Frailty and outcomes in older cancer patients
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FRAILTY AND HEALTH RELATED QUALITY OF LIFE THREE MONTHS AFTER NON-METASTATIC CRC DIAGNOSIS IN OLDER PATIENTS: A MULTI-CENTRE PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background

Health related quality of life (HRQL) is an important outcome measure in geriatric oncology. Surgery is the main treatment for colorectal cancer (CRC) but has been associated with a loss of HRQL in older patients. This study aimed to identify determinants for a decreased HRQL at three months after CRC diagnosis.

Method

This multi-centre observational cohort study (NCT04443816) included 273 patients aged ≥70 years diagnosed with non-metastatic CRC. A multi-domain frailty screening was performed in each patient. A decreased HRQL was defined as a mean difference ≥10 on the EORTC QLQ-C30 questionnaire between baseline and three months after CRC diagnosis. Determinants of a decreased HRQL were analysed using multivariable logistic regression.

Results

A decrease in HRQL occurred in 63 patients (23.1%). Non-surgical patients had the highest risk of decreased HRQL three months after diagnosis (adjusted odds ratio (OR) 6.4 (95% confidence interval (CI) 2.0-19.8)). The Charlson Comorbidity Index (CCI) (aOR 2.3 (95% (CI) 1.2-4.2)), the American Association of Anesthesiologists class (aOR 2.6 (95%CI 1.4-4.9)), impaired daily functioning (aOR 2.7 (95%CI 1.3-5.6)) and dependent living (aOR 1.9 (95%CI 1.1-4.5)) were associated with a decreased HRQL, mainly caused by non-surgical patients. In surgical patients, a major postoperative complication was a strong determinant of decreased HRQL and was associated with preoperative comorbidity and cognitive impairment (aOR 4.0 (95%CI 1.9-8.8)).

Conclusion

Frailty characteristics are highly prevalent in elderly patients at time of CRC diagnosis but not strongly associated with a decreased HRQL after three months. Non-surgical patients and patients with major postoperative complications had the highest risk of decreased HRQL.

INTRODUCTION

Colorectal cancer (CRC) is a common disease worldwide. Each year, approximately 13.000 new cases are diagnosed in the Netherlands. CRC predominantly affects older patients.[1] Increased life expectancy has increased the number of older patients with CRC that are presented for curative surgery. Improvements in surgical techniques and perioperative care have made CRC surgery feasible for elderly patients, but with increased risk for adverse outcomes.[2][3][4][5] Especially frail older patients seem to suffer from postoperative morbidity and mortality.[6][7][8] Frailty is considered a state of decreased functional reserves across multiple organ systems, that arises from cumulative physiological and pathophysiological deficits.[9] Over the past decades, frailty has been increasingly recognized as a predictor of postoperative morbidity and mortality among older cancer patients. [6][7][8]

Outcomes of cancer treatments are traditionally presented in terms of survival and disease-free status.[10] Prolonging survival is usually considered the main goal of anti-cancer treatment. However, maintaining or even improving health related quality of life (HRQL) can be equally important. Especially in older patients who have worse life expectancy in comparison with younger patients and may be less willing to exchange current quality of life for longevity. HRQL is generally accepted as a multidimensional assessment of how disease and treatment affect a patient's sense of overall function and wellbeing.[11] Change in HRQL should ideally be discussed, in addition to survival and risk of complications, when considering treatment options for CRC. To do so, accurate information on determinants of poor HRQL after CRC diagnosis in older patients is essential. Yet, the impact of frailty on HRQL after CRC diagnosis is unknown. We hypothesised that frail patients were at increased risk of a worse HRQL at three months after CRC diagnosis. Therefore, the primary aim of this research was to identify determinants for a decreased HRQL in older patients three months after non-metastatic CRC diagnosis, with a focus on frailty.

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METHODS

Design and participants
The Advanced Geriatric Evaluation – ColoRectal Cancer (AGE-CRC) study is a multi-center prospective observational cohort study carried out in six hospitals in the Netherlands (St. Antonius Hospital, Nieuwegein; Meander Medical Centre, Amersfoort; University Medical Center Utrecht, Utrecht; Diakonessenhuis, Utrecht; Tergooi Hospital, Hilversum and Hospital Rivierenland, Tiel). Patients were included from December 2017 until April 2020. All consecutive patients with a diagnosis of non-metastatic colorectal cancer were screened for eligibility. Inclusion criteria were: age ≥70 years and histologically proven non-metastatic colorectal cancer. Exclusion criteria were emergency surgery and an insufficient understanding of the Dutch language.

