COVER PAGE

Title: Improving outcomes for older cancer patients receiving external beam radiotherapy (EBRT): Developing and testing a geriatric assessment with management intervention. Part 1: A prospective observational study

NCT03071640

Date: June 9th 2021 (overall document)

Dates of protocol, revisions and analysis plans are to be found on the next page

Title

Improving outcomes for older cancer patients receiving external beam radiotherapy (EBRT): Developing and testing a geriatric assessment with management intervention.

Part 1: A prospective observational study - NCT03071640

Translation of original protocol dated 31.10.16 with minor revision 02.01.17 and 18.04.17, approved by the Norwegian Regional Committee for Medical and Health Research - South East. Revisions made 02.01.17 are marked in magenta; revisions mage 18.04.17 are marked in yellow. Introduction, background and some other paragraphs have been shortened, but all details regarding design, methods and study conduct are presented.

A new amendment (attached) was made prior to analyses and was approved by the Norwegian Regional Committee for Medical and Health Research - South East on the 09.06.2021

Detailed plans for the analyses (dated 26.05.20, 14.12.20 and 18.05.21) for the planned three first papers, respectively, are presented in Appendices 1-3.

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For the remaining representatives of the scientific project group, please see protocol page 21.

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Appendices

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2. Plan for the analyses second paper
3. Plan for the analyses third paper

Introduction

This prospective observational study is part of a larger project. The main aim of the overall project is to develop and test an intervention to improve the quality of life (QoL) and function for older patients with cancer who receive radiotherapy and to reduce their need for everyday assistance or institutional care after treatment.

Older patients with cancer ≥ 65 years represent the majority of all new cancer cases.[1] In general, older patients have poorer tolerance for cancer treatment than younger patients, and they often have other health issues that may influence the course and treatment of cancer. To offer older cancer patients good and appropriate treatment including targeted supportive measures is a great challenge.

Older patients with cancer represent a heterogeneous group in terms of health status, and treatment tolerance may vary accordingly. A systematic assessment of the older patients' vulnerability is therefore crucial for treatment decisions. The best established method for assessing vulnerability in older adults is a geriatric assessment (GA).[2] In older and/or frail patients with other illnesses than cancer, it is well documented that GA followed by targeted measures (Geriatric Assessment with Management = GAM) improves survival and function. [3-5] Although international guidelines recommend using GA for the management of older patients with cancer,[6-10] this is still not routinely implemented into clinical oncological practice, and the benefits of GAM interventions for older patients with cancer are scarcely documented.

Radiotherapy (RT) is a main modality in cancer treatment. However, during or after RT, many patients experience deterioration of function and QoL. Our main hypothesis is that an intervention based on GAM principles will have a positive impact on these outcomes in older patients receiving RT. To be efficient, however, we postulate that a GAM intervention must be carried out before, during and after RT, and that it has to be targeted towards problems and needs that affect outcomes of treatment. Based on the organization of Norwegian public health care, this means that parts of the intervention must be carried out by the municipal health services (before and after RT), and that co-operation between the specialist and municipal health service is necessary. Furthermore, it would be crucial to know, which problems and needs are most likely to affect survival, function and QoL, and thereby which patients are at highest risk of deterioration after RT and need most attention.

The knowledge base to develop, implement, test and evaluate such an invention is, however, scarce. The aim of the present prospective, observational study, is therefore to identify older patients receiving RT who are at risk of functional impairment, QoL deterioration and increased needs for health care services during and after RT, describe the prevalence of impairments that can be uncovered by GA, and investigate their impact on treatment outcomes and complications. We will also test the feasibility of GA in the municipal health services and validate a geriatric screening instrument for frailty.

Background

Cancer in older adults

Older patients represent a major proportion of the cancer population.[1] By the time of diagnosis, approximately 50% of all cancer patients are 70 years or older,[11] and due to an aging population,

the absolute number of older cancer patients is rapidly increasing.[1] Providing appropriate treatment to these patients represents a major challenge to our health services.[6] Older age is followed by reduced physiological and functional reserves and increased incidence of co-existing health problems. In comparison to their younger counterparts, older cancer patients have more complex care needs, are more vulnerable and have reduced tolerance to treatment.[12] Following cancer therapy, older patients have higher mortality and morbidity, including higher risk of geriatric events (e.g delirium, falls and fractures).[13-17] This cannot be attributed to chronological age alone. Comorbidity and functional and cognitive impairments, which vary considerably between individuals of similar age, are important contributing factors.[17,18] To avoid adverse outcomes that come at high personal and societal costs, it is necessary to assess the older patient's vulnerability and co-existing health problems, and to provide treatment, supportive care and rehabilitation accordingly. Presently no such assessments are standardised and systematically applied in Norwegian cancer care.

Geriatric assessment

Geriatric assessment (GA) addresses problems that are frequent in older age,[10,19] and includes assessment of comorbidity, medications, physical-, cognitive- and emotional function, nutritional status and social network. It is currently the most established method to identify older patients' vulnerability.[2] GA with management (GAM) refers to assessments followed by adequate management of identified vulnerabilities. GA and GAM performed as a comprehensive, multi-professional approach has well-documented success in detecting relevant problems, maintaining autonomy, reducing the need for residential care, and improving mobility, cognitive function and survival in older patients with non-malignant diseases.[3,4,20] Thus, during the last decades, GA has been adapted for cancer care. Using well-established geriatric assessment tools or more simple screening instruments, mounting evidence shows that GA may identify remediable problems, substantially affect oncological treatment decisions, and predict survival or adverse events from chemotherapy and cancer surgery.[18,21,22] Despite this, and strong recommendations from current guidelines and proposed models for care,[6,10,12,23] GA remains to be integrated into common oncology practice.[7] It has, however, been found feasible in teaching hospital centres and community cancer clinics.[24,25] All GA domains cover problems that may negatively affect outcomes of cancer and cancer treatment,[19,26-30] but that may also be prevented, alleviated or improved. Treatment of comorbidities may be optimised and inappropriately described medications withdrawn.[19,27] Rehabilitation, exercise and nutritional counselling may improve physical and nutritional deficits.[31,32] Depression can be treated, and if recognized, actions can be taken to avoid deterioration of cognitive impairments.[19] GAM interventions are therefore assumed to optimise treatment and care for older cancer patients.[7] Evidence for the potential benefits is lacking,[7] but a recent study suggests that such interventions may improve tolerance for chemotherapy.[33]

Radiotherapy

Radiotherapy is a main treatment modality in cancer, and external beam radiation (EBRT) is the most common approach. EBRT may be used with curative or palliative intent. Short and long term side effects occur in both settings. These may be local, i.e. related to the involved organ, or general, e.g. fatigue and physical deterioration.[8,34] Curative EBRT is conventionally given in

higher total doses over a longer period of time, and has more frequent side effects compared to palliative treatment. Several EBRT studies have included, or specifically targeted older patients.[8,9] Results are inconsistent, but indicate that benefits are equal to younger patients.[8] Higher toxicity rates have been noted.[9] Older patients are, however, underrepresented in clinical trials,[35] and those participating are likely to be highly selected.[8] Furthermore, studies on EBRT rarely include assessments of problems relevant for older patients, e.g. cognitive and functional deficits, and outcomes such as quality of life (QoL) and functioning are either lacking or poorly assessed.[34,36,37] A high incidence of geriatric problems in the older EBRT population is suggested by two smaller studies on head and neck cancer, identifying 49% (n = 35) [38] and up to 75% (n= 100)[39,40] of the patients as vulnerable. In comparison to fit patients, those who were vulnerable had poorer survival and QoL.[39,40] To the best of our knowledge, these are the only studies hitherto published on GA in EBRT patients. No studies on GAM for older EBRT patients have been reported.[7]

Frailty

Frailty is widely recognized as a syndrome of increased vulnerability to adverse changes in health status.[2] It is strongly associated with increased mortality and predisposes for a rapid deterioration of health status or functioning when exposed to stress factors like e.g. cancer or cancer treatment.[2]. There is, however, no general agreement on how frailty should be identified. Different approaches and indicators have been suggested and tested,[41] and in research, Fried's frailty index has been the most commonly used.[42] In clinical practice, however, GA is the best established method.[2]

In recent years, several studies have been conducted to investigate the occurrence of frailty in older patients with cancer. A recent review concluded that many of these studies are small and varying methods have been used for frailty classification, GA being the most common.[43] Median prevalence of frailty is reportedly around 40%. [43] None of the referred studies investigated the occurrence of frailty in older patients referred for RT in particular.

