The treatment of elderly patients with colorectal cancer

THE TREATMENT OF ELDERLY PATIENTS WITH COLORECTAL CANCER

A STEP TOWARDS PERSONALISED MANAGEMENT

STIJN H.J. KETELAERS

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A step towards personalised management

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ISBN:	978-94-6483-150-4
Cover design:	Stijn H.J. Ketelaers & Publiss | www.publiss.nl
Lay-out:	Publiss | www.publiss.nl
Print:	Ridderprint | www.ridderprint.nl

Printing of this thesis was financially supported by the Catharina Hospital, Maastricht University, PAJUNK® Medical Produkte GmbH, Interactive Studios, ABN Amro, Nutricia Nederland B.V., MCI Switzerland, Congress Care, Medireva, and Coloplast

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PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Pamela Habibović
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op woensdag 5 juli 2023 om 13.00 uur

door

Stijn Henricus Johannes Ketelaers
geboren op 2 mei 1997 te Nederweert

Promotor
Prof. dr. H.J.T. Rutten

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CHAPTER 1

Introduction and thesis outline

INTRODUCTION

Prevalence of colorectal cancer in the elderly

Worldwide, colorectal cancer is the third most common cancer diagnosis, with more than one million new cases each year.[1] In the Netherlands, colorectal cancer is accounting for about 12.000 to 14.000 new diagnoses, and constitutes for 4.000 to 5.000 deaths each year.[2] Approximately one third of colorectal cancer diagnoses are located in the rectum. Colorectal cancer is mainly a disease of the older population, and its prevalence increases with older age.[2] More than 50% of patients diagnosed with colorectal cancer are above 70 years of age, while more than 40% even exceeds the age of 75 years.[2,3] Due to the increased life expectancy, the proportion of elderly patients with colorectal cancer will probably increase over the coming years (Figure 1).[4] Hence, clinicians will be confronted more frequently with the challenges of managing colorectal cancer in the elderly patient.

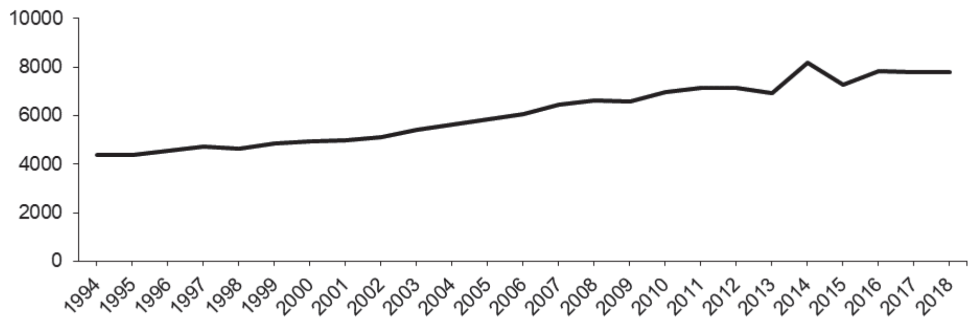

Figure 1. Incidence of colorectal cancer in the Netherlands in patients aged 70 years or older, by year of diagnosis. *Source: Netherlands Cancer Registry (NCR), IKNL.*

Comorbidity and frailty in the elderly population

Although older age is not directly interchangeable with the presence of comorbidities and frailty, their prevalences increase with older age.[5,6] Over 60% of patients aged 70 years or older suffer from at least 2 comorbidities, which rises to almost 80% in patients above 80 years of age.[6] Common comorbidities within the elderly population are hypertension (22%), cardiac (19%) and pulmonary (10%) diseases, and diabetes mellitus (11%).[7] Certain comorbidities are associated with a reduced tolerability for treatment, and an increased risk for postoperative morbidity and mortality.[8,9]

The prevalence of frailty is highly variable among literature due to differences in the used definitions. A recent meta-analyses reported that 42% of the elderly population with cancer suffered from some form of frailty, whereas individual studies reported varying frailty rates between 8% and 86%.[10] Frailty comprises a multidimensional concept, incorporating physical and psychosocial factors that synergistically contribute to the onset and progression of frailty.[5] Common factors that contribute to frailty are advanced age, the presence of multimorbidity, malnutrition, cognitive impairment, dependence in activities of daily living, and polypharmacy.[5] Frailty is characterised by a decline in functional reserve capacity across multiple physiological systems, resulting in a diminished capacity to deal with stressors.[5,11] As a result, frailty is associated with an increased risk of poor treatment outcomes, including morbidity, mortality, impaired quality of life, and functional decline.[5,12,13]

Treatment of colorectal cancer in the elderly patients

Surgery is considered as the cornerstone of the curative management of colorectal cancer. Over the last decades, developments in the treatment of colorectal cancer have resulted in improved long-term oncological outcomes.[14,15] However, the treatment of colorectal cancer has its drawbacks. Colorectal surgery is associated with morbidity, mortality, and impaired functional outcomes (e.g. bowel and urogenital dysfunction), especially in the elderly population.[16,17] Moreover, in particular in rectal cancer patients, neoadjuvant (chemo) radiotherapy may induce additional toxicity.[18] Previous studies have shown that elderly patients with colorectal cancer faced significantly increased 30-day and 1-year postoperative mortality rates when compared to younger patients, predominantly caused by treatment-related mortality.[16,19–21] Within the elderly population, one-year postoperative mortality rates up to 20-30% have been reported.[16,20] These outcomes have resulted in a tendency to withdraw elderly patients from intensive treatment regimens due to comorbidities or older age.[16,22–25] Population-based data showed that approximately 20-30% of the older population did not undergo surgery, which increased to over 50% in those older than 80 years.[24,25] Elderly patients face a risk of undertreatment. However, due to developments in the perioperative care of colorectal cancer, it is likely that the outcomes of elderly patients have improved, and that previous literature no longer reflects current clinical practice.[25]

Challenges in the treatment of elderly patients

Since elderly patients are often excluded in clinical trials, the treatment guidelines are generally based on evidence in young and fit patients, and may therefore not incorporate optimal recommendations for treating the elderly.[25] In addition, the elderly are a heterogeneous population, varying from very fit patients without any comorbidities, to severely frail patients who suffer from multimorbidity and completely depend on their caregivers.[11] The absence of data, along with the heterogeneity in the elderly population, increases the risk of undertreatment and overtreatment.[25] Elderly patients frequently prioritise quality of life and functional outcomes over oncological and survival-related outcomes, which further affects the complexity of decision-making.[26] Careful patient selection and actively involving the patient in the decision-making process is required to personalise the treatment of the elderly patient.[25] The first step to improve and personalise care would be to gain insights into the treatment outcomes of elderly patients. The next step would be to optimise patient selection, improve the perioperative care for elderly patients who undergo surgery, and explore non-operative treatment alternatives for elderly patients who prefer organ preservation or who are unable to undergo surgery.

AIM OF THIS THESIS AND THESIS OUTLINE

The aim of this thesis was to gain insights into the treatment outcomes of elderly patients with colorectal cancer, in an effort to increase shared decision-making, and further improve and personalise the treatment of elderly patients with colorectal cancer. This thesis is divided into three parts. The first part of this thesis focuses on the treatment outcomes of elderly patients. The second part focuses on improving and personalising the care for elderly colorectal cancer patients. The third part presents a summary of this thesis, a general discussion, future perspectives, and an impact paragraph.

Part I: Treatment outcomes of elderly patients with colorectal cancer

Postoperative morbidity and mortality

Previous studies have shown that postoperative mortality rates were significantly increased in elderly patients.[20] However, elderly who survived the first postoperative year had comparable cancer-related survival outcomes as younger patients.[20] Efforts have been made to improve perioperative care and reduce mortality in the first postoperative year.[25] To evaluate whether these developments have improved the outcomes of elderly patients after surgery, **chapter 2** presents a single centre, retrospective cohort study. The study evaluated the changes in postoperative morbidity and mortality over time in patients with colorectal cancer, stratified for elderly and younger patients.

The treatment of locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) requires intensive regimens of neoadjuvant (chemo)radiotherapy to downstage the tumour, often followed by extended, multivisceral rectal cancer resections. These major resections are associated with high rates of morbidity and mortality, in particular in the elderly population. **Chapter 3** presents a single centre, retrospective cohort study to investigate whether the developments over time in perioperative care have improved the postoperative outcomes of elderly patients with primary clinical T4 rectal cancer or LRRC.

Functional outcomes, quality of life, and ostomy-related outcomes

The elderly population frequently considers quality of life and functional outcomes as the most important treatment outcomes.[3,26] Adequately counselling patients about the different treatment options and their influence on functional outcomes and quality of life is crucial.

The Low Anterior Resection Syndrome (LARS) is a functional outcome that is associated with quality of life, and frequently arises after colorectal surgery.[27,28] LARS consists of a cluster of functional bowel complaints (e.g. faecal incontinence, urgency). While earlier studies have mainly reported functional bowel complaints after rectal surgery, more recent studies described that functional bowel complaints may also arise after colon surgery.[29] In **chapter 4**, the prevalence of functional bowel complaints and the impact on quality of life in elderly patients after colorectal cancer surgery is investigated in a multicentre, retrospective study.

Especially in patients with rectal cancer, attention should be paid for ostomy-related outcomes. If a primary anastomosis is performed to restore bowel continuity after a low anterior resection, a temporary diverting ostomy may be created to reduce the morbidity associated with anastomotic leakage. However, a diverting ostomy is associated with a risk of ostomy-related complications and non-reversal. In **chapter 5**, the outcomes on diverting ostomy formation and reversal in the elderly population with more advanced rectal cancer are evaluated in a single centre, retrospective cohort study.

Part II: Towards improved care in elderly patients with colorectal cancer

Patient selection and perioperative care

Chapter 6 presents a narrative review to discuss the developments that have been taken place in colorectal cancer care over the last decades and their influence on the outcomes of elderly patients. With growing evidence that most elderly patients can safely undergo curative treatment regimens, there is a need for clarity about areas that require additional attention during the treatment of elderly patients. The chapter discusses certain elements that may contribute to better patient selection and improved treatment of elderly patients with colorectal cancer, including frailty screening and frailty assessment, preoperative patient optimisation, and programmes to deal with specific tumour-related problems (e.g. bowel obstruction).

Adequate patient selection is important to optimise treatment. Frailty screening and assessment is performed to distinguish fit patients, who can be treated with standard approaches, from frail patients, who may benefit from adapted care. In **chapter 7**, a single centre, retrospective cohort study is presented to investigate the postoperative outcomes of elderly patients screened positive for frailty, and to evaluate changes in treatment after frailty screening and geriatric assessment.

The implementation of Enhanced Recovery After Surgery (ERAS) protocols have contributed to improved postoperative outcomes after colorectal cancer surgery. Adequate pain control is an important element, but is often achieved by opioids.[30] Unfortunately, opioids are associated with delayed recovery and opioid-related side effects (e.g. postoperative delirium, cognitive impairment), especially in the elderly.[30,31] **Chapter 8** comprises a multicentre, prospective observational cohort study to investigate continuous wound infusion of local analgesics as an adjunct to multimodal pain management within an ERAS protocol, in an effort to reduce opioid consumption and enhance postoperative recovery.

Given the benefits of ERAS, it is likely that ERAS protocols may also mitigate the impact associated with extended, beyond total mesorectal excision (TME) surgery in LARC and LRRC patients. However, due to the intensive treatment and extensive surgery, the implementation of, and compliance to ERAS protocols seems more challenging in patients who undergo beyond TME surgery for LARC and LRRC when compared to patients who undergo TME surgery. Specific modifications to the ERAS protocol seem warranted to suit the complexity and needs of patients who undergo beyond TME surgery for LARC and LRRC. **Chapter 9** presents a single centre, retrospective cohort study to evaluate the effect of implementing ERAS in rectal cancer patients who undergo TME surgery, and to explore the differences in ERAS-related outcomes and compliance between rectal cancer patients who underwent TME surgery, and LARC and LRRC patients who underwent beyond TME surgery. ERAS care elements that warrant specific modifications to fulfil the needs of LARC and LRRC patients who undergo beyond TME surgery were identified.

Non-operative management of elderly and frail patients

Since the introduction of the wait-and-see (W&S) approach, an increasing amount of studies have investigated non-operative treatment strategies in rectal cancer patients, in an effort to avoid major surgery.[32] Due to the beneficial outcomes related to oncological safety and quality of life, there is an increased interest in organ preservation and the non-operative management among patients and clinicians. **Chapter 10** presents a literature overview to provide an insight into the Dutch perspectives and the recent developments of organ preservation in the treatment of rectal cancer.

Although developments in the preoperative, perioperative, and postoperative care have occurred, a select group of elderly and frail patients may still be unable to undergo surgery due to severe multimorbidity, frailty, or the personal preference not to undergo surgery. These patients are at risk of undertreatment, which may result in tumour progression and the onset of debilitating symptoms, impaired quality of life, and poor survival. Non-operative treatment strategies (e.g. chemotherapy, (chemo)radiotherapy, endoluminal radiotherapy, local excision) have been explored and may provide an alternative for elderly and frail patients who are unable to undergo surgery or who prefer organ preservation.[33,34] **Chapter 11** provides a narrative review to discuss a multidisciplinary treatment approach, aiming for a personalised non-operative treatment strategy in elderly and frail patients unable to undergo rectal cancer surgery.

Part III: Summary, general discussion, future perspectives, and impact paragraph

A summary, general discussion, and future perspectives are provided in **chapter 12**. Finally, **chapter 13** presents an impact paragraph and **chapter 14** presents a Dutch summary of this thesis.

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PART

Treatment outcomes of elderly patients with colorectal cancer

CHAPTER 2

Significant improvement in postoperative and 1-year mortality after colorectal cancer surgery in recent years

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Eur J Surg Oncol. 2019 Nov;45(11):2052-2058.
doi: 10.1016/j.ejso.2019.06.017.

ABSTRACT

Background

In earlier studies, an association between older patients and higher morbidity and mortality after colorectal surgery is shown, especially in the first postoperative year. We conducted this study to investigate if there is improvement in postoperative morbidity and mortality in senior CRC patients over time.

Materials and methods

All patients, except those with distant metastasis, who received curative CRC surgery between 2006 and 2017 in the Catharina Hospital (Eindhoven, the Netherlands) were selected retrospectively. Differences in mortality and relative survival between different age groups (<75 and ≥ 75 years), period of surgery (2006–2012 and 2013–2017), and type of tumour (colon and rectum) were investigated.

Results

In total 2018 patients, of whom 57.4% is male, were selected (n = 1037 colon and n = 981 rectum). 615 (30.5%) patients were ≥75 years old. For electively treated CRC patients aged ≥75 years, 30- and 90-day mortality improved from 5.8% to 1.2% ($p = 0.004$) and 9.1% to 4.6% ($p = 0.043$) respectively, in favour of the latest time period. Relative one-year survival rates of all electively treated CRC patients were not significantly different between younger and older patients in the latest time period (95.5% vs. 94.3%, p = n.s.).

Conclusions

This study shows significant improvement in postoperative morbidity and mortality over time for both age and treatment groups. Relative survival rates improved especially for older patients and no significant differences were seen between both age groups. Senior CRC patients should not be withheld curative treatment based on age or comorbidities alone.

INTRODUCTION

The incidence of colorectal cancer (CRC) increases with age. As worldwide age is increasing, more and more older patients are diagnosed with CRC.[1] With more senior patients affected by CRC, challenges originate in treatment choices. These patients are a heterogeneous group of patients with variations in fragility and comorbidities, and with inconsistencies between physical and chronological age.[2] They are at risk for complications with increased morbidity and postoperative mortality and if complications occur, they have more devastating consequences.[3-5] Furthermore, the percentage of seniors who receive surgery decreases with older ages.[6] In daily practice these findings could lead to withholding potentially curative treatment in the older population with an increased risk for undertreatment.[7,8]

There is increasing evidence that older patients who are fit enough for surgery have the same benefit from potentially curative treatment as younger patients do.[9,10] They are able to withstand the surgical stressor better than commonly believed.[9,10] However, the risk of mortality in seniors during the first post-operative year is 20–23%.[11] If they survive the first year, their prognosis is equal to younger counterparts if they survive the first postoperative year.[11]

In senior patients, one of the most important determinating factors in decision making is frailty. This is important because this condition, defined as a state of limited reserve to undergo physical stress, is a known risk factor for postoperative complications in colorectal cancer surgery.[12] In case of increased frailty or limited functional reserve, a prehabilitation program could be beneficial for senior patients to improve their condition prior to surgery.[13] However, until now evidence on the effect of prehabilitation on postoperative outcome is varying and inconclusive.[13,14]

Improvement in earlier diagnosis, better staging, less invasive surgical techniques, pre- and postoperative care, and centralisation of complex cases have contributed to an improved outcome in the older patient.[1] Despite all these improvements, studies still report significant differences in 30-day and one-year mortality between older and younger CRC patients.[11] However, there is a possibility that these differences are changing over time.

The primary aim of this study is to investigate whether or not any improvement in short-term morbidity and mortality has occurred in senior CRC patients over the years, treated in a high-volume centre for complex CRC cases. The secondary aim is to compare these morbidity and mortality rates between younger and older CRC patients.

MATERIALS AND METHODS

Patients and treatment

The Catharina Hospital (Eindhoven, the Netherlands) is a specialised and high-volume centre for treatment of CRC and is a referral centre for locally advanced and recurrent colorectal cancer. For this study, all patients receiving curative surgery for primary non-recurrent colorectal cancer between 2006 and 2017 were selected. Almost all patients, except those undergoing emergency procedures, were adequately staged locally and systemically with histologically proven CRC and a pre-treatment CT or MRI scan. Depending on location of the tumour and cancer stage, patients received neoadjuvant and/or adjuvant treatment with (chemo)radiation, according to the Dutch National Guidelines for colorectal cancer.[15] Type of surgery (e.g. laparoscopic and open surgery) was used depending on the type and stage of the tumour and the preference of the surgeon. Patients with peritonitis carcinomatosis and distant metastasis at time of presentation were excluded in this study. All patients were assessed independently by a surgeon and an anaesthesiologist to determine whether or not they were regarded fit for surgery. Besides the standard medical history regarding previous morbidities and co-existing morbidities, nutritional assessment, drug use and a somatic and psychogeriatric screening, also the support system at home and the requirements after surgery to return home were evaluated. If needed, other disciplines were involved.

Clinical data and follow-up

Clinical and demographic data were extracted retrospectively from medical records. Complications were scored using the Clavien-Dindo classification of surgical complications.[16,17] Follow-up data was extracted from medical records or by contacting the patient, the referring hospital or patients' general practitioner by telephone. Time to follow-up was calculated as the interval from the day of surgery to death or to the date of last contact. Minimum follow-up time of the surviving patients was at least one year. The vital status of all patients was assessed through linkage with Municipal Administrative Databases, which register all deceased and emigrated persons in the Netherlands. If a patient had died during follow-up, the date and cause of death were noted.

Statistical analyses

Statistical analyses were performed using SPSS Statistics 25.0 software (IBM, Endicott, New York, USA). Patients were divided in two consecutive periods, based on year of surgery:

2006–2012 and 2013–2017. All analyses were performed separately for both colon and rectal cancer. Survival analyses were performed only for CRC patients treated with elective surgery. Comparisons within these groups were based on age (<75 and ≥ 75 years). All survival analyses were also performed for patients <80 and ≥ 80 years, and shown in supplementary data. Intergroup comparisons were analysed using chi-square tests or independent *t*-tests when appropriate. A *p*-value of <0.05 was considered statistically significant. Survival rates were analysed for colon and rectal cancer separately and were stratified by age group using the Kaplan-Meier method. To calculate disease-specific survival, we used relative survival rates, which was calculated as the absolute survival amongst CRC patients divided by the expected survival for the general population with the same sex and age structure.

RESULTS

In total, 2018 consecutive CRC patients were included. Of the 1037 colon cancer patients, 432 (41.7%) were ≥75 years old and of the 981 rectal cancer patients, 183 (18.7%) were ≥75 years old. Median follow-up time for colon cancer patients was 3.4 years and for rectal cancer patients 4.2 years. Senior (≥75 years) CRC patients had significantly more comorbidities compared to younger patients. Further clinical and demographic characteristics for both colon and rectal cancer patients are presented separately in Tables 1 and 2, respectively.

Table 1. Demographic and clinical characteristics of all 1037 colon cancer patients, stratified by age group and period of treatment.

	<75 years			≥75 years		
	2006-2012 n = 287	**2013-2017 n = 318**	***p*-value**	**2006-2012 n = 205**	**2013-2017 n = 227**	***p*-value**
	n (%)	**n (%)**		**n (%)**	**n (%)**	
Mean age in years at time of surgery (range)	64.4 (24.4-74.9)	65.4 (30.3-74.9)	0.149	81.6 (75.1-96.1)	80.6 (75.0-95.2)	0.017
Median follow-up in years (±SD)	7.1 (3.1)	2.4 (1.4)		4.9 (3.4)	2.2 (1.4)	
Male	152 (53.0)	181 (56.9)	0.329	102 (49.8)	111 (48.9)	0.859
Comorbidity			0.083			0.008
None	92 (32.1)	120 (37.7)		31 (15.1)	65 (28.6)	
1 comorbidity	54 (18.8)	73 (23.0)		34 (16.6)	35 (15.4)	
2 comorbidities	47 (16.4)	48 (15.1)		38 (18.5)	38 (16.7)	
≥3 comorbidities	94 (32.8)	77 (24.2)		102 (49.8)	89 (39.2)	
ASA classification			0.330			0.417
I-II	218 (76.0)	254 (79.9)		100 (48.8)	123 (54.2)	
III	67 (23.3)	60 (18.9)		94 (45.9)	96 (42.3)	
IV	2 (0.7)	4 (1.3)		11 (5.4)	8 (3.5)	
Type of surgery			0.137			0.165
Right hemicolectomy	125 (43.6)	117 (36.8)		106 (51.7)	122 (53.7)	
Transversum colectomy	5 (1.7)	4 (1.3)		7 (3.4)	2 (0.9)	
Left hemicolectomy	36 (12.5)	62 (19.5)		22 (10.7)	36 (15.9)	
Sigmoid	109 (38.0)	125 (39.3)		68 (33.2)	64 (28.2)	
(Sub)total colectomy	12 (4.2)	10 (3.1)		2 (1.0)	3 (1.3)	
Initial type of intervention			<0.001			<0.001
Open surgery	184 (64.1)	105 (33.0)		158 (77.1)	86 (37.9)	
Laparoscopic	103 (35.9)	213 (67.0)		47 (22.9)	141 (62.1)	
Stoma during surgery			<0.001			<0.001
Yes	29 (10.1)	40 (12.6)		29 (14.1)	30 (13.2)	
No	236 (82.2)	276 (86.8)		159 (77.6)	197 (86.8)	
Missing	22 (7.7)	2 (0.6)		17 (8.3)	-	

	<75 years			≥75 years		
	2006-2012 n = 287	2013-2017 n = 318	*p*-value	2006-2012 n = 205	2013-2017 n = 227	*p*-value
	n (%)	n (%)		n (%)	n (%)	
Emergency surgery	32 (11.1)	35 (11.0)	0.955	40 (19.5)	37 (16.3)	0.384
Extended (multivisceral) resection	34 (11.8)	31 (9.7)	0.001	23 (11.2)	21 (9.3)	0.001
Missing	18 (6.3)	51 (16.0)		7 (3.4)	30 (13.2)	
Mean hospital stay in days (±SD)	9.7 (8.9)	9.0 (10.6)	0.381	12.6 (10.8)	9.6 (7.2)	0.001
Mean ICU stay in days (±SD)	0.7 (2.1)	1.1 (5.9)	0.466	2.2 (3.5)	1.0 (2.8)	0.020
Pathological T-stage			0.023			0.915
T0-T2	75 (26.1)	110 (34.6)		52 (25.4)	60 (26.4)	
T3	156 (54.4)	145 (45.6)		117 (57.1)	125 (55.1)	
T4	56 (19.5)	59 (18.6)		36 (17.6)	42 (18.5)	
Tx	-	4 (1.3)				
Pathological N-stage			0.428			0.572
N0	178 (62.0)	191 (60.1)		146 (71.2)	153 (67.4)	
N1	62 (21.6)	82 (25.8)		36 (17.6)	49 (21.6)	
N2	47 (16.4)	45 (14.2)		23 (11.2)	25 (11.0)	
Primary anastomosis	272 (94.8)	299 (94.0)	0.690	183 (89.3)	207 (91.2)	0.501
Radical resection (R0)	287 (100.0)	317 (99.7)	0.342	205 (100.0)	227 (100.0)	N.A.

Table 2. Demographic and clinical characteristics of all 981 rectal cancer patients, stratified by age group and period of treatment.

	<75 years			≥75 years		
	2006-2012 n = 454	**2013-2017 n = 344**	***p*-value**	**2006-2012 n = 113**	**2013-2017 n = 70**	***p*-value**
	n (%)	**n (%)**		**n (%)**	**n (%)**	
Mean age in years at time of surgery (range)	61.8 (27.0-74.9)	62.2 (28.8-74.9)	0.519	79.3 (75.0-88.6)	79.7 (75.0-90.6)	0.531
Median follow-up in years (±SD)	7.1 (3.2)	2.7 (1.4)		4.5 (3.2)	1.8 (1.4)	
Male	277 (61.0)	223 (64.8)	0.270	68 (60.2)	45 (64.3)	0.578
Comorbidity			0.117			0.024
None	180 (39.6)	139 (40.4)		18 (15.9)	25 (35.7)	
1 comorbidity	107 (23.6)	70 (20.3)		23 (20.4)	10 (14.3)	
2 comorbidities	90 (19.8)	56 (16.3)		22 (19.5)	11 (15.7)	
≥3 comorbidities	77 (17.0)	79 (23.0)		50 (44.2)	24 (34.3)	
ASA classification			0.686			0.253
I-II	392 (86.3)	292 (85.2)		68 (60.2)	48 (68.6)	
III	61 (13.4)	49 (14.2)		42 (37.2)	22 (31.4)	
IV	1 (0.2)	1 (0.3)		3 (2.7)	-	
Neoadjuvant treatment			<0.001			0.659
None	51 (11.2)	59 (17.2)		33 (29.2)	17 (24.3)	
Short course radiotherapy (5 × 5 Gy)	85 (18.7)	47 (13.7)		32 (28.3)	24 (34.3)	
Chemoradiation	298 (65.6)	237 (68.9)		44 (38.9)	28 (40.0)	
Long course radiotherapy	20 (4.4)	1 (0.3)		4 (3.5)	1 (1.4)	
Type of surgery			0.489			0.263
Low anterior resection	270 (59.5)	212 (61.6)		56 (49.6)	43 (61.4)	
Abdominoperineal resection	171 (37.7)	121 (35.2)		45 (39.8)	24 (34.3)	
(Sub)total resection	2 (0.4)	-		2 (1.8)	-	
TEM	11 (2.4)	11 (3.2)		10 (8.8)	3 (4.3)	
Initial type of intervention			<0.001			<0.001
Open surgery	432 (95.2)	263 (76.5)		99 (87.6)	51 (72.9)	
Laparoscopic	11 (2.4)	70 (20.3)		4 (3.5)	16 (22.9)	

	<75 years			≥75 years		
	2006-2012 n = 454	2013-2017 n = 344	*p*-value	2006-2012 n = 113	2013-2017 n = 70	*p*-value
	n (%)	n (%)		n (%)	n (%)	
Ostomy during surgery			0.001			0.628
Yes	379 (83.5)	270 (78.5)		90 (79.6)	55 (78.6)	
No	55 (12.1)	69 (20.1)		17 (15.0)	13 (18.6)	
Missing	20 (4.4)	5 (1.5)		6 (5.3)	2 (2.9)	
Emergency surgery	6 (1.3)	4 (1.2)	0.842	3 (2.7)	1 (1.4)	0.581
Clinical T-stadium			0.990			0.633
T1-T2	67 (14.8)	50 (14.5)		23 (20.4)	16 (22.9)	
T3	183 (40.3)	136 (39.5)		48 (42.5)	24 (34.3)	
T4	203 (44.7)	157 (45.6)		39 (34.5)	29 (41.4)	
Tx	1 (0.2)	1 (0.3)		3 (2.7)	1 (1.4)	
Clinical N-stadium			<0.001			<0.001
N0	164 (36.1)	92 (26.7)		54 (47.8)	29 (41.4)	
N1	88 (19.4)	102 (29.7)		20 (17.7)	22 (31.4)	
N2	102 (22.5)	141 (41.0)		10 (8.8)	19 (27.1)	
Nx	19 (4.2)	8 (2.3)		4 (3.5)	-	
Missing	81 (17.8)	1 (0.3)		25 (22.1)	-	
Extended (multivisceral) resection	145 (29.7)	121 (35.2)	0.006	34 (30.1)	29 (41.4)	0.098
Missing	36 (7.9)	10 (2.9)		11 (9.7)	2 (2.9)	
Mean admission time in days (±SD)	11.6 (10.7)	9.4 (6.7)	0.001	14.5 (12.8)	12.7 (10.6)	0.329
Mean admission time on ICU in days (±SD)	1.7 (7.5)	0.9 (1.8)	0.129	1.9 (3.3)	2.1 (3.6)	0.798
Primary anastomosis	264 (58.1)	200 (58.1)	0.684	41 (36.3)	32 (45.7)	0.205
Radical resection (R0)	446 (98.2)	340 (98.8)	0.491	108 (95.6)	69 (98.6)	0.269

Postoperative morbidity and mortality

Senior colon cancer patients had significantly more pulmonary, cardiac, and neurological complications compared to younger patients. Clavien-Dindo grade III complications were observed in 6.0% of the older and in 9.4% of the younger patients (p = 0.046). Clavien-Dindo grade IV complications occurred in 1.9% of the older and in 2.6% of the younger patients (p = n.s.). Postoperative mortality during admission was observed in 25 (5.8%) of the older and 11 (1.8%) of the younger patients (p = 0.001).

Senior rectal cancer patients also had significantly more pulmonary, cardiac and neurological complications. The incidence of other complications was similar compared to younger patients. Of the older patients, 11.5% and 4.9% of patients developed grade III or IV complications in comparison to 11.2% and 3.1% in younger patients, respectively (p = n.s.). Postoperative mortality during admission occurred in 8 (4.4%) older and in 9 (1.1%) younger patients (p = 0.002). A detailed description of the complications in both groups is presented in Table 3.

Table 3. Complications in both colon and rectal cancer patients, stratified by age groups.

	Colon n = 1037			**Rectum n = 981**		
	<75 years n = 605	**≥75 years n = 432**	***p*-value**	**<75 years n = 798**	**≥75 years n = 183**	***p*-value**
	n (%)	**n (%)**		**n (%)**	**n (%)**	
Pulmonary	44 (7.3)	59 (13.7)	0.001	62 (7.8)	25 (13.7)	0.011
Cardiac	20 (3.3)	47 (10.9)	<0.001	35 (4.4)	18 (9.8)	0.003
Infectious	52 (8.6)	30 (6.9)	0.332	92 (11.5)	27 (14.8)	0.228
Neurological	13 (2.1)	37 (8.6)	<0.001	18 (2.3)	18 (9.8)	<0.001
Thrombosis	7 (1.2)	3 (0.7)	0.452	13 (1.6)	1 (0.5)	0.265
Clavien-Dindo grade			<0.001			<0.001
None	385 (63.6)	248 (57.4)		398 (49.9)	65 (35.5)	
Grade I-II	136 (22.5)	125 (28.9)		277 (34.7)	80 (43.7)	
Grade IIIa	13 (2.1)	9 (2.1)		29 (3.6)	2 (1.1)	
Grade IIIb	44 (7.3)	17 (3.9)		60 (7.5)	19 (10.4)	
Grade IV	16 (2.6)	8 (1.9)		25 (3.1)	9 (4.9)	
Grade V	11 (1.8)	25 (5.8)		9 (1.1)	8 (4.4)	

Development of post-operative morbidity and mortality over time

In the period 2006–2012, 9.7% and 2.8% of the older and 12.8% and 3.5% of the younger CRC patients developed grade III or grade IV complications, respectively. Postoperative mortality during admission was observed in 8.8% of the older compared to 1.3% of the younger patients ($p < 0.001$).

In the period 2013–2017, no significant differences in complications or mortality between older and younger patients were seen. Grade III or IV complications occurred in 5.4% and 2.7% of the older and 7.7% and 2.3% of the younger patients, respectively. Postoperative mortality during admission in this period occurred in 1.7% of the older and 1.5% of the younger patients ($p = 0.842$).

Overall & relative survival analysis

Comparing the 2006–2012 and 2013–2017 period, the overall 30- and 90-day mortality for senior CRC patients decreased from 5.8% to 1.2% ($p = 0.004$) and from 9.1% to 4.6% ($p = 0.043$), respectively. For patients <75 years, no differences in 30- and 90-day survival rates were seen between both time periods (Figure 1).

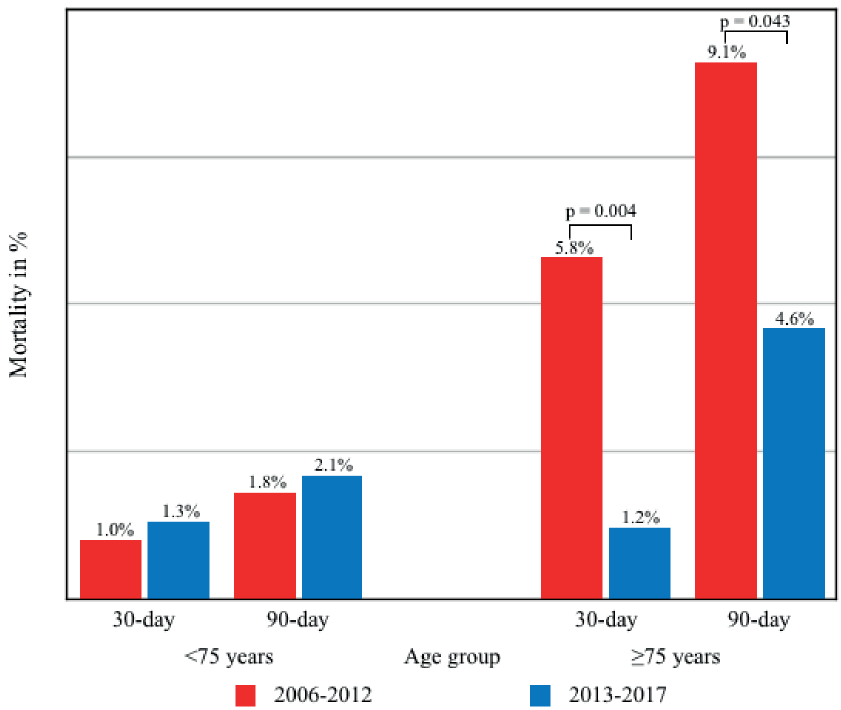

Figure 1. Improvement of short-term mortality for elderly colorectal cancer patients over the years.

In contrast to the period 2006–2012, the most recent time period showed there were no significant differences in the 30- and 90-day mortality rate between both age groups for both colon and rectal cancer patients. The 30-day and 90-day mortality rate in this period was 1.1% and 4.2% for senior colon and 1.4% and 5.8% in senior rectal cancer patients, respectively. A more detailed description of the overall survival rates for all groups is presented in Table 4.

Table 4. Absolute survival rates of both colon and rectal cancer patients with elective surgery, stratified by age groups.

	Colon n = 893			
	<75 years		**≥75 years**	
	2006-2012 n = 255	**2013-2017 n = 283**	**2006-2012 n = 165**	**2013-2017 n = 190**
1-month	0.98	0.99	0.94	0.99
3-month	0.97	0.98	0.90	0.94
6-month	0.96	0.97	0.88	0.90
1-year	0.95	0.95	0.86	0.85
	Rectum n = 967			
	<75 years		**≥75 years**	
	2006-2012 n = 448	**2013-2017 n = 340**	**2006-2012 n = 110**	**2013-2017 n = 69**
1-month	0.99	0.99	0.94	0.99
3-month	0.98	0.98	0.92	0.94
6-month	0.98	0.97	0.90	0.90
1-year	0.95	0.95	0.85	0.85

For all CRC patients, absolute one-year survival was 95.3% and 85.5% for younger and older patients in the 2006–2012 period, compared to 94.9% and 89.2% in the 2013–2017 period, respectively ($p = 0.002$). In the most recent time period, no significant differences were found in overall one-year mortality between younger and older colon cancer patients (90.5% vs. 95.1%, respectively $p = 0.055$). In rectal cancer patients there were still significant differences between older and younger patients in overall one-year mortality for the same period (85.5% vs. 94.7%, $p = 0.006$).

The relative one-year survival for senior CRC patients improved from 88.4% in the 2006–2012 period to 94.3% in the latest time period and was not significantly different compared to younger patients for this latest time period. Improvement of the relative survival was observed for both colon and rectal cancer patients. Also, in senior patients who underwent emergency surgery for CRC, similar relative one-year survival rates as their younger counterparts were seen in the period 2013–2017. The relative one-year survival rates are presented in Table 5.

Table 5. Relative one-year survival rates, stratified by age and period of surgery.

	Relative one-year survival					
	2006-2012			**2013-2017**		
	<75 years	**≥75 years**	***p*-value**	**<75 years**	**≥75 years**	***p*-value**
	%	**%**		**%**	**%**	
All CRC patients	96.5%	88.4%	<0.001	95.5%	94.3%	0.429
Colon	96.5%	87.3%	<0.001	95.3%	94.7%	0.429
Rectum	96.3%	89.4%	0.003	95.3%	91.2%	0.176
Emergency surgery	100%	69.8%	<0.001	87.2%	92.1%	0.479

DISCUSSION

Potentially curative treatment for colorectal cancer is accompanied by acceptable morbidity and low mortality rates for all patients, regardless of age.[18-21] However, earlier studies on this topic showed that morbidity in senior patients is most often higher than in their younger counterparts, and the risk for mortality is increased if a complication occurs.[3,4] Our cohort of consecutive CRC patients shows a major decrease in 90-day and one-year mortality in the older population. For the period 2006–2012, 9.1% patients aged ≥75 years died in the first 90 days compared to 4.6% in the most recent period. After correcting absolute mortality for age-related background mortality (relative survival), one-year survival rates were almost equal for younger and older patients: 95.5% and 94.3%, respectively. Although overall mortality in senior patients is higher, the impact of current CRC treatment on mortality is equal between both patient groups. We believe that improvement in perioperative and postoperative care have contributed to this positive effect. Since senior patients had significantly more comorbidities than younger patients, the differences in overall mortality between ages are most probably accountable on other diseases which affect these patients.

Older studies focusing on outcome in the older CRC population report 30-day mortality rates up to 7% in patients aged 75 years or older and one-year mortality rates of 19–26%.[18,22-25] However, this study, showed a 30-day mortality rate of 1.1% in senior colon and 1.4% in senior rectal cancer patients for the most recent period. In a population based study from The Netherlands, including patients surgically treated for CRC between 2009 and 2013, an improvement was observed in 30-day and one-year mortality for patients ≥75 years old over the years.[26] They reported mortality rates in patients ≥75 years that were slightly higher compared to our rates, 2.9–6.2% and 11.7–15.0%, respectively for one-month and one-year mortality.[26] Another recent population-based cohort study across four North European countries also showed somewhat higher 30-day, 90-day and overall one-year mortality rates for octogenarian colon and rectal cancer patients.[27] For octogenarian colon cancer patients, they reported 30-day and one-year mortality rates of 5.5–11.4% and 17.1–23.6%, respectively.[27] For the octogenarian rectal cancer patients, these rates were 4.7–7.5% and 13.6–22.1%, respectively.[27] This study also showed that short-term mortality improved over the years, which varied substantially between different countries.[27] These rates were even slightly higher than we found for patients ≥80 years old in our cohort (shown as supplementary data). A small single institution study of 85 patients from the United Kingdom including CRC patients showed a 30-day mortality rate for patients ≥75 years of 6.5%, which was almost equal to that of younger patients.[23] Others studies focusing on survival rates over the years have also shown improved survival rates in senior CRC patients.[1,22,28,29]

The reported survival rates in this study are promising, particularly as a significant proportion of the senior rectal cancer patients have locally advanced cases. These patients require intensive treatment regimens with neoadjuvant treatment and in about one third of the cases multivisceral resections. Possible explanations for improvement in short-term survival rates in senior colon cancer patients are probably due to increasing use of minimal invasive techniques and perioperative measures. However, in rectal cancer patients there is not a clear surgical explanation as most patients are treated with open surgery due to the locally advanced nature of most cases. However, increased expertise in these cases with improved perioperative care and awareness of complications will probably attribute to these improved outcomes. Another possible explanation for better short-term outcomes is the introduction and standardization of the Enhanced Recovery After Surgery (ERAS) program, that showed promising results in the postoperative phase.[27]

All patients with CRC need to be adequately staged and performance status needs to be assessed. It is known that frailty is a relevant risk factor for postoperative complications, longer hospital stay, readmission rates and lower long-term survival.[30,31] In order to prevent adverse outcomes in older CRC patients it is important to recognize frailty to determine the most appropriate therapeutic regimen. It is still a discussion how frailty should be adequately identified in the individual patient, as no specific tool is able to identify all heterogeneous aspects of frailty.[8,32] Montroni et al. recommend focusing on main predictors as functional and nutritional status and comorbidities as these are targets for prehabilitation programs.[8] Since 2012, as part of a National Patient Safety Program in the Netherlands, all patients over 70 years should be subjected to a short evaluation of four domains: undernutrition, physical impairment, delirium risk and fall risk. This short screening method is easy and less time consuming than a full geriatric assessment, but provides some important prognostic information about outcome and morbidity.[33] When patients seem to be at risk for frailty it is important to perform a complete geriatric assessment in these patients. The most eligible tool to identify frail from fit patients in the geriatric oncological group appears to be the Comprehensive Geriatric Assessment (CGA).[32] CGA uses a more multidimensional approach than ASA score does, assessing functional, psychosocial and physical health status, polypharmacy and cognition. Although time consuming, CGA has been shown to be a useful predictor for postoperative complications in senior patients.[32] In our institution, all patients are seen by the surgeon and anaesthesiologist to asses perioperative risk and to shortly evaluate the four geriatric domains. If increased risk is considered, patients are referred for a full geriatric assessment. If indicated, in some of these patients, prehabilitation programs were initiated. Nevertheless, all senior patients were advised to increase protein intake and to try to double their standard physical exercise in the waiting period for surgery.

Intense prehabilitation programs as standard care for all CRC patients have not shown to be of value yet, although in selected patients enhancing preoperative condition with prehabilitation programs could be useful in decreasing postoperative complications and improved recovery.[34,35] Studies performed in frail patients undergoing intra-abdominal surgery showed that prehabilitation decreases postoperative complications with 40–50%. Other promising results were achieved in orthopaedic and cardiac surgery patients.[13,36-38] It is believed that the frailest patients benefit most from these programs, but they are often excluded from studies and therefore the effect of these programs on older and frail CRC patients is still uncertain.[12] In addition, as our results show major improvement in postoperative mortality and outcome in the current era, and we did not implement prehabilitation programs in all patients, the effect of prehabilitation for the majority of the older population is probably small. The challenge is to find which patient in daily practice could be planned for surgery and which will benefit most from a prehabilitation program. Hopefully future studies focusing on this topic will provide more insight in the selection of patients.

The strength of this study lies in the availability of many clinical variables in a large population of patients with a low prevalence of missing values. Limitations of this study are based on its retrospective character. The report on minor complications could be underestimated due to a lack of documentation. However, we believe that the underestimation of complications was kept to a minimum by accurate studying of medical records, contact with referral hospitals and general practitioners and direct contact with patients by telephone. Assessment and screening for frailty has been implemented gradually since 2012 as it was part of a national health program. If frailty was suspected, the patients were referred for geriatric assessment. Therefore, only a few patients were assessed with a CGA and subjected to a prehabilitation program, thus we do not know the impact of prehabilitation on postoperative outcomes as this was not standard care. Over the years, we found slightly lower incidences of ≥3 comorbidities in senior patients. We believe this is due to a difference in documentation of comorbidities, rather than that outcomes have been influenced by only selecting the best patients for treatment.

As most of our rectal cancer patients are referred, there could also be an effect of selection bias for this specific patient group. Therefore, we believe that all patients with locally advanced rectal cancer cases should be discussed in a regional multidisciplinary team meeting (MDT) or should be referred to a tertiary centre before declining curative treatment.