Ethical approval was given by the local ethics committee (Medical Ethics Research Committee United, number R17.034). The study was registered at clinicaltrials.gov (NCT04443816) and performed in accordance with the declaration of Helsinki. All subjects gave written informed consent for study participation.

Geriatric assessment
After initial diagnosis of non-metastatic CRC, study information was provided by the local treating physician or oncology nurse practitioner at the outpatient clinic of each hospital. Patients were contacted by telephone after 2-3 working days to further inform them about the study and to answer study related questions. If patients were willing to participate in the study an appointment was scheduled for frailty assessment at their home or in combination with a hospital visit according to the patient's preference. Frailty assessment was performed by a medical oncologist in training (EV). Table 1 shows the tests used for all frailty characteristics with corresponding cut-off values.[12–17] The results of the assessment were not available for the treating physicians. All included patients were routinely discussed in a multidisciplinary oncology team to determine diagnoses and treatment strategy. Patients received routine perioperative care and surgical procedures were performed according to standard clinical practice.

Clinical characteristics and data collection
Baseline characteristics were collected from electronic patient records. Medication history was available from hospital pharmacy services. To assess the overall burden of comorbidities the Charlson Comorbidity Index (CCI) was calculated for each patient.[18] Secondary endpoints including major postoperative in-hospital complications (Clavien Dindo (CD) III-V) were extracted from electronic medical records. Data were managed using REDCap web application tool (Research Electronic Data Capture, Vanderbilt University, hosted by St. Antonius Hospital).

Table 1. Description of frailty tests and prevalence of frailty characteristics in the study population.

Frailty characteristics	Tests	Score range	Cut off point	Number of patients with abnormal test result (%)
Physical domain				
Daily functioning	IADL, Lawton	0-8	≤6	57 (21.2)
Nutritional status	MNA	0-14	≤11	126 (46.2)
Polypharmacy	Number of prescriptions	0-inf	≥5	164 (60.1)
Handgrip strength	Hydraulic handheld dynamometer	0-inf	gender and age	154 (56.4)
Mobility	TUGT	0-inf	≥10	108 (39.6)
Falls in past	Interview	Yes/no	Yes	31 (11.4)
Mental domain				
Cognition	6-CIT	0-28	≥6	54 (19.8)
Health related quality of life	EQ-5D-5L EQ-5D-vas	- 0-100	≥2 moderate <70	207 (75.8) 88 (32.2)
Delirium in past	Interview	Yes/no	Yes	12 (4.4)
Social domain				
Living alone	Interview	Yes/no	Yes	14 (5.1)
Living arrangement	Interview	-	Home care or residential facility	33 (12.1)
No social support system	Interview	Yes/no	No	85 (31.1)
Educational status	Interview	-	< Secondary school	104 (38.1)
Overall				
Multiple domains	G8	0-17	≤14	84 (30.8)
Multiple domains	ISAR-HP	0-5	≥2	52 (19.5)
Comorbidity	CCI	0-37	≥5	96 (35.2)

Abbreviations; IADL (Instrumental Activity of Daily Living), MNA (Mini Nutritional assessment), inf (infinity), TUGT (Timed to Get Up and Go Test), 6-CIT (6 item Cognitive Impairment Test), G8 (Geriatric 8), ISAR-HP (Identification of Seniors at Risk for Hospitalized Patients), CCI (Charlson Comorbidity Score), EQ-5D-5L (The EuroQol (European Quality of Life) Five Dimension Five Level Scale

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Outcomes

The primary outcome was a decreased HRQL three months after CRC diagnosis. A decreased HRQL was defined as a minimum detectable change of ≥10 points between baseline and 3 months follow up on the summary score of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire of Cancer patients (EORTC-QLQ-C30) questionnaire.[19] The QLQ-C30 is the most widely used questionnaire and generally accepted tool for assessing HRQL in oncology. The EORTC-QLQ-C30 questionnaire covers limitations experienced over the past week in five functional domains (physical, role, cognitive, emotional, and social functioning), a global quality of life scale, three symptom scales (fatigue, nausea and vomiting, and pain), and six single items (appetite loss, diarrhea, dyspnea, constipation, insomnia, financial impact). The scores were linearly transformed to a score between 0 and 100. The EORTC QLQ-C30 summary score is calculated as the mean of the combined 13 EORTC QLQ-C30 domains and item scores (excluding global quality of life and financial impact), with a higher score indicating a better HRQL.[19]

Patients who died within 3 months after surgery were scored with a maximum decreased HRQL. The EORTC-QLQ-C30 was surveyed twice, i.e. during frailty assessment at diagnosis and after three months of CRC diagnosis.

