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ORIGINAL ARTICLE

Differences in baseline characteristics and 1-year psychological factors between participants and non-participants in the randomized, controlled trial regarding patient-led follow-up after rectal cancer (FURCA)

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ABSTRACT

Background: The ongoing multi-center randomized FURCA-trial investigates the effect of patient-led follow-up after rectal cancer, aiming at improving management of late effects and survivorship care. The purpose of this present sub-study was to identify potential systematic differences between participants and non-participants in the FURCA-trial, in regard to demographic and clinical factors at baseline, and in quality of life (QoL) and fear of cancer recurrence (FCR) after one year.

Material and methods: The population comprised patients invited to the FURCA-trial during the first 13 months' recruitment. Clinical and demographic data was obtained at baseline and differences were significance tested. Non-participants were requested to fill in a short survey one year after primary surgery, while participants received the questionnaires as part of more comprehensive one-year follow-up.

Results: In the first 13 months of the trial, 113 out of the 262 patients invited, declined to participate. The main reason reported for this was lack of energy surplus. Participants were younger than non-participants ($p < .01$), and nonparticipation was particularly evident among patients ≥ 80 years. More than half of the invited females declined to participate. Good WHO Performance status was associated with participation ($p = .01$), yet there were no statistically significant differences in Charlson Comorbidity Index, type of surgery, oncological treatment or UICC stages between participants and non-participants. By one year after surgery, there was no difference in FCR-level ($p = .92$) and QoL ($p = .25$) between the non-participants and control group participants.

Conclusion: The sub-study found that participants and non-participants differed at baseline in regard to age, gender and performance status, which is supported by results from other studies. No between-group differences were found in psychological factors after one year. These findings are important for the generalisability of the upcoming results from the trial.

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Background

Early cancer detection and improvements in treatment for rectal cancer (RC) have led to a decrease in morbidity and mortality for this patient group [1,2]. Following this, the number of RC survivors has increased substantially, of whom many experience late effects and impaired quality of life (QoL) [3–5]. Traditional follow-up programs following RC show great variance internationally, and the evidence is low [6]. In general, the focus is on early detection and treatment of recurrent disease and metachronous cancers [6]. However, the marked drop in the risk of local recurrence and the growing number of RC survivors call for a broader purpose of cancer follow-up and survivorship care. There is a need to draw more attention to the management of late effects, and alternative approaches for patient-centered care are emerging [7–9].

In order to address this issue, a multicenter randomized trial has been launched, introducing patient-led follow-up of RC survivors (Follow-Up after Rectal CAncer - FURCA) [7–9]. The aim is to improve patient-reported QoL and symptom burden by enhancing identification and management of late effects and symptoms.

The strength of the randomized controlled design is considerable. Due to the random allocation of patients, known and unknown confounding factors are equally distributed to the intervention and control groups. This brings the ability to study the true effect from the intervention without interference from other factors that might influence on the association.

However, there is one major limitation of the randomized trial design, concerning the generalisability and interpretation of the results. The experimental nature of the design requires strict inclusion and exclusion criteria, often leading to a highly selected study population. Furthermore, interventions with an element of patient-activation can be assumed to influence on the recruitment of patients. Also fear of cancer recurrence might impact on recruitment to such trials, although research is scarce regarding this matter.

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These conditions may lead to low participation rates and systematic differences in certain characteristic between participants and non-participants.

Another concern is that such systematic differences at the time of recruitment could lead to differences in outcome between participants and non-participants, for other reasons than the intervention in scope.

The consequence may be poor generalisability of the results. Thus, analyses of non-participants are crucial in order to qualify the conclusions from clinical trials within the research field of cancer survivorship.

Only few studies have investigated non-participants in randomized trials involving cancer survivors, and these studies reported that factors such as older age [10,11], low quality of life-scores [12] and psychological morbidity [13] were associated with nonparticipation.

Alternative models for follow-up of cancer survivors gain increasing attention in Danish health policy, accompanied by a political request for reducing routine follow-up. Therefore, an early analysis of generalisability of the FURCA-intervention is highly relevant.

The first aim of this current sub-study was to identify potential systematic differences in demographic and clinical factors between patients accepting and those declining to participate in the ongoing FURCA-trial.

Furthermore, the aim was to evaluate any differences in QoL and fear of cancer recurrence (FCR) between non-participants and participants in the control group at one year after primary surgery. The underlying hypothesis was that systematic differences in participation at time of recruitment could influence on outcome after one year. The reason for restricting the participants to the control group in this second part of the analysis was the assumption that no systematic differences should emerge between these groups, as they received the same standard follow-up.