Geriatric screening tools: The Edmonton Frail Scale

GA can be both time- and resource consuming, and because of this, several screening instruments have been developed, primarily to identify patients who need a full GA. The most frequently used tools are VES-13 and G8.[44,45] Neither these nor other tested tools are found optimal in terms of sensitivity and specificity. [44,45] However, VES-13 and G8 in particular, are those most strongly recommended by the International Society of Geriatric Oncology (SIOG).[10]

The Edmonton Frail Scale (EFS) is a screening tool developed for use by clinicians without special training in GA.[83] [46] Unlike VES-13, mainly focusing on functioning and G8, having a focus on nutritional status, EFS is a broader tool that also includes testing of cognitive function (clock test) and physical function (TUG). It is easy and quick to use, and therefore relevant to test in older patients with cancer.

Inflammation, frailty and cancer

The etiology of frailty is not fully clarified, but several studies have linked frailty to increased levels of pro-inflammatory cytokines and elevated levels of C-reactive protein (CRP).[2,47] Lower levels of serum-albumin (s-alb), higher numbers of neutrophile white blood cells and lower numbers of lymphocytes have also been reported.[47,48] Furthermore, the association between systemic inflammation and cancer is well-known[49]. The prognostic impact of an index based on CRP and s-alb (Glasgow Prognostic Score = GPS) has been confirmed in several larger studies of patients with different types of cancer.[50] Few studies have investigated whether the GPS may be used to identify frailty in an oncology setting. Preliminary data from an earlier study by our research group indicates a strong association between higher GPS scores and frailty. Since CRP and s-alb are routinely assessed during treatment and follow up of patients with cancer, further investigations on the utility of GPS in identifying frailty are relevant.

Loss of muscle mass in frailty and cancer

Severe loss of muscle mass may occur due to aging, but may also be a result of diseases, including cancer.[30,51,52] In oncology settings, the phenomenon has often been referred to as sarcopenia,[53] whereas in geriatric medicine, there is a broad agreement that this term should be used for severe muscle loss in combination with either reduced muscle strength or reduced physical function.[52] In older adults with non-malignant illnesses, severe loss of muscle mass is associated with frailty, physical deterioration, falls, hospital admissions and increased mortality.[54,55] In patients with cancer, there is evidence that loss of muscle mass is common and associated with poorer survival and increased toxicity of systemic cancer treatment.[56,57] Thus, in older patients with cancer, loss of muscle mass may have several causes, but it seems relevant to assume that assessment of muscle mass would contribute to determine the patient's vulnerability and risk of adverse treatment effects. Whether this is the case for older patients receiving EBRT has, as far as we know, not been investigated.

Loss of muscle mass may also be related to an active inflammatory response.[58] Neither the underlying mechanisms nor the correlation between clinical frailty, muscle loss and active inflammation is fully clarified.

GA in the municipal health services

GA for older cancer patients have been tested and found feasible both in larger university hospital based- and smaller oncological clinics.[24,25] Whether such an assessment is feasible in the municipal health services is unknown.

Study aims

The overarching aim is to generate knowledge that may provide a basis for developing a targeted and feasible intervention to prevent adverse events during and after curative and palliative EBRT in patients $\geq$ 65 years.

Definitions: adverse events and outcomes

Adverse events are defined as reduction in QoL, physical deterioration, increased need for help in daily life activities and/or need for residential care.

Primary outcomes are global QoL and physical function as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30).79

Secondary outcomes are the ability to maintain everyday activities as measured by the Nottingham Extended Activities of Daily Living (NEADL), hospital- and nursing home admittance.

Detailed aims and hypotheses:

Primary aims and hypotheses

1. To identify patients receiving EBRT ≥ 65 years at risk of adverse events on the defined outcomes and to evaluate what characterizes these patients.
    - Our hypothesis is that patients who by GA may be classified as frail will have increased risk of adverse events as defined compared to patients who are classified as non-frail, regardless of cancer type, stage, and radiotherapy procedure (localisation, dose, field size)
2. To test the feasibility of GA in the municipal health services

Secondary aims and hypotheses:

1. To describe the prevalence of problems uncovered by GA in older patients ≥ 65 years before and after EBRT, and investigate the association between specific GA domains and adverse events.
    - Our hypothesis is that severe comorbidity, inadequate medication, malnutrition, impaired physical and cognitive functioning are factors that increase the risk of adverse events.
2. Validate the Edmonton Frail Scale (EFS) as a screening instrument to identify frail patients and patients at risk of adverse events
3. Evaluate the potential usefulness of GA carried out in the municipal health services, for older patients ≥ receiving radiotherapy

Methods

Design and setting

The study is a prospective observational study emerging from the Radiotherapy Unit and Unit of Geriatric Medicine, Innlandet Hospital Trust (SI), Gjøvik and Centre for Old Age Psychiatry Research (AFS), SI. It will be carried out in collaboration with the municipal health services in the hospital's recruitment area. All municipalities in Hedmark and Oppland will be invited to participate. The patients will be included at the Radiotherapy Unit, SI Gjøvik and followed up with self-report questionnaires. Patients from the partaking municipalities will also be followed by study specific registrations carried out by a municipal nurse after EBRT completion.

To achieve the necessary co-operation with the municipal health services, the project is linked to the existing "Network of nurses for the severely ill" in Hedmark and Oppland County. The network consists of nurses working with cancer patients, both in the municipalities and in hospital. Most municipalities have one or more nurses attached to the network, mainly referred to as "cancer contacts" or "contact nurses". The majority of these are trained oncology nurses or palliative care nurses. In addition, some hold a position referred to as "cancer coordinator", an assignment partly financed by The Norwegian Cancer Society. Regardless of education and affiliation, all these nurses are experienced, committed and dedicated, and routinely participate in the care for most cancer patients in their area. In all partaking municipalities, the "cancer contact/contact nurse" from the network will also be the project's contact nurse.

Inclusion criteria

- Age $\geq$ 65 years
- Referred to the Radiotherapy Unit, SI Gjøvik for palliative or curative radiotherapy
- Resident in Oppland or Hedmark County
- Histologically verified cancer
- Fluent in Norwegian, both oral and written
- Able to understand and answer questionnaires
- Provide written consent

Registrations, tests and forms

Patients who fulfil the inclusion criteria will be followed with study specific assessments from start of EBRT to 16 weeks after completion of treatment. With respect to survival, they will be followed for two years. The planned registrations include sociodemographic and medical data, use of municipal health care services, GAs and self-report questionnaires including physical function and QoL (primary outcomes) and need for assistance in daily living (secondary outcome). The registrations will be performed at start and end of EBRT, then 2, 8, and 16 weeks later.

During follow up after EBRT, the GA will be performed by the municipal "cancer nurse/contact nurse" (the local nurse attached to the "Network of nurses for the severely ill", see above), or another dedicated nurse in the patient`s municipality. Information that is relevant to evaluate the feasibility and usefulness of a GA performed by municipal home care nurses will be collected.

The table on the next page gives an overview over the planned registrations.

We will also collect information from the patient's hospital records (e.g. hospital admissions), the municipal health care services, The Norwegian Patient Registry, The Norwegian Cancer registry and the Norwegian Cause of Death Registry as described in detail below.

