Improving function and quality of life for older cancer patients receiving radiotherapy, a randomized controlled pilot study

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Protocol dated 09.12.2018

Amendment dated 09.03.2020

Overarching protocol with amendments[1]

Improving function and quality of life for older cancer patients receiving radiotherapy, a randomized controlled pilot study

A study emerging from Innlandet Hospital Trust in co-operation with the Norwegian University of Science and Technology (NTNU), Trondheim University Hospital Olavs Hospital, Trondheim and the primary health services in 30 municipalities in Innlandet County, Norway

Funding

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[1] Further details, please see "references", open access paper: Røyset I et al. Geriatric assessment with management for older patients with cancer receiving radiotherapy. Protocol of a Norwegian cluster-randomised controlled pilot study. J Geriatr Oncol. 2022 Apr;13(3):363-373. doi: 10.1016/j.jgo.2021.11.001. Epub 2021 Nov 12

Introduction

The current study addresses a major challenge to our health care systems, i.e. to provide good, effective and personalized health services to a large and rapidly increasing group of older cancer patient with complex needs (1).

The study is a randomised controlled pilot study for older cancer patients receiving radiotherapy (**RT**). It is designed to test the feasibility, potential effect and cost-effectiveness of an intervention aiming to improve function and quality of life (**QoL**), and thereby reduce the burden for the patients, their families and the society. The intervention program will be based on geriatric assessment with management, and comprises a targeted and personalised, primary health care based multicomponent intervention. In line with a proposal from the Norwegian Health Minister related to the new Norwegian cancer strategy (2), assigned municipal cancer nurses will serve as service coordinators to ensure a seamless treatment trajectory and a smooth transition of patients across sectors. The study will be conducted as a joint effort between specialists in geriatric and oncologic medicine as well as hospital and primary health care services, and represents the basis for a subsequent multicentre randomised trial (**RCT**).

The study is part of a larger project emerging from Innlandet Hospital Trust (SI) (Figure 1, page 2). Through this project, active collaboration is established between SI, St Olavs Hospital, 41 out 48 municipalities in Hedmark and Oppland counties and Trondheim municipality. Finances for one full-time and one part time (50%) project nurse are granted from SI. Furthermore, a 50% position for a project nurse for two years will be financed by grants from the Joint Research Committee between St. Olavs Hospital and the Faculty of Medicine and Health Sciences, NTNU. Running expenses will be covered by grants from the same committee, the Liaison Committee for Education, Research and Innovation in Central Norway and SI, jointly, and means to finance a PhD student connected to the pilot study are covered by grants from Extrastiftelsen.

Background and current knowledge

Older cancer patients ($\geq$ 65 years) represent the majority of the cancer population, and their absolute number grows due to an aging population. In comparison to their younger counterparts, older cancer patients often present with a multiplicity of problems. They frequently suffer from somatic or psychiatric comorbidities, and are often frail with impairment in mobility, daily life functioning and cognition. When diagnosed with cancer and needs of therapy, these patients are at substantial risk of complications and functional decline (3-5). Thus, following cancer treatment, older patients have higher mortality and morbidity(6-8). Recovery also takes longer and may not always be achieved (5).

To avoid adverse outcomes that come at high personal and societal costs, and to ensure that optimal cancer treatment can be administered, a systematic assessment of the older patient's overall health status and potential vulnerability is necessary (9). This is particularly important considering the result of a recent study by our study group, demonstrating that oncologists are poorly trained to recognize frailty in their patients (10). Measures should thereafter be undertaken to improve existing deficits and prevent deterioration, and targeted rehabilitation procedures should be planned and implemented. Presently no such assessments or procedures are systematically applied in Norwegian cancer care.

