Protocol amendment - 12-03-2019

Plan for statistical analyses – revised and specified

The effectiveness of the intervention will be tested by the use of patient-reported measures and tests for physical performance/mobility. Additionally, feasibility will be evaluated and the use of health care services and cost-effectiveness will be registered and evaluated. The pre-defined primary time point for outcome assessment is 8 weeks post-RT.

Primary outcome – Physical Functioning measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire-C30 (QLQ-C30)[1]

Secondary outcomes are:

- global health assessed by the EORTC QLQ-C30 global health/quality of life subscale (question 29 and 30)
- health related quality of life (HRQoL) assessed by EQ-5D-5L [2]
- physical performance/mobility assessed by the following performance tests: Short Physical Performance Battery (SPPB)[3], grip strength (measured by a dynamometer),[5]
- cost-effectiveness: the incremental cost-effectiveness ratio (ICER) i.e. the difference in mean costs divided by the difference in mean Quality Adjusted Life Years (QALYs)
- 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 general practitioner, physiotherapist, occupational therapists, and rehabilitation programs)
- feasibility at patients' and organizational level, see "Feasibility, page 3"

Other pre-defined outcomes:

- mobility assessed by the Timed Up and Go test,[4] and one-legged balance test[6]
- 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).

Primary analysis

Primary analysis will assess the difference between the control and the intervention groups in physical function measured by the EORTC QLQ-C30 questionnaire at 8 weeks after baseline. Longitudinal analysis of covariance will be performed by estimating a linear mixed model with fixed effects for baseline values, time and interaction between time and group variable. The model will include random effects for patients nested within study cluster.

Secondary analyses

The difference between the control and the intervention groups in the secondary outcomes global health (assessed by the EORTC QLQ-C30 questionnaire global health/global QoL subscale), HRQoL (assessed by the EQ-5D-5L), SPPB scores and grip strength at 8 weeks after baseline will be assessed by the same method as described for the primary analysis.

Furthermore, the differences between the control and the intervention groups in trend in the primary outcome physical functioning and all continuous secondary outcomes throughout the follow-up period (assessment points by the end of RT, and 4, 8, 16, 32 and 52 after RT) will be assessed by linear mixed model with fixed effects for baseline values, time and interaction between time and group variable. The model will include random effects for patients nested within study cluster. Differences between groups in dichotomous outcomes will be assessed by generalized linear model with the same fixed and random effects as described above.

Primarily, all analyses will be performed on intention-to-treat principle. As sensitivity analysis, per-protocol approach will be conducted as well.

We will also use the statistical approach as described for the primary and secondary analyses to compare the intervention group to a retrospective, matched controlled group from a foregoing observational study (NCT03071640/ 2016/2031 REK sør-øst A). These analyses will focus on the primary endpoint in this pilot study, i.e. physical function, and the secondary outcomes global QoL (from the EORTC QLQ-C30 questionnaire), Timed Up and Go and symptom occurrence.

Other analyses

Quantitative data will be presented by suitable descriptive statistics. Distributions of continuous outcomes will be inspected graphically by assessing the histograms. Model assumptions will be assessed by established methods. In the case of violation of assumptions necessary adjustments will be implemented.

Exploratory analyses

Following the main primary and secondary analyses, the data will be explored further to identify possible groups of patients following different trajectories of physical function, global quality of life and other relevant outcomes, and patient characteristics associated with favourable development in the defined outcomes.

Economic evaluation

We will calculate the intervention cost based on a micro-costing approach. Cost-effectiveness of the intervention will be evaluated by calculating the incremental cost-effectiveness ratio (ICER) that is the difference in mean costs divided by the difference in mean Quality

Adjusted Life Years (QALYs). We calculate QALYs by an area under the curve approach under the assumption of piecewise linear change in EQ-5D-5L-index values over time. Missing data will be imputed by multiple imputation and the uncertainty of the ICER will be assessed by performing sensitivity analysis including application of bootstrapping techniques.

Feasibility

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 patient's compliance and adherence through weekly contact with the coordinating nurse (log notes). Further data will include interviews with patients and providers. Questionnaires to involved primary health care nurses and other relevant professionals will also be used.

Sample size

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.

References

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