Overview over the study registration

A. Sociodemographic and medical data, use of health care services. Green marking: performed by project nurse. Marked red: performed by a nurse in the municipal health care service							
Domain		**Prior to EBRT Baseline**	**At completion EBRT-1***	**At completion EBRT-1****	**weeks after EBRT**		
Sociodemographic data		**x**			**2**	**8**	**16**
Medical data, including former cancer treatment and planned EBRT regimen		**x**					
Medical data, including actually received EBRT			**x**	**x**			
Use of home care services		**x**	**x**	**x**	**x**	**x**	**x**
Medical data, including ongoing cancer treatment, hospital and nursing home admissions.					**x**	**x**	**x**
ECOG performance status.		**x**	**x**	**x**			
Height (only baseline) and weight.		**x**	**x**	**x**	**x**	**x**	**x**
B. geriatric assessment (GA). Green: performed by project nurse, red: performed by municipal cancer contact nurse							
Domain	**Method/instrument**				**2**	**8**	**16**
GA domain							
Comorbidity	Charlson Comorbidity Index	**x**					
Polypharmacy	Regular medications, ATC codes	**x**	**x**	**x**	**x**	**x**	**x**
Physical function	Timed up and go (TUG),	**x**		**x**	**x**	**x**	**x**
	Number of falls	**x**			**x**	**x**	**x**
	Barthel index	**x**		**x**	**x**	**x**	**x**
Nutrtional status	Weight loss, –MNA-SF	**x**	**only weight**	**x**	**x**	**x**	**x**
Cognition	Montreal Cognitive Assessment (MoCA test)	**x**		**x**		**x**	**x**
Depression	Geriatric Depression Scale (GDS)	**x**		**x**		**x**	**x**
Frailty screening	The Edmonton Frail Scale (EFS)	**x**		**x**	**x**	**x**	**x**
C. Patient reported outcomes							
QoL and symptoms	EORTC QLQ-C30	**x**	**x**	**x**	**x**	**x**	**x**
IADL	NEADL	**x**		**x**	**x**	**x**	**x**
Activities	Pleasurable activities	**x**			**x**	**x**	**x**
D. GA – feasibility							
Time spent, completion rate, benefits and inconvenience (patient/nurse)					**x**	**x**	**x**

*Pasients receiving =< 10 radiation fractions; ** Patients receiving more than 10 fractions; *** Addition to the questionnaire to patients from municipalities not participating with follow-up GA registrations.

Sociodemographic data

These will be registered at patient enrolment, and will include age, gender, education, civil status, residence (home/residential care/nursing home) and living conditions (alone, with spouse or cohabitant +/- children, or others), number of children, number of children living in the same municipality, and smoking status. The patient will also be asked if his/her spouse/cohabitant (when existent) is fit and independent or in need of assistance. A project nurse will register these data based on information from the patient.

Medical data

Baseline

Based on information from the patient, the patient's treating physician and hospital records, the project nurse will register: cancer diagnosis, date of diagnosis, disease stage, localization of metastases, former and current cancer treatment, planned EBRT regimen (dosage, area and treatment target) and ECOG performance status. Diagnostic CT scans of thorax/abdomen that have been taken within 5 weeks prior to start of EBRT will be collected for analysis of body composition.

Results of routine blood samples (haemoglobin, white blood cell counts with differentials, creatinine, electrolytes, s-alb, liver function tests and CRP) taken within two weeks prior to EBRT will be registered. If the patient has not taken these blood samples within the last two weeks, he/she will be asked to so at enrolment.

At completion of EBRT

At this point the following will be recorded: administered radiation dose, causes of early treatment withdrawal (if relevant), any other cancer treatment that have been administered simultaneously with EBRT, plans for further cancer treatment, admission to hospital or patients' hotel during treatment, residence at the end of treatment (home, nursing home or rehabilitation institution), ECOG status and weight. The information will obtained from the patient/hospital records and/or treating oncologist.

During the follow-up

Based on information from the patients' general practitioner, treating oncologist and/or hospital records, the patients' contact nurse in the municipality or the project nurse will prospectively register information on any supplementary or new cancer treatment, new comorbidities or hospital admissions. Detailed information on supplementary or new cancer treatment (new RT, medical cancer treatment or surgical interventions) will be collected from the hospital records.

Data on hospital admissions (cause, duration and treatment received), diagnostic CT scans and relevant blood test will be obtained from the patients' hospital records.

Data on survival will be obtained from the patients' hospital records and/or municipal health service, as well as from the Norwegian Cause of Death Registry for up to two years after completion of EBRT.

Use of municipal health services

Information regarding the use of the home care services, nursing homes (number of admissions and their duration), and other health services from the municipalities will be registered at each assessment point, either by the project nurse, municipal contact nurse or by information given by the patient.

Geriatric assessment (GA)

GA will be performed by using well-documented, validated tests and questionnaires.

Comorbidity will be registered by Charlson Comorbidity Index (CCI), based on information from the hospital record, the treating oncologist, and potentially supplemented with information from the general practitioner and patient. CCI categorizes comorbid conditions based on the International Classification of Diseases (ICD). Each comorbidity category is weighted from 1-6 based on adjusted risk for mortality, and the scores are summarized into a total score. Originally, the CCI consisted of 19 categories,[59] which has later been changed to 17.[60] The list of specific ICD codes used in the categorization and the original weighting of scores have also been modified.[61],[62,63]

Medication: The project nurse will register all regular medications with name, daily dosage and ATC code in accordance with information from the patient/general practitioner/homecare nurse/hospital records. The registration will include inhalations, cremes/ointments, vitamins and eyedrops**.**

Physical functioning will be assessed by:

- Timed Up and Go (TUG),[64] which assesses the time it takes to stand up from a chair, walk 3 meters, turn, walk back and sit down again.
- Barthel ADL-indeks[65] which assesses the ability to perform basic activities of daily living (ADL). The activities include eating, personal hygiene, getting dressed and undressed, bowel- and bladder control, using the toilet and mobility. The assessment will be done by interview.
- Number of falls**:** when and where they occurred (outside or inside) and if they caused any injuries.

Cognitive function will be assessed by the Montreal Cognitive Assessment (MoCA) test.[66] The test assesses visuospatial abilities, executive functioning, attention, concentration, memory, language and orientation, and takes about 5-10 minutes to complete. The scores range from 0 (worse) to 30 (best/normal)

Depression and symptoms of depression will be assessed by the Geriatric Depression Scale (GDS).[67] Originally, the scale consisted of 30 questions. A modified version with 15 questions have been developed, and validated.[68,69] This is available in a Norwegian version,[70] which will be used in this study. GDS-15 items are answered yes/no, and the scale is scored from 0-15.

Score > 4 is considered an indication for depression. [71] GDS is suitable for self-reporting, but administration by interview has also been recommended. [72]

Nutrional status will be registered by height, weight, body mass index (BMI) (weight/height x height), and the Mini Nutrional Assessment Short Form (MNA SF).[73] The form has six items: loss of appetite, weight loss, mobility, psychological stress/acute illness, occurrence of neuropsychological illness (dementia or depression) and body mass index. Each item is scored from 0-2 or 0-3, and the scores are summarized into a total score from 0-14. Scores 12-14 indicate normal nutritional status, 8-11 risk of malnutrition and 0-7 indicate malnutrition.[74] The registrations will be based on observation and information given by the patient.

Edmonton Frail Scale (EFS) is a screening instrument developed for clinicians without special training in frailty assessment.[46] EFS includes 9 areas: cognition, health, function, social support, number of medications, nutritional status, continence (bladder control), balance and mobility, and have 11 items that are scored from 0-1 or 0-2. Item scores are summarized into a total score ranging from 0 (fit) to 17 (most severe level of frailty).