Geriatric assessment (GA) addresses problems that are frequent in older age (3, 4) and includes systematic assessment of somatic health (such as comorbidity, medications, nutrition); mental health (such as cognition, anxiety and depression); functional aspects (such

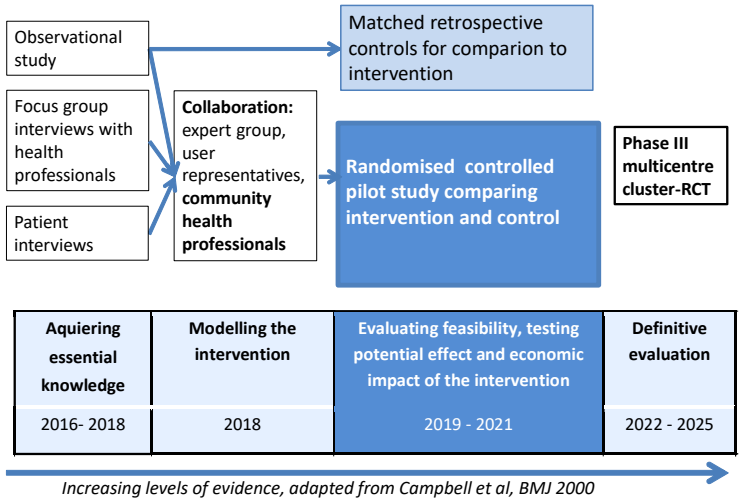
as activities of daily living (ADL) and instrumental ADL (IADL) and physical function); and social network and living situation. GA is currently the best established method to identify older patients' vulnerability (11). Performed by an interdisciplinary geriatric team and followed by adequate management of identified vulnerabilities (GA with management), the approach has documented success in improving outcomes in non-cancer populations (12, 13).

During the last decades, GA has been adapted for cancer care, and mounting evidence shows that GA may identify remediable problems, affect oncological treatment decisions and predict survival or adverse effects from chemotherapy and cancer surgery (3, 14, 15). Despite this, and strong recommendations from current guidelines (3, 9, 16), GA has not been integrated into common oncology practice.(17) All GA domains cover problems that may negatively affect outcomes of cancer and cancer treatment (4). On the other side, these problems may also be prevented, alleviated or improved. For instance may treatment of comorbidities be optimised and inappropriately described medications withdrawn (4, 18). Interdisciplinary rehabilitation addressing physical activity and nutritional counselling may improve physical and nutritional deficits (19, 20). Mobility, independency and QoL are highly prioritized by older patients (21, 22). These outcomes are interconnected and may all be promoted by tailored physical exercise (23). GA with management (**GAM**) interventions are therefore strongly recommended to optimise treatment and care for older cancer patients (17). Evidence for the potential benefits is lacking (17).

Radiotherapy in cancer treatment: RT is a main treatment modality in cancer, and may be used with curative or palliative intent. Short- and long-term side effects occur in both settings, and may be local, i.e. related to the involved organs, or general, e.g. fatigue and physical deterioration. Curative RT is conventionally given in higher total doses over a longer period of time, and have more frequent side effects compared to palliative treatment. There is evidence to suggest that older patients benefit from RT equally to younger patients (24, 25). However, high incidence of co-existing problems, higher toxicity rates, impaired QoL and physical deterioration are serious concerns (24, 25). Thus, using GA for both predictive and interventional purposes in older patients receiving RT has been advocated (24). To our knowledge, no studies on GAM interventions in this context have previously been published.

The overarching research project: The present pilot study is an essential part of a larger project designed to develop, test and evaluate a cost effective, multicomponent, interdisciplinary treatment model for older cancer patients (≥65 years) receiving RT. The project is designed in accordance with recommendations for development and evaluation of complex interventions (Fig 1) (26). To obtain sufficient knowledge to develop a feasible, targeted intervention, we have performed an observational study of older cancer patients (n = 301) receiving RT to identify needs and problems (REK SØ-A 2016/2031). The study was closed for inclusion July 2018, and results of preliminary analyses are pending. Focus group interviews with relevant hospital

Figure 1. Design of the overarching project



and primary health care professionals have been conducted (2017). Individual patient interviews to obtain detailed information about their perception of potential areas for improvement are running (REK SØ B 2018/1068). Experience, results and preliminary results from these studies represent the basis for the development of the intervention to be tested in the present pilot study.