This study shows that relative survival in the first year for senior patients undergoing CRC surgery has improved greatly over the past years. Their relative survival is even equal to that of younger patients. Therefore, all senior patients regardless of age should be adequately staged and discussed in a MDT meeting and when in doubt of frailty, patients should be referred to a geriatrician prior to declining treatment. We believe that the outcomes of this study are promising and senior patients should not be withheld curative treatment based on age or comorbidities alone.

CONCLUSION

Postoperative morbidity in senior CRC patients has decreased and survival has improved over the latest years. Currently, 30- and 90-day mortality and relative 1-year survival are almost equal for older and younger CRC patients. All senior CRC patients should be adequately staged and screened before any treatment plan is determined. Clinicians should not withheld senior patients from curative treatment based on age or comorbidities alone.

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SUPPLEMENTARY DATA OF CHAPTER 2

Supplementary Table 2.1. Complications in both colon and rectal cancer patients, stratified by age groups.

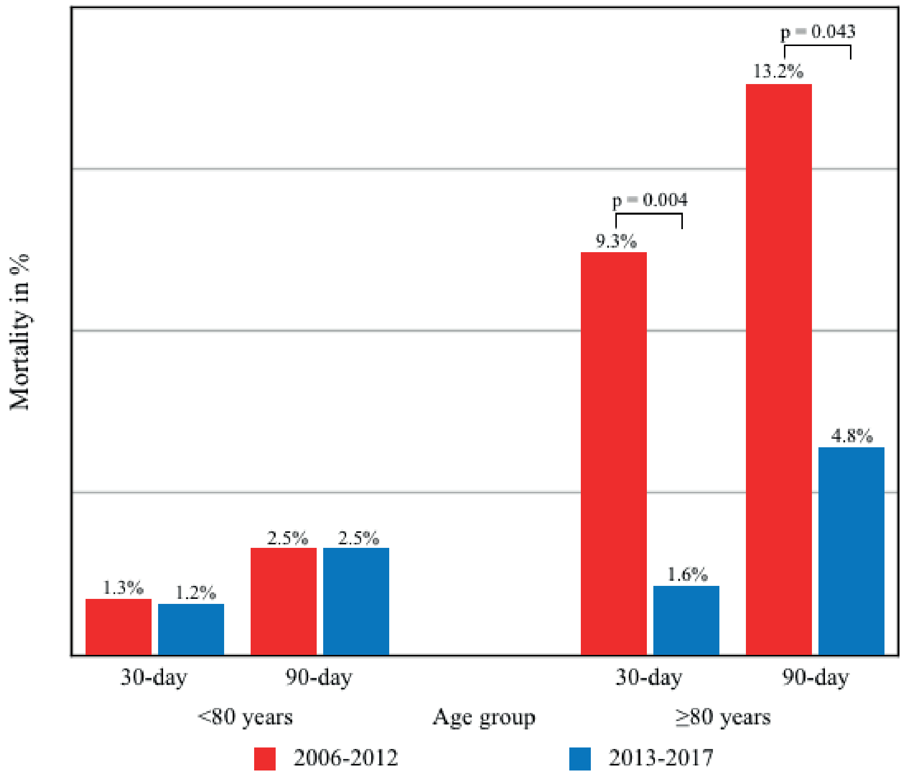
	Colon n = 1037			Rectum n = 981		
	<80 years n = 809	**≥80 years n = 228**	***p*-value**	**<80 years n = 908**	**≥80 years n = 73**	***p*-value**
	n (%)	**n (%)**		**n (%)**	**n (%)**	
Pulmonary	70 (8.7)	33 (14.5)	0.009	81 (8.9)	6 (8.2)	0.839
Cardiac	40 (4.9)	27 (11.8)	<0.001	48 (5.3)	5 (6.8)	0.570
Infectious	63 (7.8)	19 (8.3)	0.787	108 (11.9)	11 (15.1)	0.424
Neurological	24 (3.0)	26 (11.4)	<0.001	27 (3.0)	9 (12.3)	<0.001
Thrombosis	8 (1.0)	2 (0.9)	0.879	13 (1.4)	1 (1.4)	0.966
Clavien-Dindo grade			<0.001			0.046
None	519 (64.2)	114 (50.0)		435 (47.9)	28 (38.4)	
Grade I-II	186 (23.0)	75 (32.9)		326 (35.9)	31 (42.5)	
Grade IIIa	15 (1.9)	7 (3.1)		31 (3.4)	–	
Grade IIIb	52 (6.4)	9 (3.9)		72 (7.3)	7 (9.6)	
Grade IV	22 (2.7)	2 (0.9)		31 (3.4)	3 (4.1)	
Grade V	15 (1.9)	21 (9.2)		13 (1.4)	4 (5.5)	

Supplementary Table 2.2. Absolute survival rates of both colon and rectal cancer patients with elective surgery, stratified by age groups.

	Colon n = 893			
	<80 years		≥80 years	
	2006-2012 n = 333	**2013-2017 n = 378**	**2006-2012 n = 87**	**2013-2017 n = 95**
1-month	0.98	0.99	0.91	0.98
3-month	0.97	0.98	0.86	0.95
6-month	0.95	0.96	0.84	0.94
1-year	0.95	0.95	0.81	0.87
	Rectum n = 967			
	<80 years		**≥80 years**	
	2006-2012 n = 516	**2013-2017 n = 380**	**2006-2012 n = 42**	**2013-2017 n = 29**
1-month	0.99	0.98	0.91	1.00
3-month	0.98	0.97	0.88	0.97
6-month	0.97	0.96	0.83	0.93
1-year	0.95	0.93	0.76	0.89

Supplementary Table 2.3. Relative one-year survival rates, stratified by age and period of surgery.

	2006-2012			2013-2017		
	<80 years	≥80 years	*p*-value	<80 years	≥80 years	*p*-value
	%	%		%	%	
All CRC patients	95.9%	82.4%	<0.001	95.2%	94.6%	0.757
Colon	96.1%	81.8%	<0.001	96.0%	93.2%	0.198
Rectum	96.0%	81.4%	<0.001	94.4%	96.6%	0.625
Emergency surgery	94.7%	58.3%	<0.001	88.7%	91.7%	0.691



Supplementary Figure 2.1. Improvement of short-term mortality for elderly (≥80 years) colorectal cancer patients over the years.

CHAPTER 3

Age-related differences in morbidity and mortality after surgery for primary clinical T4 and locally recurrent rectal cancer

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Colorectal Dis. 2021 May;23(5):1141-1152. doi: 10.1111/codi.15542.

ABSTRACT

Aim

Outcomes in elderly patients (≥75 years) with non-advanced colorectal cancer have improved. It is unclear whether this is also true for elderly patients with clinical T4 rectal cancer (cT4RC) or locally recurrent rectal cancer (LRRC). We aimed to compare age-related differences in morbidity and mortality after curative treatment for cT4RC and LRRC.

Methods

All cT4RC and LRRC patients without distant metastasis who underwent curative surgery between 2005 and 2017 in the Catharina Hospital (Eindhoven, The Netherlands) were included. Morbidity and mortality were evaluated based on age (<75 and ≥75 years) and date of surgery (2005–2011 and 2012–2017).

Results

Overall, 72 of 474 (15.2%) cT4RC and 53 of 293 (18.1%) LRRC patients were ≥75 years. No significant differences in the incidence of Clavien–Dindo I–IV complications were observed between age groups. However, in elderly cT4RC patients, cerebrovascular accidents occurred more frequently (4.2% vs. 0.5%, $p = 0.03$). Between 2005–2011 and 2012–2017, 30-day mortality improved from 7.5% to 3.1% and from 10.0% to 0.0% in elderly cT4RC and LRRC patients, respectively. The 1-year mortality during 2012–2017 was worse in elderly than in younger patients (28.1% vs. 6.2%, $p = 0.001$ for cT4RC and 27.3% vs. 13.8%, $p = 0.06$ for LRRC). In elderly cT4RC and LRRC patients, 44.4% and 46.2% died due to non-cancer-related causes, while only 27.8% and 23.1% died due to disease recurrence, respectively.

Conclusion

Although the 30-day mortality in elderly cT4RC and LRRC patients improved after curative treatment, the 1-year mortality in elderly patients continued to be high, which requires more awareness for the elderly after hospitalisation.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide with 43% of patients being older than 75 years.[1] Approximately 10% of all CRC patients are diagnosed with locally advanced rectal cancer (LARC) and 6%–10% will eventually develop locally recurrent rectal cancer (LRRC).[2] The optimal treatment for patients with LARC and LRRC is neoadjuvant therapy followed by surgery.[3] In LRRC, in particular, involvement of the lateral and posterior pelvic wall is more common since visceral fasciae, which act as natural barriers for tumour infiltration, have already been removed during primary tumour surgery. Therefore, even more extended extra-anatomical resections are often needed in LRRC. These extended resections are associated with postoperative complication rates ranging from 41.5%−57%.[4,5]

Almost 30%–50% of surgical procedures are performed in patients >65 years old, and with the increase in the elderly population worldwide the incidence may increase further.[1,6,7] In general, elderly patients have multiple comorbidities with varying physical conditions. According to recent literature, most patients <75 years are physically healthy, whereas over 50% of patients ≥75 years have more than two chronic disorders.[8,9] The elderly often experience difficulty coping with complications and longer recovery periods along with increased mortality in the first postoperative year.[10–12] However, improvements in CRC care have led to better outcomes in elderly patients.[13–15] The difference in the postoperative and 1-year mortality rates between younger and elderly CRC patients has decreased with comparable outcomes.[11,14,15] However, it is unclear if this is also true for clinical T4 rectal cancer (cT4RC) or LRRC patients treated with curative intent.

The primary aim of this study was to evaluate the morbidity and mortality of elderly (≥75 years) and younger (<75 years) patients with cT4RC and LRRC treated with curative intent. Changes in morbidity and mortality were also analysed over time in order to evaluate whether improvements in care could have contributed to better outcomes in elderly patients.

METHODS

Patients and treatment

Patients who underwent curative surgery for primary cT4RC or LRRC at the Catharina Hospital (Eindhoven, The Netherlands), a tertiary referral centre for such patients, between 2005 and 2017 were included. Patients with peritoneal or incurable distant metastases were excluded. All patients with cT4RC had a histological diagnosis and radiological confirmation of visceral peritoneum or surrounding organ involvement. Diagnosis of LRRC was based on histology or imaging. Positron emission tomography CT was performed to exclude distant metastases and distinguish between fibrosis or LRRC when a biopsy could not be obtained and CT of chest and abdomen was performed to detect distant metastases. All patients underwent pelvic MRI for accurate staging before and after neoadjuvant treatment. Most patients with cT4RC underwent neoadjuvant treatment according to the Dutch National Guidelines for rectal cancer.[16] The majority underwent long course chemoradiation with up to 50.4 Gy in 28 fractions with concomitant oral capecitabine. LRRC patients who were previously irradiated underwent reirradiation with 30 Gy with concomitant oral capecitabine.[17] LRRC patients without a history of pelvic irradiation received a full course of irradiation (50.4 Gy) with concomitant oral capecitabine.[17] Some patients with extensive disease also received neoadjuvant induction chemotherapy followed by (re)irradiation with or without concomitant chemotherapy to achieve downstaging. Details of this treatment regimen and the influence on outcomes have been reported previously.[18] After 8–12 weeks, surgery was performed combined with intraoperative radiotherapy at a dose of 10–12.5 Gy at the margins considered at risk (perioperatively or positive margins confirmed by intraoperative frozen section analysis).

Clinical data and follow-up

Patients' characteristics, data on treatment, pathology and additional clinical (e.g., complications, hospital readmission) and demographic data were retrospectively extracted from the medical records. Complications were scored using the Clavien–Dindo classification.[19] Follow-up data were obtained from the medical records, the referral hospital or the patient's general practitioner. Follow-up was calculated as the interval between surgery and last contact or death. The minimum follow-up of all patients was 1 year (if alive). During follow-up, local recurrence and distant metastases were recorded. The Municipal Administrative Databases were consulted to obtain information on survival data. If a patient died during follow-up, the specific cause of death was investigated. Treatment-induced deterioration, as a cause of mortality, was defined as deterioration of the physiological status after hospital discharge leading to death, regardless of postoperative complications and without signs of relapsing disease, cardiopulmonary disease or cerebrovascular accidents.

Statistical analyses

Statistical analyses were performed using SPSS Statistics 25.0 software (IBM), separately for cT4RC and LRRC. The study period was divided into two time periods of 7 and 6 years, respectively (2005–2011 and 2012–2017). The primary endpoint was postoperative mortality (30-day, 90-day and 1-year). Secondary endpoints were postoperative complications (Clavien–Dindo classification) and causes of 1-year mortality. Comparisons were stratified by age (<75 and ≥75 years) and date of surgery (2005–2011 and 2012–2017). Intergroup comparisons were analysed using the chi-squared test or Fisher's exact test, when appropriate, for non-continuous data. Independent *t* tests or Mann–Whitney *U* tests were used for normally and non-normally distributed continuous data, respectively. A *p*-value of <0.05 was considered statistically significant. All tests were two-sided. Survival rates for both patient groups were estimated separately and stratified by age group using the Kaplan–Meier method and compared using the log-rank test. Relative survival rates were calculated as the absolute survival amongst cT4RC and LRRC patients divided by the expected survival for the general population with the same sex and age. In-depth analyses were performed to identify the specific cause of death.

RESULTS

A total of 767 patients were included. Of the 474 cT4RC and 293 LRRC patients, 72 (15.2%) and 53 (18.1%), respectively, were ≥75 years. The median follow-ups were 3.8 and 2.8 years for cT4RC and LRRC patients, respectively. In the LRRC group, one patient was lost to follow-up in the first postoperative year. Clinical and demographic characteristics for cT4RC and LRRC patients are presented in Tables 1 and 2, respectively. In both groups, elderly patients had significantly higher comorbidities.

Table 1. Demographic, clinical and tumour characteristics of cT4RC patients (n = 474), stratified by age (<75 and ≥75 years).

	<75 years n = 402 n (%)	≥75 years n = 72 n (%)	*p*-value
Mean age in years at time of surgery (±SD)	61.4 (8.6)	79.2 (3.6)	<0.001
Median follow-up in years (IQR)	4.0 (2.7–5.5)	2.5 (1.1–4.9)	<0.001
Male	235 (58.5)	39 (54.2)	0.50
Comorbidity			<0.001
None	148 (36.8)	9 (12.5)	
1 comorbidity	121 (30.1)	18 (25.0)	
2 comorbidities	64 (15.9)	18 (25.0)	
≥ 3 comorbidities	53 (13.2)	23 (31.9)	
Missing	16 (4.0)	4 (5.6)	
ASA classification			0.02
I-II	328 (81.6)	50 (69.4)	
III	60 (14.9)	21 (29.2)	
Missing	14 (3.5)	1 (1.4)	
Neoadjuvant treatment			<0.001
None	-	2 (2.8)	
Short course radiotherapy (5 × 5 Gy)	17 (4.2)	9 (12.5)	
Long course radiotherapy	10 (2.5)	9 (12.5)	
Chemoradiation	358 (89.1)	46 (63.9)	
Other	17 (4.2)	6 (8.3)	
Type of surgery			<0.001
Low anterior resection	184 (45.8)	25 (34.7)	
Abdominoperineal/abdominosacral resection	176 (43.8)	34 (47.2)	
Hartmann resection	8 (2.0)	8 (11.1)	
Pelvic exenteration[a]	32 (8.0)	3 (4.2)	
Other	2 (0.5)	2 (2.8)	
Extended (multivisceral) resection[b]	200 (49.8)	50 (69.4)	0.01
Intra operative radiotherapy	278 (69.2)	47 (65.3)	0.51
Radical resection (R0)	356 (88.6)	56 (77.8)	0.01

Abbreviations: ASA, American Society of Anaesthesiologists; cT4RC, clinical T4 rectal cancer; Gy, Gray; IQR, interquartile range; SD, standard deviation.

[a] Pelvic exenteration was defined as an en bloc resection of the rectum including complete removal of the bladder and reproductive organs (prostate/seminal vesicles, or uterus, ovaries and/or vagina).[2]

[b] Extended (multivisceral) resection is used for other combinations of resections than exenteration

Table 2. Demographic, clinical and tumour characteristics of LRRC patients (n = 293), stratified by age (<75 and ≥75 years).

	<75 years n = 240	**≥75 years n = 53**	***p*-value**
	n (%)	**n (%)**	
Mean age in years at time of surgery (±SD)	62.7 (8.2)	78.6 (3.2)	<0.001
Median follow-up in years (IQR)	2.8 (1.4–4.1)	2.3 (0.9–3.9)	0.09
Male	161 (67.1)	36 (67.9)	0.91
Comorbidity			0.01
None	90 (37.5)	9 (17.0)	
1 comorbidity	70 (29.2)	14 (26.4)	
2 comorbidities	44 (18.3)	16 (30.2)	
≥ 3 comorbidities	36 (15.0)	14 (26.4)	
ASA classification			0.36
I-II	204 (85.0)	41 (77.4)	
III	28 (11.7)	10 (18.9)	
Missing	8 (3.3)	2 (3.8)	
Neoadjuvant treatment			0.09
None	16 (6.7)	5 (9.4)	
Re-irradiation only	7 (2.9)	1 (1.9)	
Re-irradiation with concomitant chemotherapy	143 (59.6)	23 (43.4)	
Full course irradiation with concomitant chemotherapy	69 (28.8)	20 (37.7)	
Full course irradiation only	5 (2.1)	4 (7.5)	
Type of surgery			0.01
Low anterior resection	37 (15.4)	6 (11.3)	
Abdominoperineal/abdominosacral resection	91 (37.9)	22 (41.5)	
Hartmann resection	10 (4.2)	4 (7.5)	
Pelvic exenteration[a]	38 (15.8)	7 (13.2)	
Debulking	60 (25.0)	8 (15.1)	
Other	4 (1.7)	6 (11.3)	
Extended (multivisceral) resection[b]	131 (54.6)	28 (52.8)	0.82
Intra operative radiotherapy	208 (86.7)	38 (71.7)	0.01
Radical resection (R0)	139 (57.9)	38 (71.7)	0.06

Abbreviations: ASA, American Society of Anaesthesiologists; IQR, interquartile range; LRRC, locally recurrent rectal cancer. Also see comment in Table 1 about abbreviations SD and Gy.

[a] Pelvic exenteration was defined as an en bloc resection of the rectum including complete removal of the bladder and reproductive organs (prostate/seminal vesicles, or uterus, ovaries and/or vagina).[2]

[b] Extended (multivisceral) resection is used for other combinations of resections than exenteration

Postoperative morbidity

No significant differences were observed in the incidence of Clavien–Dindo Grade I–IV complications based on age in either the cT4RC or LRRC groups, but patients <75 years were more likely to have an uncomplicated postoperative course than patients ≥75 years ($p = 0.02$ for cT4RC and $p = 0.001$ for LRRC). More pulmonary complications were observed among cT4RC and LRRC patients ≥75 years than among patients <75 years (22.2% vs. 8.7%, $p = 0.001$ for cT4RC, and 26.4% vs. 14.2%, $p = 0.03$ for LRRC). Older cT4RC patients experienced more postoperative delirium and cerebrovascular accidents than younger patients (11.1%

vs. 1.0%, $p < 0.001$ for delirium, and 4.2% vs. 0.5%, $p = 0.03$ for cerebrovascular accidents). More delirium was also observed in LRRC patients ≥75 years than in patients <75 years (17.0% vs. 2.5%, $p < 0.001$). Other than fascial dehiscence in LRRC patients (9.4% vs. 1.7%, $p = 0.01$), surgical complications and reintervention rates (endoscopic, radiological and surgical) were not significantly different between elderly and younger cT4RC and LRRC patients (16.7% vs. 18.4%, $p = 0.72$, and 41.5% vs. 28.7%, $p = 0.07$, respectively). A more detailed description of complications in both groups is presented in Table 3.

Table 3. Details on postoperative outcomes of cT4RC and LRRC patients, stratified by age (<75 and ≥75 years).

	cT4RC		LRRC	
	<75 years n = 402	**≥75 years n = 72**	**<75 years n = 240**	**≥75 years n = 53**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Median admission time in days (IQR)	9.0 (7.0–14.0)	9.0 (7.0–16.0)	12.0 (7.0–17.0)	12.0 (8.0–20.5)
Median admission on ICU in days (IQR)	1.0 (0.0–1.0)[a]	1.0 (1.0–2.0)[a]	1.0 (1.0–2.0)	1.0 (1.0–2.5)
Surgical complications[b]	136 (33.8)	26 (36.1)	130 (54.2)	35 (66.0)
Anastomotic leakage	19 (4.7)	4 (5.6)	10 (4.2)	3 (5.7)
Clavien-Dindo ≥III	3 (0.7)	2 (2.8)	7 (2.9)	2 (3.8)
Presacral Abscess	46 (11.4)	5 (6.9)	48 (20.0)	12 (22.6)
Clavien-Dindo ≥III	28 (7.0)	2 (2.8)	36 (15.0)	9 (17.0)
Intra-Abdominal abscess	15 (3.7)	1 (1.4)	23 (9.6)	6 (11.3)
Clavien-Dindo ≥III	9 (2.2)	–	14 (5.8)	6 (11.3)
Ileus	49 (12.2)	14 (19.4)	62 (25.8)	13 (24.5)
Clavien-Dindo ≥III	1 (0.2)	2 (2.8)	2 (0.8)	–
Fascial Dehiscence	8 (2.0)	2 (2.8)	4 (1.7)[a]	5 (9.4)[a]
Wound infection	44 (10.9)	9 (12.5)	57 (23.8)	15 (28.3)
Abdominal	24 (6.0)	4 (5.6)	27 (11.3)	4 (7.5)
Perineal	20 (5.0)	5 (6.9)	30 (12.5)	11 (20.8)
Non-surgical complications[b]	136 (33.8)[a]	39 (54.2)[a]	111 (46.3)[a]	34 (64.2)[a]
Urologic	95 (23.6)	20 (27.8)	79 (32.9)	24 (45.3)
Pulmonary	35 (8.7)[a]	16 (22.2)[a]	34 (14.2)[a]	14 (26.4)[a]
Cardiac	25 (6.2)	9 (12.5)	15 (6.3)	5 (9.4)
Venous thromboembolism	11 (2.7)	–	5 (2.1)	1 (1.9)
Neurological				
Cerebrovascular accident (CVA)	2 (0.5)[a]	3 (4.2)[a]	1 (0.4)	1 (1.9)
Delirium	4 (1.0)[a]	8 (11.1)[a]	6 (2.5)[a]	9 (17.0)[a]
Complication grade according to Clavien-Dindo				
None	154 (38.3)[a]	17 (23.6)[a]	55 (22.9)[a]	2 (3.8)[a]
Grade I-II	167 (41.5)	38 (52.8)	108 (45.0)	25 (47.2)
Grade IIIa+IIIb	57 (14.2)	8 (11.1)	60 (25.0)	16 (30.2)
Grade IV	14 (3.5)	4 (5.6)	10 (4.2)	4 (7.5)
Grade V	6 (1.5)[a]	5 (6.9)[a]	4 (1.7)[a]	4 (7.5)[a]
Missing	4 (1.0)	–	3 (1.3)	2 (3.8)

Abbreviations: cT4RC, clinical T4 rectal cancer; ICU, intensive care unit; IQR, interquartile range; LRRC, locally recurrent rectal cancer.

[a] $p < 0.05$

[b] Number of patients that had at least one surgical or one non-surgical complication, respectively.

Mortality

The 30-day mortality decreased over time for both cT4RC and LRRC patients ≥75 years, from 7.5% and 10.0%, respectively, for the period 2005–2011, to 3.1% and 0.0%, respectively, for the period 2012–2017. Comparable 30-day mortality rates were observed for cT4RC and LRRC patients <75 years in both time periods (0.5% vs. 1.5% for cT4RC, respectively, and 2.9% vs. 1.4% for LRRC, respectively). The 30-day mortality rates were significantly different between cT4RC patients <75 and ≥75 years in the period 2005–2011, but were comparable for the latter period (p = 0.01 and p = 0.46, respectively). Among LRRC patients, no significant differences in 30-day mortality were observed based on age in either time period. The 90-day mortality rates did not improve over time. For cT4RC patients, the 90-day mortality rates in the period 2012−2017 were 9.4% and 2.1% for patients ≥75 years and those <75 years, respectively. The corresponding rates for patients with LRRC were 9.1% and 2.2%, respectively.

The 1-year mortality rate for cT4RC patients ≥75 years was significantly worse than for patients <75 years and did not improve over time (22.5% vs. 5.8%, p = 0.002 for 2005–2011, and 28.1% vs. 6.2%, p = 0.001 for 2012–2017). Among LRRC patients <75 years, the 1-year mortality improved non-significantly over time (20.6% vs. 13.8%, p = 0.16) and no improvements over time were observed among elderly patients. The differences in 1-year mortality between the two age groups for LRRC were not significant (p > 0.99 for 2005–2011 and p = 0.06 for 2012–2017). For both cT4RC and LRRC patients, assessing relative survival did not change these results. A more detailed description of mortality rates during the first year and overall and cancer-specific survival for the entire study period is presented in Tables 4 and 5, respectively. In Figure 1−4, Kaplan−Meier curves on absolute 1-year survival for the different time periods are presented. The causes of death in the first postoperative year are summarised in Table 6.

Table 4. Absolute mortality rates of both cT4RC and LRRC patients after surgery, stratified by age (<75 and ≥75 years) and period of surgery (2005–2011 and 2012–2017).

			2005-2011			
	cT4RC			**LRRC**		
	<75 years n = 207	**≥75 years n = 40**	***p*-value**	**<75 years n = 102**	**≥75 years n = 20**	***p*-value**
30-day	0.5%	7.5%	0.01	2.9%	10.0%	0.19
90-day	1.4%	10.0%	0.01	2.9%	10.0%	0.19
1-year	5.8%	22.5%	0.002	20.6%	20.0%	>0.99
			2012-2017			
	cT4RC			**LRRC**		
	<75 years n = 195	**≥75 years n = 32**	***p*-value**	**<75 years n = 138**	**≥75 years n = 33**	***p*-value**
30-day	1.5%	3.1%	0.46	1.4%	0.0%	>0.99
90-day	2.1%	9.4%	0.06	2.2%	9.1%	0.09
1-year	6.2%	28.1%	0.001	13.8%	27.3%	0.06

Abbreviations: cT4RC, clinical T4 rectal cancer; LRRC, locally recurrent rectal cancer.

Table 5. Overall, cancer-specific and disease-free survival rates for cT4RC and LRRC patients stratified by age (<75 and ≥75 years) for the period 2005–2017.

Overall survival				
	cT4RC <75 years	**cT4RC ≥ 75 years**	**LRRC <75 years**	**LRRC ≥ 75 years**
1-year	0.94	0.75	0.83	0.76
3-years	0.79	0.54	0.56	0.45
5-years	0.65	0.37	0.31	0.17
	$p < 0.001$		$p = 0.06$	
Cancer-specific survival				
	cT4RC <75 years	**cT4RC ≥ 75 years**	**LRRC <75 years**	**LRRC ≥ 75 years**
1-year	0.95	0.83	0.87	0.82
3-years	0.82	0.66	0.61	0.56
5-years	0.73	0.56	0.35	0.32
	$p = 0.001$		$p = 0.56$	
Disease-free survival				
	cT4RC <75 years	**cT4RC ≥ 75 years**	**LRRC <75 years**	**LRRC ≥ 75 years**
1-year	0.83	0.82	0.60	0.66
3-years	0.69	0.55	0.33	0.44
5-years	0.62	0.48	0.25	0.41
	$p = 0.10$		$p = 0.08$	

Abbreviations: cT4RC, clinical T4 rectal cancer; LRRC, locally recurrent rectal cancer.

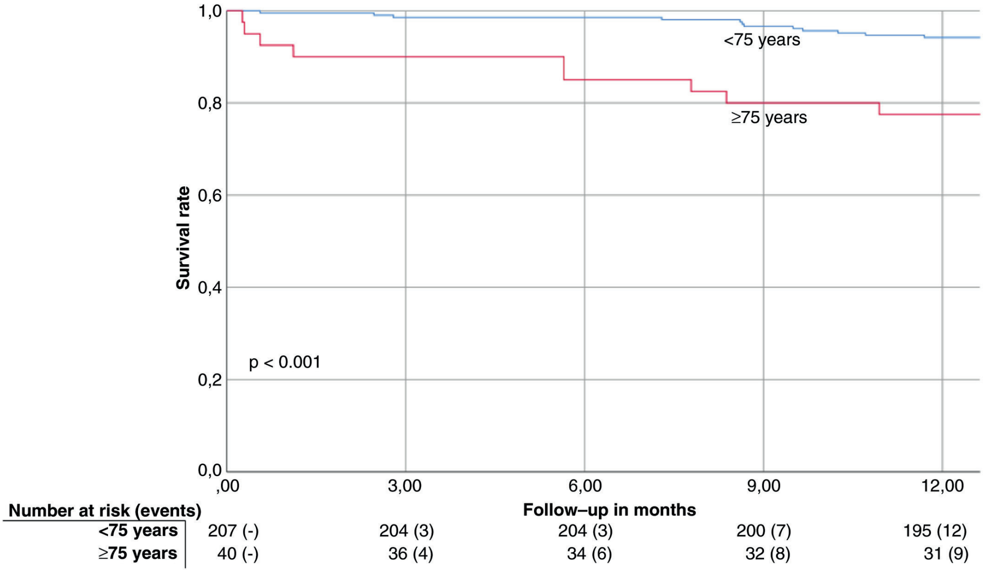

Figure 1. Kaplan–Meier curve for absolute 1-year survival for cT4RC patients for the period 2005–2011 (n = 247), stratified by age (<75 and ≥75 years).

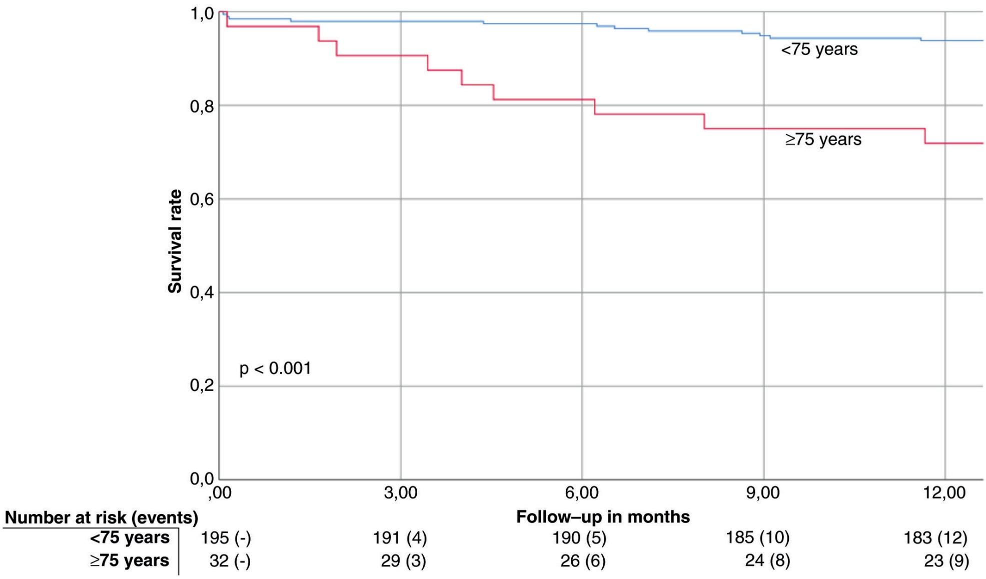

Figure 2. Kaplan–Meier curve for absolute 1-year survival for cT4RC patients for the period 2012–2017 (n = 227), stratified by age (<75 and ≥75 years).

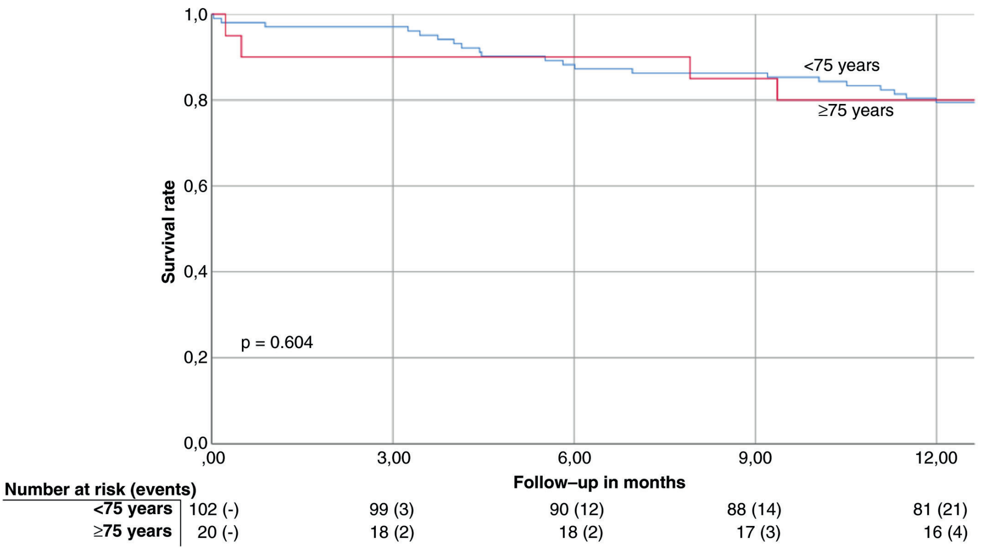

Figure 3. Kaplan–Meier curve for absolute 1-year survival for LRRC patients for the period 2005–2011 (n = 122), stratified by age (<75 and ≥75 years).

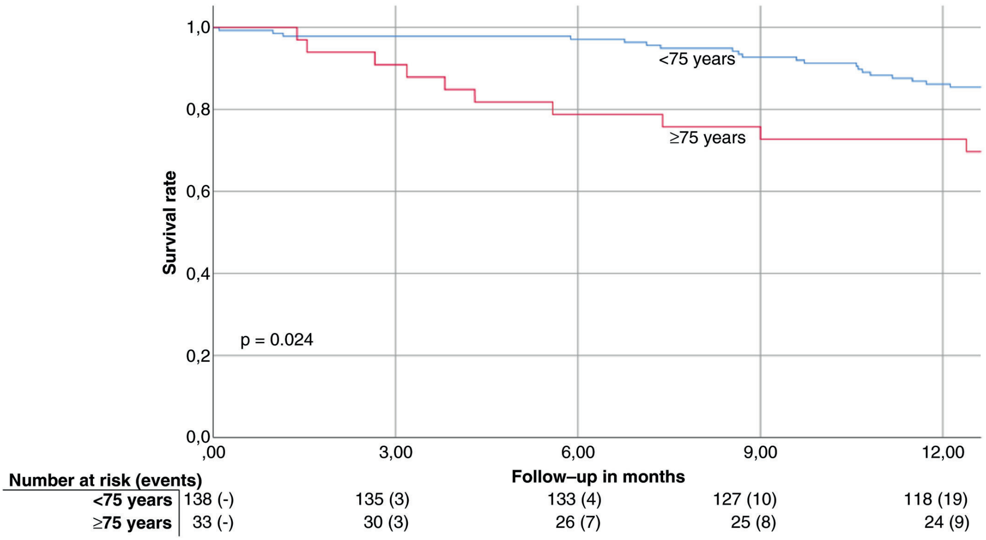

Figure 4. Kaplan–Meier curve for absolute 1-year survival for LRRC patients for the period 2012–2017 (n = 171), stratified by age (<75 and ≥75 years).

Table 6. Causes of death of all cT4RC and LRRC patients who died in the first year postoperatively, stratified by age (<75 and ≥75 years).

	cT4RC		LRRC	
	<75 years n = 24	**≥75 years n = 18**	**<75 years n = 40**	**≥75 years n = 13**
	n (%)	**n (%)**	**n (%)**	**n (%)**
In-hospital mortality[a]	6 (25.0)	5 (27.8)	4 (10.0)	4 (30.8)
Out-of-hospital mortality				
Treatment-induced deterioration[b]	1 (4.2)	2 (11.1)	6 (15.0)	4 (30.8)
Relapsing disease	11 (45.8)	5 (27.8)	25 (62.5)	3 (23.1)
Cardiopulmonary disease	–	2 (11.1)	2 (5.0)	2 (15.4)
Other	–	1 (5.6)	–	–
Unknown	6 (25.0)	3 (16.7)	3 (7.5)	–

Abbreviations: cT4RC, clinical T4 rectal cancer; LRRC, locally recurrent rectal cancer.

[a] Any combination of complications leading directly or indirectly to death during hospital admission (e.g. renal insufficiency, cardiac failure, respiratory failure etc.). In-depth analyses did not show specific major groups of complications.

[b] Deterioration of the physiological status of the patient after discharge from the hospital, leading to death without signs of relapsing disease, cardiopulmonary disease or cerebrovascular accidents.

DISCUSSION

In this study, we compared the morbidity and mortality of elderly and younger cT4RC and LRRC patients and analysed differences over time. In elderly cT4RC and LRRC patients, the 30-day mortality rates improved over the years to 3.1% and 0.0%, respectively, which were comparable with younger patients. Unfortunately, the 90-day and 1-year mortality rates were still significantly worse for elderly patients. Approximately 25% of elderly cT4RC or LRRC patients died in the first postoperative year, compared to 6.0% and 16.7% of younger patients, respectively, over the entire study period. Of the elderly patients who died in the first postoperative year, most died due to treatment-induced or non-cancer-related causes. Disease recurrence, however, was the main cause of death in patients <75 years.

More non-surgical complications were observed in elderly patients; however, no significant differences in the incidence of surgical complications and reinterventions were observed between the two age groups. Clavien–Dindo Grade ≥III complications occurred in 19% and 31% of young cT4RC and LRRC patients, and in 24% and 45% of elderly cT4RC and LRRC patients, respectively, which is comparable to other studies in which 25% of cT4RC and 36% of LRRC patients experienced Grade ≥III complications.[20,21] Although the morbidity of elderly patients remains high, the 30-day mortality has improved over time, which is observed for all stages of colon and rectal cancer and probably reflects improved perioperative and postoperative care.[14,15,22-25] The literature also showed improvements in 1-year mortality and comparable survival for elderly and younger patients with Stage I–III CRC, but in this study of cT4RC and LRRC patients no improvements in 90-day and 1-year overall mortalities were observed.[14,15] We found no significant influence of postoperative complications on mortality among elderly patients and, as many patients died after hospitalisation due to deterioration, a delayed effect of treatment on the physical condition of these patients could be hypothesised. Among patients with LRRC, higher mortality rates were also observed among the elderly, but the differences were smaller compared with patients <75 years than those observed among cT4RC patients. It is likely that poor oncological behaviour of these recurrent tumours has a relatively large influence on survival for both age groups.

The mortality rates presented in this study are based on relatively small patient groups, but are supported by population-based studies on outcomes in LARC in Northern European countries and the USA, where reported 30- and 90-day mortality rates range from 4.0%−14.5%, depending on stage.[13,26] Another Dutch study with LARC and LRRC patients treated with total pelvic exenteration found 90-day mortality rates similar to ours.[2] Our 1-year mortality rates are also in accordance with other studies which range from 21%−26.5% for locally advanced cases.[2,13]

In our institution, surgery for cT4RC and LRRC is performed open with extended or multivisceral resections, whereas minimally invasive surgery is the standard of care for non-advanced cases. Extended tumour involvement in the pelvic wall was more often observed in LRRC than cT4RC, requiring more extensive extra-anatomical exenterations such as unilateral or bilateral pelvic side wall or sacral resections (Table S1). It has been hypothesised that when stressors reach a certain threshold and homeostatic mechanisms are no longer able to compensate, functional decline with impaired health status and further diminishment of physiological reserve capacity may occur, leading to decreased resilience to future stressors.[27] The impact of major rectal surgery and hospitalisation could therefore induce increased vulnerability with a higher risk of death in the first postoperative year when other stressors appear. Although this effect is more often seen in frail people, this phenomenon could explain the higher mortality rates seen in this study in contrast to other studies of Stage I–III CRC patients.[14,15]

Patients' physiological status was evaluated preoperatively by a surgeon and an anaesthesiologist, and multidisciplinary team meeting decisions were based on tumour and patient characteristics and preferences. If the surgeon or anaesthesiologist suspected a poor physiological status, the patient was referred to a geriatrician for a more comprehensive geriatric screening and to improve performance status. Identifying frailty in elderly patients is important as it is a predictor of postoperative complications and shorter life expectancy.[28,29] Although all elderly patients in this study were preoperatively considered fit for multimodality treatment and surgery, the 1-year mortality rates remained high, which shows how extremely difficult it is to distinguish elderly patients at risk for increased mortality in the first postoperative year from those who are not. As not all of our patients underwent a geriatric assessment, estimating frailty and 1-year mortality risk should be considered for every elderly patient with cT4RC or LRRC.

Another possible intervention to improve outcomes could be prehabilitation. Supervised prehabilitation programmes have shown promise in improving physical condition and outcomes in patients unfit for surgery, but the role of these programmes in this specific patient group remains unclear.[30,31] In our study, all patients were instructed to increase their protein intake and physical activity in the preoperative period, but a supervised prehabilitation programme was not standard of care during the study period.

The most benefit towards improving mortality rates in elderly patients may be gained in the period after hospitalisation. Our results show that a major part of the 1-year mortality in elderly patients occurs in this period, regardless of postoperative complications or disease progression. Elderly patients who are hospitalised after surgery spend a considerable time in bed, leading to rapid muscle loss.[32,33] Sarcopenia has been associated with decreased physical reserve capacity and increased 1-year mortality.[34] Preserving muscle mass in both the early and late postoperative phases may increase physical functioning and prevent 1-year mortality in this specific age group. Therefore, rehabilitation programmes should be part of a total prehabilitation, Enhanced Recovery After Surgery and rehabilitation pathway and must be initiated immediately after surgery and continue after discharge.[33] A pilot study showed that elderly patients who received rehabilitation after abdominal emergency surgery had better 'Timed Up and Go' outcomes at 6 weeks after discharge in comparison with those receiving standard care.[32] As high 'Timed Up and Go' scores are a risk factor for both long-term institutionalisation and mortality in senior patients, improving this with a rehabilitation programme may result in reduced vulnerability and mortality.[35,36] Additionally, in patients undergoing other types of major gastrointestinal surgery, improvements have been seen in relevant parameters for cardiorespiratory fitness (e.g., VO_2 max and the 6-min walking test) after a multidisciplinary rehabilitation programme, although the influence of these programmes on postoperative outcomes and survival remains unclear.[37] In elderly patients with cT4RC or LRRC, survival outcomes may be improved by combining prehabilitation, enhanced recovery, and rehabilitation programmes. Studies focusing on this topic in cT4RC or LRRC patients are lacking, and future studies would be of interest.

Other than oncological and survival outcomes, functional outcomes including quality of life can also play a major role in the decision-making process, especially in the elderly population. It is known that the quality of life in elderly CRC patients improves after surgery and is comparable to that in younger patients.[38] Unfortunately, in our study we did not have information about the quality of life. However, earlier studies performed by our research group showed that patients with LRRC had lower health-related quality of life outcomes after surgery compared with patients with non-advanced disease or LARC, regardless of age.[39] More outcomes with respect to the quality of life and functional outcomes of this patient group should be addressed in future prospective studies.

This paper will help educate clinicians and elderly cT4RC and LRRC patients about the possible outcomes and expectations after surgery. In our study, a median length of 9 days of hospital admission for elderly cT4RC patients was observed, with only 24% having major complications (Clavien–Dindo ≥III) and 18% undergoing reinterventions (endoscopic, radiological and surgical). For elderly LRRC patients, median length of hospital admission was 12 days, 45% of them had major complications (Clavien–Dindo ≥III) and 42% had to undergo reinterventions (endoscopic, radiological and surgical). Although postoperative mortality is low, clinicians should be aware of the increased vulnerability and mortality in these elderly patients in the first postoperative year.

The strength of this study lies in the availability of many clinically relevant variables in a unique population of cT4RC and LRRC patients with a low prevalence of missing values. Although this is one of the largest single-centre studies with detailed data in this specific population without interhospital variations, the relatively small patient population could have resulted in less statistical power and it could be argued that it lacks generalisability to other centres. An important limitation of this study is that we were only able to study those patients who underwent surgery, with no information on patients who died preoperatively or were not eligible for, or declined, surgery. Furthermore, as we are a referral centre for these advanced and recurrent cases, the referral of patients could have resulted in some selection bias. The retrospective nature of this study is another limitation, with underestimation of minor complications due to lack of documentation. However, by accurately and thoroughly studying the medical records and contact with referral hospitals and general practitioners, an underestimation of complications was kept to a minimum.