As an addition to the 11 items, we will register which of the activities mentioned in the item "how many of the following activities do you need help with……"), the patient is not able to perform independently**.**

Fatigue will not be assessed as part of GA, but is included in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), see below.

Questionnaires for self-report

The EORTC QLQ-C30 [75] is a 30-item questionnaire developed for QoL assessment in cancer patients. It is widely used and thoroughly tested. The questionnaire includes scales for physical function (5 items), emotional function (4 items), role function (2 items), social function (2 items), cognitive function (2 items) and global health/QoL (2 items). In addition, there are three symptom scales, i.e. nausea/vomiting (2 items), fatigue (3 items) and pain (2 items), and six single items assessing symptoms that are common in patients with cancer and the financial impact of the disease . Before analysis, scale/item scores are transformed into scales ranging from 0 to 100. A change of 10 points or more on each scale/item is considered clinically significant.[76]

Nottingham Extended Activities of Daily Living (NEADL)[77] assesses functional status. It includes 20 items covering four main areas: mobility (6 items including use of transportation), eating/drinking/preparing food (5 items), household activities (5 items, including laundry, shopping, handling money) and leisure activities (6 items). Each item is answered on a categorical scale ranging from 0 (activity cannot be performed) to 3 (performs without help). Item scores are summarized into a scale ranging from 0 to 66. The smallest change considered to be of clinical relevance is between 2,4 and 6,1 points.[78]

Pleasurable activities. The patient's participation in pleasurable activities will be registered with a short questionnaire (5 items) from the DemiNor study, a study from the Norwegian National

Advisory Unit on Ageing and Health and the Centre for Old Age Psychiatry Research. The purpose is that such knowledge may be useful for the development of rehabilitation interventions.

Feasibility of geriatric assessment in the municipal health services

We will register how many of the municipalities in Hedmark and Oppland that agrees to participate in the study. At each assessment point (2, 8 and 16 weeks after EBRT), the contact nurse in the partaking municipalities will register if GA was done or not (completely or partly), reasons for lack of completion, if the registrations were found useful or burdensome (for the patient and the nurse), and if any measures were undertaken based on GA findings.

Registry data

In addition to data retrieved from patients' hospital records, we plan to retrieve data on hospital admissions during follow-up from the Norwegian Patient Registry (NPR). As described, information regarding cancer diagnosis and treatment, survival and death will be extracted from patient records, but we also plan to obtain data from the Norwegian Cancer Registry (cancer diagnosis, stage of disease and treatment) and The Norwegian Cancer Registry (date, place and cause of death) to ensure data quality. Survival data will contribute to identify patients with short life expectancy, who potentially may benefit more from purely palliative measures than from a GAM intervention.

Implementation

Enrolment

A project nurse will have the daily responsibility for all data collection.

All patients who are 65 years or older and have been referred to the Radiotherapy Unit, SI Gjøvik, will receive brief information about the study together with the letter summoning them to their first consultation. This consultation is usually meant for information and treatment planning (CT dose planning), whereas the treatment itself normally starts several days, sometimes weeks, later. Eligible patients will be identified at the first consultation. The treating oncologist will ensure that the inclusion criteria are fulfilled, and that the patient is capable of providing informed consent. The project nurse will present the study for the patient both orally and in writing. If the patient consents to participation, baseline registrations will be performed on the same day (i.e. if the EBRT is expected to start within one week), or in connection with start of treatment.

~~Baseline registrations (i.e. the GA) includes a test of cognitive function (MoCA test). If the MoCA score is below 20 (possible dementia), the patients' treating oncologist will be consulted to re-evaluate the patients' capability to give informed consent before the baseline procedures are completed. However, since patients with mild to moderate dementia may also have sufficient capability to provide an informed consent, no definite MoCA score limit is set for inclusion/exclusion.~~

Baseline registrations include a test of cognitive function (MoCA test). If the test gives reason to believe that the patient has cognitive impairment (score $\leq$ 18), and the project nurse (an

experienced cancer nurse), based both on the MoCA score and the conversation with the patient, finds reasons to question the patients capability to provide informed consent despite the oncologist's former evaluation, a re-in collaboration with the treating oncologist will be performed before completing the baseline registrations. If the MoCA score is ≤ 16, the patient's capability to provide informed consent will in any case be re-evaluated. However, since patients with mild to moderate dementia may also have sufficient capability to provide informed consent, no definite MoCA score limit is set for inclusion/exclusion.

Emergency referrals to EBRT is not a defined exclusion criterion. Emergency patients are usually managed as inpatients and may be included if they meet the inclusion criteria. It is, however, a prerequisite that the treating oncologist do not consider the inclusion procedure too burdensome for the patient.

In addition to ask for consent to all study procedures and data collection, the patients will be asked for permission to inform the project contact nurse in the patient's municipality about his/her study inclusion and the planned schedule of his/her follow up registrations.

Non-included patients will be registered by age, gender, diagnosis and cause of exclusion (does not wish to participate/does not fulfil the inclusion criteria/is considered too ill/incapable of participation).

Follow up

The patients will be followed with study specific registrations for 16 weeks after completion of EBRT. As the length of the treatment period may vary from one day (single fraction) to 5-7 (8) weeks for some patients receiving curative treatment, the length of the period from baseline to 16 weeks after treatment will also vary from 16 to 22-23 (24) weeks. With respect to survival, the patients will be followed for two years after completion of EBRT.

At completion of EBRT

At completion of EBRT, the project nurse will perform a repeated GA and hand out the scheduled self-report questionnaire. If the patient prefers to fill in the questionnaire at home, he/she will be given the questionnaire along with a pre-paid return envelope.

~~Patients who have received less than six radiation fractions (about one week of treatment), will only fill in the questionnaire since a new GA after such a short period is likely to add little new information~~

Patients who have received less than 10 radiation fractions (treatment duration two weeks or less), will only fill in the self-report questionnaire since a new GA after such a short period is likely to add little new information.

Further follow-up

The self-report questionnaires, scheduled at 2, 8 and 16 weeks after completion of EBRT, will be administered by post to all patients with a prepaid return envelope attached. If no answer is received within 2 weeks, a reminder will be sent.

Apart from this, the follow-up will vary somewhat depending on whether the health services in the patients' municipality have consented to participate with GA or not.

1. For patients from non-consenting municipalities who does not have any contact with the municipal home care services, the project nurse will offer to contact them (or the municipal cancer contact nurse) by the end of EBRT. The purpose is to ensure that the patient receives a follow up according to the municipality's routine.

   Moreover, for these patients, a few questions will be added to the self-report follow-up questionnaires. The patients will be asked if they have any questions or needs that makes a phone call from the project nurse or a cancer nurse at the Radiotherapy Unit warranted, and about their use of municipal health care services. If the information about the latter is lacking or incomplete, the project nurse will take contact with the municipality services directly.

2. For patients from municipalities participating in the project with GA, the project nurse will inform the municipal cancer /contact nurse when the patients' EBRT is completed. The contact nurse will get in touch with the patient to make an appointment for the next registration procedure, 2 weeks after completion of EBRT. The GA performed at this point will be limited to registration of medications, nutritional status, physical functioning (TUG, Barthel Index and falls) and the Edmonton Frail Scale. For the next registrations at 8 and 16 weeks, all parts of GA will be included except comorbidity. The contact nurse is encouraged to make the appointments for subsequent registrations in advance. All registrations will preferably take place at the patients' current residence (at home or in a nursing home), but if the patient wishes to meet at another suitable place, this can be arranged. The patients should, however, not be summoned to any particular location (e.g. family physician's or a nurses' office) specifically for the registrations.

   After each registration, the nurse will fill in a special form to evaluate feasibility (see "Feasibility of a geriatric assessment in the municipal health services, page 14). She/he will also register any measures or interventions undertaken due to GA findings.