Rationale for a pilot study: Before embarking on a larger multicenter RCT, the conduct of a pilot study is paramount. Although GAM has proven successful in other contexts (12, 13), there is no universally accepted recipe for how such an intervention should be performed and implemented. To be feasible and efficient, adjustments according to patient population, health care organization and available resources are necessary. A pilot study is needed to provide evidence for the feasibility from a patient as well as an organizational perspective. It is crucial to know if the intervention may be more relevant for some subgroups than others, to ensure that patients are able to adhere to all aspects of the intervention or if adjustments are needed, and to ensure that the intervention may be implemented within existing services and resources. A pilot study is also needed to enable adjustment of methods for evaluation and outcome assessment, and to enable precise sample size estimations for a future multicenter RCT.

Study aims and objectives

The present PhD-project will be conducted to provide the evidence needed to implement a cost-effective GAM intervention for older cancer receiving RT on a larger scale, aiming at improving QoL and function and thereby reduce the burden for the patients, their families and the society.

The detailed objectives are to:

1. assess the potential short- and long term effect of the intervention on global QoL and physical functioning for older cancer patients receiving RT
2. assess the feasibility of the intervention
    a. at the patients' level (recruitment, compliance and adherence)
    b. at the organizational level (structures facilitating or impeding implementation and collaboration across sectors and between professionals)
3. study the use of health care services and related costs in the intervention and control group

Scientific significance and new knowledge that can be derived from the project

The present study will provide new knowledge on the needs of elderly cancer patients receiving RT, the feasibility of performing a multicomponent intervention based on collaboration across sectors and between disciplines, and on the potential benefits of GAM interventions on outcomes of particular relevance to older patients. Thus, the study will contribute to fill several knowledge gaps. Studies evaluating GAM interventions for cancer care are missing, and there is an urgent need to implement GA into routine clinical practice, and to establish the feasibility. Moreover, studies on older patients addressing treatment outcomes such as functioning and QoL are scarce, but highly advocated. The knowledge generated from the study will therefore be of major international interest, and essential for future planning of health services for an increasing number of patients with complex needs.

Furthermore, introducing GA to the hospital and primary health care services will increase awareness and knowledge on geriatric problems, and provide experience with assessments and interventions that are beneficial for older patients in general**.** Likewise, the study includes

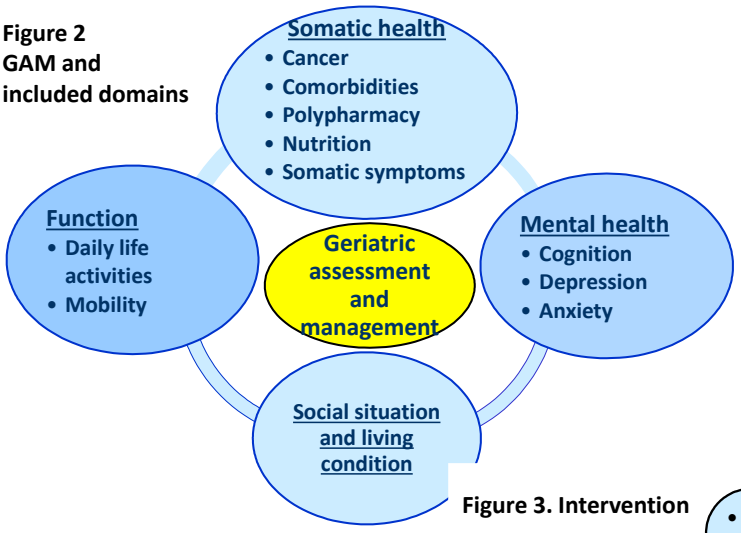
collaboration with a range of municipalities of varying size and health care organization, and involves hospital with different level of expertise. Overall, the results will be broadly applicable for the management of older patients.

Design, methodology and analyses

The intervention[2]

The intervention is developed by the interdisciplinary, experienced research group of this study in close collaboration with user representatives and hospital and primary health care professionals (reference group, page 12), and based on experience, results and preliminary results from the foregoing studies of the overarching project (Fig 1). Additionally, we have taken advantage of experience and results from another observational study by our study group " Cancer in the elderly; a prospective, observational study" (REK SØ C 2012/104) (10, 27) as well as studies evaluating GAM interventions in older, non-cancer patient conducted by members of our study group (12, 28, 29).