CONCLUSION

Advances in rectal cancer care have led to equal short-term postoperative outcomes in elderly and younger patients, but 90-day and 1-year mortality rates did not improve over time. Approximately one out of four elderly cT4RC and LRRC patients died in the first postoperative year and, as the majority died after hospitalisation without disease recurrence, more awareness is needed towards patient care in the period after hospitalisation.

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SUPPLEMENTARY DATA OF CHAPTER 3

Supplementary Table 3.1. Details on the extent of exenteration, stratified by age group for both cT4RC and LRRC patients.

	cT4RC		LRRC	
	<75 years n = 32	**≥75 years n = 3**	**<75 years n = 38**	**≥75 years n = 7**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Sacral resections	3 (9.4)	–	20 (52.6)	5 (71.4)
Pelvic side wall resections				
Unilateral	12 (37.5)	–	18 (47.4)	1 (14.3)
Bilateral	1 (3.1)	–	10 (26.3)	3 (42.9)

CHAPTER 4

Functional bowel complaints and the impact on quality of life after colorectal cancer surgery in the elderly

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Front Oncol. 2022 Feb 9;12:832377. doi: 10.3389/fonc.2022.832377.

ABSTRACT

Background

The Low Anterior Resection Syndrome (LARS) is commonly reported after colorectal cancer surgery and significantly impairs quality of life. The prevalence and impact of LARS in the elderly after rectal cancer as well as colon cancer surgery is unclear. We aimed to describe the prevalence of LARS complaints and the impact on quality of life in the elderly after colorectal cancer surgery.

Materials and methods

Patients were included from seven Dutch hospitals if they were at least one year after they underwent colorectal cancer surgery between 2008 and 2015. Functional bowel complaints were assessed by the LARS score. Quality of life was assessed by the EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires. Outcomes in patients ≥70 years were compared to a reference group of patients <70 years.

Results

In total, 440 rectal cancer and 1183 colon cancer patients were eligible for analyses, of whom 133 (30.2%) rectal and 536 (45.3%) colon cancer patients were ≥70 years. Major LARS was reported by 40.6% of rectal cancer and 22.2% of colon cancer patients ≥70 years. In comparison, patients <70 years reported major LARS in 57.3% after rectal cancer surgery ($p = 0.001$) and in 20.4% after colon cancer surgery ($p = 0.41$). Age ≥70 years was independently associated with reduced rates of major LARS after rectal cancer surgery (OR 0.63, $p = 0.04$). Patients with major LARS reported significantly impaired quality of life on almost all domains.

Conclusion

Elderly should not be withheld a restorative colorectal cancer resection based on age alone. However, a substantial part of the elderly colorectal cancer patients develops major LARS after surgery, which often severely impairs quality of life. Since elderly frequently consider quality of life and functional outcomes as one of the most important outcomes after treatment, major LARS and its impact on quality of life should be incorporated in the decision-making process.

INTRODUCTION

As a consequence of the improved treatment and outcomes in elderly colorectal cancer patients over the last decades, elderly pay more attention to long-term functional outcomes and quality of life.[1,2] In fact, elderly frequently consider outcomes related to quality of life and functional recovery at least as important as survival-related outcomes.[3,4]

The Low Anterior Resection Syndrome (LARS) is an organ-specific functional outcome that is strongly associated with quality of life.[5] LARS includes a cluster of functional bowel complaints including faecal incontinence, increased stool frequency, and urgency, and is prevalently observed among patients after colorectal surgery.[6–8] Although LARS typically arises after rectal cancer surgery, recent studies also described these complaints after colon cancer surgery.[9–11]

Functional bowel complaints after rectal cancer surgery have been described increasingly over the last decades.[7,9,10,12,13] However, studies on the prevalence of LARS and the impact on quality of life among the elderly after rectal cancer as well as colon cancer surgery are scarce. It has been described earlier that faecal incontinence impairs quality of life in the elderly.[14] However, the impact of LARS in the elderly, which also includes other symptoms that may impair quality of life, such as urgency and increased stool frequency, is unclear. In order to adequately counsel elderly colorectal cancer patients, more knowledge is needed with regard to functional bowel complaints and the impact on quality of life in the elderly.

The primary aim of this study was to describe the prevalence of LARS complaints among elderly (≥70 years) patients after rectal cancer as well as colon cancer surgery. The secondary aim was to investigate the impact of LARS on quality of life and to compare the results in the elderly with a reference group of younger patients (<70 years).

MATERIAL AND METHODS

Population and data collection

All consecutive patients that underwent colorectal cancer surgery with primary anastomosis between 2008 and 2015 in seven hospitals in The Netherlands were selected retrospectively. Patients ≥18 years who were at least 1 year after primary surgery or ostomy reversal were included. Since relapsing disease has a profound impact on quality of life, patients with metastatic or recurrent disease were excluded.[15,16] Other exclusion criteria were: presence of a (temporary) ostomy, cognitive disability or dementia, death prior to the start of the study, or a local excision, a subtotal or total colectomy, or an unknown procedure.

Patient characteristics, data on treatment and pathology, and additional clinical and demographic data were retrospectively extracted from the medical records. Complications occurring in the first 30 postoperative days or before hospital discharge were scored using the Clavien-Dindo classification.[17] Patients received treatment according to the national treatment guidelines for colorectal cancer.[18] Therefore, neoadjuvant long-course chemoradiotherapy or short-course radiotherapy was proposed in patients with stage II-III rectal cancer. Adjuvant treatment was advised in stage III colon cancer patients. Participants were approached via a letter that explained the aim of the study, together with the questionnaires and a prepaid return envelope. The study was reviewed and approved not to be subject to the Medical Research Involving Human Subjects Act (Medical Research Ethics Committees United – Nieuwegein, registration number W20.322).

Measurement instruments

The LARS score was used to assess bowel dysfunction after surgery. The LARS score is a validated questionnaire regarding functional bowel complaints.[5,19,20] Although the LARS score was originally developed for patients after a low anterior resection, recent studies also applied the LARS score in patients after colon resections.[9,10] The questionnaire includes 5 questions with a total score ranging between 0 and 42. Based on the total score, patients are classified into: no LARS (0-20 points), minor LARS (21-29 points), or major LARS (30-42 points).[19] The European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-CR29 were used to assess health-related quality of life. The EORTC QLQ-C30 questionnaire includes 30 questions on global quality of life, functional scales, and symptom assessment.[21] The EORTC QLQ-CR29 includes 29 questions specifically for patients with colorectal cancer.[22] For EORTC QLQ-C30 and QLQ-CR29, a high score on functional scales represents a high level of functioning and a high score on symptom scales represents a high level of symptoms.

Statistical analyses

The primary endpoint was the prevalence of LARS in the elderly population. Secondary endpoints were the impact of LARS complaints on quality of life, the differences in LARS outcomes between the elderly (≥70 years) and a reference group of younger patients (<70 years), and factors associated with major LARS. Statistical analyses were performed using SPSS Statistics 25.0 software (IBM, Endicott, New York, USA). Demographics were presented for all patients. Continuous data were reported as mean with standard deviation (SD) or as median with interquartile range (IQR), depending on the parameter distribution. Categorical data were reported as count with percentage (%).

Intergroup comparisons between patients ≥70 years and a reference group of patients <70 years were performed using chi-squared test or Fisher's exact test for categorical data, when appropriate. Unpaired *t*-tests and Mann-Whitney *U* tests were used for normally and non-normally distributed continuous data. A *p*-value of <0.05 was considered statistically significant. All tests were two-sided.

The following factors possibly associated with major LARS were tested in univariable binary logistic regression analyses: gender, age at time of surgery, American Society of Anaesthesiologists (ASA) classification, time since surgery, neoadjuvant treatment (in rectal cancer), surgical procedure, surgical technique, distance of tumour from anal verge on MRI or colonoscopy in centimetres from the anal verge (in rectal cancer), temporary diverting ostomy during primary surgery, pathological tumour stage, anastomotic leakage, postoperative complications (Clavien-Dindo scale), and adjuvant chemotherapy (in colon cancer). Multivariable logistic binary regression analyses were used to test for the independent association of potential factors associated with major LARS. Only variables that were possibly associated with major LARS in univariable binary regression analysis ($p < 0.10$) were included in multivariable binary regression analysis. In case the missing values of a variable in univariable and multivariable binary regression analyses exceeded 5% and were considered to be missing at random or completely at random, multiple imputation was performed to impute the missing data.[23]

The EORTC Health-Related Quality of Life subdomains were scored according to the standard scoring guidelines and were compared between LARS groups (no/minor or major LARS) using Mann-Whitney *U* test. Earlier studies showed that the impact of LARS complaints on quality of life was comparable between patients with no and minor LARS, as well as between patients with colon and rectal cancer.[9,24] Therefore, these groups were combined in quality of life outcomes.

RESULTS

In total, 5036 patients underwent colorectal cancer surgery between 2008 and 2015 in the participating hospitals. Patients were excluded due to recurrent locoregional or systemic disease (n=1159), presence of an ostomy (n=568), cognitive disability or dementia (n=71), death prior to the start of the study (n=695), local excision (n=120), subtotal or total colectomy (n=37), or unknown procedure (n=8).

Eventually, 2378 patients were included in this study. A total of 1658 patients returned their EORTC QLQ-C30, EORTC QLQ-CR29, as well as their LARS questionnaires (75.6%

of patients <70 years vs. 62.9% of patients ≥70, $p < 0.001$). Since the primary endpoint was the prevalence of LARS, 35 patients who returned incomplete LARS questionnaires were excluded from analyses. This resulted in 1623 (68.3%) patients who were eligible for analyses. Figure 1 presents a patient disposition flowchart.

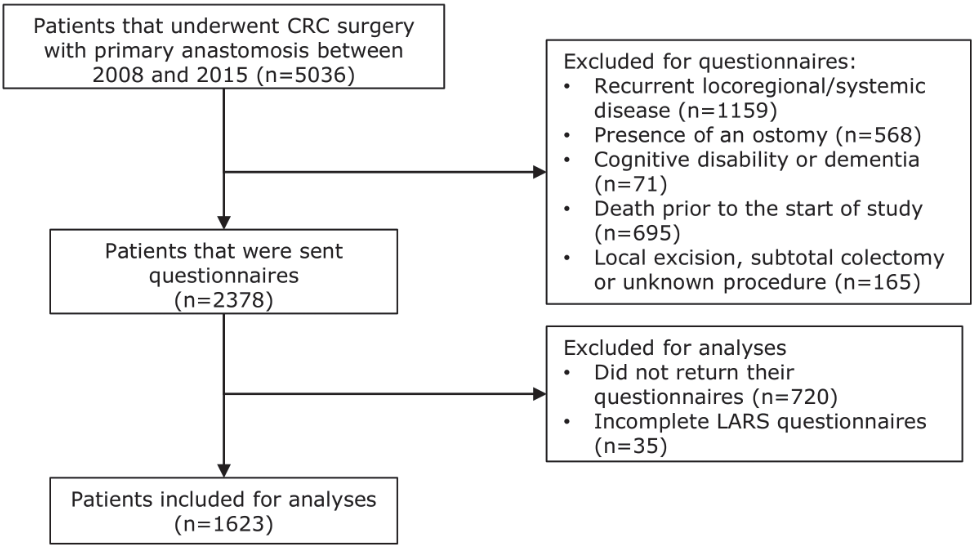

Figure 1. Patient disposition flowchart. Out of 5036 patients in total who underwent colorectal cancer surgery with primary anastomosis between 2008 and 2015, 2378 were sent questionnaires due to the inclusion and exclusion of patients based on the mentioned criteria. In total, 720 patients did not return their questionnaires and 35 patients returned incomplete LARS questionnaires. Overall, 1623 patients were included for analyses regarding LARS complaints and quality of life.

Of the 440 rectal cancer patients, 133 (30.2%) patients were ≥70 years and 307 (69.8%) patients were <70 years. The formation of a temporary diverting ostomy during primary surgery was less often observed in patients ≥70 years than in patients <70 years (63.9% vs. 75.6%, $p = 0.01$). The mean follow-up since surgery was 5.2 years (SD 2.1) for both age groups. Table 1 presents further details on demographic outcomes in rectal cancer patients.

4

Table 1. Demographic, clinical and tumour characteristics of rectal cancer patients (n = 440), stratified by age groups (<70 years and ≥70 years).

	<70 years n = 307	**≥70 years n = 133**	***p*-value**
	n (%)	**n (%)**	
Median age in years at time of surgery (IQR)	62.2 (55.8 – 66.6)	74.5 (72.2 – 77.5)	<0.001
Mean time since surgery in years (SD)	5.2 (2.1)	5.2 (2.1)	0.94
Male	180 (58.6)	93 (69.9)	0.03
ASA classification			0.01
I-II	288 (93.8)	114 (85.7)	
≥III	13 (4.2)	16 (12.0)	
Missing	6 (2.0)	3 (2.3)	
Tumour stage			0.41
Stage 0	11 (3.6)	5 (3.8)	
Stage I-II	196 (63.8)	93 (69.9)	
Stage III-IV	100 (32.7)	35 (26.3)	
Neoadjuvant treatment			0.01
None	97 (31.6)	47 (35.3)	
Short-course radiotherapy	96 (31.3)	57 (42.9)	
Long-course chemoradiotherapy	113 (36.8)	29 (21.8)	
Distance of tumour from anal verge (cm)			0.18
<5 cm	45 (14.7)	9 (6.8)	
5 – 9.9 cm	116 (37.8)	50 (37.6)	
10 – 14.9 cm	84 (27.4)	41 (30.8)	
≥15 cm	20 (6.5)	9 (6.8)	
Missing	42 (13.7)	24 (18.0)	
Technique of surgery			0.10
Open	164 (53.4)	68 (51.1)	
Laparoscopic	134 (43.6)	55 (41.4)	
Converted to open	8 (2.6)	10 (7.5)	
Missing	1 (0.3)	–	
Type of surgery			0.52
Rectosigmoid resection	12 (3.9)	7 (5.3)	
(Low) anterior resection	295 (96.1)	126 (94.7)	
Temporary diverting ostomy during primary surgery	232 (75.6)	85 (63.9)	0.01
Median time until ostomy reversal in months (IQR)	4.3 (2.9 – 8.0)	4.3 (3.2 – 5.6)	0.27
Anastomotic leakage	21 (6.8)	9 (6.8)	0.98
Postoperative Complications (Clavien-Dindo)			0.80
Grade 0 (No complication)	176 (57.3)	80 (60.2)	
Grade I-II	83 (27.0)	35 (26.3)	
Grade III	39 (12.7)	13 (9.8)	
Grade IV	9 (2.9)	5 (3.8)	

Of the 1183 colon cancer patients, 536 (45.3%) patients were ≥70 years and 647 (54.7%) patients were <70 years. The formation of a temporary diverting ostomy during primary surgery was less often observed in patients ≥70 years than in patients <70 years (7.3% vs. 11.9%, respectively, p = 0.01). The mean follow-up since surgery was 4.9 years (SD 2.0) for patients ≥70 years and 4.8 years (SD 2.0) for patients <70 years (p = 0.83). Table 2 presents further details on demographic outcomes in colon cancer patients.

Table 2. Demographic, clinical and tumour characteristics of colon cancer patients (n = 1183), stratified by age groups (<70 years and ≥70 years).

	<70 years n = 647	**≥70 years n = 536**	***p*-value**
	n (%)	**n (%)**	
Median age in years at time of surgery (IQR)	63.5 (58.7 – 66.8)	76.1 (73.3 – 80.2)	<0.001
Mean time since surgery in years (SD)	4.8 (2.0)	4.9 (2.0)	0.83
Male	370 (57.2)	281 (52.4)	0.11
ASA classification			<0.001
I-II	590 (91.2)	427 (79.7)	
≥III	48 (7.4)	101 (18.8)	
Missing	9 (1.4)	8 (1.5)	
Tumour stage (pathological)			0.01
Stage 0	1 (0.2)	–	
Stage I-II	421 (65.1)	389 (72.6)	
Stage III-IV	225 (34.8)	147 (27.4)	
Technique of surgery			0.01
Open	218 (33.7)	209 (39.0)	
Laparoscopic	385 (59.5)	275 (51.3)	
Converted to open	42 (6.5)	52 (9.7)	
Missing	2 (0.3)	-	
Type of surgery			<0.001
Right hemicolectomy	251 (38.8)	276 (51.5)	
Transverse/left hemicolectomy	80 (12.4)	53 (9.9)	
Sigmoid resection	305 (47.1)	200 (37.3)	
Anterior resection	11 (1.7)	7 (1.3)	
Temporary diverting ostomy during primary surgery	77 (11.9)	39 (7.3)	0.01
Median time until ostomy reversal in months (IQR)	8.2 (4.6 – 10.1)	4.8 (3.5 – 9.4)	0.03
Anastomotic leakage	40 (6.2)	28 (5.2)	0.48
Post-operative Complications (Clavien-Dindo)			0.056
Grade 0 (No complication)	453 (70.0)	335 (62.5)	
Grade I-II	122 (18.9)	119 (22.2)	
Grade III	56 (8.7)	66 (12.3)	
Grade IV	16 (2.5)	15 (2.8)	
Missing	-	1 (0.2)	
Adjuvant chemotherapy	262 (40.5)	123 (22.9)	<0.001

LARS outcomes

In rectal cancer patients ≥70 years, major LARS was reported by 40.6% of patients, while minor LARS was reported by 17.9% of patients. In comparison, in patients <70 years, major LARS was reported by 57.3% (p = 0.001) of patients and minor LARS by 19.5% (p = 0.58) of patients.

In colon cancer patients ≥70 years, major LARS was reported by 22.2% of patients and minor LARS by 17.2% of patients. In patients <70 years, major LARS was reported by 20.4% (p = 0.41) of patients and minor LARS by 22.6% (p = 0.02) of patients. Figure 2 presents the subscales of the LARS score, separately for colon and rectal cancer patients.

Associated factors for major LARS

Age ≥70 years was independently associated with reduced rates of major LARS in rectal cancer patients (OR 0.63, p = 0.04). In colon cancer patients, a left hemicolectomy (OR 0.52, p = 0.01) was independently associated with lower rates of major LARS. Female gender (OR 2.00 for rectal cancer, p = 0.002 and OR 1.68 for colon cancer, $p < 0.001$) and a temporary diverting ostomy during primary surgery (OR 2.54 for rectal cancer, $p < 0.001$ and OR 1.71 for colon cancer, p = 0.03) were independently associated with increased rates of major LARS in both rectal as well as colon cancer patients. Tables 3 and 4 present further details of the univariable and multivariable binary regression analysis on factors associated with major LARS in rectal and colon cancer patients.

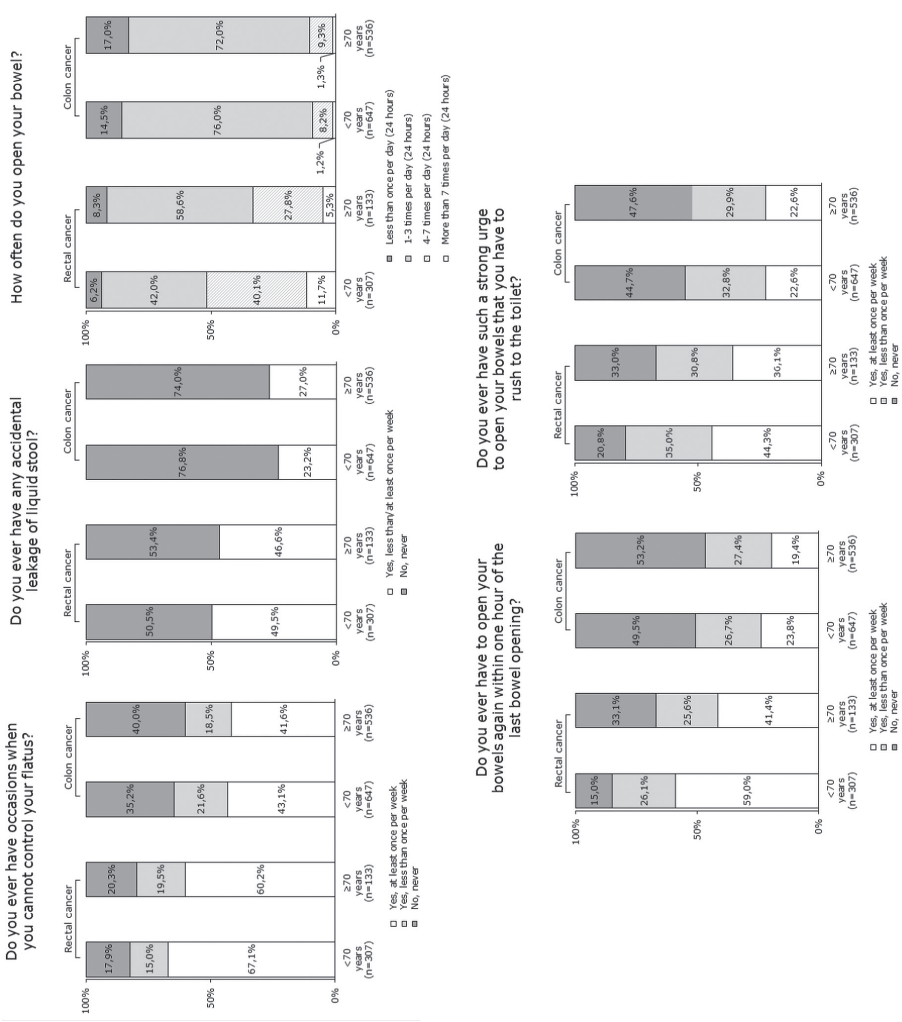

Figure 2. LARS subscale items, separately for rectal and colon cancer patients, stratified by age groups (<70 years and ≥70 years).

Table 3. Univariable and multivariable logistic regression analyses on associated factors for major LARS in rectal cancer patients (n = 440).

		Univariate			Multivariable		
	n (%)	**OR**	**95%-CI**	***p*-value**	**OR**	**95%-CI**	***p*-value**
Gender							
Male	273 (62.0)	1.00			1.00		
Female	167 (38.0)	1.85	1.25 – 2.74	0.002	2.00	1.30 – 3.07	0.002
Age							
<70 years	307 (69.8)	1.00			1.00		
≥70 years	133 (30.2)	0.51	0.34 – 0.77	0.01	0.63	0.40 – 0.98	0.04
ASA classification							
I-II	402 (91.4)	1.00					
III	29 (6.6)	1.11	0.52 – 2.38	0.78			
Missing	9 (2.0)						
Time since surgery							
2-3 years	121 (27.5)	1.11	0.70 – 1.76	0.65			
4-5 years	134 (30.5)	1.18	0.76 – 1.85	0.46			
>5 years	185 (42.0)	1.00					
Neoadjuvant treatment							
None	144 (32.7)	1.00			1.00		
Radiotherapy	153 (34.8)	1.35	0.86 – 2.13	0.20	0.95	0.57 – 1.59	0.84
Chemoradiotherapy	142 (32.3)	2.00	1.25 – 3.21	0.004	0.94	0.53 – 1.64	0.82
Surgical procedure							
Rectosigmoid resection	19 (4.3)	1.00					
LAR	421 (95.7)	1.93	0.75 – 5.00	0.18			
Surgical technique							
Laparoscopy	189 (43.0)	1.00					
Open	232 (52.7)	1.03	0.70 – 1.51	0.88			
Converted to open	18 (4.1)	0.93	0.35 – 2.44	0.88			
Missing	1 (0.2)						
Distance of tumour from anal verge (cm)*							
<5.0 cm	60 (13.6)	4.48	2.00 – 10.07	<0.001	2.80	0.82 – 9.58	0.10
5.0-9.9 cm	183 (41.6)	2.07	1.02 – 4.18	0.04	1.41	0.64 – 3.10	0.40
10.0-14.9 cm	151 (34.3)	1.10	0.48 – 2.49	0.82	0.87	0.35 – 2.13	0.75
≥15cm	50 (11.4)	1.00			1.00		
Temporary diverting ostomy	317 (72.0)	3.10	2.00 – 4.82	<0.001	2.54	1.51 – 4.29	<0.001
Tumour stage							
Stage 0	16 (3.6)	0.82	0.29 – 2.33	0.72			
Stage I-II	289 (65.7)	0.87	0.57 – 1.30	0.49			
Stage III-IV	135 (30.7)	1.00					
Anastomotic leakage	30 (6.8)	1.21	0.57 – 2.55	0.62			
Clavien-Dindo complication grade							
Grade 0	256 (58.2)	1.00			1.00		
Grade I-II	118 (26.8)	1.22	0.79 – 1.89	0.37	1.05	0.64 – 1.71	0.85
Grade III-IV	66 (15.0)	1.99	1.13 – 3.49	0.02	1.51	0.82 – 2.80	0.19

*Multiple imputation was performed due to a high amount of missing values.

Table 4. Univariable and multivariable logistic regression analyses on associated factors for major LARS in colon cancer patients (n = 1183).

		Univariable			Multivariable		
	n (%)	**OR**	**95%-CI**	***p*-value**	**OR**	**95%-CI**	***p*-value**
Gender							
Male	651 (55.0)	1.00			1.00		
Female	532 (45.0)	1.65	1.25 – 2.18	<0.001	1.68	1.26 – 2.23	<0.001
Age							
<70 years	647 (54.7)	1.00					
≥70 years	536 (45.3)	1.13	0.85 – 1.49	0.41			
ASA classification							
I-II	1017 (86.0)	1.00					
III	149 (12.6)	0.84	0.54 – 1.31	0.45			
Missing	17 (1.4)						
Time since surgery							
2-3 years	384 (32.5)	0.89	0.63 – 1.24	0.48			
4-5 years	347 (29.3)	1.15	0.82 – 1.60	0.42			
>5 years	452 (38.2)	1.00					
Surgical procedure							
Right hemicolectomy	527 (44.5)	1.00			1.00		
Left/transverse hemicolectomy	133 (11.2)	0.55	0.33 – 0.92	0.02	0.52	0.31 – 0.88	0.02
Sigmoid resection	505 (42.7)	0.77	0.57 – 1.04	0.08	0.75	0.55 – 1.03	0.07
Anterior resection	18 (1.5)	0.89	0.29 – 2.75	0.84	0.78	0.25 – 2.44	0.67
Surgical technique							
Laparoscopy	660 (55.8)	1.00					
Open	427 (36.1)	1.06	0.79 – 1.43	0.69			
Converted to open	94 (7.9)	0.82	0.47 – 1.43	0.49			
Missing	2 (0.2)						
Temporary diverting ostomy	116 (9.8)	1.54	1.00 – 2.37	0.049	1.71	1.05 – 2.79	0.03
Tumour stage							
Stage I-II	810 (68.5)	1.22	0.90 – 1.66	0.20			
Stage III-IV	372 (31.4)	1.00					
Anastomotic leakage	68 (5.7)	1.59	0.92 – 2.73	0.095	1.27	0.70 – 2.32	0.43
Clavien-Dindo complication grade							
Grade 0	788 (66.6)	1.00					
Grade I-II	241 (20.4)	1.26	0.89 – 1.77	0.20			
Grade III-IV	153 (12.9)	1.34	0.89 – 2.01	0.16			
Missing	1 (0.1)						
Adjuvant chemotherapy	385 (32.5)	0.81	0.60 – 1.10	0.17			

Impact of LARS on quality of life

Major LARS significantly impaired global quality of life in both patients ≥70 years and <70 years when compared with patients with no or minor LARS. Besides, patients with major

LARS scored worse on almost all functional and symptom scales of the EORTC QLQ-C30 and EORTC QLQ-CR29 in comparison with patients with no or minor LARS. Figures 3 and 4 present EORTC QLQ-C30 and EORTC QLQ-CR29 outcomes in both elderly and younger patients.

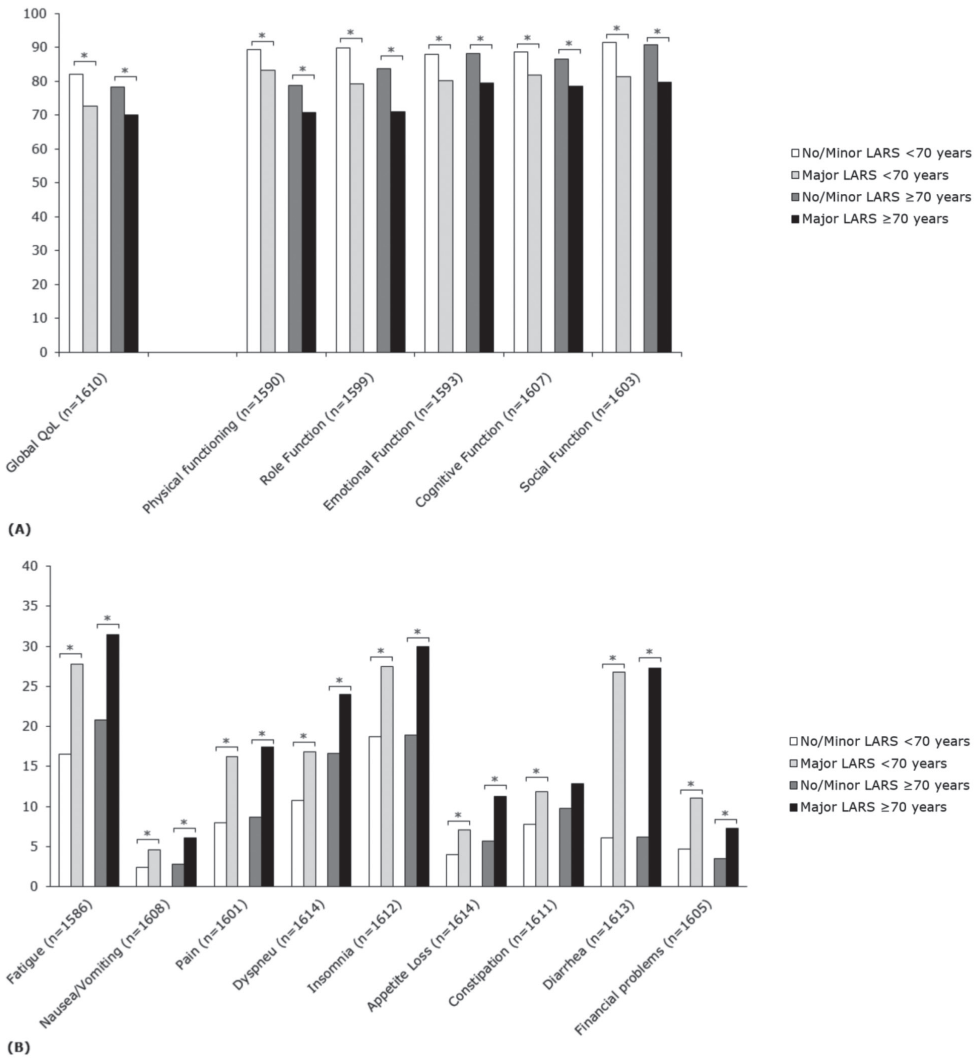

Figure 3. Mean scores of EORTC QLQ-C30 subscales for patients <70 years and ≥70 years, stratified by LARS group. **(A)** Functional scales: A higher score represents a better level of functioning. **(B)** Symptom scales: A higher score represents a higher level of symptoms. Significant differences are indicated by an asterisk; *p*-value <0.05.

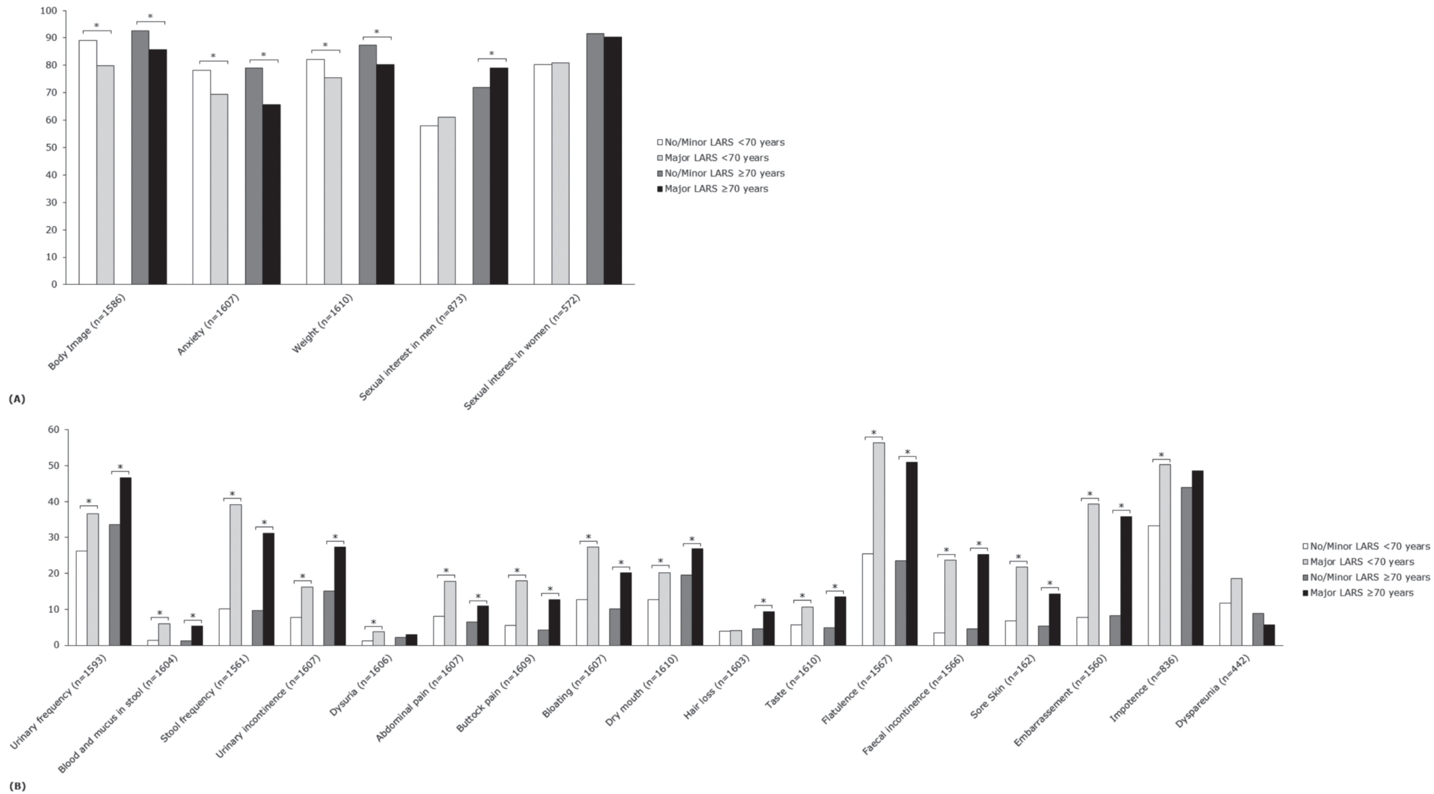

Figure 4. Mean scores of EORTC QLQ-CR29 subscales for patients <70 years and ≥70 years, stratified by LARS group. **(A)** Functional scales: A higher score represents a better level of functioning. **(B)** Symptom scales: A higher score represents a higher level of symptoms. Significant differences are indicated by an asterisk; *p*-value < 0.05.

DISCUSSION

This study examined the prevalence of LARS and the impact on quality of life among elderly patients after rectal cancer as well as colon cancer surgery and addresses several important issues. Firstly, major LARS was not only prevalent in more than 40% of elderly rectal cancer patients, but also in more than 20% of elderly colon cancer patients after surgery. Secondly, our data suggest that elderly do not report major LARS more often after rectal as well as colon cancer surgery when compared with younger patients. Finally, patients that suffered from major LARS reported significantly impaired quality of life on almost all domains.

Functional bowel complaints are frequently observed after colorectal cancer surgery, especially in the first postoperative year.[6,7,9,10] Similar to our results, earlier studies also reported major LARS in 34–48% of patients after rectal cancer surgery and in 20% of patients after colon cancer surgery.[6,9,11,24] The pathophysiology of LARS after rectal as well as colon cancer surgery seems to be multifactorial.[6,25] After rectal cancer surgery, LARS is probably caused by the diminished rectal reservoir capacity, along with anal sphincter dysfunction and colonic dysmotility.[6] While colonic dysmotility seems to contribute to LARS after colon cancer surgery as well, the reduced absorptive capacity of electrolytes and water probably results in more liquid stool, increased bowel frequency and the risk for faecal incontinence.[9,25–27] In accordance to the existing literature, the present study observed that LARS complaints were most prevalent in colon cancer patients after a sigmoid resection or right hemicolectomy.[9,11,25,27,28] Most likely, the reduced reservoir capacity of the rectum when incorporated in an anastomosis is an additional factor contributing to these complaints after a sigmoid resection.[10] While after a right hemicolectomy, the loss of the right colon, which is considered as the main site for water absorption, might contribute to the increased risk for complaints.[25,28] Besides, the loss of the ileocaecal valve and its sphincter function, the consequent ileocolic dysmotility, and the increased malabsorption of bile acids in the terminal ileum may also declare the increased bowel complaints observed after a right hemicolectomy.[25,28] However, it should also be noted that among the general population without a history of abdominal surgery, 8–15% suffers from major LARS as well.[7,29] Therefore, the reported LARS rates after surgery may not be fully attributable to the treatment alone and may be pre-existent to a certain extent in some patients.

Apart from focusing on the prevalence of major LARS, it is also important to consider the impact of major LARS on quality of life. Comparing the findings of the present study with earlier studies confirms that major LARS significantly impairs quality of life on almost all domains.[6,13,14] However, it can be hypothesised that elderly patients experience functional bowel complaints differently than younger patients. A recent study showed that elderly, especially female patients experienced less disturbances from their bowel complaints than their younger equivalents.[7] A possible explanation might be that older patients more commonly suffer from a poor sphincter function, bowel complaints, or faecal incontinence on forehand.[14,30] Consequently, they might be less perceptive for a deterioration of these complaints after treatment.[31] Besides, elderly patients seem to adapt more rapidly to their bowel disturbances after treatment than the younger population.[7] However, it must be noted that almost 50% of the elderly still considered their complaints as problematic after 2 years.[7]

Clinicians often underestimate the risk and the impact of functional bowel complaints.[32] However, based on the data in this study, it might be suggested that in current clinical practice, more attention is paid to functional bowel complaints in the elderly than in the younger population. Younger patients, which were used as a reference population in this study, reported major LARS significantly more often after rectal cancer surgery. Although some studies also found a reduced risk for major LARS in older patients, most studies did not observe any influence of age.[24,31,33] Besides, the elderly suffer more commonly from pre-existent bowel complaints and poor sphincter function.[7,29,30] Therefore, the reduced rates of major LARS in the elderly in this study are most likely caused by better preoperative patient selection, rather than a physiological cause.[31,33] Probably, the elderly at risk for major LARS were more often refrained from a restorative rectal cancer resection or diverting ostomy reversal when compared to younger patients.[7,24,31,33,34] Since patients in whom an ostomy was still present were not included in this study, this may also clarify that temporary diverting ostomy creation was less often observed during primary surgery in the elderly when compared to the younger population. Lastly, the outcomes related to the prevalence of LARS in the elderly may also have been influenced by age-related bias, since elderly had a significantly lower response rate to the questionnaires than younger patients.

It is important for both colon and especially rectal cancer patients to be informed about major LARS and its influence on quality of life when the benefits and risks of either a restorative or non-restorative rectal cancer resection are weighed. Major LARS results in poor functional outcomes, reduced quality of life and lower levels of independency. Particularly elderly patients consider these outcomes related to functional complaints, quality of life and the maintenance of independency as one of the most important outcomes of a treatment strategy.[3,35,36] Another aspect that should be considered in particularly in the elderly when the benefits and risk of either a restorative or non-restorative procedure are weighed, is the risk for anastomotic leakage. Especially since the elderly are at increased risk for devastating consequences if an anastomotic leakage occurs, with reported mortality rates up to 30%.[37,38] Moreover, it should be noted that a permanent end ostomy is not only well tolerated by most elderly, it also results in a quality of life that is comparable to the quality of life in the general population.[39] On the contrary, there are also studies that describe an increased level of functional dependency and worse survival in rectal cancer patients with a permanent end ostomy when compared to patients with a primary anastomosis.[40] Although these studies did not incorporate confounding factors that may have influenced both the decision to perform an end ostomy as well as survival, certain aspects related to an end ostomy such as the need for ostomy care, the risk for ostomy-related complications, and survival should also be taken into consideration during the decision-making process.

Preoperatively discussing functional bowel complaints is crucial to set and manage expectations and to support the decision that patients have to make. The Pre-Operative Low Anterior Resection Syndrome Score (POLARS) may help as a consent aid to estimate the risk for functional bowel complaints. Apart from the value of the POLARS in counselling patients and helping them to decide between a restorative or a non-restorative resection, it may also help clinicians to identify those patients that may benefit most from a permanent end ostomy.[41]

The strength of this study was the availability of real-world data from a large population of 669 elderly colorectal cancer survivors among different hospitals in The Netherlands, of whom 155 patients were older than 80 years old. Besides, we included a reference group of younger patients to put the outcomes in the elderly into perspectives. The mean time after surgery of 5 years was another strength of this study, since this has given insights in functional outcomes and the impact on quality of life on the mid- and long-term of both rectal as well as colon cancer patients.

Since data regarding patient characteristics of the excluded patients were absent and we performed a retrospective study, we did not have data regarding the preoperative patient selection, which is considered as one of our main limitations. The use of the LARS score in patients after colon resections might also be considered as a limitation, as the questionnaire was originally developed for patients after anterior resections.[5] However, the application of the LARS score in colon cancer patients seems justified, since the symptoms described in the questionnaire are often reported and clinically relevant in patients after colon resections as well.[9,11,25] This was also observed in the present study, as approximately 20% of the colon cancer patients reported major LARS, which significantly impaired quality of life. A reference population of patients without previous surgery was absent, and could have given insights in the functional bowel complaints of the general elderly population. Unfortunately, we also had some missing values. Although we had to perform multiple imputation on the distance of the tumour from the anal verge in rectal cancer patients due to a high amount of missing values, most variables had no missing values at all. Despite these limitations, this study incorporated the real clinical patient selection during the included period of time. Moreover, this is the first study that reported LARS outcomes and the impact of major LARS on quality of life in a large population of elderly patients after rectal as well as colon cancer surgery. Therefore, this study provides important data that should be used in current clinical practice among elderly colorectal cancer patients. Further research is needed to better identify those elderly patients who benefit most from either an end ostomy or a primary anastomosis.

In conclusion, elderly patients should not be withheld from a restorative colorectal cancer resection based on age alone. Nevertheless, almost half of the elderly rectal cancer and one out of five elderly colon cancer patients reported major LARS after surgery, which significantly impaired quality of life. Since elderly frequently consider quality of life and functional outcomes at least as important as oncological outcomes, the risk of major LARS should be considered. When the risks and benefits of either a restorative or non-restorative procedure are weighed, counselling patients about the risk for major LARS and its impact on quality of life may be helpful.

ACKNOWLEDGEMENTS

We would like to thank the contributing partners of the participating hospitals (Maastricht University Medical Centre+ (Maastricht), Maxima Medical Centre (Veldhoven), Zuyderland Medical Centre (Sittard and Heerlen), Laurentius Medical Centre (Roermond), VieCuri Medical Centre (Venlo), and Catharina Hospital (Eindhoven) for data collection.

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CHAPTER 5

Outcomes on diverting ostomy formation and reversal after low anterior resection in the older more advanced rectal cancer patient

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Eur J Surg Oncol. 2022 Jun;48(6):1414-1420. doi: 10.1016/j.ejso.2021.12.020.

ABSTRACT

Background

To decrease morbidity caused by anastomotic leakages after a low anterior resection (LAR) with primary anastomosis, a diverting ostomy is often created. Reversal of a diverting ostomy is associated with morbidity, which may result in non-reversal, particularly in the elderly. This study aimed to describe the diverting ostomy-related outcomes in elderly patients with more advanced rectal cancer after LAR.

Materials and methods

All rectosigmoid and rectal cancer patients ≥70 years who underwent LAR with primary anastomosis between 2006 and 2019 in the Catharina Hospital (Eindhoven, The Netherlands) were included for analyses. Reversal rates, ostomy-related complications, morbidity and mortality after ostomy reversal, and definitive ostomy rates were evaluated.

