Frailty and outcomes in older cancer patients

Vlies, E. van der

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IN OLDER CANCER PATIENTS

ELLEN VAN DER VLIES

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COLOFON

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GENERAL INTRODUCTION

GENERAL INTRODUCTION

Ageing of the cancer population

Life expectancy of the Dutch population has increased significantly over the last century.[1] Nowadays, life expectancy has increased to eighty years for men and eighty-four years for women. Consequently, the number of older patients diagnosed with cancer has steadily increased. In 2019, more than one-hundred thousand cancer patients (excluding skin cancer) were diagnosed in The Netherlands. Fifty percent of these patients was aged seventy years or older. (Figure 1) Currently, cancer is the leading casus of death among older Dutch patients. Half of the patients ≥70 years die because of cancer.[2]

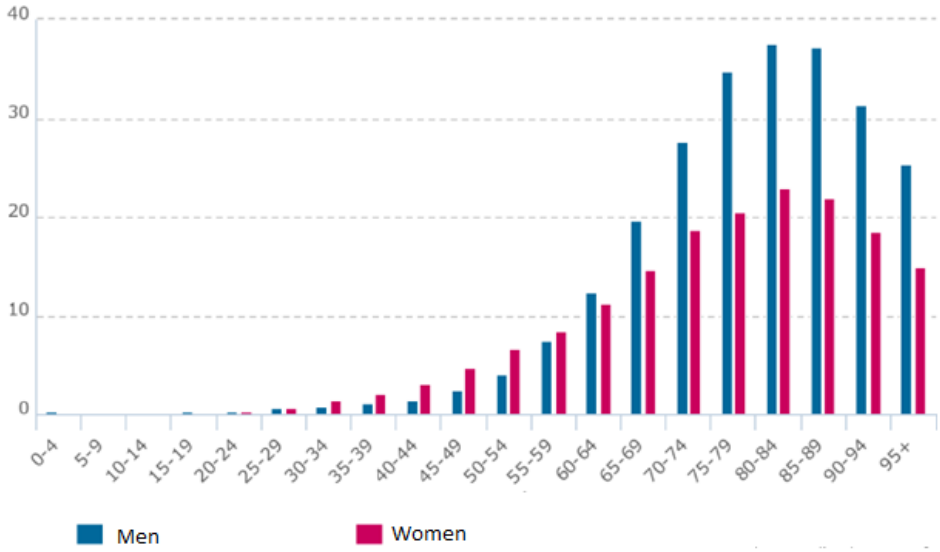

Figure 1. Incidence of cancer in the Netherlands in 2019, by age and gender.

Source: Netherlands Cancer registry

Challenges in older patients with cancer

The ageing of the population has a major impact on oncological care. Overall health and functional status can vary largely between older patients, including the presence and extend of comorbidity and geriatric impairments.[3] This heterogeneity has led to the exclusion of older cancer patients from the majority of clinical trials.[4] Although substantial progress has been made in cancer treatment, it is unclear whether older patients benefit from these improvements. The under-representation of the older patients has led to a lack of knowledge with regard to efficacy and safety of anti-cancer treatment resulting in a risk of both under- and over treatment. As a result, current treatment decisions often

lack a scientific basis and are often based on clinical judgement. Clinical judgment varies between clinicians and may be subject to bias.[5] Besides, treatment decisions are usually based on oncological guidelines, while older patients are complex and often suffer from multiple chronic diseases and frailty which demands for a patient-centred treatment plan.[6] The age definition of an older person is arbitrary. Most of the literature uses 70 year and older as cut-off point, based on retrospective evidence that the incidence of geriatric impairments increases sharply after 70 years and older.[7]

Outcomes of cancer treatments traditionally focus on survival and disease-free status. However, for older patients, maintaining health related quality of life (HRQL) is often more valuable than longevity. When discussing different options for cancer treatment, impact on HRQL should ideally be discussed in addition to survival and complications. However, patient reported outcomes were hardly ever part of large oncological trials.[8]

The increasing complexity of the management of older cancer patients and concerns of adverse outcomes demand accurate risk assessment. Chronological age alone is often a poor indicator of the physiological and functional status of older adults, and thus should not solely define treatment decisions in oncology.[8 9] Current risk assessment tools do not predict outcomes such as loss of quality of life or functional decline. Significant progress has been made in risk stratifying older cancer patients beyond age and traditional performance scales such as the ECOG (Eastern Cooperative Oncology Group) Performance Score. The American Society of Clinical Oncology (ASCO), The International Society of Geriatric oncology (SIOG) and other cancer-focused organisations now recommend a geriatric assessment for all older patients to detect physical, functional, and psychological impairments that can increase the risk of adverse outcomes of cancer therapy.[10]

Frailty

Frailty is an age related state of functional decline. The syndrome of frailty is closely related to comorbidity and disability, and often occurs simultaneously. The aetiology of frailty is largely unknown, but contributing factors include malnutrition, muscle wasting, fatigue, sarcopenia, chronic inflammation, immuno-senescence, and hormonal deficits.[11–13]

In reality, frailty is complex, multidimensional and highly prevalent. Accumulations of deficits on the somatic, physical, mental, and social domain lead to a diagnosis of frailty. (Figure 2)

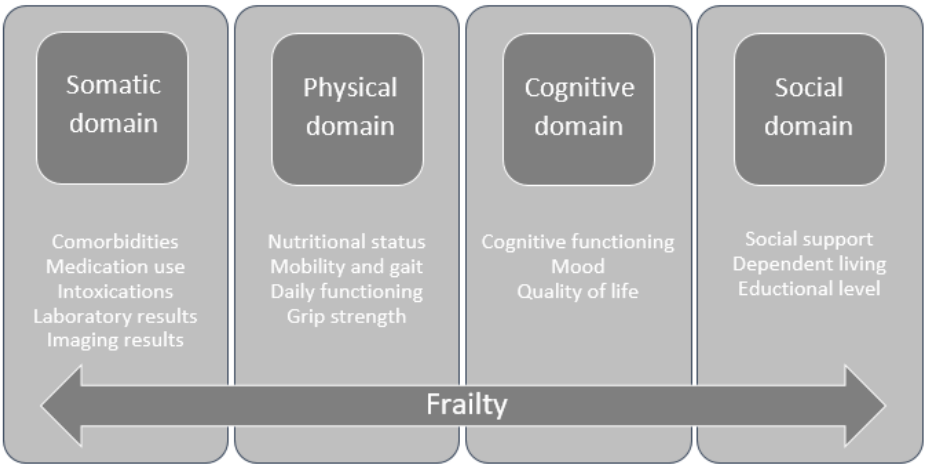

Figure 2. Frailty domains and characteristics

In the setting of geriatric oncology, research suggests that frail patients have increased risk of postoperative complications, chemotherapy toxicity and death.[14] Therefore, The International Society of Geriatric Oncology and the National Comprehensive Cancer Network recommend performing a geriatric assessment to screen for frailty in all patients older than 70 years and those with significant weight loss (>5%) because of chronic illness.[7] Which frailty measurement tool is optimal for screening and assessment, however, is not clear.[15] This is also caused by different outcome measurements such as postoperative complications, chemotherapy intolerance, functional decline and loss of quality of life. Over seventy different measures of frailty have been proposed. Currently, a comprehensive geriatric assessment is the most accepted method to assess frailty. However, a comprehensive geriatric assessment is time consuming. Given the rise in number of older patients, and the already high workload of medical professionals, this seems often unfeasible in the regular clinical practice.

Frailty is associated with a number of different clinical outcomes such as postoperative complications, chemotherapy intolerance, disease progression and death.[14] However, associations are dependent on the type and stage of cancer, anti-cancer treatment and the tests that are used to diagnose frailty. As older age and comorbidities are often associated with frailty, it seems essential to take frailty characteristics into account in order to improve shared decision making and to guide possible prehabilitation interventions in the growing cohort of patients.

Thesis objectives

The main objectives of this thesis are:

I) To study survival and tolerability outcomes in non-surgically treated older cancer patients.

II) To assess the association between frailty and (functional) adverse outcomes in cancer patients.

III) To describe the implementation of a preoperative multidisciplinary team care for frail cancer patients.

Outline of this thesis

Chapter 2 describes in a Dutch population-based study the survival in non-surgical and surgical patients aged ≥70 years with non-metastatic colorectal cancer. **Chapter 3** assesses the tolerability and outcomes of combined therapy with neoadjuvant chemoradiotherapy and surgery in older patients with locally advanced rectal cancer. In **Chapter 4** the association of chemotherapy intolerance and frailty characteristics in patients treated with palliative chemotherapy is prospectively studied. **Chapter 5** describes the influence of preoperative multidisciplinary care for frail older patients with colorectal cancer on preoperative decision making and postoperative outcomes. **Chapter 6** determines the value of preoperative frailty screening in predicting postoperative severe complications and 1-year mortality in patients undergoing radical cystectomy. In **Chapter 7** the association between frailty and decreased health-related quality of life in older patients with colorectal cancer is investigated in a multicenter observational cohort study including patients aged ≥70 years diagnosed with non-metastatic colorectal cancer. Finally, overall conclusions and recommendations for clinical practice are summarized in **Chapter 8**.

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2

SURVIVAL IN SURGICAL AND NON-SURGICAL OLDER PATIENTS WITH NON-METASTATIC COLORECTAL CANCER; A POPULATION-BASED STUDY IN THE NETHERLANDS

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ABSTRACT

Background

Surgery is the primary treatment for non-metastatic colorectal cancer (CRC) but is omitted in a proportion of older patients. Characteristics and prognosis of non-surgical patients are largely unknown.

Objective

To examine the characteristics and survival of surgical and non-surgical older patients with non-metastatic CRC in the Netherlands.

Methods

All patients aged ≥70 years and diagnosed with non-metastatic CRC between 2014 and 2018 were identified in the Netherlands Cancer Registry. Patients were divided based on whether they underwent surgery or not. Three-year overall survival (OS) and relative survival (RS) were calculated for both groups separately. Relative survival and relative excess risks (RER) of death were used as measures for cancer-related survival.

Results

In total, 987/20.423 (5%) colon cancer patients and 1.459/7.335 (20%) rectal cancer patients did not undergo surgery. Non-surgical treatment increased over time from 3.7% in 2014 to 4.8% in 2018 in colon cancer patients (P=0.01) and from 17.1% to 20.2% in rectal cancer patients (P=0.03). 3 year RS was 91% and 9% for surgical and non-surgical patients with colon cancer, respectively. For rectal cancer patients this was 93% and 37%, respectively. In surgical patients, advanced age (≥80 years) did not decrease RS (colon; RER 0.9 (0.7-1.0), rectum; RER 0.9 (0.7-1.1)). In non-surgical rectal cancer patients, higher survival rates were observed in patients treated with chemoradiotherapy (OS 56%, RS 65%), or radiotherapy (OS 19%, RS 27%), compared to no treatment (OS 9%, RS 10%).

Conclusion

Non-surgical treatment in older Dutch CRC patients has increased over time. Because survival of patients with colon cancer is very poor in the absence of surgery, this treatment decision must be carefully weighed. (Chemo-)radiotherapy may be a good alternative for rectal cancer surgery in older frail patients.

INTRODUCTION

Colorectal cancer (CRC) is one of the most frequently diagnosed cancer types in the Netherlands, with approximately 14.000 new cases each year.[1] More than half of the CRC patients are aged ≥70 years at the time of diagnosis. Surgery is the main curative treatment for non-metastatic CRC. However, older patients are at increased risk of adverse outcomes, including postoperative complications, functional decline and worse quality of life after surgery.[2 3 4] In order to carefully weigh the risks and benefits of surgery, detailed information on outcomes in older cancer patients is needed.

In the past years, there has been much attention for patient-centred treatment plans to reduce undesired outcomes in older oncology patients.[5] Older patients have a relatively short life expectancy, in comparison to younger patients, and often value quality of life over longevity.[6] Therefore, information on cancer and non-cancer related survival is crucial for shared decision making. Yet, survival rates in non-surgical CRC patients and its influence on alternative treatment options are largely unknown. The aim of this Dutch population-based study was to examine the characteristics and survival of surgical and non-surgical older patients diagnosed with non-metastatic CRC.

METHODS

Study population

In this nationwide population-based study, all patients aged ≥ 70 years diagnosed with non-metastatic CRC (cM0) between 2014 and 2018 in the Netherlands were included. Patients for whom disease stage or date of resection was unknown, who were treated with local therapy such as polypectomy, transanal endoscopic microsurgery (TEM), transanal excision (TAE), or who were diagnosed with a neuro-endocrine tumor were excluded. Patients with a double tumor were excluded from the analyses if the dates of resection differed. For patients with a double tumor with the same date of resection, the most extensive tumor was designated as the index tumor. Patients were divided into five age groups: 70-74, 75-79, 80-84, 85-89, ≥90 years. Treatment was categorized as follows, for colon cancer: 1. Surgery; 2. No surgery. For rectal cancer: 1. Surgery; 2. Surgery with neoadjuvant chemoradiotherapy (CTRT); 3. Surgery with radiotherapy (RT); 4. No surgery; 5. No surgery, chemoradiotherapy (CTRT); 6. No surgery, radiotherapy (RT).

Data collection

Data were extracted from the Netherlands Cancer Registry (NCR), managed by the Netherlands Comprehensive Cancer Organisation (IKNL). This registry contains data of all newly diagnosed cancer patients in the Netherlands. Data on patient and tumor characteristics, diagnosis and treatment strategies are routinely extracted from the medical records by trained registration clerks of IKNL. Tumor localization is categorized into colon (C18) and rectum (C19-C20) and further divided into anatomical subsites: proximal colon (coecum, ascending colon, hepatic flexure, transverse colon and splenic flexure; C18.0, C18.2-18.5), distal colon (descending colon and sigmoid; C18.6-18.7) and other/NOS (not other specified) (C18.8-18.9). Tumors are staged as defined by the TNM (Tumor-Nodes-Metastases) classification valid at time of diagnosis.[7] Clinical stage is used when pathological stage is missing. Anatomical site is registered according to International Classification of Disease–Oncology (ICDO).[8] The Charlson Comorbidity Index (CCI) and the American Society of Anaesthesiologists (ASA) classification are collected to assess the overall weight of comorbidities.[9] Patients' vital status is obtained by linking the NCR to the Municipal Personal Records Database (BRP). Information on cause of death was not available in this registry.

Outcomes

Survival was defined as the time from diagnosis to the date of death or last follow up for patients who were still alive (February 1, 2020). 3-year overall survival (OS) was defined as the time from diagnosis to death or date of last follow up. 3-year relative survival (RS) was used to estimate the probability of surviving from cancer.

Statistical analysis

Description of patient and tumor characteristics and analyses were performed separately for colon cancer and rectum cancer. Differences in baseline characteristics were compared among surgical and non-surgical patients using the Chi-square test for categorical variables and the Student's t-test or Mann-Whitney U test for continuous variables, as appropriate.

A Kaplan-Meier survival analysis was conducted to determine the crude 3-year overall survival (OS) for surgical and non-surgical patients.

To estimate cancer-specific survival, 3-year relative survival (RS) was calculated for both groups using the Pohar Perme method.[10] We defined RS as the ratio of the observed survival in cancer patients to the expected survival in the general population (based on age, gender and calendar year). Expected survival was calculated from population life tables from the Netherlands.[11] OS and RS was also calculated for each of the treatment strategies in rectal cancer patients. Relative excess risks (RER) of death were estimated for surgical and non-surgical treated patients using a multivariable generalized linear model with a Poisson error structure, based on collapsed relative survival data, using exact survival times.[10] Models were adjusted for age (in 3 categories: 70-74, 75-79 and ≥80 years because in 5 categories the model did not converge), gender, year of diagnosis, comorbidities (CCI), disease stage, ASA classification and emergency surgery (the latter two for surgical patients only). (CT)RT was included in both the surgical and non-surgical models regarding rectum cancer and adjuvant CT was included for analyses in surgical colon patients.

Throughout the analyses, a *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using R statistics version 3.5.1 (2018-07-02, R, Inc., for Windows).

RESULTS

Characteristics of older non-surgical patients

During the study period, 987/20.423 (5%) colon cancer patients and 1.459/7.335 (20%) rectal cancer patients did not undergo surgery (Figure 1). Non-surgical patients were characterized by advanced age, multi-morbidity and higher disease stage (Table 1). Surgery was more frequently omitted when age increased. The proportion of non-surgical patients increased over time, from 3.7% in 2014 to 4.8% in 2018 for colon cancer (p=0.01), and from 17.1% to 20.2% for rectal cancer (p=0.03), respectively. For rectal cancer patients, this was primarily caused by an increase in chemoradiotherapy followed by a wait and see approach for complete responders (0% in 2014 vs 4.0% in 2018).

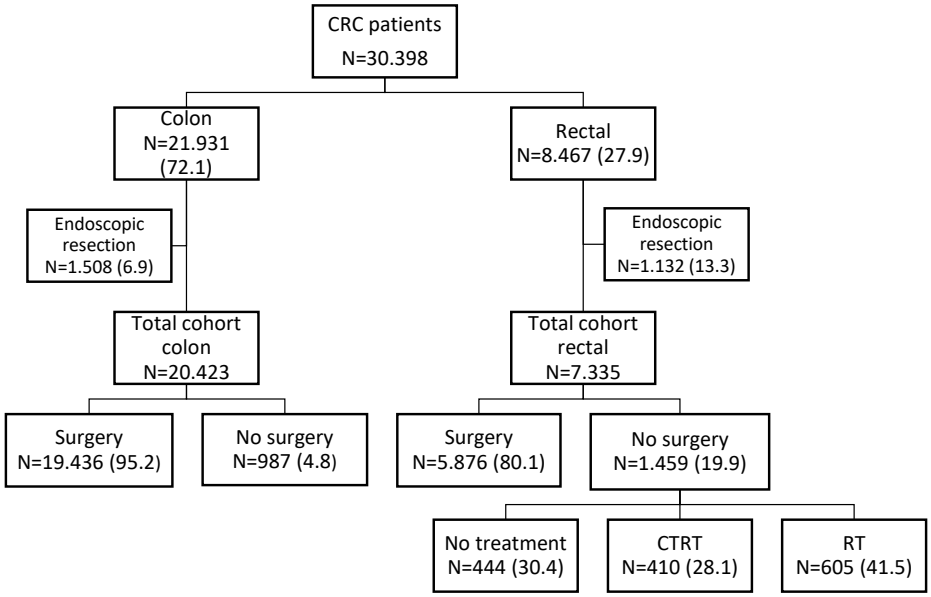

Figure 1. Flowchart non-metastatic CRC patients ≥70 years in 2014-2018. (N (%))

The majority (70%) of patients of 80 years or older that did not receive surgical treatment neither received alternative treatment (Supplementary Table 1). Patients with complete response after (CT)RT (n=147, 10.1%) were younger and had less comorbidities, compared to other non-surgical patients with rectal cancer.

Survival of older colon cancer patients

After a median follow up of 33 months [interquartile range (IQR) 20-51], 5.757/19.436 (28%) surgical patients deceased versus 899/987 (91%) non-surgical patients (P<0.01). The crude 3-year OS and RS were 78% and 91% for surgical patients and 7% and 9% for non-surgical patients, respectively (Figure 2a).

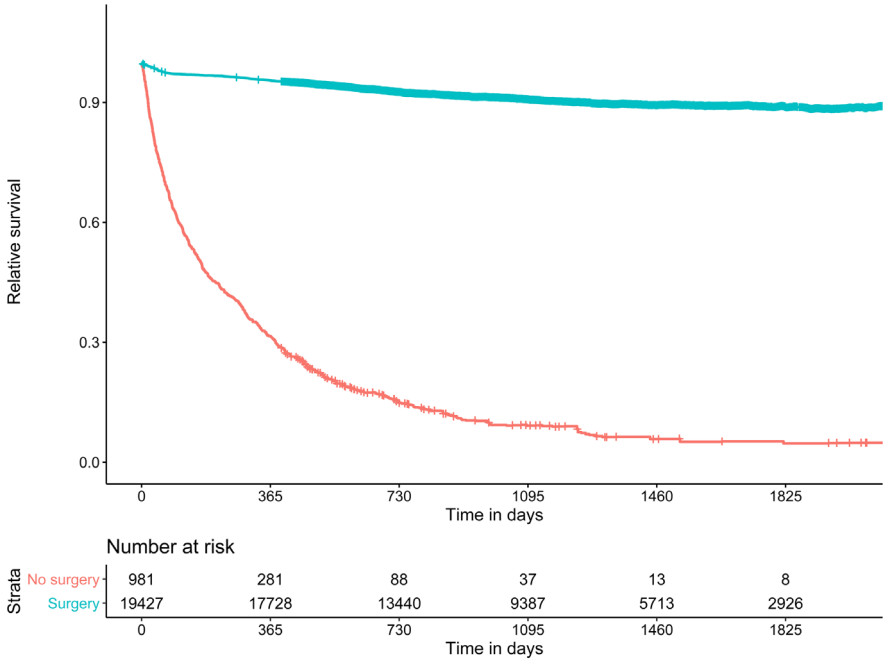

Figure 2a. Relative survival colon cancer patients according to surgery and non-surgery.

The 3-year OS and RS in surgical and non-surgical colon cancer patients according to patient and tumor characteristics are shown in Table 2. A decrease in OS in both surgical and non-surgical patients was related to advanced age, multi-morbidity and higher disease stage. However, no age-related differences were observed for RS. Surgical patients had a worse RS with increasing disease stage (stage III; RER 2.6 (95%CI 2.0-3.2) and comorbidities (ASA 4; RER 2.0 (95%CI 1.3-3.1)) (Table 2). In non-surgical patients, disease stage increased the risk of cancer-related death almost three-fold (stage III; RER 2.7 (95%CI 2.0-3.2)).

Table 1. Baseline characteristics according to surgical and non-surgical patients for colon and rectal cancer.

	Colon patients (N=20.423)		P-value
	Surgical (N=19.436)	**Non-surgical (N=987)**	
Age			<0.01
70-74	6709 (34.5)	125 (12.7)	
75-79	6197 (31.9)	154 (15.6)	
80-84	4201 (21.6)	286 (29.0)	
85-90	1898 (9.8)	284 (28.7)	
≥90	431 (2.2)	138 (14.0)	
Gender, male	9415 (48.4)	568 (57.5)	<0.01
ASA			<0.01
I	901 (4.6)	52 (5.3)	
II	7998 (41.2)	195 (19.8)	
III	5042 (25.9)	177 (17.9)	
IV	378 (1.9)	86 (8.7)	
Unknown	5117 (26.4)	477 (48.3)	
CCI (median)	1 (0-2)	1 (0-2)	<0.01
CCI			<0.01
0	3332 (17.1)	104 (10.6)	
1	2891 (14.9)	125 (12.7)	
≥2	2043 (10.5)	121 (12.2)	
Unknown	11.170 (57.5)	637 (64.5)	
Year of diagnosis			<0.01
2014	4156 (21.4)	161 (16.3)	
2015	3616 (18.6)	173 (17.5)	
2016	4038 (20.8)	181 (18.3)	
2017	3840 (19.7)	197 (20.0)	
2018	3786 (19.5)	275 (27.9)	
Stage			<0.01
I	4896 (25.2)	165 (16.7)	
II	8150 (41.9)	407 (41.2)	
III	6390 (32.9)	415 (42.1)	
Localisation			<0.01
Proximal colon	11841 (60.9)	614 (62.2)	
Distal colon	7261 (37.4)	332 (33.6)	
Other/NOS	334 (1.7)	41 (4.2)	
Emergency surgery	1008 (5.2)	-	-

	Rectal patients (N=7.335)		P-value
	Surgical (N=5.876)	**Non-surgical (N=1.459)**	
			<0.01
	2497 (42.5)	296 (20.3)	
	1853 (31.5)	304 (20.9)	
	1107 (18.8)	390 (26.7)	
	386 (6.6)	342 (23.5)	
	33 (0.6)	126 (8.6)	
	2184 (37.2)	610 (41.8)	<0.01
			<0.01
	366 (6.2)	256 (17.5)	
	2762 (47.0)	337 (23.1)	
	1206 (20.5)	251 (17.3)	
	57 (1.0)	75 (5.1)	
	1485 (25.3)	540 (37.0)	
	1 (0-1)	1 (0-2)	<0.01
			<0.01
	1124 (19.1)	194 (13.3)	
	863 (14.7)	214 (14.6)	
	521 (8.9)	180 (12.4)	
	3368 (57.3)	871 (59.7)	
			<0.01
	1306 (22.2)	270 (18.5)	
	1126 (19.2)	256 (17.5)	
	1131 (19.2)	295 (20.2)	
	1169 (19.9)	297 (20.5)	
	1144 (19.5)	341 (23.3)	
			<0.01
	1492 (25.4)	202 (13.8)	
	1514 (25.8)	431 (29.5)	
	2870 (48.8)	826 (56.7)	
			<0.01
	-	-	
	-	-	
	-	-	
	34 (0.6)	-	-

Table 1. Continued.

	Colon patients (N=20.423)		P-value
	Surgical (N=19.436)	Non-surgical (N=987)	
Treatment modalities			-
Surgery only	16342 (84.1)	-	
Adjuvant CT	3094 (15.9)	-	
Neoadjuvant CTRT	-	-	
Neoadjuvant RT	-	-	
CTRT	-	-	
RT	-	-	

Abbreviations: ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Score, CT: chemotherapy, RT: radiotherapy

Table 2. Crude 3 year overall and relative survival percentages and relative risks of dying among surgical (N=19.436) and non-surgical (N=987) treated colon cancer patients, stratified by risk facors.