The questionnaire was filled out at home on paper or through a digital patient tracking system PROFILES (Patient Reported Outcomes Following Initial Long term treatment and Survivor Ship) if a patient was also participating in the Prospective Dutch Colorectal Cancer cohort (PLCRC).[20] In case of incomplete or missing follow up questionnaires patients were contacted by phone by a member of the study team and when necessary questionnaires were sent a second time to collect missing data. Secondary outcome was the occurrence of a major postoperative in-hospital complication defined as a Clavien Dindo grade ≥ 3.

Statistical analysis

Data are presented as frequencies and percentages for categorical data and as median with interquartile range (IQR) for continuous data. Differences between patients with preserved and decreased HRQL at three months after CRC diagnosis were tested with the Chi square test for dichotomous or categorical variables and the Mann-Whitney U test for continuous variables. Univariable analyses were performed to compare frailty characteristics among patients with decreased HRQL and preserved HRQL using the Chi square test.

Thereafter, the association between individual frailty characteristics and decreased HRQL were analysed by multivariable logistic regression analyses. Associations were adjusted for baseline HRQL, CCI≥5 (including comorbidities and age), gender and surgical approach (no surgery/surgery/surgery with stoma).[21] Odds ratios (OR) are presented with accompanying 95% confidence intervals (CI). A subgroup analysis was performed without patients who deceased within 3 months after diagnosis.

Similar analyses were performed for the association between individual frailty characteristics and in-hospital major complications (Clavien Dindo Grade≥ 3) after CRC surgery.

All scores of different HRQL domains were compared using paired Student's t-test among patients with and without a major in-hospital complication between baseline and three months after diagnosis. Mean differences (MD) were calculated between HRQL EORTC-QLQ-C30 domains on baseline and after 3 months and compared to the clinical relevance as estimated by the consensus-based guidelines of Cocks et al.[22]

A p-value of < 0.05 was considered statistically significant. Data analysis were performed using IBM SPSS Statistics version 23 for Windows (IBM Corp. Armonk, New York).

Sample Size Analysis
Guidelines for the clinical effect size are provided for the EORTC-QLQ-C30 subscales. This sample size calculation is based on a small difference (10 points) in EORTC-QLQ-C30 score.[23] This difference is considered subtle but clinically relevant. Based on the literature and the alpha of 0.05/power of 90%, a sample size of 265 patients would be sufficient.
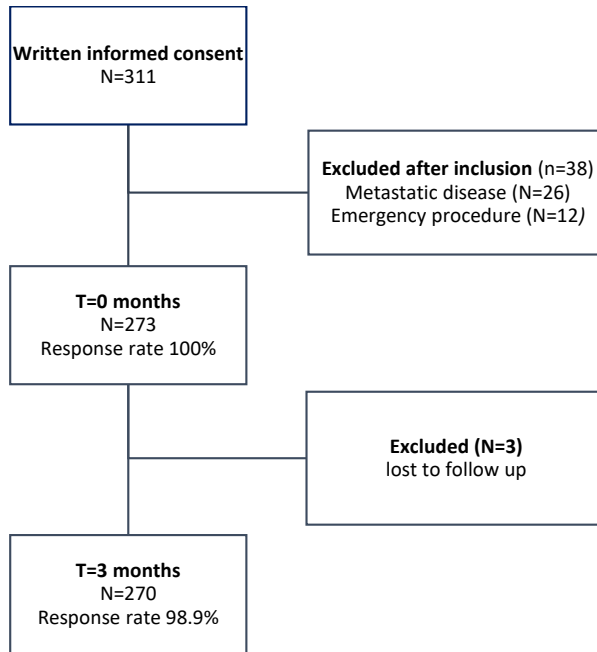
Figure 1. Flowchart of patient inclusion.

RESULTS

Study population and frailty
A total of 273 CRC patients were included (Figure 1). Baseline data and frailty assessment were complete in all patients. The response rate for the HRQL questionnaire after three months was 98.9% (n=270). Age ranged from 70 to 99 years and 107 patients (39.2%) were octogenarian. Ninety-six patients (35.2%) had five or more comorbidities. Eighty patients (29.3%) were diagnosed with rectal cancer of whom 17 patients (21.3%) received neoadjuvant (chemo)radiotherapy. The most common surgery for colon cancer was a right hemicolectomy (40.7%) and 18 patients (9.3%) were treated with adjuvant chemotherapy (Table 2). Seventeen patients (6.2%) did not undergo CRC surgery. Reasons for non-surgical treatment were poor performance status (n=11) and patient preference (n=6). None of the non-surgical patients died within three months. Overall, physical frailty was most common and consisted primarily of decreased grip strength (56.4%), risk of malnutrition (46.2%) and slow TUGT (39.6%). One out of five patients had impaired cognition and 33 patients (12.1%) were dependent on home care or lived in an assisted living facility. More than five frailty characteristics were present in all non-surgical patients compared to 29.6% of surgical patients (p=0.03).