Results

In total, 164 patients were included, of which 150 (91.5%) underwent primary or secondary ostomy creation. Ostomy-related complications were reported in 34.7% (95%-CI 27.1–42.9%). In total, 72.5% (95%-CI 64.2–79.7%) reversed their diverting ostomy. Non-reversal was mostly due to relapsing disease (52.6%). Median time to ostomy reversal was 3.2 months (IQR 2.3–5.0). No or minor complications after ostomy reversal were observed in 84.0% (95%-CI 75.3–90.6%). Over time, ostomy recreation was performed in 15.0% (95%-CI 8.6–23.5%), and ultimately 65.8% (95%-CI 57.8–73.2%) were ostomy-free after the median follow-up of 3.8 years.

Conclusion

Although most elderly successfully reversed their diverting ostomy after LAR with limited morbidity, attention should be paid for the risk of non-reversal and ostomy recreation over time. Preoperative patient counselling is important in every individual to be able to decide if LAR with primary anastomosis or a permanent end colostomy is preferred.

INTRODUCTION

In rectal cancer surgery, either a low anterior resection (LAR) or an abdominoperineal resection (APR) is performed. In patients with proximal or mid rectal cancer a low anterior resection (LAR) with or without restoration of bowel continuity is preferred. In those with very distal rectal cancer or sphincter involvement, an abdominoperineal resection (APR) is necessary, leading to a permanent end colostomy. In case a LAR is technically possible, patient characteristics such as age, physical condition, neoadjuvant treatment, sphincter function, comorbidities and perioperative findings influence the decision to create a primary anastomosis or a permanent end colostomy. A LAR with primary anastomosis is less often performed in elderly than in younger patients, probably due to concerns for both functional outcomes and the risk for anastomotic leakage.[1,2]

Anastomotic leakage occurs in 11–15% of rectal cancer patients with a primary anastomosis and may have devastating consequences, especially in the elderly population.[3–6] In order to minimise the morbidity associated with an anastomotic leakage, a temporary diverting ostomy is often created.[7–9] A diverting ostomy is, however, associated with a risk for ostomy-related complications, which may negatively affect quality of life.[8,10,11] A diverting loop colostomy (DLC) is associated with ostomy prolapse and parastomal hernia, while a diverting loop ileostomy (DLI) is in particularly associated with the risk for high-output ostomy.[12,13] Besides, in approximately 20% of patients the diverting ostomy will not be reversed and becomes permanent.[14–16] Although studies on this topic in elderly are scarce, population-based data from the Netherlands Cancer Registry reports non-reversal rates up to 40% in elderly rectal cancer patients.[11]

In order to optimise the decision-making process in elderly patients with more advanced rectal cancer that undergo rectal resection with or without restoration of bowel continuity and a protecting diverting ostomy, it is beneficial for both clinicians and patients to gain knowledge on ostomy-related outcomes.

The aim of this study was to evaluate ostomy-related outcomes in elderly patients with more advanced rectal cancer after a LAR with primary anastomosis.

MATERIALS AND METHODS

This study was conducted at the Catharina Hospital (Eindhoven, the Netherlands), a high-volume centre for the treatment of colorectal cancer (CRC) and a tertiary referral centre for advanced rectal cancer. This study was approved by the local medical ethics board (Medical Research Ethics Committees United – Nieuwegein, registration number

W20.322). Patients ≥70 years treated with curative intent for rectal or rectosigmoid cancer (stage I-IV) between 2006 and 2019 were selected. The cut-off age was based on other studies describing ostomy-related outcomes in elderly patients.[11] Patients who underwent emergency resection, had locally recurrent rectal cancer or underwent previous rectal or rectosigmoid resection because of benign causes were excluded.

Treatment and definitions

Most patients in our centre had locally advanced rectal cancer and underwent neoadjuvant chemoradiotherapy (or short-course radiotherapy), according to the Dutch National Guidelines for colorectal cancer.[17] The majority of patients received a primary diverting loop colostomy (DLC), a diverting loop ileostomy (DLI) was only performed when a colostomy was technically difficult or not feasible. A primary ostomy was defined as an ostomy present before or created during LAR, and a secondary ostomy was defined as an ostomy created in an additional procedure following LAR (e.g. due to anastomotic leakage in a patient without a primary diverting ostomy). Ostomy recreation was defined as recreation of an ostomy after reversal. Preoperatively, all patients were consulted by a specialised ostomy nurse to determine the ideal location of the ostomy and to receive information about ostomy care. Before ostomy reversal was performed, the anastomotic integrity was confirmed by additional diagnostic modalities such as contrast enema or endoscopy. In line with other studies, a permanent diverting ostomy due to non-reversal was defined as a persistent diverting ostomy at 18 months after creation.[18,19] Delayed reversal was defined as reversal after more than 6 months after creation.[20]

Clinical data and follow-up

Patient characteristics, data on treatment, and additional clinical and demographic data were retrospectively extracted from medical records. Complications occurring in the first 30 postoperative days or before hospital discharge were scored using the Clavien-Dindo classification.[21] Follow-up data were extracted from medical records, or by contacting the referring hospital or the patient's general practitioner. Follow-up was calculated as the interval between the date of surgery and last contact or death. Minimal follow-up was 12 months (if alive). Patients with a persistent diverting ostomy after 12 months were minimally followed-up until 18 months or the date of ostomy reversal (if earlier than 18 months). During follow-up, ostomy reversal, ostomy-related complications, ostomy recreation, and the development of local recurrence and distant metastases were recorded. The Municipal Administrative Databases were consulted to obtain information on survival data.

Statistical analyses

Statistical analyses were performed using SPSS Statistics 25.0 software (IBM, Endicott, NY, USA). The primary endpoint was the proportion of patients that underwent ostomy reversal within 18 months since creation. Secondary endpoints were ostomy-related complications, morbidity and mortality after ostomy reversal, ostomy recreation rates, and definitive ostomy rates. Proportions were calculated for the whole population and 95% Confidence Intervals (95%-CI) were calculated using Clopper-Pearson interval for the primary and secondary endpoints. To determine differences between patients 70–74 and ≥75 years, comparisons between proportions were also stratified for age. Intergroup comparisons were analysed using chi-squared test or Fisher's exact test, when appropriate, for non-continuous data. Independent *t*-tests or one-way ANOVA were used for normally distributed continuous data, and Mann-Whitney *U* tests or Kruskal-Wallis test were used for non-normally distributed continuous data, when appropriate. A *p*-value of <0.05 was considered statistically significant. All tests were two-sided. Ostomy reversal and definitive ostomy rates were calculated using the Kaplan-Meier method. Ostomy reversal rates were stratified by age group and compared using the log-rank test. Definitive ostomy rates were calculated since the date of ostomy creation. The specific causes for non- or delayed reversal and ostomy recreation were analysed.

RESULTS

In total, 363 patients ≥70 years underwent curative rectal cancer surgery with LAR or APR between 2006 and 2019 (43 LAR without primary anastomosis, 156 APR, and 164 LAR with primary anastomosis). Patients that underwent LAR without the formation of a primary anastomosis were significantly older than patients that underwent APR or LAR with primary anastomosis (79.4 vs. 76.2 vs. 75.0 years, $p < 0.001$). No significant differences were observed in comorbidities and ASA classification between these treatment groups. Of the 43 patients that underwent LAR without a primary anastomosis, in 23 patients the decision was made preoperatively based on pre-existent incontinence, patient preferences, or patient and treatment characteristics (e.g. age or neoadjuvant treatment). In the other 20 patients, the decision was made during surgery based on low tumour height, pelvic fibrosis, or the suspicion of insufficient blood supply to the anastomosis. As no primary anastomosis was performed, these patients were excluded from any further analyses on diverting ostomy-related outcomes.

This resulted in 164 patients that underwent LAR with primary anastomosis that were included for analysis, of which 94 (57.3%) patients were 70–74 years and 70 (42.7%) patients were ≥75 years old. Median follow-up was 3.8 years. Comorbidities were present in 79.9% of patients and were comparable between both age groups (p = 0.29). Clinical and demographic characteristics are presented in Table 1.

Table 1. Demographic, clinical and tumour characteristics of rectal cancer patients (n = 164), stratified by age (70–74 and ≥ 75 years).

	70–74 years n = 94	**≥75 years n = 70**	***p*-value**
	n (%)	**n (%)**	
Mean age in years at time of surgery (±SD)	72.2 (1.4)	78.7 (3.0)	<0.001
Median follow-up in years (IQR)	4.4 (2.5 – 6.6)	3.3 (1.8 – 4.9)	0.03
Male	53 (56.4)	46 (65.7)	0.23
Comorbidity			0.29
None	23 (24.5)	10 (14.3)	
1 comorbidity	24 (25.5)	21 (30.0)	
2 comorbidities	21 (22.3)	13 (18.6)	
≥3 comorbidities	26 (27.7)	26 (37.1)	
ASA classification			0.053
I-II	80 (85.1)	51 (72.9)	
III	14 (14.9)	19 (27.1)	
Tumour stage (clinical)			0.06
I–II	30 (31.9)	35 (50.0)	
III–IV	61 (64.9)	34 (48.6)	
Missing	3 (3.2)	1 (1.4)	
Neoadjuvant treatment			0.15
None	11 (11.7)	13 (18.6)	
Short course radiotherapy (5 × 5 Gy)	27 (28.7)	28 (40.0)	
Chemoradiation	51 (54.3)	27 (38.6)	
Other	5 (5.3)	2 (2.9)	
Type of LAR			0.12
Open surgery	80 (85.1)	54 (77.1)	
Transanal TME	4 (4.3)	1 (1.4)	
Laparoscopic surgery	10 (10.6)	15 (21.4)	
Conversion to open surgery	1 (1.1)	6 (8.6)	0.04
Extended (multivisceral) resection	38 (40.4)	23 (32.9)	0.32
Intraoperative treatment			
Hyperthermic intraoperative peritoneal chemotherapy	2 (2.1)	–	0.51
Intraoperative radiotherapy	39 (41.5)	17 (24.3)	0.02
Radical resection (R0)	91 (96.8)	65 (92.9)	0.29

In 145 of 164 (88.4%) patients a diverting ostomy was constructed during primary surgery, 127 (87.6%) of these were DLC and 18 (12.4%) were DLI. Of the 19 patients without a primary diverting ostomy, a secondary ostomy was created in 5 patients, of which in 4 a DLC and in 1 a permanent end colostomy was created. Anastomotic leakage was the cause for secondary ostomy creation in all of these patients. In 2 of the 145 patients with a primary diverting ostomy, a permanent end colostomy was created secondarily in the postoperative period, either due to bowel perforation and anastomotic leakage. In Figure 1, a flowchart on patient selection and ostomy creation is presented.

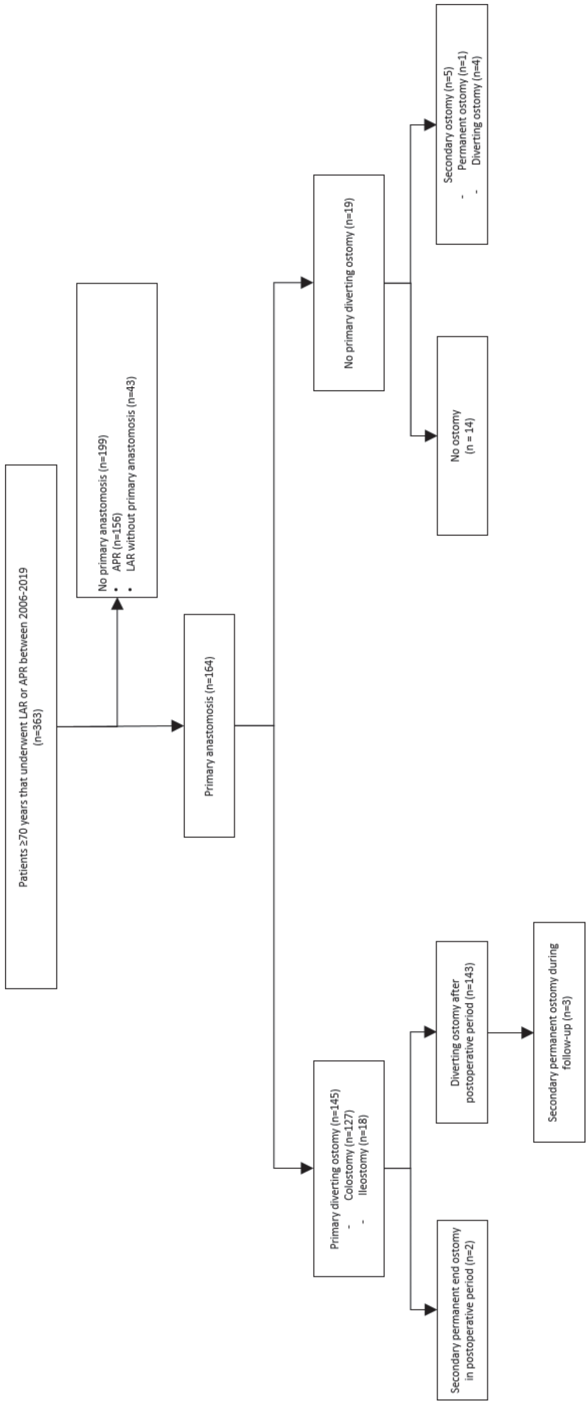

Figure 1. Patient disposition flowchart of all elderly (≥70 years) rectal cancer patients that underwent surgery with curative intent between 2006 and 2019 (n = 363).

After the postoperative period, 147 patients had a primary or secondary diverting ostomy and 3 had a permanent end colostomy. Ostomy-related complications were observed in 34.7% (95%-CI 27.1–42.9%). In Table 2, ostomy-related complications are described in more detail.

Table 2. Details on ostomy-related complications reported by patients with an ostomy, either primary or secondary, after low anterior resection with primary anastomosis.

	n = 150	
	n (%)	**95%-CI**
None	98 (65.3)	57.1 – 72.9
Peristomal skin problems	25 (16.7)	11.1 – 23.6
Stomal obstruction	5 (3.3)	1.1 – 7.6
Ostomy prolapse	8 (5.3)	2.3 – 10.2
High-output ostomy	10 (6.7)	3.2 – 11.9
Parastomal hernia	7 (4.7)	1.9 – 9.4

Postoperative anastomotic leakage or presacral abscess was observed in 16.5% of patients. Supplementary Table 1 presents the treatment of patients with anastomotic leakage or presacral abscess. In total, 8 (4.9%) patients died due to postoperative complications, of which 7 had a diverting ostomy and 1 an end colostomy. These patients were excluded from further analyses, along with 2 patients that were lost to follow-up. In Table 3, details on postoperative outcomes after low anterior resection with primary anastomosis are presented.

Table 3. Details on postoperative outcomes of all rectal cancer patients (n = 164) after low anterior resection with primary anastomosis.

	n = 164
	n (%)
Median admission time in days (IQR)	8.5 (6.0 – 15.0)
Median admission on ICU in days (IQR)	1.0 (0.0 – 2.0)
Complication Grade according to Clavien-Dindo	
None	50 (30.5)
Grade I-II	76 (46.3)
Grade IIIa+IIIb	20 (12.2)
Grade IV	10 (6.1)
Grade V	8 (4.9)
Surgical complications	
Anastomotic leakage / presacral abscess	27 (16.5)
Clavien-Dindo ≥III	13 (7.9)
Intra Abdominal abscess	6 (3.7)
Clavien-Dindo ≥III	4 (2.4)
Ileus	27 (16.5)
Clavien-Dindo ≥III	3 (1.8)
Fascial Dehiscence	7 (4.3)
Wound infection	17 (10.4)

Diverting ostomy reversal

Of the remaining 138 patients with a diverting ostomy, 72.5% (95%-CI 64.2–79.7%) reversed their ostomy successfully, with no significant differences between patients 70–74 and ≥ 75 years (74.1% vs. 70.2%, $p = 0.61$). Median time until reversal was 3.2 months (IQR 2.3–5.0). Figure 2 presents a Kaplan-Meier curve on diverting ostomy reversal rates, stratified by age groups. Non-reversal of the ostomy occurred in 38 patients, mostly due to relapsing disease. Details on the reasons for non-reversal are presented in Table 4.

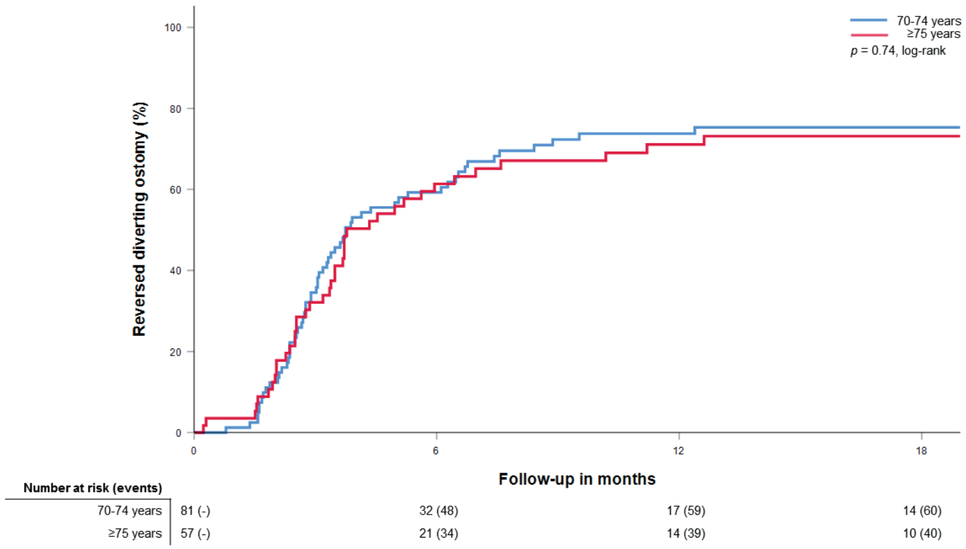

Figure 2. Kaplan-Meier curve on diverting ostomy reversal of rectal cancer patients undergoing a low anterior resection with primary anastomosis with either a primary or secondary diverting ostomy (n = 138), stratified by age groups.

Table 4. Reasons for non-reversal at 18 months of a diverting ostomy after low anterior resection with primary anastomosis.

	n = 38
	n (%)
Relapsing disease (local/systemic)	20 (52.6)
Persistent anastomotic problems	5 (13.2)
Patient's preference	4 (10.5)
Death	1 (2.6)
Other, such as patient being unfit for surgery	5 (13.2)
Unknown	3 (7.9)

After ostomy reversal, median time of hospital admission was 3.0 days (IQR 3.0–4.0). The majority of patients had no or minor (Grade 0–II) complications (84.0% [95%-CI 75.3–90.6%]). Severe complications (Grade ≥IIIB) occurred in 8.0% (95%-CI 3.5–15.2%). Postoperative complications did not significantly differ between age groups. Table 5 presents further data on ostomy reversal and hospital admission.

Table 5. Details on the outcomes of ostomy reversal in patients with a primary or secondary diverting ostomy (n = 100), after low anterior resection with primary anastomosis.

	n = 100	
	n (%)	**95%-CI**
Median time until ostomy reversal in months (IQR)	3.2 (2.3–5.0)	
Ostomy reversal <6 months	82 (82.0)	73.1–89.0
Ostomy reversal ≥6 months, reasons for delayed reversal	18 (18.0)	11.0–26.9
Persistent anastomotic problems	8 (8.0)	
Adjuvant chemotherapy or treatment of metastatic disease	4 (4.0)	
Prolonged physical recovery	2 (2.0)	
Patient's preference	1 (1.0)	
Unknown	3 (3.0)	
Median hospital admission in days (IQR)	3.0 (3.0–4.0)	
Complication grade according to Clavien-Dindo		
No complications	62 (62.0)	51.7–71.5
Grade I-II	22 (22.0)	14.3–31.4
Grade IIIA + IIIB	8 (8.0)	3.5–15.2
Grade IV	1 (1.0)	0.0–5.4
Missing	7 (7.0)	
Complications		
Surgical site infection	8 (8.0)	3.5–15.2
Anastomotic leakage	3 (3.0)	0.6–8.5
Ileus/Gastroparesis	16 (16.0)	9.4–24.7
Missing	7 (7.0)	

Ostomy recreation and ostomy-free survival

During follow-up, 15 of 100 (15.0% [95%-CI 8.6–23.5%]) patients that reversed their diverting ostomy underwent ostomy recreation. Median time from reversal to recreation was 16.3 months (IQR 1.4–34.1). The reasons for ostomy recreation were severe functional bowel complaints (n = 5), chronic anastomotic problems (n = 4), local tumour recurrence (n = 2), surgical complications (n = 3) and enterocutaneous fistula (n = 1).

Of all patients that underwent LAR with primary anastomosis, 69.5% (95%-CI 61.6–76.6%) were ostomy-free at one year after primary surgery, and 65.8% (95%-CI 57.8–73.2%)

after follow-up (median 3.8 years). No significant differences in definitive ostomy rates between age groups were observed. Supplementary Figure 1 presents a Kaplan-Meier curve on definitive ostomy rates.

DISCUSSION

In this study, investigating ostomy-related outcomes in more advanced elderly rectal cancer patients that underwent curative LAR with primary anastomosis, 72.5% of patients had their ostomy reversed successfully, with limited morbidity in the majority of patients. Over time, 15% of patients underwent ostomy recreation and after the median follow-up of 3.8 years, 65.8% of patients that underwent LAR with primary anastomosis were ostomy-free.

Previous studies described diverting ostomy reversal rates of 72.5–83% after LAR in patients of all ages.[16,18,20,22–24] However, data from the Netherlands Cancer Registry suggested that 68% of patients 71–80 years and 59.8% of patients ≥81 years reversed their diverting ostomy successfully, which is slightly lower compared to the reversal rates in this study.[11] The inferior reversal rates in elderly when compared with younger patients may be explained by the fear for a secondary procedure for ostomy reversal, along with earlier acceptance of a permanent diverting ostomy.[16] In this study, the main reason for non-reversal was relapsing disease (local or systemic), which is not age-dependent, and non-reversal was less often due to the patient's physical capacity, preferences, or chronic anastomotic problems.[25,26] Previous studies showed that relapsing disease and older age were both associated with non-reversal of a diverting ostomy.[10,16] Besides, ostomy reversal was less often performed in patients with ASA classification ≥2, advanced rectal cancer, certain comorbidities (e.g. anaemia, renal dysfunction), secondary ostomy creation and perioperative and postoperative complications.[10,16,23] These factors should be incorporated during decision-making to determine whether a diverting ostomy is a feasible option for the individual patient.

Ostomy reversal is accompanied with morbidity and mortality, which may be feared by the older patient and the surgeon. Complications after ostomy reversal are described in 20–40% of patients, with severe (Grade ≥IIIb) complications occurring in 7–9% and a reported mortality rate of 0.4–3%.[11,27–29] The morbidity described in earlier studies on patients of all ages was comparable to our results. Moreover, a recent study confirmed that older age is not associated with an increased risk for morbidity after ostomy reversal.[30] However, patients should be informed about the need for a secondary procedure for ostomy reversal and the associated risk for complications before deciding to undergo a LAR with a primary anastomosis and the formation of a diverting ostomy.

In 88.4% of our patients, a primary diverting ostomy was present after surgery, which is higher than the wide range of primary diversion after LAR of 15–74% reported in other studies.[8,16,22,31] As the present study was conducted in a referral centre for advanced rectal cancer cases, many included patients underwent neoadjuvant treatment followed by extensive surgery, probably contributing to the increased rates of primary diversion. The value of primary diversion in decreasing the absolute risk of anastomotic leakage is unclear, therefore the routine use of a diverting ostomy after bowel restoration is still a matter of debate. Nonetheless, the clinical outcomes of an anastomotic leakage are found to be better in patients with a primary diverting ostomy, with increased success rates of conservative treatment and less multiple organ failure.[7–9] However, as anastomotic leakage only occurs in the minority of patients, some patients will not experience the clinical benefits, but only the potential risks related to a diverting ostomy.[4–6] Careful selecting those patients benefiting most from a diverting ostomy is essential and many studies have been performed to identify predictive factors associated with anastomotic leakage, such as age, comorbidities or neoadjuvant treatment.[4,32] In the majority of hospitals in the Netherlands, primary diversion is therefore considered standard of care after neoadjuvant treatment. Besides, elderly are more at risk for the devastating consequences of an anastomotic leakage.[3,32] Therefore, especially in the elderly with more advanced rectal cancer who require neoadjuvant treatment followed by extensive surgery, primary diversion seems beneficial. Yet, identifying the patients benefitting most from a diverting ostomy still seems important.

Intestinal diversion may be performed by a DLC or DLI and the decision often depends on the surgeon's preferences. In our hospital, a DLC is standard of care, and a DLI was only performed when a colostomy was technically not feasible or when already present preoperatively. Most studies evaluating the outcomes after DLC and DLI did not show clear significant overall benefits of one over the other.[12,13] Although a DLC is associated with more ostomy prolapses, parastomal hernias and surgical wound infections, a DLI increases the risk for peristomal dermatitis and high-output ostomy.[12,33] Moreover, the readmission rate after a DLI is up to 17%, mostly due to dehydration.[34,35] Especially the elderly may be more prone for the consequences of a high-output ostomy. In fact, a recent study showed that a DLI may result in long-term renal dysfunction in elderly patients, which even persisted after ostomy reversal.[36] Therefore, it could be argued that particularly in the elderly a DLC is preferred. Especially when considering the risk of a diverting ostomy becoming permanent.[16]

Functional outcomes should also be discussed during shared decision making when a LAR with primary anastomosis is considered. The low anterior resection syndrome (LARS), a cluster of symptoms including faecal incontinence and urgency after sphincter-preserving surgery, can severely impact quality of life.[37,38] Although it could be speculated that older patients have increased risks to develop LARS, most studies found no association of age.[39] In this study, 5 patients underwent ostomy recreation due to severe LARS complaints, however it may be expected that invalidating symptoms may have been present in more patients. Unfortunately, this study does not have more detailed data on functional bowel complaints.

To avoid the risk of anastomotic leakage, the need to undergo a secondary procedure for ostomy reversal, and functional bowel complaints, the avoidance of a primary anastomosis and the formation of a permanent end colostomy may be preferred in the elderly. Moreover, one third of patients eventually ends up with an ostomy after LAR with primary anastomosis, either due to a permanent diverting ostomy or ostomy recreation. Especially the latter group may be prone for a prolonged period of impaired quality of life due to severe LARS complaints or persistent anastomotic problems before ultimately deciding to undergo ostomy recreation. Furthermore, health-related quality of life seems comparable between patients with a permanent end colostomy and patients without or the general population, showing that most elderly are well able to cope with a permanent ostomy.[40,41]

This study highlights that a diverting ostomy after LAR with primary anastomosis can be performed relatively safely in most older patients with almost three quarters of the patients reversing their ostomy with limited additional morbidity. However, a permanent end colostomy should be considered in every older patient with more advanced rectal cancer, since 27.5% of patients will not reverse their diverting ostomy. Besides, a further 15% undergoes ostomy recreation over time, which may even underestimate the total population of patients having severe complaints after ostomy reversal. Hence, it is essential that for every individual patient the risk of anastomotic leakage, functional bowel complaints, a secondary procedure, the potential burden of non-reversal and the risk for ostomy recreation should be weighed against the consequences of a permanent end colostomy. Counselling patients, setting the right expectations and composing a tailor-made treatment plan is therefore essential.

The strength of this study lies in the availability of many clinically relevant variables with barely missing values of a unique population in a tertiary referral centre for advanced rectal cancer. A major limitation of this study is the retrospective character of this study, which could have led to an underestimation of ostomy-related complications or ostomy recreation during follow-up. By thoroughly studying the medical records, contacting the referral hospitals and general practitioners, this was kept to a minimum. Furthermore, this study was conducted in a tertiary referral centre for advanced rectal cancer. Although we aimed to describe the elderly with more advanced rectal cancer, this could have resulted in selection bias. Future studies on functional bowel complaints and the quality of life of patients with or without a diverting or permanent ostomy are warranted to further improve patient counselling.

CONCLUSIONS

Almost three out of four elderly patients were able to reverse their diverting ostomy with limited additional morbidity after LAR with primary anastomosis for rectal cancer. However, a permanent end colostomy should be discussed in every older patient as approximately one third of the elderly ends up with an ostomy due to either non-reversal or ostomy recreation. Adequately counselling patients about the potential risks for anastomotic leakage, non-reversal, ostomy recreation and functional outcomes is essential to be able to conscientiously decide if LAR with primary anastomosis or a permanent end colostomy is preferred.

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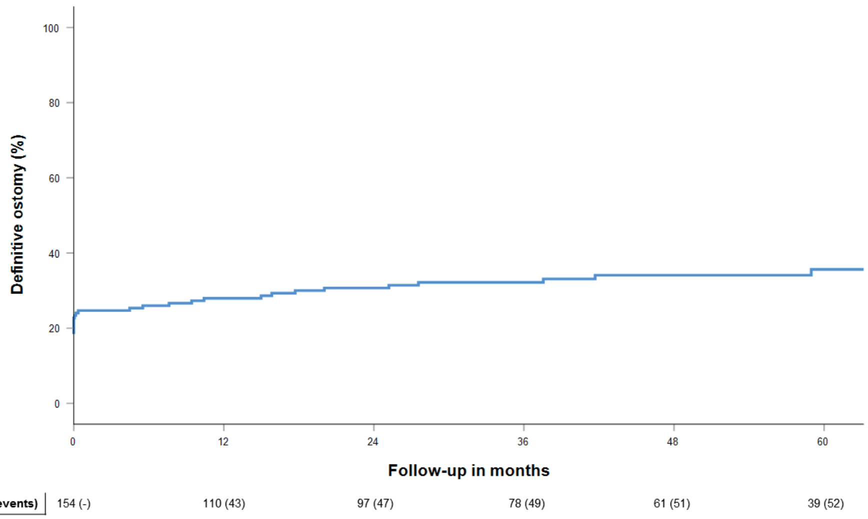
SUPPLEMENTARY DATA CHAPTER 5

Supplementary Table 5.1. Treatment of patients with anastomotic leakage or presacral abscess, stratified for patients with and without a primary diverting ostomy (n = 27).

	Primary diverting ostomy n = 22	**No primary diverting ostomy n = 5**
	n (%)	**n (%)**
No treatment	6 (27.3)	–
Antibiotics only	6 (27.3)	1 (20.0)
Transanal drainage	2 (9.1)	–
Transgluteal drainage	5 (22.7)	–
Transabdominal drainage	1 (4.5)	–
Diverting ostomy	–	3 (60.0)
Disconnection of anastomosis and permanent end ostomy	1 (4.5)	1 (20.0)
Unknown	1 (4.5)	–



Supplementary Figure 5.1. Kaplan-Meier curve on definitive ostomy rates due to either non-reversal of a diverting ostomy or ostomy recreation in rectal cancer patients undergoing a low anterior resection with primary anastomosis (n = 154), calculated from the day of ostomy creation.

PART II

Towards improved care in elderly patients with colorectal cancer

CHAPTER 6

When and how should surgery be performed in senior colorectal cancer patients?

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Eur J Surg Oncol. 2020 Mar;46(3):326-332. doi: 10.1016/j.ejso.2020.01.007.

ABSTRACT

Older studies reported high rates of postoperative morbidity and mortality in the senior population, which lead to a tendency to withhold curative surgery in the older population. However, more recent studies showed impressing developments in postoperative outcomes in seniors. Probably, these improvements are due to enhancements in both surgical and non-surgical aspects in the pre-, peri- and postoperative period, such as minimally invasive techniques and anaesthesiological insights. The postoperative survival gap seen earlier between younger and older patients is fading. For optimal treatment in the older population, special awareness and care on several aspects is needed. As only a minority of the seniors are frail, a quick frailty assessment is crucial to distinguish the fit from the frail in the decision-making process. In addition, it could be valuable to improve the lacks in physical condition in the preoperative period with the use of prehabilitation programs. Furthermore, it is important to evolve an emergency to an elective setting by postponing emergency surgery to prevent any high-risk situation. In conclusion, based on modern insights, surgery is a valid option in the curative treatment of colorectal cancer in seniors, however individual attention and care is required.

INTRODUCTION

Colorectal cancer (CRC) is mainly a disease of the older population, with the highest incidence around the age of 80 years old.[1] With increasing life expectancy of the worldwide population, this will result in aging of the population and higher rates of CRC in the oldest population.[1] Therefore, it is not unthinkable that clinicians have to deal more and more commonly with these senior CRC patients.

In older papers, after introduction of TME surgery, seniors did not seem to benefit as much as their younger counterparts.[2] It had been postulated that higher postoperative mortality rates were mainly responsible for this lack of benefit. However, the tide has turned recently. Population-based cohorts from Belgium, Denmark, Sweden, and The Netherlands showed that short-term mortality rates are improving over time.[3] Other recent studies show that fit senior patients can be treated the same as younger patients and, when operated on, they have the same outcomes as their younger equivalents.[4,5] Unfortunately, senior patients are less likely to undergo surgery and intensive treatment regimens than their younger counterparts.[5-7] They are believed that they cannot deal with these treatment regimens, due to comorbidities or age.[2,4,6] However, these assumptions are based on older studies who reported worse outcomes than nowadays.[8,9]

With growing evidence that fit senior patients can deal the stress of curative treatment regimens and increasing numbers of seniors that are affected by CRC, there is a need for clarity about the areas of concern during treatment of these patients.[10-12] Age itself should not lead to withhold curative treatment before the physical status of the senior patients is assessed.[4-6] As senior patients are not included in most clinical trials, evidence is based on younger patients.[5,6] Fortunately, there are expert recommendations on how to treat this senior population, as standard guidelines focus particularly on middle aged patients.[6,13]

In this paper, a surgery-focused recommendation is outlined why, when and how we should treat the senior CRC patient.

WHICH CHANGES HAVE BEEN MADE OVER THE YEARS TO IMPROVE OUTCOMES AFTER COLORECTAL CANCER SURGERY?

Minimally invasive surgery

Laparoscopic colorectal cancer surgery is safe and has comparable oncological results as open surgery.[6,14] There is no difference between laparoscopic and open surgery in harvested lymph nodes, circumferential resection margins, recurrence rates, and overall and disease-free survival.[14,15] In addition, minimal invasive surgical techniques evoke less intensive immune response than open surgery, thus reducing the surgical stressor.[16] This could be an explanation for the improved recovery seen after laparoscopic surgery with less postoperative pain, shorter hospital admissions and less postoperative and cardiopulmonary complications.[5,15,17,18] Also in the older population, laparoscopic CRC surgery is safe and goes with less postoperative morbidity.[18-20]

In select cases, organ-sparing techniques like polypectomy, transanal excisions (TAE) and transanal endoscopic microsurgery (TEM) can be the solution.[6] Organ-sparing techniques have less morbidity and excellent functional results, with acceptable oncological results.[6] For rectal cancer, good oncological outcomes with local excisional techniques are achieved in T1 tumours with minimal submucosal and no lymphovascular invasion, when no poor differentiation, mucinous histology and budding is present.[6] For malignant colorectal polyps in general, similar oncological results after radical polypectomy were seen as after surgical resections.[21] It is important to weigh balances between both oncological and surgical outcomes before choosing for these local techniques. As some senior patients are frail or could prefer good functional outcomes over survival benefit, it is important to discuss this with the patient using shared decision making.

Organ preservation in rectal surgery

In about 20% of the patients treated with neoadjuvant treatment, complete pathological response is observed.[22] When complete response is achieved after neoadjuvant rectal cancer treatment, there is a possibility for a watch-and-wait approach.[23] Complete responders of neoadjuvant chemoradiotherapy are assessed and followed with MRI and endoscopy.[22] With this more conservative approach with intensive surveillance, acceptable rates of local recurrence and high rates of survival are found in clinical responders.[22,24,25] About 10–30% need delayed salvage surgery to resect regrowth and only a small percentage of them had unresectable recurrences, so in highly selected patients it could be an effective method to avoid surgery.[23,25]

The standard for treating rectal cancer remains surgery with or without neoadjuvant treatment.[22] Although watch-and-wait procedures have similar cancer-specific and overall survival rates, surgery is associated with higher rates of disease-free survival and a smaller risk of technically unresectable recurrences.[25] However, in patients who are at risk to undergo surgery or when functional outcomes and the avoidance of a permanent stoma are important, it could be better to have a more conservative approach that only consists of neoadjuvant treatment followed by the watch-and-wait protocol.[22,25] In short, in selected patients with clinical complete response, the watch-and-wait protocol could be an adequate surrogate to surgery.[22]

Effect of colorectal differentiation on outcome

One of the effects seen of subspecialisation in surgery is improved surgery-related outcomes.[26] Higher CRC volumes and colorectal subspecialisation improves outcomes and survival.[27-29] Specialised and high-volume surgery is also related to less anastomotic leakages, lower postoperative mortality, and recurrence rates.[28,30,31] Especially in more complex surgery, like advanced rectal cancer surgery, high-volume and specialised surgery is associated with more sphincter-preserved surgery, lower rates of permanent stoma formation, better local control, and increased survival.[26,32] Only in those senior patients with advanced cases, or seniors in whom an increased risk of morbidity or mortality is expected, a referral can be considered.

Need for changing the perspective of surgical treatment of the senior patient with colorectal cancer

The current belief that seniors could not manage curative treatment regimens is based on older studies that show associations between senior patients and high rates of postoperative morbidity and mortality.[2,33] These outcomes lead to a decrease in older patients receiving curative surgery, enlarging the risk of undertreatment.[6,34] Fortunately, there is increasing evidence showing seniors who are fit for surgery, have the same benefit from curative treatment as younger patients do.[9,11,35] With improving the surgical circumstances over the years, declining rates of postoperative morbidity and mortality have been described for this population.[8,9,36] In earlier studies, high rates of one-year mortality in senior patients of about 19–26% were reported and were much higher than in younger patients.[37-39] A population-based study from The Netherlands showed an improvement in short-term mortality after CRC surgery in the senior population between 2009 and 2013.[36] For colon and rectal cancer patients ≥75 years, 1-year mortality decreased from 18.5% to 15.0% and from 15.3% to 11.7%, respectively. Nevertheless, these rates were still much higher than in younger patients.[36] Another population-based study across four North-European countries and also other population-based studies showed improvement in short-term mortality rates over time.[3,40,41]

Possible explanations for this major improvement in short-term mortality rates for seniors are better staging, increased use of minimally invasive techniques, perioperative care, awareness of complications, expertise and high-volume care.[9,36] Other possible contributing factors are insights in perioperative anaesthesiological factors, which include administration of antibiotics, preservation of body temperature and adequate fluid balances.[42,43]

More recently, a study using Dutch population-based data analysed the developments of postoperative mortality and 1-year relative survival in CRC patients between 2005 and 2016.[8] Improvements in 30-day mortality for senior patients to 4.0% and 2.7% were seen, for colon and rectal cancer, respectively.[8] The relative 1-year survival rates improved to 94.6% and 97.2%, for colon and rectal cancer respectively.[8] (Figure 1). These rates were almost comparable to those in younger patients.[8] In addition, a recently published study from a high-volume centre for complex cases showed 30-day mortality rates for senior CRC patients of 1.2% (1.1% for senior colon and 1.4% for senior rectal cancer patients) and 1-year relative survival rates of 94.3%.[9] These rates were also comparable to younger patients.[9] (Table 1).

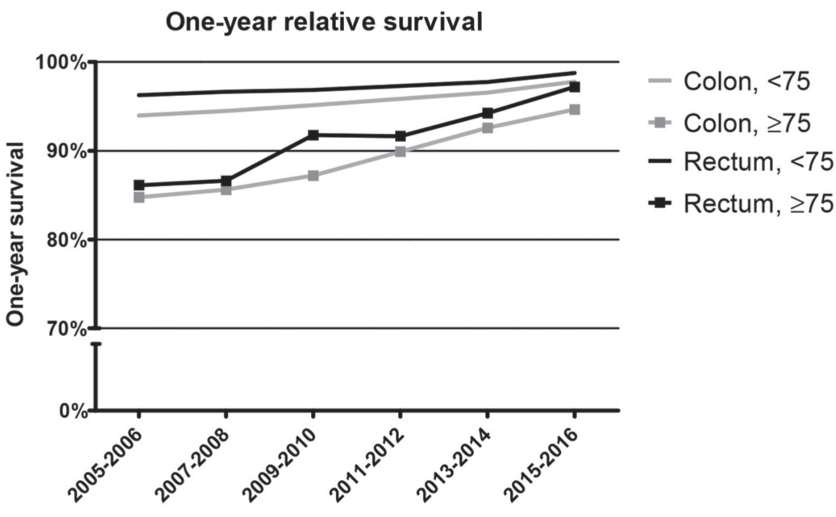

Figure 1. Relative one-year survival rates for both colon and rectal cancer patients after receiving surgery between 2005 and 2016 in the Netherlands, as published by Brouwer et al.[8]

Table 1. Relative one-year survival rates, stratified by age and period of surgery, for all patients who underwent CRC surgery (n = 2018) between 2006 and 2017 in the Catharina Hospital, Eindhoven.[9]

	2006-2012			2013-2017		
	<75 years	≥75 years	*p*-value	<75 years	≥75 years	*p*-value
	%	%		%	%	
All CRC patients (n = 2018)	96.5%	88.4%	<0.001	95.5%	94.3%	0.429
Colon (n = 1037)	96.5%	87.3%	<0.001	95.3%	94.7%	0.429
Rectum (n = 981)	96.3%	89.4%	0.003	95.3%	91.2%	0.176
Emergency surgery (n = 158)	100%	69.8%	<0.001	87.2%	92.1%	0.479

While one-year mortality after CRC surgery has been a major concern in the past for seniors, recent studies show a major increase in survival, both for specialised and general CRC surgical centres.[2,8,9] The earlier reported mortality rates in seniors should no longer be used to form a basis to withhold CRC treatment in older patients.[8,9] However, we are aware that special care and attention is needed in this population and that individual differences in frailty levels need to be assessed preoperatively.

WHEN AND HOW TO TREAT?

Staging

Treatment for all colorectal cancer patients starts with adequate staging of the primary tumour and an estimation of the patient's performance status. Primary diagnosis is done by colonoscopy and biopsy for histological examination on the characteristics of the tumour.[44] A Computed Tomography (CT) is advised for tumour staging and to examine the possibility of lymph node involvement and/or (extra)hepatic metastasis.[44] In rectal cancer, the Magnetic Resonance Imaging (MRI) provides detailed views of dissection planes, pelvic organs and mesorectal fascia and circumferential margins (CRM).[45]

Frailty assessment

In senior patients, an estimation of their performance status is important to reveal frailty. Frailty is defined as a state of diminished physiological reserve capacity across multiple organ systems.[46] As a result of frailty, the capacity to withstand stressors, such as intensive treatment, is reduced, which is associated with postoperative complications, hospitalisation, and reduced survival after surgery.[6,47-49]

It has to be clear that only a small percentage of the senior population is considered frail. Therefore, in the older population it is important to distinguish the frail from the fit senior.

But it is not clear how to identify frailty in the individual patient, as no one tool is accurate enough to include all differences between older patients.[6,50] Extensive and comprehensive assessment of frailty on a routinely basis is time-consuming and resource intensive, as many geriatricians are needed to be involved to evaluate every older patient who undergoes CRC surgery.[12,45] For most hospitals it is difficult to implement this as standard care. Therefore, other less time-consuming tools are needed in daily practice to screen for frailty and to distinguish those patients that benefit from an assessment by a geriatrician prior to treatment.[6] In the most recent published expert opinion on how to treat senior rectal cancer patients, the focus should lie on identifying the main predictors of frailty and postoperative complications such as functional status, nutritional status, and comorbidities.[6]

Functional status is easily assessed during the patient's visit with the timed-up-and-go test (TUG), since a high TUG is able to predict the risk of postoperative complications.[51] Also a history of falls in the last 6 months before surgery is associated with a higher risk of postoperative complications.[12] Other possible tools given by the expert group are the G8 score to determine health and nutritional status and medication use, and the Mini-Cog score for the evaluation of cognitive status.[6] Since 2012, as part of a National Patient Safety Program, all patients over 70 years in the Netherlands should be screened for frailty by assessing the following domains: undernutrition, physical impairment, delirium risk and fall risk.[52] Other important factors to evaluate could be the mental status, alcohol and smoking habits, supporting system and the willing to fight for recovery of the patient. As it could be possible that some seniors tend to give up earlier when feeling bad, discussing that some symptoms like fatigue, nausea, or weakness are normal during recovery after colorectal surgery, could be of significance.