	Surgical patients		
	Overall survival	Relative survival	
	Crude 3 year %	Crude 3 year %	RER* (95% CI)
Age, years			
70-74	85.8	91.7	1.0 (ref)
75-79	81.3	90.6	1.1 (0.8-1.4)
≥80	67.1	90.0	0.9 (0.7-1.1)
Gender			
Female	78.9	90.3	1.0 (ref)
Male	77.3	91.3	1.1 (0.8-1.3)
ASA			
I	89.1	100	1.0 (ref)
II	84.1	96.5	1.2 (0.8-1.8)
III	71.1	84.8	1.4 (1.0-2.1)
IV	48.7	58.9	2.0 (1.3-3.1)
CCI			
0	82.6	95.8	1.0 (ref)
1	77.2	90.0	1.3 (0.9-1.7)
≥2	67.5	79.5	1.0 (0.7-1.4)
Stage			
I	89.0	101	1.0 (ref)
II	80.8	95.5	2.1 (1.6-2.6)
III	66.4	76.7	2.6 (2.0-3.2)

Rectal patients (N=7.335)		P-value
Surgical (N=5.876)	Non-surgical (N=1.459)	
		-
2899 (49.3)	-	
-	-	
1448 (24.6)	-	
1630 (27.7)	-	
-	410 (28.1)	
-	605 (40.2)	

	Non-surgical patients	
Overall survival	Relative survival	
Crude 3 year %	Crude 3 year %	RER* (95% CI)
8.5	9.0	1.0 (ref)
8.6	9.8	1.1 (0.8-1.2)
6.2	9.1	0.9 (0.7-1.0)
5.6	7.6	1.0 (ref)
8.5	11.3	1.2 (1.0-1.4)
-**	-	-
-	-	-
-	-	-
-	-	-
5.3	8.0	1.0 (ref)
2.8	3.7	1.3 (1.1-1.7)
1.1	1.6	1.0 (0.9-2.5)
17.8	22	1.0 (ref)
6.7	9.2	2.1 (1.7-2.9)
2.7	4.2	2.7 (2.0-3.2)

Table 2. Continued.

	Surgical patients		
	Overall survival	**Relative survival**	
	Crude 3 year %	**Crude 3 year %**	**RER* (95% CI)**
Localisation			
Proximal	76.8	89.7	1.0 (ref)
Distal	70.3	92.7	0.6 (0.6-0.7)
Other/NOS	74.8	86.8	1.0 (0.6-1.4)
Adjuvant CT	81.8	89.9	0.3 (0.1-0.5)

Abbreviations: ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Score, CT: chemotherapy

Table 3. Crude 3 year overall and relative surival percentages and hazard ratios for death and relative risks of dying among surgical (N=5.876) and non-surgical rectal (N=1.459) cancer patients, stratified by risk facors.

	Surgical patients		
	Overall survival	**Relative survival**	
	Crude 3 year %	**Crude 3 year %**	**RER* (95% CI)**
Age, years			
70-74	89.2	93.4	1.0 (ref)
75-79	85.7	93.0	1.0 (0.8-1.3)
≥80	74.8	92.9	0.8 (0.5-1.1)
Gender			
Female	83.2	93.1	1.0 (ref)
Male	80.7	93.1	0.9 (0.7-1.3)
ASA			
I	92	100	1.0 (ref)
II	87.7	95.8	1.8 (0.8-4.1)
III	81.1	88.0	2.7 (1.2-6.3)
IV	63.2	67.6	3.8 (1.2-12.6)
CCI			
0	89.6	100	1.0 (ref)
1	82.1	91.3	2.1 (1.3-3.4)
≥2	76.1	84.4	2.5 (1.5-4.2)
Stage			
I	90.5	100	1.0 (ref)
II	84.7	94.6	7.1 (1.8-28.0)
III	80.5	88.4	16.5 (4.2-64.4)
CTRT	86.3	91.9	0.8 (0.6-1.0)
RT	69.9	91.8	0.8 (0.6-1.1)

Abbreviations: ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Score, CT: chemotherapy, RT: radiotherapy

Non-surgical patients		
Overall survival	**Relative survival**	
Crude 3 year %	**Crude 3 year %**	**RER* (95% CI)**
5.7	7.5	1.0 (ref)
9.5	12.8	0.8 (0.7-1.0)
2.9	3.1	1.1 (0.8-1.6)
-	-	-

*Adjusted for variables listed and additionally for period of diagnosis, emergency surgery
** ASA was not reported for non-surgical patients due to the high amount of missings

Non-surgical patients		
Overall survival	**Relative survival**	
Crude 3 year %	**Crude 3 year %**	**RER* (95% CI)**
49.8	53.4	1.0 (ref)
36.5	41.0	1.0 (0.8-1.2)
20.2	29.7	0.9 (0.7-1.1)
26.7	33.7	1.0 (ref)
31.3	38.9	0.9 (0.8-1.1)
-**	-	-
-	-	-
-	-	-
-	-	-
43.9	54.0	1.0 (ref)
31.6	38.9	1.2 (0.8-1.6)
22.6	27.9	1.6 (1.2-2.0)
30.8	43.1	1.0 (ref)
30.4	38.0	1.8 (1.4-2.4)
28.6	34.5	2.1 (1.6-2.7)
64.1	46.5	0.1 (0.0-0.2)
38.5	47.0	0.4 (0.3-0.4)

*Adjusted for variables listed and additionally for period of diagnosis, emergency surgery
** ASA was not reported for non-surgical patients due to the high amount of missings

Survival of older rectal cancer patients

In total, 1.356/5.876 (23%) surgical patients with rectal cancer deceased versus 1.006/1.459 (69%) non-surgical patients. The crude 3-year OS and RS were 82% and 93% for surgical patients and 30% and 37% for non-surgical patients, respectively. In non-surgical patients, lower survival rates were observed in patients without alternative treatment (OS 9%, RS 10%) compared to patients treated with CTRT (OS 56%, RS 65%) or RT (OS 19%, RS 27%) (Figure 2b). In contrast to OS, advanced age did not influence RS (RER 0.8 (95%CI 0.5-1.1) for age ≥80 years (Table 3). Non-surgical patients with comorbidities (CCI≥2; RER 1.6 (95%CI 1.2-2.0)) and higher disease stage (Stage III; RER 2.1 (95%CI 1.6-2.7)) had a worse RS. Advanced age did not worsen the RS in non-surgical patients (RER 0.9 (95%CI 0.7-1.1)).

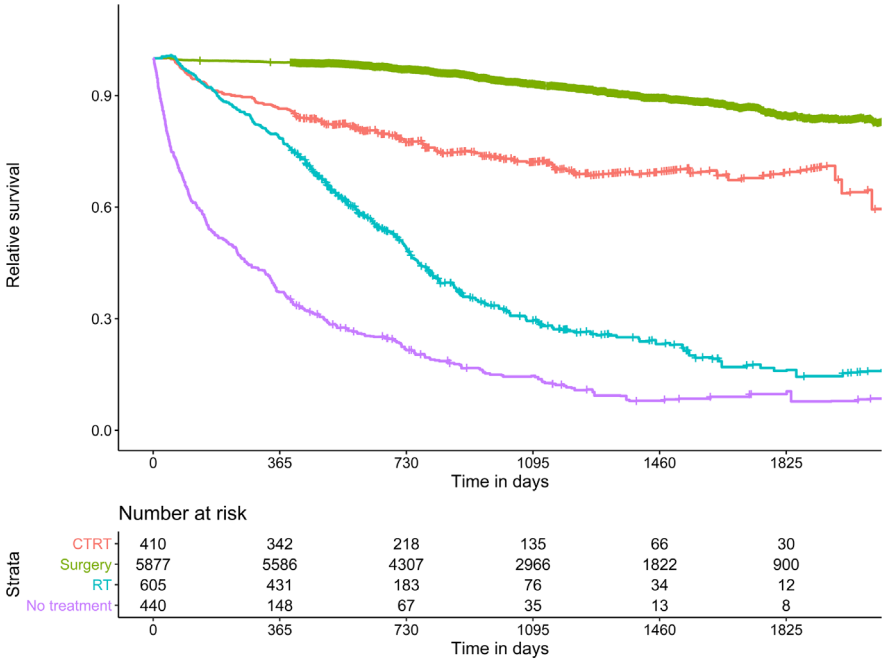

Figure 2b. Relative survival rectal cancer patients according to surgery and non-surgery divided in radiotherapy, chemoradiotherapy and no treatment.

DISCUSSION

This Dutch population-based study examined the survival and characteristics of older surgical and non-surgical patients (≥70 years) with non-metastatic CRC and addressed several important issues. First, survival is poor in non-surgical CRC patients. Three years after diagnosis, nine out of ten (91%) non-surgical patients with colon cancer and seven out of ten (69%) non-surgical rectal cancer patients had died. Second, despite a poor prognosis the number of non-surgical CRC patients increased significantly over time. Third, although no age-related differences in surgical and non-surgical patients were observed in 3 year-cancer related survival (RS), non-surgical approach was chosen more often with advanced age. Fourth, irrespective of age, survival was increased for rectal cancer patients treated with CTRT or RT when compared to patients without any treatment.

More than half of the CRC patients are aged ≥70 years at the time of diagnosis. Ageing often comes with multi-morbidity and frailty leading to a higher risk of adverse events after surgery, including disability and worse health related quality of life (HRQL).[12,13–15] Therefore improvement of informed decision-making has high priority to reduce undesired treatment outcomes. Information about expected survival of surgical and non-surgical strategies is essential in this process.

Older patients have been shown to receive inappropriate care, with treatment decisions motivated on chronological age alone resulting in under-treatment and treatment decisions irrespective of degree of frailty resulting in overtreatment.[16] Lower risk and less aggressive interventions may appear a more attractive option to physicians, in order to avoid patient morbidity or mortality. As a result, this study showed that older patients (≥80 years) are often treated less aggressively than younger patients (70-79 years). In our cohort, the 3 year cancer-related survival was similar in older (≥80 years) and younger patients (70-79 years) in both surgical and non-surgical patients. [17 18] Previous studies have demonstrated that poor survival in older CRC patients is mainly due to differences in mortality during the first year, and that the excess mortality is highest in patients with postoperative complications.[19–22]

Therefore, it is important to distinguish frail older patients from fit patients who could benefit from curative therapy. Currently, surgery is the only curative treatment option in colon cancer patients with stage I-II. For patients with stage III colon cancer, the standard treatment is surgery followed by adjuvant chemotherapy. For rectal cancer patients, treatment may involve surgery only and for patients with locally advanced disease preoperative RT or CTRT with subsequent surgical resection. A small part

of these patients treated with CT(RT) achieved a complete clinical response which justifies a wait and see approach. When patients are considered too vulnerable for surgery, alternative treatment options should be considered to preserve or optimize quality of life. Except for a palliative stoma to control local symptoms, no alternative treatment options are available in colon cancer patients. In rectal cancer patients there are alternative treatment modalities such as CTRT, and short- and long course RT. Currently, the optimal non-surgical treatment strategy in older rectal cancer patients is unclear.[23] In frail patients the general trend is to propose a short course of RT, as CTRT is too toxic and a long course RT is too time-demanding. [24 25 26] Our results suggests that older patients treated with these alternative treatment modalities have better survival rates compared to patients without any treatment. This could be a result of carefully selected patients for alternative treatments who may be less vulnerable compare to patients without any treatment. As shown in our study, the 3 year OS of surgical rectal cancer with high ASA class or multi-morbidity (CCI ≥2) is reduced and probably affected by other cause mortality or even mortality due to complications. Similar OS rates are reported for patients treated with CTRT only. This may imply that alternative treatment modalities should be considered in rectal cancer patients with multi-morbidity.

The decision regarding a patient's fitness for surgery has traditionally been based on subjective judgement, which is limited by the inability to predict adverse outcomes. Prevention of under-and over-treatment in older CRC patients should be considered. Individualization is critical in this heterogeneous population. In recent years, the development of patient-centred treatment plans, that includes frailty characteristics, to optimize shared decision making and reduce adverse outcomes has gained interest.[5,27] This may be an explanation why the number of non-surgical CRC patients increased significantly over time.

Due to the absence of high-quality outcome data in frail older patients, clinical consensus using a multidisciplinary team (MDT) approach may offer the best available advice to guide patient selection for CRC treatment. A MDT approach based on a geriatric assessment and patient preference can be beneficial in the development of a patient-centred treatment plan to improve survival and HRQL in frail patients.[5 28 29]

A strength of this study is the large number of older patients with a histologically proven CRC diagnosis included in the analyses, that are representative of the general older cancer population. This allowed for analysis of non-surgically treated older CRC patients and provided an unique insight into the treatment strategies in daily practice. Nevertheless, some limitations should be addressed. First, information on frailty and

patient preferences were not registered in the NCR and comorbidity status (CCI)/ASA score were frequently missing in non-surgical patients. Second, we did not have specific information on the fractionation and duration of RT (short course vs. long course), dosage of CT and other cancer therapy such as brachytherapy in the non-surgical treatment group. Third, the NCR data does not contain specific follow-up data of patients such as burden of disease, hospital visits/hospitalizations, cause of death and health related quality of life. For future research, we recommend to collect these outcomes in addition to survival.

In conclusion, non-surgical treatment in older Dutch CRC patients has increased over time despite a poor prognosis. Because survival of patients with colon cancer is very poor in the absence of surgery, this treatment decision must be carefully weighed. (Chemo-)radiotherapy may be a good alternative for rectal cancer surgery in older frail patients.

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SUPPLEMENTARY TABLE

Supplementary Table 1. Baseline characteristics of non-surgical patients with rectal cancer according to treatment modalities.

	Surgery (N=5.876)	CTRT (N=410)	RT (N=605)	No treatment (N=444)
Age				
70-74	2497 (42.5)	191 (46.6)	52 (8.6)	54 (12.2)
75-79	1853 (31.5)	142 (34.6)	91 (15.0)	71 (16.0)
80-84	1107 (18.8)	63 (15.1)	192 (31.7)	136 (30.6)
85-89	386 (6.6)	13 (3.2)	196 (32.4)	133 (30.0)
≥90	33 (0.6)	2 (0.5)	74 (12.2)	50 (11.3)
Gender, male	101 (38.7)	131 (32.0)	286 (47.3)	251 (56.5)
ASA				
I	366 (6.2)	177 (43.2)	54 (8.9)	25 (5.6)
II	2762 (47.0)	107 (26.1)	158 (26.1)	72 (16.2)
III	1206 (20.5)	20 (4.8)	144 (23.8)	87 (19.6)
IV	57 (1.0)	4 (1.0)	35 (5.8)	36 (8.1)
Missing	1485 (25.3)	102 (24.9)	214 (35.4)	224 (50.5)
CCI (median [IQR])	1 [0-2]	0.5 [1-2]	1 [1-3]	1 [1-3]
Number of comorbidities				
0	1124 (19.1)	96 (23.4)	61 (10.1)	37 (8.3)
1	863 (14.7)	62 (15.1)	80 (13.2)	72 (16.2)
≥2	521 (8.9)	36 (8.8)	91 (15.0)	52 (11.9)
Missing	3368 (57.3)	216 (52.7)	373 (61.7)	282 (63.5)
Year of diagnosis				
2014	1306 (22.2)	69 (16.8)	106 (17.5)	96 (21.6)
2015	1126 (19.2)	55 (13.4)	118 (19.5)	83 (18.7)
2016	1131 (19.2)	95 (23.2)	109 (18.0)	91 (20.5)
2017	1169 (19.9)	85 (20.7)	132 (21.8)	80 (18.0)
2018	1144 (19.5)	106 (25.9)	140 (23.2)	94 (21.2)
Stage				
I	1492 (25.4)	24 (5.8)	85 (14.1)	92 (20.7)
II	1514 (25.8)	106 (25.9)	195 (32.2)	131 (29.5)
III	2870 (48.8)	280 (68.3)	325 (53.7)	221 (49.8)

Abbreviations: ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Score, CT: chemotherapy, RT: radiotherapy


3

TOLERABILITY, SAFETY AND OUTCOME OF NEOADJUVANT CHEMORADIOTHERAPY WITH CAPECITABINE IN PATIENTS AGED 70 YEARS OR OLDER WITH LOCALLY ADVANCED RECTAL CANCER

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ABSTRACT

Background

In studies of colorectal cancer, the elderly have been frequently underrepresented because comorbid conditions and functional status often lead to study exclusion. For elderly patients with an indication for neoadjuvant chemoradiotherapy (nCRT), physicians usually decide using clinical factors whether nCRT should be offered. The aim of the present retrospective study was to assess the tolerability of nCRT with capecitabine and the surgical outcomes in patients aged ≥70 years with locally advanced rectal cancer.

Methods

Data from 1372 rectal cancer patients diagnosed from 2002 to 2012 at 4 Dutch hospitals were used. Patients aged ≥ 70 years were included if they had received nCRT, and their data were analyzed for treatment deviations, postoperative complications, mortality, disease-free survival (DFS), and overall survival (OS). The data were stratified into 3 age groups (70-74, 75-79, and ≥ 80 years).

Results

We identified 447 patients aged ≥ 70 years. Of these patients, 42 had received nCRT, and 37 (88%) had completed nCRT. Radiation dermatitis, fatigue, and diarrhea were reported in 62%, 57%, and 43% of the 42 patients, respectively. Of the 42 patients, 40 (95%) underwent surgery, 1 patient refused resection, and 1 patient died during nCRT of severe mucositis due to dihydropyrimidine dehydrogenase deficiency. The postoperative complication rate was 30%, and the 30-day mortality rate was 0%. A pathologic complete response was found in 7.5%. The 2- and 5-year DFS and OS rates were 58.5% and 40.7% and 81.0% and 58.2%, respectively.

Conclusion

The results of the present multicenter study have shown that if selected on clinical factors, nCRT with capecitabine is safe and well tolerated in elderly patients. No negative effect on surgical outcome was measured, and the beneficial effect (pathologic complete response, DFS, and OS) seemed comparable to that for younger age groups. We believe that elderly patients should not be excluded from nCRT on the basis of age only.

INTRODUCTION

Colorectal cancer (CRC) is a common disease worldwide, representing the third most commonly diagnosed malignancy.[1] With the improved life expectancy of elderly in general, the better diagnostic and staging techniques, and the CRC screening programs, physicians will increasingly see patients with CRC.[2,3] CRC predominantly affects elderly patients. The median age at diagnosis is 69-72 years, with 60% to 70% of all cases diagnosed in patients aged ≥65 years.[4-7] However, the aging process is associated with physiological, sociological and psychological transitions. As such, the risk of chemotherapy- and radiotherapy- related toxicity and postoperative morbidity could be increased. In addition, neoadjuvant chemoradiotherapy (nCRT) only affects the local recurrence rate but not the overall survival of rectal cancer patients; thus, the benefit for elderly patients is doubtful.[8]

In the past decade, several randomized controlled studies have confirmed the efficacy of nCRT and total mesorectal excision (TME) surgery resulting in a lower risk of local recurrence in rectal cancer patients.[8-16] In the Netherlands, nCRT for rectal cancer was introduced in 2006. Patients with a suspected positive resection margin along the mesorectal fascia and/or ≥4 suspected lymph nodes within the mesorectum and/or lymph nodes outside the mesorectal fascia on magnetic resonance imaging are considered eligible for nCRT. However, in studies on CRC, older patients have been frequently underrepresented because a comorbid condition and/or functional status often led to study exclusion.[17,18] In leading intervention studies such as the German Rectal Cancer study group and the ACCORD 12/PRODIGE 2 phase III study the median age of included patients is 62 and 63 years, respectively.[14,19] Few data on safety and beneficial effects of nCRT in the elderly are available.

The Dutch guidelines for CRC have advocated that the treatment principles of rectal cancer should not be different for younger and older patients. They should, however, be adapted when comorbidities and/or physiological changes are present.[20] In elderly rectal cancer patients with an indication for nCRT according to T/N stage, physicians usually decide on clinical factors whether nCRT should be offered to individual patients.

The aim of the present retrospective study was to assess the tolerability of nCRT with capecitabine and surgical outcomes in patients aged ≥70 years with locally advanced rectal cancer (LARC). We also assessed postoperative complications, mortality, disease-free survival (DFS) and OS.

METHODS

Patient population

The present retrospective multicenter study included data from the Dutch Comprehensive Cancer Centre of all patients with histologically confirmed rectal adenocarcinoma (stadium I-IV) from January 1, 2002 to December 31, 2012 from 4 Dutch hospitals (i.e. St. Antonius Hospital Nieuwegein and Utrecht, Diakonessenhuis Hospital Utrecht, Meander Medical Centre Amersfoort and University Medical Centre Utrecht) in the region of Utrecht, Netherlands. All patients aged ≥70 years who had received nCRT were included. The patient and treatment characteristics were obtained from the medical records. The medical ethics research committee approved the present study. (registration no., W13.018).

Treatment regimen

Patients received nCRT according to the applicable guidelines.[21] Clinical staging was determined by radiologic evaluation and the clinical TNM classification valid at diagnosis. The treatment of all patients was discussed in a multidisciplinary team that included oncologists, surgeons, radiation oncologists, gastroenterologists, pathologists and radiologists.

nCRT consisted of a regimen of chemotherapy and radiotherapy for 5 weeks followed by surgery 8 to 10 weeks later. The external beam radiotherapy dose was 50 Gy, delivered in 25 daily fractions of 2 Gy 5 times each week in supine position. Concomitant chemotherapy consisted of the oral 5-fluorouracil derivate capecitabine, 825 mg/m^2 twice daily, 7 days weekly.[21] Radical rectal resection was performed using to the TME technique by experienced colorectal surgeons specializing in colorectal oncology.[16]

Patient evaluation and follow up

Patients were monitored during and after nCRT for adverse events. The medical records were reviewed for gastro-intestinal, hematological and cardiac events, dermatitis, hand-foot syndrome, fatigue and death. The hematological toxicity was evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.[22]

The primary endpoint was the tolerability of nCRT and surgical outcomes in patients aged ≥70 years with LARC, including postoperative complications, mortality, DFS, and OS. Tolerability was defined as the number of treatment deviations with nCRT. The relative dose intensity was calculated and used as a reflection of treatment deviations, defined as the ratio of the actual delivered dose intensity of capecitabine to the standard

dose intensity of capecitabine (mg/m^2/week). The decision to deviate from the intended treatment schedule was the responsibility of the treating physician and not determined by a standardized protocol.

Statistical methods

The data were stratified by patient age into three groups (70-74, 75-79 and ≥80 years). The chi-square test and Fisher's exact test were used to analyze differences in proportions. All tests were two-sided and p-values (P<0.05) were considered to indicate statistical significance. DFS and OS were calculated using the Kaplan-Meier method and were calculated from the first day of nCRT. The statistical analysis was performed using SPSS Statistics for Windows, version 22.0 (IBM, Corp, Armonk, NY).

RESULTS

Baseline patient characteristics

A total of 447 rectal cancer patients aged ≥70 years were identified, with a median follow-up of 51 months [range 1-99 months]. Of these, 42 patients (9.4%) had received nCRT, with a median age of 74 years (interquartile range, 72-78). The cases of LARC were all diagnosed from 2006 to 2012. The Eastern Cooperative Oncology Group (ECOG) performance score was favorable for 88% of the patients at diagnosis. The distribution of distal tumors (≤5cm from the anal verge) and proximal tumors (>5cm from the anal verge) in the study cohort was equal. Baseline characteristics are listed in Table 1.

Table 1. Baseline Clinical Characteristics (N=42).

Characteristics	Patients (%)
Age	
70-74	23 (54.7)
75-79	12 (28.6)
≥80	7 (16.6)
Gender	
Male	26 (61.9)
Female	16 (38.1)
ECOG Performance score	
0	20 (47.6)
1	17 (40.5)
2	3 (7.1)
>2	2 (4.8)
Clinical T stage	
T1 or T2	3 (7.1)
T3	22 (52.4)
T4	17 (40.5)
Clinical N stage	
N0	6 (14.3)
N1	20 (47.6)
N2	16 (38.1)
Tumor height	
Lower rectum (≤5cm)	21 (50.0)
Higher rectum (>5cm)	21 (50.0)

Abbreviation: ECOG: Eastern Cooperative Oncology Group

Tolerability of nCRT

Overall, 37 patients (88.1%) completed the planned nCRT with capecitabine without treatment deviations, with no significant differences between the three age groups. The remaining 5 patients (11.9%) received ≤75% of the intended dose of capecitabine because of severe diarrhea (n=2), neutropenic fever (n=1), or severe mucositis due to dihydropyrimidine dehydrogenase (DPD)-deficiency (n=1). The patient with DPD-deficiency died of mucositis in the third week of nCRT. The intended radiation dose was given to all patients, except for the patient with DPD deficiency. Two patients required a dose delay because of diarrhea and fatigue. Patients with comorbidity or an ECOG performance status ≥2 did not experience more treatment deviations than the other patients (*P*=0.516 and *P*=0.231, respectively). Most patients (95.2%) experienced adverse events, with radiation dermatitis (61.9%), fatigue (57.1%) and diarrhea (42.9%) the most common (Table 2).

Table 2. Adverse events during nCRT according to age group (70-74, 75-79 and ≥80 years).