Surgical patients
Median length between diagnosis and surgery was 28 days (IQR 18-34). A major postoperative complication occurred in 36/258 patients (14.0%) that underwent surgery for CRC. Twelve patients (4.7%) developed an anastomotic leakage. Twenty-three patients (8.9%) had a re-operation and 21 patients (8.1%) were admitted to the intensive care unit. Mortality was 2.3% (n=6) during hospital stay and 2.7% (n=7) after three months. Median length of hospital stay was 5 days (IQR 4-8) and 111 patients (43.0%) were discharged with home care or to a residential facility. ASA ≥3 (adjusted odds ratio (aOR) 2.3 (95% confidence interval (95%CI) 1.1-4.8)) and cognitive impairment (aOR 2.4 (95%CI 1.1-5.5)) were associated with a major postoperative complication. (Table 3)

Health related quality of life
A decreased HRQL occurred in 63 patients (23.1%), of whom twelve patients (4.4%) deceased and three patients (1.1%) had metastatic disease three months after diagnosis. Physical functioning (mean difference (MD) -7.7, P<0.01), social functioning (MD -5.0, P<0.01) and cognitive functioning (MD -10.4, P<0.01) were most commonly affected in patients with a decreased HRQL.

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Table 2. Baseline characteristics in CRC patients with and without a decreased HRQL after 3 months.

	Preserved HRQL N=207 (%)	Decreased HRQL N= 63 (%)	P-value
Age, median (IQR)	77 (73-82)	79 (74-83)	0.28
Male gender	133 (64.3)	39 (61.9)	0.74
ASA ≥3	80 (38.6)	38 (60.3)	<0.01
CCI ≥ 5	65 (31.4)	30 (47.6)	0.05
Comorbidities			
Cardiovascular disease	58 (28.0)	13 (20.6)	0.24
Pulmonary disease	37 (17.9)	15 (23.8)	0.36
Diabetes Mellitus	58 (28.0)	16 (25.4)	0.75
Atrial fibrillation	32 (15.5)	15 (23.8)	0.13
Intoxication			
Current smoking	22 (10.6)	8 (12.7)	0.65
Alcohol use	20 (9.7)	6 (9.5)	0.97
Stage			0.83
I	83 (40.1)	23 (36.5)	
II	72 (34.8)	22 (34.9)	
III	52 (25.1)	18 (28.6)	
Tumor site			0.83
Colon	145 (70.0)	45 (71.4)	
Rectum	62 (30.0)	18 (28.6)	
Type of surgery			0.37
No surgery	5 (2.4)	12 (19.1)	0.02
High/low anterior resection	42 (20.3)	6 (9.5)	0.01
APR	26 (12.6)	8 (12.7)	0.85
Hemicolectomy right	81 (39.1)	29 (46.0)	0.72
Hemicolectomy left	19 (9.2)	3 (4.8)	0.35
Sigmoid resection	32 (15.5)	4 (6.3)	0.41
(Sub)total colectomy	2 (1.0)	1 (1.6)	0.88
Neoadjuvant/adjuvant therapy	14 (6.8)	3 (4.8)	0.66
Chemoradiotherapy	11 (7.8)	2 (5.9)	0.57
Adjuvant chemotherapy			

Abbreviations: HRQL (Health Related Quality of Life), IQR (Interquartile Range), ASA (American Society of Anesthesiologists), CCI (Charlson Comorbidity Index), APR (abdominoperineal resection)

Table 3. Association of frailty characteristics with in hospital complications adjusted for gender, Charlson comorbidity index and type of surgery. (N=258)