Material and methods

The methodology for the ongoing FURCA-trial is described briefly here, yet a more detailed description is published elsewhere [12].

In the patient-led program, prescheduled outpatient visits are replaced by structured patient-education and access to point of need care by self-referral to a project nurse. Patients allocated to the control group follow the standard follow-up program with prescheduled outpatient rectoscopies and no option for self-referral. Chest and abdominal computed tomography (CT) are performed according to Danish national guidelines [14] in both allocation groups at 1 and 3 years after surgery, supplemented with a CEA-test.

Patients

The population for the current sub-study comprised all patients, being invited to participate in the FURCA-trial during the first 13 months of the trial inclusion period (from 1 February 2016 to 1 March 2017). The total inclusion period for the FURCA-trial was 2 years and 5 months.

For the FURCA-trial, patients (≥18 years) were invited after treatment for primary, non-metastatic and radically resected RC. The recruitment took place in four surgical centers, covering the treatment service to all patients in the Central Denmark Region and the North Denmark Region. That equals one third of all RC patients treated in Denmark.

Exclusion criteria for the FURCA-trial were: lacking ability to understand the Danish language, dementia or other significant impairment of cognitive functioning, residual life expectancy less than two years, synchronous cancer and participation in other research studies adding extra prescheduled control-visits and other contacts in the follow-up-period.

All patients declining to participate in the FURCA-trial were encouraged to give a self-defined reason for the non-participation. For the analysis, this information was synthesized into categories by two observers and displayed in a table.

Procedures

FURCA-non-participants were approached by postal mail shortly prior to the one-year CT-scan, with an invitation to attend in a brief survey, filling in a paper-questionnaire and returning it in a pre-paid envelope. A reminder was sent by postal mail, if the patient did not respond within 10 days. No further approach was made for non-participants who didn't respond to the reminder.

Patients with a change in medical or cognitive condition, and thus meeting one or more of the exclusion criteria from the FURCA-trial were not invited to fill in the one-year questionnaire. This criterion was conferred for each patient with the department in charge of treatment.

Only participants allocated to the FURCA control group were included in the one-year analysis, and data for this group were derived from the one-year FURCA-questionnaire, administered as part of the trial.

Non-participants and control group participants attended similar follow-up programs during the first year after surgery, hence only participants allocated to the FURCA control group were included in the one-year analysis. Data for this group was derived from the one-year FURCA-questionnaire, administered as part of the trial.

Baseline data

Baseline data included clinical and demographic variables at the time of invitation.

Data regarding *type of surgery, oncological treatment and UICC-stages* was derived from patient charts.

Information about American Society of Anesthesiologist Physical Status Classification System (ASA-score), WHO Performance Status and Charlson Comorbidity Index-score was collected from the database of the Danish Colorectal Cancer Group (DCCG) [15]. Clinical information for colorectal cancer patients treated at Danish hospitals is collected for the Danish Colorectal Cancer Group-database. The ASA-score and the WHO Performance Status at the time of diagnosis

are reported real time to the database by clinicians, while the Charlson Comorbidity Index is derived from the Danish National Patient Register [15].

The ASA-score: It is a subjective assessment of the patient's overall health. The score is based on five classes, ranging from the completely fit and healthy patient (I) to a moribund patient who is not expected to live 24 h with or without surgery (V) [16].

The WHO performance status scale: It classifies a patient according to the functional impairment and ability to self-care. The scale ranges from the fully active patient with the same habitus as pre-disease (status 0), to dead patient (status 5) [17]. In the DCCG database, the latter class is not included, and the highest status refers to the completely disable patient, not being able to carry out any self-care (status 4) [15].

The Charlson Comorbidity Index (CCI): It is a method for measuring disease burden and predicting mortality by weighting comorbid conditions [18]. A CCI-score of "0" equals no comorbidity, while higher scores indicate greater comorbidity. For this analysis, the index scores were categorized into three groups, according to the categories used in the DCCG database [15].