Adverse events	70-74 years (n=23)	75-79 years (n=12)	≥80 years (n=7)	P-value
Constipation	3 (13.0)	1 (8.3)	0	0.310
Diarrhea	9 (39.1)	5 (41.7)	4 (57.1)	0.448
Nausea/vomiting	2 (8.7)	0	3 (42.8)	0.067
Anorexia	4 (17.4)	2 (16.7)	1 (14.3)	0.856
Dehydration	0	0	1 (14.3)	0.067
Leucopenia	0	0	0	-
Thrombocytopenia				
CTC grade 1	1 (4.3)	1 (8.3)	0	0.821
Anemia				0.918
CTC grade 1	1 (4.3)	0	0	
CTC grade 2	0	1 (8.3)	0	
CTC grade 3	0	1 (8.3)	0	
Neutropenic fever	0	0	1 (14.3)	0.167
Dysuria-painful urination	3 (13.0)	5 (41.7)	1 (14.3)	0.482
Radiation dermatitis	15 (65.2)	7 (58.3)	4 (57.1)	0.649
Allergy	0	0	0	-
Hand-foot syndrome	1 (4.3)	1 (8.3)	0	0.821
Fatigue	13 (56.5)	6 (50.0)	5 (71.4)	0.641
Cardiac	0	0	0	-
Death	0	0	1 (14.3)	0.236

Abbreviation: CTC: Common toxicity criteria

Surgery procedures, postoperative complications, mortality and adjuvant chemotherapy
Of the 42 patients, 40 patients underwent surgery (95.2%); 1 patient refused resection and 1 patient died of DPD deficiency during nCRT. The median interval between the last day of nCRT and surgery 49 days [range 32-126 days]. Among the 40 patients, 10 patients (23.8%) had received a diverting stoma before starting nCRT. A primary anastomosis was performed in 3 patients, and the remaining group received a permanent colostomy. The pathology report showed R0 resections in 36 patients (90%). A pathologic complete response (pCR) was observed in 3 patients (7.5%).

Postoperative complications developed in 12 patients (30%), with 6 patients (15%) requiring reoperation because of anastomotic leakage (n=2) or drainage of a presacral abscess (n=4). Patients aged 70 to 74 years were significantly more often hospitalized within <30 days compared with the other patients (*P*=0.041). The reasons for repeat hospitalization were anastomotic leakage (n=1), wound infection (n=1), pneumonia (n=2) and presacral abscess (n=2). Postoperative intensive care admissions were indicated for only 2 patients (5%), 1 for a transfusion reaction and 1 because of respiratory problems. Patients aged ≥80 years were significantly longer, owing to discharge to a nursing home and a longer recovery period required for postoperative complications (*P*=0.034). The remaining postoperative complications and treatment efficacy did not significantly differ among the three age groups (Table 3). The overall 30-day mortality rate after surgery was 0%. Adjuvant chemotherapy was given to 8 patients. Of these 8 patients, 5 received capecitabine monotherapy and 3 received capecitabine and oxaliplatin (Table 3).

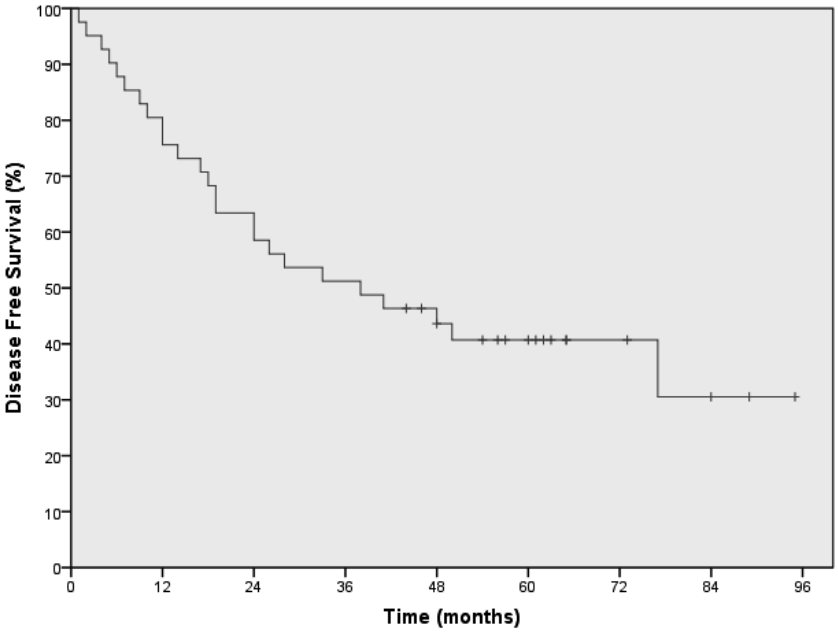
DFS and OS rates
The 2- and 5-year DFS rates were 58.5% and 40.7%, respectively, with a median of 38 months (SE 13.8, 95% CI 11.0-65.0) (Figure 1A). No significant differences were found in DFS among the three age groups (log rank *P*-value 0.468; figure 1B). Of the 42 patients, 31 patients (73.8%) developed disease recurrence, with 4 patients having local recurrence (9.5%) and 27 patients, distant metastasis (64.3%). The 2- and 5-year OS rates in all 42 patients were 81.0% and 58.2%, respectively, with a median OS of 67 months (Standard Error (SE) 13.5, 95% Confidence Interval (CI) 40.3-93.7%) (figure 2A). No significant differences were found in OS among the three age groups (log rank *P*-value 0.212; figure 2B).

Table 3. Surgery procedures and postoperative complications according to age group (70-74, 75-79 and ≥80 years).

	70-74 years (n=23)	**75-79 years (n=12)**	**≥80 years (n=7)**	**P-value**
Surgery	23 (100)	12 (100)	5 (71.4)	0.208
No surgery	0	0	2 (28.6)	
Diverting stoma	6 (26.1)	3 (25.0)	1 (14.3)	0.572
Type surgery				0.206
LAR	12 (52.2)	3 (25.0)	2 (40.0)	
APR	10 (43.5)	9 (75.0)	2 (40.0)	
Hartmann procedure	1 (4.3)	0	1 (20.0)	
Permanent colostomy	21 (91.3)	11 (91.7)	5 (100)	-
Temporary Ileostomy	0	0	0	
R0 resection rate	20 (86.9)	12 (100)	4 (80.0)	0.322
Days hospitalized, median(range)	7 (5-9)	7 (4-16)	10 (5-35)	0.034
Postoperative IC visit	1 (4.3)	0	1 (14.3)	0.124
Complications	9 (39.1)	1 (8.3)	2 (40.0)	0.440
Anastomotic leak	1 (4.3)	0	1 (20.0)	
Ileus	3 (8.7)	0	1 (20.0)	
Wound infection	1 (4.3)	1 (8.3)	0	
Pre-sacral abscess	4 (17.4)	0	0	
Re-hospitalization <30 days	6 (26.1)	0	0	0.041

Abbreviations; LAR: low anterior resection, APR: abdominoperineal resection, IC: intensive care

1A



1B

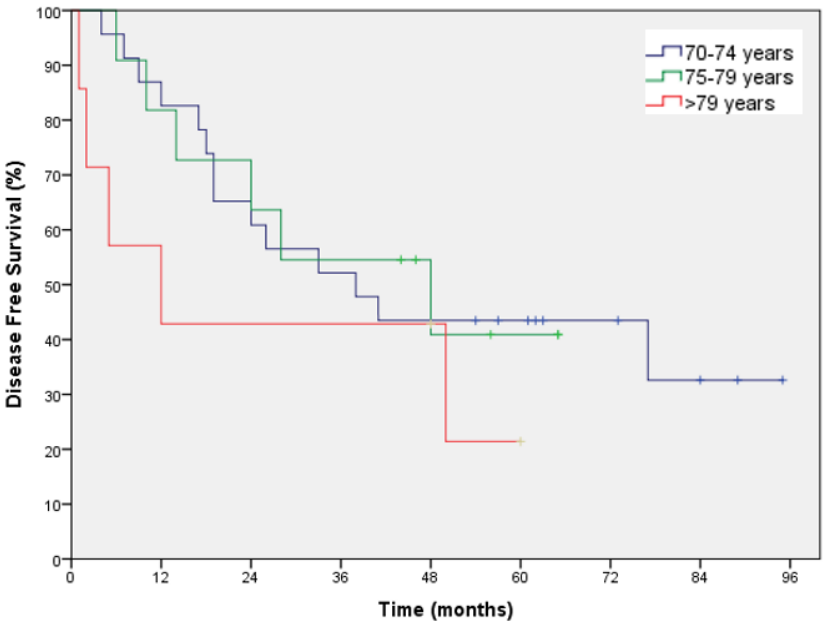
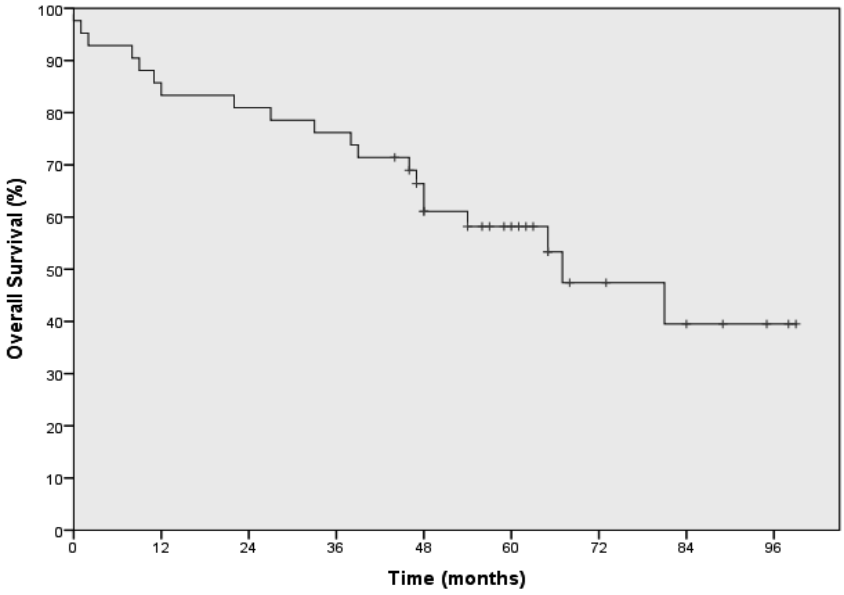


Figure 1. Kaplan-Meier estimates of DFS in all 42 patients (A) and age groups (B).

2A



2B

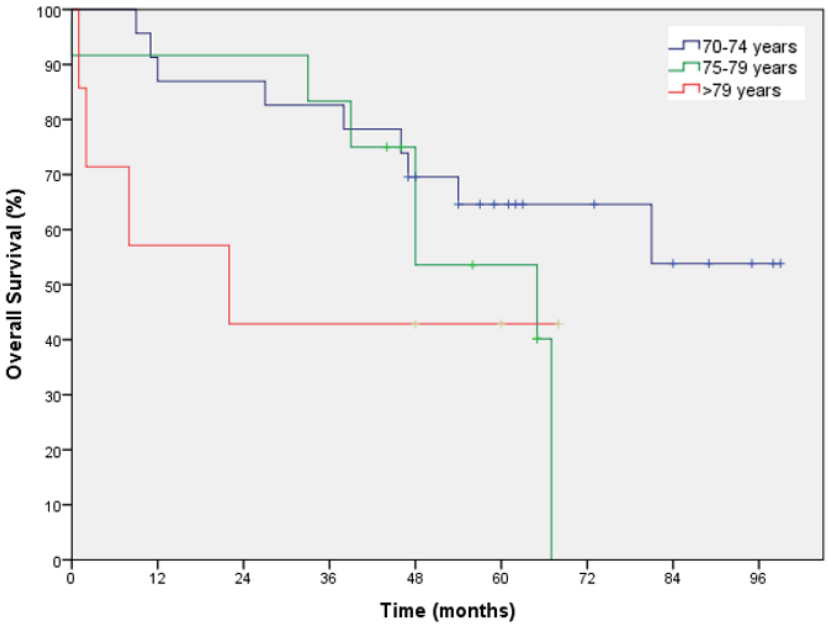


Figure 2. Kaplan-Meier estimates of OS in all 42 patients (A) and age groups (B).

DISCUSSION

The combination of nCRT with TME is the standard of care for patients with LARC in the Netherlands. To the best of our knowledge, the present multicenter study is the first to retrospectively evaluate the tolerability, safety and outcomes of nCRT with capecitabine in elderly patients with LARC.

Our results suggest that elderly patients with rectal cancer can receive nCRT followed by surgery because the tolerability of nCRT and the postoperative morbidity seemed acceptable. The clinical benefit, together with the good tolerability profile of nCRT, has been widely demonstrated in younger patients.[10-12,23] However, little is known about the tolerability of nCRT with capecitabine in the geriatric population with rectal cancer compared to the younger population. Kim et al. studied 45 younger patients (median age, 55 years) that reported that 95% of the patients completed nCRT with capecitabine.[24] The most commonly seen grade 3 adverse events were hand-foot syndrome (7%), fatigue (4%) and diarrhea (4%). No grade 3 or 4 hematological adverse events were observed, similar to our study in which 1 patient developed grade 3 anemia. Grade 3 nonhematological toxicity is a frequent reason for dose modification; however, these modifications were not often seen in the present study.

In general, the chemotherapeutic toxicity in our patients was comparable to that reported by retrospective studies of younger patients with LARC.[25,26] The ACCOR12/PRODIG 2 phase III trial compared the tolerability of nCRT with either capecitabine or capecitabine combined with oxaliplatin between older (≥70 year n=142) and younger patients (<70 patients n=442). Preoperative chemoradiotherapy resulted in a greater incidence of grade 3 toxicity (25.6% versus 15.8%, p=0.01) in the elderly. The grade 3 hematological toxicity rate was similar in the two age groups (<70 years: 4.1% vs. ≥70 years: 10.1%, p=0.66). Hematological toxicity was more common in the ACCORD/PRODIGD 2 phase III trial, which is likely explained by the addition of oxaliplatin. In the ACCORD/PRODIGD 2 phase III trial, 94.4% of the patients received the planned doses of capecitabine, similar to our study.[27]

Most of the studies that evaluated the geriatric population were small and used different radiotherapy techniques and/or chemotherapy schedules.[23,28-33] Only one study investigated the same schedule nCRT with capecitabine in elderly. Cefaro et al. retrospectively analyzed the data from 26 patients with a median age of 74 years. All patients completed the chemotherapy course as planned, expect for 1 patient, who developed hematologic toxicity. The tolerability of chemotherapy regimen in our study was lower, with 5 patients who received less than 75% of the planned

doses. The most frequent nonhematological toxicity in the study by Cefaro et al. was diarrhea in 62% of the patients. The incidence of diarrhea in our study was slightly lower (42.8%); however, the incidence of acute hematological toxicity was similar in both studies.[34]

A great concern exists that if elderly patients undergo nCRT and TME, they will be at an increased risk of postoperative complications and mortality compared with younger patients. Younger rectal cancer patients who undergo nCRT and surgery have a postoperative complication rate of 22.1% and a 30-day mortality rate of 0.7%.[35,36] This is comparable to the incidence of postoperative complications and the excellent 30-day mortality rate that we found in elderly patients (30% vs 0%, respectively).

Anastomotic leakage, which is considered the most severe surgical complication, is of particular interest. In our cohort, 3 patients received a primary anastomosis, and 2 of these patients developed anastomotic leakage (66.7%). This incidence is high compared with the incidence of anastomotic leakage after nCRT and surgery reported by Valenti et al. (4.2%).[36] Moreover, McDermott et al, in a systematic review, reported that the anastomotic leakage rate after rectal cancer surgery in general was 1% to 19% [37]. The rate was 8.4% according to the Dutch Surgical Colorectal Audit [38]. However, with only 3 patients with a primary anastomosis in our study cohort, the small sample size was too small to draw firm conclusions. Nevertheless, anastomotic leakage after low anterior resection has been associated with increased mortality in elderly patients.[39] Furthermore, mortality at 6 months in general increased significantly in patients ≥75 years compared to patients <75 years (57.1% versus 8.2%, relative risk = 6.94 (95% CI 2.99-16.11)), although no difference in the frequency of anastomotic leakage was observed between the two groups (11.5% versus 10.1%).[39]

In addition to these favourable surgical outcomes, we found a pCR in 3 patients (7.5%). This is slightly lower than pCR rates in previous published studies of capecitabine pretreatment 16% and 24%, respectively).[23,40] However, the number of patients in our study with pCR was too small to draw meaningful conclusions. We found a 5-year DFS rate of 40.7% and a 5-year OS rate of 58.2%, with no significant differences among the three age groups. These are comparable to the DFS and OS rates reported in previous studies of younger patients. A study by Kim et al. found a 5-year DFS of 52% and an OS rate of 58.1% in patients treated with nCRT and TME.[41] National studies of rectal cancer patients from Sweden, Denmark, the United Kingdom and Norway have reported overall 5-year OS rates between 44.8% and 63.4%.[42-45]

The major limitation of the present study was the retrospective design with a relatively small number of patients selected using clinical factors. Also, we were not informed about the outcomes of elderly patients who did not receive nCRT most likely because of age, comorbidity and/or frailty.

The results of the present multicentre study have shown that if elderly patients are selected using clinical factors, nCRT will be safe and well tolerated. We found no 30-day mortality after surgery and the beneficial effect (pCR, DFS and OS) seemed comparable to those for younger age groups. Therefore, we believe that elderly patients should not be withheld neoadjuvant treatment only because of age. Individual patient evaluation using a validated comprehensive geriatric assessment could be a useful tool in the decision-making process to prevent either under- and overtreatment of the elderly population with LARC.

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4

THE RELEVANCE OF GERIATRIC ASSESSMENT FOR OLDER PATIENTS RECEIVING PALLIATIVE CHEMOTHERAPY

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ABSTRACT

Objective

No tools accurately discriminate between older patients who are fit and those who are frail to tolerate systemic palliative treatment. This study evaluates whether domains of geriatric assessment (GA) are associated with increased risk of chemotherapy intolerance in patients who were considered fit to start palliative chemotherapy after clinical evaluation by their treating clinician.

Methods

This prospective multicenter study included patients ≥70 years who started first line palliative systemic treatment. Before treatment initiation, patients completed GA including Activities of Daily Life (ADL), Instrumental Activities of Daily Life (IADL), Mini-Mental State Examination (MMSE), Mini Nutritional Assessment (MNA), Geriatric Depression Scale (GDS-15) and the Timed Up and Go Test (TUGT). Primary endpoint was treatment modification, defined as inability to complete the first three sessions of systemic treatment as planned. Secondary endpoint was treatment related toxicity ≥ grade 3 (CTCAE Version 4). The association between GA and endpoints were assessed using univariable and multivariable logistic regression analysis.

Results

Ninety-nine patients with median age of 77 (+/- 8) years underwent GA. 48% of the patients required treatment modification and grade 3 toxicity occurred in 53% of patients. One or more geriatric impairments were present in 71% of patients and 32% of patients were frail in two or more domains. Only TUGT was associated with treatment modifications (OR 2.9 [95% CI 1.3-6.5]) and grade 3 toxicities (OR 2.8 [95% CI 1.2-6.3]).

Conclusion

Frailty was common in older patients who were considered fit to receive palliative chemotherapy. Treatment modification was necessary in half of the patients. Only TUGT was significantly associated with treatment modifications and grade 3 chemotherapy toxicities.

INTRODUCTION

Due to an improved life expectancy, physicians will see an increasing number of older patients with malignant disease.[1] In the past decades, substantial progress has been made in the treatment of cancer. However, it is unclear whether all age groups benefit from these improvements due to exclusion of older patients in clinical trials. Less than 10% of the patients with cancer aged ≥ 75 years were enrolled in clinical trials. [2] In the setting of geriatric oncology, research suggests that frail older patients have an increased risk of chemotherapy toxicity, which can severely impact quality of life.[3]

Currently, physicians often use clinical judgement to recommend palliative chemotherapy, because a short clinical tool to identify patients at risks of treatment toxicity is not widely used. Frailty may be hard to detect by clinical judgment, and conversely most oncologists consider very few patients as frail. Oncologists need an objective and validated clinical tool to discriminate between fit and frail older patients in palliative setting to avoid chemotherapeutic major adverse events that severely impact the quality of life, or that withhold patients from the beneficial effects of chemotherapy due to treatment modifications. This may be especially relevant for older patients who are treated in the palliative setting, as quality of life may be considered more important than length of life.

International guidelines recommend that clinicians take geriatric assessment (GA) results into account when recommending chemotherapy in older patients.[4] GA has been developed to discriminate between fit and frail older patients by providing information on physical function, comorbidity, nutrition and cognition. Previous studies have shown the additional value of a comprehensive GA for the identification of patients who are at risk of chemotherapy intolerance in combined palliative and curative setting.[3] However, a comprehensive GA is a time-consuming method (as it may take up to an hour of more per patient). A short GA may improve its applicability in daily clinical practice, but it remains unclear which frailty characteristics are the most predisposing for adverse events. In addition, the use of GA in palliative setting is poorly investigated and weighing risks from benefits from chemotherapeutic treatment is likely different in palliative patients compared to patients who are treated in the curative setting.[4] A predictive (screening) model in which geriatric oncologic frailty can be assessed may help to discriminate between patients who will benefit of chemotherapeutic treatment in daily clinical practice. Furthermore, it may help guide the implementation of health interventions that aim to optimize pre-chemotherapeutic condition.

This study evaluates whether domains of a geriatric assessment are associated with increased risk of chemotherapy intolerance within the first three cycles of chemotherapy in patients who were considered fit to start palliative chemotherapy after clinical evaluation by their treating physician.

METHOD

Patients

This prospective multicenter study included patients between November 2012 and September 2014 in the St. Antonius Hospital Nieuwegein and the Tergooi Hospital Hilversum in The Netherlands. Patients were eligible for participation if they were aged ≥ 70 years and diagnosed with metastatic cancer for whom first line palliative chemotherapy was prescribed by an experienced (≥5 years) medical oncologist or hematologist. In addition, also patients with non-Hodgkin lymphoma and multiple myeloma receiving chemotherapy (with or without targeted therapy) were eligible for participation. Because of older age, patients with multiple myeloma were considered ineligible for stem cell transplantation.

Other inclusion criteria was an understanding of Dutch language due to the use of Dutch questionnaires. Patients with metastases in the central nervous system were excluded from this study. Patients diagnosed with breast or colorectal cancer could have received previous chemotherapy (neoadjuvant or adjuvant) if >6 months before study participation. This study was approved by the Medical Research Ethics Committees United (MEC-U) in Nieuwegein. All patients provided written informed consent in accordance with the Declaration of Helsinki.

Geriatric assessment

Before initiating the systemic treatment, all patients were prospectively assessed using a GA that consisted of 6 preselected geriatric assessments. The elements of the GA were chosen based on previously validated, standardized, mostly survey-based measures, testing several geriatric domains. The cognitive domain included the questionnaire Mini-Mental State Examination (MMSE). Depressive symptoms were assessed using the 15 item Geriatric Depression Scale (GDS-15). Physical functioning was assessed using the Activities of Daily Life (ADL) and the Instrumental Activities of Daily Life (IADL) questionnaires. The IADL assesses independent living skills. These skills are considered more complex than the basic activities of daily living. To assess nutritional status, the Mini Nutritional Assessment (MNA) was used. The Timed Up and Go Test (TUGT) evaluates gait and balance and requires a person to stand up, walk 3 meters, turn, walk back and sit down. Polypharmacy was defined as the use of ≥4 drugs per day. All GA measures were completed by a nurse practitioner or a member of the research team and did not require a specialized training background for administration. The treating physician was not aware of the results of the GA and it did not affect treatment decisions or interventions. All elements of the used GA have predefined cut off points for frailty. (Table 2)

Endpoints

The primary endpoint (treatment modification) was defined as the inability to complete the first three sessions of chemotherapy as planned. This included any early discontinuation of treatment, dose reduction or dose delay (≥5 days) based on reported toxicities as graded by de National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[5] Treatment discontinuations due to death from any cause or disease progression were not considered treatment modifications due to CTCAE toxicity, and were therefore not included in the primary endpoint. The cutoff point of three cycles of chemotherapy was chosen because in daily clinical practice the response of chemotherapy is most commonly evaluated after three cycles. The secondary endpoint was treatment related toxicity ≥ grade 3.

Statistical analysis

Patient characteristics were described in means ± standard deviation (SD) for continuous variables if normally distributed, medians and interquartile range (IQR) if not normally distributed, and percentages or numbers for categorical or ordinal variables. To test for differences between mono versus combination chemotherapy and the primary and secondary endpoints, we used a Chi-square test. Furthermore, we used the Chi-square test to analyze the cumulative effect of geriatric impairments on primary and secondary outcome. Subsequently, we assessed the relation between treatment modification and grade 3 toxicity in a univariable logistic regression analysis. The geriatric assessments that reached a P-value less than 0.1 were further examined in a multivariable logistic regression model with clinically relevant, empirically chosen confounders including age at inclusion continuously, sex (male / female) and type of cancer (solid versus hematological). Unadjusted and adjusted Odds Ratios (OR) were calculated with corresponding 95% confidence intervals (95% CI).

Finally, because patients with hematological malignancies may have a different prognosis compared to patients with solid metastasized malignancies, chemotherapeutic treatment considerations may be different. Different treatments may lead to different toxicity profiles and different risks of treatment modifications, which may potentially impact on the relation between GA and outcomes. To investigate potential differences in the relation between GA and outcomes between patients with hematologic and non-hematologic malignancies, we repeated the previous analyses including only the group of patients with solid metastasized malignancies. The group of hematologic malignancies (n=18) was considered too small to conduct a subgroup analysis.