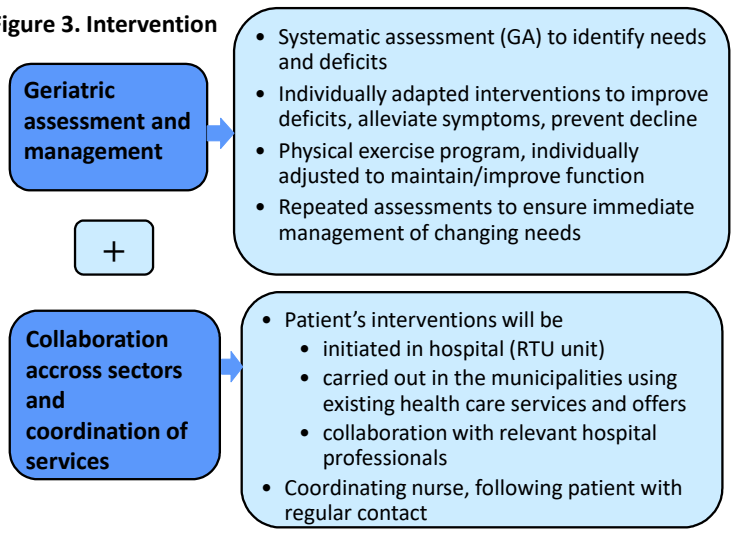
Figure 2
GAM and included domains



The intervention is a multicomponent GAM intervention (Fig 2) that will be adjusted to each patient's needs and capacity to comply. It focuses on somatic and mental health, function and social situation including living condition. Measures adapted to each patient will target these areas according to needs and deficits identified by a systematically applied GA.

According to results from a former study by our group(10), as well as preliminary data from the foregoing studies (Fig 1), evaluation of comorbidities and medications, appropriate treatment of depressive and somatic symptoms, nutritional counselling and physical rehabilitation will be important components of the intervention.

Figure 3. Intervention



[2] Details on the intervention and intervention procedure were written in Norwegian in a protocol attachment and are to be found in the protocol paper: Røyset et al. Geriatric assessment with management for older patients with cancer receiving radiotherapy. Protocol of a Norwegian cluster-randomised controlled pilot study. JGO 2022

The initial GA and start of the intervention will be handled by the PhD student or project nurse before RT commences. Pre-planned guidelines will be followed, and contribution from relevant hospital professionals will be sought according to needs. Then the intervention will be offered in the primary health care taking advantage of existing services, e.g. home care, meal delivery, rehabilitation services, exercise groups etc.

A coordinating nurse will follow the patients with regular contact throughout RT and to end of intervention and 8 weeks post-RT. In Hedmark and Oppland this task will be assigned to those who are "cancer co-ordinators" or have a dedicated role as a "contact nurse" for cancer patients in their municipality. Repeated assessments will be performed by the end of RT and after 4 weeks to ensure that the intervention is properly adjusted to changing need (see also Fig 4).

Before recruitment of patients to this pilot study starts, seminars will be arranged for information and training of involved primary health care professionals. Through the foregoing observational study (Fig 1), the relevant nurses in the SI catchment area are all extensively familiar with GA.

Setting

The primary study center is the Radiotherapy Unit (**RTU**) at SI providing RT to the population in Oppland and Hedmark counties (380 000 inhabitants), and treating about 700 patients per year, 2/3 are ≥65 years. Palliative RT represents about 60 % of the patients, and is administered independent of diagnosis. Curative treatment is given to breast, prostate, lung and skin cancers only. Hedmark and Oppland comprise 48 municipalities, and 30 of these have consented to participate in the present study. The RTU, St Olavs hospital, Trondheim will be the second study center. This RTU provides all RT services to the inhabitants in the catchment area including Trondheim municipality (180 000 inhabitants). RT is administered to about 250 patients ≥65 years from Trondheim per year. The municipality of Trondheim is organized into 4 health care districts.