1 -year follow-up data

QoL was measured using the self-report instrument Functional Assessment of Cancer Therapy – colorectal (FACT-C). The 35-item questionnaire comprises five subscales, which all sums up to a total score, ranging from 0–136. The subscales measure psychological, social, emotional and functional well-being as well as colorectal cancer-specific items. All items are rated on a 5-point Likert scale [19]. FACT-subscales were prorated if missing values were less than 50%. Observations with more than 50% missing values in one or more subscales were excluded from that part of the analysis. The handling of missing data was according to the FACIT scoring-manual [20].

FCR was measured using the severity subscale of the Fear of Cancer Recurrence Inventory (FCRI) [21]. The multidimensional FCRI includes seven subscales, of which the 9-item severity subscale measures the extent of FCR. A 5 point Likert scale is used for rating of all the items [21]. The severity subscale also provides a cutoff value for identifying clinical FCR, indicating the point when the level of FCR shift from a normal psychological reaction, to a clinical condition that impairs quality of life, daily functioning and psychological well-being [22,23]. Observations with more than 50% missing values in the severity subscale were excluded, according to instructions from the original author [21].

The current sub-study was approved by the Danish Data Protection Agency.

Statistical analysis

The statistical analyses were performed using Stata version 15. Descriptive statistics were performed by calculating mean values for continuous characteristics, and counts and proportions for categorical ones. Differences between participants and non-participants at baseline were tested with Student's *t*-test for continuous variables under the assumption of normally distributed data, and Chi-squared test for dichotomous and categorical variables. Patient-reported outcomes at one year after surgery were adjusted in a multiple linear regression model for the scores, and a multiple logistic regression model for the dichotomous variable clinical FCR. Independent variables for this adjusted analysis were chosen a priori, and included age, gender and performance status at time of diagnosis. For this analysis, performance status was dichotomized into status 0 (good) and status $\geq$1 (impaired), based on clinical considerations. In order to be eligible for curatively intended treatment, patients should have a good or fairly good performance status at the time of diagnosis. It was, therefore, assumed that few patients in this sub-study had performance $>$1.

Results

A total number of 262 patients were invited to participate in the FURCA trial, during the time period from 1 February 2016 to 1 March 2017. Of these, 149 joined the trial, while 113 declined (43%). The patient-reported reasons for declining participation are shown in Table 1.

No reason was given from 44 non-participants (39%). The most frequent reasons given were lack of energy to enter

Table 1. Reported reasons for declining participation in the FURCA-trial regarding patient-led follow-up after rectal cancer ($n = 113$).

Reasons	Non-participants, n (%)
Did not have the energy/wish to complete FURCA questionnaire	12 (10.6)
Did not have the energy/wish to enter the intervention	7 (6.2)
Lacked surplus energy to enter the project as such	20 (17.7)
Had enough in coping with comorbidity	5 (4.4)
Preferred the standard follow-up program	7 (6.2)
Preferred follow-up by general practitioner	1 (0.8)
Did not want to be part of research	2 (1.8)
Had mental problems, that hampered participation	3 (2.7)
Felt too old for participating	3 (2.7)
Did not want to participate (no further reason reported)	4 (3.5)
Other[a]	5 (4.4)
No reason given	44 (38.9)

[a]Thought the study was too small/Died before enrollment/Was not invited/Was inaccessible after being invited to participate.