RESULTS

Patient, tumor and treatment characteristics

Between 2012 and 2014, a total of 99 patients were included. The median age was 77 (IQR 8) years and 34% was octogenarian. Two-thirds of the patients were male. A minority of patients (14%) were restricted in daily activities (ECOG ≥ 2). Almost all patients lived at home (94%) and the majority together with a partner (70%). The most common tumor types were colorectal (21%), urogenital (19%) and Non-Hodgkin Lymphoma(NHL) or Multiple Myeloma(MM) (18%). Most patients received combination chemotherapy (62%) and six patients started with an upfront dose reduction of chemotherapy. Combination therapy included: taxane-based chemotherapy (20%) was the most frequently prescribed therapy after platinum based (18%) and anthracycline (11%) based chemotherapy. Baseline characteristics are depicted in Table 1.

Geriatric assessment

Table 2 shows the results of the GA prior to the chemotherapy. All enrolled patients participated in the GA. One or more geriatric impairments were present in 71% of patients and 32% patients were frail in two or more domains. Eleven subjects were not able to carry out the TUGT, due to various reasons and were considered physically impaired. A slow gait speed, cognitive impairment and risk of malnutrition were the most commonly observed impairments and occurred in 52%, 14% and 15% of patients respectively. The median score of the TUGT was 10.5 (7.4) seconds, and 52% of the patients were considered impaired. The median score of the ADL was 6 (IQR 1), and 9% of patients required assistance during simple daily living activities such as feeding and dressing, and 8% of the patients required help with instrumental activities of daily life. Few patients were considered cognitively impaired (14%) and 9% of patients scored high on the GDS-15 questionnaire. Malnutrition occurred in 15.2% of the older patients.

Treatment modifications

In total, 47 of the 99 patients (48%) required one or more treatment modifications during the first three cycles of chemotherapy. 18 patients received a dose reduction (18%), 21 patients required a delay in chemotherapy administration (21%) and 21 patients discontinued treatment (21%) (Figure 1).

Table 1. Baseline table of patients receiving palliative chemotherapy (n=99).

Characteristics	Total patients (%)
Age, median (IQR)	77 (IQR 8)
Sex - male	62 (63)
St. Antonius hospital	62 (63)
Tergooi hospital	37 (37)
ECOG performance score	
0	44 (44)
1	41 (41)
2	12 (12)
3	2 (2)
BMI, mean (±SD)	26 (±4)
Underweight (<18.5)	3 (3)
Normal (18.5-25)	47 (48)
Overweight (25-30)	37 (37)
Obese(≥30)	12 (12)
Type of malignancy	
Colorectal cancer	21 (21)
Urogenital cancer	19 (19)
Hematological cancer	18 (18)
Gynecological cancer	13 (13)
Upper gastrointestinal cancer	11 (11)
Lung cancer	11 (11)
Breast cancer	5 (5)
Melanoma	1 (1)
Type chemotherapy	
Mono	37 (37)
Combination	62 (63)
Adaptive chemotherapy schedule at baseline	6 (6)
Polypharmacy ≥4	67 (68)
Living with partner	68 (69)
Living at home	96 (97)

Abbreviations: IQR, Interquartile Range; ECOG, Eastern Cooperative Oncology Group; SD, Standard Deviation; BMI, Body Mass Index; GI, Gastrointestinal

Most patients required a dose reduction after the first cycle (11/18, 61%) and the most common causes for dose reductions were diarrhea (5/18, 28%), malaise (4/18, 22%) and neutropenic fever (4/18, 22%). Most of the patients discontinued the chemotherapy after the first cycle (15/21, 71%), most frequently due to malaise (7/21, 33%), diarrhea

(5/21, 24%) and neutropenic fever (2/21, 10%). Chemotherapy delay (median 10 (IQR 8) days) was most frequently observed after cycle 3 (14/21, 67%) and most frequently caused by neutropenia (5/21, 24%), infections (4/21, 19%) and diarrhea (3/21, 14%). There was no significant difference between patients receiving mono versus combination chemotherapy and the risk of dose reductions (p=0.14), delay (p=0.34) or treatment discontinuations (p=0.11).

Table 2. GA specifics and outcomes according to all patients (n=99).

Questionnaire or test	Score range	Cut off point for frailty	Median (25^{th}, 75^{th})	Number of frail patients (%)
ADL	0-6	≤4	5 (5, 6)	9 (9)
IADL	0-14	≤7	13 (11, 14)	8 (8)
GDS-15	0-15	≥6	2 (1, 4)	9 (9)
TUGT	0-inf	≥10	10 (8, 15)	41 (41)
MMSE	0-30	≤24	28 (26, 29)	14 (14)
MNA	0-30	≤17	20 (18, 24)	15 (15)

Abbreviations: ADL, Activities of Daily Life; IADL, Instrumental Activities of Daily Life; MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment; GDS-15, Geriatric Depression Scale; TUGT, Timed Up and Go Test.

Table 3 shows the number of patients who were considered impaired per each individual GA test, the number of treatment modifications, and the association between GA and treatment modifications. Most patients who were considered impaired on any of the GA tests required a treatment modifications, except for patients who were considered impaired by the MMSE test (43% of the impaired patients and 48% of the non-impaired patients required a treatment modification). In the univariable logistic regression analysis, the TUGT was the only significant factor associated with treatment modifications (OR 2.9 [95% CI 1.3-6.5], p=0.01). The TUGT remained significantly associated for treatment modifications (OR 3.1 [1.3-7.2], p=0.01) after correcting for the potential confounders of age, sex and type of tumor (data not shown). No significant associations among the other geriatric assessments were found. By repeating the previous analyses, including only the patients with solid tumors, we did not find any important differences in the relation between GA and treatment modifications compared to the total group of patients. (Supplementary Table 1)

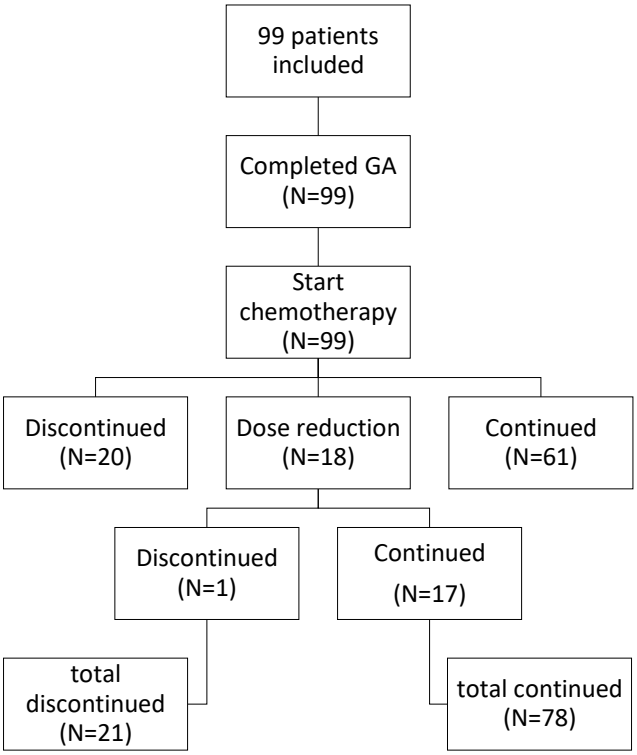

Figure 1. Flow chart of included patients and chemotherapy administration(n=99).

Finally, the proportion of patients who required a treatment modification was not associated with an increasing number of impaired GA (p=0.556). (Figure 2) Of the patients without geriatric impairments, 38% required a treatment modification, while in patients with 1, 2 of 3+ geriatric impairments grade 3 toxicity was reported in 47%, 55% and 59% respectively.

Grade ≥3 toxicity

Grade 3 toxicity occurred in 53 patients (54%) (Table 4). Grade 4 and 5 toxicities were not observed. Most patients (89%) who experienced a grade 3 toxicity required a treatment modification. Grade 3 hematologic and non-hematologic toxicity occurred in 14% and 40% of patients, respectively. The most common grade 3 toxicities were diarrhea (25%), neutropenia (23%) and (neutropenic) infection (21%). Among the 6 patients who started with an upfront dose reduction, grade 3 toxicity occurred in 3 patients (50%) due to hematological toxicities.

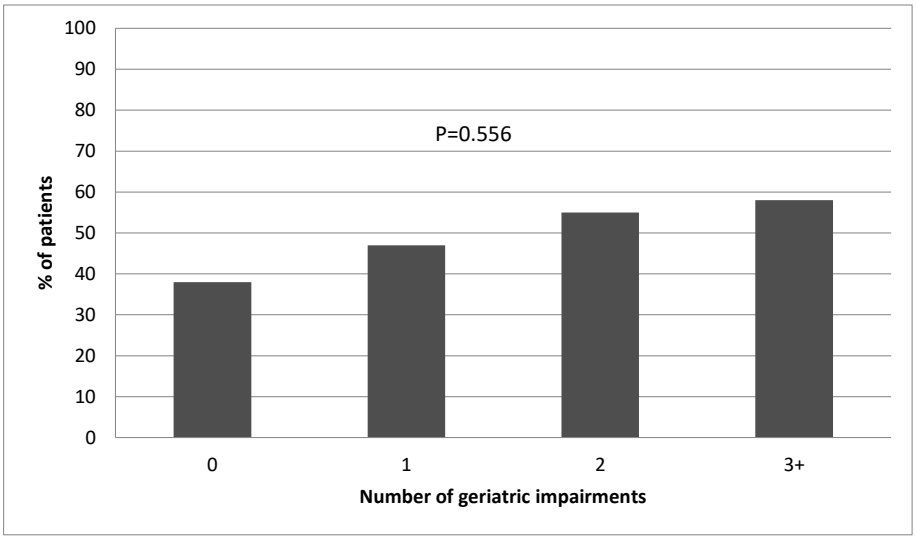

Figure 2. Association between number of impaired geriatric assessments and percentages of patients with treatment modifications.

Twenty-eight patients (28%) with an adverse event were admitted to the hospital, with a mean time of hospitalization of 7.8 days (+/-SD 2.3) The most frequent reasons for hospitalization were diarrhea and neutropenic fever. Three patients developed a delirium.

The association between individual GA tests and grade 3 toxicity are depicted in Table 4. Patients with an impaired GA test experienced more often a grade 3 toxicity compared to patients with a normal GA test, except for the patients with an impaired MMSE: 43% of the impaired patients versus 53% of the non-impaired patients experienced toxicity. In the univariable analysis, again only the TUGT was significantly associated with treatment related grade 3 toxicity (OR 2.8 [95% CI 1.2-6.3], p=0.01). After correction for confounders, the TUGT (2.8 [95% CI 1.3-7.2]), p=0.01) remained significantly associated with the occurrence of grade 3 toxicity. Finally, the subgroup analysis in which only patients with solid tumors were included did not show differences in the relation to GA and the occurrence of grade 3 toxicity compared to the total group of patients. (Supplementary Table 1)

Table 3. Association between GA and treatment modification/grade 3 toxicity (n=99).

Geriatric assessment	Patients with treatment modification/total patients (n (%))	Treatment modification OR (95% CI)
ADL		
Impaired	6/9 (67)	2.4 (0.6-10.2)
Independent	41/90 (45)	1.0
IADL		
Impaired	6/8 (75)	3.7 (0.7-19.1)
Independent	41/91 (45)	1.0
GDS-15		
Impaired	6/9 (67)	2.4 (0.6-10.2)
Independent	41/90 (45)	1.0
TUGT		
Impaired	31/52 (60)	2.9 (1.3-6.5)
Independent	16/47 (34)	1.0
MMSE		
Impaired	6/14 (43)	0.8 (0.3-2.5)
Independent	41/85 (48)	1.0
MNA		
Impaired	9/15 (60)	1.8 (0.6-5.6)
Independent	38/84 (40)	1.0

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; ADL, Activities of Daily Life; IADL, Instrumental Activities of Daily Life; MMSE, Mini-Mental State Examination;

Table 4. Treatment related grade 3 toxicity (n=53).

Grade 3 toxicity	Patients (%)
Non-hematological (n=39)	
Diarrhea	13 (25)
Malaise	12 (23)
Infection	6 (11)
Neutropenic infection	5 (9)
Ileus	1 (2)
Allergic reaction	1 (2)
Sensory neuropathy	1 (2)
Hematological (n=14)	
Neutropenia	8 (15)
Anemia	3 (6)
Thrombocytopenia	3 (6)

P-value	Patients with grade 3 toxicity/ total patients (n (%))	Grade 3 toxicity OR (95% CI)	P-value
0.24			0.41
	6/9 (67)	1.8 (0.4-7.8)	
	47/90 (52)	1.0	
0.12			0.12
	6/8 (75)	0.9 (0.7-1.0)	
	47/91 (51)	1.0	
0.24			0.23
	6/9 (67)	1.1 (0.9-1.3)	
	47/90 (52)	1.0	
0.01			0.01
	34/52 (65)	2.8 (1.2-6.3)	
	19/47 (40)	1.0	
0.70			0.29
	8/14 (43)	0.9 (0.8-1.0)	
	45/85 (53)	1.0	
0.30			0.10
	9/15 (60)	0.9 (0.8-1.0)	
	44/84 (52)	1.0	

MNA, Mini Nutritional Assessment; GDS-15, Geriatric Depression Scale; TUGT, Timed Up and Go Test.

DISCUSSION

The present study analyzes the association between GA and chemotherapy intolerance in older patients receiving first line palliative systemic treatment for both solid and hematologic malignancies. Our data show that half of the patients who were considered fit to start palliative systemic chemotherapy required treatment modifications and/or experienced grade 3 treatment related toxicity during the first three cycles of treatment. Of all investigated geriatric domains, only an impaired TUGT was significant associated with a three times increased risk of chemotherapy intolerance in patients who are considered fit to start chemotherapy.

Despite multiple studies that investigated the predictive value of GA for mortality, studies on the predictive value of GA for chemotherapeutic intolerance are limited. [3] [4] The first, of Aaldriks and colleagues, investigated the predictive value of GA for treatment modification in a heterogenic population, in which 55% of the 202 included patients were treated in the palliative setting.[6] Impaired MNA in this study was associated with an increased probability of treatment modification. Two other studies, both in patients with metastatic ovarian carcinoma, found that better functional, quality of life and social activity scores were associated with a greater likelihood of completing four cycles of chemotherapy.[7] [8]

Two studies developed and externally validated predictive models for chemotherapy toxicity.[9] [10] Both studies included patients treated in both the curative and palliative setting. The CARG (Cancer and Aging Research Group) developed a "chemotherapy toxicity calculator," which is a risk score consisting of 11 items, taking less than 5 minutes to complete.[9] In this study the TUGT was also significantly associated with the occurrence of grade 3 to 5 toxicity. In another study including 187 older patients with various types of malignancies stage 1-4, the CRASH score (Chemotherapy Risk Assessment Scale for High-age Patients i.e. 70 years or older) was developed.[10] In this study results from several GA tools were combined to predict severe toxicity, including functional, nutritional and cognition tools, taking up to 20 to 30 minutes to complete. They observed an association with IADL, MNA and the occurrence of toxicity. Additional predictors in this study for toxicity were hemoglobin, creatinine clearance, albumin, self-rated health, ECOG performance and chemotoxicity score (i.e. a score to rate the likelihood of experiencing toxicity based on the intensity of treatment). Three other studies investigated the association between GA and chemotherapy toxicity in more homogeneous patients populations with either advanced colorectal, breast or lung cancer.[11] [12] [13] In these studies IADL and MMSE were considered most strongly related with toxicities.

In contrast to the CRASH score and the later 2 studies, we did not find a relation between toxicity and IADL or MMSE scores, which may be explained by the low number of patients with an impaired test in our study, or because the CRASH score used a very strict cut off point for frailty in the MMSE questionnaire of <30 rather than the more commonly used cut-off point of 24. Finally, all these studies, except the CARG study, did not include the TUGT or other functional tests, which was the test that was most strongly related with grade 3 toxicity in our study. The observed high risk of treatment modifications and grade 3 toxicities is comparable to the risk that were observed in several other studies. [2] [3] [4]

Frailty is caused by the cumulative decline across multiple organs systems and resulting in a decreaed resistance to stressors such as chemotherapy. This suggests that the accumulation of geriatric impairments may results in higher risks of chemotherapy intolerance, which was also observed in several previous studies.[14] In contrast, we only observed a numerical, but non-significant, association between the number of geriatric impairments and treatment modifications.

Frailty may be hard to detect by clinical judgment, and conversely most oncologists consider very few patients as frail.[15] The current standard of functional status assessment by using the ECOG performance score has been shown to poorly predict functional impairment in older patients. A GA can detect health problems that may be associated with unfavorable outcomes, which may otherwise go unrevealed. For example this may be relevant for the need for assistance in daily functioning or malnutrition, as a large study of 1820 patients showed that 51.2% of patients, who suffer from unknown geriatric problems, primarily suffered from impaired physical functioning (40.1%) and malnutrition (37.6%).[16] These are both geriatric domains that are easily assessed by MNA and ADL questionnaires, and also potentially modifiable by interventions which may optimize patient's condition.

In this study we included a heterogeneous study population, consisting of patients with different types of tumors, who received different palliative systemic treatment regimens, rather than patients suffering from a certain type of tumor. The reason for including a heterogeneous study population is that we wanted to determine whether there are common factors of vulnerability for treatment modifications and severe toxicities in a broad range of older patients who are treated for their cancer, as this may improve its ability for all oncologists to use it in daily clinical practice. However, the heterogeneity in the patient population and chemotherapy treatments may also lead to different types of toxicity and therefore different risks of treatment modification. However, our subgroup analysis in patients with solid tumors did not reveal any important differences in the

relation between GA and outcomes. Another limitation is the relative small sample size, which may impact the significance of associations between GA components and outcomes. Finally, we have no data on characteristics of patients who were eligible for study inclusion but declined participation. As frail patients are more likely to decline study participation, there is a possibility that we included a patient population with favourable prognosis, i.e. only patients with good clinical condition, which may impact the generalizability of our results.

As pointed out by the international guidelines, evidence is increasing for the use of GA to aid physicians in daily clinical practice in several ways: by identifying impairments, clarifying patients priorities, predicting survival and toxicity risk, establishing a pretreatment baseline, and developing GA guided interventions. All these elements may influence treatment decisions (i.e. upfront dose adjustments) and help to guide in shared decision making.[4 17] This also implies that although the majority of the individual GA test were not significantly associated with treatment modifications or grade 3 toxicity, a GA can still be relevant for the before mentioned purposes.

Finally, an important next step would be to investigate whether future intervention studies that aim to improve geriatric domains also have the potential to decrease the risk of chemotherapy toxicity and improve treatment tolerance.

In conclusion, frailty was common in patients with metastatic cancer who were considered fit to receive palliative chemotherapy. Treatment modification was necessary in half of the patients. The TUGT was significantly associated with treatment modifications and grade 3 toxicities.

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SUPPLEMENTARY TABLE

Supplementary Table 1. Association between GA and treatment modifications/grade 3 toxicity in patients with solid cancer (n=81).

Geriatric assessment	Patients with treatment modification/total patients (n (%))	Treatment modification OR (95% CI)
ADL		
Impaired	3/5 (60)	0.5 (0.0-7.0)
Independent	36/76 (47)	1.0
IADL		
Impaired	4/6 (67)	2.7 (0.3-27.9)
Independent	35/75 (47)	1.0
GDS-15		
Impaired	5/7 (71)	2.7 (0.4-16.8)
Independent	34/74 (46)	1.0
TUGT		
Impaired	26/42 (62)	3.2 (1.2-8.2)*
Independent	13/39 (33)	1.0
MMSE		
Impaired	6/12 (50)	0.8 (0.2-3.3)
Independent	33/69 (48)	1.0
MNA		
Impaired	7/12 (58)	1.3 (0.3-5.4)
Independent	32/69 (46)	1.0

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; ADL, Activities of Daily Life; IADL, Instrumental Activities of Daily Life; MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment; GDS-15, Geriatric Depression Scale; TUGT, Timed Up and Go Test.

P-value	Patients with grade 3 toxicity/ total patients (n (%))	Grade 3 toxicity OR (95%)	P-value
0.57			0.63
	3/5 (60)	0.5 (0.1-6.8)	
	41/76 (54)	1.0	
0.34			0.57
	4/6 (67)	1.9 (0.2-16.5)	
	40/75 (53)	1.0	
0.30			0.93
	4/7 (57)	0.9 (0.2-5.2)	
	40/74 (54)	1.0	
0.02			0.03
	18/42 (43)	2.9 (1.1-7.2)**	
	16/39 (41)	1.0	
0.70			0.95
	7/12 (58)	0.9 (0.2-4.0)	
	37/69 (54)	1.0	
0.68			0.46
	8/12 (67)	1.7 (0.4-7.0)	
	36/69 (52)	1.0	

*Adjusted (age/gender) OR 3.4 (95% CI [1.4-8.9], p=0.02)

**Adjusted (age/gender) OR 2.8 (95% CI [1.2-7.1], p=0.00)


5

Implementation of a preoperative multidisciplinary team approach for frail colorectal cancer patients: influence on patient selection and outcome

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ABSTRACT

Objective

To determine the influence of a preoperative multidisciplinary evaluation for frail older patients with colorectal cancer (CRC) on preoperative decision making and postoperative outcomes.

Background

Surgery is the main treatment for CRC. Older patients are at increased risk for adverse outcomes. For complex surgical cases, a multidisciplinary team (MDT) approach has been suggested to improve postoperative outcome. Evidence is lacking.

Methods

Historical cohort study from 2015-2018 in surgical patients ≥70 years with CRC. Frailty screening was used to appraise the somatic, functional and psychosocial health status. An MDT weighed the risk of surgery versus the expected gain in survival to guide preoperative decision making and initiate a prehabilitation program. Primary endpoint was the occurrence of a Clavien-Dindo (CD) Grade III-V complication. Secondary endpoints included the occurrence of any complication (CD II-V), length of hospital stay, discharge destination, readmission rate and overall survival.

Results

466 patients were included and 146 (31.3%) patients were referred for MDT evaluation. MDT patients were more often too frail for surgery compared to non-MDT patients (10.3% vs 2.2%, P=0.01). Frailty was associated with overall mortality (aOR 2.6 95% CI 1.1-6.1). Prehabilitation was more often performed in MDT patients (74.8% vs 23.4% in non-MDT patients). Despite an increased risk, MDT patients did not suffer more postoperative complications (CD III-V) than non-MDT patients (14.9% vs 12.4%; P=0.48). Overall survival was worse in MDT patients (35 (32-37) vs 48 (47-50) months in non-MDT patients; P<0.01).

Conclusion

Implementation of preoperative MDT evaluation for frail patients with CRC improves risk stratification and prehabilitation, resulting in comparable postoperative outcomes compared to non-frail patients. However, frail patients are at increased risk for worse overall survival.

INTRODUCTION

Colorectal cancer (CRC) is common and affects approximately 15.000 new cases each year in The Netherlands. Population ageing and a national cancer screening program has increased the number of older patients with CRC that are presented for surgery.[1] Although CRC surgery is considered relatively safe in older patients, overall complication rates remain high.[2] Especially frail older patients with multiple comorbidities seem to suffer from adverse outcomes.[3 4] Frailty is a state of functional decline, characterized by weight loss, muscle wasting and reduced functional capacity.[5] In geriatric oncology frailty has been associated with toxicity of chemotherapy, postoperative complications, disability and decreased cancer survival.[6 7 8 9] The increasing complexity of the management of frail older patients undergoing CRC surgery and concerns of adverse outcomes have given rise to a preoperative multidisciplinary team (MDT) approach.

Although evidence for the effectiveness of a preoperative MDT meeting for older patients with cancer is currently lacking, MDT care for oncological patients is widely accepted and a mandatory component of cancer care. Several studies have shown that multidisciplinary oncology meetings can improve a patient's quality of life and even survival.[10] Similarly, the involvement of medical specialties that contribute to a patient-centered perioperative treatment plan can be used to improve risk assessment, decision-making and prehabilitation in older surgical patients. Prehabilitation is an important component of a preoperative MDT approach. Although it remains uncertain if prehabilitation improves outcome in patients with CRC, the results of recent studies in abdominal surgery are in favor of prehabilitation programs.[11] With this in mind, a specific preoperative MDT was implemented in 2015 for frail older patients with CRC in St. Antonius hospital, The Netherlands. This study presents the results of the implementation of a preoperative MDT approach for frail older surgical patients with CRC on patient selection, prehabilitation and outcome.

METHODS

Design

This historical cohort study describes the implementation of an MDT approach for frail patients with colorectal cancer (CRC). In November 2015, representatives of the departments of Anesthesiology and Intensive Care, Surgery and Internal Medicine of St. Antonius Hospital (a large non-university teaching hospital in The Netherlands) initiated an MDT approach for frail patients with CRC to improve postoperative outcomes.

Since patients were not subjected to investigational actions and treated according to standard guidelines the need for informed consent was waived by the local review board of the ethical committee (Medical research Ethics Committee United, number W17.139). The study was performed in accordance with the principles of the Declaration of Helsinki.

Population

All patients ≥70 years with histologically confirmed colorectal adenocarcinoma (Stadium I-IV) suitable for elective curative surgery between 2015 and 2018 were included. Patients with neuroendocrine tumors or transanal endoscopic microsurgery were excluded. All patients with CRC were routinely discussed in a multidisciplinary oncology team to determine treatment strategy. Surgical procedures were performed according to standard clinical practice by experienced colorectal surgeons and their trainees. According to hospital protocol, all patients aged ≥80 years were routinely admitted to an intensive care unit after surgery until the first postoperative day.