Frailty characteristics	Major postoperative complication (N=36)			
	OR (95%CI)	P-value	aOR (95%CI)	P-value
ASA ≥3	2.2 (1.1-4.6)	0.03	2.3 (1.1-4.8)	0.03
CCI ≥5	1.0 (0.5-2.1)	0.97	0.8 (0.4-1.8)	0.60
G8	1.8 (0.5-4.2)	0.15	2.1 (0.9-5.2)	0.09
ISAR-HP	0.5 (0.2-1.1)	0.14	0.4 (0.1-1.1)	0.08
IADL	0.6 (0.3-1.3)	0.17	0.5 (0.2-1.2)	0.14
MNA	0.6 (0.3-1.2)	0.14	0.5 (0.2-1.0)	0.06
Anemia	0.9 (0.5-1.9)	0.87	0.8 (0.4-1.7)	0.54
Polypharmacy	0.8 (0.4-1.6)	0.51	0.8 (0.4-1.6)	0.51
Handgrip	0.6 (0.3-1.3)	0.21	0.7 (0.3-1.5)	0.34
TUGT	1.1 (0.5-2.2)	0.88	1.0 (0.4-2.0)	0.90
Falls	2.3 (0.5-9.9)	0.28	1.9 (0.4-8.8)	0.38
6-CIT	2.1 (1.0-4.7)	0.06	2.5 (1.1-5.6)	0.03
EQ-5D-5L	0.5 (0.2-1.4)	0.19	0.5 (0.2-1.2)	0.48
EQ-5D-vas	0.9 (0.4-1.9)	0.83	0.9 (0.4-1.8)	0.70
Delirium in past	1.3 (0.2-10.8)	0.80	1.3 (0.2-11.2)	0.80
Living alone	2.6 (1.0-6.4)	0.04	2.4 (0.9-6.6)	0.08
Living arrangement	0.5 (0.2-1.4)	0.20	0.4 (0.1-1.2)	0.10
No social support system	0.8 (0.2-3.8)	0.78	0.7 (0.1-3.4)	0.65
Educational status	1.1 (0.5-2.2)	0.84	0.8 (0.4-1.8)	0.46

Abbreviations; ASA (American Society of Anesthesiologists), CCI (Charlson Comorbidity Score), G8 (Geriatric 8), ISAR-HP (Identification of Seniors at Risk for Hospitalized Patients), IADL (Instrumental Activity of Daily Living), MNA (Mini Nutritional assessment), TUGT (Timed to Get Up and Go), 6-CIT (6 item Cognitive Impairment Test), EQ-5D-5L (The EuroQol (European Quality of Life) Five Dimension Five Level Scale)

Non-surgical patients more often reported a decreased HRQL (64.7% vs 20.5% in surgical patients, p<0.01) with a larger decline (MD -30.8 vs -2.4 in surgical patients, p<0.01) between baseline and three months after CRC diagnosis (Supplementary Table 1). After adjustment for confounding factors a non-surgical approach was associated with a six-fold increased odds for a decreased HRQL (aOR 6.4 (95% CI 2.0-19.8). Frailty characteristics in patients with and without a decreased HRQL are presented in Table 4, corrected for gender, comorbidity, treatment strategy (no surgery/surgery), and

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baseline HRQL. Comorbidity (i.e. CCI and ASA), impaired IADL and dependent living were associated with a decreased HRQL (Figure 2). Subgroup analysis without deceased patients showed similar associations between frailty characteristics and HRQL, however the association with impaired IADL was weaker (aOR 2.0 (95%CI 1.2-2.5).

Table 4. Frailty according to HRQL.

Frailty characteristics	Preserved HRQL N=207 (%)	Decreased HRQL N= 63 (%)	P-value
G8	70 (33.8)	14 (22.2)	0.08
ISAR-HP	32 (15.5)	20 (31.7)	0.07
IADL	36 (17.4)	22 (34.9)	<0.01
MNA	90 (43.5)	33 (52.4)	0.22
Anemia	112 (54.1)	37 (58.1)	0.52
Polypharmacy	123 (59.4)	39 (61.9)	0.72
Handgrip	115 (55.6)	36 (57.1)	0.89
TUGT	80 (38.6)	26 (42.3)	0.77
6-CIT	40 (19.3)	14 (22.2)	0.62
EQ-5D-5L	155 (74.9)	50 (79.4)	0.50
EQ-5D-vas	66 (31.9)	21 (33.3)	0.83
Delirium in past	7 (3.4)	5 (7.9)	0.13
Living alone	64 (30.9)	20 (31.7)	0.90
Living arrangement	21 (10.1)	12 (19.0)	0.05
No social support system	12 (5.8)	2 (3.2)	0.41
Educational status	77 (37.2)	25 (39.7)	0.72

Abbreviations; HRQL (Health related Quality of Life), ASA (American Society of Anesthesiologists), CCI (Charlson Comorbidity Score), G8 (Geriatric 8), ISAR-HP (Identification of Seniors at Risk for Hospitalized Patients), IADL (Instrumental Activity of Daily Living), MNA (Mini Nutritional assessment), TUGT (Timed to Get Up and Go Test), 6-CIT (6 item Cognitive Impairment Test), EQ-5D-5L (The EuroQol (European Quality of Life) Five Dimension Five Level Scale)