If no frailty is expected, the patient should be offered an optimal treatment. When after the previous mentioned, quick and easily applicable screening methods, the patient is at risk, the selected patient should be referred to a geriatrician to perform a full comprehensive geriatric assessment. This full assessment evaluates the multiple domains of frailty, such as physical, nutritional, functional and psychosocial health status, cognition and polypharmacy.[50] When after this geriatric assessment the patient seems fit, standard curative care can be performed. However, in case the patient is considered frail, prehabilitation programs should be started to increase the patient's condition before surgery is performed or the treatment regimen should be fine-tuned to the health status of the individual patient. In addition, when the patient is considered frail, it could be of importance to discuss the patient in a regional multidisciplinary team meeting (MDT) with incorporated geriatricians for the whole decision-making process.

Prehabilitation

Older patients who undergo CRC surgery are at risk for delayed recovery, and prehabilitation could enhance the capacity to tolerate surgery and to recover earlier.[53] It seems to be a promising method to increase the physical condition of the senior patients prior to surgery, and reductions of about 50% in postoperative complications are seen in intra-abdominal surgery.[54] Although, clear evidence on postoperative outcomes in colorectal cancer surgery is still lacking.[49]

Especially in selected patients, improvement of preoperative physical status could be beneficial in improving postoperative outcomes.[55] Seniors with lack of physical condition and muscle strength have an increased risk for postoperative complications, and therefore these are targets for prehabilitation programs.[12,49] In particular senior patients with the lowest baseline fitness benefit most from these programs.[56] Until now, it is still not exactly known which aspects the best prehabilitation programs should include and what the optimal timing and duration of these programs should be.[6] Probably, these programs should contain multimodal interventions such as physical training, smoking cessation, nutritional support and psychological support.[53,56,57]

The prehabilitation program should start with assessing where the patient is lacking in condition and what the situation and possibilities of the patient are. As home-based training has shown some good results in prehabilitation programs, training at home could be considered if preferred by the patient.[58] While in other cases, it could be preferred to train with a physiotherapist. Ideally, these programs should take place in the waiting period between diagnosis and surgery. This period can be used optimally by letting patients participate in prehabilitation programs to improve their condition. In case of advanced rectal cancer where neoadjuvant treatment is needed, this period is often longer and can extend up to 12 weeks, which makes it feasible to perform a longer and possibly more effective prehabilitation program to improve the patient's condition. Although prehabilitation needs time to take its effect, until now it is not clear whether long prehabilitation programs are more effective than short programs.[59] However, it is believed that these programs should be given to patients where there is at least about 2 weeks, and ideally 4–6 weeks, prior to surgery.[59] Participating in prehabilitation programs can help to lower the impact of neoadjuvant regimens on physical condition.[60] In patients that are considered frail, response to prehabilitation can also help to determine if they can receive curative treatment with surgery or it is better to perform best supportive/palliative treatment.

Nutritional status

About one in five CRC patients is malnourished before surgery.[61] Poor nutritional state is associated with adverse postoperative outcomes, while good nutritional status is important for muscle gain and recovery.[49,53,62] So, improving nutritional status preoperatively seems important to create an anabolic instead of a catabolic state. Supplementation of proteins in addition to physical training could be beneficial to increase muscle gain.[57] Additionally, some proteins have shown some anti-inflammatory and immune-modulating effects.[53] Supplementation of vitamin D and multivitamins, which are often deficient in seniors, could be beneficial as vitamin D is associated with muscle mass and strength.[57,63] Although the use of nutritional interventions has not yet been proven, it seems that when nutritional interventions are integrated with other prehabilitation modalities, clinically meaningful enhancements could be made in outcomes.[62,64]

Comorbidity

Older patients with CRC often have other chronic diseases to deal with, about 60% of CRC patients over 70 years suffer from any comorbidity.[65] Each comorbidity has a different impact on physical function and postoperative outcomes, but patients with comorbidities in general do not especially develop more surgical complications than those without comorbidities.[65,66] As having comorbidities is not the same as frailty, and frailty is influenced only by a few specific comorbidities, it is important to know the impact of each comorbidity on postoperative outcomes.[65,67] Most seniors with CRC have comorbidities like cardiovascular and pulmonary diseases, which both increase the operative and postoperative risk of morbidity and mortality.[67,68] Patients with colorectal cancer and a preoperative diagnosis of deep venous thrombosis (DVT) also have an increased risk of developing postoperative complications.[65] Therefore, when patients suffer preoperatively from a DVT, it is important to give extra attention to regulate their haemostasis both pre- and postoperatively to prevent complications and to increase survival.[65,68] Also neurological comorbidities in the presence of CRC increases the risk of negative postoperative outcomes.[68] Other prevalent comorbidities seen in CRC patients are hypertension, diabetes, and previous malignancies, but these have minimal impact on frailty and postoperative outcomes.[65,69] However, some comorbidities do play a role in survival and must be taken into account during the decision-making process. Preoperative treatment and regulation of the patients’ comorbidities is important and may reduce the peri- and postoperative morbidity and mortality.[70]

Emergency surgery

About 15% of colon cancer patients present with acute obstruction.[71] Emergency surgery is considered as a major risk factor for postoperative mortality in comparison to elective surgery, especially in the senior CRC patient.[71] In addition, they died earlier after surgery and had higher rates of complications compared to younger patients.[71] However, it has been shown that relative survival rates do not differ between older and younger obstructed colon and rectal cancer patients, which implicates that curative treatment of these seniors is beneficial.[9,71] Even in emergency cases, age itself should not be the most important factor in decision-making.[9,71]

In obstructed colon cancer, surgery is also the primary treatment modality.[71] However, it is still not known which surgical technique is the best and whether stent as bridge to surgery should be performed or not.[71] The rationale behind stenting as bridge to surgery is to initially decompress the distended colon to transform an emergency resection into an elective procedure with optimised circumstances.[72] Although guidelines even recommend the use of stent placement as bridge to surgery for seniors who are at risk, it is not frequently performed because of safety concerns.[72] Recently, it is shown that the use of a stent as bridge to surgery is safe and provides an alternative to emergency resections, especially in high-volume centres.[72] In addition, it is associated with higher rates of laparoscopy and lower rates of postoperative morbidity and permanent stomas than after emergency resection.[72,73] Although not statistically significant, a meta-analyses showed a tendency to higher tumour recurrence rates in the stent group than after emergency surgery. However, short-term mortality and overall and disease-free survival rates were not impaired in the stent-group.[72,73]

Another alternative to emergency surgery is the obstruction protocol, which has been developed by some of the authors (M.F., A.S.).[74] (Figure 2). This protocol aims to postpone surgery for several weeks allowing proper prehabilitation. Especially in the older patient who is in an emergency situation and thus depleting their physical reserves, prehabilitation is important to reduce postoperative morbidity. The obstruction protocol consists of reduction of pre-stenotic dilatation and abdominal pain, thus preventing emergency surgery and providing time for prehabilitation, both in regards to physical and nutritional status. The pre-stenotic distention of the bowel wall and the stenosis of these patients causes pain and malabsorption leading to chronic insufficient intake and lethargy which in turn causes suboptimal physical and nutritional condition.[75] In this obstruction protocol, patients that present with obstructed colon cancer receive dietary adjustments and oral laxatives to reduce the amount of stool produced. The reduced volume of stool can more easily pass the obstructive bowel. This will reduce pre-stenotic bowel wall distension and consequently abdominal pain. In the absence of bowel wall distension and abdominal pain the need for emergency surgery disappears. Surgery can be postponed, planned electively after preferably 3 weeks, and conducted by a specialised colorectal surgeon, laparoscopically or robot-assisted. It also provides time for proper prehabilitation of the patient such as improving physical status, smoking cessation and reduction of alcohol consumption prior to elective surgery. The dietary measures that were given to reduce the amount of stool also covered all the nutritional needs of the patient and subsequently ensured adequate caloric intake, which resulted in the patient leaving the catabolic state. According to the severity of obstruction the patients are given diets ranging from residue-low diet to total parenteral nutrition. In the senior patient, these measures that can enhance nutritional and physical condition can make an important difference. Promising results have been shown in a pilot study and are now further investigated in a multicentre setting.[74]

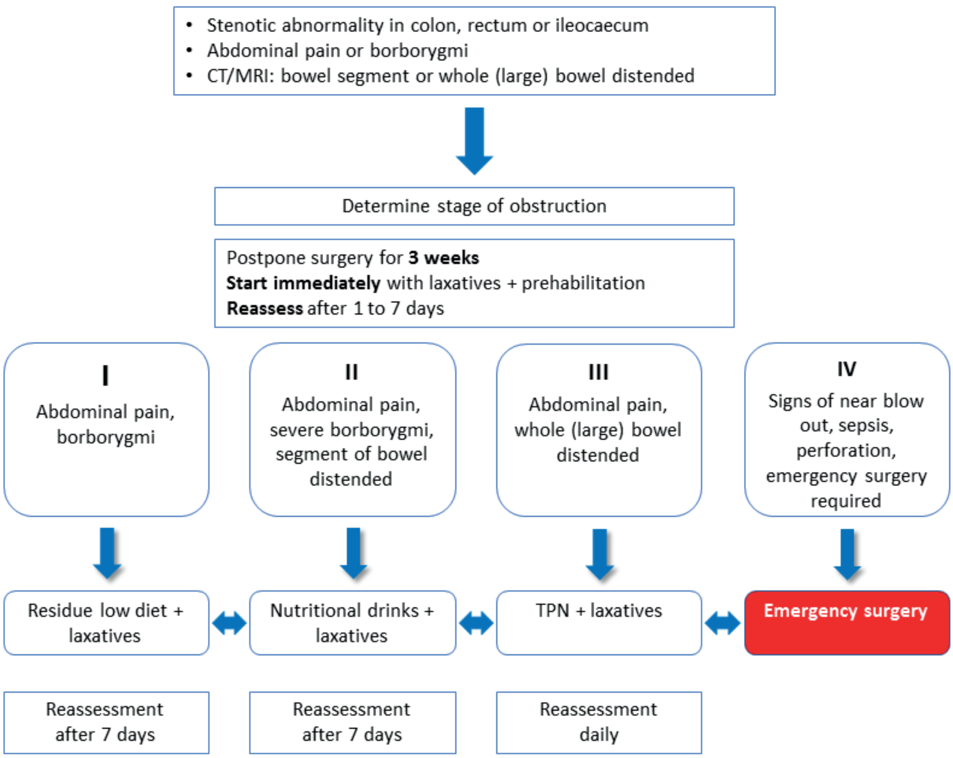

Figure 2. Flowchart for postponing emergency surgery in case of obstruction, as described by Fahim and Smits et al.[74]

In obstructed rectal cancer with an impending cecum blow-out, it seem necessary to perform a deviating stoma first and to perform resectional surgery in an elective setting after adequate staging and neoadjuvant treatment, when needed.[45] During this period, it could also be possible to use the obstruction protocol to improve the circumstances and the patients' condition as a bridge to definitive surgery.

CONCLUSION

The poor outcomes in the past of colorectal surgery do not reflect daily practice anymore. Colorectal surgery can be performed safely without increased postoperative morbidity and mortality and without excess one-year mortality. Several changes in the management have contributed to this lapse in outcome i.e.: better preoperative assessment and prehabilitation, less traumatic surgery and non-surgical organ preservation treatments, perioperative care focussing on nutritional, electrolyte and fluid balance, new anaesthesiological techniques, early postoperative mobilization etc. The most important contribution solving this problem was the understanding that a multidisciplinary approach is necessary, and the recognition that actions may be needed to be taken before any invasive treatment.

Within this multidisciplinary setting, even more frail patients may undergo treatment. The development of special MDTs for seniors, who have to undergo major surgery, with a dedicated team encompassing not only a surgeon and anaesthesiologist, but also a geriatrician has to be applauded.

Programs to deal with specific problems like acute obstruction, which still carries the highest risks for senior people, have to be developed further and implemented on a major scale.

If surgery is necessary for cure, surgery is a valid option for most senior citizens with colorectal cancer. Counselling and shared decision making should be based on modern insights in surgical outcomes rather than on outdated data.

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CHAPTER 7

An evaluation of the postoperative outcomes and treatment changes after frailty screening and geriatric assessment in a cohort of older patients with colorectal cancer

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Submitted to Journal of Geriatric Oncology

ABSTRACT

Introduction

Adequate patient selection is crucial within the treatment of older patients with colorectal cancer (CRC). While previous studies reported increased morbidity and mortality in older patients screened positive for frailty, improvements in the perioperative care and postoperative outcomes have raised the question of whether older patients screened positive for frailty still face worse outcomes. This study aimed to investigate the postoperative outcomes of older patients with CRC screened positive for frailty, and to evaluate changes in treatment after frailty screening and geriatric assessment.

Materials and methods

Patients ≥70 years with primary CRC who underwent frailty screening between 1 January 2019 and 31 October 2021 were included. Frailty screening was performed by the Geriatric-8 (G8) screening tool. If the G8 indicated frailty (G8 ≤14), patients were referred for a comprehensive geriatric assessment (CGA). Postoperative outcomes and changes in treatment based on frailty screening and CGA were evaluated.

Results

A total of 170 patients were included, of whom 74 (43.5%) patients were screened positive for frailty (G8 ≤14). Based on the CGA, the initially proposed treatment plan was altered to a less intensive regimen in 5 (8.9%) patients, and to a more intensive regimen in 1 (1.8%) patient. Surgery was performed in 87.8% of patients with G8 ≤14 and 96.9% of patients with G8 >14 (p = 0.03). Overall postoperative complications (46.2% vs. 47.3%, p = 0.89) were similar between patients with G8 ≤14 and G8 >14. Postoperative delirium was observed in 7.7% of patients with G8 ≤14 and 1.1% of patients with G8 >14 (p = 0.08). No differences in 30-day mortality (1.1% vs. 1.5%, p > 0.99), and 1-year and 2-year survival rates were observed (log rank, p = 0.26).

Discussion

Although patients screened positive for frailty less often underwent CRC surgery, those considered eligible for surgery can safely undergo CRC resection within current clinical care pathways, without increased morbidity and mortality. Efforts to optimise perioperative care and minimise the risk of postoperative complications, in particular delirium, seem warranted. A multidisciplinary onco-geriatric pathway may support tailored decision-making in patients at risk of frailty.

INTRODUCTION

Adequate patient selection is crucial to prevent undertreatment and overtreatment in older patients with colorectal cancer (CRC).[1] Due to the wide heterogeneity in health among the older population, the decision-making is often challenging.[1,2]

A comprehensive geriatric assessment (CGA) is often performed to improve patient selection and decision-making. A CGA consist of a multidimensional evaluation of medical, psychosocial, and functional aspects, aiming to assess frailty status, the presence of geriatric syndromes, patient preferences, and treatment goals.[2] However, performing a CGA in every older patient would be expensive and time-consuming.[3,4] Therefore, frailty screening is performed to identify patients who benefit most from a CGA due to an increased risk of poor outcomes.[4] The Geriatric-8 (G8) is a validated screening tool for frailty.[5,6] Previous studies have reported that patients screened positive for frailty by the G8 (G8 ≤14) face increased morbidity, prolonged lengths of hospital stay, higher rates of postoperative delirium, and increased one-year mortality rates.[5,7–9]

However, over the recent years, the implementation of minimal invasive surgery and Enhanced Recovery After Surgery (ERAS) protocols have contributed to shortened lengths of hospital stay, and reduced morbidity and mortality.[10,11] CRC surgery is nowadays considered a safe treatment approach in most older patients.[10,11] Given these improvements in the perioperative care and postoperative outcomes of older patients, the question has been raised of whether even those at risk of frailty can safely undergo CRC surgery within current clinical care pathways.

The aim of the present study was to investigate the postoperative outcomes of older patients with CRC who were screened positive for frailty, and to evaluate changes in treatment after frailty screening and geriatric assessment.

MATERIALS AND METHODS

Study design and population

A retrospective single centre, observational cohort study was conducted at the Catharina Hospital (Eindhoven, the Netherlands). This study was reviewed and approved not to be subject to the Medical Research Involving Human Subjects Act (Medical Research Ethics Committees United – Nieuwegein, registration number W22.021). Patients ≥70 years with primary CRC who underwent frailty screening between 1 January 2019 and 31 October 2021 were included. Patients with peritoneal or distant metastases, or locally recurrent rectal cancer were excluded.

Frailty screening and CGA

According to the Dutch guidelines, frailty screening should be performed in patients ≥70 years. Frailty screening was performed by using the G8 screening tool.[12,13] The G8 screening tool consists of 8 items, dealing with age, food intake, weight loss, mobility, neuropsychological problems, body mass index (BMI), medication use, and self-perception of health.[12] The total score ranges from 0–17. A G8 score ≤14 indicated a positive score for frailty.[12] In patients with G8 ≤14, a CGA by a geriatrician was indicated.

The CGA consisted of a multidimensional evaluation of medical, psychosocial, and functional capabilities, to assess the patient's frailty status, treatment goals, and preferences. Health domains were evaluated by various clinimetric tests and score lists. Comorbidities were classified by the Charlson Comorbidity Index (CCI).[14] The CCI comprises of 19 disease-categories, each assigned between 1 and 6 points, according to the adjusted risk of 1-year mortality.[14] CRC diagnoses were excluded from the CCI. Katz-ADL was used to assess the level of independency in activities of daily living (ADL).[15] Katz-ADL consists of 6 questions, with a total score range between 0 (completely independent) and 6 (completely dependent).[15] A score ≥1 on the Katz ADL questionnaire indicated an increased level of dependency in ADL.[12,16] Fillenbaum-IADL was used to assess the level of independency in instrumental activities of daily living (IADL).[17] Fillenbaum-IADL consists of 7 questions with a total score range between 0 (completely dependent) and 14 (completely independent).[17] A score ≤12 indicated an increased level of dependency in IADL.[17] The Mini Nutritional Assesment Short-Form (MNA-SF) was used to assess nutritional status.[18] MNA-SF consists of 6 questions and the total score is categorised in: 0–7 (severe malnutrition), 8–11 (at risk for malnutrition), and 11–14 (no malnutrition).[18] The Mini Mental State Examination (MMSE) was used to assess the cognitive status.[19] The MMSE consists of 30 questions on the cognitive function.[19] A score ≤23 indicated cognitive impairment.[19] The 4-meter gait speed (4MGS) test measures the time that a patient needs to walk 4 meters at a normal pace.[20] A 4MGS <1.00 m/s was considered abnormal.[21]

Based on the criteria of Balducci and Extermann, by considering the patient's clinical, functional, and mental status, and the outcomes on frailty assessment instruments, patients were classified into three groups: fit, intermediate frail, or frail.[22] Fit patients were functionally independent and did not suffer from any relevant comorbidities, or had a G8 score >14.[22] Intermediate frail patients were dependent in one or more IADL domains and/or suffered from 1 or 2 relevant comorbidities.[22] Frail patients were dependent in one or more ADL domains, and/or suffered from 3 or more relevant comorbidities, and/or suffered from at least one geriatric syndrome (i.e. dementia, previous delirium, depression, previous falls (>3 times per month), neglect and abuse, spontaneous bone fractures).[22]

Data collection and follow-up

Patient characteristics, outcomes of frailty screening and geriatric assessment, and data on treatment and postoperative outcomes were retrospectively extracted from the medical records. Geriatric interventions were divided in oncological treatment alterations and non-oncological interventions. Non-oncological interventions were aimed to optimise the patient's health status or minimise the risk of complications (e.g. delirium-preventive strategies, interventions to improve mobility or nutrition). New diagnoses found during the CGA were scored. Postoperative complications occurring in the first 30 postoperative days or before hospital discharge were scored by using the Clavien-Dindo classification.[23] Length of postoperative hospital stay, 30-day readmission rate, the destination of discharge, and the need for home nursing care services were extracted from the medical records. Follow-up data were extracted from medical records, by contacting the referring hospital, or the patient's general practitioner. Follow-up was calculated as the interval between the date of surgery and last contact or death. The Municipal Administrative Databases were consulted to obtain data on survival.

Statistical analyses

Statistical analyses were performed by using SPSS Statistics 25.0 software (IBM, Endicott, NY, USA). The primary endpoint was the overall postoperative complication rate. Secondary endpoints were the Clavien-Dindo grades, oncological treatment alterations and non-oncological interventions, length of hospital stay, destination of discharge, need for home nursing care services, readmissions, and survival outcomes. Continuous data were reported as mean with standard deviation (SD) or as median with interquartile range (IQR), depending on parameter distribution. Categorical data were reported as count with percentage (%). Comparisons were stratified by G8 score (≤14 versus >14). Subanalyses were performed to compare postoperative outcomes between fit, intermediate frail, and frail patients, based on the CGA. Independent *t*-tests or one-way ANOVA were used for normally distributed continuous data, and Mann-Whitney *U* tests or Kruskal-Wallis test were used for non-normally distributed continuous data, when appropriate. A *p*-value of <0.05 was considered statistically significant. All tests were two-sided. Survival rates were analysed for patients who underwent surgery by using the Kaplan–Meier method and compared by the log-rank test, stratified by G8 score (≤14 and >14) and geriatric classification (fit, intermediate frail, frail).

RESULTS

A total of 170 older patients with CRC who underwent frailty screening between January 2019 and October 2021 were included, of whom 74 (43.5%) patients were screened positive for frailty (G8 ≤14) and 96 (56.5%) were screened negative for frailty (G8 >14). The median follow-ups of patients with G8 ≤14 and G8 >14 were 20.7 (IQR 12.4–28.3) and 22.8 (IQR 14.4–31.2) months, respectively (p = 0.12). Patients with G8 ≤14 were significantly older (81.8 years vs. 76.3 years, $p < 0.001$), and suffered more often from polypharmacy (62.2% vs. 32.3%, $p < 0.001$), anaemia (51.4% vs. 24.0%, $p < 0.001$), and higher scores on the Charlson Comorbidity Index (p = 0.002) (Table 1).

Table 1. Clinical patient characteristics of all included older patients with CRC (n = 170), stratified by G8 score (>14 and ≤14).

	G8 >14 **n = 96**	**G8 ≤14** **n = 74**	***p*-value**
	n (%)	**n (%)**	
Median follow-up since diagnosis in months (IQR)	22.8 (14.4–31.2)	20.7 (12.4–28.3)	0.12
Mean age in years at time of diagnosis (±SD)	76.3 (4.3)	81.8 (5.6)	<0.001
Male	47 (49.0)	27 (36.5)	0.10
Charlson Comorbidity Index score			0.002
0	60 (62.5)	27 (36.5)	
1–2	33 (34.4)	40 (54.1)	
≥3	3 (3.1)	7 (9.5)	
Median Charlson Comorbidity Index score	0.0 (0.0–1.0)	1.0 (0.0–2.0)	<0.001
Median Geriatric-8 score	15.0 (15.0–16.0)	12.3 (11.0–13.6)	<0.001
Anaemia at baseline	23 (24.0)	38 (51.4)	<0.001
Treated	21 (91.3)	32 (84.2)	0.70
Polypharmacy	31 (32.3)	46 (62.2)	<0.001
Location of tumour			0.74
Colon	69 (71.9)	51 (68.9)	
Rectum	27 (28.1)	23 (31.1)	

Abbreviations: IQR = interquartile range, SD = standard deviation

Influence of frailty screening and geriatric assessment on treatment decisions

Of the 74 patients with G8 ≤14, 56 (75.7%) were referred for a CGA. A total of 18 patients screened positive for frailty were not referred for a CGA (e.g. considered fit by treating physician) (Table 2). Table 3 presents the outcomes of the frailty assessment instruments in the CGA. Based on frailty screening and/or CGA, 108 (63.5%) patients were classified as fit, 28 (16.5%) were classified as intermediate frail, and 16 (9.4%) were classified as frail.

Table 2. Reasons patients screened positive for frailty were withdrawn from a Comprehensive Geriatric Assessment (CGA) (n = 18).

	n = 18
	n (%)
Considered fit by treating physician (although screened as frail)	4 (22.2)
Urgent surgery needed (e.g. due to bowel obstruction)	5 (27.8)
Patient denies referral for a CGA	5 (27.8)
Recently underwent a comprehensive assessment	2 (11.1)
Unknown	2 (11.1)

Abbreviations: CGA = Comprehensive Geriatric Assessment

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Table 3. The outcomes of the scoring tools used in the Comprehensive Geriatric Assessment (CGA) in older patients screened positive for frailty (n = 56).

	n = 56
	n (%)
Katz ADL score ≥1	17 (30.4)
Missing	–
Fillenbaum IADL score ≤12	34 (60.7)
Missing	1
MNA-SF score	
At risk for malnutrition (8–11)	29 (51.8)
Malnutrition (0–7)	3 (5.4)
Missing	4
MMSE score ≤23	10 (17.9)
Missing	10
4-meter gait speed <1.00 m/s	23 (41.1)
Missing	15
Charlson Comorbidity Index score	
0	19 (33.9)
1-2	32 (57.1)
≥3	5 (8.9)

Abbreviations: ADL = activities of daily living, IADL = instrumental activities of daily living, MNA-SF = Mini Nutritional Assessment Short Form, MMSE = Mini-Mental State Examination

Based on the CGA, the oncological treatment plan was altered in 6 (10.7%) out of 56 patients. In 5, the treatment was altered to a less intensive regimen due to frailty, of whom 3 were withdrawn from surgery and 2 underwent local excision instead of total mesorectal excision. The oncological treatment plan was intensified from palliative radiotherapy to surgical resection in 1 patient. Non-oncological interventions were recommended in 36 (64.3%) patients and mostly included delirium-preventive measures (n = 21), and interventions to improve nutritional status (n = 17) or mobility (n = 16). In 16 (28.6%) patients, the CGA revealed new diagnoses (Table 4). In 15 of 16 patients, the newly found diagnosis did not influence the proposed treatment regimen.

Table 4. Oncological treatment alterations, recommended non-oncological interventions and newly found diagnoses, based on the Comprehensive Geriatric Assessment (CGA) in older patients screened positive for frailty (n = 56).

	n = 56
	n (%)
Oncological interventions	6 (10.7)
More intensive treatment	1 (1.8)
Less intensive treatment	5 (8.9)
Non-oncological interventions	36 (64.3)
Nutritional interventions	17 (30.4)
Interventions aimed at mobility and falls	16 (28.6)
Psychological interventions	3 (5.4)
Delirium-preventive measures	21 (37.5)
Medication optimisation	7 (12.5)
Geriatric consultation during hospital admission	8 (14.3)
Interventions aimed at postoperative discharge / rehabilitation	3 (5.4)
Newly identified comorbidities	16 (28.6)
Cardiac murmur	5 (8.9)
Cognitive dysfunction	9 (16.1)
Other (e.g. psychiatric problems, wound healing problems)	2 (3.6)

Surgical treatment and postoperative outcomes

Surgery was performed in 65 (87.8%) of 74 patients with G8 ≤14 and in 93 (96.9%) of 96 patients with G8 >14 (p = 0.03). Minimal invasive surgery was performed in 90.8% of patients with G8 ≤14 and in 83.9% of patients with G8 >14 (p = 0.21). A primary anastomosis was significantly less often performed in patients with G8 ≤14 (73.8% vs. 87.1%, p = 0.04). (Table 5). Supplementary Table 1 presents the clinical characteristics of patients who underwent surgery, separated for colon and rectal cancer.

Table 5. Clinical characteristics of all included older patients with CRC that underwent surgery (n = 158), stratified by G8 score (>14 and ≤14).

	G8 >14 n = 93 n (%)	G8 ≤14 n = 65 n (%)	*p*-value
Location of tumour			0.63
Colon	69 (74.2)	46 (70.8)	
Rectum	24 (25.8)	19 (29.2)	
Neoadjuvant treatment			0.95
No neoadjuvant treatment	72 (77.4)	53 (81.5)	
Long-course chemoradiotherapy	16 (17.2)	9 (13.8)	
Short-course radiotherapy	2 (2.2)	1 (1.5)	
Other	3 (3.2)	2 (3.1)	
Elective surgery	90 (96.8)	57 (87.7)	0.052
Surgical technique			0.25
Laparotomy	15 (16.1)	6 (9.2)	
Robot-assisted	15 (16.1)	12 (18.5)	
Laparoscopy	63 (67.7)	45 (69.2)	
Local excisional procedure	–	2 (3.1)	
Surgical procedure			0.56
Right hemicolectomy	43 (46.2)	33 (50.8)	
Left hemicolectomy	11 (11.8)	4 (6.2)	
Sigmoid resection	9 (9.7)	8 (12.3)	
Low anterior resection	20 (21.5)	13 (20.0)	
Abdominoperineal resection	9 (9.7)	5 (7.7)	
(Sub)total colectomy	1 (1.1)	–	
Local excision	–	2 (3.1)	
Multivisceral resection	18 (19.4)	8 (12.3)	0.24
Intra-operative radiotherapy	7 (7.5)	3 (4.6)	0.53
Primary anastomosis	81 (87.1)	48 (73.8)	0.04
Adjuvant chemotherapy	12 (12.9)	4 (6.2)	0.18

No differences in overall complication rates were observed between patients with G8 ≤14 and G8 >14 (46.2% vs. 47.3%, p = 0.89). Clavien-Dindo ≥III complications occurred in 13.8% of patients with G8 ≤14 and in 18.3% of patients with G8 >14 (p = 0.46). Cardiac complications were more often observed in patients with G8 ≤14 (15.4% vs. 4.3%, p = 0.02). Postoperative delirium was observed in 7.7% of patients with G8 ≤14 and in 1.1% of patients G8 >14 (p = 0.08). No significant differences in postoperative complications were observed between patients classified as fit, intermediate frail, and frail. (Table 6). Supplementary Table 2 presents the postoperative outcomes, separated for colon and rectal cancer.

Table 6. Postoperative outcomes of all colorectal cancer patients ≥70 years that underwent surgery (n = 158), stratified by G8 score (>14 and ≤14) and geriatric classification (fit, intermediate frail, frail).

	Frailty screening n = 158			Geriatric classification n = 142			
	G8 >14	**G8 ≤14**	***p*-value**	**Fit**	**Intermediate frail**	**Frail**	***p*-value**
	n = 93	**n = 65**		**n = 105**	**n = 26**	**n = 11**	
	n (%)	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Postoperative complications							
Cardiac	4 (4.3)	10 (15.4)	0.02	5 (4.8)	4 (15.4)	1 (9.1)	0.12
Pulmonary	8 (8.6)	2 (3.1)	0.20	9 (8.6)	–	–	0.32
Urological	13 (14.0)	7 (10.8)	0.55	14 (13.3)	1 (3.8)	1 (9.1)	0.43
Delirium	1 (1.1)	5 (7.7)	0.08	2 (1.9)	1 (3.8)	1 (9.1)	0.17
Wound infection	11 (11.8)	5 (7.7)	0.44	11 (10.5)	–	–	0.16
Gastroparesis/ileus	18 (19.4)	11 (16.9)	0.70	19 (18.1)	6 (23.1)	1 (9.1)	0.70
Intra-abdominal/presacral abscess	10 (10.8)	1 (1.5)	0.03	10 (9.5)	–	–	0.25
Anastomotic leakage	11 (11.8)	1 (1.5)	0.02	11 (10.5)	–	–	0.16
Clavien-Dindo classification			0.59				0.51
Grade 0	49 (52.7)	35 (53.8)		58 (55.2)	13 (50.0)	7 (63.6)	
Grade I-II	27 (29.0)	21 (32.3)		28 (26.7)	10 (38.5)	3 (27.3)	
Grade IIIa+IIIb	14 (15.1)	5 (7.7)		16 (15.2)	1 (3.8)	1 (9.1)	
Grade IV	2 (2.2)	3 (4.6)		2 (1.9)	2 (7.7)	–	
Grade V	1 (1.1)	1 (1.5)		1 (1.0)	–	–	
Median length of hospital stay in days (IQR)	3.0 (2.0–6.5)	4.0 (2.0–6.0)	0.91	3.0 (2.0–6.0)	5.0 (2.0–7.0)	3.0 (1.0–4.0)	0.33
Destination of discharge			>0.99				0.27
Institutional care facility	6 (6.5)	4 (6.3)		7 (6.7)	–	1 (9.1)	
Home	86 (93.5)	60 (93.8)		97 (93.3)	26 (100.0)	10 (90.9)	
Need for home nursing care services[1]	14 (16.3)	14 (23.3)	0.39	14 (14.4)	11 (42.3)	3 (30.0)	0.01
30-day readmission	11 (12.0)	5 (7.8)	0.39	11 (10.6)	1 (3.8)	2 (18.2)	0.33
Mortality							
30-day	1 (1.1)	1 (1.5)	>0.99	1 (1.0)	–	–	>0.99
90-day	1 (1.1)	1 (1.5)	>0.99	1 (1.0)	–	–	>0.99

Abbreviations: IQR = interquartile range

[1]Calculated for patients discharged to home;

The median length of hospital stay was similar between patients with G8 ≤14 and G8 >14 (4.0 days vs. 3.0 days, $p = 0.91$). The majority of patients with G8 ≤14 and G8 >14 (93.8% vs. 93.5%, $p > 0.99$) were discharged to home. The need for home nursing care services was comparable between both groups (23.3% vs. 16.3%, $p = 0.39$). However, patients classified as frail and intermediate frail required home nursing care services significantly more often than patients classified as fit (42.3% vs. 30.0% vs. 14.4%, $p = 0.01$).

The 1-year and 2-year overall survival rates were comparable between patients with G8 ≤14 and patients with G8 >14 (Figure 1A), and between fit, intermediate frail, and frail patients (Figure 1B).

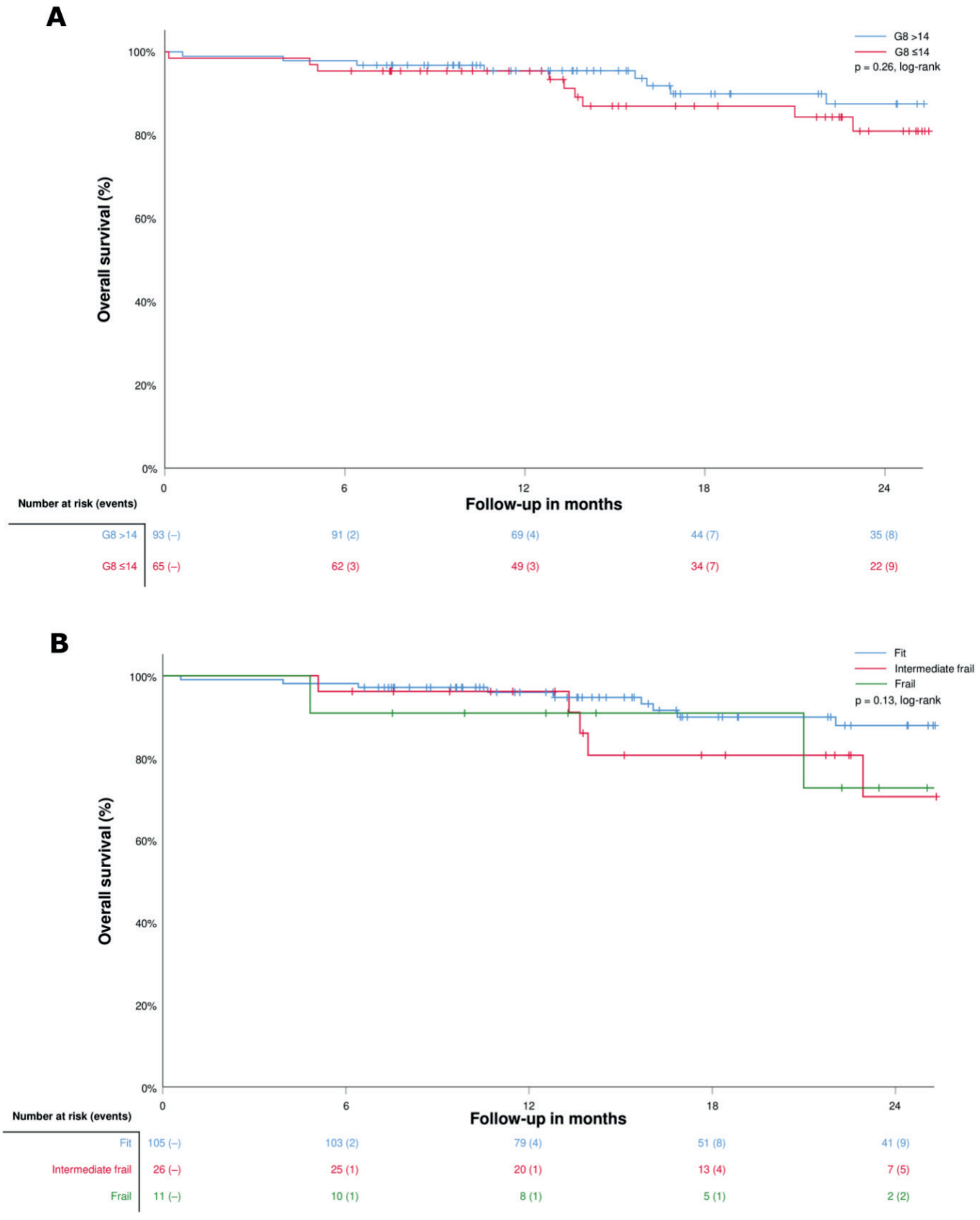

Figure 1. Kaplan-Meier curve on the absolute overall survival for older patients with CRC who underwent surgery during the first 2 years after surgery, stratified by **A)** G8 score (>14 and ≤14) and **B)** Geriatric classification (fit, intermediate frail, frail).

DISCUSSION

This study investigated the differences in postoperative outcomes between patients with G8 ≤14 and G8 >14, and evaluated the changes in treatment after frailty screening and geriatric assessment in older CRC patients. Of the 170 older patients with CRC who underwent frailty screening, 74 were screened positive for frailty (G8 ≤14). Over 75% of the patients with G8 ≤14 were referred for a CGA, which resulted in less intensive treatment regimens in 9% of patients due to frailty, and more intensive treatment regimens in 2% of patients. Surgery was performed in 88% of patients with G8 ≤14 and 97% of patients with G8 >14. No differences were observed in overall postoperative complications (46% vs. 47%), Clavien-Dindo ≥III rates (14% vs. 18%), length of hospital stay (4 days vs. 3 days), patients discharged to home (94% vs. 94%), and survival rates.

Only few studies have reported on the correlation between the G8 and postoperative complications after CRC surgery.[24,25] Bessems et al. included 149 older patients eligible for surgery and reported an increased risk of postoperative complications (62% versus 28%) in patients with abnormal G8 and/or 4MGS.[7] The addition of the 4MGS test may have improved the accuracy to predict postoperative complications.[7] Although not statistically significant, patients with abnormal 4MGS in our cohort also seemed to have an increased risk of postoperative complications (45% versus 29%). Fagard et al. reported on 190 older patients who underwent surgery and observed a significant association between abnormal G8 and increased complications.[8] Another recent study among 112 older patients observed a significantly higher overall complication (52% versus 17%) and 1-year mortality rate (30% versus 8%) in patients with G8 ≤14 when compared to G8 >14.[9] Patients with abnormal G8 were in particular more prone for minor (Clavien-Dindo I-II) and non-surgical complications.[7–9] In the earlier mentioned studies, minimal invasive surgery was performed in 40-70% of patients, whereas 87% of patients in our cohort underwent minimal invasive surgery, which could have contributed to the beneficial outcomes in the current study. Nevertheless, it was found that patients with G8 ≤14 were more prone to develop cardiac complications (e.g. cardiac rhythm disorders, fluid congestion) and postoperative delirium when compared to G8 >14. The increased susceptibility for these complications might be caused by an increased prevalence of cardiopulmonary comorbidities and reduced cognitive capacity in patients at risk of frailty.[26]

Although the definition of frailty lacks standardisation, a median frailty prevalence of 42% has been described among cancer patients in a recent meta-analysis, with a wide range among studies between 6–86%.[27] According to these studies, frail patients faced increased postoperative morbidity and mortality when compared to fit patients.[25,27,28] In our study, the prevalence of frailty and intermediate frailty were 9.4% and 16.5%, respectively, which may have positively influenced our outcomes. Nevertheless, 79% of the patients in our cohort who were screened positive for frailty were classified as either frail or intermediate frail by the geriatrician, of whom 84% underwent CRC surgery. In contrast to earlier literature, patients classified as frail or intermediate frail in our cohort had comparable postoperative outcomes as fit patients.[25,27,28] This underlines that even in frail and intermediate frail patients considered eligible for surgery, colorectal resection seems a safe treatment option nowadays.

Improvements in perioperative care, including the implementation of minimal invasive surgery and ERAS protocols, has greatly benefitted the older population.[10,11] Given the reduced surgical stress and the improved postoperative outcomes after minimal invasive surgery, this should be the first choice of treatment in the older patient, especially in those at risk of frailty.[29] An increasing amount of literature has shown that ERAS protocols are feasible in older patients and result in a shorter length of hospital stay and less complications.[30,31] The preoperative workup that is part of ERAS might be beneficial for older patients. Screening for malnutrition, correction of anaemia, and informing the patient and their caregivers about the postoperative period, including the benefits of early mobilisation, and the importance of delirium prevention, can favour their recovery.[30] In those suffering from frailty, polypharmacy, or multimorbidity, geriatric co-management may help to suit perioperative treatment to their needs.[32,33] Implementing a geriatrician in the multidisciplinary team during the postoperative phase has shown to be associated with improved outcomes and reduced 90-day mortality.[34] Efforts should be integrated to increase overall adherence to ERAS protocols. Within our hospital, a dedicated ERAS protocol has been implemented, with an overall adherence rate of above 70%. This may have contributed to the beneficial outcomes in patients with G8 ≤14.[35] The median length of hospital stay was 4 days, whereas previous studies among similar patients reported a length of stay of 6–10 days.[7,8,24,36–38] The overall delirium rate of 3.8% was also reduced in comparison to the 8–14% reported in other CRC cohorts.[38–40] Nevertheless, still 8% of patients with G8 ≤14 developed a postoperative delirium. As a result, additional attention should be paid for preoperative delirium risk screening and delirium-preventive strategies, in particular in patients at risk of frailty.[38,41]

Patient selection is key in the treatment of older patients. Frailty screening and a CGA may help to identify patients who benefit from standard versus adapted treatment. A CGA is associated with improved decision-making, treatment outcomes, quality of life, and a reduced risk of institutionalisation after treatment, especially in the frail.[42–44] The additional value of frailty screening and a CGA on the treatment decisions in older patients with cancer has been investigated previously. A systematic review by Hamaker et al. included 61 studies with different types of cancer and reported oncological treatment alterations in a median of 31%, mostly resulting in less intensive treatment.[44] Treatment decisions were in particularly changed when geriatric assessment was implemented in multidisciplinary team evaluations.[44] In our cohort, geriatric assessment strictly altered the treatment regimen in 11% of patients, but geriatric risk factors appeared to have influenced perioperative decision-making. More than 90% of patients with G8 ≤14 were treated with minimal invasive techniques. In addition, they were more often refrained from a primary anastomosis, which may have contributed to the reduced rates of anastomotic leakages, and intra-abdominal or presacral abscesses when compared to fit patients.

Frailty screening and a CGA may also help to identify impaired health areas. There is growing evidence that adequate preoperative strategies to optimise the patient's health status can improve the outcomes of older patients, especially in the frail.[45–48] In the present cohort, non-oncological interventions were recommended in 64% of the patients referred for a CGA, and mostly aimed at delirium prevention, or at improving the nutritional status or mobility. Other studies reported non-oncological interventions in 63-83% of patients after geriatric assessment.[7,36,44] Although non-oncological interventions could have contributed to the beneficial outcomes in patients screened positive for frailty, clear evidence on the value of these interventions is still awaited.[36,46] The retrospective character of our study and the absence of data on the adherence to non-oncological interventions have limited insights into the causality between these interventions and the postoperative outcomes.

Rather than chronological age or comorbidities, treatment decisions should be based on the level of frailty, patient preferences, and treatment goals. If no frailty is suspected, older patients can safely be offered standard approaches. If patients are at risk of frailty, a CGA should be considered. In a select group of patients with only minor and easy targetable health deficits and no clinical signs of frailty, targeted interventions based on validated clinimetric tests might be sufficient to optimise the patient's preoperative health status. In these patients, the need for a time-consuming CGA might be reduced. Close alignment of care and effective communication between the geriatrician, the surgeon, and the rest of the multidisciplinary is crucial to tailor treatment. The geriatrician is a crucial part of the multidisciplinary team. This was also supported by a recent Dutch study, which showed that the implementation of a multidisciplinary onco-geriatric approach improved patient selection, prehabilitation, and outcomes of frail CRC patients.[49] A select group of the most frail patients still face high risks of poor postoperative outcomes, even after optimising the entire treatment pathway. In these patients, a personalised non-operative treatment strategy should be considered, aiming for an optimal treatment to obtain local control of the primary tumour and maintain quality of life, based on individual treatment goals and preferences.[50]

The main strength of this study was the inclusion of a relatively large cohort of older patients with the availability of many clinical variables. Limitations were mainly based on the retrospective character of the study, which may have impaired insights into the causality between frailty screening, interventions and outcomes. Another main limitation was that we only studied patients in whom frailty screening was performed and investigated the outcomes of patients who were considered eligible for surgery by the surgeon and/or geriatrician. This could have resulted in selection bias. Nevertheless, the current study provides important data on the beneficial postoperative outcomes of older patients at risk of frailty. Since frailty screening is standard care in the older patient, it is expected that only a minority of patients were not included due to absent frailty screening.