Preoperative geriatric assessment

All patients were pre-screened for frailty characteristics during intake at the surgical outpatient clinic. Dedicated oncology nurse specialists used clinical judgement and validated screening questionnaires (Geriatric 8 (G8) questionnaire (cut-off ≤14) and 6 Item Cognitive Impairment Test (6-CIT) (cut-off ≥6) to screen for frailty characteristics. [12 13] Patients who were considered frail by clinical judgement of the oncology nurse specialist (e.g. apparent weakness or slowness during physical examination), were referred to the MDT irrespective of the results of frailty screening. Patients at risk for frailty were referred for a comprehensive preoperative geriatric assessment, which was performed directly after routine preoperative assessment by a nurse specialist and an anesthesiology (LV) or internal medicine (EV) resident. The preoperative geriatric assessment was supervised by an anesthesiologist dedicated to preoperative screening and consisted of a compilation of validated tools to assess physical, mental and social frailty.[14] Analysis of physical frailty included nutritional status (Mini Nutritional Assessment (MNA); weight loss ≥3kg), gait speed (Timed to Get up and Go Test (TUGT), impaired mobility (unable to walk 5 minutes

without rest or dyspnea, unable to climb 1 stair without rest or dyspnea, unable to walk without mobility aids); polypharmacy (≥5 medicines), daily functioning (Instrumental activities of daily functioning (IADL) and Activities of Daily Living (ADL) questionnaires) and grip strength.[15 16 17] Screening for mental impairments included an assessment of cognition (6-CIT ≥6; diagnosis of dementia), health related quality of life (HRQL) (Short Form 12 (SF-12) or EQ-5D questionnaire), estimate of delirium risk and motivation for surgery.[18] To assess social frailty we evaluated a patient's living situation and social support system. The results of the geriatric assessment provided input for the MDT meeting.

Multidisciplinary Team Meeting

The MDT consisted of at least one representative of each of the following medical specialties: anesthesiology, surgery, medical oncology and geriatrics. In addition, a clinical pharmacist, physiotherapist, dietician and nurse specialist were part of the MDT. Meetings were held on a weekly basis. MDT results were discussed with the patient by a nurse specialist and surgeon.

Members of the MDT estimated the risk of a surgical procedure by evaluating a patient's medical history, comorbidities, frailty characteristics and severity of disease. In addition, the American College of Surgeons (ACS) NSQIP risk calculator was used.[19]

Prehabilitation program

When patients were considered eligible for surgery, a prehabilitation program was initiated based on comorbidity and frailty characteristics. Prehabilitation was initiated if a patient had a frailty characteristic that was suitable for prehabilitation. Elements of prehabilitation were: nutrition (referral to dietician, tube or parenteral feeding); mobility (referral to physiotherapist); cognition (delirium prevention or comprehensive geriatric assessment); medication (alterations in current medication); anemia (IV iron or transfusion); intoxication (alcohol or smoking cessation); interdisciplinary consultation. The aim of the prehabilitation program was to improve cardiovascular, respiratory, muscular and mental condition over a period of weeks prior to surgery. A reasonable time frame for prehabilitation was determined by a surgeon and medical oncologist and consensus between members of the MDT. For patients with severe frailty a second MDT meeting was held after the prehabilitation program was completed. During prehabilitation patients were monitored by their nurse specialist.

Clinical characteristics and data collection
Baseline and frailty characteristics of MDT patients were prospectively collected during AGE.

Demographic and clinical characteristics of non-MDT patients were retrospectively collected from electronic medical records. Medication history was available from hospital pharmacy services. To assess the overall weight of comorbidities, the Charlson Comorbidity Index (CCI) was calculated for each patient.[20] The American Society of Anesthesiologists (ASA) classification was used to assess the fitness of patients before surgery.[21] The Revised Cardiac Risk Index (RCRI) was used to determine the risk on postoperative cardiac complications.[22] Data were registered in an electronic database (RedCAP (Research Electronic Data Capture) hosted by St. Antonius hospital).

Endpoint definitions
Primary endpoint was the occurrence of a severe postoperative complication (Clavien-Dindo (CD) Grade III-V). Secondary outcomes were any postoperative complication (CD grade II-V), length of hospital stay, discharge destination, readmission rate and overall survival. Primary and secondary endpoints were extracted from electronic medical records. Overall survival was collected from the municipal Personal Records Database (BRP).

Statistical analysis
Categorical data are stated as number and percentages. Continuous data are described as mean ± standard deviation or median and interquartile range (IQR) depending on normality. Normality was tested using visual inspection of histograms and Kolmogorov-Smirnov test. Differences between MDT and non-MDT patients were tested using Chi square test for dichotomous or categorical variables and Mann-Whitney U test or Student's t-test for independent continuous variables. The linear by linear association was used to test for trends in complication incidences over time. Differences between mild versus severe complications were calculated using Chi square test.

Overall survival was estimated using Kaplan Meier plot and the log-rank test was used to 1. test for differences in survival among non-MDT, MDT and non-surgical patients, and 2. test for differences according to severity of frailty (fit= ≤1 frailty characteristics, intermediate=2-3 frailty characteristics and frail ≥4 frailty characteristics). The association between frailty and overall mortality was assessed using logistic regression analysis adjusted for ASA classification. P- value <0.05 was considered statically significant. For statistical analysis IBM SPSS version 22 (IBM Corp. Armonk, New York) was used.

RESULTS

Patient selection for surgery

A total of 466 patients with CRC were included, of which 146 (31.3%) were referred for AGE MDT (MDT patients). Forty nine patients had one frailty characteristic, but did not meet the referral criteria for MDT evaluation. In fifteen MDT patients, risk for adverse outcome outweighed the potential benefits of surgery, in two patients this conclusion was drawn after unsuccessful prehabilitation. Three patients that were eligible for surgery refused an operation due to fear for adverse events and one patient reported a lack of motivation (Figure 1). MDT patients were more often considered too frail for surgery compared to non-MDT patients (15/146 (10.3%) vs 7/320 (2.2%), P=0.01). MDT patients that did not have surgery were characterized by advanced age, multi-morbidity, functional dependency and poor mobility (Supplementary table 1). In all of these patients, cancer symptoms did not affect their quality of life at time of diagnosis. The MDT advice to withhold surgical treatment was generally agreed upon by the treating physicians and their patients, except for one patient with dementia and impaired disease awareness.

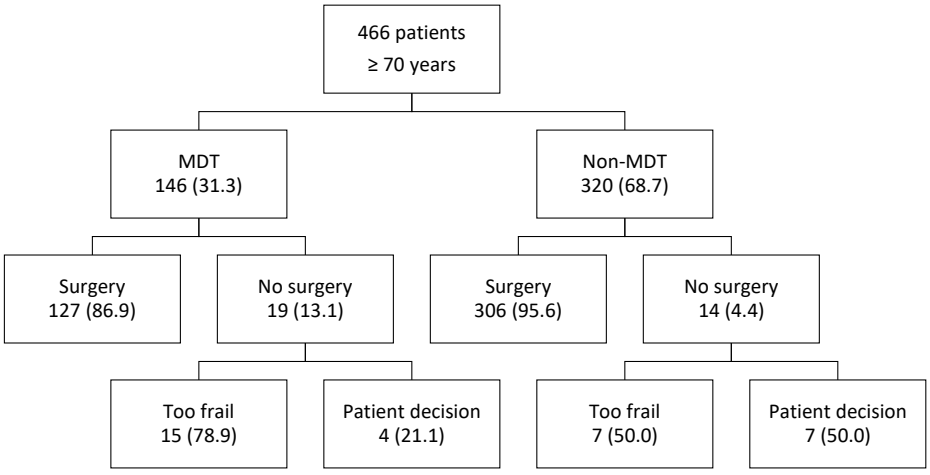

Figure 1. Flow chart of study patients.

Surgical population, frailty and prehabilitation

In total, 433 (92.9%) patients underwent CRC surgery. Median age was 75 (73-80) years, 118 (27.3%) patients were older than 80 years and a majority (59.1%) was male. 124/433 (28.6%) patients were classified ASA ≥3 and 195/433 (45.0%) patients had impairments in at least one domain. During the study period the number of patients with severe systemic disease and polypharmacy significantly increased (ASA ≥3 23/116 (19.8%)

in 2015 compared to 53/124 (42.7%) in 2018, P<0.01; polypharmacy 57/116 (49.1%) in 2015 compared to 83/124 (66.9%) in 2018, P=0.04). Baseline characteristics of MDT and non-MDT patients are presented in Table 1. MDT patients were older and had more comorbidities compared to non-MDT patients. According to the ACS risk classification 70.9% (90/127) of MDT patients versus 20.6% (63/306) of non-MDT patients were classified as high risk for developing a postoperative complication (P=0.03). MDT patients were also more often frail than non-MDT patients (Table 1). The most common impairment was polypharmacy. In 100/127 (78.7%) MDT patients two or more impairments on geriatric assessment were present. Prehabilitation was more frequently performed in MDT patients compared to non-MDT patients (74.8% (95/127) vs 23.4% (71/306), P <0.01). Iron infusion, exercise training and nutritional support were performed most often and 63.1% (80/127) of MDT patients received multiple domain interventions (Table 2). The median time between an MDT meeting and surgery was 17 (11-29) days.

Table 1. Baseline and frailty characteristics of MDT and non-MDT surgical patients.

	MDT patients N=127 (%)	**Non-MDT patients N=306 (%)**	**P-value**
Age, median (IQR)	80 (75-83)	75 (72-78)	<0.01
Male Gender	65 (51.2)	191 (62.4)	0.03
Risk scores, median (IQR)			
CCI	7 (6-8)	6 (5-7)	<0.01
RCRI	1 (0-2)	0 (0-1)	0.03
ACS, predicted any complication	16 (12.3-21.0)	9.7 (8.5-9.7)	<0.01
ASA	3 (2-3)	2 (2-2)	<0.01
Comorbidities			
Cardiovascular disease	65 (51.2)	101 (33)	<0.01
Pulmonary disease	35 (19.7)	39 (12.7)	0.06
Atrial fibrillation	21 (16.5)	37 (12.1)	0.22
Diabetes Mellitus	43 (33.9)	60 (19.6)	<0.01
Intoxication			
Current smoking	13 (10.2)	25 (8.2)	0.49
Alcohol use	6 (4.7)	38 (12.4)	0.02
TNM stage			0.81
TNM 0	0 (0)	3 (1)	
TNM I	44 (34.6)	109 (35.6)	
TNM II	40 (31.5)	100 (32.7)	
TNM III	38 (29.9)	84 (27.5)	
TNM IV	5 (3.9)	10 (3.3)	

Table 1. Continued

	MDT patients N=127 (%)	Non-MDT patients N=306 (%)	P-value
Neoadjuvant			
Radiotherapy	10 (7.9)	21 (6.9)	0.71
Chemoradiotherapy	7 (5.5)	23 (7.5)	0.46
Type of surgery			0.04
LAR	14 (11)	52 (17)	
APR	14 (11)	55 (18)	
Hemicolectomy right	67 (52.8)	123 (40.2)	
Hemicolectomy left	10 (7.9)	18 (5.9)	
Sigmoid resection	18 (14.2)	55 (18)	
Subtotal colectomy	4 (3.1)	3 (1)	
Symptoms at diagnosis	18 (14.2)	95 (31)	<0.01
Weight loss	64 (50.4)	106 (34.6)	<0.01
Impaired mobility	78 (61.4)	84 (27.5)	<0.01
Impaired cognition	19 (15)	6 (2)	<0.01
Polypharmacy	108 (85)	135 (44.1)	<0.01
Living alone	87 (18.9)	63 (20.9)	0.69
Independently at home	96 (75.6)	294 (96.1)	<0.01
At home with home care	26 (20.5)	8 (2.6)	
Residential facility	5 (3.9)	4 (1.3)	
No social support system	4 (1.3)	4 (3.1)	0.24
Anemia	99 (78)	156 (50.1)	<0.01
Renal impairment	41 (32.2)	34 (11.1)	<0.01

Abbreviations; MDT, Multidisciplinary team; non-MDT, Non multidisciplinary team; IQR, Interquartile Range; CCI, Charlson Comorbidity Score; RCRI, Revised Cardiac Risk Index; ACS, American College of Surgeons; ASA, American Society Anesthesiologists; LAR, Low Anterior Resection; APR, Abdominoperineal resection.
Anemia< 8mmol/l; renal impairment; eGFR CKD-EPI <45

Outcome

Overall, 57 (13.2%) patients were diagnosed with at least one severe complication and six (1.4%) patients died within 30 days after surgery. The number of patients with a severe complication did not change during the study period (Supplementary Figure 1, P=0.89). A severe postoperative complication occurred in 14.9% (19/127) of MDT patients compared to 12.4% (38/306) of non-MDT patients (P=0.48). MDT patients more often suffered from pneumonia while non-MDT patients had more abdominal infections (Table 3). MDT patients were more often discharged with home car or to a residential facility.

Readmission rates were similar between MDT and non-MDT patients and were most frequently caused by an infectious complication. During the study period the ratio of mild versus severe complications changed significantly in non-MDT patients. The number of severe complications steadily decreased from 18.7% (20/107) in 2015 to 5.2% (3/58) in 2018 (P<0.01) while the number of mild complications did not change significantly (23.4% (25/107) in 2015 vs 32.8% (19/58) in 2018 (P=0.14, Supplementary Figure 2a). In MDT patients the severity of complications did not change over time, 33.3% (1/3) had a severe complication in 2015 vs 22.4% (13/58) in 2018 (P=0.15), while 66.6% (2/3) had a mild complication in 2015 vs 24.1% (14/58) in 2018 (P=0.33, Supplementary Figure 2b).

Table 2. Elements of prehabilitation in MDT patients and non-MDT surgical patients.

	MDT patients N=127 (%)	**Non-MDT patients N=306 (%)**	**P-value**
Nutrition			
Referral to dietician	42 (33.1)	65 (21.2)	<0.01
Tube feeding	7 (5.5)	12 (3.9)	0.46
TPN	3 (2.4)	6 (2)	0.73
Mobility			
Referral to physiotherapist	34 (28.6)	59 (19.3)	0.08
Cognition			
Delirium prevention	48 (37.8)	11 (3.6)	<0.01
Comprehensive geriatric assessment	9 (7.1)	0 (0)	<0.01
Medication			
Alteration in current medications	7 (5.5)	0 (0)	<0.01
Anemia			
IV Iron	59 (46.5)	35 (11.4)	<0.01
Transfusion	24 (11)	28 (9.2)	0.76
Intoxication			
Alcohol and smoking cessation	21 (16.5)	12 (3.9)	<0.01
Interdisciplinary consultation	26 (20.5)	30 (9.8)	<0.01

Abbreviations; TPN, total parenteral nutrition; IV, intravenous

After a median follow up time of 25 (14.5-38) months, 21/127 (16.5%) MDT patients had died vs 35/306 (11.4%) of non-MDT patients (P=0.15). Overall survival was worse in MDT patients compared to non-MDT patients (Figure 2a). Frail patients had a more than two-fold increased risk of overall mortality compared to non-frail patients (adjusted OR 2.6 and 95% CI 1.1-6.1). (Figure 2b)

Table 3. Postoperative outcomes in MDT and non-MDT patients.

	MDT patients N=127 (%)	**Non-MDT patients N= 306 (%)**	**P-value**
Severity of complications			0.32
Clavien Dindo II	37 (29.1)	81 (26.5)	
Clavien Dindo III	5 (3.9)	18 (5.9)	
Clavien Dindo IV	11 (8.7)	17 (5.6)	
Clavien Dindo V	3 (2.4)	3 (1)	
Reoperation	11 (8.7)	30 (9.8)	0.71
Type of complications			
Anastomotic leakage	4 (3.1)	8 (6.3)	0.06
Infection	34 (26.8)	62 (20.3)	0.14
Pneumonia	20 (15.7)	15 (4.9)	0.01
Urinary tract infection	6 (4.7)	15 (4.9)	0.81
Wound infection	4 (3.1)	7 (2.3)	0.76
Abdominal infection	3 (2.4)	24 (7.8)	0.05
Other	1 (0.8)	1 (0.3)	0.21
Delirium	18 (14.2)	25 (8.2)	0.06
Cardiac	16 (12.6)	23 (7.5)	0.09
Gastroparesis	19 (15)	48 (15.7)	0.85
Blood transfusion	24 (18.9)	43 (14.1)	0.20
Unplanned ICU admission	12 (9.4)	19 (6.2)	0.23
Length of stay, median (IQR)	7 (5-8)	6 (5-7)	0.08
30 days mortality	3 (2.4)	3 (1)	0.58
Readmission within 30 days	15 (11.8)	31 (10.1)	0.61
Required new home care or residential care after surgery	60 (47.2)	112 (36.6)	0.03

Abbreviations; IQR, Interquartile Range; ICU, Intensive Care Unit

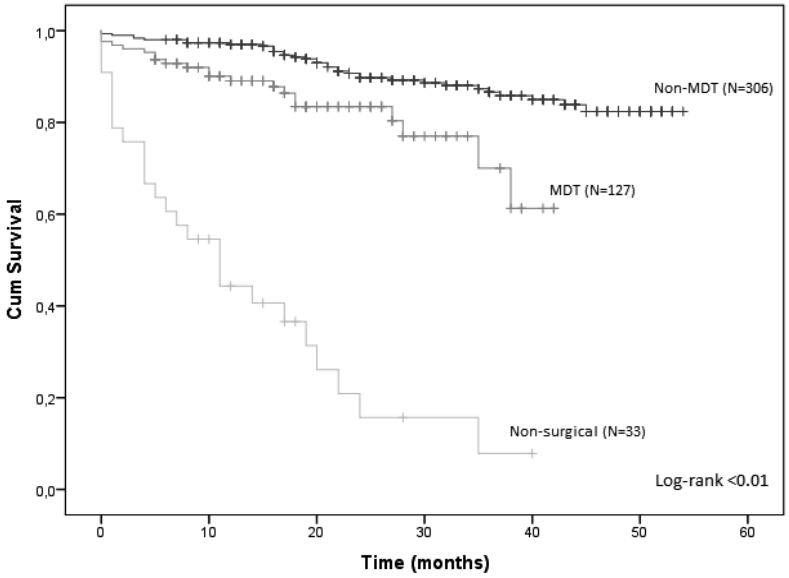

Figure 2a. Kaplan Meier plot for overall survival in MDT patients, non-MDT patients and patients without surgery.

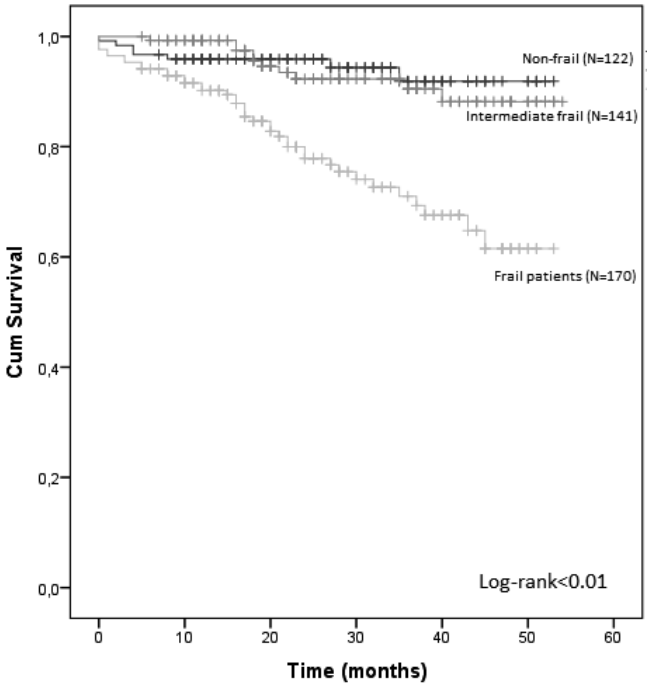

Figure 2b. Kaplan Meier plot for overall survival according to frailty.

DISCUSSION

This study evaluated the implementation of a preoperative MDT approach for frail patients with CRC on patient selection and outcome. Our main findings were that an MDT meeting improved preoperative risk stratification, facilitated prehabilitation and resulted in an overall similar severe postoperative complication rate compared to non-MDT patients, despite an increased surgical risk. However, frail patients showed worse overall survival compared to non-frail patients.

CRC surgery in older patients aims to improve survival while maintaining health related quality of life and daily functioning. A majority of older patients seems to be willing to undergo surgical treatment for CRC when risk of adverse outcome is acceptable. However, preoperative risk stratification in frail patients with CRC is complicated because robust outcome data are currently lacking. Besides, the risk that a patient is willing to take varies greatly between patients, which demands a personal treatment plan that includes shared decision making regarding whether or not to operate. In our study, one out of ten MDT patients was denied surgery due to frailty. These results are in agreement with the non-resection rates in a recent study from The Netherlands cancer registry in CRC patients ≥75 years with multi-morbidity.[23]

In addition to commonly used risk models, preoperative geriatric assessment has been used to identify patients for whom the risks of surgery outweigh the benefits. Our results show that frailty is common in older patients with CRC and associated with worse overall survival, which underlines the importance of a preoperative geriatric assessment. During the study period, frailty screening resulted in a selection of high risk CRC patients that were referred for MDT evaluation. Also, patient selection led to a decrease of severe complications in non-MDT patients over time. These results can be used for full informed consent in both frail and non-frail surgical patients and improve shared decision making.

During the last two decades, MDTs have become the cornerstone of global cancer care. Several studies showed that MDT meetings for patients with gastrointestinal cancer are used to discuss the optimal oncological and surgical treatment.[10 24]

Whether or not surgical patients can benefit from preoperative MDT evaluations to assess risk of complications remains unclear. The results of our study confirm that implementation of a preoperative MDT affected patient management. A majority of MDT patients underwent multi-domain prehabilitation. Considering that frailty is a risk factor for adverse outcome, it seems reasonable to focus on prehabilitation in order to

reduce postoperative complications. In this respect, an MDT is more likely to deliver a tailored prehabilitation program than an individual physician, considering the growing complexity of care for geriatric surgical patients.

It remains uncertain if prehabilitation is effective in decreasing the number of severe complications in frail surgical patients.[25 26 27] Our results demonstrate that MDT evaluation can lead to similar rates of postoperative complications in frail and non-frail patients. This might be the effect of prehabilitation, as most single intervention studies showed that prehabilitation has a positive effect on functional capacity. However, most of these studies investigated younger patients than we did and did not include patients with multiple comorbidities.[28 29 30] A 20% reduction in complications was shown in a meta-analysis that investigated the effectiveness of multimodal prehabilitation in older ASA 3-4 patients undergoing abdominal surgery.[25] The favorable effect of prehabilitation are further abstracted by a recent study, demonstrating that a pre- and rehabilitation program in patients with CRC resulted in a postoperative severe complication rate of 16%[31]. This percentage is comparable to our results (14.9%).

The following limitations should be considered. This study described the results of an implementation of MDT evaluation which was modified over time. Experience gained during the study period, has likely affected patient referral and prehabilitation strategies. The number of MDT patients increased over time which may have influenced our results. Similarly, increasing experience with perioperative care for frail patients led to a change in prehabilitation management of MDT and non-MDT patients. It is likely that patients were more often fully prehabilitated at the end of the study period. In addition, this study was not powered to demonstrate an effect of prehabilitation on postoperative outcomes. Furthermore, information on the cause of death was not available. However, it seems likely that frail patients died of their comorbidities instead of CRC, because cancer stages were similar at baseline in non-frail and frail surgical patients. Last, information on frailty and prehabilitation in non-MDT patients were retrospective collected and could have introduced information bias. Despite these limitations, this study showed a detailed overview of four years of experience in preoperative MDT evaluation and adds important outcome information on treatment of frail patients with CRC.

In conclusion, an increasing number of complex older surgical patients is being referred for CRC surgery. Implementation of MDT evaluation can be used to improve the management of frail older patients with CRC, including shared decision making and tailored perioperative care. This may lead to favorable postoperative outcomes in frail patients despite an increased preoperative risk.

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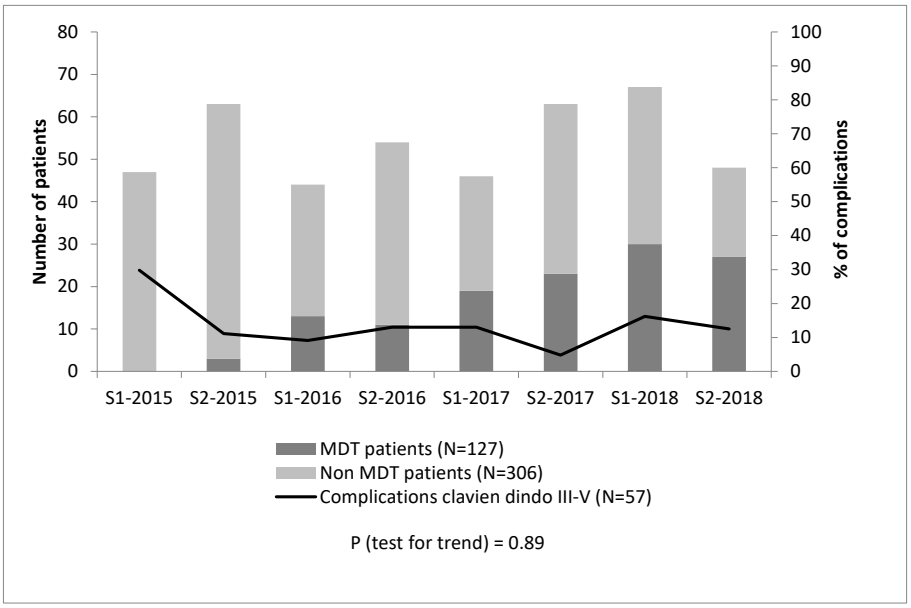
SUPPLEMENTARY TABLE

Supplementary Table 1. Baseline and frailty characteristics in non-surgical MDT patients.