In an univariate subgroup analysis of surgical patients, none of the frailty characteristics were associated with decreased HRQL. Patients with a complicated hospital stay after surgery more often had a decreased HRQL after three months (44.4% vs 20.1% in patients without a complication, P<0.01), and the occurrence of a major postoperative complication increased the odds for a decreased HRQL four-fold (aOR 4.0 (95%CI 1.9-8.8)). Change in HRQL scores according to the six functional subscales of EORTC-QLQ-C30 for surgically treated patients are shown in Figure 3. Occurrence of major postoperative complications resulted in significant declines (p<0.01) in all six subscales.
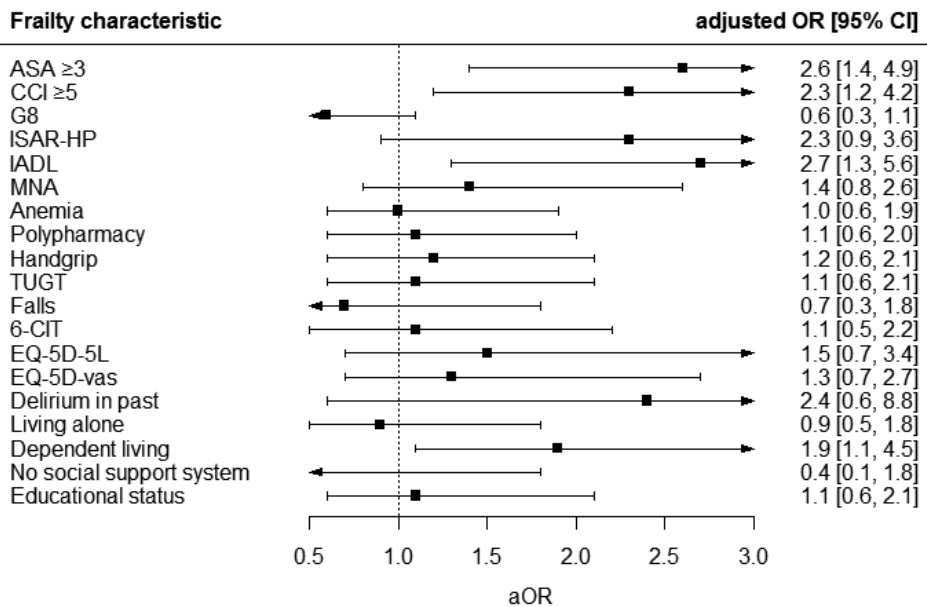

Figure 2. Frailty characteristics and decreased HRQL after three months. All characteristics were independently adjusted for gender, comorbidity, surgical approach and baseline HRQL.

