

Statistical analysis plan – Geriatric intervention before colorectal cancer surgery in elderly patients – a randomised controlled trial.

Note: This statistical analysis plan was written prior to any unblinding of treatment allocation

1. Introduction

The aim of the study is to evaluate the effect of a preoperative geriatric assessment followed by an individualized intervention in older patients with colorectal cancer (CRC). The study is registered in ClinicalTrials.gov (NCT01321658). The aim of this document is, prior to any unblinding of the data, to recapitulate the protocol, and establish details of the statistical analysis that were not finished when the protocol was written.

Inclusion and exclusion criteria

All patients aged 65+ and scheduled for colorectal cancer surgery were eligible for the study.

Eligible patients went through a screening for frailty procedure, composed of two items:

- 1) VES-13 screening for frailty form [1], where a score > 2 points was used as criterion for frailty
- 2) Assessment of comorbidity. Established diagnoses of heart failure or other symptomatic heart disease, COPD, dementia, kidney failure, malnutrition (BMI<20 or loss of >5% body weight in the last six months) or polypharmacy (>5 systemic medications in daily use) was used as criterion for frailty.

If patients were considered frail by any one of the two criteria, they were invited to enter into the study.

Patients were excluded if surgery for colorectal cancer was performed as an emergency procedure, if they were considered moribund, if they were not able to give informed consent, or if patient or next of kin denied registration.

Randomisation procedures

The randomisation was based on computer-generated random numbers, and carried out by a research coordinator without any contact with the patients or the personnel involved in the inclusion. We used block randomisation (blocks of variable and unknown size) to ensure equal group size. The randomisation was stratified with respect to cancer type (colon or rectum cancer) in order to balance the groups, as surgery for rectum cancer traditionally carries a higher risk for postoperative complications than colon cancer surgery. The allocation of each patient (intervention group or control group) was by sealed, opaque, numbered envelopes that were held in the surgical ward (different colours for the two stratification groups). The randomisation envelopes were drawn by the study physician (NO) or a research coordinator. A study nurse was responsible for registration of post-operative outcome, and was blinded for group allocation. For each randomised patient, the study physician (NO) controlled that the randomisation envelope with the lowest number was used.

Consent and inclusion procedures were carried out by the study nurse, the study physician (NO) or a research coordinator.

Primary effect variable

Severe postoperative complications (defined as grade 2 or higher according to the Clavien-Dindo scoring system) [2] during the first 30 days post surgery. Patients who die before the 30 days follow-up, will according to this system be registered with grade 5 complication.

Secondary effect variables

- Any complication at 30 days post surgery
- Grade 2 and higher complications, excluding lower urinary tract infections, at 30 days
- Very severe complications (Grade 3 or higher) at 30 days
- Living at home at 3 months
- Reoperation at 30 days and at 3 months post surgery
- Readmittance to hospital at 30 days and at 3 months post surgery
- Length of stay
- Survival at 30 days and at end of study
- Physical and emotional function, global health status and global quality of life at 3 months, assessed by EORTC QLQ-C30 [3]

Data registration

All complications and mortality 30 days post surgery were registered prospectively by the study nurse. 3 months post surgery, data on quality of life and subjective health status, location of current stay (nursing home, private home, hospital or other), need of formal help, reoperation or recurrence of disease were collected.

At the end of the study inclusion period, survival and recurrence data were collected.

Blinding

All variables at follow-up during the first 30 days post surgery and at three months post surgery were collected by a study nurse blinded to allocation. One of the research physicians (SR) was blinded to group allocation, and performed the Clavien-Dindo complications scoring. The other research physician (NO) performed the Geriatric assessment and intervention, and could not be blinded. The personnel of the surgical department were also made aware of group allocation in order to perform the recommended interventions during the hospital stay.