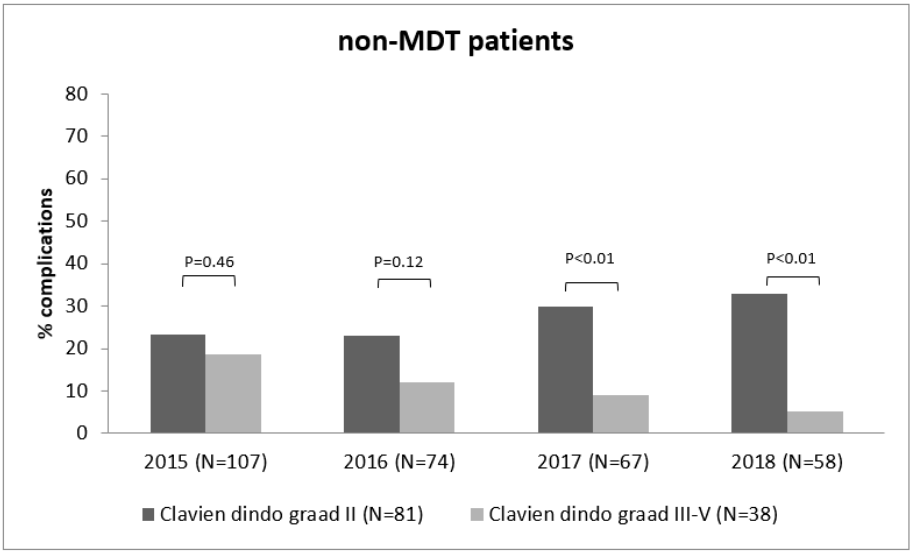
	MDT patients N=19 (%)
Age, median (IQR)	79 (73-85)
Male Gender	13 (68.4)
Risk scores, median (IQR)	
CCI	7 (7-9)
ACS, predicted any complication	19.4 (18-21.8)
ASA ≥ 3	18 (94.7)
Comorbidities	
Cardiovascular disease	14 (73.7)
Pulmonary disease	8 (42.1)
Atrial fibrillation	2 (10.5)
Diabetes Mellitus	7 (36.8)
TNM stage	
TNM 0	0
TNM I	5 (26.3)
TNM II	9 (42.1)
TNM III	5 (26.3)
TNM IV	0
Polypharmacy	17 (89.5)
Impaired mobility	19 (100)
Impaired cognition	5 (26.3)
Living alone	10 (52.6)
At home, independently	4 (21.1)
At home, with homecare	12 (63.2)
Residential facility	3 (15.8)

Abbreviations; MDT, Multidisciplinary team; IQR, Interquartile Range; CCI, Charlson Comorbidity Score; RCRI, Revised Cardiac Risk Index; ACS, American College of Surgeons; ASA, American Society Anaesthesiologists.

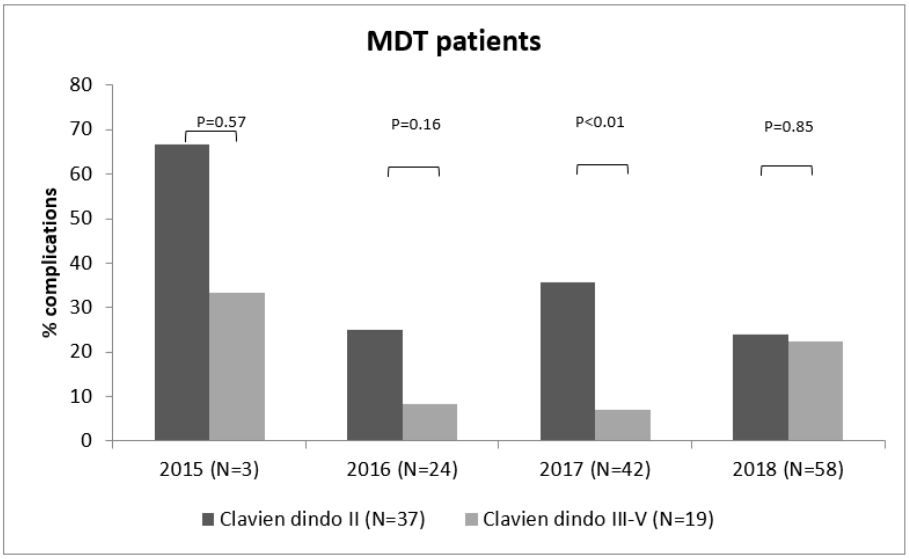
SUPPLEMENTARY FIGURES



Supplementary Figure 1 . Severe complications in MDT and non-MDT patients stratified to semesters.



Supplementary Figure 2a. Mild versus severe complications in non-MDT patients.



Supplementary Figure 2b. Mild versus severe complications in MDT patients.

6

PREOPERATIVE FRAILTY AND OUTCOME IN PATIENTS UNDERGOING RADICAL CYSTECTOMY

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ABSTRACT

Objective

To determine the value of preoperative frailty screening in predicting postoperative severe complications and 1 year mortality in patients undergoing radical cystectomy.

Methods

Prospective cohort single centre study in patients undergoing radical cystectomy from September 2016-December 2017. Preoperative frailty screening was implemented as standard care and was used to guide shared decision making during multidisciplinary team meeting. Frailty screening consisted of validated tools to assess physical, mental and social frailty. Patients were considered frail when having ≥2 frailty characteristics. Primary endpoint was the composite of a severe complication (Clavien Dindo (CD) grade III-V) within 30 days and 1 year all-cause mortality. Secondary endpoints included any complication (CD II-V), length of stay, readmission within 30 days and all-cause mortality. Logistic regression analysis and the concordance statistic were used to describe the association and predictive value of preoperative frailty screening.

Results

63 patients were included; 39 patients (61.9%) were considered frail. Preoperative frailty was associated with a seven-fold increased risk for a severe complication or death one year after surgery (adjusted OR 7.36 (95% CI 1.7-31.8) (22 patients). Compared to American Society of Anesthesiologists score and Charlson Comorbidity Index, frailty showed the best model performance (Nagelkerke R^2 0.20) and discriminative ability (c-statistics 0.72, $p<0.01$) for the primary endpoint. After adding frailty to the conventional ASA risk score, the c-statistics improved by 11% ($p<0.01$). Overall survival was significantly worse in frail patients (23.2 months (95% CI 18.7-30.1)) versus non-frail patients (32.9 months (95% CI 30.0-35.9), P=0.01).

Conclusion

Frail patients undergoing radical cystectomy are at high risk for postoperative adverse outcomes including death. Preoperative frailty screening improves preoperative risk stratification and may be used to guide patient selection for radical cystectomy.

INTRODUCTION

Bladder cancer is frequently diagnosed worldwide and a common cause of death. Approximately, 30% of all new diagnosed patients present with muscle invasive bladder cancer.[1] Radical cystectomy is the gold standard for patients with muscle-invasive bladder cancer and patients with recurrent high risk non-muscle invasive disease. [2,3] Although radical cystectomy is a common urologic surgical procedure, postoperative morbidity and mortality rates remain high.[4–6] Especially frail patients with multiple comorbidities seem to suffer from adverse outcomes. [7–9]

Frailty is an age related state of functional decline, characterized by weight loss, muscle wasting and reduced functional capacity. Frailty has been associated with postoperative complications, disability, loss of health related quality of life (HRQL) and decreased cancer survival.[8] With ageing of the population, the incidence of bladder cancer will continue to rise, and physicians will encounter the dilemma of treatment decisions in older and more frail patients. The increasing complexity of the management of frail patients undergoing radical cystectomy, and concerns of adverse outcomes demand accurate preoperative risk assessment.

Current traditional risk assessment tools, such as the American Society of Anesthesiologists (ASA) score or the Charlson Comorbidity Score (CCI) are used to guide selection of surgical candidates. However, these predictors focus primarily on medical comorbidities and do not take frailty characteristics into account. There is an unmet need for a preoperative risk stratification tool, with specific attention for frailty, to identify patients at high risk for poor outcomes. The purpose of this prospective study was to determine the predictive value of preoperative frailty screening on short- and long term postoperative outcomes in patients undergoing radical cystectomy.

METHODS

Design

The current study was a single centre prospective cohort study. In 2016, the St. Antonius Hospital, a large teaching hospital and regional referral centre for uro-oncologic surgery, implemented frailty screening as standard care for patients scheduled for radical cystectomy. The results were discussed in a multidisciplinary team (MDT) meeting, with representatives of the departments of Anaesthesiology and Intensive Care, Urology, Internal Medicine, Medical Oncology and Geriatrics.[10] Since patients were treated according to standard local guidelines, the need for informed consent was waived by the local review board of the ethical committee (Medical research Ethics Committee United, number W17.139). The study was performed in accordance with the principles of the Declaration of Helsinki.

Patients

All patients who were scheduled for radical cystectomy between September 2016 and December 2017 in the St. Antonius hospital were eligible for inclusion. All patients were routinely discussed in a multidisciplinary urologic oncology team to determine treatment strategy. Each surgical procedure was performed according to standard clinical practice by two experienced urologists.

Preoperative frailty screening

Preoperative frailty screening was performed directly after routine preoperative assessment by an anesthesiology (LV) or internal medicine (EV) resident. Frailty screening was supervised by an anesthesiologist dedicated to preoperative screening, and consisted of validated tools to assess physical, mental and social frailty. Analysis of physical frailty included nutritional status (Mini Nutritional Assessment (MNA), gait speed (Timed to Get up and Go Test (TUGT)), polypharmacy (≥5 medicines), daily functioning (NAGI scale) and grip strength.[11–13] Screening for mental frailty included an assessment of cognition (6-CIT) and HRQL (Short Form 12 (SF-12).[14,15]

To assess social frailty we evaluated a patient's living situation and social support system. Frailty characteristics were considered normal or abnormal according to predefined cut off points based on literature. Patients were considered frail when two or more frailty characteristics were present.

Clinical characteristics and data collection

During routine preoperative assessment baseline characteristics, medical history and laboratory tests were routinely collected. Muscle invasive disease was defined as a clinical T stage of ≥T2. To assess the overall weight of comorbidities, the age

adjusted CCI and the ASA classification were calculated for each patient.[16] Data were registered in an electronic database (RedCAP (Research Electronic Data Capture), Vanderbilt University, hosted by St. Antonius hospital).

Endpoint definitions

Primary endpoint was the composite of a severe complication (Clavien Dindo (CD) grade III-V) within 30 days after surgery or death after one year. Secondary endpoints were any complication (CD II-V), length of stay, readmission within 30 days after surgery and all-cause mortality. Primary and secondary endpoints were extracted from electronic medical reports. Mortality was collected from the municipal Personal Records Database.

Statistical analysis

Data are presented as frequencies and percentages (%) for categorical data, and as median with first and third quartile (IQR) or mean with standard deviation (SD) for continuous data. Normal distribution of the variables was assessed with visual inspection of the histograms and Q-Q plots. Differences between frail and non-frail patients were tested using Chi square test for dichotomous or categorical variables and Mann-Whitney U test or Student's t-test for independent continuous variables.

The association between separate risk scores, individual frailty characteristics and the endpoints were analysed with univariable logistic regression. Because age and tumor stage (muscle invasive versus non-muscle invasive) were a priori expected to be related with the endpoints and the investigated risk scores, all models were adjusted for those variables resulting in adjusted odds ratios (OR) with 95% confidence intervals (CI).

To assess the discriminatory ability of separate risk scores and the added value of frailty, the c-statistic was used. The C-statistic is an index of predictive discrimination, with a value of 0.5 indication random prediction, and a value of 1 indicating perfect prediction. Overall model performance was reported by Nagelkerke's R^2. Nagelkerke's R^2 ranges from 0 to 1, with higher values indicating better model performance.

Kaplan-Meier curves were used for survival analysis. Differences in Kaplan-Meier curves between frail and non-frail patients were analysed with log-rank test. Finally, cox regression analysis were used to adjust for muscle invasiveness, because patients with muscle invasive disease have a poor prognosis compared to patients with non-muscle-invasive disease.

P-values <0.05 were considered statistically significant. All data analyses were performed using IBM SPSS Statistics for Windows version 22 (IBM Corp. Armonk, NY, USA).

RESULTS

Population and outcome

A total of 64 patients were scheduled for cystectomy and underwent preoperative frailty screening. One patient was excluded, because surgery was abandoned after reassessment of the cancer stage by the pathologist. The final cohort consisted of 63 patients, with a median age of 67 (IQR 61-74) years. Two patients (3.2%) had surgery for non-oncologic diseases: one patient had chronic bladder pain syndrome, and another patient had iatrogenic ureteral injury after rectal amputation.

Of all oncologic patients, 61.9% was diagnosed with muscle invasive disease. Five patients (7.9%) received neo-adjuvant chemotherapy. 24 Patients (38.1%) underwent a robot assisted laparoscopic radical cystectomy with intracorporal urinary diversion. In all other patients a complete open surgical procedure was performed. Twenty-one percent (13/63) of patients was classified ASA ≥3, and median CCI was 5 (4-6). Baseline characteristics of frail and non-frail patients are presented in table 1. Overall, 22 patients (34.9%) had a severe complication or died (CD III-V) within one year after surgery. Any complication occurred in 42/63 patients (66.7%). Fascial dehiscence (5/10 patients) or other acute abdominal signs (caused by rectal, small bowel or urostoma lesions in 3/10 patients) were the most common reasons for reoperation. The operation technique (laparoscopic versus open) was not associated with the occurrence of a severe complication (P=0.34). More than half of the patients (58.7%) were diagnosed with an infection, including eight (8/37) patients with urosepsis. Urosepsis was the most common reason for readmission to the ICU, and readmission within 30 days after discharge. One third (22/63) of patients died within two years.

Preoperative frailty

Table 2 presents the prevalence of preoperative frailty characteristics in the study population.

Age of the study population ranged from 45 to 82 years, 3.2% (2/63) of patients were octogenarians. One or more frailty characteristics were present in 52 (82.5%) patients. Physical frailty was more common (51 patients, 81%) than mental or social frailty (38 patients, 60.3%) and 0 patients respectively). Multidomain frailty was present in 39 (61.9%) patients.

Physical frailty consisted primarily of impaired grip strength, anemia or polypharmacy. Of the anemic patients, 2/19 (10.5%) were diagnosed with severe anemia (Hb≤6 mmol/l) and 1/19 (5.3%) developed anemia after neoadjuvant chemotherapy.

Table 1. Baseline characteristics (N=63)

	Frail patients (N=39) (%)	**Non-frail patients (N=24) (%)**	***P*-value**
Age, mean (±SD)	69 (± 8)	62 (± 8)	<0.01
Male gender	30 (76.9)	18 (75)	0.86
BMI, mean (±SD)	25.5 (± 3.5)	26.4 (± 3.6)	0.36
Age adjusted CCI, mean (±SD)	5 (± 1.5)	4 (± 1.1)	<0.01
ASA classification			<0.01
1	5 (12.8)	10 (41.7)	
2	21 (53.8)	14 (58.3)	
≥ 3	13 (33.3)	0 (0)	
Comorbidities			
Cardiovascular disease	23 (59)	16 (41)	<0.05
Pulmonary disease	8 (20.5)	0 (0)	<0.05
Diabetes Mellitus	4 (10.3)	2 (8.3)	1.00
Renal failure (GFR <60)	7 (17.9)	1 (4.2)	0.14
Stroke	4 (10.3)	1 (4.2)	0.64
Intoxication			
Current smoking	18 (46.2)	2 (8.3)	<0.01
Alcohol use*	11 (28.2)	4 (16.7)	0.30
cT stage			0.42
Muscle-invasive	26 (66.7)	13 (54.1)	
Non-muscle-invasive	14 (35.9)	13 (54.2)	0.35
Lymph node positive	9 (23.1)	3 (12.5)	1.00
Non-oncological	1 (2.6)	1 (4.2)	
Neoadjuvant chemotherapy	4 (10.3)	1 (4.2)	0.64
Type of surgery			0.65
Robot cystectomy	14 (35.9)	10 (41.7)	
Open cystectomy	25 (64.1)	14 (58.3)	

Abbreviations: SD: standard deviation; CCI: Charlson Comorbidity Score; ASA: American Society of Anesthesiologists; cT: Clinical T stadium. *woman >2 units/day, men>3 units/day

Median number of prescriptions were 3 (1-5) and 20 (31.7%) patients had ≥5 prescribed medications. Mental frailty was characterized by loss of HRQL; more than half of the patients reported a HRQL below the population mean. None of the patients were considered frail on social domain. Although 20% of the patients lived alone, all patients had a strong social support system. Overall, 39 patients (61.9%) were considered frail (≥2 frailty characteristics).

Table 2. Frailty characteristics (N=63)

Variable	Score range	Cut off point for frailty	Median (IQR)	Number of frail patients (%)
Age	0-inf	≥ 75 years	67 (61-74)	14 (22.2)
6-CIT	0-28	≥ 6	0 (0-2)	5 (7.9)
SF-12 PCS (N=54)	0-100	< 50	51.5 (42.2-55.7)	26 (48.1)
SF-12 MCS (N=54)	0-100	< 50	47.4 (42.6-51.3)	37 (68.5)
NAGI	0-7	≥ 3	0 (0-0)	4 (6.3)
MNA	0-30	≤ 7	11 (9-11)	8 (12.7)
TUGT	0-inf	≥ 10 sec	8.6 (7.58-9.80)	13 (20.6)
Grip strength	0-inf	Age dependent	-	20 (31.7)
Polypharmacy	0-inf	≥ 5 drugs	3 (1-5)	20 (31.7)
Anemia	0-11	< 8 mmol/l	8.6 (7.6-9.1)	19 (30.6)
Living alone	Yes-no	-	-	20 (31.7)
At home with home care	Yes-no	-	-	6 (9.5)
No social support system	Yes-no	-	-	0 (0)

Abbreviations: IQR, Interquartile Range; 6-CIT, 6 Item Cognitive Impairment Test; SF-12, Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary; MNA, Mini Nutritional Assessment; TUGT, Timed to Get and Go test; inf, infinity

Preoperative frailty and outcome

A severe complication or death after one year was more common in frail patients (48.7% versus 12.5% in non-frail patients, P<0.01) (Table 3). After adjustment for age and muscle invasiveness preoperative frailty was associated with a seven-fold increased risk for a severe complication or death after one year (Table 4). Compared to ASA and CCI, frailty showed the best model performance, and discriminative ability for the primary endpoint. After adding frailty to the conventional ASA risk score, the discrimination slope increased by 11% (c-statistic 0.75, p<0.01). Individual frailty characteristics were not associated with the primary or secondary endpoints. Of all frailty characteristics, polypharmacy showed the best model performance (Nagelkerke R^2 0.08).

After a median follow up time of 26 (IQR 14-31) months, overall survival was worse in frail patients (mean 23.2 months (95% CI 18.7-30.1) versus 32.9 months (95% CI 30.0-35.9) for non-frail patients (P=0.01); Figure 1) Overall survival was worse for patients with muscle invasive disease (22.8 months (95% CI 18.2-27.5)) compared to patients with non-muscle invasive disease (32.3 months (95% CI 28.9-35.8), P<0.01. Frailty remained associated with worse overall survival after adjustment for muscle invasiveness (adjusted HR 3.2 (95% CI 1.1-9.4), P=0.04.

Table 3. Post-operative outcomes (N=63)

	Frail patients (N=39) (%)	Non-frail patients (N=24) (%)	*P*-value
Severity of complications			0.30
Clavien Dindo II	16 (41)	12 (50)	
Clavien Dindo III	4 (10.3)	3 (12.5)	
Clavien Dindo IV	4 (10.3)	0 (0)	
Clavien Dindo V	3 (7.7)	0 (0)	
Reoperation	9 (23.1)	1 (4.2)	0.07
Inplanned ICU admission	7 (17.9)	0 (0)	0.04
Length of stay, median (IQR)	14 (11-27)	13 (11-16)	0.21
30 days mortality	3 (7.7)	0 (0)	0.28
Readmission within 30 days	5 (12.8)	3 (12.5)	1.00
Required new home care or residential care after surgery	29 (74.4)	19 (79.2)	0.66
1 year mortality	12 (30.8)	1 (4.2)	0.01
2 year mortality	18 (46.2)	4 (16.7)	0.02

Abbreviations: IQR: Interquartile Range; ICU, Intensive care Unit

Table 4. Results of risk scores and components of the preoperative frailty screening on the prediction of severe complications and 1 year all-cause mortality.

Model	OR (95% CI)*	*P*-value	Nagelkerke R^2	C-statistic*	*P*-value
Single risk score					
ASA score (<3, ≥3)	4.28 (1.13-16.17)	0.03	0.12	0.64	0.07
CCI score (<5, ≥5)	1.53 (0.45-5.19)	0.49	0.03	0.57	0.37
Frailty model (<2, ≥2)	7.36 (1.70-31.84)	<0.01	0.20	0.72	<0.01
ASA + frailty model	3.58 (1.52-8.41)	<0.01	0.22	0.75	<0.01
Frailty characteristics					
Polypharmacy	2.72 (0.88-8.45)	0.08	0.08	0.63	0.09
Anemia	1.39 (0.44-4.40)	0.57	0.03	0.59	0.27
6-CIT	1.28 (0.20-8.37)	0.80	0.02	0.56	0.47
TUGT	2.55 (0.70-9.33)	0.16	0.06	0.62	0.12
Hand grip strength	1.89 (0.63-5.73)	0.26	0.05	0.59	0.27
NAGI	1.95 (0.25-15.14)	0.52	0.03	0.57	0.35
MNA	2.05 (0.46-9.25)	0.35	0.04	0.60	0.20
SF12 PCS	1.83 (0.63-5.31)	0.27	0.05	0.61	0.17
SF12 MCS	0.43 (0.15-1.26)	0.12	0.07	0.63	0.10
Living alone	0.98 (0.32-3.00)	0.97	0.02	0.55	0.50

Abbreviations: CCI: Charlson Comorbidity Score; ASA: American Society of Anesthesiologists; 6-CIT, 6 Item Cognitive Impairment Test; SF-12, Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary; MNA, Mini Nutritional Assessment; TUGT, Timed to Get up and Go Test. *All models were adjusted for age and muscle invasiveness

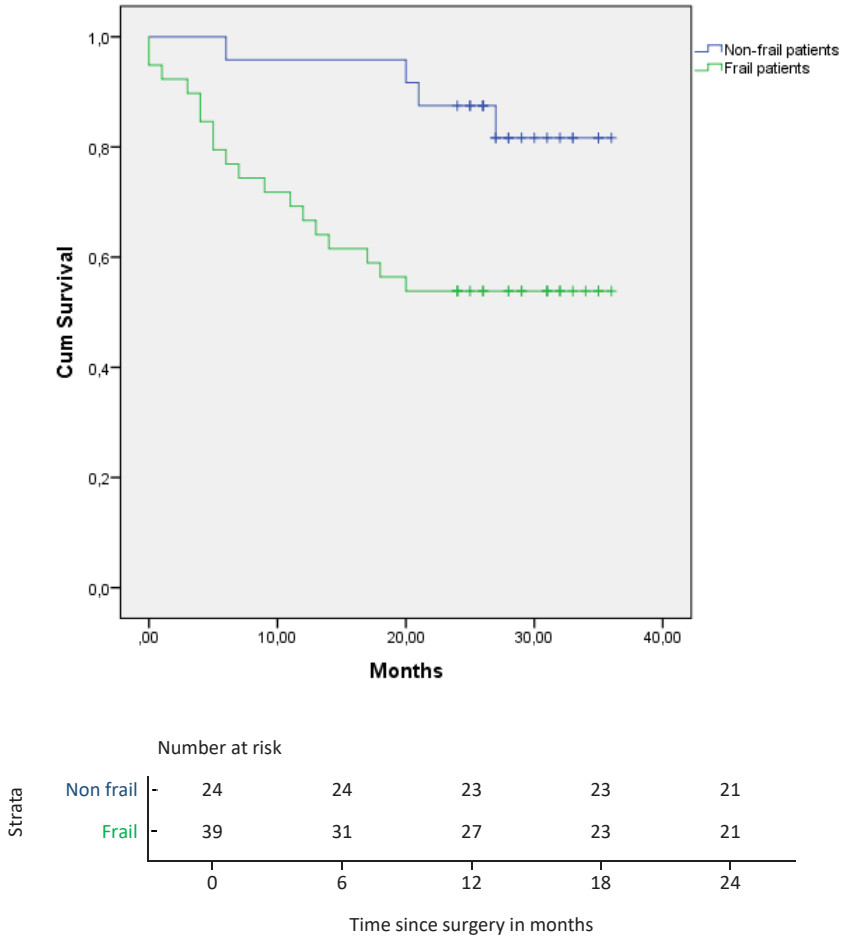

Figure 1. Kaplan meier plot for frail versus non-frail patients.

DISCUSSION

This study determines the value of preoperative frailty screening to predict postoperative severe complications and one year all-cause mortality in patients undergoing radical cystectomy. Frailty was commonly present and associated with a seven-fold increased risk of severe postoperative adverse outcomes, including one year mortality. Furthermore, preoperative frailty screening improved risk prediction for severe complications or death one year after surgery, and may be useful for preoperative shared decision making in patients scheduled for radical cystectomy.