Design

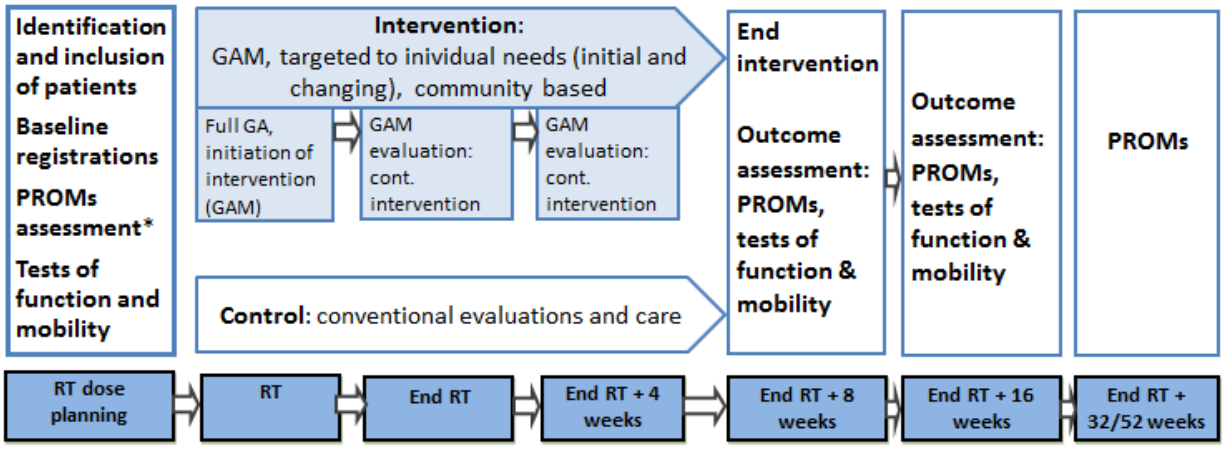
The present study is a controlled cluster-randomized pilot study. Cluster-randomization is chosen to avoid contamination of the control group. It is paramount that control and intervention patients are not handled by the same primary health care professionals, and this can only be achieved by randomizing municipalities (or health care districts).

Before patient recruitment commences, a selection of 32 municipalities/city districts (= clusters) will be stratified into blocks in accordance with number of inhabitants. The selection will include city districts, large and smaller municipalities to ensure sample size and representativity. Clusters within each block will be randomly assigned to one of the groups by using a computer-generated code, 16 in each group.

Eligible patients from clusters assigned to intervention will enter the intervention group and enter the intervention program. Patients from control clusters will enter the control group.

These patients will receive treatment and care in accordance with usual routines and standards

Figure 4. Study design



* PROMs (patient reported outcome mesures): will also be applied in both groups at end RT and at end RT + 4 weeks

Consenting, eligible patients will be included when admitted to planning of RT. Baseline assessments will be performed by a project nurse/the PhD student at start of RT. As we believe that the intervention may have both a short- and long term impact on patients' QoL and functioning, the patients will be followed for 52 weeks with specific study assessments and for survival up to 5 years. The main outcomes assessments will take place at 8 and 16 weeks after the end of RT. A blinded assessor will be used to assess outcomes other than those that are patient reported (**PROMs**) at these time points.

Patients

Patients will be consecutively recruited at the RTU, Gjøvik and St. Olavs hospital.

The inclusion criteria are:[3]

- ≥65 years of age
- confirmed cancer diagnosis (histology/cytology)
- living in one of the participating municipalities in the catchment area of SI or in the municipality of Trondheim
- referred for palliative or curative RT
- fluency in Norwegian, orally and in writing
- ability to fill in self-report questionnaires
- provide written informed consent

The exclusion criteria are

- severely ill with a life expectancy < 3months
- referred to receive one fraction of RT only (one day treatment)

Outcomes and assessments

The effectiveness of the intervention will be tested by the use of patient-reported measures and tests for physical performance/mobility. Additionally, the use of health care services will be

[3] A minor change of the inclusion criteria were made by February 2020 to include patients with a cancer diagnosis without cytological/histological confirmation, i.e. in cases where the referring oncologist affirmed the malignant diagnosis based on medical history, imaging and blood analyses, see attached amendment.

registered and evaluated. The pre-defined primary time point for outcome assessment is 8 weeks post-RT.