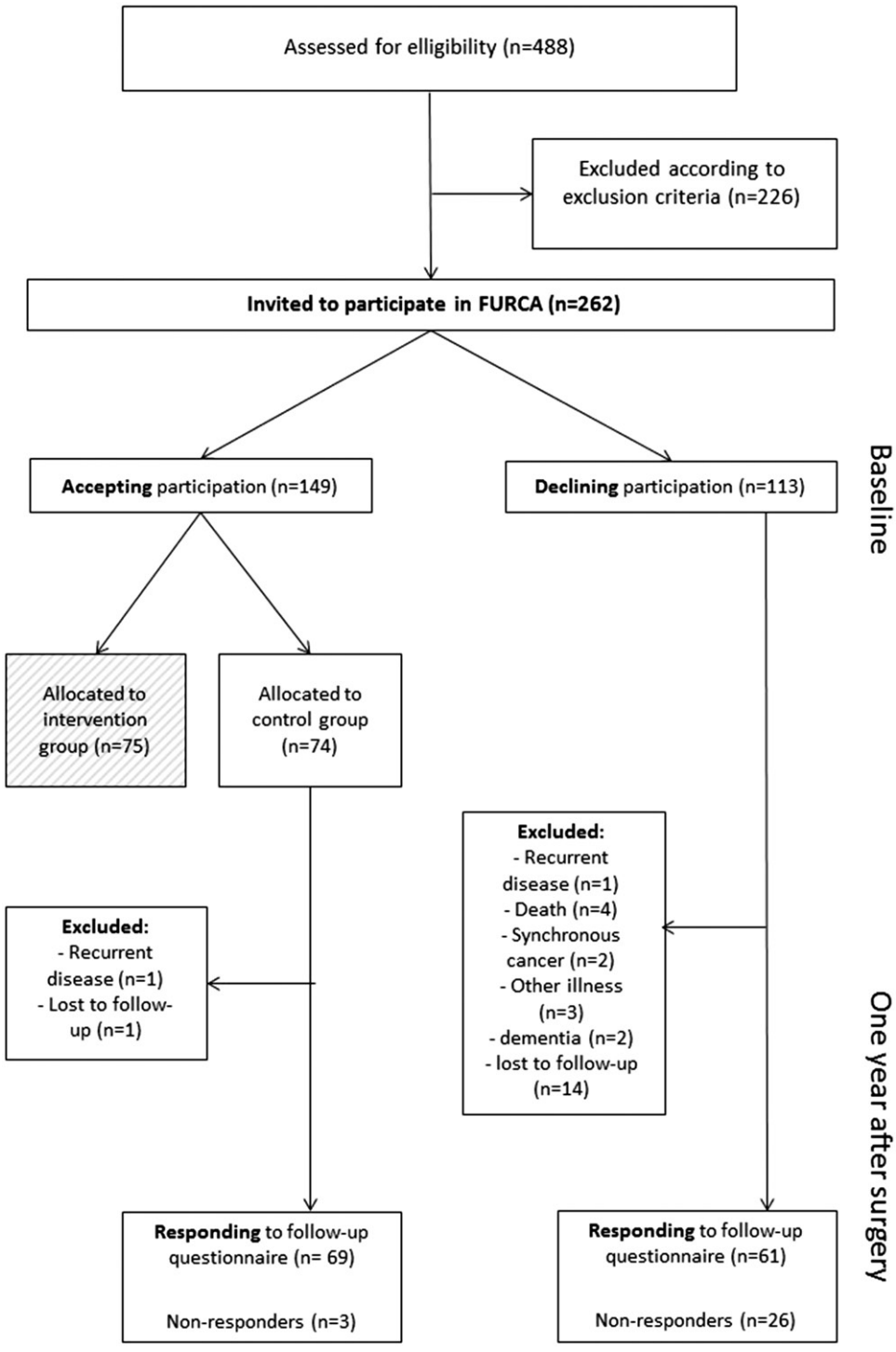

Figure 1. Recruitment of participants to the FURCA-trial and to the current sub-study.

the project as such (%) and lack of energy or wish to complete the FURCA-questionnaires (%). The following most frequent reasons were: no energy to enter the intervention (%), and a preference for standard follow-up (%).

Details about the participation are displayed in Figure 1.

Characteristics of participants and non-participants at the time of invitation to the FURCA-trial are displayed in Table 2. Participants were younger than non-participants at the time of surgery, were more likely to be male and had a better health status. Nonparticipation was particularly high among older patients with 77% of the invited patients at the age of $\geq$80 years declining. Participation also differed statistically significant between genders, shown by more than half of the invited females declining participation.

Moreover, non-participants had a worse WHO Performance Status than participants ($p = .01$), and worse ASA-score, yet the latter difference was not statistically significant. There were no statistically significant differences in Charlson Comorbidity Index, type of surgery, oncological

Table 2. Characteristics of participants and non-participants at baseline.