Although radical cystectomy provides the best long term oncological prognosis in muscle invasive- and recurrent high risk non-invasive bladder cancer, surgical morbidity and mortality are high. Especially in frail patients, radical cystectomy has been associated with poor postoperative outcomes. [7–9,17–19]

Contemporary series from high volume centres report complication rates that range from 25-80%, with major complications occurring in approximately one third of the patients.[4,5] Furthermore, comparable results of 30 days mortality (2-4%) and long term mortality (5 years overall survival 42-58%) were observed in several other studies. [6,19,20] As presented in our study, frailty is common in patients scheduled for radical cystectomy. [8] In our cohort the majority of patients had at least one frailty characteristic and two-third of patients were frail in two out of three domains. This can be expected in a population which is characterized by older age and multimorbidity. Bladder cancer patients have the highest median age at time of diagnosis in all types of cancers and a median of eight chronic comorbidities, compared to a median of four in the general population. [21] As older age and comorbidities are often associated with frailty, it seems essential to take frailty characteristics into account in order to make the right treatment decisions in the growing cohort of patients undergoing radical cystectomy.

A majority of the patients is willing to undergo surgical treatment for bladder cancer when risk of adverse outcome is acceptable. Information on expected changes in daily functioning and quality of life after surgery is more likely to influence preoperative decision making than the often limited cancer related overall survival. However, this type of outcome data in frail patients with bladder cancer is currently lacking, which makes risk stratification complicated. Besides that, preoperative risk management consist of traditional risk assessment tools, such as the American Society of Anesthesiologists (ASA) score or the Charlson Comorbidity Score (CCI) and do not take frailty characteristics into account, leading to an underestimation of perioperative risk. The majority of the studies that examine frailty in patients undergoing radical cystectomy are population

based, single centre historical cohort studies.[8] Most studies use the simplified Frailty Index or the Modified Frailty index, which are solely based on functional status and comorbidities.[7,17,18,22] Prospective studies that cover all frailty domains (physical, mental and social), such as our study, are scarce. In one prospective study of 123 bladder cancer patients the Fried Frailty Criteria were predictive of high-grade complications.[19] Our study results showed that an assessment of frailty in multiple domains was strongly associated with adverse outcome, and that adding frailty to the ASA classification improved discrimination for the primary outcome by 11%.

In addition to an improved preoperative risk stratification, frailty screening has the ability to identify potentially modifiable risk factors. Considering that frailty is associated with adverse outcome, it seems reasonable to focus on prehabilitation in order to reduce postoperative complications. However, it is uncertain if prehabilitation is effective in decreasing postoperative outcomes in high risk patients. A recent randomized controlled study of seventy patients undergoing a radical cystectomy concluded that multimodal prehabilitation resulted in faster functional recovery after surgery.[23] In contrast, preoperative exercise-based programs failed to show significant improvement in physical and surgical outcomes.[24] Additionally, a preoperative risk profile that includes frailty may contribute to shared decision making by better informing the surgeon and patient on risk of adverse outcomes.

High risk patients may be better candidates for bladder-sparing approaches, such as (chemo)radiation.[25] In order to optimize preoperative shared decision making and to ensure the complexity of the management of frail patients, a MDT approach can be beneficial in the development of such patient-centered treatment plan.[10] Due to the absence of high quality outcome data in frail patients, clinical consensus in the form of a MDT approach (experienced based medicine) may the best available evidence to guide patient selection for radical cystectomy.

The following limitations should be considered. Although data were prospectively and consecutively collected, our sample size is limited. As a result we were unable to determine which individual frailty characteristics were most strongly associated with adverse outcome. As a full frailty screening is time consuming, a short frailty screening would improve its applicability in daily practice. Although a clear recommendation cannot be made based on our data, we would suggest the use of a screening tools that cover both the physical and mental domains of frailty. Furthermore, to avoid overfitting the multivariable analysis we were not able to add more variables such as operation technique. This also applies for the cox regression analysis where we adjust only for muscle invasiveness while variables such as older age, smoking and N+ stage may have influenced survival.

Finally, information on the long term cause of death was not available, which makes it impossible to distinguish between non cancer – and cancer related survival. However, frailty remained associated with one year mortality after adjustment of tumor stage in the cox regression analysis. Despite these limitations, this study showed a detailed overview of one year of experience in multidomain frailty screening and adds important information on risk prediction of frail patients undergoing radical cystectomy.

In conclusion, our study confirmed that frailty is common in patients undergoing radical cystectomy and strongly associated with severe complications and all-cause mortality. Preoperative frailty screening has the ability to improve risk stratification and may be used to guide patient selection for radical cystectomy. However, larger prospective trials are necessary to confirm our findings.

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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.

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

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.

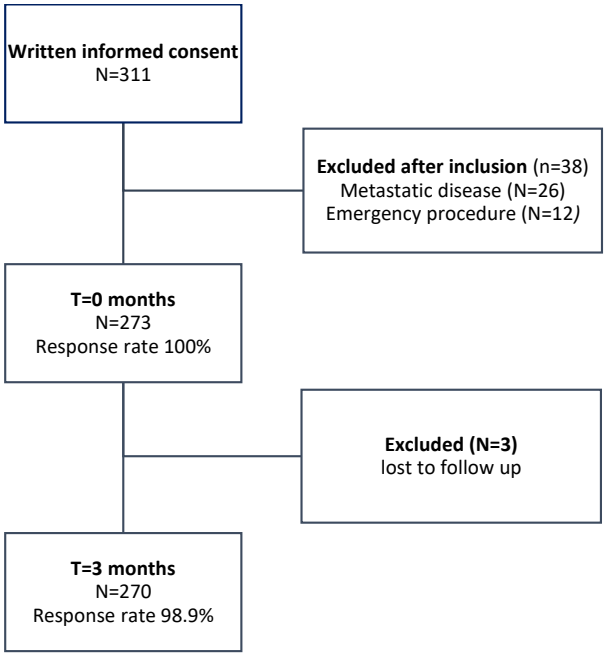

Figure 1. Flowchart of patient inclusion.

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.

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

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.

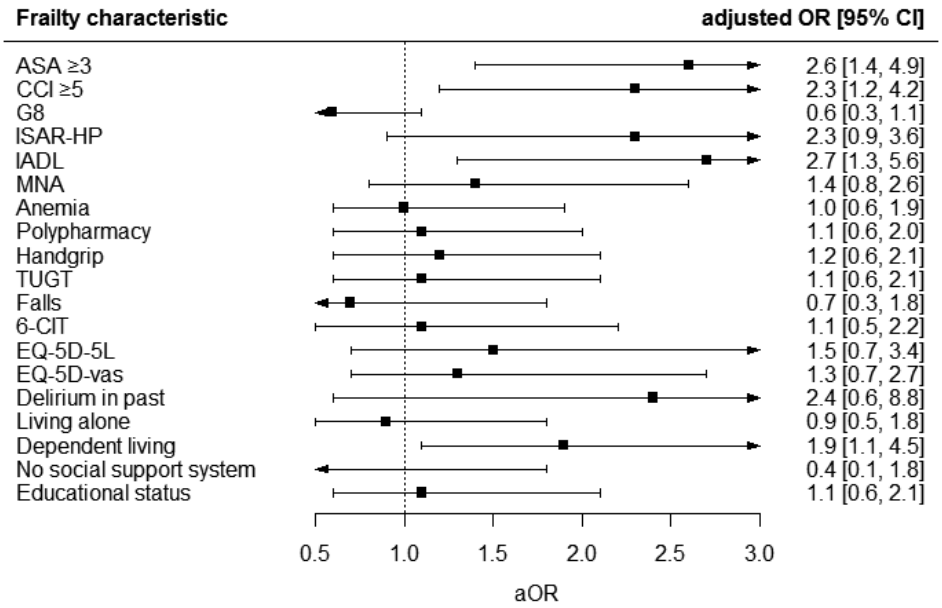

Figure 2. Frailty characteristics and decreased HRQL after three months. All characteristics were independently adjusted for gender, comorbidity, surgical approach and baseline HRQL.

*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

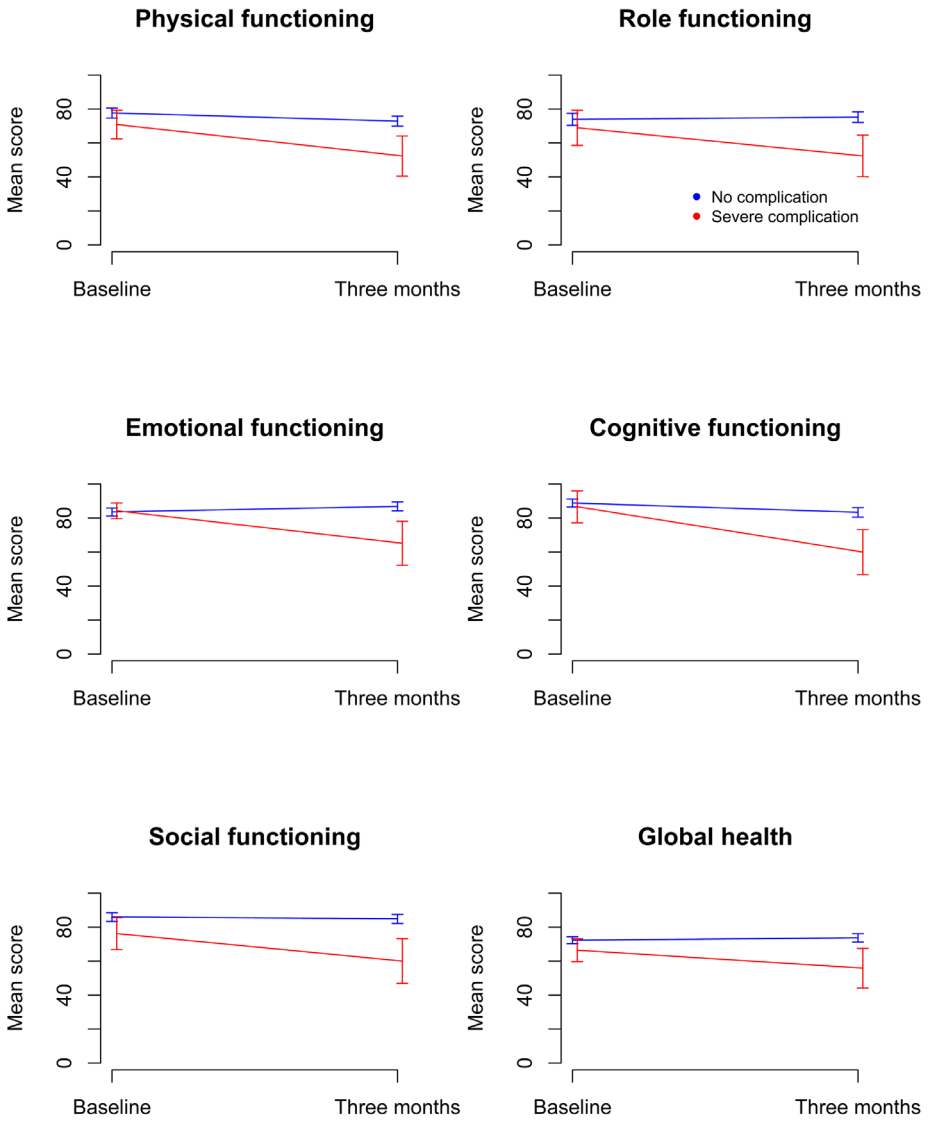

Figure 3. Function domains and summary HRQL score in patients with and without major complications, assessed with the EORTC-QLQ-C30 questionnaire. Results are presented in mean scores. All P-values are <0.01.

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

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

GENERAL DISCUSSION

GENERAL DISCUSSION

This thesis addresses current treatment strategies in older cancer patients, as well as the consequences of these decisions for clinical outcomes. In addition, this thesis investigated the value of frailty assessment in different cancer populations and described the implementation of a multidisciplinary team approach in frail older cancer patients.

In this final chapter, reflections on our findings are presented, placed in a broader perspective and recommendations for future research are given. The case presented in box 1 will be referred to throughout the discussion.

Box 1: clinical scenario
A 73-year old women with a history of diabetes mellitus type II, hypertension, chronic obstructive pulmonary disease gold III (COPD), atrial fibrillation, left ventricular ejection fraction of 30% and a transient ischemic attack was referred for a right sided hemicolectomy because of a symptomatic T3N1 colon carcinoma. The surgeon doubted whether she was fit for surgery. In order to obtain more information on her general health status and to aid in preoperative decision making, she was referred for a comprehensive geriatric assessment and multidisciplinary team (MDT) meeting. Geriatric assessment revealed a risk for malnutrition due to recent weight loss, slow gait speed and low grip strength. The patient used nine prescription drugs, including oxazepam twice daily for anxiety. Her physical complaints were abdominal pain and rectal blood loss. She lived alone, since her husband passed away three years ago. She used to play bridge three times a week at the local church. Since three months she spent most of her days inside her house watching television. She was unable to run her household, without the help of her two daughters. Cognitive screening revealed a mild cognitive impairment, which increased the risk of postoperative delirium. Laboratory results revealed a hemoglobin level of 6.4 mmol/l, ferritin 7ug/l and a glucose of 15.1 mmol/l (HbA1c 73 mmol/mol). The patient was very motivated to undergo surgery, but emphasized that independent living (good enough to play bridge and see her friends), without suffering from rectal blood loss and abdominal pain was most important.

Box 1: Continued

At the preoperative MDT meeting the pros and cons of surgery were carefully weighed. The risk of losing functional capacity and independency after surgery was considered high. The prehabilitation program consisted of exercise and respiratory muscle training, nutritional support and treatment with intravenous iron. A pulmonologist and internist were consulted to optimize treatment of COPD and diabetes. Anticoagulants were temporarily discontinued to reduce rectal bleeding and oxazepam use was tapered off by the general practitioner. After 4 weeks, rectal bleeding was largely reduced and the hemoglobin level was increased to 7.4 mmol/l. Her mobility and grip strength had improved and she resumed to play bridge. She gained two kilograms in body weight and her blood glucose curves were acceptable. Oxazepam use was limited to twice weekly, to help her cope with stress. After a reassessment by the MDT, the patient was considered fit for surgery, although the risk of adverse outcome remained high due to multiple chronic diseases. Despite non-pharmacological delirium prevention, surgery was complicated by a mild delirium. She stayed in hospital stay for 7 days after which she was discharged with home care. Her self-reported physical Health Related Quality of Life (HRQL) was better three months after surgery, but her mental HRQL was lower. Six weeks after surgery she played her first game of bridge again.

Anti-cancer treatment in older patients

In an ageing population the number of older patients that are diagnosed with cancer has increased.[1] The ageing of the population has a major impact on oncological care. One of the challenges in treating older cancer patients is their heterogeneity in multiple domains, including overall health, functional status, severity of comorbidities and presence of geriatric syndromes.[2,3] These characteristics increase the risk of adverse outcomes.[4–9] Anti-cancer treatment in older patients aims to improve survival while maintaining health related quality of life and daily functioning. Therefore, a careful consideration of treatment options regarding risks for adverse outcome versus survival gains are essential in order to make the right treatment decision. Risk stratification in older cancer patients is complicated because robust outcome data are currently lacking. Besides, acceptable risk varies greatly between patients.

In the past years, the development of a patient-centered treatment plan, including frailty characteristics, to optimize shared decision making and reduce adverse outcomes has gained interest.[10–12] Concurrently, different treatment strategies have been developed

to make cancer treatment more appropriate for the older population. If a treatment that is less harmful is preferred, it does not always mean that there are no treatment options. For instance, endoscopic resection of early stage tumors in colorectal cancer (CRC) patients, short-course radiotherapy with delayed or no surgery in rectal cancer patients, offering monotherapy chemotherapy instead of combination chemotherapy and bladder-sparing approaches such as (chemo)radiation in older bladder cancer patients.[4,13–15] The oncologic effect might not be as strong as the standard treatment, but the risk of adverse events will be less pronounced. An illustration of treatment changes in Dutch cancer patients is shown in **Chapter 2**. This population-based study in Dutch CRC patients aged 70 years and older showed that non-surgical treatment was more often performed over time. In 2014, 3.7% of colon cancer patients had non-surgical treatment compared to 4.8% in 2018. Similar results were shown in rectal cancer patients (17.1% vs 20.2%).

Furthermore, survival benefits were reported for rectal cancer patients treated with (chemo)radiotherapy compared to the no-treatment group, which implies that less invasive and harmful treatment options should be considered in frail older CRC patients. Current treatment decisions are often based on clinical judgement, because the evidence for evidence based medicine of anti-cancer treatment in older patients is lacking.[16] Consequently, treatment decisions vary between clinicians, resulting in a risk of over- or under treatment.[17] The results in **chapter 3** support the hypotheses of the possible risk of under treatment in Dutch older rectal cancer patients.[18] Although neoadjuvant chemoradiotherapy was well tolerated, a small proportion (9%) of patients was received this treatment.

Furthermore, treatment decision are often more complicated in older patients, because of a limited life expectancy, multiple comorbidities, geriatric impairments and a large variety in treatment goals (e.g. longevity, disability-free survival, satisfactory health related quality of life). Therefore, treatment decisions in geriatric oncology cannot depend on the clinical judgment of a single physician.[19,20] This is supported by our findings in **chapter 4**.[21] Half of the older patients who were examined by an experienced physician (oncologist/oncological surgeon) and considered fit for palliative chemotherapy, experienced grade 3 toxicity and/or needed treatment modifications. Apparently, clinical judgement by a single physician is not always sufficient to predict adverse outcomes in older patients. Understanding the influence of frailty on adverse outcomes in patients undergoing anti-cancer treatment is therefore essential in order to improve treatment decisions.

Frailty

Frailty is an age-related clinical syndrome that is commonly defined as a state of reduced functional capacity and occurs as a consequence of the cumulative decline in many physiological systems over a lifetime.[22] Frail patients are vulnerable for external stressors such as anti-cancer treatment (e.g. surgery, chemotherapy, radiotherapy). As older age and comorbidities are often associated with frailty, it seems reasonable to take frailty characteristics into account to improve treatment decisions in the growing cohort of older cancer patients.[23]

In this thesis frailty was evaluated in different older cancer populations. Geriatric impairments were highly prevalent in older Dutch cancer patients and were associated with adverse outcomes. One or more geriatric impairments were present in 71% of patients undergoing palliative chemotherapy **(Chapter 4)** and 45% of non-metastatic colorectal cancer (CRC) patients **(Chapter 5)**.[21,24] The incidence of one or more geriatric impairments was the highest (82.5%) in patients undergoing radical cystectomy **(Chapter 6)**.[25] In all of these studies frailty was associated with adverse outcome, including postoperative complications, worse survival and a clinically relevant deterioration in health related quality of life **(Chapter 4, 5, 6, 7)**.

These findings stress the importance to screen for geriatric impairments and incorporate frailty characteristics in anti-cancer treatment decision making. However, the implementation of frailty into routine oncologic care has been hampered. Frequently used arguments against use of a (comprehensive) geriatric assessment are that it is time and resource consuming. Besides that, the lack of consensus on the best instrument to diagnose frailty is another barrier. This thesis aimed to construct a comprehensive frailty model to aid decision making in Dutch older cancer patients. However, in our studies the associations between individual frailty characteristics and adverse outcomes were not uniform.

Of the physical frailty tests, the Timed to Get Up en Go test (TUGT) was associated with treatment modifications and grade 3 toxicities in older patients treated with palliative treatment **(Chapter 4).** Polypharmacy showed the strongest predictor in bladder cancer patients **(Chapter 6).**

And most important determinants for a decreased HRQL in CRC patients were comorbidity, impaired daily functioning and dependent living **(Chapter 7).**

There are several explanations for these different findings. First, frailty is not only dependent of an age-related decline. The cancer related burden of disease may induce 'cancer-related frailty'. As shown in box 1, the patient suffered from a bleeding

tumor resulting in anemia. This reduced gait speed, mobility and muscle strength. Consequently, the type of cancer and the cancer related symptoms likely affect the association between frailty characteristics and outcome. Another explanation could be that our selection of frailty questionnaires and tests may not reflect the full frailty status of the patient. Also the differences in anti-cancer treatment may influence the association between frailty and adverse outcomes. Finally, adverse outcomes such as complications, deterioration in HRQL and chemotherapy intolerance depend not only on frailty related factors.

Although the results are heterogeneous, frailty tests predict adverse outcomes **(Chapter 4, 5, 6, 7)**. This indicates that frailty screening and decision making in older patients demand a personalized approach. We advocate the implementation of a quick frailty screening in older cancer patients. Several two-stepped models have been described in literature, in which all patients undergo short simple frailty screening, and only those with abnormal test scores undergo a complete comprehensive geriatric assessment. For example, the G8 (Geriatric 8) and the 6-CIT (6 item Cognitive Impairment Test) have a good sensitivity for detecting geriatric impairments and for identifying the patients who will benefit from a complete comprehensive geriatric assessment.[26,27] This was confirmed in **Chapter 5**. Such frailty screening can categorise patients into 'non-frail' patients in with low chances of adverse events and 'frail' patients who have a higher risk. Subsequently, a complete risk profile including comorbidities, frailty characteristics and expectations/priorities of the frail patients should be constructed. Results of the complete risk profile should discussed in a MDT meeting. Similar to other medical specialties, a collaborative approach of multiple specialties in a MDT seems suitable in these complex patients.

The outcomes of de MDT meeting should be discussed with the patient and care-givers. In addition to improving risk assessment for adverse outcomes, frailty screening has the ability to facilitate targeted prehabilitation.

Prehabilitation

Prehabilitation, defined as a multimodal approach to enhance a patient's condition prior to treatment has gained interest over the past years. The objectives of prehabilitation are: to reduce adverse outcomes, to enhance and speed up recovery and to improve health related quality of life (HRQL). Prehabilitation is so intuitive that a layman might wonder why prehabilitation programs are scarcely present in daily practice. The answer to this question is twofold: there is a lack of evidence for behavioral interventions and it requires a multi-disciplinary collaboration which is often experienced as a logistical challenge.

The goal of anti-cancer treatment in older patients is to prolong life while maintaining their level of daily functioning and HRQL. However, the ability to endure anti-cancer treatment requires substantial physical and psychological resilience of the human body. Considering that frailty is a risk factor for adverse outcome, it seems reasonable to focus on prehabilitation in order to reduce adverse outcomes **(Chapter 5)**. Improving baseline functioning may even make oncological treatment feasible that appeared too risk full. Furthermore, anti-cancer treatment often comprises of different treatment steps. This is why prehabilitation during the complete treatment course to retain fitness is essential. For example, neoadjuvant chemoradiotherapy in rectal cancer patients may reduce physical fitness, which potentially results in the transition of a patient from low to high risk for postoperative complications.

Prehabilitation also provides an opportunity for patients to be involved in their health journey. Prehabilitation can shift the classic 'waiting period' to a time frame in which patients improve their health, and thus increase their chances on improved outcome. In the clinical example shown in box 1, the patient was motivated to improve her physical condition, not only to prevent postoperative complications but also to increase her activity level. In most studies, the time interval for prehabilitation is 4 to 8 weeks, with shorter time periods for patients with high burden of disease.

Short preoperative timeframes can be a problem. However, fitness improvements can be made in as little as 2 to 4 weeks.[28] As shown in box 1, after 4 weeks the patient experienced a better physical condition. As a results, she was able to walk to church and resume playing Bridge. This example illustrates that an personalised prehabilitation program targets the physical, mental and social domains.

In recent years, research on prehabilitation has received considerable attention which has resulted in a wide range of mixed results.[29–32] Prior studies focused on single modal programs often on nutritional status or exercise training. Most studies concluded an improvement in physical and nutritional status, but demonstrated no significant effect on the reduction of adverse outcomes.[33,34] However, considering the multifactorial origins of a patient's vulnerability, a multimodal approach combining nutritional support, exercise training, physiological support, smoking cessations and anemia correction, might be more effective. In this respect, a multidisciplinary team (MDT) approach, as shown in **Chapter 5**, is more likely to deliver a tailored prehabilitation program than an individual physician. **Chapter 5** demonstrates that MDT care, that includes a prehabilitation program, can lead to similar rates of postoperative complications in frail and non-frail CRC patients.

Health Related Quality of Life

Prolonging survival is usually considered the main goal of anti-cancer treatment. However, maintaining or even improving quality of life 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. Change in health related quality of life (HRQL) should ideally be discussed, in addition to survival and risk of complications, when considering anti-cancer treatment options.[35]

Studies on change in postoperative HRQL in surgical cancer patients show that most patients benefit from surgery, but a significant number of patients experience a decrease in HRQL after surgery.[36–39] **Chapter 7** reported the short term outcomes (3 months follow up) of the multicentre prospective AGE-CRC (Advanced Geriatric Evaluation-ColoRectal Cancer) study. Ultimately, this study aimed to identify determinants for a decreased HRQL at one year after CRC diagnosis. Our findings confirmed that three months after CRC diagnosis, a significant proportion of older patients experienced a decreased HRQL. Patients with a non-surgical approach and those who experienced severe postoperative complications were prone to experience a deterioration of short term HRQL. Most important determinants of decreased HRQL were comorbidity, impaired daily functioning and dependent living at time of CRC diagnosis.

An important finding is that most preoperative determinants, including frailty, were poorly associated with a deterioration in HRQL (**Chapter 7).** The causes of a deterioration of HRQL are multifactorial and can vary over time, which makes HRQL a complex outcome measurement. This makes prediction of deterioration in HRQL challenging. Patient reported outcome measures (PROMs) are susceptible to subjectivity. Survivors of cancer 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.[40] Furthermore, cognitive disorders can lead to difficulty with understanding HRQL questionnaires, comorbidity and frailty may have a larger impact on HRQL than cancer itself.