Future studies in larger cohorts are warranted to support the findings of this study and investigate the value of frailty screening and assessment in a prospective setting. In addition, future studies should focus on predictive factors that correlate with post-treatment outcomes, including functional recovery and quality of life, to identify which patients benefit most from a CGA. Studies on the treatment and outcomes of older and frail patients unfit for surgery are also warranted. The currently ongoing RESORT study will probably provide insights into the decision-making, treatment, and outcomes of those unable to undergo surgery.[50]

CONCLUSION

Although patients screened positive for frailty (G8 ≤14) less often underwent CRC surgery, those considered eligible for surgery can safely undergo CRC surgery within current clinical care pathways, without increased morbidity and mortality. Efforts to optimise perioperative care and minimise the risk of postoperative complications, in particular delirium, seem warranted. A multidisciplinary onco-geriatric pathway may support tailored decision-making in patients at risk of frailty.

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SUPPLEMENTARY DATA CHAPTER 7

Supplementary Table 7.1. Clinical characteristics of older patients with colon and rectal cancer that underwent surgery separately (n = 158), stratified by G8 score (>14 and ≤14).

	Colon			Rectum		
	G8 >14	**G8 ≤14**	***p*-value**	**G8 >14**	**G8 ≤14**	***p*-value**
	n = 69	**n = 46**		**n = 24**	**n = 19**	
	n (%)	**n (%)**		**n (%)**	**n (%)**	
Neoadjuvant treatment			0.65			0.45
No neoadjuvant treatment	66 (95.7)	45 (97.8)		6 (25.0)	8 (42.1)	
Long-course chemoradiotherapy	–	–		16 (66.7)	9 (47.4)	
Short-course radiotherapy	–	–		2 (8.3)	1 (5.3)	
Other	3 (4.3)	1 (2.2)		–	1 (5.3)	
Elective surgery	66 (95.7)	38 (82.6)	0.03	24 (100.0)	19 (100.0)	>0.99
Surgical technique			0.89			0.17
Laparotomy	2 (2.9)	1 (2.2)		13 (54.2)	5 (26.3)	
Robot-assisted	7 (10.1)	3 (6.5)		8 (33.3)	9 (47.4)	
Laparoscopy	60 (87.0)	42 (91.3)		3 (12.5)	3 (15.8)	
Local excisional procedure	–	–		–	2 (10.5)	
Surgical procedure			0.46			0.25
Right hemicolectomy	43 (62.3)	33 (71.7)		–	–	
Left hemicolectomy	11 (15.9)	4 (8.7)		–	–	
Sigmoid resection	9 (13.0)	8 (17.4)		–	–	
Rectosigmoid resection	5 (7.2)	1 (2.2)		–	–	
Low anterior resection	–	–		15 (62.5)	12 (63.2)	
Abdominoperineal resection	–	–		9 (37.5)	5 (26.3)	
(Sub)total colectomy	1 (1.4)	–		–	–	
Local excision	–	–		–	2 (10.5)	
Multivisceral resection	6 (8.7)	4 (8.7)	>0.99	12 (50.0)	4 (21.1)	0.051
Intra-operative radiotherapy	–	1 (2.2)	0.40	7 (29.2)	2 (10.5)	0.26
Primary anastomosis	69 (100.0)	45 (97.8)	0.40	12 (50.0)	3 (15.8)	0.02
Adjuvant chemotherapy	12 (17.4)	4 (8.7)	0.20	–	–	N.A.

Supplementary Table 7.2. Postoperative outcomes of older patients with colon and rectal cancer separately (n = 158), stratified by G8 score (>14 and ≤14).

	Colon			Rectum		
	G8 >14	G8 ≤14	*p*-value	G8 >14	G8 ≤14	*p*-value
	n = 69	n = 46		n = 24	n = 19	
	n (%)	n (%)		n (%)	n (%)	
Postoperative complications						
Cardiac	4 (5.8)	9 (19.6)	0.02	1 (4.2)	2 (10.5)	0.58
Pulmonary	4 (5.8)	2 (4.3)	>0.99	4 (16.7)	–	0.12
Urological	5 (7.2)	5 (10.9)	0.52	8 (33.3)	2 (10.5)	0.15
Delirium	1 (1.4)	2 (4.3)	0.56	–	3 (15.8)	0.08
Wound infection	7 (10.1)	4 (8.7)	>0.99	4 (16.7)	1 (5.3)	0.36
Gastroparesis/ileus	9 (13.0)	8 (17.4)	0.52	9 (37.5)	3 (15.8)	0.12
Intra-abdominal/presacral abscess	7 (10.1)	–	0.04	3 (12.5)	1 (5.3)	0.62
Anastomotic leakage	7 (10.1)	1 (2.2)	0.14	4 (16.7)	–	0.12
Clavien-Dindo classification			0.15			0.045
Grade 0	42 (60.9)	23 (50.0)		7 (29.2)	12 (63.2)	
Grade I-II	17 (24.6)	19 (41.3)		10 (41.7)	2 (10.5)	
Grade IIIa+IIIb	8 (11.6)	2 (4.3)		6 (25.0)	3 (15.8)	
Grade IV	1 (1.4)	2 (4.3)		1 (4.2)	1 (5.3)	
Grade V	1 (1.4)	–		–	1 (5.3)	
Median length of hospital stay in days (IQR)	3.0 (2.0–4.0)	3.0 (2.0 – 6.0)	0.39	6.0 (4.0–10.0)	5.0 (3.0–6.5)	0.16
Destination of discharge			>0.99			0.69
Institutional care facility	2 (2.9)	2 (4.3)		4 (16.7)	2 (11.1)	
Home	66 (97.1)	44 (95.7)		20 (83.3)	16 (88.9)	
Need for home nursing care services[1]	8 (12.1)	9 (20.5)	0.24	6 (30.0)	5 (31.3)	>0.99
30-day readmission	9 (13.2)	5 (10.9)	0.69	2 (8.3)	–	0.50
Mortality						
30-day mortality	1 (1.4)	–	>0.99	–	1 (5.3)	0.44
90-day mortality	1 (1.4)	–	>0.99	–	1 (5.3)	0.44

[1]calculated for patients who were discharged to home;

CHAPTER 8

A prospective cohort study to evaluate continuous wound infusion with local analgesics within an enhanced recovery protocol after colorectal cancer surgery

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Colorectal Dis. 2022 Oct;24(10):1172-1183. doi: 10.1111/codi.16201.

ABSTRACT

Aim

To reduce detrimental opioid-related side effects, minimising the postoperative opioid consumption is needed, especially in older patients. Continuous wound infusion (CWI) with local analgesics appears to be an effective opioid-sparing alternative. However, the added value of CWI to an enhanced recovery protocol after colorectal cancer (CRC) surgery is unclear. The aim of this study was to evaluate the outcomes of CWI after CRC surgery within a strictly adhered to enhanced recovery protocol.

Methods

In this multicentre prospective observational cohort study, patients who underwent CRC surgery between May 2019 and January 2021 were included. Patients were treated with CWI as adjunct to multimodal pain management within an enhanced recovery protocol. Postoperative opioid consumption, pain scores, and outcomes regarding functional recovery were evaluated.

Results

A cohort of 130 consecutive patients were included, of whom 36.2% were ≥75 years. Postoperative opioids were consumed by 80 (61.5%) patients on postoperative day 0, and by 28 (21.5%), 27 (20.8%), and 18 (13.8%) patients on postoperative days 1, 2, and 3, respectively. Median pain scores were <4 on all days. The median time until first passage of stool was 1.0 (IQR: 1.0–2.0) day. Postoperative delirium occurred in 0.8%. Median length of hospital stay was 3.0 days (IQR: 2.0–5.0).

Conclusion

In patients treated with CWI, low amounts of postoperative opioid consumption, adequate postoperative pain control, and enhanced recovery were observed. CWI seems a beneficial opioid-sparing alternative and may further improve the outcomes of an enhanced recovery protocol after CRC surgery, which seems especially valuable for older patients.

INTRODUCTION

Adequate postoperative pain control after colorectal cancer (CRC) surgery is an essential element within the enhanced recovery after surgery (ERAS) programme.[1,2] However, in current clinical practice, this is often achieved by opioids.[3] Unfortunately, opioids are associated with various detrimental side effects that hamper recovery, such as delayed return of bowel function and prolonged sedative effect.[3,4] Older patients in particular are most prone to these side effects, especially with regard to the risk of delirium and cognitive impairment.[4–6] In order to further improve the postoperative outcomes within an enhanced recovery protocol, minimising the opioid consumption is necessary.[6]

Epidural analgesia is no longer recommended as an opioid-sparing alternative due to its delaying effects on recovery in minimally-invasive CRC surgery, while abdominal wall blocks are mainly limited by their short duration of action.[2,7,8] Continuous wound infusion (CWI) of local analgesics is a promising opioid-sparing technique that is gaining acceptance.[9,10] Several studies have described the benefits of CWI after different types of abdominal surgery.[10–13]

It is hypothesised that CWI has the most benefit within a strictly adhered to and continuously audited enhanced recovery protocol, in which all ERAS elements work synergistically to improve postoperative outcomes.[1,10,14] However, most studies that investigated CWI in patients after CRC surgery were performed in the absence of a strictly adhered to and multidisciplinary enhanced recovery protocol.[10–13] Consequently, outcomes regarding postoperative recovery were mostly not adequately reported.[10]

The aim of this prospective observational cohort study was to evaluate the outcomes of patients treated with CWI as an adjunct to multimodal pain management within an enhanced recovery protocol after CRC surgery, by evaluating postoperative opioid consumption, pain scores and outcomes regarding functional recovery.

METHODS

Study design

This multicentre prospective observational cohort study was conducted to evaluate the outcomes of patients treated with CWI as an adjunct to multimodal pain management within a strictly adhered to enhanced recovery protocol. The use of CWI as an adjunct to multimodal pain management has been initiated since May 2019 as standard of care within the participating hospitals. The study was performed in the Catharina Hospital

(Eindhoven, The Netherlands) and VieCuri Medical Centre (Venlo, The Netherlands) between May 2019 and January 2021.

This study was reviewed and approved not to be subject to the Medical Research Involving Human Subjects Act (Medical Research Ethics Committees United – Nieuwegein, registration number W22.021). Since the study evaluated the recently implemented standard of care, the requirement for written informed consent for participation was waived by the medical ethical committee.

Participants

Consecutive patients who underwent curative open, laparoscopic, or robot-assisted CRC surgery were included. Patients were excluded if they underwent multivisceral organ resections, intraoperative radiation therapy or hyperthermic intraperitoneal chemotherapy, or if they had known allergy to the used local analgesics (bupivacaine or ropivacaine).

Treatment and enhanced recovery protocol

Except from the introduction of CWI as part of multimodal pain management in May 2019, the enhanced recovery protocol that was followed was initiated in March 2018. All patients received standard of care according to the ERAS protocol.[2] Table 1 presents the enhanced recovery protocol that was used in the participating hospitals.

All surgical procedures were performed by dedicated colorectal surgeons. Postoperative pain management was multimodal and included the use of CWI. At the end of the surgical procedure, the wound catheter (InfiltraLong) was introduced in a standardised manner by trained surgeons, a few centimetres away from the Pfannenstiel or laparotomy wound and was positioned in the pre-peritoneal layer. Subsequently, a bolus of 10 ml bupivacaine 1.25 mg/ml or 20 ml ropivacaine 2 mg/ml was injected through the catheter. The wound catheter was connected to the infiltration pump (FuserPump), filled with 350 ml of either bupivacaine 1.25 mg/ml or ropivacaine 2 mg/ml. The standard CWI infusion rate was set at 5 ml/h, and could be adjusted depending on pain scores to either 8 or 3 ml/h, respectively. CWI was continued until the infiltration pump was empty (mostly on postoperative day 3) or until hospital discharge. Apart from CWI, the postoperative analgesia plan included a standard dose of paracetamol 1000 mg 3–4 times daily. In one of the participating hospitals, metamizole 1000 mg was administered 3 times daily during the first three postoperative days. Short-acting opioids were only given as rescue medication in case of uncontrolled pain.

Table 1. The enhanced recovery protocol after colorectal cancer surgery used in the participating hospitals.

Preadmission patient education regarding the protocol	All patients receive extensive information and education with an informational packet and an educational consult with a specialised nurse
Preadmission screening and optimisation for nutritional deficiency, frailty, tobacco cessation, and alcohol use	Patients are screened for nutritional deficiency using the MUST or PG-SGA scoring system, and for frailty by using the G8 scoring system. Patients are referred preoperatively for tobacco and alcohol counselling. Anaemia screening is performed and if applicable, iron replacement treatment is given.
Fasting and carbohydrate loading guidelines	Normal diet until 6 h preoperatively, clear liquids until 2 h preoperatively, preoperative carbohydrate treatment 2 h preoperatively.
Pre-emptive medication (dose, route, timing) and antibiotics prophylaxis	1000 mg paracetamol oral in preoperative ward. No preoperative sedatives. Standard iv antibiotic prophylaxis within 60 minutes before incision.
Anti-emetic prophylaxis (dose, route, timing)	1 mg granisetron and 4 mg dexamethasone given intravenously preoperatively
Intraoperative fluid management strategy	Minimal intraoperative fluid administration. No guidance
Types, doses, and routes of anaesthetics administered	Continuous propofol, intravenous lidocaine, and low-dose ketamine infusion, no volatile anaesthesia Hospital 1: continuous propofol, sufentanil, esketamine, lidocaine, and rocuronium. Hospital 2: continuous propofol, remifentanil, rocuronium, and morphine. Anaesthesia was maintained based on the bispectral index (BIS), targeting between 40 and 60.
Patient warming strategy	Forced warm air
Management of postoperative fluids	Limited and guided by clinical necessity
Postoperative analgesia and anti-emetic plans	Continuous pre-peritoneal wound infusion of bupivacaine 0.125% or ropivacaine 0.2%, 1000 mg acetaminophen every 6 h orally. Patient-controlled analgesia only if postoperative pain control was persistently insufficient with multimodal pain management. 3 times 1 mg granisetron or 3 times 10 mg metoclopramide on postoperative day 1, from day 2 subsequently when necessary
Plan for opioid minimisation	No standard opioids. Short-acting opioids (5 mg oral oxycodone) for breakthrough pain.
Drain and line management	No routine wound drains, Foley catheter removed in OR. Infusion line stopped after first successful diuresis and start of intake
Early mobilisation strategy	Patients ambulate direct on surgical ward. At least rising from bed on day 0, out of bed all meals, out of bed at least 6 h per day starting from postoperative day 1
Postoperative diet and bowel regimen management	Clear liquids and regular diet beginning on postoperative day 0
Criteria for discharge	Tolerating oral intake, independent diuresis, pain well controlled on oral medication, ambulating in hallways, no signs of complications
Tracking of post-discharge outcomes	Follow-up by telephone on day 2 after discharge. Follow-up at 1 week after discharge, and at 1 month after discharge.

Data collection

Baseline patient characteristics, data on treatment, pain management, pain scores, complications, and postoperative recovery (e.g., time until first passage of stool, mobilisation, length of stay) were extracted from the medical records and from a prospectively maintained database, the ERAS Interactive Audit System (EIAS). The primary outcome was the postoperative opioid consumption during the first three postoperative days. The consumed opioid doses were converted to mg of intravenous morphine equivalents.[15,16] Secondary outcomes were postoperative pain scores and outcomes related to functional recovery (e.g., time until mobilisation or first passage of stool). The postoperative pain scores were scored using the numerical rating scale (NRS), ranging from 0–10, during the first three postoperative days.[17] Adequate pain control per patient was defined as a daily mean NRS score < 4.[18] Postoperative nausea (requiring treatment) and vomiting were recorded, as well as the time until successful mobilisation, until the first passage of stool, and the date of hospital discharge. Successful mobilisation was defined as at least getting out of bed (i.e. to walk or sit in chair). Complications occurring in the first 30 postoperative days or until hospital discharge were scored using the Clavien-Dindo (CD) classification.[19] CWI catheter-related complications (e.g., dislocation, leakage) were recorded. All patients had at least a follow-up of 30 days after surgery.

Statistical analyses

Statistical analyses were performed using SPSS Statistics 25.0 software (IBM). The primary endpoint was the proportion of patients that used postoperative opioids on the day of surgery and the first three postoperative days, which was reported using 95% confidence intervals (95% CI). Secondary endpoints were the consumed doses of postoperative opioids, postoperative NRS pain scores on the first three postoperative days, the proportion of admitted patients with adequate pain control (mean NRS per patient < 4), postoperative complications, parameters on functional recovery, and length of hospital stay. Demographics are shown for all patients. Continuous data are reported as mean with standard deviation (SD) or as median with interquartile range (IQR), depending on the parameter distribution. Categorical data are reported as count with percentage (%).

Since the elderly are most prone to opioid-related side effects and seem to benefit most from opioid reduction, post-hoc analyses were performed to evaluate the outcomes between different age groups. Elderly patients were defined as patients aged ≥75 years, since the prevalence of multimorbidity (≥2 comorbidities) increases with age and exceeds 50% in patients aged 75 years or older.[20] Intergroup comparisons regarding the abovementioned outcomes between age groups (<65 years, 65–74 years and ≥75 years) were analysed using Chi-squared or Fisher's exact tests, when appropriate, for non-continuous data. One-way ANOVA or Kruskal-Wallis tests, when appropriate, were used for normally and not-normally distributed continuous data. A *p*-value of <0.05 was considered statistically significant. All tests were two-sided.

RESULTS

A cohort of 130 consecutive CRC patients was included. The median age at time of surgery was 70.2 (IQR: 59.8–78.3) years. Of the patients included in the study, 48 (36.9%) patients were aged <65 years, 35 (26.9%) were 65–74 years and 47 (36.2%) were ≥75 years. Preoperative opioid consumption was observed in eight (6.2%) patients. The majority of patients underwent a right hemicolectomy, sigmoid resection, or low anterior resection. Surgery was mostly performed laparoscopically or robot-assisted (96.9%). Table 2 presents the patient demographics. The mean duration of surgery was 141.9 (SD: 51.2) min, and 121 patients (93.1%) underwent total intravenous anaesthesia. Table 3 presents details on intraoperative anaesthesia.

Table 2. Demographic, clinical and tumour characteristics of all consecutive colorectal cancer surgery patients treated with CWI (n = 130), stratified by age groups (<65 years, 65–74 years and ≥75 years).

	Age groups				
	Overall	**<65 years**	**65-74 years**	**≥75 years**	***p*-value**
	n = 130	**n = 48**	**n = 35**	**n = 47**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Median age in years at time of surgery (IQR)	70.2 (59.8 – 78.3)	57.0 (52.4–61.1)	70.2 (67.0–73.3)	80.5 (77.7 – 84.1)	<0.001
Male	67 (51.5)	33 (68.8)	20 (57.1)	14 (29.8)	0.001
ASA classification					<0.001
I-II	88 (67.7)	42 (87.5)	29 (82.9)	17 (36.2)	
III	42 (32.3)	6 (12.5)	6 (17.1)	30 (63.8)	
BMI (kg/m^2)					0.45
<18.5	3 (2.3)	1 (2.1)	1 (2.9)	1 (2.1)	
18.5 – 24.9	51 (39.2)	13 (27.1)	17 (48.6)	21 (44.7)	
25.0 – 29.9	53 (40.8)	24 (50.0)	12 (34.3)	17 (36.2)	
≥30	23 (17.7)	10 (20.8)	5 (14.3)	8 (17.0)	
Preoperative use of opioids	8 (6.2)	1 (2.1)	3 (8.6)	4 (8.5)	0.31
Tumour stage (pathological)					0.31
0–II	89 (68.5)	29 (60.4)	25 (71.4)	35 (74.5)	
III–IV	41 (31.5)	19 (39.6)	10 (28.6)	12 (25.5)	
Surgical procedure					0.02
Right hemicolectomy	52 (40.0)	11 (22.9)	16 (45.7)	25 (53.2)	
Left hemicolectomy	9 (6.9)	4 (8.3)	3 (8.6)	2 (4.3)	
(Sub)total colectomy	1 (0.8)	–	–	1 (2.1)	
Sigmoid resection	36 (27.7)	13 (27.1)	10 (28.6)	13 (27.7)	
Low anterior resection	30 (23.1)	19 (39.6)	5 (14.3)	6 (12.8)	
Abdominoperineal resection	2 (1.5)	1 (2.1)	1 (2.9)	–	
Surgical technique					0.04
Open surgery	3 (2.3)	–	2 (5.7)	1 (2.1)	
Robot-assisted surgery	20 (15.4)	12 (25.0)	5 (14.3)	3 (6.4)	
Laparoscopic surgery	107 (82.3)	36 (75.0)	28 (80.0)	43 (91.5)	
Conversion to open surgery	7 (5.4)	3 (6.3)	2 (5.7)	2 (4.3)	>0.99

Table 3. Anaesthesiological characteristics of all consecutive colorectal cancer surgery patients treated with CWI (n = 130), stratified by hospital.

	Hospital A	Hospital B
	n = 78	**n = 52**
	n (%)	**n (%)**
Mean duration of surgery in minutes (±SD)	116.6 (41.3)	179.7 (40.2)
PONV[a] prophylaxis administered	78 (100.0)	50 (96.2)
Intraoperatively used sedatives/analgesics		
Inhalational anaesthetics	9 (11.5)	-
Propofol	69 (88.5)	52 (100.0)
Median induction dose in mg/kg (IQR)	2.3 (1.8–2.7)	1.3 (0.3–2.5)
Median maintenance dose in mg/kg (IQR)[b]	18.3 (12.2–31.7)	N.A.
Median maintenance dose in mcg/mL (IQR)[b]	N.A.	2.0 (2.0–2.0)
Remifentanil	-	51 (98.1)
Median dose micrograms/kg (IQR)	-	0.6 (0.2–1.6)
Sufentanil	77 (98.7)	1 (1.9)
Median dose in milligrams (IQR)	40.0 (30.0–50.0)	25.0 (25.0–25.0)
Morphine	7 (9.0)	40 (76.9)
Median dose milligrams (IQR)	10.0 (5.0–10.0)	10.0 (9.3–14.8)
Esketamine	74 (94.9)	1 (1.9)
Median dose milligrams (IQR)	35.0 (26.2–50.0)	30.4 (30.4–30.4)
Lidocaine	72 (92.3)	35 (67.3)
Median dose milligrams (IQR)	427.9 (277.3–663.8)	40.0 (40.0–40.0)
Bupivacain loading dose	78 (100.0)	–
Levobupivacain loading dose	–	32 (61.5)
Ropivacain loading dose	–	12 (23.1)

Abbreviation: N.A., not applicable

[a]Perioperative nausea and vomiting

[b]Different dosing schemes of propofol maintenance were used between hospitals

Opioid consumption

On the day of surgery, 80 (61.5% [95% CI: 52.6%–69.9%]) patients used opioids postoperatively. The number of patients that used opioids decreased to 28 (21.5% [95% CI: 14.8%–29.6%]) on postoperative day 1, 27 (20.8% [95% CI: 14.2%–28.8%]) on postoperative day 2, and 18 (13.8% [95% CI: 8.4%–21.0%]) on postoperative day 3 (Figure 1). In total, 39 patients (30.0% [95% CI: 22.3%–38.7%]) did not use any postoperative opioids at all. Figure 2 presents the daily opioid consumption (in mg of intravenous morphine equivalents) in patients who used postoperative opioids. The median cumulative opioid consumption in these patients was 10.0 (IQR: 4.0–18.0) mg. Table 4 presents details on postoperative pain management.

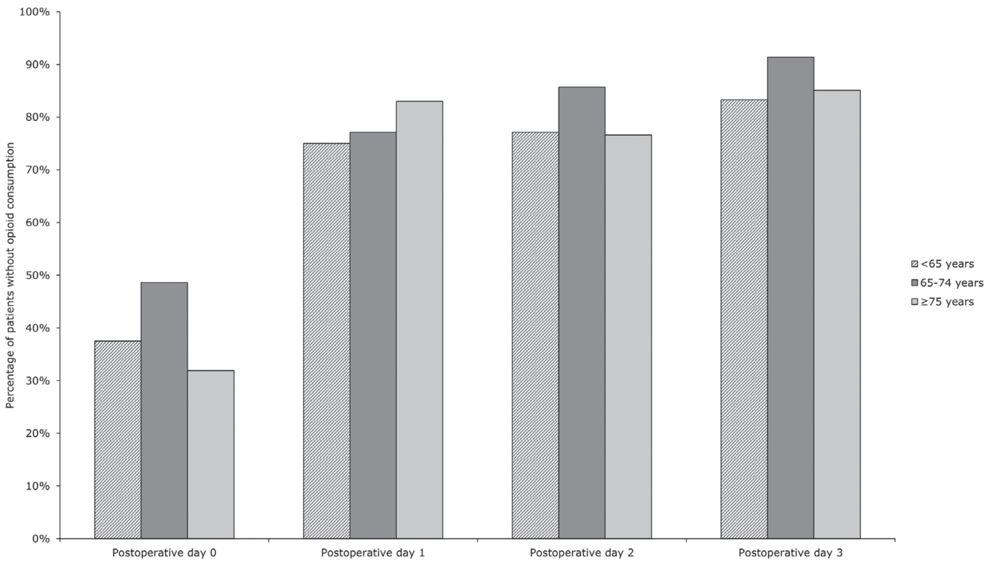

Figure 1. Percentage of colorectal cancer surgery patients treated with CWI without opioid consumption on postoperative day 0 until postoperative day 3, stratified by age groups (<65 years, 65–74 years, ≥75 years). No statistically significant differences were observed between the age groups.

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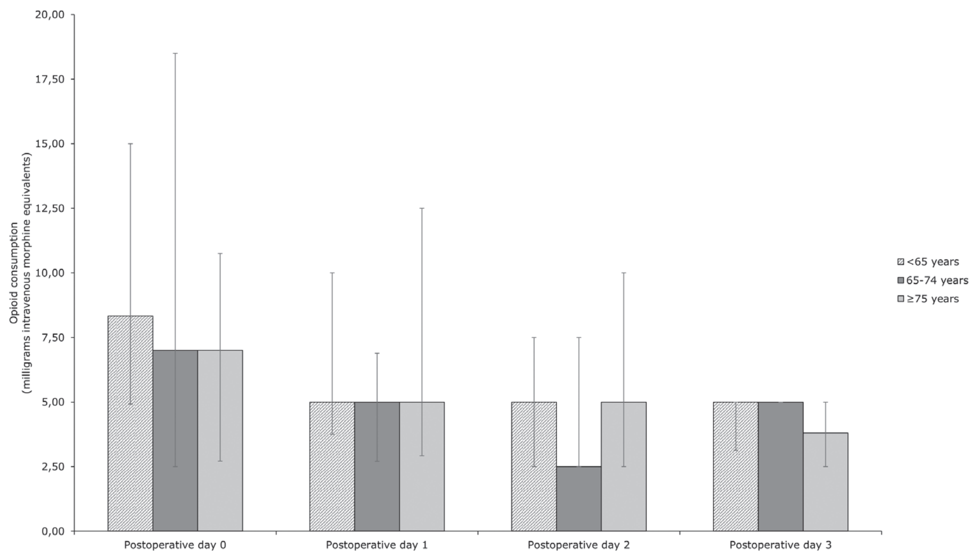

Figure 2. Median opioid consumption in milligrams of intravenous morphine equivalents in colorectal cancer surgery patients treated with CWI who used opioids on postoperative day 0 (n = 80), postoperative day 1 (n = 28), day 2 (n = 27), and day 3 (n = 18), stratified by age groups (<65 years, 65–74 years, ≥75 years). No statistically significant differences were observed between the age groups.

Table 4. Postoperatively used analgesics (other than paracetamol) in all consecutive colorectal cancer surgery patients treated with CWI (n = 130), stratified by age groups (<65 years, 65–74 years and ≥ 75 years).

		Age groups			
	Overall	**<65 years**	**65-74 years**	**≥75 years**	***p*-value**
	n=130	**n = 48**	**n = 35**	**n = 47**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Opioid consumption					
Postoperative day 0	80 (61.5)	30 (62.5)	18 (51.4)	32 (68.1)	0.30
Postoperative day 1	28 (21.5)	12 (25.0)	8 (22.9)	8 (17.0)	0.62
Postoperative day 2	27 (20.8)	11 (22.9)	5 (14.3)	11 (23.4)	0.54
Postoperative day 3	18 (13.8)	8 (16.7)	3 (8.6)	7 (14.9)	0.55
NSAID use (metamizole)					
Postoperative day 0	64 (49.2)	30 (62.5)	16 (45.7)	18 (38.3)	0.055
Postoperative day 1	20 (15.4)	13 (27.1)	3 (8.6)	4 (8.5)	0.02
Postoperative day 2	8 (6.2)	6 (12.5)	1 (2.9)	1 (2.1)	0.11
Postoperative day 3	1 (0.8)	1 (2.1)	-	-	>0.99
Patient-controlled intravenous analgesia					
Postoperative day 0	11 (8.5)	3 (6.3)	4 (11.4)	4 (8.5)	0.62
Postoperative day 1	10 (7.7)	3 (6.3)	3 (8.6)	4 (8.5)	0.85
Postoperative day 2	9 (6.9)	3 (6.3)	2 (5.7)	4 (8.5)	0.92
Postoperative day 3	4 (3.1)	3 (6.3)	-	1 (2.1)	0.45
Epidural analgesia	1 (0.8)	1 (2.1)	-	-	>0.99

Pain scores

The median postoperative pain scores (NRS) were <4 during the day of surgery and the first three postoperative days. Figure 3 presents the postoperative pain scores. Adequate pain control was reported by 99 (76.2%) of the admitted patients on the day of surgery, by 115 (88.5%) patients on postoperative day 1, by 110 (91.7%) on postoperative day 2 and by 75 (94.9%) on postoperative day 3. Tables S1–S3 present the pain scores and opioid consumption between the different wound types that were used as extraction site, the different surgical procedures, and the different surgical techniques.

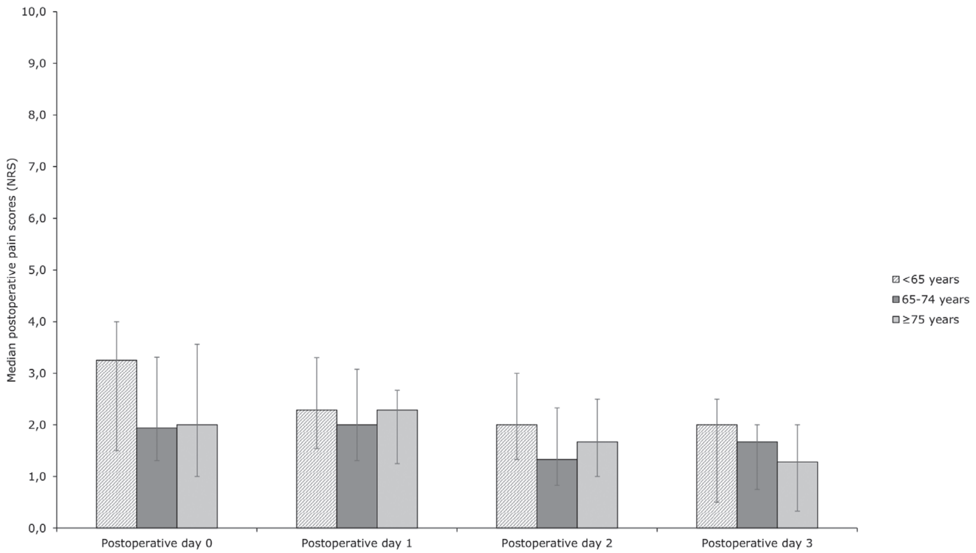

Figure 3. Median postoperative pain scores on the first three postoperative days in all consecutive colorectal cancer surgery patients treated with CWI (n = 130), stratified by age groups (<65 years, 65–74 years, ≥75 years). No statistically significant differences were observed between the age groups.

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Functional recovery

On the day of surgery, 78 (60.0%) patients could be mobilised successfully. The median time until first passage of stool was 1.0 (IQR: 1.0–2.0) day. During the time of hospital admission, nausea (requiring treatment) was observed in 34 (26.2%) patients and vomiting in 20 (15.4%) patients.

Postoperative outcomes and complications

The median length of hospital stay was 3.0 days (IQR: 2.0–5.0). No or minor (grade I–II) complications were observed in 119 (91.5%) patients. Two patients died in the postoperative period, one as a result of myocardial infarction and one as a result of anastomotic leakage. Paralytic ileus was observed in 11 (8.5%) patients. Postoperative delirium was observed in one (0.8%) patient. Table 5 presents the outcomes on functional recovery and postoperative complications.

Table 5. Outcomes on functional recovery and postoperative complications of all consecutive colorectal cancer surgery patients treated with CWI (n = 130), stratified by age groups (<65 years, 65–74 years and ≥75 years).

	Age group				p-value
	Overall	**<65 years**	**65-74 years**	**≥75 years**	
	n=130	**n = 48**	**n = 35**	**n = 47**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Median hospital admission in days (IQR)	3.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	4.0 (3.0–6.0)	0.01
Median time until mobilisation in days (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.45
Patients mobilizing on postoperative day 0	78 (60.0)	32 (66.7)	20 (57.1)	26 (55.3)	0.49
Median time until first stool in days (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.08
Nausea (requiring treatment)	34 (26.2)	9 (18.8)	11 (31.4)	14 (29.8)	0.34
Vomiting	20 (15.4)	10 (20.8)	3 (8.6)	7 (14.9)	0.31
Reinsertion of nasogastric tube	16 (12.3)	5 (10.4)	4 (11.4)	7 (14.9)	0.79
Complication grade according to Clavien-Dindo					0.45
No complications	88 (67.7)	34 (70.8)	25 (71.4)	29 (61.7)	
Grade I-II	31 (23.8)	8 (16.7)	7 (20.0)	16 (34.0)	
Grade IIIa + IIIb	8 (6.2)	4 (8.3)	2 (5.7)	2 (4.3)	
Grade IV	1 (0.8)	1 (2.1)	–	–	
Grade V	2 (1.5)	1 (2.1)	1 (2.9)	–	
Complications					
Cardiac complications	7 (5.4)	1 (2.1)	2 (5.7)	4 (8.5)	0.39
Pneumonia	1 (0.8)	–	–	1 (2.1)	0.63
Urinary retention	9 (6.9)	5 (10.4)	3 (8.6)	1 (2.1)	0.30
Surgical wound infection	12 (9.2)	4 (8.3)	3 (8.6)	5 (10.6)	0.93
Intra-abdominal/presacral abscess	5 (3.8)	2 (4.2)	1 (2.9)	2 (4.3)	>0.99
Anastomotic leakage	5 (3.8)	3 (6.3)	1 (2.9)	1 (2.1)	0.63
Paralytic ileus	11 (8.5)	2 (4.2)	2 (5.7)	7 (14.9)	0.19
Delirium	1 (0.8)	–	–	1 (2.1)	0.63
Thromboembolic complications	–	–	–	–	
Readmissions	8 (6.2)	5 (10.4)	2 (5.7)	1 (2.1)	0.28

Outcomes among different age groups

The median age of patients aged <65 years, 65–74 years, and ≥75 years was 57.0 (IQR: 52.4–61.1) years, 70.2 (IQR: 67.0–73.3) years, and 80.5 (IQR: 77.7–84.1) years, respectively (Table 2). Post-hoc analyses between age groups showed comparable outcomes regarding postoperative opioid consumption, pain control, functional recovery, and postoperative outcomes (Tables 4 and 5; Figures 1-3).

Continuous wound infusion catheter-related outcomes

The wound catheter was removed after a median time of 2.0 days (IQR: 2.0–3.0). CWI catheter-related complications occurred in eight patients (6.2%) and included dislocation (n = 4), leakage (n = 2), and catheter obstruction (n = 2).

DISCUSSION

This prospective observational cohort study evaluated the outcomes of patients treated with CWI as part of multimodal pain management within an enhanced recovery protocol. The present prospective cohort study included 130 consecutive patients. In the present cohort, low postoperative opioid consumption, adequate pain control and enhanced recovery were observed in all age groups. This suggests that CWI is a beneficial opioid-sparing alternative as an adjunct to multimodal pain management. The results also suggest a favourable contribution of CWI to the functional recovery of patients when used within an enhanced recovery protocol.

Continuous wound infusion as an adjunct to multimodal pain management seems beneficial in minimising the postoperative opioid consumption, which is strongly associated with enhanced recovery.[1,21] In the present study, patients treated with CWI as part of multimodal pain management consumed low amounts of postoperative opioids. Almost 80% of patients did not use any opioids after the day of surgery and 30% of patients did not use any postoperative opioids at all. Moreover, the opioid consumption in patients that did use opioids was relatively low, with a converted cumulative dose of 10 mg of intravenous morphine. In comparison, other cohorts that incorporated ERAS, but did not use CWI, reported postoperative opioid consumptions of approximately 15–35 mg of intravenous morphine.[22–24] The low opioid consumption observed in this study further confirms the opioid-sparing effect of CWI that has been described in several earlier studies among patients after different types of abdominal surgery, including colorectal surgery.[9–11,25,26] In these studies, the postoperative opioid consumption in patients treated with CWI was significantly lower than those of patients treated with patient-controlled analgesia or placebo, while it was comparable to those treated with epidural analgesia.[11,25–27] The promising outcomes of CWI that have been described in multiple cohorts after abdominal surgery may support the transition of CWI to standard of care.

Despite the low postoperative opioid consumption in the present cohort, adequate pain control was maintained. The median pain scores were below 4 on all postoperative days. Adequate pain control was obtained in over 75% of patients on the day of surgery, which even improved to 95% on the third postoperative day. The observed adequacy of CWI in achieving postoperative pain control is supported by earlier studies in patients after abdominal surgery.[9,10] Although epidural analgesia is often considered as the most effective modality to reduce postoperative pain, earlier studies showed comparable pain scores between patients treated with CWI and patients treated with epidural or patient-controlled analgesia.[9,10]

As a non-opioid based analgesic, CWI fits in the multimodal pain management as recommended by the ERAS guidelines.[2] The concept of multimodal pain management is based on treating pain through multiple non-opioid analgesics to reduce opioid consumption.[28] As a result, multimodal pain management is correlated with enhanced recovery.[1] In the enhanced recovery protocol that was followed in this study, non-opioid based multimodal pain management was pursued. Patients were standardly treated with paracetamol and CWI. In one of the participating centres, metamizole, an NSAID, was also administered. While NSAIDs are proven to be opioid-sparing, some studies suggest an increased risk for anastomotic leakage after CRC surgery, whereas other studies are inconclusive.[2,29–31] Although clear evidence is lacking, metamizole seems more safe than other NSAIDs with regard to anastomotic healing and gastrointestinal side effects.[32,33] To diminish opioid-related side effects and its influence on postoperative recovery, short-acting opioids were only prescribed if non-opioid based pain management was insufficient, while long-acting opioids were avoided as much as possible.

Another beneficial effect that supports the use of CWI is that it seems to contribute to enhanced recovery.[9,10] A recent meta-analysis in patients after different types of abdominal surgery showed that CWI was associated with lower rates of postoperative hypotension, nausea, vomiting and urinary retention when compared with epidural or patient-controlled analgesia.[9,10,13] Unfortunately, most of the earlier performed studies regarding CWI in CRC surgery were not conducted within a strictly adhered to multidisciplinary enhanced recovery protocol and data regarding functional recovery in these patients is therefore scarce.[10] In the present study, patients were treated with CWI within an enhanced recovery protocol, and high rates of early mobilisation, fast recovery of bowel function, and low rates of nausea and vomiting were observed. Whereas other studies in CRC patients report the first passage of stool after 3–5 days, the median time until the first passage of stool in this cohort was only one day.[9,25,34,35] While a paralytic ileus is commonly described in 12%–17% of patients after CRC surgery, only 8.5% of patients suffered from a paralytic ileus in this study.[36,37]

Apart from multimodal pain management and other elements of the enhanced recovery protocol, the intraoperative anaesthesia protocol might also influence postoperative recovery. Total intravenous anaesthesia, which was used in both hospitals, is associated with less nausea and vomiting and reduced length of hospital stay when compared to inhalational anaesthesia.[38,39] Moreover, particularly in older patients, the intraoperative use of short-acting instead of long-acting opioids and cerebral monitoring during anaesthesia seems to be associated with a reduced postoperative sedative effect and delirium, which might benefit recovery.[2]

As mentioned earlier, older patients are most prone to opioid-related side effects.[4,5] In the present study, low amounts of opioid consumption and adequate postoperative pain control were observed among all age groups. When specifically evaluating the postoperative outcomes in the elderly (≥75 years), the morbidity in the present study was relatively low in comparison to earlier cohorts.[40–42] Despite almost 40% of patients being 75 years or older, postoperative delirium was observed in 0.8% of patients, which is considerably lower than the 10%–14% risk that is reported in similarly aged CRC populations.[43–45] Moreover, Clavien-Dindo III complications only occurred in 4.3% of elderly patients, and no Clavien-Dindo IV complications or postoperative mortality were observed in the elderly population. The median time until the first passage of stool in patients aged 65–74 years and ≥75 years was 2 days and might also suggest a beneficial effect of opioid reduction and enhanced recovery on the return of bowel function in relatively older patients.[1,25] Moreover, the median length of hospital stay in the elderly was 4 days, with a readmission rate of only 2.1%. In comparison, other studies among elderly, laparoscopically-treated CRC patients mostly report a length of stay of at least 5–9 days, and readmission rates of 4%–7%.[40,46–48]

While concerns may exist regarding CWI catheter-related complications, these were scarcely observed.[10,25] In the present study as well as in the literature, catheter-related complications were uncommon and the risk of wound infection was comparable between patients treated with CWI and those without.[10,25] In accordance to earlier studies, none of our patients developed toxic side effects of the local analgesics.[49]

Our study had some limitations. Since we performed a prospective observational cohort study regarding the recently implemented standard of care, we did not include a control arm to compare our results. Another limitation may be the multicentre setting of the study, which could have resulted in heterogeneity in perioperative treatment between hospitals. Although small differences were observed in the rate of early mobilisation and the anaesthesia protocol, further analyses regarding the differences in treatment and outcomes between hospitals was limited by small subgroups. Earlier studies have reported that compliance to the enhanced recovery protocol is necessary to improve outcomes.[14] Although both hospitals had a dedicated multidisciplinary and frequently audited enhanced recovery protocol, clear data on compliance rates were only available in one of the participating hospitals. The overall ERAS compliance rate in this hospital was 78.1%, whereas the compliance to certain elements (i.e., intraoperative protocol) exceeded 90%. The relatively high compliance to the ERAS guidelines could have positively influenced the outcomes. Nevertheless, by including consecutive patients and performing a multicentre study, we aimed to improve the generalisability of our data. Lastly, an underestimation of the parameters of postoperative recovery could have occurred, but this was kept to a minimum by informing physicians and nurses to routinely document these outcomes in the medical records and the prospectively collected database.

While CWI has been investigated earlier, the novel aspect of this study is that we have investigated the addition of CWI as an adjunct to multimodal pain management within a strictly adhered to and audited multidisciplinary enhanced recovery protocol. The presented outcomes regarding the opioid consumption and enhanced recovery have not been described before and suggest a beneficial contribution of CWI on the postoperative recovery when used within an enhanced recovery protocol. Since this study investigated the current clinical patient care, it reflects the actual heterogeneous CRC population with almost 40% of patients aged ≥75 years.[6] Moreover, we were able to include a relatively large patient population in two hospitals.

Due to the promising outcomes presented in this study, continuous wound infusion is still standard of care in our centres. Moreover, the presented outcomes increase the need for future studies in larger populations regarding the implementation and outcomes of patients treated with CWI in a more intensified opioid-sparing enhanced recovery protocol. Although CWI seems cost-effective according to an earlier study, further research is warranted.[50]

In conclusion, low amounts of postoperative opioid consumption and enhanced recovery were observed in patients treated with CWI, while adequate postoperative pain control was maintained. CWI seems a beneficial opioid-sparing alternative and may therefore contribute to a further improvement of the outcomes of patients treated within an enhanced recovery protocol after CRC surgery, which seems especially valuable in older patients.