*CCI ≥5 was not adjusted for comorbidity

Abbreviations; OR (odds ratio), ASA (American Society of Anesthesiologists), CCI (Charlson Comorbidity Score), G8 (Geri atric 8), ISAR-HP (Identification of Seniors at Risk for Hospitalized Patients), IADL (Instrumental Activity of Daily Living), MNA (Mini Nutritional assessment), TUGT (Timed to Get Up and Go Test), 6-CIT (6 item Cognitive Impairment Test), EQ-5D-5L (The EuroQol (European Quality of Life) Five Dimension Five Level Scale
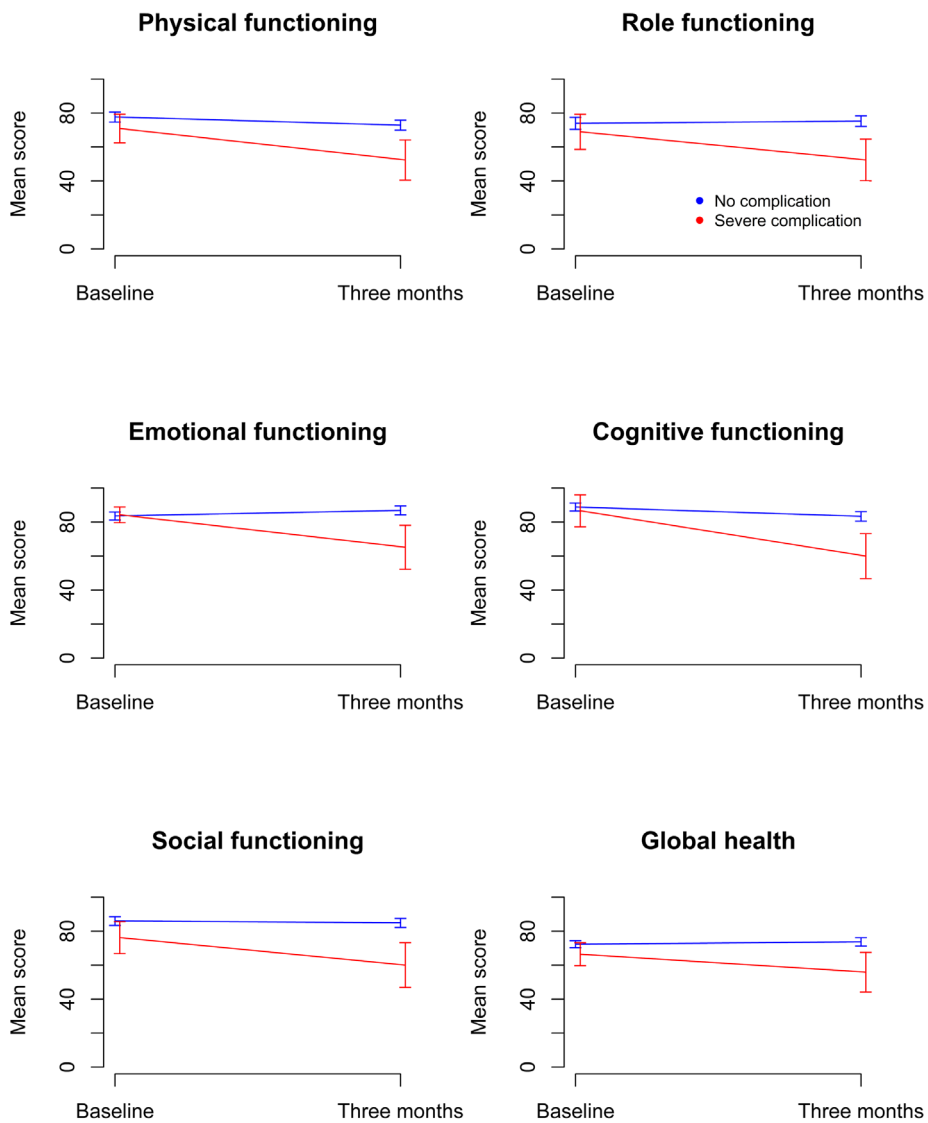
Physical functioning

Role functioning

Emotional functioning

Cognitive functioning

Social functioning

Global health

Figure 3. Function domains and summary HRQL score in patients with and without major complications, assessed with the EORTC-QLQ-C30 questionnaire. Results are presented in mean scores. All P-values are <0.01.

DISCUSSION

This multi-center observational study used detailed information on frailty to identify determinants for a decreased HRQL three months after non-metastatic CRC diagnosis in elderly patients. Frailty was highly prevalent, with almost half of the patients having one or multiple frailty characteristics, and one out of four patients reported a clinically relevant decrease in HRQL three months after CRC diagnosis. Patients that did not undergo surgery or with a major postoperative complication had the highest risk for a decreased HRQL. Other important determinants were comorbidity, impaired daily functioning and dependent living but were more common in non-surgical patients. Although frailty was common in our study population, none of the other frailty characteristics were associated with a decreased HRQL after three months.

Poor health outcomes are often feared by older patients diagnosed with non-metastatic CRC, as treatment can have a significant impact on physical, mental and social well-being. Identifying risk factors for adverse functional outcome, including HRQL, are valuable to make informed shared decisions and increase the number of patients that benefit from surgery. Prior studies investigated HRQL in older surgical CRC patients showed similar results; shortly after surgery a decrease of HRQL. However, in most patients recovery occurs one year after surgery. [24] [25] Although the results of our study do show that elderly CRC patients are at risk for a decreased HRQL shortly after diagnosis, this decline is most significant in patients who do not undergo surgery, either due to poor performance status or personal preference. These patients showed large declines in physical, social and cognitive functioning, which is likely explained by advanced age, pre-existing multi-morbidity and frailty or disease progression.

By contrast, the overall decline in HRQL in the surgically treated patients was relatively small and consisted of slight impairments in physical and cognitive functioning. In line with other studies, a major postoperative complication was a strong determinant of decreased HRQL after three months.[26,15] Only preoperative comorbidity and cognitive impairment were associated with major postoperative complications.