Physical function (PF) measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire-C30 (QLQ-C30)(30) is the defined primary outcome.

Secondary outcomes are:

- QoL assessed by the EORTC QLQ-C30 global QoL scale and EQ-5D-5L(31)
- Physical performance/mobility assessed by the following performance tests: Short Physical Performance Battery (SPPB)(32), Timed Up and Go test(33), Grip Strength (measured by a dynamometer)(34), and one legged balance test (35)
- Use of health care services (hospital in- and outpatient services and municipality services in terms of home care, nursing home care and use of other services such as physiotherapist, occupational therapists, and rehabilitation programs)

Other defined outcomes:

- Symptom occurrence assessed by the EORTC QLQ-C30, specifically fatigue, pain, dyspnea, and sleeping disturbances
- Emotional function assessed by the EORTC QLQ-C30
- Nutritional abnormalities assessed by BMI, weight loss and loss of appetite (subscale of the EORTC QLQ-C30).

Patient reported outcomes (EORTC QLQ-C30 and EQ-5D-5L) will be assessed at baseline, by the end of RT, and thereafter 4, 8, 16, 32 and 52 weeks after RT. Performance tests will be applied at baseline and 8 and 16 weeks after the end of RT. Data on primary care service utilization (home based and institutional care) and hospital services will be registered throughout the intervention period and during follow-up (one year, week 52).

Feasibility will be assessed by a process evaluation aiming to identify facilitators and barriers for a successful implementation, using mixed methodology. Measures recommended for each patient's intervention plan will be consecutively registered, as will patients' compliance and adherence through weekly contact with the coordinating nurse (log notes). Further data will include interviews with patients and provider. Questionnaires to involved primary health care nurses and other relevant professionals will also be applied.

Economic evaluation will be based on a comparison of costs and effects as measured by the main outcome measures, EQ-5D-5L particular. Costs include direct costs associated with GAM (intervention costs), as well as costs related to hospital admissions, home care and nursing home care. Data on service utilization will be obtained from hospital and municipal registers, respectively. Both intervention costs (GAM) and conventional care will be calculated in detail..

Sample size[4]

Sample size estimations are based on a block-randomised cluster RCT. A total of 57 patients distributed in 16 clusters (proportionally to cluster size) in each group will enable the detection of a clinically significant difference (12 points)(36) on the physical functioning QLQ-C30 scale with a standard deviation (SD) of 22 at the significance level of 5% and a power of 80%, given an intracluster correlation (ICC) of 5%. The ICC is assumed to be small

[4] For detail see statistical analyses plan dated 12-3-19 and protocol amendment dated 9-3-20.

as the intervention primarily will be applied by municipal cancer nurses with similar training in collaboration with hospital specialists, similar to all intervention patients. According to a former study on older cancer patients by this study group, we expect an attrition of about 15-20% at 16 weeks of follow-up post-RT. Furthermore, it is paramount to ensure that all municipalities are represented by included patients. To take this and attrition into account, we aim at including 81 patients in each group, i.e. a total of 162 patients. See also statistical analyses plan dated 12-3-19 and attached protocol amendment dated 9-3-20.

Statistics

All analyses will be pre-planned in collaboration with the study statistician before start of the study, and will follow the intention-to-treat principle. Descriptive statistics will be used to investigate quantitative data related to feasibility, compliance and adherence. Associations will be assessed by using suitable regression models. Interviews will be analysed by an interpretative approach, aiming at capturing interviewees' experiences with the intervention. To investigate the intervention effect, the trend in pre-defined outcomes will be compared between intervention and control groups by estimating linear mixed models accounting for intra-patient (due to repeated measurements per patient) and intra-municipality variations. The results will further be adjusted for relevant covariates.

Due to the potential heterogeneity of the study sample, the effect of the intervention will also be tested against a retrospectively matched control group, extracted from the observational study in the first part of the overarching project (see Fig 1). Patients in the foregoing observational study have given their consent to this comparison, and the observational study makes use of the same patient-related outcome measures, assessed on the same points of time as the current study.

