6%)		Fair (N=86, 29.3%)		Good (N=80, 27.2%)		Excellent (N=47, 16.0%)	
	RC (SE)	p-value	RC (SE)	p-value	RC (SE)	p-value	RC (SE)	p-value
Intercept	37.9 (1.6)	<0.001	66.9 (1.5)	<0.001	90.2 (1.6)	<0.001	120.4 (0.4)	<0.001
Linear	-1.1 (0.5)	0.024						
Quadratic	0.06 (0.02)	0.019						
Av.prob.	0.95		0.90		0.89		0.94	

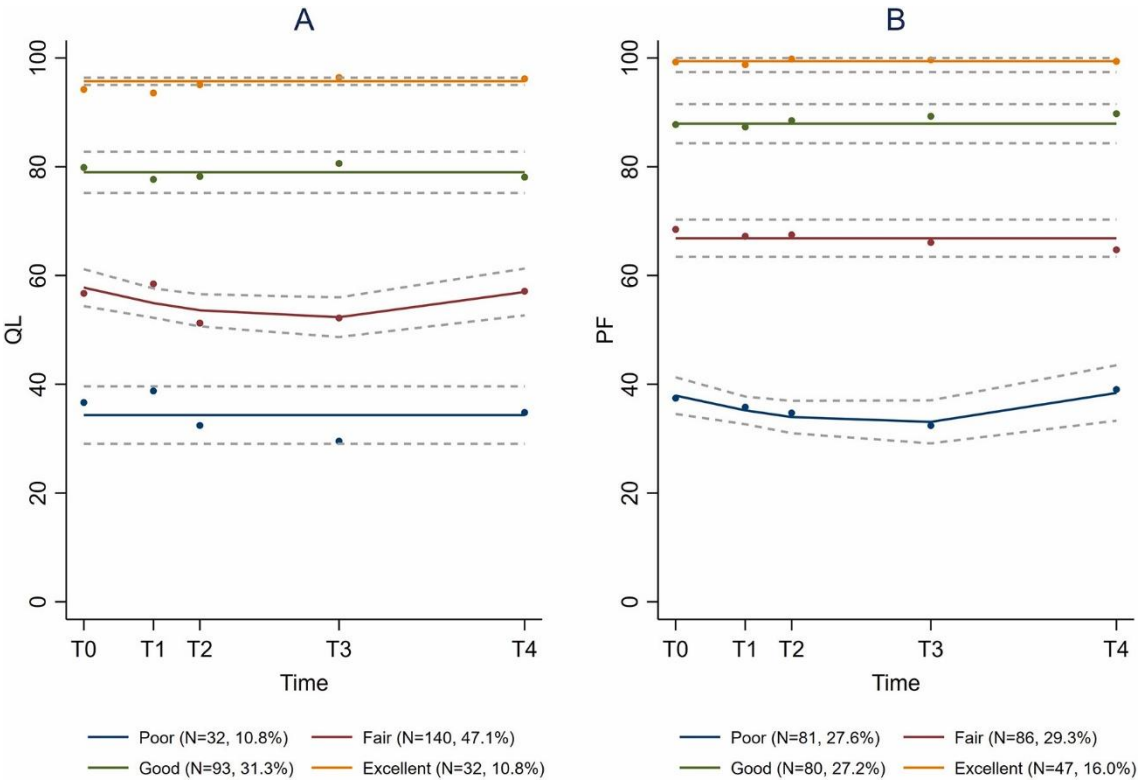
Abbreviations: EORTC QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality-of-Life Core Questionnaire RC, regression coefficient; SE, standard error; Av.prob, average group-probability;

Supplementary table S-B. Baseline characteristics of the four groups with distinct trajectories in global quality of life and physical function.