Actions due to GA findings

The study is an observational study, but if the GA uncovers problems or needs requiring management, actions should be undertaken in collaboration/consultation with the patient. No measure can, however, be initiated without the patient's consent. Furthermore, the information acquired during the GA cannot be passed on to the health professionals who normally take care of the patient without the patient's informed consent. A general instruction has been attached to GA registration forms to ensure that this information reaches all contact nurses performing GA in the municipalities.

GA findings indicating that actions are required may vary from patient to patient, dependent on established support, care and treatment from the involved health care services. Simple, general guidelines have been developed, stating when actions should be considered and/or undertaken.

Patient selection and sample size

The Radiotherapy Unit, SI Gjøvik offers EBRT to patients with cancer from Oppland and Hedmark Counties (approximately 380 000 inhabitants) and treats about 700 patients each year. About 2/3 of these are 65 years or older. Palliative treatment represents about 60% of all treatment, and is offered regardless of cancer type. Curative treatment is administered only to patients with breast-, prostate-, lung- or skin cancer. Patients with other types of cancer in need of EBRT with curative intent, or patients who need stereotactic or internal radiotherapy are referred to Oslo University Hospital

***Sample size estimates*:** The prevalence and impact of problems uncovered by GA in older Norwegian patients receiving EBRT are not known. Neither is the frequency of the defined adverse outcomes. Thus, estimates of the sample size needed to reliably define characteristics of patients at risk for adverse outcomes cannot be made. Furthermore, our sample will be heterogeneous and several demographic, medical and GA characteristics will have to be taken into account.

Based on these considerations, we will extend the inclusion period to one year and aim at including 325 patients. This cohort, we believe, will be a representative sample, large enough to ensure that all participating municipalities are represented for the evaluation of the feasibility of GA. To achieve 325 enrolled patients within one year, we presume that 70% of the patients 65 years or older who are treated at the RTU will consent to participation.

Our hypothesis is that patients, who are classified as frail, will have increased risk of deterioration in global QoL and physical functioning (PF), assessed by the corresponding EORTC QLQ-C30 scales ranging from 0-100. A difference of 10 points on these scales is considered a clinically significant difference.[76] Based on the reported prevalence of frailty in studies of other cohorts of older patients with cancer,[18,43] one may assume that about 40% will be frail and 60% non-frail. To detect a difference of 10 points in global QoL and PF between the two groups at 8 weeks follow up, standard deviation (SD) = 30 (a conservative estimate), power 80% and significance level 5%, 119 patients will be needed in the frail group and 178 patients in the non-frail group, in total 297 patients. To document a difference of 11 points, 247 patients are needed. Based on these estimates, and taking into account that some drop out will occur, we find that including 325 patients will be satisfactory.

Strategy for the analyses

Adverse events are defined as described under Study aims, page 7-8. The patients will be classified as frail or non-frail based on GA at baseline. Primary and secondary outcomes will be compared between the non-frail and frail using bivariate regression analyses. Since the study cohort will be heterogeneous and several factors most likely will affect the outcomes, we will also estimate multivariate regression models, adjusted for these factors. The most important factors will be type of cancer, stage of disease, gender and radiotherapy regimen. Time trend models will be estimated in order to assess the development in the primary outcomes for non-frail/frail patients during the follow up period. We will also estimate bi- and multivariate regression models to assess the impact of each individual factor in GA (i.e. comorbidity, physical function, nutritional status) on the defined outcomes. Furthermore, we will use descriptive statistics to compare sociodemographic and medical data and GA findings between patients experiencing and not experiencing adverse events.

The sensitivity and specificity of EFS in identifying frail patients will be tested against the full GA. EFS ability to predict adverse events on the defined outcomes will be assessed with uni- and multivariate regression analysis, controlled for relevant co-variates (e.g. type of cancer, stage of disease, and radiotherapy regimen).

To assess the feasibility of GA for the municipal health care service, we will partly lean on the RE-AIM Framework,[79] and evaluate the proportion of consenting and participating municipalities and explore potential difference between them. We will also evaluate the number and completeness of the GAs that are actually performed in relation to those planned. For each assessment, the municipal contact nurse, who performs the assessment, will answer a short questionnaire addressing time spent, obstacles, facilitators, patients' opinion on relevance and convenience, and actions taken due to identified problems. These data will be linked to the individual patients and thereby contribute to identify patients who may benefit the most from GA. For analyses, we will use descriptive statistics.

***Analysis of muscle mass and inflammation markers*:** Muscle mass will be quantified by analyses of diagnostic CT scans taken within five weeks prior to start of EBRT. The analyses will be performed with special soft-ware developed for this purpose (Slice-O-Matic software V4.3 - Tomovision, Montreal, QC, Canada).[30,51,53,80] As an indicator of inflammation, we will use the Glasgow Prognostic Score (GPS) which is based on C-reactive protein (CRP) and serum-albumin (s-alb) and is scored on a scale from 0 to 2 (0 = CRP < 10 + s-alb> 35, 1 = CRP> 10, any s-alb value, 2 = CRP > 10 + s-alb< 35). [50] The association between frailty defined by GA, GPS and muscle mass will be assessed using descriptive statistics and correlation analyses. Regression analyses will be used to assess the association with survival.

***Comparison with outcomes in a subsequent pilot study*:** The plan is that an intervention targeting patients at risk of adverse events will be developed based on the results from the present study, and that this intervention will be tested in a pilot study before embarking on a larger randomised trial. The pilot study will have a cluster-randomized design, randomising municipalities to either control or intervention to avoid that the same staff treats both control and intervention patients. In a smaller pilot study, a cluster-randomised design may results in an imbalance in characteristics between control and intervention patients. Although this may partly be adjusted for in the analyses, it may be relevant to draw comparisons to a matched control group from the present cohort. This potential use of study data is explicitly stated in the patient information and consent form.

Data storage and protection

Data storage and management are described in detail in the Norwegian protocol with the purpose of informing the Ethical Review Board and the Data Protection Officials. In short, data storage and use will follow Norwegian laws and regulations and be approved by both the Norwegian Ethical Review Board, Health Region South-East, and the Privacy Protection Official at Innlandet Hospital Trust before study start. According to Norwegian regulations, data sharing is not possible before data are anonymised, i.e. unless the patients are specifically informed through the patient information and consent form.

Ethics

Study approval and data storage will be applied for to The Regional Committee for Medical Research Ethics, Health Region South-East (REK HSØ) and the Data Protection Official at Innlandet Hospital Trust before start of study. The study will be performed according to the rules of the Helsinki-declaration, and registered in the ClinicalTrials.gov database. Participation will not inflict upon the patients' cancer treatment and will not imply any health risks or deviation from good clinical practice. The patients will receive treatment and care according to routine practice, and all participants will provide written informed consent.

Besides the inconvenience of providing potential sensitive information and spending time to fill in questionnaires and to perform the study test, study participation inflicts little burden on the patients. The registrations are kept as simple as possible, and represent no health risks. Even so, certain ethical aspects are still relevant to discuss. Being an observational study, it is from a methodological point of view important that study participation and registrations inflict as little as possible upon the patients' routine care. However, thorough evaluations like GA will potentially uncover problems and needs that it will be ethically unacceptable not to act upon. As formerly stated, we have therefore prepared general guidelines for the project nurse and our contact nurses in the municipalities stating when actions should be considered or carried out (with patients' informed consent). These actions and the undertaken measures will be registered, both to clarify the needs for GA in older patients with cancer receiving EBRT, and also in order to interpret the results.