For the economic evaluation, we measure outcome in terms of Quality Adjusted Life Years (QALY) by combining the preference based Health Related Quality of Life index from EQ-5D-5L and the corresponding time periods. We evaluate cost-effectiveness by estimating the incremental cost-per-QALY ratio defined as the mean cost per patient for the intervention group minus mean cost per patient for the control group, divided by mean QALY intervention group minus mean QALY control group. We apply non-parametric bootstrapping methods to assess uncertainty and use cost-effectiveness plane and cost-acceptability curves for presentation of results.

See also detailed statistical analyses plan dated 12-3-19.

User involvement

User involvement is essential for this project. At SI, a group of four user representatives is established, and have participated in the planning and conduct of the observational study. For the conduct of the present study, an additional representative from Board of senior citizens in Trondheim is contracted. These user representatives will participate in the design of the intervention and implementation procedures. They will further contribute during the study conduct, to the interpretation of results by evaluating the relevance for the users, and participate in the dissemination of results to the public, patients and relatives. Regular meetings are implemented and will continue during the overall study conduct.

Ethics

The study was approved by The Regional Committee for Medical Research Ethics, Health Region South-East (2018/2515/REK sør-øst A) and the Data Protection Official for

Research,Innlandet Hospital Trust and Trondheim University Hospital. The pilot study will be performed according to the rules of the Helsinki-declaration. Participation will not inflict upon the patients' cancer treatment and not imply any health risks or deviation from good clinical practice. Patients in the control group will receive care according to routine. However, a more thorough assessment followed by advice according to findings may, however, contribute to improved care. Written informed consent will be provided.

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Protocol amendment – 29-02-20

Adjustment of inclusion criteria

We have realized that some patients are referred for radiotherapy for a cancer disease that has not been confirmed histologically or cytologically. In these cases, the referring oncologist has affirmed the malignant diagnosis based on medical history, imaging and blood analyses.

As participating in the study does not have any impact on the patients' cancer treatment, and neither the intervention, its results, or the patients potential benefit of the intervention program are in any way dependent on how the cancer diagnosis has been confirmed, we have decided to make a minor change of the inclusion criteria.

Formerly stated criteria for eligibility (according to original protocol)

Patients

Patients will be consecutively recruited at the RTU, Gjøvik and St. Olavs hospital.

The inclusion criteria are:

- ≥65 years of age
- confirmed cancer diagnosis (histology/cytology)
- living in one of the participating municipalities in the catchment area of SI or in the municipality of Trondheim
- referred for palliative or curative RT
- fluency in Norwegian, orally and in writing
- ability to fill in self-report questionnaires
- provide written informed consent

The exclusion criteria are

- severely ill with a life expectancy < 3months
- referred to receive one fraction of RT only (one day treatment)

Adjustment of inclusion criteria

Bullet point two "confirmed cancer diagnosis (histology/cytology" is changed to: "Confirmed cancer diagnosis (preferrably histologically or cytologically, but patients referred for radiotherapy for cancer based on medical history, imaging and blood analyses are also eligible»

Otherwise, there are no changes to the inclusion and exclusion criteria.

Adjustment of timing for baseline registrations

According to original protocol, amendment 1, page 16, baseline registrations should be completed within the second day of treatment. We have realized that this is not feasible for all patients due to practical constraints. The patients often have several appointments during the first period of treatment like seeing their oncologist and/or cancer nurses, and are also often in short of time to be able to comply with scheduled transportation. As this study is not only a pilot study testing the potential effect of the intervention program, but also a feasibility study,

these circumstances have to be taken into account to enable inclusion of all patients who potentially may benefit from the intervention program. Thus, we have decided on the following:

- Patients who receive a radiotherapy regimen with less than 15 fractions (short term treatment, usually 10 fractions or less) should have their baseline registrations completed by the third day of treatment
- Patients who receive radiotherapy with 15 fractions or more (long term treatment) should have their baseline registrations completed within the sixth day of treatment

As any negative impact of radiotherapy generally occur by the end of treatment, we believe that these changes would not have any effect on the registrations or our results.