	Global quality of life				Physical function			
	Poor	Fair	Good	Excellent	Poor	Fair	Good	Excellent
Treatment intent (%)								
Curative	10 (31.3)	52 (37.1)	70 (75.3)	28 (87.5)	19 (23.5)	41 (47.7)	58 (72.5)	43 (91.5)
Palliative	22 (68.8)	88 (62.9)	23 (24.7)	4 (12.5)	62 (76.5)	45 (52.3)	22 (27.5)	4 (8.5)
Age, mean (SD)	73.6 (5.5)	74.6 (6.8)	72.8 (6.0)	71.7 (5.2)	75.9 (6.8)	74.2 (6.9)	72.4 (5.2)	70.9 (4.9)
Sex, n (%)								
Male	20 (62.5)	69 (49.3)	53 (57.0)	15 (46.9)	44 (54.3)	46 (53.6)	38 (47.5)	26 (55.3)
Female	12 (37.5)	71 (50.7)	40 (43.0)	17 (53.1)	37 (45.7)	40 (46.5)	42 (52.5)	21 (44.7)
ECOG PS, n (%)								
0-1	21 (65.6)	109 (77.9)	91 (97.8)	32 (100)	44 (54.3)	81 (94.2)	80 (100)	47 (100)
2-4	11 (34.4)	31 (22.1)	2 (2.2)	0	37 (45.7)	5 (5.8)	0	0
Cancer type, n (%)								
Breast	3 (9.4)	41 (29.3)	35 (37.6)	15 (46.9)	15 (18.5)	21 (24.4)	38 (47.5)	21 (44.7)
Prostate	6 (18.8)	23 (16.4)	33 (35.5)	10 (31.3)	10 (12.3)	19 (22.1)	23 (28.7)	20 (42.6)
Lung	14 (43.8)	39 (27.9)	12 (12.9)	0	30 (37.0)	23 (26.7)	8 (10.0)	1 (2.1)
Others	9 (28.1)	37 (26.4)	13 (14.0)	7 (21.9)	26 (32.1)	23 (26.7)	11 (13.8)	5 (10.6)
No.of impairments, n (%)	2 (6.5)	6 (4.3)	25 (27.2)	48 (16.3)	2 (2.5)	4 (4.7)	20 (25.0)	22 (46.8)
0	0	27 (19.4)	32 (34.8)	67 (22.8)	4 (4.9)	15 (17.4)	33 (41.3)	15 (31.9)
1	2 (6.5)	23 (16.5)	20 (21.7)	50 (17.0)	6 (7.4)	21 (24.4)	16 (20.0)	7 (14.9)
2	8 (25.8)	30 (21.6)	7 (7.6)	48 (16.3)	11 (13.6)	27 (31.4)	7 (8.8)	3 (6.4)
3	19 (61.3)	53 (38.1)	8 (8.7)	81 (27.6)	58 (71.6)	19 (22.1)	4 (5.0)	0
≥4								

Abbreviations: SD, standard deviation; ECOG PS Eastern cooperative oncology group performance status.

Supplementary figure S-A. Trajectories in the four groups in global quality of life (QL) (a), and physical function (PF) (b) identified by the growth mixture models.



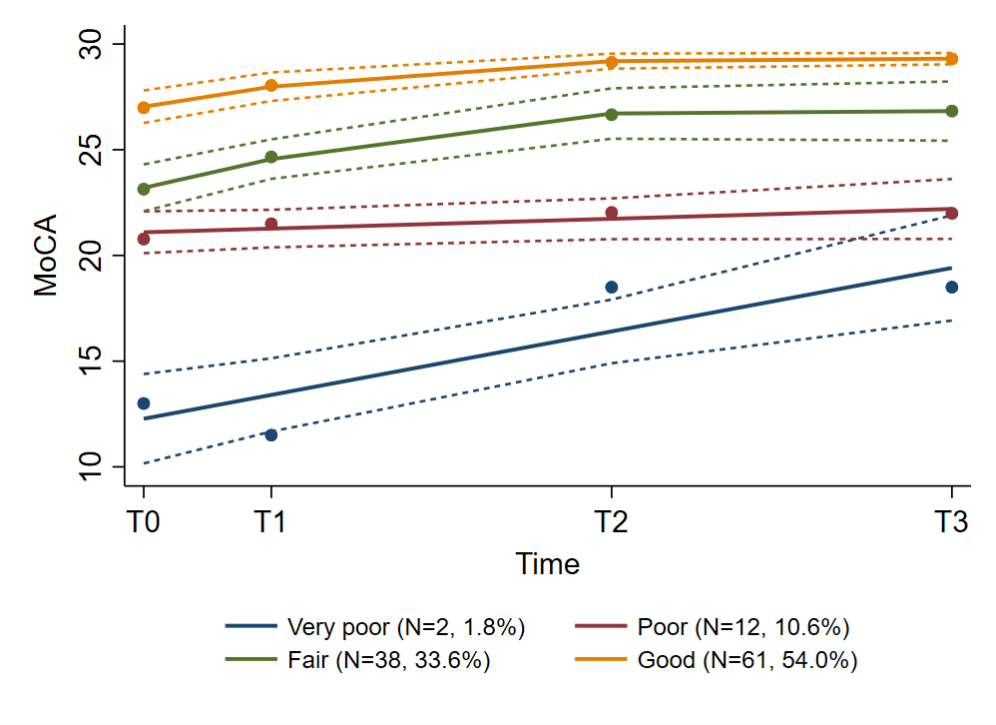
Supplementary figure S-A legend:

Abbreviations: QL, quality of life; PF, physical function. QL and PF assessed by The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ-C30). Scale range 0-100, higher scores indicate better QL and PF. Mean values, dotted lines indicate 95 % CIs. T0=baseline, T1= at RT completion, T2= two, T3= eight, T4= sixteen weeks after completing RT.

Supplementary Table S1. Spearman´s rho correlation for factors included in the linear regression models.

Spearman's rho		2	3	4	5	6	7	8	9	10	11	12	13	14
MoCA	1	-0.05	0.07	0.14	-0.36	-0.25	-0.05	-0.12	-0.34	0.14	0.37	-0.24	-0.29	-0.14
Endocrine therapy	2		-0.01	-0.27	-0.01	0.06	-0.04	0.04	0.14	-0.20	0.02	-0.03	0.10	0.01
Other systemic cancer therapy	3			0.11	0.10	0.32	-0.03	0.36	-0.05	0.08	-0.07	-0.02	0.11	0.16
Cancer surgery/RT	4				-0.10	-0.13	0.07	0.01	-0.14	0.31	0.01	-0.14	-0.11	0.06
Number of physical impairments	5					0.44	0.19	0.45	0.21	-0.01	-0.13	0.27	0.51	0.39
RT treatment intent	6						0.26	0.31	0.21	-0.21	-0.06	0.19	0.29	0.16
Cancer/metastases in the brain	7							0.05	-0.06	-0.05	0.04	-0.05	0.01	0.14
Fatigue	8								0.11	0.13	-0.04	0.20	0.40	0.45
Age	9									-0.12	-0.14	0.18	0.25	0.05
Gender	10										-0.01	-0.20	-0.05	0.05
Educational level (three categories)	11											-0.18	-0.18	-0.05
Comorbidity, CCI	12												0.56	0.08
Number of daily medications	13													0.27
Geriatric depression scale ≥5	14													

Supplementary Figure S1. Second sensitivity analysis, growth mixture model including only patients who completed MoCA at all time points assessed, n=113.



Supplementary Table S2. Results of growth mixture model, second sensitivity analysis only including patients who completed MoCA at all time points assessed.

	Very poor N=2[a] (1.8%)		Poor N=12 (10.6%)		Fair N=38 (33.6%)		Good N=61 (54.0%)	
	RC (SE)	p-value	RC (SE)	p-value	RC (SE)	p-value	RC (SE)	p-value
Intercept	12.28 (1.08)	<0.001	21.10 (0.50)	<0.001	23.20 (0.56)	<0.001	27.10 (0.29)	<0.001
Linear	0.38 (0.10)	<0.001	0.06 (0.04)	0.182	0.50 (0.10)	<0.001	0.40 (0.08)	<0.001
Quadratic					-0.02 (0.005)	0.002	-0.01 (0.004)	0.002
Av.prob.	0.99		0.92		0.86		96	

Abbreviations: RC, regression coefficient; SE, standard error; T0, baseline; T1, at RT completion; T2, 8 weeks after RT; T3, 16 weeks after RT. Av.prob, average group-probability. [a]The very poor group contains only two patients, but none of the applied statistical criteria (except for reasonable group size) suggests that this group could be merged with another one.