Prior studies showed that frailty characteristics measured on a full geriatric assessment were associated with postoperative complications.[6] However, a full geriatric assessment is time consuming and a clinical assessment of frailty by an experienced physician may suffice.[27] Considering the growing number of elderly patients and the already high workload of medical professionals, we suggest a targeted preoperative work-up to identify patients at risk for adverse outcomes after CRC diagnosis. In our opinion, this should be done by an experienced physician/nurse and focus on comorbidity, daily

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functioning, self-dependence and cognition. We recommend a collaborative approach of multiple specialties in a multidisciplinary team (MDT) meeting in complex patients.[28] A MDT approach can be useful to weigh the risks and benefits of treatment, incorporating frailty into treatment decision making and discuss options for prehabilitation in order to optimize preoperative shared decision making and reduce postoperative complications.

Experience with patients reported outcomes measurements (PROMs) for older CRC patients are limited and heterogeneous.[29] The EORTC QLQ-C30 questionnaire is widely used as PROM but was investigated mostly in younger patients. Therefore, the validity of the EORTC QLQ-C30 for the older population is a point of debate. HRQL domains that are impaired vary by age, i.e. HRQL is worse with increasing age for physical functioning, and better with increasing age for social functioning and financial problems.[30] Furthermore, our results illustrate that studying change in HRQL in cancer patients is complex. PROMs are susceptible to subjectivity and different reasons may have affected the reported HRQL after three months. Survivors of CRC have often described the period after treatment as more difficult than treatment itself. It brought feelings of uncertainty about the future and fear of cancer recurrence, while others experienced more positive feelings by resuming normal life.[31] Furthermore, cognitive disorders can lead to difficulty with understanding HRQL questionnaires, comorbidity and frailty may have a larger impact on HRQL than cancer itself, and starting adjuvant chemotherapy or changes in social environment (e.g. loss of a partner, or family member) can negatively impact HRQL. Also, a patient's perception of their internal standards, values and conceptualization of HRQL may be reframed over time, this is also known as response shift.[32,33] In our study, a large decline in HRQL was witnessed in a small group of non-surgical patients. High-risk for postoperative morbidity and poor health were the main reasons why surgery was omitted. In non-surgical patients decreased HRQL was likely the result of a fragile general health instead of CRC progression.

Strengths of the current study include the thorough frailty assessment and the large number of frailty tests, which were all performed by the same researcher. Response bias was limited due to a minimum loss to follow up. Furthermore, our sample size is one of the largest to date and follow-up was complete in 99% of patients. Nevertheless, some limitations should be addressed. First, although the prevalence of frailty characteristics are comparable with other studies, it is conceivable that frail patients more often denied to participate in the study. However, percentage of non-surgical patients, who are often frail, are comparable with population based studies in CRC patients which makes our study cohort generalizable. Second, our study sample consisted of patients with colon and rectal cancer, with differences in symptoms, surgery and (neo)adjuvant treatment. Although (neo)adjuvant therapy and type of surgery can affect postoperative outcomes

including HRQL, our cohort is representative of a real-world CRC population. Third, depending on type of surgery, timing of surgery and adjuvant chemotherapy, it seems plausible that some patients need more than three months to fully recover from cancer treatment. Nevertheless, insight in short term HRQL results is valuable information for shared decision making process in future patients. Long term HRQL results will be published in the future.

In conclusion, frailty characteristics are highly prevalent in elderly patients at time of CRC diagnosis but not strongly associated with a decreased HRQL after three months. Non-surgical patients were at highest risk of decreased HRQL three months after diagnosis. Comorbidity, impaired daily functioning and dependent living were most important determinants of decreased HRQL which was mainly caused by the non-surgical patients. In surgical patients, the occurrence of a major postoperative complication was a strong determinant of decreased HRQL and was associated with preoperative comorbidity and cognitive impairment. The results of our study highlight the importance of identifying those patients at risk for postoperative complications and advocate for a targeted routine assessment of preoperative frailty.

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SUPPLEMENTARY TABLE

Supplementary Table 1. Mean difference of HRQL domains and symptoms scales between baseline and 3 months in patients with and without surgery, assessed with the EORTC-QLQ C30 questionnaire.

	MD without surgery (N=17)	P-value	MD with surgery (N=263)	P-value
Physical functioning	-24.6	0.01	-6.7	0.01
Role functioning	-31.3	0.01	-1.1	0.60
Emotional functioning	-32.8	0.01	0.2	0.87
Cognitive functioning	-42.7	0.01	-8.4	0.01
Social functioning	-33.3	0.01	-3.2	0.06
Global health	-29.7	0.01	-0.16	0.91
Fatigue	-4.2	0.69	5.1	0.04
Pain	5.2	0.57	-2.6	0.02
Nausea and vomiting	-3.1	0.57	-2.1	0.11
Summary score	-30.8	0.01	-2.4	0.06

Abbreviation: MD Mean Difference

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