Power calculation

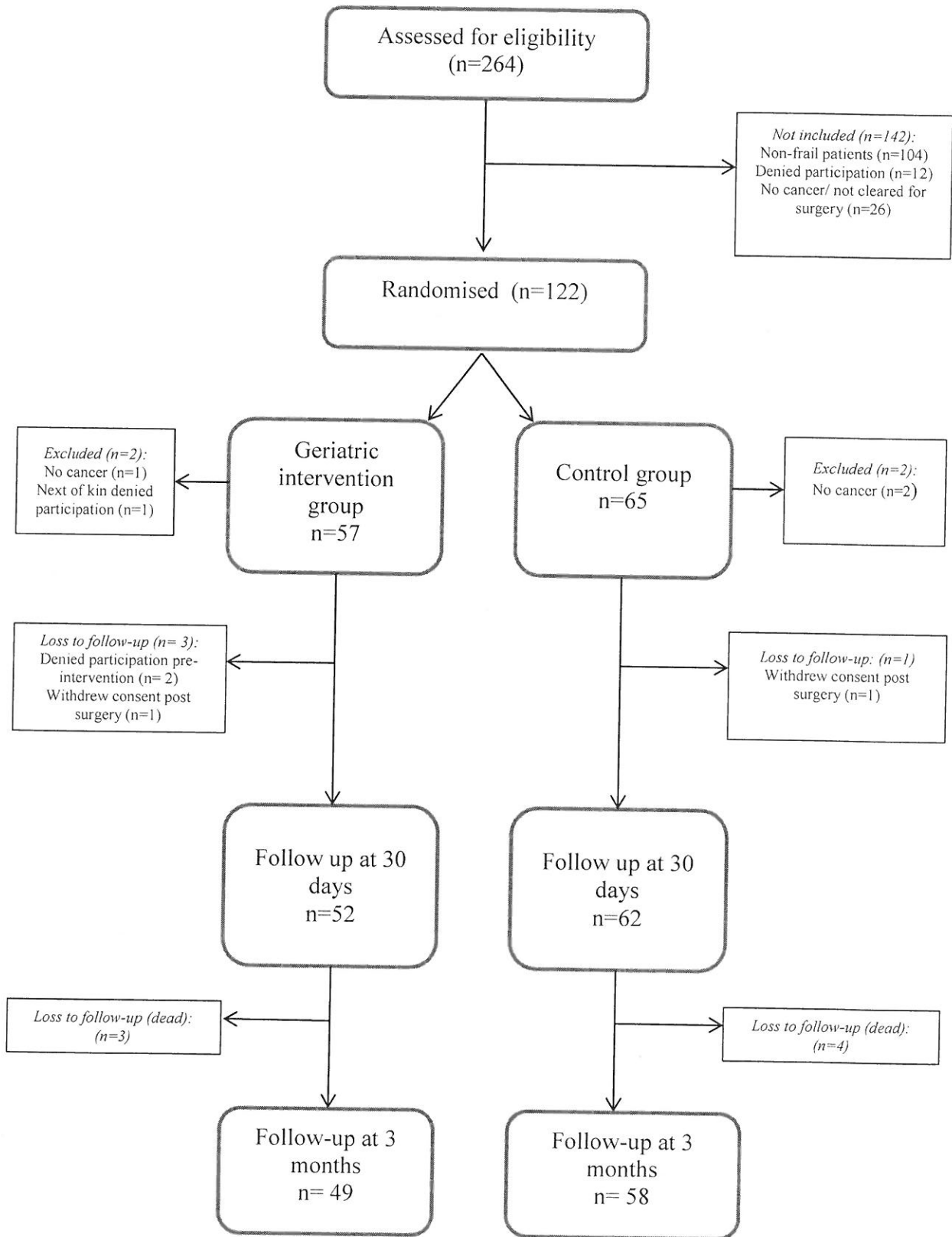
No data were available allowing us to carry out precise power estimates based on our primary effect variable. Based on our previous observational study [4], we found that 76% of frail patients had postoperative complications after CRC surgery. To be able to demonstrate a reduction in complication rate by 20% with a 5% level of significance and test power of 80%, we estimated that 86 patient should be randomized into each group.

Due to fewer patients being eligible for inclusion than what we had estimated, the inclusion period was prolonged from the originally planned period from 2011 to 2012, to an inclusion period reaching from January 2011 to June 2014. At that time, inclusion had to be terminated at a total of 122 included patients because of lack of further funding.