Amendment B[5]

Revision of sample size estimate 09.03.20

The original estimates as stated in Amendment 8 (12-03-19) were as follows:

Sample size estimations are based on a block-randomized cluster RCT. A total of 53 patients distributed in 16 clusters (proportionally to cluster size) in each group will enable the detection of a clinically significant difference (12 points)[8] in the physical functioning QLQ-C30 scale at week 8 with a standard deviation (SD) of 24 in each group at the significance level of 5% and a power of 80%, given an intra-cluster correlation (ICC) of 10%. The ICC is assumed to be small as the intervention primarily will be applied by municipal cancer nurses with similar training in collaboration with hospital specialists, similar to all intervention patients. Power calculation was performed for analysis of covariance, adjusting difference between groups for baseline values, and assuming the correlation between baseline and follow-up measurements to be 0.5. According to a former study on older cancer patients by this study group, we expect an attrition of about 15-20% at 16 weeks of follow-up post-RT. Furthermore, it is paramount to ensure that all municipalities are represented by included patients. To take this and attrition into account, we aim at increasing sample size by about 28% and including 81 patients in each group, i.e. a total of 162 patients.

Revision of estimates

Background:

The present study is a block cluster-randomized study where 32 municipalities/city districts have been allocated to either control or intervention using a computer generated code. Due to large differences in number of inhabitants between municipalities/city districts, the

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randomization units were stratified according to number of inhabitants prior to randomization (5 strata). Based on strata sizes and the estimated sample size, the preplanned number of study participants varied from 2 to 16 in different strata (as explained in the original application to the Ethical Review Board, attachment 7).

Before embarking on the study, the following considerations were made (Original protocol amendment 5, page 34 -35):

- the enrolment was estimated to take one year
- the number of eligible patients referred for radiotherapy from each randomized unit would depend on/vary according to chance
- there was a risk that there would not be enough eligible patients from the small municipalities to enable inclusion of the pre-planned number
- it was thus likely that it would be necessary to increase the number of patients from some municipalities (most likely the larger ones), and reduction in number of strata would also require a larger number of patients

Current status of inclusion

Based on these considerations, the inclusion rate, in particular the inclusion from each municipality, has been continuously monitored.

By the 25th of February 2020, the status was:

- a total of 111 patient were included
- one of the municipalities has withdrawn before including any patient
- another four municipalities with preplanned two patients had not included any of the patients so far
- in five other randomized smaller municipalities with preplanned two patients for inclusion, only one patient had been included from each so far

This implies that the number of strata will be seriously reduced. Hence, sample size has to be adjusted correspondingly. Furthermore, to be able to include a required number of patients according to the new estimates the period for recruitment has to be extended.

New sample size estimate

The revised sample size estimate is based on the same end-point, assumed difference and SD estimates as well as requirements for significance and power as the original. However, due to the reduction in number of strata and smaller number of patients than preplanned from some strata, the new estimate indicates that at least 69 patients must be included in each trial arm. Considering attrition, as described for the original sample size estimates, we now estimate that a total of 186 patients, i.e. 93 patients in each trial arm, will be required to show the statistically significant difference between groups given it exists.

Conclusion:

We aim at including a total of 186 patients, i.e. 24 patients more than originally estimated. It also means that more patients than preplanned will have to be included from some of the participating municipalities, i.e. from those that during the inclusion period present with eligible patients.

For the analysis of the primary outcome, however, we need at least 138 evaluable patients, i.e. patients where the primary outcome is registered. Thus, by closely monitoring the inclusion and response rate, it may be possible to stop the enrolment before the end of Sep 2020, and before we reach 186 patients. We may also need to enroll more than the estimated 186 patients to reach the target number of evaluable patients, and in this case, a new application to the Ethical Review Board will be submitted.

To be noted: Due to the increase in sample size, the inclusion period was extended primarily to Sep 2020. However, study recruitment had to be paused in March 2020 due to the covid pandemic, and was thereafter opened again in the autumn 2020, please see published protocol paper .