Demographic factors	Participants $n = 149$	Non-participants $n = 113$	p-value
Age at time of surgery, mean (sd)	65.6 (8.7)	70.0 (10.0)	<.01
Age groups (years), n (%)			
<50	4 (2.7)	4 (3.5)	<.01
50–59	35 (23.5)	11 (9.7)	
60–69	66 (44.3)	42 (37.2)	
70–79	38 (25.5)	36 (31.9)	
≥80	6 (4.0)	20 (17.7)	
Gender, *n* (%)			
Female	45 (30.2)	53 (46.9)	<.01
Male	104 (69.8)	60 (53.1)	
Disease- and treatment-related factors			
Type of surgery[a], *n* (%)			
TME	64 (43.0)	43 (38.1)	.56
PME	31 (20.8)	22 (19.5)	
APE/Hartmann	52 (34.9)	44 (38.9)	
Other	2 (1.3)	4 (3.5)	
Stage (UICC)[b], *n* (%)			
Stage 0	5 (3.4)	3 (2.7)	.32
Stage I	58 (38.9)	32 (28.3)	
Stage II	34 (22.8)	30 (26.5)	
Stage III	52 (34.9)	48 (42.5)	
Charlson comorbidity index	($n = 145$)	($n = 107$)	
No comorbidity (score 0)	113	75	.28
Moderate comorbidity (score 1–2)	29	27	
Severe comorbidity (score ≥ 3)	3	5	
ASA-score at time of diagnosis, *n* (%)	($n = 143$)	($n = 107$)	
ASA I	44 (30.8)	26 (24.3)	.07
ASA II	89 (62.2)	64 (59.8)	
ASA III	10 (7.0)	17 (15.9)	
WHO performance status at time of diagnosis, *n* (%)	($n = 143$)	($n = 105$)	
Status 0	118 (82.5)	74 (70.5)	.01
Status 1	25 (17.5)	23 (21.9)	
Status 2	0	7 (6.7)	
Status 3	0	1 (0.9)	
Neoadjuvant[c] oncological treatment, *n* (%)			
Yes	35 (23.5)	29 (25.7)	.69
No	114 (76.5)	84 (73.3)	
Adjuvant[d] oncological treatment, *n* (%)			
Yes	49 (32.9)	33 (29.2)	.52
No	100 (67.1)	80 (70.8)	

[a]TME: Total mesorectal excision; PME: partial mesorectal excision; APE: abdomino-perineal excision.
[b]UICC-stages: Stage 0 = T0/N0M0, Stage I = T1/T2N0M0, Stage II = T3/T4N0M0, Stage III = any T-stageN1/N2M0.
[c]Chemo-irradiation therapy prior to surgery.
[d]Chemotherapy after surgery.

treatment or UICC stages between participants and non-participants.

The one-year questionnaire was sent to 87 non-participants of whom 61 (70%) responded. Among the 72 participants in the control group, the response rate was 96%. Details regarding loss to follow-up are provided in Figure 1.

The mean time since surgery to filling out the 1-year questionnaire was 349 days in both groups (non-participants and control group-participants), with standard deviations of 19 and 22 respectively.

Eight observations were excluded from the analysis of QoL, due to extensive number of missing.

None of the one-year outcomes differed systematically between non-participants and control group participants, when adjusted for age, gender and performance status (Table 3). The FCRI severity-score was 11.8 in the control group and slightly lower among non-participants (10.9). Moreover, control group participants had a lower FACT-C score (111.4) than non-participants (116.7). Although none of these differences were statistically significant.

Discussion

This sub-study set out to identify potential systematic differences in demographic, clinical and psychosocial factors between patients accepting and patients declining to participate in the ongoing FURCA-trial. Results showed significant differences in gender, age and performance status at time of diagnosis.

Other studies have investigated patterns of participation in clinical trials [10,12,24]. In a comprehensive population-based analysis of participation in cancer clinical trials in the US, systematic variations were found in regard to racial/ethnic factors, gender and age. There was a clear inverse relation between age and participation, meaning that younger patients were more likely to participate than older. Female

Table 3. Patient-reported FCR and QoL at one year after surgery.

	Score range	Participants (control group)	Non-participants	*p*-value[a]
Fear of Cancer Recurrence (FCRI)		*n* = 69	*n* = 61	
Severity score, mean (sd)	0–36	11.8 (7.0)	10.9 (7.1)	.92
Clinical FCR[b], *n* (%)	–	21 (30)	15 (25)	.75
Functional Assessment of Cancer Therapy (FACT-C)		*n* = 65	*n* = 57	
Total score, mean (sd)	0–136	111.4 (14.7)	116.7 (15.6)	.25
Trial Outcome Index – TOI mean (sd)	0–84	69.4 (9.1)	72.2 (10.8)	.39

[a]Multiple regression model, including age and performance status at the time of surgery, and gender.
[b]Clinical FCR was defined by a score of ≥16 on the FCRI severity subscale.

colorectal cancer patients participated less than men ($p < .01$) [24].

In a Danish trial among survivors of head-and-neck cancer, factors associated with participation were identified. These factors were young age, high education, being a cohabitant and life-style factors. There was no difference between genders in participation [10]. And a third trial regarding patient-led follow-up for breast cancer patients reported age differences between participants and non-participants (mean age 57 and 71 years respectively) [12].