It is possible that the extra attention the structured assessments entails, may benefit the participating patient. Hence it might be seen as problematic that patients from non-participating municipalities do not receive the same follow up as those from municipalities agreeing to perform GA during follow-up. We find, however, no reason to believe that these GA registrations will have a significant clinical impact. Firstly, all patients will be registered and tested in the same way prior to and at completion of EBRT. Secondly, there is currently no documentation indicating that GA without management provides significant benefits for the patients. On the contrary, a recently published study[81] of lung cancer patients randomized for GA or not did not report any impact of GA, except for a little less toxicity from chemotherapy. This latter finding may be explained by the fact that fewer patients in the GA group received such treatment. Thirdly, patients from non-participating municipalities will be given the opportunity to keep in touch with the project nurse or cancer nurse at the Radiotherapy Unit if they report any need for it through the questionnaire especially added for these patients. Overall, we believe that participating in this study will have the same impact on all patients.

The knowledge generated by this study will be beneficial for future patients, and we find that the possible inconvenience for the participants is exceeded by the potential benefit for the participants and for the overall group of older patients with cancer receiving EBRT.

Organization

The project is organized with a project leader, an assistant project leader, a scientific (main) and a local project group, a reference group, and user representatives. Participants and details appear in section "Project group and collaboration" below. The study will provide the basis for a doctoral thesis, completed by a PhD student, financed by the Research Department, Innlandet Hospital Trust and connected to The Research Centre for Old Age Psychiatry (AFS). AFS will also serve as the project office.

A project nurse in a full-time position, financed by the Research Department, Innlandet hospital trust will be employed before the study starts in February 2017. He/she will be a professional cancer nurse and will have the daily responsibility for the data collection. Furthermore, he/she will be a key person in the collaboration with the municipal health services, and will have a co-responsibility for training of the municipal contact nurses who will perform the follow-up GA registrations. The project nurse will continuously be available for the municipal health services for guidance, and will have all necessary access to academic expertise from local geriatrists, geriatric nurses, cancer nurses and oncologists, all represented in the scientific and the local project group. If the project nurse is intermittently absent (holidays etc.), the PhD student (a physician) will be responsible for patient inclusion, registrations and data collecting. The PhD student will receive the necessary training from the project nurse and participants in the project group.

The study conduct will depend on a good collaboration with the municipal health services in Hedmark and Oppland counties. To achieve this, the project is linked to the existing "Network of nurses for the severely ill", as formerly explained (page 9). Four nurses from this network have collaborated with the scientific project group in the study design (including the scheduled registrations), and will continue to participate in the further study conduct. There is also established a larger reference group comprising municipal cancer contact nurses and cancer coordinators. Before the study commences, a cancer contact nurse, preferably a cancer nurse, from each participating municipality will be assigned to the project and the reference group. Additionally, participants in the reference group from general practitioners (GPs) in the area arewarranted. To achieve this, the plan is to contact the local GPs union in the two counties.

Participation in the study must be anchored to the health care management in each municipality. Thus, all 46 municipalities in Hedmark and Oppland have received written information about the study, and a final confirmation or rejection of their participation will be retrieved before study start.

Future contact with the municipal health care service will be maintained through email, phone, video conferences, and established meeting points. For those nurses who will participate in GA registrations, meetings/seminars for training will be arranged. Participation will not be charged, and travel expenses will be covered.

User participation

A group of four user representatives has been established. So far, they have participated in the planning of the study, and also evaluated and approved the scheduled registrations. These representatives will continue their collaboration throughout the study conduct, and will also participate in interpreting and dissemination of results.

Project group and collaboration

The project emerges from Innlandet Hospital Trust (SI) and will be performed in collaboration with the municipalities in Hedmark and Oppland counties and several internal and external partners, including the Norwegian University of Science and Technology (NTNU) Campus Gjøvik. Marit S Jordhøy (prof., MD, oncologist), SI will lead the project. Co-leader is Øyvind Kirkevold (prof, ass. research director), Faculty of Health, Care and Nursing, NTNU Gjøvik and The Research Centre for Old Age Psychiatry (AFS), SI.

The scientific project group: Anne Hjelstuen (MD, PhD), Unit of Geriatric Medicine, SI Gjøvik contribuing with expertise in internal and geriatric medicine. Katharina Lederer (MD), leading radiation oncologist, The Radiotherapy Unit, SI Gjøvik contributing with expertise in radiation oncology. Sverre Bergh (MD, PhD, leader of research) and Lene Kirkhus (MD, PhD student), AFS, SI contributing with broad experience from large studies involving health resources, depression and dementia, and from the ongoing SI study on older cancer patients receiving chemotherapy, respectively. Aud Obstfelder (prof. leader of Centre for Care Research) and Øyvind Kirkevold (prof), The Faculty of Health, Care and Nursing, NTNU Gjøvik provide expertise on health organisation research, technology and quantitative methodology, and broad experience from research involving community health care, including large national and international cohort studies, respectively. The following additional members all contribute with expertise from their area of work, in which they all have long lasting clinical and research experience and are also frontline experts: Ingvild Saltvedt (geriatrician, PhD), Dept. of Geriatric Medicine (Head of Dept.), St Olav's Hospital and Dept. of Neuroscience, NTNU; Bjørn Henning Grønberg (oncologist, PhD), Dept of Cancer Research and Molecular Medicine, NTNU and Clinic of Oncology, St. Olav's Hospital; Line Oldervoll (prof., rehabilitation medicine), Dept. of Social Work and Health Science, NTNU and Norwegian Heart and Lung Patient Organization (NHL) (leader of research); Asta Bye (PhD, nutritionist) Oslo and Akershus University College (HiOA), Astrid Bergland (prof, PhD, physiotherapist) (HiOA) and Siri Rostoft (MD, PhD, geriatric oncology), Dept. of Geriatric Medicine, Oslo University Hospital. The project's statistician is senior researcher, PhD, Jūratė Šaltytė Benth, University of Oslo and Akershus University Hospital.

The local project group provides local clinical and organizational expertise, ensures the co-operation with the involved health services and thereby the project implementation and conduct. The group includes a geriatrician and specialized geriatric nurse from the Unit of Geriatric Medicine, SI Gjøvik, a radiation technologist, RTU Gjøvik, a nutritionist, four cancer contact nurses representing SI, and Gjøvik, Stange and Valdres municipalities.

International collaboration is established with the University of Alberta, Edmonton, Canada including the developer of the Edmonton Frail Scale, Darryl Rolfson (prof, geriatrician), Dept. of Geriatric Medicine.

User representatives: Our aim is to establish a group of 6 members (3 of each gender) > 65 years of age with experience from EBRT. Currently 4 members have been assigned from the local Breast Cancer Society and the local Prostate Society, respectively.

Reference group: Presently the group includes 11 cancer nurses and cancer co-ordinators representing 16 municipalities. We are aiming at including the remaining cancer coordinators (6-8) in the SI catchment area as well as representatives for the GPs.

Financial support

The study is fully financed by the Research Department at Innlandet Hospital Trust. No other financial partner is involved.

Time schedule

Start of enrolment is planned for February 2017 and will continue for 12 months or until the planned number of participants are included. The patients will be followed with study specific registrations for 16 weeks after the end of EBRT. Data on survival will be retrieved for up to 2 years after completion of EBRT. Furthermore, a PhD student and a project nurse will be contracted from the time of study start.

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Amendment 1-3

These amendments have not been translated from Norwegian. Amendments 1-2 were added due to the revision of the protocol on the 18.04.17 and concerns evaluation of the patients' capability of providing informed consent, and MoCA score cut-offs for when a re-evaluation of the patients capability should be performed. The resulting changes in the protocol are marked in yellow.

Amendment 3 was written as some additional data collection was planned, but this was never carried out due to practical problems with the planned registrations.

Amendment 4: Amendments prior to data analyses.

Several years have passed since the original protocol was written, and during this time, the field of geriatric oncology has evolved considerably. Thus, before embarking on the analyses, the analytic strategy has been discussed in the scientific group, and some amendments have been made.

1. We have decided to report overall survival (OS) among palliative versus curative patients, and investigate the association between GA domains and OS in the first paper emerging from this study.