In addition, 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.[41,42] This concept is known as a response shift. For example, a patient may initially experience a worse mental HRQL after surgery. But, over time, the patient adapts and grows accustomed to the new circumstances and HRQL recovers to baseline. These variations in HRQL between and within patients, make predictions difficult and could partly explain the lack of associations with preoperative determinants.

Despite the difficulties in predicting HRQL, nowadays it is essential to implement such measurements not only in clinical trials, but also in the perioperative practice. HRQL assesses the impact of an intervention on a patient's life, rather than just their body or a single organ; information which is very relevant when counselling a patient on expected recovery.

Multidisciplinary team approach
Currently, most decisions regarding a treatment of cancer are first discussed in an oncological multidisciplinary team (MDT) meeting with the focus on the cancer diagnosis, rather than taking patients related factors such as frailty into account. Large differences in overall health and functional status, severity of comorbidities and presence of geriatric syndromes, raise the question of how to incorporate frailty screening and assessment in an oncological MDT meeting.

The increasing complexity of the management of older cancer patients and concerns of adverse outcomes demands accurate risk assessment.[43] Due to the absence of high-quality outcome data in frail patients, clinical consensus in the form of a MDT approach (experienced based medicine) may be the best available advice to guide patient selection for anti-cancer treatment **(Chapter 5)**. Older patients often suffer from multiple chronic diseases which demands a broader multidisciplinary approach. Similar to other medical specialties, a collaborative approach of multiple specialties in a MDT seemed suitable in these complex patients.

A MDT approach based on a geriatric assessment and patient preference can be beneficial in the development of a patient-centered treatment plan which is described in **chapter 5** of this thesis. **Chapter 5** showed that the implementation of such preoperative MDT care for frail patients with CRC improves risk stratification and prehabilitation, resulted in comparable short term outcomes for frail and non-frail patients.

Facilitators and barriers to the implementation of MDT care
With these goals in mind, a weekly MDT meeting in the St. Antonius Hospital for high risk surgical patients was set up in 2016. Prior to MDT meetings a comprehensive geriatric assessment is performed in patients to be discussed. The assessment includes tests or questionnaires in four domains **(Table 1, Chapter 5)**. During MDT meetings a team of dedicated (para)medical specialists including a medical and surgical oncologist, anesthesiologist, geriatrician, pharmacologist, physiotherapist, dietician and nurse specialist interpret pretreatment risk factors and construct a patient's tailored plan. The geriatric assessment can identify potentially modifiable risk factors. During the MDT meeting the following topics were addressed: indication of treatment, possible

less invasive treatment options, severity of comorbidities and frailty, burden of disease, expected prognosis with and without treatment, patient motivation, possibilities and time frame of prehabilitation. After the MDT meeting the treatment plan is discussed with the patient and care-givers by the treating specialist and nurse according to shared decision making principles.

Several benefits of MDT care for complex cancer patients are described above. Additional lessons can be learned from our experience. First, the implementation of a MDT approach demands a significant effort from every specialty. Time, preparation and attendance at MDT meetings is necessary in order to make optimal treatment decisions in complex cases. Second, accurate selection of high-risk patients to be discussed in MDT meetings is essential. Inappropriate referral may delay treatment in healthy patients in whom MDT involvement is redundant.

To limit the strain on available resources and prevent an unnecessary increase in patient burden, MDT care should be targeted at complex patients at high risk for adverse outcome. For example, the patient from the clinical example had multiple comorbidities and several impairments in frailty characteristics. As a result of the MDT meeting, her surgery was postponed and a prehabilitation program was considered and discussed with the patient. Her physical condition, nutritional status, anemia, COPD, diabetes mellitus and polypharmacy were optimised. The postsurgical course was only complicated by a mild delirium.

Anti-cancer treatment might be postponed when a prehabilitation program is advised. Ideally, patients must start their anti-cancer treatment within short time after diagnosis, because delaying this treatment can have major consequences such as the increase cancer related symptoms or the risk of tumor progression.

Last, to limit the increasing workload of physicians, standardized frailty screening tests as preparation for the MDT can be done by trained nurses. Although for a group of older patients with complex multi-morbidity, cognitive disorders or comprehensive geriatric syndromes a full comprehensive geriatric assessment by a geriatrician should be performed.

FUTURE DIRECTIONS

Individualization is critical in the heterogeneous population of the older patients with cancer; one size does not fit all. Clinical consensus in the form of a MDT approach may be the best available advice for optimal cancer care in frail older patients. The findings of this thesis and the clinical experiences with the MDT meetings lead to the following considerations on development of clinical research for these patients and opportunities for clinical improvement.

Frailty characteristics are important when making treatment decisions in older cancer patients. A two-step frailty assessment that consists of a quick screening and more thorough assessment on indication seems logical. Future research should focus on these two-step models. Frailty characteristics should be reported systematically in clinical studies on cancer treatment in older patients. In trial designs frail older patients with multiple comorbidities are often excluded from participation, resulting in a limited generalizability of the results. Therefore, to increase the number of older cancer patients and to avoid selection bias of fit older patients participating in large trials, studies should be conducted differently. For instance, by applying less stringent exclusion criteria, development of specific trials for older patients and making studies more accessible for older patients. An additional practical solution is to do research visits at home as we have done in the AGE-CRC study, so older patients are more willing to participate. Willingness to participate can further be increased by incorporating research activities during routine hospital visits, and by providing follow up by telephone. When studying diseases in older patients, collaboration with other hospitals is essential. To perform studies in older CRC patients participation in the Prospective Dutch Colorectal Cancer Cohort (PLCRC) project will be helpful.[44] In this project systematic registration and collection of data is facilitated.

Offering all patients a 'one-size fits all' intervention fails to take individual needs into account which can lead to low compliance. However, each part of the prehabilitation program (e.g. nutrition or physical activity) needs to be standardized. Subsequently, data of all patients should be systemically collected to contribute to real world evidence.

The lack of evidence for MDT care in frail patients is a restricting factor for its implementation in standard care. Studies comparing MDT care with regular care are needed to assess potential benefits on adverse events and PROMs. A solution to add to evidenced based medicine in MDT care is to use a multi-centre and step-wedge design. Each centre includes a part of the control group, then implements the intervention and includes the intervention group. This reduces bias caused by changes in health care and contamination bias.

The following opportunities for daily clinical practice should be considered; first of all, careful patient selection is necessary for MDT care, otherwise it is too costly and time consuming. Using the G8 and 6-CIT questionnaires for patient selection seems appropriate and resulted in an average referral of two CRC patients a week for MDT care in our centre with 250 CRC surgeries annually.

Second, a complete risk profile of the patients is needed to facilitate a profound discussion during MDT meetings and during shared decision making with the patient. Regardless of the frailty assessment of choice, it is essential to evaluate the somatic problems of the patient, and to obtain information about the other three (physical, mental and social) main geriatric domains. These assessments need to be performed prior to the MDT meeting. Third, patient reported outcomes should be measured before and after anti-cancer treatment. Important outcome measures in older patients such as HRQL can be measured using PROMs. Yet PROMs are not structurally incorporated in clinical practice and the large amount of disease specific questionnaires might counteract compliance in patients with multimorbidity. These outcomes should be measured with validated tools from a perspective that matters to the patients and that is relevant to the intervention.

A solution could be one standard set of PROMs specific for older patients and their disease. It is important that the most sensitive PROM is selected for each disease and double questions are avoided. For instance, the International Consortium for Health Outcomes Measurements (ICHOM) assembled an international working group of health professional and patients representatives to develop a standardized minimum set targeted for clinical use.[45] [46] The effect of treatment on HRQL should be discussed and used in counselling patients.

Last, the general practitioner (GP) should be invited to participate in the MDT when their own patient is discussed. In complex cases, the GP can provide information on the patient's personal and social history, which is important to ensure that the MDT treatment proposals are in line with the patient's needs and wishes. In this way, the GP can be involved in drafting the personal treatment plan and may participate in shared decision making, monitoring prehabilitation programs or advanced care planning.

This thesis described several steps to improve treatment decisions and prehabilitation in older cancer patients. It provides new understandings on frailty in older cancer patients. Findings from this thesis could be used to design new studies in older cancer patients and inspire to further improve care for older cancer patient using MDT care.

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APPENDIX

SUMMARY

SUMMARY

The ageing of the population has a major impact on oncological care. In an ageing population the number of older patients diagnosed with cancer has increased. One of the challenges in treating older cancer patients is their heterogeneity in multiple domains, including overall health, functional status, severity of comorbidities and presence of geriatric syndromes. These characteristics increase the risk of adverse outcomes. This thesis addresses current treatment strategies in older cancer patients, as well as the consequences of these decisions for clinical outcomes. In addition, this thesis discussed the value of frailty assessment in different cancer populations and described the implementation of a multidisciplinary team approach in frail older cancer patients.

Surgery is the primary treatment for non-metastatic colorectal cancer (CRC) but is omitted in a proportion of older patients. Characteristics and prognosis of non-surgical patients are largely unknown. Therefore, in **Chapter 2** we investigated the characteristics and survival of surgical and non-surgical older patients with non-metastatic CRC in the Netherlands between 2014 and 2018. In total, 987/20.423 (5%) colon cancer patients and 1.459/7.335 (20%) rectal cancer patients did not undergo surgery. Non-surgical treatment in older Dutch CRC patients has increased over time despite a poor prognosis. Because survival of patients with colon cancer is very poor in the absence of surgery, this treatment decision must be carefully weighed. In rectal cancer patients there are alternative treatment options. The prognosis of patients treated with alternative treatments such as (chemo)radiotherapy were better compared to patients without any treatment. Therefore, (chemo-)radiotherapy may be a good alternative for rectal cancer surgery in older frail patients.

In the past decades, substantial progress has been made in cancer treatment. An example of these improvements is the efficacy of neoadjuvant chemoradiotherapy (nCRT) resulting in a lower risk of developing a local recurrence in patients with locally advanced rectal cancer. However, since older patients are frequently underrepresented in clinical trials, it is unclear whether older patients benefit from these improvements. This led to our research in **Chapter 3** where the tolerability of nCRT with capecitabine and the surgical outcomes in older patients diagnosed with locally advanced rectal cancer were investigated. In this retrospective multicentre study of 1372 CRC patients, 9% of the patients were treated with nCRT of whom 95% underwent surgery. The results showed that nCRT is safe and well tolerated. No negative effect on surgical outcome was measured, and the beneficial effect (pathologic complete response, disease free survival and overall survival) were comparable to those in younger age groups. The results suggest that older patients should not be excluded from nCRT based exclusively on age.

No tools accurately discriminate between older patients who are fit enough and those who are too frail to tolerate systemic palliative chemotherapy. **Chapter 4** describes a multicenter prospective study investigating whether domains of geriatric assessment are associated with increased risk of chemotherapy intolerance in 99 patients who were considered fit to start palliative chemotherapy after clinical evaluation by their treating clinician. The results show that half of the patients who were considered fit to start palliative systemic chemotherapy required treatment modifications and/or experienced grade 3 treatment related toxicity during the first three cycles of treatment. One or more geriatric impairments were present in 71% of patients and 32% of patients were frail in two or more domains. Of all investigated geriatric domains, only an impaired timed to get up and go test (TUGT) was associated with a three times increased risk of chemotherapy intolerance. This research suggest that the clinical judgment may not sufficient to predict adverse outcomes and a frailty assessment should be considered.

The increasing complexity of the management of older cancer patients and concerns of adverse outcomes demand accurate risk assessment. Due to the absence of high-quality outcome data in frail patients, clinical consensus in the form of a multidisciplinary team (MDT) approach (experienced based medicine) may be the best available advice to guide patient selection for anti-cancer treatment. **Chapter 5** shows the results of the implementation of MDT care between 2015-2018 for frail older patients with CRC on preoperative decision making and postoperative outcomes. In this historical cohort study 466 patients were included. One hundred and forty six (31.3%) frail patients were referred for MDT evaluation. Based on the results of this study, implementation of MDT care can be used to improve the management of frail older patients with CRC, including shared decision making and tailored perioperative care including prehabilitation. This leads to favorable postoperative outcomes in frail patients despite an increased preoperative risk.

MDT care was also implemented for patients undergoing radical cystectomy. This led to our study described in **chapter 6** where the value of preoperative frailty screening in predicting postoperative severe complications and 1-year mortality in 63 patients undergoing radical cystectomy was investigated. Frailty was commonly present (61.9%) and associated with a seven-fold increased risk of severe postoperative adverse outcomes, including one year mortality. Furthermore, preoperative frailty screening improved risk prediction for severe complications or death one year after surgery, and could be useful for preoperative shared decision making in patients scheduled for radical cystectomy.

Prolonging survival is usually considered the main goal of anti-cancer treatment. However, maintaining or even improving quality of life can be equally important, especially in older patients who have shorter life expectancy in comparison with younger patients and may be less willing to exchange current quality of life for longevity. In **Chapter 7** the short term outcomes (3 months follow up) of the multicentre prospective AGE-CRC (Advanced Geriatric Evaluation-ColoRectal Cancer) study are reported . We show that 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 are prone for a decreased HRQL. Most important determinants of decreased HRQL were comorbidity, impaired daily functioning and dependent living at time of CRC diagnosis. The results of this study highlight the importance of identifying those patients at risk for postoperative complications and advocate a targeted routine assessment of preoperative frailty.

To place the findings of the research presented in this thesis in a wider context **Chapter 8** provides a reflection on our results and offers recommendations for clinical care and further research.

APPENDIX

NEDERLANDSE SAMENVATTING

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In de vergrijzende samenleving neemt het aantal ouderen dat gediagnosticeerd wordt met kanker toe. Dit heeft een grote impact op de zorg voor kankerpatiënten. Een aanzienlijk deel van deze oudere kankerpatiënten is namelijk kwetsbaar, waardoor het risico op sterfte, complicaties en/of functionele achteruitgang na de behandeling toeneemt. Dit proefschrift beschrijft de huidige behandelstrategieën bij de oudere kankerpatiënt, evenals de gevolgen van behandel beslissingen voor klinische resultaten. Daarnaast onderzoekt dit proefschrift wat de waarde van kwetsbaarheidsscreening is in verschillende kankerpopulaties en beschrijft het de implementatie van een multidisciplinaire benadering bij de kwetsbare, oudere kankerpatiënten.

Chirurgie is de belangrijkste behandeling om niet-uitgezaaide darmkanker te genezen. Bij een gedeelte van de oudere darmkankerpatiënten wordt van een operatie afgezien, vaak omdat de overlevingswinst niet opweegt tegen de mogelijke negatieve effecten van de operatie, zoals ernstige complicaties of verlies van kwaliteit van leven. In **hoofdstuk 2** onderzochten we de karakteristieken en overleving van geopereerde en niet-geopereerde patiënten ≥70 jaar in Nederland die tussen 2014 en 2018 werden gediagnosticeerd met niet-uitgezaaide darmkanker. In totaal werd 5% van de dikke darmkankerpatiënten en 20% van de endeldarmkankerpatiënten niet geopereerd. Over de jaren heen en met toename van leeftijd werd er vaker afgezien van een operatie. Niet-geopereerde patiënten met dikke darmkanker hadden een zeer slechte prognose; dit maakt een goed afgewogen beslissing om niet te opereren van groot belang. Bij patiënten met endeldarmkanker zijn er alternatieve behandelingen mogelijk zoals bestraling, al dan niet in combinatie met chemotherapie. Deze behandelingen gaven een betere prognose ten opzichte van helemaal geen behandeling en zouden een goed alternatief kunnen zijn als patiënten te kwetsbaar zijn voor een operatie.

In de afgelopen decennia is een aanzienlijke vooruitgang gemaakt in de behandeling van kanker. Een voorbeeld van deze verbetering is het gebruik van neoadjuvante chemoradiotherapie (chemotherapie en bestraling voor de operatie) bij patiënten met lokaal gevorderd endeldarmkanker. Dit wordt toegepast om de kans op een recidief na de behandeling te verkleinen. Aangezien oudere patiënten vaak ondervertegenwoordigd zijn in wetenschappelijke onderzoeken, is het onduidelijk of zij ook baat hebben bij deze vooruitgang. Het is algemeen bekend dat er vaker wordt afgezien van deze behandeling bij oudere patiënten, voornamelijk vanwege de angst voor bijwerkingen. Dit leidde tot het onderzoek dat beschreven staat in **hoofdstuk 3**. Van de 1372 oudere patiënten werd 9% behandeld met deze behandeling, van wie 95% daarna een operatie onderging. De resultaten toonden aan dat de voorbehandeling met chemotherapie en bestraling goed

werd verdragen. Het aantal complicaties en de overleving was vergelijkbaar met jongere leeftijdsgroepen. Deze resultaten suggereren dat oudere patiënten niet uitsluitend op basis van leeftijd mogen worden uitgesloten van deze behandeling.

Er zijn geen instrumenten die nauwkeurig onderscheid maken tussen oudere patiënten die fit genoeg zijn om een kankerbehandeling te ondergaan en patiënten die te kwetsbaar daarvoor zijn. In **hoofdstuk 4** werd onderzocht of kwetsbaarheidskenmerken geassocieerd zijn met een verhoogde risico op palliatieve chemotherapie intolerantie bij 99 oudere patiënten die fit genoeg werden geacht door hun behandeld arts om de behandeling te ondergaan. De resultaten toonden aan dat de helft van de patiënten ernstige bijwerkingen ervaarde of een aanpassing kreeg in het behandelplan. Driekwart van de patiënten was kwetsbaar op tenminste één domein. Van alle onderzochte kwetsbaarheidskenmerken was de Timed Up and Go Test geassocieerd met een driemaal verhoogd risico op chemotherapie intolerantie. Dokters moeten niet alleen op hun klinische blik varen, maar ook kwetsbaarheidskenmerken laten meewegen in hun behandelbeslissingen.

De toenemende complexiteit van de behandeling bij oudere kankerpatiënten door de verhoogde kans op nadelige gevolgen vraagt om een nauwkeurige risico inschatting. Vanwege het ontbreken van hoogwaardig wetenschappelijk bewijs bij kwetsbare patiënten, kan klinische consensus in de vorm van een multidisciplinaire benadering zorgen voor een gepersonaliseerd behandeladvies. **Hoofdstuk 5** toont de resultaten van de implementatie van multidisciplinaire zorg voor kwetsbare ouderen met darmkanker tussen 2015 en 2018 in het St. Antonius Ziekenhuis. In deze studie werden 466 patiënten geïncludeerd, waarvan een derde verwezen werd voor de multidisciplinaire aanpak. Deze patiënten werden uitgebreid op kwetsbaarheid gescreend en vervolgens werden deze resultaten besproken in een multidisciplinair overleg. De postoperatieve uitkomsten bij de kwetsbare patiënten waren vergelijkbaar met de niet-kwetsbare groep, ondanks dat de kwetsbare groep een verhoogd risico had op slechtere uitkomsten. De resultaten van de studie suggereren dat de behandeling, inclusief gedeelde besluitvorming, gepersonaliseerde zorg rondom de operatie en prehabilitatie door deze aanpak de zorg voor kwetsbare ouderen verbeteren.

Deze multidisciplinaire aanpak werd ook geïmplementeerd voor patiënten met een indicatie voor het verwijderen van de blaas (radicale cystectomie). **(Hoofdstuk 6)** Alle 63 patiënten die in 2017 een indicatie hadden voor het verwijderen van de blaas in het St. Antonius Ziekenhuis werden verwezen voor de kwetsbaarheidsscreening en multidisciplinaire aanpak. Kwetsbaarheid kwam veel voor (61.9%) en was geassocieerd met een zevenvoudig verhoogd risico op ernstige postoperatieve complicaties en/

of 1-jaars overlijden. Bovendien verbeterde de kwetsbaarheidsscreening de risico inschatting voor ernstige complicaties inclusief 1-jaars overlijden. Deze studie impliceert dat een kwetsbaarheidsscreening nuttig kan zijn in de besluitvorming voor het verwijderen van de blaas.

Het verlengen van het leven wordt meestal beschouwd als het belangrijkste doel van kankerbehandeling. Het behoud of zelfs het verbeteren van de kwaliteit van leven kan echter net zo belangrijk zijn. Vooral bij oudere patiënten die bij voorbaat al een slechtere levensverwachting hebben in vergelijking met jongere patiënten. Deze patiënten zijn vaak minder bereid de huidige kwaliteit van leven in te ruilen voor een langer leven met mogelijk verminderde kwaliteit van leven. **Hoofdstuk 7** beschrijft de korte termijnresultaten (3 maanden follow up) van de AGE-CRC (Advanced Geriatric Evaluation-ColoRectal Cancer) studie. De resultaten laten zien dat kwetsbaarheidskenmerken veel voorkomen bij oudere patiënten op moment van darmkanker diagnose, maar niet sterk geassocieerd zijn met een verminderde kwaliteit van leven 3 maanden na de diagnose. Niet-geopereerde patiënten en patiënten met complicaties na de operatie hebben het grootste risico op verlies van kwaliteit van leven. De belangrijkste factoren die waren geassocieerd met verminderde kwaliteit van leven waren comorbiditeit (bestaande ziekten) en niet zelfstandig zijn in het dagelijks leven op het moment van diagnose. Deze studie laat zien dat het voorspellen van complicaties belangrijk is voor de kwaliteit van leven op korte termijn.

Concluderend beschrijft dit proefschrift verschillende stappen om behandelbeslissingen bij ouderen kankerpatiënten te verbeteren. Daarnaast biedt het nieuwe inzichten over kwetsbaarheid bij deze oudere populatie. De bevindingen uit dit proefschrift kunnen worden gebuikt om nieuwe studies bij oudere kankerpatiënten te ontwikkelen, en is een inspirator om de zorg voor oudere kankerpatiënten verder te verbeteren met behulp van een multidisciplinaire benadering waarin kwetsbaarheidskenmerken en kwaliteit van leven centraal staan.

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LIST OF PUBLICATIONS

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van der Vlies E, Jacobs L, Ten Bokkel Huinink D, Bloemendal H, Intven M, Smits AB, Weusten BLAM, Siersema PD, van Lelyveld N, Los M
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Ned Tijdschr Oncol 2014;11:92-99.

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LIST OF ABBREVIATIONS

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5-FU	5-fluorouracil
6-CIT	6 Item Cognitive Impairment Test
ACS	American College of Surgeons
ADL	Activities of Daily Living
AGE	Antonius Geriatric Evaluation
AGE-CRC	Advanced Geriatric Evaluation – ColoRectal Cancer
aOR	Adjusted odds ratio
APR	Abdominoperineal Resection
ASA	American Society of Anesthesiologists
BRP	Personal Records Database
CARG	Cancer and Aging Research Group
CCI	Charlson Comorbidity Index
CD	Clavien Dindo
CI	Confidence Interval
DPD	Dihydropyrimidine dehydrogenase
CRASH	Chemotherapy Risk Assessment Scale for High-age Patients
CRC	Colorectal cancer
CTC-AE	Common Terminology Criteria for Adverse Events
DFS	Disease free survival
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	The EuroQol (European Quality of Life) Five dimension level scale
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire of Cancer patients
G8	Geriatric 8
GA	Geriatric Assessment
GDS- 15	15 item Geriatric Depression Scale
GP	General Practitioner
Gy	Gray
HR	Hazard ratio
HRQL	Health Related Quality of Life
IADL	Instrumental Activities of Daily Functioning
ICHOM	International Consortium for Health Outcomes Measurements
ICU	Intensive Care Unit
IKNL	Dutch Comprehensive Cancer Centre
ISAR-HP	Identification of Seniors at Risk for Hospitalized Patients
IQR	Interquartile Range
LAR	Low Anterior Resection

LARC	Locally Advanced Rectal Cancer
MD	Mean Difference
MDT	Multidisciplinary Team
MEC-U	Medical Research Ethics Committees United
MM	Multiple myeloma
MMSE	Mini Mental State Examination
MNA	Mini Nutritional Assessment
MRI	Magnetic Resonance Imaging
NHL	Non-Hodgkin Lymphoma
nCRT	Neoadjuvant chemoradiotherapy
OR	Odds ratio
OS	Overall survival
pCR	Pathological complete response
PLCRC	Prospective Dutch Colorectal Cancer cohort
Profiles	Patient Reported Outcomes Following Initial Long term treatment and Survivor Ship
PROMs	Patient reported outcome measures
RedCAP	Research Electronic Data Capture
RCRI	Revised Cardiac Risk Index
RDI	Relative Dose Intensity
RS	Relative Survival
SD	Standard deviation
SE	Standard Error
SF-12	Short Form 12
SPSS	Statistical Package for the Social Sciences
TME	Total Mesorectal Excision
TUGT	Timed to Get up and Go Test

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DANKWOORD

DANKWOORD

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CURRICULUM VITAE

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Ellen van der Vlies was born on April 12th 1990 in Eindhoven, the Netherlands. She grew up in Son en Breugel, where she attended high school (Bisschop Bekkers college, Eindhoven) and graduated in 2008. She started medical school at Utrecht University and obtained her medical degree in 2015.

Her interest in research developed in the last year of medical training during a science internship under supervision of Dr. M. Los. After graduation she started her training in Internal Medicine at the St. Antonius Hospital in Nieuwegein under supervision of Dr. A.B.M. Geers and Dr. P.Chr. de Jong. In 2017 she started with her PhD trajectory under supervision of Dr. M. Los, Dr. P.G. Noordzij and Prof. Dr. W.J.W. Bos. After careful consideration she switched career. In September 2020 she started the internship in Utrecht to become general practitioner.