Patient flow

Patient flow is illustrated in Figure 1.

Figure 1. Patient flow



2. Primary effect analysis

The primary analyses will be done in a modified intention-to-treat analysis, excluding the four patients that were erroneously randomized (n=118, see flowchart).

The primary outcome will be analysed by a chi square test, with randomisation group as the explanatory variable. A two sided p-value below .05 will be taken as an indicator of statistical significance, and the relative risk of a severe complication in the intervention group as compared to the control group with its 95% confidence interval will be reported.

3. Handling of protocol violations

3.1 Wrongly included patients (n=4)

Inclusion of patients who did not undergo resection (n=3) and patients where next of kin denied participation (n=1). These patients will be excluded before the primary analysis. They will, however, be included in sensitivity analyses for the primary endpoint, imputing values as if they all got severe complications ("worst case scenario").

3.2 Patients not handled according to randomisation (n=2)

Two patients were included and randomised to intervention, but withdrew consent before intervention. We will perform two sets of analyses with respect to the primary effect variable; one set excluding these two patients, another set including the two patients in the group to which they were originally randomised, and assuming worst case scenario, that is both patients suffering severe complications. Both sets of analyses will be reported.

3.3 Patients who withdrew consent > 2 weeks post surgery (n=2)

These patients will be included in the primary analyses with last observation carried forward (LOCF).

4. Sensitivity analyses

4.1. Variables for adjustment

Variables with known or believed prognostic influence upon the outcome will be included in regression models, one by one in addition to the randomisation group. If their introduction to the model changes the effect estimate for the randomisation variable with 10% or more, they will be introduced in a final model including all variables with an effect of this size. The following variables will be subject to such analyses:

- Age
- Cancer type (rectum/colon)
- TNM stage (0-II, III or IV)
- Surgery; open vs laparoscopy
- VES-13 score

4.2. Handling of missing data

Data for patients missing for other reason than death will be imputed as worst possible outcome, and comparison of analyses including these patients and analyses excluding them will be performed to evaluate their potential influence on the results. Patients who die during the 28 days follow-up, will be registered with a grade 5 complication.

5. Analyses of secondary effect variables

Continuous variables will be analysed by two-sample t-test if the distribution is deemed approximately normal. Should there be obvious deviations from the assumption of normality, Mann-Whitney tests will be applied. Categorical variables will be analysed by chi-square tests, and survival data by Kaplan-Meyer plots and Cox regression models. The secondary effect variables will be analysed after exclusion of the four erroneously included patients as well as the two patients who withdrew their consent pre surgery, whereas the two patients who withdrew consent after surgery will be included and data imputed based on LOCF.

6. Blind analysis

The study physician (NO) has been active in data acquisition, and has performed the intervention, and might theoretically understand from the clinical data from a given patient who the patient is and whether the patient belongs to the control or the intervention group. The principal investigator (SR) has, however, had no role in data acquisition, and was blinded to randomisation group. To prevent bias due to the project administrator's expectations, we will adhere to the following procedure: The study physician (NO), witnessed by a research coordinator (AG), allocates a random letter to patients in the intervention group and another to the patients in the control group. The code is written and stored safely, but not delivered to principal investigator. The principal investigator receives the dataset with these codes for the randomisation variable, and carries out the primary analyses. When the principal investigator has concluded upon the results of the analysis, group allocation will be unmasked.

7. References

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2. Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. *Annals of Surgery* 2004; 240(2):205-213
3. Aaronson NK, Ahmedzai S, Bergman B., et al.: The European Organization for research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical trials in Oncology. *J Natl Cancer Inst* 1994;85:365-376,
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8. Signatures

We hereby vouch for the fidelity of the study to this statistical analysis plan.

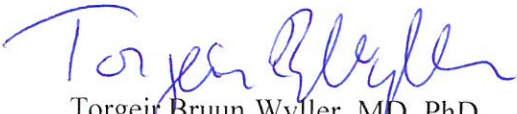
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