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SUPPLEMENTARY DATA CHAPTER 8

Supplementary Table 8.1. Postoperative pain scores and opioid consumption in all consecutive colorectal cancer surgery patients treated with CWI (n = 130), stratified for the wound types used as extraction site.

	Pfannenstiel/ Transverse incision	**Midline laparotomy**	**Infraumbilical midline laparotomy**	**Other (e.g. perineal only, incision in previous scar)**	***p*-value**
	n=117	**n = 6**	**n = 4**	**n = 3**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Postoperative opioid consumption (Yes)					
Postoperative day 0	70 (59.8)	4 (66.7)	4 (100.0)	2 (66.7)	0.46
Postoperative day 1	26 (22.2)	-	1 (25.0)	1 (33.3)	0.49
Postoperative day 2	24 (20.5)	2 (33.3)	-	1 (33.3)	0.52
Postoperative day 3	15 (12.8)	1 (16.7)	1 (25.0)	1 (33.3)	0.30
Median opioid consumption (opioid consumers) in mg of intravenous morphine equivalents (IQR)					
Postoperative day 0	7.0 (3.1–15.0)	16.5 (11.3–20.1)	7.3 (5.4–10.8)	8.8 (2.5–8.8)	0.21
Postoperative day 1	5.0 (3.1–8.1)	-	5.0 (5.0–5.0)	3.3 (3.3–3.3)	0.67
Postoperative day 2	5.0 (2.5–7.5)	2.5 (2.5–2.5)	-	7.5 (7.5–7.5)	0.19
Postoperative day 3	5.0 (2.5–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	0.89
Median postoperative pain scores (IQR)					
Postoperative day 0	2.00 (1.25–3.67)	3.75 (0.80–6.17)	3.32 (2.43–4.29)	2.33 (1.00–2.33)	0.44
Postoperative day 1	2.25 (1.33–3.00)	1.75 (0.38–3.25)	2.33 (1.75–2.67)	3.50 (3.00–3.50)	0.10
Postoperative day 2	1.67 (1.00–2.50)	1.38 (0.00–2.33)	2.00 (2.00–2.00)	2.67 (1.33–2.67)	0.35
Postoperative day 3	1.33 (0.33–2.00)	1.88 (0.81–2.00)	2.00 (1.67–2.00)	2.00 (1.50–2.00)	0.28

Supplementary Table 8.2. Postoperative pain scores and opioid consumption in all consecutive colorectal cancer surgery patients treated with CWI (n = 130), stratified for surgical procedure.

	Right hemicolectomy	Left hemicolectomy	(Sub)total colectomy	Sigmoid resection	Low anterior resection	Abdominoperineal resection	*p*-value
	n=52	n = 9	n = 1	n = 36	n = 30	n = 2	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Postoperative opioid consumption (Yes)							
Postoperative day 0	27 (51.9)	5 (55.6)	1 (100.0)	23 (63.9)	22 (73.3)	2 (100.0)	0.33
Postoperative day 1	10 (19.2)	4 (44.4)	-	4 (11.1)	9 (30.0)	1 (50.0)	0.11
Postoperative day 2	9 (17.3)	1 (11.1)	-	6 (16.7)	10 (33.3)	1 (50.0)	0.32
Postoperative day 3	5 (9.6)	3 (33.3)	-	3 (8.3)	6 (20.0)	1 (50.0)	0.12
Median opioid consumption (opioid consumers) in mg of intravenous morphine equivalents (IQR)							
Postoperative day 0	6.0 (2.5–12.0)	4.2 (2.9–8.3)	4.0 (4.0–4.0)	7.5 (5.0–15.0)	10.0 (6.9–16.5)	8.8 (2.5–8.8)	0.27
Postoperative day 1	5.0 (3.8–8.5)	4.2 (2.7–5.0)	-	6.3 (3.1–7.5)	5.0 (3.8–12.5)	3.3 (3.3–3.3)	0.63
Postoperative day 2	5.0 (2.5–10.0)	5.0 (5.0–5.0)	-	5.0 (2.5–5.6)	5.0 (2.5–8.5)	7.5 (7.5–7.5)	0.89
Postoperative day 3	5.0 (3.8–7.1)	2.5 (1.7–2.5)	-	5.0 (2.5–5.0)	5.0 (3.5–5.0)	5.0 (5.0–5.0)	0.39
Median postoperative pain scores (IQR)							
Postoperative day 0	2.0 (1.3–3.6)	2.8 (1.6–4.1)	3.5 (3.5–3.5)	2.6 (1.4–4.2)	2.4 (1.3–3.8)	2.5 (1.0–2.5)	0.75
Postoperative day 1	2.3 (1.3–3.0)	2.3 (1.5–3.3)	2.0 (2.0–2.0)	2.0 (1.3–2.9)	2.3 (1.5–3.4)	4.5 (3.0–4.5)	0.48
Postoperative day 2	1.3 (1.0–2.0)	2.5 (2.0–3.5)	-	1.6 (1.0–2.3)	1.8 (1.2–3.0)	3.3 (2.7–3.3)	0.02
Postoperative day 3	1.1 (0.0–2.0)	2.0 (2.0–3.1)	1.0 (1.0–1.0)	1.3 (0.6–2.0)	1.8 (0.5–2.0)	1.5 (0.4–1.8)	0.14

Supplementary Table 8.3. Postoperative pain scores and opioid consumption in all consecutive colorectal cancer surgery patients treated with CWI (n = 130), stratified for surgical technique.

	Open surgery	**Robot-assisted surgery**	**Laparoscopic surgery**	***p*-value**
	n = 3	**n = 20**	**n = 107**	
	n (%)	**n (%)**	**n (%)**	
Postoperative opioid consumption				
Postoperative day 0	2 (66.7)	16 (80.0)	62 (57.9)	0.16
Postoperative day 1	-	6 (30.0)	22 (20.6)	0.45
Postoperative day 2	1 (33.3)	7 (35.0)	19 (17.8)	0.15
Postoperative day 3	-	5 (25.0)	13 (12.1)	0.30
Median opioid consumption (opioid consumers) in mg of intravenous morphine equivalents (IQR)				
Postoperative day 0	15.4 (10.0–15.4)	7.9 (2.5–14.5)	7.0 (3.8–15.0)	0.36
Postoperative day 1	-	2.9 (2.3–5.0)	5.0 (4.8–10.0)	0.02
Postoperative day 2	2.5 (2.5–2.5)	2.5 (2.5–7.5)	5.0 (2.5–7.5)	0.42
Postoperative day 3	-	5.0 (2.5–5.0)	5.0 (3.2–5.0)	0.51
Median postoperative pain scores (IQR)				
Postoperative day 0	3.8 (1.6–3.8)	3.0 (1.4–4.0)	2.0 (1.3–3.7)	0.37
Postoperative day 1	2.0 (0.0–2.0)	3.2 (2.5–5.0)	2.0 (1.3–2.9)	<0.001
Postoperative day 2	0.0 (0.0–0.0)	3.0 (2.0–4.0)	1.7 (1.0–2.3)	<0.001
Postoperative day 3	0.5 (0.5–0.5)	2.0 (2.0–2.5)	1.1 (0.3–2.0)	<0.001

CHAPTER 9

Enhanced Recovery After Surgery protocols in rectal cancer patients who undergo beyond TME and TME surgery: a comparison of outcomes and compliance

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Submitted to Colorectal Disease

ABSTRACT

Background

Patients requiring a beyond total mesorectal excision (bTME) for locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) will probably benefit from ERAS protocols. However, the implementation is considered challenging. The aim of this study was to evaluate the colorectal ERAS protocol in rectal cancer patients who underwent TME, and explore differences in ERAS-related outcomes between TME and bTME patients.

Methods

Rectal cancer patients who underwent curative surgery between 2019–2021 in the Catharina Hospital were included. Patients were divided in three groups: rectal cancer patients who underwent TME before (TME pre-ERAS) and after ERAS implementation (TME post-ERAS), and LARC and LRRC patients who underwent bTME.

Results

In total, 156 TME and 75 bTME patients were included. After ERAS implementation, the overall compliance in TME patients improved from 54.7% to 85.6%. Shortened lengths of stay (4.0 vs. 3.0 days, $p < 0.001$) were observed in TME patients after ERAS implementation, without compromising post-operative complications (52.1% vs. 37.3%, $p = 0.077$). In bTME patients, the overall ERAS compliance was significantly less in comparison to TME pre-ERAS and post-ERAS patients (44.4% vs. 54.7% vs. 85.6%, $p < 0.001$), whereas length of stay was longer (9.0 days, $p < 0.001$) and major post-operative complications were higher (21.9% vs. 12.2% vs. 40.0%, $p < 0.001$).

Conclusion

The implementation of a strict ERAS protocol in TME patients has resulted in improved compliance and enhanced recovery. A tailored, multimodal ERAS protocol with specific modifications is warranted to suit the complexity of the treatment of LARC and LRRC patients who undergo bTME surgery.

INTRODUCTION

In colorectal surgery, Enhanced Recovery After Surgery (ERAS) protocols are well established.[1–6] Given the beneficial outcomes, patients who undergo extended rectal cancer surgery for locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) will probably benefit from ERAS as well. However, the implementation of, and the compliance to ERAS protocols in LARC and LRRC is considered challenging.[1,2,7–9]

In LARC and LRRC, the tumour commonly invades pelvic organs and tissues, requiring neoadjuvant therapy, followed by extensive rectal cancer surgery. Beyond total mesorectal excisions (bTME) are frequently deemed necessary, consisting of multivisceral resections that often involve sacral and pelvic sidewall excisions.[10,11] The treatment of LARC and LRRC is associated with prolonged lengths of hospital stay, and high rates of morbidity and mortality, especially in the elderly. Previous studies reported lengths of hospital stay of 9–14 days and major complication (Clavien-Dindo ≥III) rates of 20–40% after LARC and LRRC surgery.[12–15]

Specific modifications to the ERAS protocol seem warranted to suit the complexity of bTME surgery.[13,16–18] Since ERAS-related outcomes of LARC and LRRC patients have not yet been studied nor compared with those of rectal cancer patients who undergo TME surgery, the outlines of these modifications are still unclear.

The aim of this study was to evaluate the implementation of the colorectal ERAS protocol in rectal cancer patients who underwent TME surgery, and to explore the differences in ERAS-related outcomes and compliance between these patients and patients who underwent bTME surgery for LARC and LRRC. Care elements that warranted specific modifications to fulfil the needs of LARC and LRRC patients were identified.

METHODS

Patients and treatment

Patients who underwent rectal cancer surgery with curative intent in the Catharina Hospital Eindhoven between 2019 and 2021 were included. Patients were treated according to the Dutch National Guidelines for colorectal cancer.[19] TME patients were defined as patients with primary rectal cancer who were suitable for a partial or total mesorectal excision (PME or TME) without additional resections (without or after neoadjuvant therapy). Patients who underwent bTME surgery for LARC were standardly treated with neoadjuvant (chemo)radiotherapy, whereas LRRC patients underwent neoadjuvant chemoradiotherapy or chemo re-irradiation (in case of previous pelvic irradiation). Some patients with highly extensive disease received induction chemotherapy before chemoradiotherapy.[20,21] bTME surgery was defined as a multivisceral TME, with at least the resection of the pelvic sidewall and/or adjacent organs, including partial or total pelvic exenterations. Surgery was often combined with intra-operative radiotherapy (10–12.5 Gy) at the margins considered at risk. Other surgical specialists were consulted if urological, plastic, or vascular reconstructions were required. Since the Catharina Hospital Eindhoven is a tertiary referral hospital for LARC and LRRC in the Netherlands, most patients who underwent bTME surgery were referred from other centres due to the extent of disease.

From January 2019 until December 2019, TME patients (TME pre-ERAS group) and bTME patients (bTME group) were treated according to the traditional perioperative management. From March 2020 onwards, TME patients were treated in accordance to a strictly adhered to ERAS protocol (TME post-ERAS group).[1]

This study was reviewed and approved not to be subject to the Medical Research Involving Human Subjects Act (Medical Research Ethics Committees United – Nieuwegein, registration number W22.021).

Data collection and follow-up

Patient and tumour characteristics, data on ERAS elements, complications, and functional recovery (e.g., time until first passage of stool, mobilisation, length of hospital stay) were retrospectively extracted from the medical records and from the prospectively maintained ERAS Interactive Audit System (EIAS®). Pre-admission (e.g. patient education, optimisation of patient's health status), pre-operative (e.g. antibiotic and perioperative nausea and vomiting prophylaxis), intra-operative (e.g. surgical approach, blood loss, fluid management), and post-operative (e.g. nasogastric tube management, pain management, oral intake) ERAS-related outcomes were collected. Complications occurring the first 30 post-operative days were scored using the Clavien-Dindo classification.[22] All patients had at least a follow-up of 30 days after surgery.

Statistical analyses

Statistical analyses were performed using SPSS Statistics 25.0 software (IBM, Endicott, NY, USA). The primary endpoints were the ERAS compliance and ERAS-related outcomes. Secondary endpoints were related to functional recovery and post-operative complications.

Demographics were presented for all patients. Continuous data were reported as mean with standard deviation or as median with range, depending on parameter distribution. Categorical data were reported as count with percentage. Intergroup comparisons between patient groups (i.e. TME pre-ERAS, TME post-ERAS, bTME) were analysed using Chi-squared or Fisher's exact tests, when appropriate, for non-continuous data. One-way ANOVA or *t*-test, and Kruskal-Wallis or Mann-Whitney *U* test were used for normally and not-normally distributed continuous data, when appropriate. A p-value of < 0.05 was considered statistically significant. All tests were two-sided.

RESULTS

A total of 231 rectal cancer patients underwent surgery between 2019 and 2021, of whom 156 patients underwent TME, and 75 patients underwent bTME for LARC (n=43) or LRRC (n=32). Among TME patients, 73 patients were included before and 83 patients after ERAS implementation. (Figure 1). Patient and treatment characteristics are shown in Table 1. No differences were observed regarding age, gender, ASA, and comorbidities. bTME patients more often underwent induction chemotherapy (60.0% vs. 27.4% vs. 15.7%, $p < 0.001$) and neoadjuvant radiotherapy (100% vs. 53.4% vs. 31.3%, $p < 0.001$) when compared to TME pre-ERAS and post-ERAS patients.

Table 2 presents the surgical details of bTME patients. Intra-operative radiotherapy was performed in 74.7% of bTME patients. The median duration of bTME surgery was 250.0 minutes, which was significantly longer than in TME surgery (120.0 minutes pre-ERAS and 133.0 minutes post-ERAS). Significantly more blood loss was observed in bTME patients when compared to TME pre-ERAS and post-ERAS patients ($p < 0.001$).

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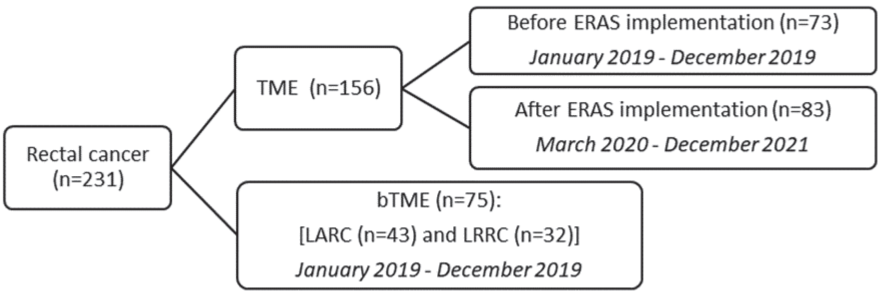

Figure 1. Flowchart of inclusion

Table 1. Patient and treatment characteristics, stratified by patient group.

	TME pre-ERAS n = 73 n (%)	TME post-ERAS n = 83 n (%)	bTME n = 75 n (%)	*p*-value
Mean age in years at time of surgery (SD)	66.8 (9.7)	65.8 (12.2)	64.7 (10.7)	0.513
Sex				0.836
Male	45 (61.6)	48 (57.8)	47 (62.7)	
Female	28 (38.4)	35 (42.2)	28 (37.3)	
ASA classification				0.067
I	2 (2.7)	7 (8.4)	–	
II	52 (71.2)	58 (69.9)	56 (74.7)	
III	19 (26.0)	18 (21.7)	17 (22.7)	
IV	–	–	2 (2.7)	
Diabetes mellitus	5 (6.8)	7 (8.4)	9 (12.0)	0.575
Severe heart disease	2 (2.7)	12 (14.3)	2 (2.7)	0.012
Severe pulmonary disease	–	2 (2.4)	3 (4.0)	0.283
WHO score				<0.001
0	52 (71.2)	53 (63.9)	46 (61.3)	
1	11 (15.1)	30 (36.1)	27 (36.0)	
2	1 (1.4)	–	2 (2.7)	
Missing	9 (12.3)	–	–	
Alcohol				<0.001
Yes	23 (31.5)	15 (18.1)	22 (29.3)	
Stopped*	–	15 (18.1)	1 (1.3)	
Smoker				
Yes	5 (6.9)	3 (3.6)	7 (9.3)	0.642
Stopped*	2 (2.8)	4 (4.8)	3 (4.0)	
Neoadjuvant (chemo)radiotherapy	39 (53.4)	26 (31.3)	75 (100)	<0.001
Induction chemotherapy	20 (27.4)	13 (15.7)	45 (60.0)	<0.001
Primary diagnosis				<0.001
Primary tumour	73 (100)	83 (100)	43 (57.3)	
Recurrence	–	–	32 (42.7)	
Pathological Tumour stage**				<0.001
T0-T2	42 (57.5)	37 (45.1)	13 (30.2)	
T3-T4	31 (42.5)	44 (54.9)	30 (69.8)	
Missing	–	1	–	
Pathological Nodal stage**				<0.001
N0	54 (74.0)	50 (61.0)	25 (58.1)	
N+	19 (26.0)	32 (39.0)	18 (41.9)	
Missing	–	1	–	

* Because of surgery

** Only for primary tumours

Table 2. Surgical details of advanced rectal cancer patients who underwent bTME.

	n = 75
	n (%)
Main procedure	
APR	37 (49.3)
LAR or re-resection with anastomosis	19 (25.3)
Posterior exenteration	4 (5.3)
Total exenteration	7 (9.3)
Tumour resection n.o.s.*	8 (10.7)
Bladder resection	
Partial	2 (2.7)
Complete	7 (9.3)
Urologic reconstruction	
Psoas hitch	5 (6.7)
Bricker reconstruction	7 (9.3)
Sacral resection	
> S2	1 (1.3)
> S3	3 (4.0)
> S4	1 (1.3)
> S5	2 (2.7)
Coccyx	9 (12.0)
Prostate resection (male only)	
Partial	8 (17.0)
Complete	8 (17.0)
Seminal vesicles resection (male only)	
Unilateral	9 (19.1)
Both sides	10 (21.3)
Uterus resection (female only)	9 (33.3)
Ovarian resection (female only)	
Unilateral	1 (3.7)
Both sides	7 (25.9)
Vaginal resection (female only)	
Posterior wall	19 (67.9)
Total	2 (7.1)
Lateral lymph node resection	
Lymph node dissection	10 (13.3)
Lymph node picking	6 (8.0)
Vascular resection	
Partial	15 (20.0)
With reconstruction	1 (1.3)
Small bowel resection	6 (8.0)
Omentoplasty	48 (64.0)
Plastic reconstruction	
VRAM without skin	1 (1.3)
Gluteus flap	1 (1.3)

* Tumour resection n.o.s. = resection not otherwise specified

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Comparison of ERAS-related outcomes: pre-admission and pre-operative elements

In TME patients, all pre-admission and pre-operative elements improved significantly after ERAS implementation (Table 3a and Figure 2).

Among bTME patients, 25.3% received pre-admission education about the planned hospitalisation and surgery, and 64.0% received stoma counselling. Screening for anaemia and malnutrition was assessed in 70.7% and 74.6%, respectively.

Table 3a. Pre-admission and pre-operative elements relevant in ERAS compliance.

	TME pre-ERAS	**TME post-ERAS**	**bTME**
	n = 73	**n = 83**	**n = 75**
	n (%)	**n (%)**	**n (%)**
Anaemia			
Yes	4 (5.5)	13 (15.7)	15 (20.0)
No	47 (64.4)	70 (84.3)	38 (50.7)
Not assessed	22 (30.1)	–	22 (29.3)
Treatment of anaemia[ns2]			
Yes	–	9 (10.8)	4 (5.3)
No	26 (35.6)	4 (4.8)	33 (44.0)
Not applicable	47 (64.4)	70 (84.3)	38 (50.7)
Pre-op oral carbohydrate[ns2]			
Yes	34 (46.6)	81 (97.6)	28 (37.3)
No	4 (5.5)	2 (2.4)	14 (18.7)
Missing/unknown	35 (47.9)	–	33 (44.0)
Antibiotic prophylaxis	66 (90.4)	82 (98.8)	75 (100)
PONV prophylaxis	66 (90.4)	82 (98.8)	67 (89.3)
Pre-admission education	6 (8.2)	83 (100)	19 (25.3)
Stoma counselling			
Yes	61 (83.6)	49 (59.0)	48 (64.0)
Not applicable	1 (1.4)	27 (32.5)	4 (5.3)
Nutritional status[ns2]			
Normal status	23 (31.5)	67 (80.7)	20 (26.7)
Risk of malnutrition	25 (34.2)	7 (8.3)	33 (44.0)
Malnourished	1 (1.4)	1 (1.2)	3 (4.0)
Not assessed	24 (32.9)	8 (9.6)	19 (25.4)

[ns1] = no significant differences between TME pre-ERAS and TME post-ERAS

[ns2] = no significant difference between bTME and TME pre-ERAS

[ns3] = no significant difference between bTME and TME post-ERAS

Comparison of ERAS-related outcomes: intra-operative elements

In TME patients, the use of intra-operative opioids diminished (p < 0.001) after ERAS implementation, while local analgesic modalities were used more frequently instead of epidural analgesia (p < 0.001). Postoperative urinary drainage was performed in 68.5% of

TME pre-ERAS and in 1.2% of TME post-ERAS patients ($p < 0.001$). Resection-site drainage was performed in 30.1% of TME pre-ERAS patients and in 26.5% of TME post-ERAS patients.

In bTME patients, epidural analgesia was used in 97.3%, while 98.7% needed vasoactive medication to prevent hypotension. Postoperative urinary drainage was performed in 96.0% of bTME patients, and resection-site drainage in 76.0%. (Table 3b).

Table 3b. Intra-operative elements relevant in ERAS compliance.

	TME pre-ERAS	**TME post-ERAS**	**bTME**
	n = 73	**n = 83**	**n = 75**
	n (%)	**n (%)**	**n (%)**
Surgical approach			
Open	14 (19.2)	1 (1.2)	75 (100)
Laparoscopy	56 (76.7)	32 (38.2)	–
Robotic	–	50 (60.2)	–
Main procedure			
LAR or re-resection with anastomosis	49 (67.1)	74 (89.2)	19 (25.3)
APR	22 (30.1)	9 (10.8)	37 (49.3)
Posterior exenteration	–	–	4 (5.3)
Total exenteration	–	–	7 (9.3)
Tumour resection n.o.s.*	2 (2.7)	–	8 (10.7)
Additional resections	–	–	57 (76)
IORT	–	–	56 (74.7)
Median length of operation in minutes (range) [ns1]	120 (66-304)	133 (48-267)	250 (90-518)
Median intra-operative blood loss in mL (range) [ns1]	0 (0-850)	50 (50-1500)	1400 (200-10.000)
Urinary drainage			
No drainage	23 (31.5)	82 (98.8)	3 (4.0)
Urethral catheter	48 (65.8)	1 (1.2)	63 (84.0)
Suprapubic catheter	2 (2.7)	–	3 (4.0)
Nephrostomy	–	–	6 (8.0)
Resection-site drainage [ns1]	22 (30.1)	22 (26.5)	57 (76.0)
Systemic opioids during surgery			
Yes, short acting	26 (35.6)	63 (75.9)	70 (93.3)
Yes, long acting	47 (64.4)	20 (24.1)	4 (5.3)
Vasoactive drugs	51 (69.9)	10 (12.0)	74 (98.7)
Epidural	12 (16.1)	–	73 (97.3)
Nerve blocks/local anaesthesia	39 (53.4)	81 (97.6)	4 (5.3)
Median core temperature at end of surgery in °C (range) [ns1,2,3]	36.3 (34.7-38.6)	36.3 (35.2-38.8)	36.4 (34.7-37.8)
Median minimal temperature during surgery in °C (range) [ns1,3]	36 (34.7-36.7)	35.9 (35.9-35.9)	35.6 (34.6-37.7)

[ns1] = no significant differences between TME pre-ERAS and TME post-ERAS

[ns2] = no significant difference between bTME and TME pre-ERAS

[ns3] = no significant difference between bTME and TME post-ERAS

*Tumour resection n.o.s. = resection not otherwise specified

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Comparison of ERAS-related outcomes: post-operative elements

In TME patients, postoperative nasogastric tubes were less often inserted after ERAS implementation (6.8% vs. 0.0%, $p < 0.001$), while reinsertion rates were similar (12.3% vs. 13.0%, $p > 0.999$). Comparable NRS pain scores were observed during the first three post-operative days in TME post-ERAS and TME pre-ERAS patients, while opioid consumption diminished ($p < 0.001$). Time until the first passage of stool (2.0 vs. 1.0 days, $p = 0.044$) and length of stay (4.0 vs. 3.0 days, $p < 0.001$) was significantly reduced in TME post-ERAS patients. Postoperative complications were observed in 52.1% of TME pre-ERAS patients and in 37.2% of TME post-ERAS patients ($p = 0.077$). (Table 3c).

In bTME patients, a postoperative nasogastric tube was inserted in 64%. A median of 5609.0 ml of intravenous fluids were administered on the day of surgery, which was significantly more than in TME pre-ERAS (1642.0 ml) and TME post-ERAS (1682.0 ml) patients (p < 0.001). Time until the first passage of stool (3.0 days, $p < 0.001$) and length of stay (9.0 days, $p < 0.001$) were significantly longer in the bTME group when compared to both TME groups. Major (Clavien-Dindo III-V) complications were observed in 40.0% of bTME patients, while surgical reinterventions were required in 20.0%, and 39.6% were readmitted after discharge. (Table 3c).

Table 3c. Post-operative elements relevant in ERAS compliance.

	TME pre-ERAS	TME post-ERAS	bTME
	n = 73	n = 83	n = 75
	n (%)	n (%)	n (%)
Nasogastric tube placement	5 (6.8)	–	48 (64.0)
Nasogastric tube reinserted[ns1]	9 (12.3)	9 (13.0)	25 (33.3)
Median total IV fluids on day of surgery in mL (range)[ns1]	1642 (0-7110)	1682 (600-5228)	5609 (420-19.540)
Median duration of IV fluids in days (range)	1 (0-24)	1 (0-19)	4 (0-19)
IV fluids restarted during admission[ns1,2]	8 (11.0)	5 (7.2)	15 (20.0)
Opioid use			
Postoperative day 0[ns1,3]	69 (94.5)	58 (84.1)	57 (76.0)
Postoperative day 1	52 (71.2)	15 (21.7)	16 (21.3)
Postoperative day 2	45 (61.6)	12 (17.4)	29 (38.7)
Postoperative day 3	43 (58.9)	7 (10.1)	64 (85.3)
Median time to passage stool in days (range)	2 (0-6)	1 (0-5)	3 (0-9)
Median time to tolerating solid food in days (range)	2 (0-16)	1 (0-24)	5 (1-23)
Median time to recover ADL in days (range)	3 (0-20)	2 (0-26)	6 (2-31)
Median time to terminate epidural in days (range)	2 (1-5)	NA	3 (1-4)
Successful block of epidural[ns2]	10 (76.9)	NA	55 (77.5)
Median time to oral pain control in days (range)[ns1]	1 (0-31)	2 (0-7)	3 (2-23)

	TME pre-ERAS	TME post-ERAS	bTME
	n = 73	n = 83	n = 75
	n (%)	n (%)	n (%)
Mean NRS pain score (SD)			
Postoperative day 0	3.7 (2.6)	4.8 (2.6)	1.4 (2.1)
Postoperative day 1[ns1]	4.3 (2.8)	4 (2.1)	2.7 (2.6)
Postoperative day 2[ns1,2,3]	3.3 (2.1)	2.8 (1.7)	3 (2.6)
Postoperative day 3[ns2]	3.5 (2.1)	2.6 (1.7)	3.6 (2.2)
Median time to termination urinary drainage in days (range)	2 (0-58)	0 (0-0)	5 (1-140)
Median length of post-operative ICU stay in days (range)	NA	NA	1 (0-16)
Median length of primary stay in days (range)	4 (1-27)	3 (1-45)	9 (5-57)
Complications at all[ns1]	38 (52.1)	31 (37.3)	64 (85.3)
Most severe complication (Clavien-Dindo)[ns1]			
0-II	57 (78.1)	72 (87.8)	45 (60.0)
III-V	16 (21.9)	10 (12.2)	30 (40.0)
Reoperations[ns1,2]	13 (17.8)	7 (8.4)	15 (20.0)
Readmissions	14 (22.6)	4 (6.3)	19 (39.6)
Mobilisation at all on day of surgery	37 (50.7)	61 (73.5)	4 (5.3)
Mobilisation at least 1 hour			
Postoperative day 1	10 (13.7)	35 (42.2)	1 (1.3)
Postoperative day 2	3 (4.1)	15 (18.1)	1 (1.3)
Postoperative day 3	3 (4.1)	15 (18.1)	3 (4.0)

[ns1] = no significant differences between TME pre-ERAS and TME post-ERAS

[ns2] = no significant difference between bTME and TME pre-ERAS

[ns3] = no significant difference between bTME and TME post-ERAS

NA = not applicable

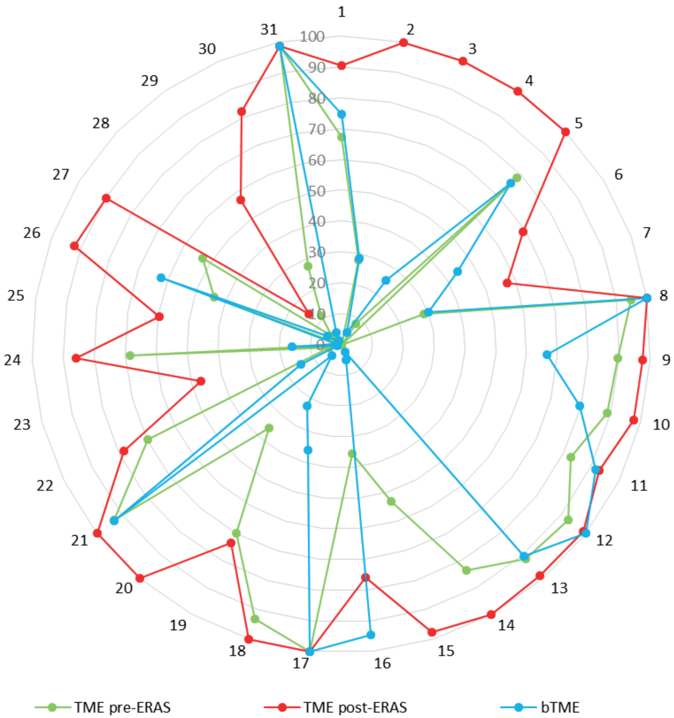
ERAS compliance

The pre-admission, pre-operative, intra-operative, and post-operative ERAS compliance improved significantly in patients who underwent TME after ERAS implementation. The overall compliance after ERAS implementation was 85.6% versus 54.7% before implementation ($p < 0.001$).

In bTME patients, the overall compliance to ERAS was 44.4% ($p < 0.001$). (Table 4). Figure 2 presents the compliance rates of separate ERAS care elements.

Table 4. Mean ERAS compliance of all patient groups

	TME pre-ERAS	TME post-ERAS	bTME	*p*-value
Pre-admission compliance in % (SD)	30.1 (31.6)	88.1 (17.7)	44.1 (26.5)	<0.001
Pre-operative compliance in % (SD)	90.1 (4.2)	97.6 (2.5)	88.1 (12.9)	<0.001
Intra-operative compliance in % (SD)	72.6 (24.6)	91.2 (26.1)	43.6 (43.4)	<0.001
Post-operative compliance in % (SD)	42.5 (34.7)	75.4 (26.1)	25.4 (37.0)	<0.001
Overall compliance in % (SD)	54.7 (35.5)	85.6 (20.5)	44.4 (38.9)	<0.001



		TME pre-ERAS	TME post-ERAS	bTME
	Preadmission compliance care elements	%	%	%
1	Preoperative nutritional status assessed	67,1	90,4	74,6
2	Preoperative nutritional treatment in case of (risk for) malnutrition	28	100	28,57
3	In case of alcohol overconsumption (quitted before surgery)	0	100	4,35
4	Preadmission patient education	8,2	100	25,33
5	Patient screened for anaemia preoperatively	78,46	100	75,71
6	Anaemia treatment given when applicable	0	69,23	44,44
7	Smoker (quitted before surgery)	28,57	57,14	30
	Preoperative compliance care elements	%	%	%
8	No oral bowel preparation used unless patients received a LAR	94,87	100	100
9	Preoperative oral carbohydrate treatment	89,47	97,59	66,67
10	No preoperative sedative medication	88,89	97,59	79,73
11	Thrombosis prophylaxis administered, untill outpatient to 28 days	82,86	92,77	91,78
12	Antibiotic prophylaxis before incision	92,96	98,8	100
13	PONV prophylaxis administered	91,67	98,8	90,54
	Intraoperative compliance care elements	%	%	%
14	No epidural or spinal anaesthesia	83,56	100	2,67
15	Nerve blocks or local anaesthesia	53,42	97,59	5,33
16	No long-acting systemic opioids given	35,62	75,9	94,67
17	Forced-air heating cover used	100	100	100
18	No nasogastric tube at end of operation and standard after	93,15	100	36
19	No resection-site drainage placed	69,86	73,49	22,67
	Postoperative compliance care elements	%	%	%
20	Termination of urinary drainage at end of operation	35,71	100	4,76
21	Stimulation of gut motility	92,86	100	93,15
22	Balanced fluids POD 0 (≤2500 ml)	69,86	78,26	14,67
23	Weighted on POD 0	4,11	46,99	1,33
24	IV fluid infusion till POD 1	68,49	86	16
25	Energy intake on POD 0, postoperatively ≥300kCal (200ml)	0	59,65	1,56
26	Energy intake on POD 1 ≥ 300kCal (200ml)	43,9	92,19	62,16
27	Mobilisation at all on day of surgery	52,86	89,71	5,41
28	Mobilisation on POD1 (≥6 h)	4,1	14,49	1,36
29	Mobilisation on POD2 (≥6 h)	11,36	56,94	1,41
30	Mobilisation on POD3 (≥6 h)	27,66	82,19	4,11
31	Follow up control performed around 30 days postoperatively	98,63	98,7	98,67

**POD = Postoperative day*

Figure 2. ERAS care elements according to compliance rates (%), stratified by patient group

DISCUSSION

This study evaluated the implementation and outcomes of the colorectal ERAS protocol in rectal cancer patients who underwent TME surgery, and explored the differences in ERAS-related outcomes and compliance between TME and bTME patients. In TME patients, the overall compliance improved from 54.7% to 85.6% after ERAS implementation, which resulted in enhanced recovery and improved post-operative outcomes. The current study revealed the significant differences in tumour characteristics, treatment, ERAS compliance, and post-operative outcomes between TME and bTME patients, underlining the extensiveness of bTME surgery, and the complexity of the treatment and perioperative care of LARC and LRRC.

The outcomes of the colorectal ERAS protocol in TME surgery

A significant increase in ERAS compliance was observed after the implementation phase, underlining the feasibility of the current colorectal ERAS protocol in TME surgery. The improvements in post-operative outcomes after implementing a dedicated ERAS protocol in colorectal surgery are supported by earlier literature.[23,24] Similar to our results, previous studies have demonstrated that ERAS protocols are effective in reducing post-operative complications, improving recovery, and shorten lengths of hospital stay.[3,5,18] Most of these studies included a heterogeneous group of colon and rectal cancer patients, while data on the feasibility and effectiveness of ERAS in rectal cancer specifically is more scarce.[15,16] Nevertheless, few earlier studies among rectal cancer patients also reported comparable compliance and improvements in outcomes after ERAS implementation, especially in those undergoing minimal invasive surgery.[5,18,25,26]

Differences in treatment, ERAS compliance, and outcomes between TME and bTME surgery

The complexity of the neoadjuvant, surgical, and perioperative treatment of LARC and LRRC patients is underlined by the differences in treatment characteristics and outcomes between bTME patients and TME patients in our cohort. While only 30–50% of TME patients received neoadjuvant treatment, neoadjuvant (chemo)radiotherapy was performed in all bTME patients. In addition, 75% of bTME patients underwent intra-operative radiotherapy. Extended pelvic organ, vascular, and sacral resections were commonly performed in bTME surgery, with or without reconstructive procedures (e.g. urinary reconstruction). Consequently, the duration of surgery, the amount of blood loss, intravenous fluid administrations, and intra-operative opioid use, and the need for vasoactive medication was significantly increased in bTME patients when compared to TME patients. The intensive neoadjuvant treatment and the extensive surgical treatment seem to hamper postoperative recovery and limit the applicability of the colorectal ERAS protocol in bTME surgery. This was supported by the finding that bTME patients took significantly longer to recover from surgery and were discharged after a median of 9 days, whereas TME patients were discharged after a median of 3 to 4 days. Major post-operative complications were observed in 40% of bTME patients, of whom 20% needed a surgical reintervention. In contrast, 12-22% of TME patients suffered from major post-operative complications.

ERAS in bTME surgery

In accordance to a few earlier studies, the current study showed that compliance to the standard colorectal ERAS protocol in bTME surgery is challenging.[2,17,27] The overall compliance to ERAS in bTME patients was only 44.4%, while compliance in the post-operative period was even less. These findings emphasise the need to optimise the ERAS protocol for patients who undergo bTME surgery. This was also underlined in a recent feasibility study by Harji et al., in which the implementation of an ERAS protocol for patients who underwent pelvic exenteration was investigated.[13] Harji et al. developed a tailored enhanced recovery protocol for pelvic exenterations, and highlighted the need for specific modifications to the currently existing protocols to fulfil the needs and complexity of patients who undergo extensive pelvic surgery. The implementation of a dedicated, tailored ERAS protocol for bTME surgery will probably benefit the postoperative recovery of LARC and LRRC patients. Therefore, multiple meetings were arranged in our centre with the entire treatment team. In collaboration with pelvic surgeons, urologists, plastic surgeons, anaesthesiologists, nurses from the surgical ward, intensive care physicians, dieticians and physiotherapists, a tailored ERAS protocol is currently being developed for LARC and LRRC patients who undergo bTME surgery.

While the entire ERAS protocol should be optimised, the outcomes of this study revealed that certain elements seem to require additional attention in bTME surgery. In bTME patients, the opioid consumption is increased due to longer surgical procedures and increased postoperative pain. A multimodal perioperative analgesia protocol may contribute to reduced opioid consumption. The intra-operative use of ketamine, lidocaine and local wound infiltration seems associated with reduced intra-operative and post-operative opioid consumption.[28–30] Methadone seems a promising alternative for epidural analgesia, and may reduce postoperative hypotension, thereby enhancing early mobilisation.[31] Continuous wound infusion of local analgesics is associated with reduced opioid consumption and enhanced recovery, and could have an important role in multimodal pain management.[32,33] In addition, protocols on the use and removal of resection-site drainage could be standardised to prevent delay of removal and drain-related infections.[34–38] Due to damage of pelvic nerves and/or the resection and reconstruction of urological organs, bTME patients are prone to develop urinary retention. The use of a suprapubic catheter might be beneficial in those at high risk of urinary retention.[39] In our cohort, the majority of bTME patients standardly received a post-operative nasogastric tube. However, a more selective approach, in which a nasogastric tube is not inserted standardly, might be beneficial to stimulate early oral intake. Nevertheless, bTME patients are prone to develop paralytic ileus, and 33.3% of the bTME patients in our cohort needed reinsertion of the nasogastric tube. Close attention for the early detection of paralytic ileus is important, and bTME patients may benefit from starting oral intake gradually rather than having a restriction-free diet. In an effort to stimulate early postoperative mobilisation, standardised mobilisation schedules with the guidance of a physiotherapist should be encouraged from the day of surgery.

Strengths and limitations

The main strength of this study is that we included a relatively large cohort of rectal cancer patients with the availability of many variables that were related to ERAS and post-operative recovery. To our knowledge, this is one of the first studies that investigated outcomes related to ERAS in patients undergoing bTME surgery for LARC and LRRC, in an effort to gain insights into the perioperative treatment of these patients. The retrospective character of this study is one of the main limitations. In addition, since this study involves a single-centre study in a tertiary referral centre for LARC and LRRC, the generalisability of the study may have been limited.

Currently, a tailored ERAS protocol is being developed in our hospital for bTME patients. After developing and implementing the ERAS protocol in bTME patients, a prospective observational cohort study is planned to evaluate the feasibility and outcomes.

CONCLUSION

The implementation of a strict ERAS protocol in rectal cancer patients who underwent TME surgery has resulted in improved overall compliance and enhanced recovery. In patients who underwent bTME surgery for LARC and LRRC, the compliance to ERAS was significantly reduced and post-operative recovery was worse, underlining the complexity of the disease and treatment. In an effort to improve the outcomes of patients who undergo bTME surgery, a tailored, multimodal ERAS protocol with specific modifications is warranted.

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CHAPTER 10

Organ preservation in rectal cancer: an overview of the Dutch perspective and recent developments

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Clin Oncol (R Coll Radiol). 2022 Oct 14:S0936-6555(22)00464-2.
doi: 10.1016/j.clon.2022.09.055.

ABSTRACT

Although current guidelines on rectal cancer treatment often recommend rectal resection with or without neoadjuvant (chemo)radiotherapy, there is growing interest in organ-preserving treatment approaches among patients and clinicians in the Netherlands. Currently, multiple ongoing studies are investigating the value of different non-operative treatment modalities to improve tumour response rates and increase the chance of successful organ preservation. Papillon contact X-ray brachytherapy is a promising treatment modality to improve the chance of organ preservation, which seems especially relevant for elderly and frail patients unable or refusing to undergo total mesorectal excision surgery. The elderly and frail patient with rectal cancer poses a significant challenge and warrants a thorough multidisciplinary approach to provide the most optimal organ-preserving treatment. In this overview, an insight into the Dutch perspectives and developments within the field of organ preservation and the set-up of a Papillon facility to complete the spectrum of organ-preserving treatment options in a tertiary referral centre for rectal cancer treatment has been provided.

INTRODUCTION

New developments in the rectal cancer field have expanded the collection of treatment options for patients in the last decades. As a result, doctors have the ability to provide a more tailored treatment for their patients that is based on the patient's needs and wishes, as well as their physical and mental status. The theme of organ preservation is more frequently becoming a subject of conversation between patient and doctor. The main reason for this increase in interest is the promise of the preservation of anorectal function, particularly for patients with distal rectal tumours who would otherwise receive a colostomy. Moreover, it has become clear that elderly age or frailty does not necessarily exclude the possibility for treatment, whether it be by surgery/excision, (chemo) radiotherapy or a combination of both. Shared decision-making is an important tool in this evolving landscape in order to make a well-balanced decision. It is thereby essential to understand the implications of the results from the many recent and ongoing rectal cancer studies. Here we describe the challenges often presented in the diagnosis and management of rectal cancer and we provide an overview of the Dutch perspective as well as developments within the field of organ preservation.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

Depending on tumour stage, current guidelines recommend total mesorectal excision (TME) with or without neoadjuvant (chemo)radiotherapy. The standard treatment approach for patients with T2 and early T3 rectal cancer without pathological lymph nodes (stage I–II) consists of a radical rectal resection, either a low anterior resection or an abdominoperineal resection, without neoadjuvant (chemo)radiotherapy. TME surgery is associated with morbidity and mortality.[1–3] Anastomotic leakage after a low anterior resection has been described in 10–15% of patients after rectal cancer surgery.[4–6] Mortality rates of 4–16% are described in patients with anastomotic leakage, which even increase up to 30% in the elderly population.[6,7] Moreover, 30–60% of patients suffer from long-term anorectal, urogenital and sexual dysfunction after rectal cancer surgery.[8–11] In patients with more advanced rectal cancer, about 35% of patients end up with a permanent end colostomy during follow-up.[12,13] Since low tumour height increases the risk of pelvic organ dysfunction and the risk of anastomotic leakage, the dilemma to choose for a distal anastomosis is even higher with rectal tumours close to the anorectal junction. Doctors and patients must choose between a colostomy on the one hand and the risk of a malfunctioning anastomosis and long-term pelvic organ dysfunction on the other.