Although patients declining to participate in the FURCA-trial were asked to give a reason, 39% of them did not give a reason (Table 1). The most frequent reasons given was lack of energy surplus, or reasons related to practical issues of participating. Seven patients explained that they did not wish to enter the patient-led follow-up, and other seven patients stated that they preferred standard follow-up. These statements indicate that although 14 patients reported concern regarding the patient-led intervention, the majority reported reasons related to more overall health issues. This is supported by the described differences between the groups in regard to Performance status and ASA-score.

The number of patients lost to follow-up differed between participants (control group) and non-participants by one year after surgery. The difference might be explained by the fact that non-participants tended to be older and have a worse performance and health status, thus leading to more events in the follow-up than in the group of more healthy participants.

In the adjusted analyses at one year after surgery, no between-group differences were found. These findings corresponded with the a priori assumption that outcomes should not differ, because the follow-up program was equal in the two groups.

Only few studies have looked into the potential association between enrollment in cancer survivorship trials and psychological and QoL factors [12,13]. FCR is a plausible factor influencing participation in clinical trials regarding follow-up, due to the fairly high prevalence of FCR in cancer survivors. A recent study found that 29% of Danish colorectal cancer survivors reported clinical levels of FCR [25]. However, the influence from FCR on study participation is sparsely investigated.

An association between low quality of life-score and non-participation has previously been shown [12], and Kamphoff et al found a lower level of psychological distress among participants than non-participants in a randomized trial regarding physical exercise for cancer survivors [13]. Nevertheless, such associations need to be further investigated in order to draw more firm conclusions.

Although 100% inclusion is desirable, high rates of non-participation is a known problem in clinical trials involving active involvement from the patient. In a controlled intervention study testing a computer-based, patient self-report screening-model for physical and psychosocial problems in survivors of head and neck cancer, 52% of the invited patients declined to participate [10]. Likewise, the recruitment was 50% in a randomized trial, investigating the effect of patient-led follow-up versus routine outpatient control of breast cancer survivors [26]. Yet, in another trial, also comparing point of need-access to routine control visits for breast cancer survivors, the rate of nonparticipation was as low as 28% [12].

The number of non-participants during the first 13 months of the FURCA-trial was 43%. A possible explanation for this slightly high rate might be that the patients might prefer one specific follow-up strategy over the other, as hesitantly supported by the reasons given for nonparticipation. The high number of patients not giving a reason for nonparticipation hampers a more firm conclusion. However, the FURCA-trial intervention is patient-led follow-up, and implies symptom monitoring, self-referral and end of routine follow-up. This might induce a sense of insecurity and trigger FCR in some patients, thus preferring the regular outpatient visits. On the other hand, some might welcome the intervention as a possibility to gain more information about the disease and late effects, and a closer affiliation to the hospital. And others again, feeling in general healthy and cured, may be interested in avoiding regular hospital visits and having the freedom to point of need access.

This assumption is supported by the results in a British survey among researchers in trial recruiting centers for head and neck cancer surgery [27]. The study found that the most significant barrier to trial recruitment was the patient's preference for one arm of the trial [27].

A limitation of this sub-study might be the validity of the register-based data regarding Performance status and ASA-score. The patient and data completeness in the DCCG-database is high, reaching about 95% for the ASA-score and Performance status [28]. However, the validity of register-based clinical data is an issue for concern. Fortunately, an upcoming study is investigating the validity of several variables in the database, although results are not yet available.

A main strength of this sub-study is that it includes patients from a well-defined population covering all centers treating rectal cancer patients in two large regions, thus covering more than one third of all RC patients in Denmark.

Other strengths are the patient-reported data with a fairly high response rate among non-participants one year after surgery and the use of validated questionnaires. The FACT-C has shown good psychometric properties, although the Danish version has not yet been validated. In a recent study, the Danish version of the FCRI has been initially validated, showing acceptable properties [25].

Conclusion

In conclusion, this sub-study found statistically significant differences in age, gender and performance status between participants and non-participants for the FURCA-trial at time of baseline.

By the time of one-year's follow-up after surgery, FCR and QoL did not differ significantly between the non-participants and the control group participants. These findings are important when assessing the generalisability of the upcoming results from the FURCA-trial.

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The Danish Colorectal Cancer Group granted access to data regarding ASA-score and Performance status.

Disclosure statement

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