   This first paper will fulfil the secondary aim of our study reading as follows: "*To define the prevalence of problems uncovered by GA in older patients ≥ 65 years before and after EBRT, and investigate the association between GA domains and adverse events*", except that OS and not deterioration in QoL and physical function (PF) will be the main outcome and only GA findings at baseline will be included.

   Explanation for changes:

   Although the study includes a two-year follow-up with respect to survival, OS was not a pre-defined outcome in this observational study. The exception was a plan to investigate the association between CT based muscle measure, inflammation and survival (protocol, page 18: "*Analysis of muscle mass and inflammation markers* "). One reason for this omission was that the association between GA defined frailty and OS was relatively well-documented in 2016, and thereby assumed to be of less interest than the outcomes QoL and PF.

   The association between frailty/GA impairments and survival in older patients receiving EBRT is, however, currently still scarcely investigated, and therefore of interest. Furthermore, the overarching aim of the present study was to "*generate knowledge that may provide a basis for developing a targeted and feasible intervention to prevent adverse events during and after curative and palliative EBRT in patients ≥ 65 years*". Although not pre-defined as such in our study, death is the ultimate adverse event, and a gold standard endpoint in cancer studies. Hence, we found that investigating whether GA impairments are associated with mortality risk is both appropriate and pertinent, and well in line with the study purpose. Several of the impairments that may be identified by GA, are remediable. If any of these could have an impact on OS in patients with cancer receiving curative or palliative EBRT, developing and/or implementing interventions that specifically target these impairments would be highly important, i.e. in hope of improving an endpoint of major importance for the patients. Finally, when investigating the impact of GA impairments on global QoL, physical function and need for daily life assistance, it is crucial to know, whether the same impairments also affect OS.

   Before any analysis for the first paper was conducted, a detailed analysis plan was prepared(**Appendix 1**). Subsequently, however, the definition of OS was corrected from "time from end of EBRT to death or last observation" to "time from inclusion to death or last

observation", and we also decided to explore the association between number of GA impairments and OS.

2. <u>OS will also be used as an outcome in the validation of the Edmonton Frail Scale, i.e. the planned second paper</u>

   The second secondary aim of our study is to "*Validate the Edmonton Frail Scale (EFS) as a screening instrument to identify frail patients and patients at risk of adverse events*" (see page 8).

   The plan for the analyses was: "*The sensitivity and specificity of EFS in identifying frail patients will be tested against the full GA. EFS' ability to predict adverse events on the defined outcomes will be assessed with uni- and multivariable regression analyses, controlled for relevant co-variates (e.g. type of cancer, stage of disease, and radiotherapy regimen"*(see page 17)

   Partly based on the considerations stated under point 1, we have now decided to perform the validation by investigating the association between the instrument's scores and OS in addition to association with GA findings. Another strong argument for this is that other well-known and widely used frailty screening instruments, e.g. the G8, have been widely tested against patients' survival.[1-5] Thus, for comparison, which is important, we will do likewise.

   Before embarking on these analyses, a detailed plan has also been prepared (**Appendix 2**).

3. <u>We have decided not to use the term "frailty" when classifying the patients according to GA. Hence, we will not define the patients as frail or non-frail, but instead classify them according to their number of identified GA impairments.</u>

   Our primary hypothesis (page 8) has been revised accordingly, now reading: *"Our hypothesis is that increasing number of GA impairments is associated with increased risk of adverse events as defined, regardless of cancer type, stage, and radiotherapy procedure (localisation, dose, field size)*

   This hypothesis and the primary aim of our study will be addressed in paper 3, for which a detailed plan for the analyses has also been prepared (**Appendix 3**)

   This amendment also affects paper 2 as the sensitivity and specificity of Edmonton Frail Scale will be evaluated against number of geriatric deficits, not against a classification of frail vs. non-frail patients.

Explanation:

The concept of frailty has received increasing attention in oncology research since the start of the present study, and the understanding of the syndrome has also increased considerably. There is, however, still no consensus on how frailty should be defined based on GA. Former studies have used various numbers of GA impairments (from one to four) to identify patients as frail.[6] Thus choosing a more or less arbitrary number to define frailty, we have realised, makes little sense. Furthermore, it is increasingly clear that frailty is developed as a

continuum from vulnerability to severe frailty.[7] A classification as frail vs. non-frail therefore gives a poor description of the patients' vulnerability status, whereas this is reflected more correctly by number of geriatric deficits.

4. The fourth paper so far being planned is a description of the MoCA test results at baseline and during follow-up, and simultaneously an evaluation of the feasibility of this test for older patients with cancer. A detailed plan for the analyses has not yet been prepared.

   This fourth paper will partly contribute to fulfil our primary aim 2 (evaluating the feasibility of GA performed in the municipalities) and secondary aim (describing the prevalence of geriatric problems after EBRT).

   The reasons why we have chosen to look specifically on cognitive function and MOCA scores before evaluating the feasibility of the remaining GA registrations are:

   - The MoCA test was assessment reported to cause most inconvenience for both patients and nurses. Patients with cancer, when consulting health care professionals, are not used to being cognitively evaluated, and some patients objected to this. For the same reason, some of the nurses also found it difficult to repeat the test after EBRT.
   - Whether the MoCA test is relevant and appropriate for patients with cancer referred for new treatment, is poorly assessed. It is important to investigate if there might be a trend towards improvement from baseline through follow-up at home after EBRT, i.e. indicating that scores obtained before start of new treatment may not appropriately reflect the patients' cognitive function. According to some of the testing nurses, the scores seemed to be significantly affected by distress related to start of new treatment or other cancer-related problems.
   - Overall, the trajectory of MoCA scores obtained from older patients with cancer receiving EBRT is scarcely described.

   The overall feasibility of GA performed in the municipality, after EBRT, in this patient cohort will be evaluated in a subsequent paper.

5. We have decided not to assess the patients' muscle mass from available CT scans (as stated in the protocol page 17), hence these scans have not been retrieved.

   The reason for this is our experience from a former study[8] in another cohort of older patients with cancer. From that study, it was clear that as long as a baseline CT scan is not an obligatory part of the study design, or the procedures for such scans are not clearly defined, a large number of patients will not have scans taken within a reasonable time frame or at the appropriate body level including the overall body circumference. Hence, it is highly likely that the number of patients having non-available CT scans would be just as high in the present cohort as in our former study. Hence, the sample size for the planned analyses would most likely be too small. Furthermore, our former study, as well as another one recently

published,[9] have found no association between muscle mass and frailty as defined by GA. Further investigations on the issue therefore seems futile.

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Appendix 1

Dated 26-05-20

Statistical analysis plan for the first paper from the study: Improved quality of life and function for older cancer patients receiving radiotherapy – a prospective observational study

A total of 301 patients were included, 165 (54.8%) patients received radiotherapy (RT) with curative intent, and 136 (45.2%) received palliative RT.

The aims of this first paper are to:

1) describe the characteristics of this older population referred for RT in terms of demographics, cancer diagnosis, stage, former and planned treatment, and deficits/needs identified by a geriatric assessment (GA),
2) compare the overall and 1-, 3- and 6-month survival of the patients treated with curative versus palliative intent
3) investigate if frailty indicators assessed as part of the GA can predict overall survival in the curative and palliative group, respectively.

The GA includes the following factors

Cognition assessed by MoCA test

Physical function

- Activites of daily living assessed by Barthel Index
- Instrumental activities of daily living (IADL) assessed by the Nottingham Extended Activities of Daily (NEADL)
- Mobility assessed by the Timed Up and Go (TUG)
- Number of falls the last 6 months

Comorbidity assessed by Charlson Comorbidity Index (CCI)

Depressive symptoms assessed by the Geriatric Depression Scale-15 (GDS-15)

Medications: Number of regular, prescribed medications

Nutritional status assessed by the Mini Nutritional Assessmennt MNA

Statistics

Patient characteristics will be presented as means, standard deviations (SD), minimum and maximum values for continuous variables, and frequencies and percentages for categorical variables. Survival time, defined as time from end of radiotherapy (last fraction) to death or censoring (last observation) will be assessed by Kaplan-Meier plot and compared between groups using log-rank test. Bivariate and multiple Cox regression models will be used to investigate if frailty indicators specified above may predict the overall survival. The estimates will be adjusted for age, gender, type of cancer (lung cancer/breast cancer/prostate cancer/others), ECOG performance status and treatment intent (palliative versus curative intent).

To assess whether the predictors act differently in two treatment groups, the interactions between treatment intent variable and all other variables will be included. The Akaike's Information Criterion will be used to reduce the multiple model for excessive interactions. A significant interaction would imply that certain predictor predicts the overall survival differently in two treatment groups.

Appendix 2

Dated 14-12-20

Paper 2 from the study: Improving Quality of Life and Function for Older Cancer Patients Receiving Radiotherapy: an observational study

Paper investigating the relationship between Edmonton Frail Scale (EFS) scores and overall survival and the construct validity of EFS in relation to a geriatric assessment (GA)

Part 1: EFS in relation to survival in older patients receiving radiotherapy

The aims are to

A) investigate if the Edmonton Frail Scale (continuous, scores 1-17) assessed at baseline is predictive of survival independent of age, gender and major cancer-related prognostic factors (treatment intent (curative vs. palliative), diagnostic groups and ECOG status)
B) assess the survival of groups of patients classified according to proposed cut-off points for EFS scores (see below), and explore the data to find cut-off point(s) (potentially new) that best divide our cohort into groups with respect to survival

   Proposed cut-off points and categories for the EFS scores
   - 0-3 Fit
   - 4-5 Vulnerable
   - 6-7 Mild Frailty
   - 8-9 Moderate Frailty
   - 10+ Severe Frailty

Hypotheses

A) EFS scores are independently predictive of survival in older patients referred for curative or palliative radiotherapy
B) The survival of older patients with cancer referred for curative or palliative radiotherapy differ between the groups defined by formerly used/suggested cut-off points

Methods

A) Cox proportional hazards regression model will be estimated
B) Receiver Operating Characteristics curve analysis, Akaike's Information Criterion

Part II: Evaluate the concurrent validity of the EFS in a cohort of patients receiving radiotherapy

The aims are to

A) describe the number and type of GA deficits within each of the formerly proposed categories of EFS (see above)
B) assess the association between the formerly proposed EFS categories and number of GA deficits, and explore the data to find the cut-off point of EFS score that is most relevant to use in a screening procedure to ensure that the majority of patients in need of a full geriatric assessment are captured

Hypotheses

A) the number of GA deficits increases according to the formerly proposed EFS categories (fit, vulnerable, mild frailty, moderate frailty and severe frailty) with patients with moderate/severe frailty having the highest number of GA deficits
B) there is a significant association between EFS categories and number of GA deficits, and the proposed cut point EFS>=6 for frailty is the appropriate cut-off point to ensure that a full GA is applied in patients where this is needed (based on number of GA deficits)

Methods

A) Descriptive statistics
B) ANOVA

Baseline data for EFS scores and the geriatric assessment will be used.

Appendix 3

Dated 18-05-21

Plan for analyses, paper no.3

Preliminary title:

Is the presence of geriatric impairments associated with quality of life and physical function after radiotherapy in older cancer patients? - A prospective observational study.

Main objectives:

In a cohort of older patients with cancer, referred for curative or palliative RT, we will**:**

1. assess the trend in quality of life (QoL) and physical function prior to and after RT for palliative and curative patients, and investigate if there is a significant difference in trend between the two groups
2. assess the trend in QoL and physical function prior to and after RT stratified on number of geriatric impairments present at baseline, and investigate if there is a significant difference in trend depending on the number of geriatric impairments

Predefined outcomes:

Primary: Global quality of life (QoL) and physical function as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global QoL (glQoL) and physical functioning (PF) scale.

Secondary:

- Instrumental Activities of Daily Living (ADL)-function assessed by Nottingham Extended Index of Activities of Daily Living (NEADL) based on patients' self-report.
- Role function as assessed by the EORTC QLQ-C30 role function (RF) scale
- Fatigue and pain as assessed by the EORTC QLQ-C30 corresponding symptom scales (FA = fatigue)(PA = Pain)

Exploratory: Functioning and symptom scales/items of the EORTC QLQ-C30 that are not defined as primary or secondary outcomes will be assessed for explorative purposes

Hypotheses:

1. Patients referred for palliative RT have poorer scores for all primary and secondary outcomes prior to and after RT compared to patients referred for curative treatment
2. There is a significant difference in trend in outcomes for palliative and curative patients:
    a. patients referred for palliative RT will experience an improvement in the primary outcomes global QoL and PF, and the secondary outcomes RF, NEADL and pain (PA) within 8 weeks after RT.
    b. patients referred for curative RT will experience a deterioration in the primary outcomes global QoL and PF and the secondary outcomes RF, NEADL and

fatigue (FA) scores from baseline to 2 weeks after RT. Thereafter the scores will return to baseline values within 16 weeks.

3. There is a significant difference in trend in outcomes depending on number of geriatric impairments
    - **a.** scores for the primary outcomes global QoL and PF, and the secondary outcome RF decreases with increasing number of geriatric impairments
    - b. there is a significant association between number of geriatric impairments and the primary outcomes global QoL and PF as well as the secondary outcome RF scores

Timeline for the assessments: Patients answered EORTC QLQ-C30 and NEADL at five different time points: baseline, when completing RT (except palliative patients who received only a single fraction were per protocol test schedule not asked to answer EORTC QLQ-C30, and patients who received <10 fractions were not asked to answer NEADL), and 2, 8 and 16 weeks after RT. We will exclude the assessment of NEADL at the end of RT from our analyses because patients with short courses of RT did not fill in this questionnaire.

Statistical approach

Categorical baseline characteristics of curative and palliative patients will be described with frequencies and percentages, while continuous with means and standard deviations (SD) or median and min-max values.

Raw scores for all QLQ-C30 scales/items will be transformed into scales ranging from 0-100 in accordance with the official manual for this questionnaire. NEADL item scores will be summarized into a scale ranging from 0-66. Missing NEADL items scores will be imputed as follows:

The missing values are assumed to be missing at random (MAR), and will be imputed if at least half of the items of the scale had been answered. The imputation will be 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.

To answer Study aim 1 and test our first hypothesis, the primary outcomes, global QoL and PF will be assessed by linear mixed model with fixed effects for (non-linear) time, treatment group (curative vs. palliative) and the interaction between the two. Random effects for patients will be included. The models will be adjusted for age, gender, performances status (ECOG PS) and cancer type. The secondary outcomes RF, NEADL and pain scores will be evaluated by similar models.

To answer Study aim 2 and test our second hypothesis, similar models to those describe for aim 1 will be performed for the primary outcomes global QoL and the secondary outcome RF. However, these models will use number of geriatric impairments as a stratification variable instead of treatment intent (palliative vs curative). The models will be adjusted for age, gender, cancer type, treatment intent (curative vs palliative) and ECOG PS.

Sensitivity analyses to estimate models for non-imputed variables for NEADL will be also be performed.

For explorative purposes linear mixed model with fixed effects for (non-linear) time, treatment group (curative vs. palliative) and the interaction between the two will be estimated to assess differences in trend between palliative and curative patients for emotional function (EF, insomnia, appetite loss). Similar models will also be estimated to assess possible differences in trend in pain, fatigue, insomnia, and appetite loss between groups defined according to number of geriatric impairments. For these models number of geriatric impairments will be used for stratification instead of treatment intent. No adjustments will be made in any of the explorative models.