After Habr-Gama et al.[14] first introduced the watch-and-wait (W&W) strategy for patients with rectal cancer with a clinical complete response (cCR) after neoadjuvant chemoradiotherapy, several cohort studies have shown the impact of omitting surgery on different outcomes.[15–17] The beneficial oncological and functional outcomes have led to a paradigm shift towards W&W and organ-preserving strategies in the treatment of rectal cancer. Apart from patients with distal rectal cancer who should undergo an abdominoperineal resection with the formation of a permanent colostomy, elderly or frail patients may also ask not to undergo major surgery regardless of the tumour location. Moreover, some patients may be unable to undergo TME surgery due to advanced age or frailty. Over 50% of patients diagnosed with rectal cancer are older than 70 years, and the proportion of elderly patients will probably increase due to improved life expectancy.[18] Earlier studies have shown that more than 50% of the elderly patients suffer from at least two comorbidities.[19] Although many comorbidities do not increase the risk of morbidity and mortality after surgery, certain comorbidities are associated with significantly worse postoperative outcomes.[20] The heterogeneity of the elderly and frail population increases the risk of undertreatment and overtreatment.[21,22] The main challenge for clinicians is therefore to optimise the balance between the patient's preferences, health status and the most optimal oncological outcomes. The recently described and currently ongoing developments in organ-preserving strategies may provide a beneficial alternative for these patients to avoid major surgery.

DUTCH PERSPECTIVES ON ORGAN PRESERVATION IN RECTAL CANCER

Literature has shown that radiotherapy-based treatment regimens may result in favourable tumour responses and local control of the primary tumour.[23,24] Some patients may even be cured without the need for surgery. Studies on external beam radiotherapy revealed relatively high local control and organ-preservation rates.[25–29] Recent developments in non-operative treatment modalities might further increase the possibilities for organ preservation by increasing the tumour response and reducing the risk of regrowth.[30] These developments include the exploration of (chemo)radiotherapy in early rectal cancer patients. Table 1 and Table 2 provide an overview of recent and currently ongoing, prospective studies on organ preservation in rectal cancer.[31–44]

Table 1. Overview of recent, prospective studies on the organ preserving treatment of rectal cancer

Trial	N	Phase	Age (y)	Follow-up (months)	Stage	Treatment	Treatment regimen	Tumour response	Successfull organ preservation (%)	LR (%)	Survival (%)
CARTS[31,32]	55	II	Median 64 (range 39–82)	Median 53 (IQR 39–57)	cT1-3N0M0	CRT → TEM	Capecitabine + 50 Gy or 50.4 Gy → TEM	pCR 38% ypT0-1 54.5%	57% no indication for (additional) TME	5-year LR 8%	5-year DFS 82% 5-year OS 83%
GRECCAR-2[37,38]	148	III, R	A: Median 61 (range 35-84) B: Median 64 (range 40-88)	A: Median 60 (IQR 58–60) B: Median 60 (IQR 57–60)	T2-3N0-1, ≤ 40 mm, with good clinical response (≤20 mm) after CRT	A: CRT → LE B: CRT → TME	A: Capecitabine + oxaliplatin + 50 Gy → LE B: Capecitabine + oxaliplatin + 50 Gy → TME	A: ypT0-1 41/74 B: ypT0-1 45/68	A: 39/74 no indication (additional) TME after LE B: N.A.	A:5-year LR 7% B: 5-year LR 7%	A: 5-year DFS 70% 5-year OS 84% B: 5-year DFS 72% 5-year OS 82%
TREC[39]	55	II, R	A: 65 (52-79) B: 65 (49-83)	Median 51 (IQR 39-60)	T1-2N0, ≤30 mm	A: SCRT → TEM B: TME	A: 5 × 5 Gy → TEM B: TME	A: pCR/cCR 30% ypT0-1 48% B: N.A.	A: 70% B: N.A.	A: 3-year LR 9% B: 3-year LR 0%	A: 3-year DFS 76% 3-year OS 88% B: 3-year DFS 85% 3-year OS 93%
	61	Observational, OP arm	74 (53-89)	Median 49 (IQR 38-56)	T1-2N0, ≤30 mm	SCRT → TEM	5 × 5 Gy → TEM	pCR + cCR 41% ypT0-1 63%	92%	3-year LR 9%	3-year DFS 76% 3-year OS 86%

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Trial	N	Phase	Age (y)	Follow-up (months)	Stage	Treatment	Treatment regimen	Tumour response	Successfull organ preservation (%)	LR (%)	Survival (%)
STAR-TREC[40,*]	120	II, R	n.r.	n.r.	cT1-3bN0M0, ≤40 mm	A: TME B: SCRT → W&W/ TEM (if partial response)/ TME (poor response) C: CRT → W&W/ TEM (if partial response)/ TME (poor response)	A: TME B: 5 × 5 Gy → W&W/ TEM (if partial response) / TME (poor response) C: Capecitabine + 50 Gy → W&W / TEM (if partial response)/ TME (poor response)	n.r.	A: 0% B/C (pooled): 60%	n.r.	A: 2-year DFS 91% 2-year non-regrowth DFS 86% B/C (pooled): 2-year DFS 75% 2-year non-regrowth DFS 90%
OPERA[41,*]	144	III, R	A: 68 B: 69	Median 34	cT2-3abN0-1, <50 mm	A: CRT → EBRT boost B: Tumour <3 cm: CXB → CRT Tumour ≥3 cm: CRT → CXB	A: Capecitabine + 45 Gy → 9Gy boost B: T <3 cm: 3 × 30 Gy (endorectal) → Capecitabine + 45 Gy T ≥3 cm: Capecitabine + 45 Gy → 3 × 30 Gy (endorectal)	A: cCR 61% B: cCR 90%	A: 3-year OP 60% B: 3-year OP 81%	n.r.	n.r.

Trial	N	Phase	Age (y)	Follow-up (months)	Stage	Treatment	Treatment regimen	Tumour response	Successfull organ preservation (%)	LR (%)	Survival (%)
HERBERT[42]	38	I	Median 83 (range 57-94)	Median 30 (range 21-86)	cT2-4N0-1M0-1, unfit for surgery	EBRT → HDR-BT	13 × 3 Gy → 3 × 5-8 Gy (endorectal)	cCR 20/33	n.r.	1-year LP 36% 3-year LP 80%	1-year OS 82% 3-year OS 27%
ReSARCh[43]	160	Observational study	Median 65 (IQR 60-72)	Median 24 (IQR 17-30)	mCR or cCR after neoadjuvant treatment	A: Neoadjuvant treatment → LE (if mCR / cCR) B: Neoadjuvant treatment → W&W (if cCR)	A: Neoadjuvant treatment → LE B: Neoadjuvant treatment → W&W	A: pCR 58% ypT0-1 81% B: cCR 98%	A: no indication for (additional) TME after LE 73.5% B: n.r.	A: n.r. B: Regrowth end of follow-up 24%	n.r.
ACOSOG Z6041[44]	79	II	62 (range 30-83)	56 (IQR 46-63)	cT2N0, <40 mm	CRT → LE	Capecitabine + oxaliplatin + 45 Gy + 9 (or 5) Gy boost → LE	pCR 49% ypT0-1 63%	4/76 indication for (additional) TME after LE	LR end of follow-up 4%	3-year DFS 88% 3-year OS 95%

*Preliminary data

Abbreviations: cCR = complete clinical response; mCR = major clinical response; pCR = pathological complete response; CRT = chemoradiotherapy; CXB = contact X-ray brachytherapy; DFS = disease-free survival; EBRT = external beam radiotherapy; HDR-BT = high-dose rate endorectal brachytherapy; IQR = interquartile range; LE = local excision; LP = local progression; LR = local recurrence/local regrowth; N.A. = not applicable; n.r. = not reported; OP = organ preservation; OS = overall survival; R = randomised study; SCRT = short-course radiotherapy; TEM = transanal endoscopic microsurgery; TME = total mesorectal excision; W&W = watch and wait

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Table 2. Overview of currently ongoing, prospective studies on the organ preserving treatment of rectal cancer

Trial	N (sample size)	Phase	Patient and tumour characteristics	Aim	Treatment	Treatment regimen	Treatment outcomes	Status
TESAR[33]	302	III, R	Intermediate risk T1-T2 rectal cancer after complete LE	Compare OP strategy and completion TME	A: TME B: Adjuvant CRT	A: TME B: Capecitabine + 45 Gy	Primary: 3-year LR Secondary: morbidity, 3-year and 5-year DFS and OS, stoma-free survival, QoL, cost-effectiveness	Recruiting
STAR-TREC[34]	300	III, patient preference	cTX-3bNX-0MX-0, ≤40 mm in diameter	Evaluate two organ preserving strategies (SCRT or CRT) for treatment of early rectal cancer	A: TME B: SCRT or CRT (randomised) → W&W (if cCR) / LE (if good, but incomplete response)	A: TME B: 5x5 Gy / Capecitabine + 50 Gy → W&W (if cCR) / LE (if good, incomplete response)	Primary: Successful OP at 30 months after start treatment Secondary: toxicity, response rates, LE rates, non-regrowth pelvic tumour control, metastasis, survival, patient-reported outcome measures	Recruiting
OPAXX[35]	336	II, R	Intermediate risk or locally advanced rectal cancer with good, but incomplete clinical response after neoadjuvant treatment	Investigate two different strategies to treat ncCR or small residual tumour after neoadjuvant treatment	A: CXB B: Prolonged waiting interval with re-assessment → LE (if small remaining lesion)	A: 3 x 30 Gy (endorectal) B: prolonging the waiting interval with 6-8 (+/- 4) weeks → LE (if small remaining lesion)	Primary: successful OP at 1 year after randomisation Secondary: toxicity, morbidity, oncological and functional outcomes at 1, 2, and 5 year	Recruiting

Trial	N (sample size)	Phase	Patient and tumour characteristics	Aim	Treatment	Treatment regimen	Treatment outcomes	Status
HERBERT II[36]	110	III, R	cT1-3N0-1M0-1, unfit for surgery	Investigate the added value of a brachytherapy boost compared to external beam radiotherapy alone for rectal cancer patients unfit for surgery	A: EBRT B: EBRT → HDR-BT / CXB (will be added as an amendement)	A: 13 x 3 Gy B: 13 x 3 Gy → 3 x 7 Gy (endorectal) / 3 x 30 Gy (endorectal; will be added as an amendement)	Primary: composite QoL (local sypmtoms, deterioriation in QoL / maintenance of ADL) Secondary: local control, survival, retreatment, symptoms and QoL	Recruiting

Abbreviations: ADL = activities in daily living; cCR = complete clinical response; ncCR = near-complete clinical response; CRT = chemoradiotherapy; CXB = contact X-ray brachytherapy; DFS = disease-free survival; EBRT = external beam radiotherapy; HDR-BT = high-dose rate endorectal brachytherapy; LE = local excision; LVI = lymphovascular invasion; LR = local recurrence/local regrowth; OP = organ preservation; OS = overall survival; QoL = quality of life; R = randomised study; SCRT = short-course radiotherapy; SM = submucosal invasion; TME = total mesorectal excision; W&W = watch and wait

The TESAR study (NCT02371304) is investigating the possibilities for organ preservation after a local excision in patients with an intermediate risk of recurrence.[33] Local excision is considered an oncologically safe treatment option in patients with low-risk T1 rectal tumours. However, the risk of lymph node metastases and local recurrences are increased in those with unfavourable histological characteristics (e.g. poor differentiation, tumour budding, lymphovascular invasion) or with a pathological T2 stage.[45,46] In these patients, completion TME surgery is often required.[45] The TESAR study randomises patients with an intermediate-risk T1–2 rectal tumour after local excision between adjuvant chemoradiotherapy or a completion TME.[33]

In the international STAR-TREC (NCT02945566) phase II study, patients were randomised between surgery and an organ-preserving approach.[34] As most patients preferred organ preservation over surgery, the STAR-TREC phase III trial was initiated. The STAR-TREC phase III trial is based on the patient's preference for either organ preservation or surgery. If patients prefer organ preservation, they will be randomised between chemoradiotherapy (25 × 2 Gy with daily oral capecitabine 850 mg/m2 bid) and short-course radiotherapy 5 × 5 Gy.[34] If a good response is observed after (chemo)radiotherapy, patients can be followed-up in a W&W trajectory, whereas small residual disease can be treated with transanal surgery.[34] The STAR-TREC trial will thereby provide valuable insights in the organ-preserving treatment of patients with early rectal cancer [T1-3b (<4 cm) N0 M0, EMVI–, MRF–].

Another important development to improve organ-preserving treatment approaches includes the exploration of additional treatment modalities to improve tumour responses, such as by the addition of systemic chemotherapy or dose escalation of radiotherapy.

Multiple cohort studies among rectal cancer patients have described promising effects of adding systemic chemotherapy before or after (chemo)radiotherapy on the tumour response rates.[47–51] These studies reported complete response rates of 22–30% in patients with locally advanced rectal cancer, and up to 53.5% in patients with early rectal cancer.[47–51] Based on these outcomes, randomised trials have been carried out to explore the effect of adding systemic chemotherapy in the neoadjuvant treatment phase, such as the RAPIDO and the PRODIGE-23 trials.[52,53] However, due to the risk of toxicity and the lack of data in the elderly and frail, the use of additional systemic chemotherapy will probably be limited in these patients.

Dose escalation by administering a local radiotherapy 'boost' has been described as a way to improve the cCR rates in selected cases.[54] Papillon contact X-ray brachytherapy

(CXB) is considered a feasible treatment modality to escalate radiotherapy doses directly to the tumour.[55,56] CXB can be used as primary treatment in small rectal tumours or as an additional modality after (chemo)radiotherapy to treat residual tumours smaller than 3 cm.[55,56] The international OPERA trial, the definitive results of which are expected soon, compared the effect of an external radiotherapy boost to a CXB boost for patients in good condition having received neoadjuvant chemoradiotherapy with smaller rectal tumours (cT2-cT3ab). The preliminary results revealed complete response rates in 90% of patients treated with CXB and in 60% of patients treated with an external radiotherapy boost.[41] The 3-year organ-preservation rates in patients treated with CXB versus an external radiotherapy boost were 81% versus 60%, respectively.[41] Published studies on CXB show acceptable toxicity that is limited to the rectal wall.[57] The phase III Lyon R96-02 trial showed that for operable patients, a CXB boost can improve the cCR rate as well as sphincter and organ preservation for patients with a T2-T3 rectal tumour. This effect remained significant after a 10-year follow-up.[58,59] Although CXB has been investigated mainly in early rectal cancer, the role of this modality in more advanced tumours is relatively unexplored. The OPAXX study was initiated in 2021.[35] This study is designed to investigate the value of additional CXB versus extending the waiting interval and local excision in patients with a good clinical response after neoadjuvant (chemo) radiotherapy for intermediate-risk or locally advanced rectal cancer to preserve the rectum. Patients with a near-complete response or small residual tumour mass (<3 cm) and no pathological lymph nodes (cN0) after (chemo)radiotherapy will be randomised between CXB (3 × 30 Gy), given within 12 weeks after external beam radiotherapy, or extension of the waiting interval with another 6 weeks followed by a W&W approach, local excision or TME surgery, depending on the response evaluation.

Since the arrival of the attractive concept of organ-sparing treatment, significant improvements have been made in quality of life for many patients with rectal cancer. However, the challenge remains of predicting which patients are good candidates, and which patients are not suitable for a W&W strategy. Achieving a cCR after neoadjuvant chemoradiotherapy has been shown to be a good starting point for patients willing to partake in the W&W pathway.[15] However, for patients who do not warrant neoadjuvant (chemo)radiotherapy according to 'protocol', for example, those with a small T2–T3 tumour, it has become less clear how to move forward, especially as more and more patients explicitly ask for organ-sparing treatment. The TREC study was one of the first trials to explore the feasibility of a trial comparing major surgery or organ-preserving treatment for patients with small rectal tumours.[39] Along with showing that high levels of organ preservation were achieved, it proved that short-course radiotherapy is an effective option with acceptable toxicity to consider in the organ-sparing toolbox. Many organ-sparing studies prove that the oncological risk of the W&W strategy remains small, as a good salvage treatment (major surgery) often remains available in the case of local failure.[15] Although this is good news, it does make the feasibility of a large-scale trial difficult, as patients often will not accept randomisation between organ-sparing treatment and major surgery.[60] Studies in the future will therefore need to cater to the needs and wishes of patients. A good illustration of this is the adaptation of the STAR-TREC protocol, described above, to a patient-preference study. This type of consideration will ensure the possibility of large-scale trials in the future, which are greatly needed to further explore which patients will benefit most and, importantly, which will not benefit at all, from organ-sparing treatment.

The phase I HERBERT study investigated the outcomes of definitive radiotherapy in elderly and frail rectal cancer patients.[42] Patients were treated with 13 × 3 Gy external beam radiotherapy followed by 3 × 5–8 Gy of high-dose rate endorectal brachytherapy (HDR-BT).[42] The study concluded that definitive radiotherapy can provide good tumour response rates but has a substantial risk for toxicity in the elderly and frail.[42] To further assess the benefits and risk of a HDR-BT boost above external beam radiotherapy alone in elderly or frail patients, the HERBERT-II study (Netherlands Trial Register: NL7795) was designed as a phase III trial. The study outcomes of the HERBERT-II study focus on efficacy, toxicity, quality of life and functional capacity. Elderly and frail patients, unfit for or refusing surgery, with a rectal adenocarcinoma, less than two-thirds of the circumference and without extension into the anal canal, N0-1 M0, and sufficient lumen to allow positioning of the brachytherapy applicator are eligible for inclusion. Prior to inclusion, patients >70 years of age or considered frail by their treating physician will undergo a geriatric pre-screening test. If the geriatric pre-screening is abnormal, referral to the department of geriatrics and gerontology will follow for a more comprehensive geriatric assessment. Participating patients will receive 13 × 3 Gy external beam radiotherapy within 2.5 weeks, followed by response evaluation after 11–15 weeks. After excluding patients with progressive disease, the remaining patients will be randomised between an observational arm and an interventional arm. In the interventional arm, an additional local radiotherapy boost with HDR-BT (3 × 7 Gy, one fraction per week) will be administered. An amendment will follow to include CXB (3 × 30 Gy, one fraction every 2 weeks) as an alternative local treatment option in the interventional arm for small residual tumours (<3 cm).

As the number of elderly and frail patients will probably further increase over the coming years, tailor-made treatment regimens will become of greater importance. Due to the complexity of treating these patients and the heterogeneity within this group, the care for these patients is best organised in multidisciplinary teams with expertise on the non-operative management of elderly and frail patients. These multidisciplinary teams should include at least a surgeon, a medical oncologist, a radiation oncologist, a geriatrician, a physician assistant and, in some cases, an anaesthesiologist. In the Catharina Hospital, a dedicated multidisciplinary clinical care pathway has been initiated. Elderly and frail patients are comprehensively evaluated by the entire multidisciplinary team during day care admission. At the end of the day, a multidisciplinary and patient-centred treatment advice will be formulated and communicated with the patient and their caregivers. The RESORT study (A Prospective Registry of the Non-Invasive Multimodality Treatment in Inoperable Rectal Cancer Patients: Evaluating the Current Treatment Strategies in Rectal Cancer Patients Unable to Undergo TME Surgery) is a single-centre prospective observational cohort study to evaluate the treatment and outcomes of elderly and frail rectal cancer patients who are unable to undergo TME surgery. Patients who are unable or unwilling to undergo TME surgery and who are treated within the multidisciplinary care pathway in the Catharina Hospital are eligible for inclusion. The study outcomes focus on the decision-making process, the treatment, local control of disease, survival, quality of life and functional outcomes of elderly and frail patients treated non-operatively.

PAPILLON FACILITY AT THE CATHARINA HOSPITAL

The summarised literature above confirms the growing tendency for an organ-preserving approach in the Netherlands. Especially for elderly and frail rectal cancer patients, and for patients with distal rectal tumours, the advantages of avoiding surgery might be great. Improving the chance of a cCR by increasing the radiotherapy dose locally can be seen as a valid option for selected patients. As the Catharina Hospital is well known for its expertise in treating complex rectal cancer, a logical step was to set up a Papillon facility at the Radiotherapy Department. This way, the hospital could offer all possible treatment modalities (including organ-sparing approaches) to its own rectal cancer patients and those in the surrounding regions.

In 2020, the Catharina Hospital purchased the Papillon+ machine produced by Ariane Medical Systems, and set up a Papillon facility within the Radiotherapy Department. Potential candidates are selected by the multidisciplinary team and, if possible, included in the abovementioned OPAXX or HERBERT-II studies. Treatments are administered in accordance with the recently published GEC-ESTRO International Guidelines.[56] The radiation oncologists are often joined by the gastroenterologist and/or surgeon to aid in target volume localisation. An additional rectal endoscopy is often carried out prior to the treatment. In the near future, the feasibility and added value of an endorectal ultrasound prior to treatment in order to gain more insights into tumour depth will be carried out, as recommended by the GEC-ESTRO guidelines.[56]

CONCLUSION

There is growing interest in an organ-preserving treatment approach for patients with rectal cancer in the Netherlands, as shown by the increase in studies regarding organ preservation over recent years. The elderly and/or frail patient with rectal cancer poses a significant challenge for the treating clinicians, and warrants a thorough multidisciplinary approach, including a comprehensive geriatric assessment. The addition of a Papillon facility completes the spectrum of organ-sparing treatment options for patients with rectal cancer at the Catharina Hospital.

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CHAPTER 11

A multidisciplinary approach for the personalised non-operative management of elderly and frail rectal cancer patients unable to undergo TME surgery

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Cancers (Basel). 2022 May 11;14(10):2368. doi: 10.3390/cancers14102368.

ABSTRACT

Despite it being the optimal curative approach, elderly and frail rectal cancer patients may not be able to undergo a total mesorectal excision. Frequently, no treatment is offered at all and the natural course of the disease is allowed to unfold. These patients are at risk for developing debilitating symptoms that impair quality of life and require palliative treatment. Recent advancements in non-operative treatment modalities have enhanced the toolbox of alternative treatment strategies in patients unable to undergo surgery. Therefore, a proposed strategy is to aim for the maximal non-operative treatment, in an effort to avoid the onset of debilitating symptoms, improve quality of life, and prolong survival.

The complexity of treating elderly and frail patients requires a patient-centred approach to personalise treatment. The main challenge is to optimise the balance between local control of disease, patient preferences, and the burden of treatment. A comprehensive geriatric assessment is a crucial element within the multidisciplinary dialogue. Since limited knowledge is available on the optimal non-operative treatment strategy, these patients should be treated by dedicated multidisciplinary rectal cancer experts with special interest in the elderly and frail. The aim of this narrative review was to discuss a multidisciplinary patient-centred treatment approach and provide a practical suggestion of a successfully implemented clinical care pathway.

INTRODUCTION

Although total mesorectal excision (TME) surgery is the optimal approach for curation, elderly and frail rectal cancer patients may not always be able to undergo a surgical procedure.[1–3] In these patients, decision making is challenging, and no standardised treatment regimen or guideline is available.[4–6] Frequently, patients receive no treatment at all and doctors and patients wait out the natural course of the disease.[1,7,8] This often results in tumour progression and the onset of debilitating symptoms that impair quality of life. Palliative treatment may then be offered to alleviate symptoms, if possible.[7,9]

However, improvements in chemotherapeutic and radiotherapeutic treatment modalities provide alternative non-operative treatment strategies for patients who are unable to undergo TME surgery.[10,11] These strategies may provide long-term local control of the primary tumour and avoid the early-onset of debilitating symptoms, improve quality of life, and prolong survival. In some patients, curation might even be possible.

Various evidence-based and expert-based recommendations exist on how elderly and frail rectal cancer patients should be treated surgically. However, the optimal treatment approach for patients who are unable to undergo TME surgery is still unknown. The patient complexity, as well as the risk for undertreatment or overtreatment require a patient-centred approach to propose the most optimal treatment strategy, considering the patient's level of frailty, personal preferences, and treatment goals.

The aim of this narrative review was to discuss a multidisciplinary patient-centred approach for the personalised non-operative management of elderly and frail rectal cancer patients unable to undergo TME surgery.

Current treatment of elderly and frail rectal cancer patients

Epidemiological data show that over 50% of rectal cancer patients are older than 70 years. Due to an improved life expectancy, this proportion of elderly patients will probably increase over the coming years.[12] The elderly population is characterised by a wide variety in health status, ranging from vital and fit to frail and unable to undergo even minor surgical procedures.[4–6] This heterogeneity results in a difficult balance between oncological outcomes, the burden of treatment, and functional outcomes.

Considerations on the surgical treatment of elderly rectal cancer patients

TME surgery is generally accepted as the best curative treatment for rectal cancer.[13] While older studies reported high rates of postoperative morbidity and mortality in the elderly, the outcomes have improved significantly over recent years.[14,15] In a Dutch retrospective cohort of 2018 patients, the postoperative mortality of elderly patients (≥75 years) improved from 8.8% between 2006–2012 to 1.7% between 2013–2017, whereas the 1-year relative survival rates were no longer different between elderly and younger patients.[15] Similar improvements have been described by population-based data from the Netherlands Cancer Registry (NCR), which reported an improvement of the 1-year relative survival in the elderly (≥75 years) rectal cancer patient from 86.1% between 2005–2006 to 97.2% between 2015–2016.[14] These results support the paradigm shift that patients should not be withheld surgery based on chronological age alone.[14,15]

Particularly in the treatment of elderly and frail patients, the concept of personalised care is essential. Elderly and frail patients often consider that maintaining independence, quality of life, and functional outcomes are at least as important as oncological outcomes and survival.[16–18] These aspects should be discussed and incorporated in the decision-making process. Although the survival of elderly patients has improved significantly, clinicians should consider that the overall one-year mortality is still 10–15%.[14,15] In the most frail, the risks are even higher and may outweigh the benefits, with 2-year mortality rates above 40%.[19] TME surgery may also result in undesirable functional outcomes that impair quality of life. Various cohorts have reported severe functional bowel complaints (e.g., faecal incontinence, urgency) in 30–40% of patients.[20,21] Urinary dysfunction (e.g., incontinence, urgency) is reported by 30–60% of patients, while more than half of patients reported sexual dysfunction after treatment.[22–25] A Scottish population-based study showed that 12% of patients older than 80 years did not return to their preoperative living situation after surgery, while other studies showed that a significant part of the elderly experienced a deterioration in their functional status.[26–30]

Epidemiology of the non-surgical treatment of the elderly and frail

Population-based data showed that 6–30% of patients of all ages with curable, stage I-III rectal cancer will not undergo surgery.[2] According to literature, there are several reasons why patients do not undergo TME surgery. Age is still considered the primary reason.[3,17] While approximately 30% of the patients aged 70 years or older did not undergo surgery, this percentage rose to more than 60% in those older than 80 years.[1,4] Patients with multiple or severe comorbidities also underwent less surgery.[1,8] While population-based studies have shown that most comorbidities are not predictive for poor outcomes, certain comorbidities (e.g., chronic cardiopulmonary disease, liver cirrhosis) severely increase the risk for treatment-induced morbidity and mortality or impair toleration for anaesthesia.[31–33] Advanced disease stages also resulted in higher non-resection rates, especially in the elderly.[1,2,8] Lastly, some patients refuse TME surgery despite being fit for reasons varying from personal convictions and preferences to fear of consequences (i.e., poor functional outcome or an ostomy).

The fate of elderly and frail rectal cancer patients refrained from treatment

Although the number of patients treated with alternative modalities has increased over the years, data from the NCR still show that 30.4% of the older patients (≥70 years) who did not undergo surgery received no treatment at all.[1] This percentage increased to 37.1% and 40.9%, respectively, in those older than 80 years and those with multimorbidity (≥2 comorbidities).[1] The 3-year overall and relative survival rates of these patients were 9% and 10%, respectively.[1] Although scarce, a few other studies reported on untreated rectal cancer patients. A retrospective study by Bethune et al. investigated the outcomes of 35 patients (mean age 87 years) and reported a mean overall survival of 18 months.[7] Another study among 79 patients (mean age 79.4 years) reported a median overall survival of 10.7 months and 2-year mortality rates of 76%.[8] Although selection bias might have occurred in these studies, not offering patients any treatment at all seems to be associated with a very poor survival.[19,34]

Apart from poor survival rates, patients with untreated rectal cancer often develop severe symptoms that affect their lives significantly, which was also observed in the cohort of Bethune et al.[7] Patients may present themselves with various symptoms related to tumour progression. In a group of 180 patients with incurable disease, the most commonly observed symptoms were bowel obstruction and rectal bleeding.[35] Approximately 10–25% of patients with stage IV disease presented with symptoms related to bowel obstruction.[9,35–37] If bowel obstruction results in colonic perforation, emergency surgery is usually required, which is associated with increased mortality in the elderly and frail and should be avoided.[38] Rectal tumour perforation may result in localised problems, such as pelvic abscesses, fistulae or pelvic pain, often requiring drainage.[36] Rectal bleeding and anaemia are also frequently observed, particularly in patients using anticoagulants.[36] An earlier study reported rectal bleeding in 24% of patients with incurable colorectal cancer, while an additional 12% suffered from anaemia.[35] In two retrospective cohorts, 37–43% of untreated patients needed at least one blood transfusion during follow-up.[7,8]

The need for a personalised non-operative treatment approach

Elderly and frail rectal cancer patients unable to undergo TME surgery are at risk for undertreatment, which results in poor outcomes. However, progress has been made in non-operative treatment modalities.[5,10,11] Studies have explored the use of systemic chemotherapy, external beam radiotherapy (EBRT), endoluminal radiotherapy, and local excision with promising outcomes. The performed studies reported local control rates up to 60–90% and 1-year, 2-year, and 3-year overall survival rates of 82–100%, 63–88% and 27–82%, respectively.[39–43]

The promising developments in the non-operative management of rectal cancer patients in general raises the question of whether these options should be considered in patients for whom surgery is not possible. It seems logical that maximal treatment effectiveness can be achieved when the available modalities are optimally allocated in each individual patient. This may result in improved local control of the primary tumour, thus aiming to prevent the onset of debilitating symptoms, improve quality of life, and prolong survival. Due to the heterogeneity in the elderly and frail population, a patient-centred approach, in which the patient is comprehensively evaluated by dedicated multidisciplinary experts, is required to optimise and personalise treatment.

In this narrative review, three main topics to discuss a patient-centred approach for elderly and frail rectal cancer patients unable to undergo TME surgery will be addressed: (i) the multidisciplinary patient approach; (ii) the non-operative treatment options; (iii) the response evaluation and follow-up. Based on the literature review in the main topics, we provided a practical suggestion of a successfully implemented multidisciplinary clinical care pathway and a prospective observational cohort study that has been initiated by the authors of the study.

THE MULTIDISCIPLINARY PATIENT APPROACH

Treatment outcomes in the elderly and frail

While the treatment outcomes of fit patients are generally more focused on the oncological results, the elderly and frail frequently prioritise maintaining quality of life and functional recovery.[18] Although curation might be the best oncological outcome, this is often not the main priority for the elderly and frail who are unable to undergo TME surgery. Setting the right expectations is important, since the burden of treatment and the expected impact on quality of life and functional recovery often determine the patient’s preferences.[44]

As mentioned by Saur and Montroni et al., functional recovery can be divided in organ-specific functional recovery and the individual ability to regain or maintain independence.[45] Bowel, bladder, and sexual dysfunction are frequently observed after rectal cancer treatment and can severely impair quality of life. Considering the impact of the available treatment modalities on these organ functions is essential and should be discussed with the patient. Several scoring tools are available to evaluate pelvic organ functions, such as the Low Anterior Resection Syndrome (LARS) score, the International Prostate Symptoms Score (IPSS), and the International Index of Erectile Function (IIEF).[46–51] Implementing these questionnaires at baseline, during treatment, and during follow-up may help to personalise the decision-making process, set the right expectations, and/or initiate treatment when symptoms arise.

Elderly patients value functional independence as one of the most important factors related to their well-being.[52] The loss of independence is considered as a detrimental burden of treatment.[52] Several studies have reported that 24–60% of elderly patients experienced a decline in their level of independence after treatment.[27–30] Clinicians should, consequently, prioritise the prevention of functional decline over obtaining curation when treating these patients. Moreover, preventing hospitalisation and institutionalisation, maintaining physical and cognitive functioning, and minimising the burden of disease and treatment for the patient and their relatives are also important parameters to consider. The geriatric frailty assessment can help to identify health domains at risk for deterioration and is considered a crucial element to personalise treatment.[53]

Geriatric assessment

Frailty is defined as a state of diminished physiological reserve capacity across multiple organ systems, resulting in a reduced capacity to compensate for stressors.[54] Frailty is a strong predictor for treatment-induced toxicity, reduced tolerance, loss of quality of life, and increased mortality.[55,56] Many factors contribute to frailty, including age and comorbidities.[56] Population-based data reported that 58.3–70.6% of patients aged 70–74 years suffer from multimorbidity (≥2 comorbidities), increasing to more than 80% in patients above 85 years.[57] While age and comorbidities contribute to frailty, they do not equal frailty.[58] Many elderly patients are not frail and can be treated safely by standard approaches, whereas only a few comorbidities contribute to poor outcomes.[58,59] Therefore, distinguishing the frail from the fit is crucial to optimise treatment.[60]

Comprehensive geriatric assessment (CGA)

The CGA consists of a multidimensional evaluation of the patient's health status.[54,61] A CGA can identify health problems and vulnerable areas that increase the risk of frailty, functional decline, toxicity, and mortality.[61] A systemic review among 35 studies by Hamaker et al. described that a CGA resulted in a changed treatment plan in 28% of elderly cancer patients.[62] A CGA was associated with increased treatment compliance and a reduced risk for toxicity.[62] A Cochrane review showed that a CGA resulted in improved decision-making and a diminished rate of institutionalisation after treatment.[63] A CGA can also identify health areas in need for improvement, leading to targeted interventions.

Several domains that contribute to the onset and progression of frailty are evaluated in a CGA (Table 1).[12] Multiple validated scoring tools are available to assess these health domains.[64] The presence of geriatric risk factors and syndromes (e.g., risk to fall, the risk of delirium), the living situation, the level of social support and the availability of a caregiver are also part of the CGA. Moreover, the exploration of the patient's preferences and treatment goals (e.g., maintaining independence, reducing symptoms, maximising quality of life, prolonging survival, etc.) is considered crucial. By combining all of these outcomes, the benefits and risks of each treatment modality can be analysed within the multidisciplinary team.

Table 1. Elements of the comprehensive geriatric assessment within the non-operative management of elderly and frail rectal cancer patients.

Geriatric domain	**Examples of scoring tools**
Age	-
Functional status	Eastern Cooperative Oncology Group (ECOG) Performance status [65] Karnofsky Performance status [66]
Level of independency	Katz scale of Activities of Daily Living (ADL) [67] Lawton and Brody scale of Instrumental Activities of Daily Living (IADL) [68]
Comorbidity	Charlson Comorbidity Index (CCI) [69]
Medication use	Number and type of medication use
Physical function and mobility	4-Meter Gait Speed [70] Handgrip strength [71] Timed Up and Go (TUG) [72]
Cognitive function	Six-item Cognitive Impairment Test (6-CIT) [73] Mini-Cog [74] Visual Association Test (VAT) [75] Clock Drawing Test (CDT) [76] Mini Mental State Examination (MMSE) [77]
Emotional function	Patient Health Questionnaire (PHQ-2) [78] Geriatric Depression Scale-15 (GDS-15) [79] Hospital Anxiety and Depression Scale (HADS) [80]
Nutritional status	Mini-Nutritional Assessment Short Form (MNA-SF) [81] Body Mass Index (BMI)

Geriatric domain	Examples of scoring tools
Social status	Living arrangements (independent, institutionalized, hospitalized) Availability of an informal and formal caregivers (number of days with home care)
Geriatric risk factors or syndromes	Risk to fall/fall history Risk of delirium Vision or hearing difficulties Pain Urinary and/or faecal incontinence
Treatment goals and preferences	E.g. Minimising/improving local complaints related to the tumour Maintaining/improving quality of life Maintaining/improving functional status Prolonging survival

Multidisciplinary evaluation

The multidisciplinary evaluation has an important role in the treatment of rectal cancer, especially in the elderly and frail.[17,82] There are no accurate guidelines available on the non-operative management of elderly and frail rectal cancer patients and most evidence is based on data from clinical trials that excluded the elderly and frail.[6] Clinical consensus within a dedicated multidisciplinary team with expertise on the non-operative management of elderly and frail rectal cancer patients may most likely provide the optimal treatment advice.[12,17,83]

In a patient-centred approach, the patient should be considered as the core of the decision-making process and should be involved actively. Informing patients about the benefits and risks of the available treatment options is an important element for shared-decision making.[84] An individual assessment by each member of the multidisciplinary team might be beneficial to improve the multidisciplinary discussion.[84] The geriatrician is an indispensable member of the multidisciplinary team and the CGA should have a central role within the multidisciplinary dialogue.[83,85,86] From the start of treatment until the end of follow-up, the multidisciplinary team should consider the patient's health status, treatment goals, and preferences as central elements to personalise treatment.[12]

Prehabilitation

Prehabilitation refers to the optimisation of the patient's health status to prevent a future decline.[87] The compliance to and the response of prehabilitation may also contribute to better patient selection and improved decision-making. Prehabilitation often aims at improving the general health status, but the CGA can optimise prehabilitation by identifying specific areas of impairment. A systematic review showed that a CGA resulted in targeted interventions in 72% of patients.[62] A randomised study showed that a CGA with subsequent targeted interventions can effectively reduce frailty.[88] Moreover, a study among 106 colorectal cancer patients showed that particularly the frail had the largest benefit from prehabilitation.[89] Earlier studies mainly investigated prehabilitation in patients scheduled for surgery, but it is conceivable that patients scheduled for non-operative treatment also benefit from prehabilitation.[90] While the effects on the toxicity and compliance of non-operative treatment modalities are unexplored, increasing evidence shows favourable health benefits of prehabilitation programmes during chemotherapy and radiotherapy.[91,92] The improved health status achieved by prehabilitation is associated with an improved quality of life and may increase the probability for an escalation of treatment or even TME surgery.[87]

NON-OPERATIVE TREATMENT OPTIONS

The non-operative management of rectal cancer in elderly and frail patients unable to undergo TME surgery should not be considered the same as palliative treatment. In palliative treatment, the natural course of the disease is often awaited and symptoms are treated when they arise, whereas the non-operative management is a more active approach with clear treatment goals to obtain local control of the primary tumour and prevent the onset of symptoms.

The advancements in chemotherapeutic and radiotherapeutic treatment modalities over the recent years have improved tumour responses.[10,11,93,94] Radiotherapy-based treatment strategies may result in adequate local control of the primary tumour. In fact, some patients can even be cured without the need for surgery. This has been supported by data from the International Watch and Wait Database. They reported 5-year overall and cancer-specific survival rates of 85% and 94%, respectively, among 880 patients with a clinical complete response.[95] A recent study by Haak et al. investigated the effectiveness of a watch-and-wait strategy among 43 elderly patients.[96] After a minimal follow-up of 2 years, the complete response was sustained in 88%, while the 3-year overall survival was 97%.[96]

The beneficial outcomes have led to increased interest in the non-operative management of rectal cancer patients, which is especially relevant for elderly and frail patients who are not able to undergo TME surgery.[5,6] While curation would be the best possible outcome, the treatment of these patients mostly aims at achieving local control of the primary tumour.

Improved tumour responses can be obtained by increased radiotherapeutic doses, which can be delivered endoluminally.[5,10,94,97] The addition of systemic chemotherapy may also improve tumour response, while local excision can be performed to treat small residual disease.[43,98,99] Multiple studies have explored the advantages and disadvantages of non-operative treatment modalities in selected groups of patients. Most of the performed studies reported on complete or near-complete response rates, rather than on local control. Nevertheless, the complete or near-complete response rates associated with a non-operative treatment modality may indicate its effect on the tumour response and the probability to obtain local control.

It has become clear that each modality may benefit each patient differently, supporting the need for a personalised treatment strategy.[100] Despite separate modalities as well as certain combinations having been explored, the optimal allocation in the elderly and frail is unknown. Centralisation of care to a dedicated centre with expertise on all non-operative treatment modalities in the elderly and frail seems warranted.

Systemic chemotherapy

Adding systemic chemotherapy before or after (chemo)radiotherapy seems to improve local tumour response and may increase local control. Over recent years, the addition of systemic chemotherapy has been explored increasingly in studies on total neoadjuvant treatment.[11,101] Although some studies only reported small effects, promising response rates have been described in several randomised trials and cohort studies.[102–106] Calvo et al. reported significantly higher rates of tumour downstaging after adding systemic chemotherapy, which was also observed in a phase II study by Markovina et al.[107,108] Meta-analyses by Petrelli et al. and Kasi et al. reported a pooled complete response rate of 22.4–29.9% in patients with locally advanced rectal cancer in whom systemic chemotherapy was added to (chemo)radiotherapy.[98,109] In patients with lower stages of rectal cancer, the complete response rates seem even higher. A study by Cercek et al. reported a complete response in 53.5% of patients with stage II disease.[103] However, the benefits of the addition of systemic chemotherapy for achieving local control and survival are unclear, especially in the elderly and frail.

Systemic chemotherapy may induce toxicity, resulting in morbidity and decreased physical reserve capacity, particularly in the elderly and frail. The performed studies showed high compliance rates of 80–100% and similar toxicity rates when compared to chemoradiotherapy, but these studies were mostly conducted in relatively young and fit patients with a median age between 57 and 69 years.[98,109] Many studies investigated oxaliplatin-based chemotherapy, which is, particularly in the elderly, known for its adverse effects.[110] Studies exploring the effectiveness, the toxicity, and compliance of adding systemic chemotherapy in the elderly and frail are lacking. While it may be beneficial in relatively fit patients who refuse surgery, the absence of data and the potential toxicity probably limits its use in the non-operative management of the elderly and frail.

External beam radiotherapy (EBRT)

EBRT is most commonly administered in two different schedules: long-course chemoradiotherapy (45–50.4 Gy in fractions of 1.8–2.0 Gy with concomitant capecitabine) or short-course radiotherapy (SCRT) (25 Gy in fractions of 5 Gy).

Both schedules are associated with beneficial tumour response rates and form a viable basis for combinations in the non-operative management of rectal cancer. When compared to chemoradiotherapy, SCRT seems to result in slightly lower response rates. After chemoradiotherapy, a complete response is reported in 15–27% of patients with cT3–T4 rectal cancer.[111,112] Two population-based studies on data from the NCR showed that SCRT combined with a waiting interval of 4–5 weeks resulted in fewer complete (6.4–9.3% vs. 16.2–17.5%) and good (yT0–1) (11.0–17.5% vs. 20.6–22.6%) responses than chemoradiotherapy.[113,114] The Stockholm III trial reported significantly increased tumour regression rates in patients with a delayed interval (median 6.4 weeks) until surgery after SCRT, with a complete response in 11.4% of patients.[115] Response evaluation at 4–5 weeks after SCRT may be too early to evaluate the tumour response adequately. Furthermore, tumour response rates seem correlated with the initial tumour stage. In a pooled analyses by Maas et al. that included 3105 patients who underwent chemoradiotherapy, complete responses were observed in 58% of cT1, 28% of cT2, and 16% of cT3 tumours.[112] Most studies were performed in locally advanced rectal cancer and the response rates of chemoradiotherapy and SCRT in early stage tumours (cT1–3bN0) are relatively unexplored. The currently ongoing STAR-TREC phase II/III study (NCT02945566) is investigating the effects of chemoradiotherapy and SCRT on early stage rectal cancer and may provide valuable insights on the non-operative management of rectal cancer patients.[116]

Earlier studies have shown that elderly patients treated with chemoradiotherapy achieved comparable response rates, disease-free survival, and tolerability in relation to their younger counterparts.[6] Data from the ACCORD12/PRODIGE2 phase 3 trial by François et al. reported that elderly patients treated with chemoradiotherapy had increased rates of grade 3 and 4 toxicity (25.6% vs. 15.8%) when compared to younger patients.[117] Still, 95.8% of the elderly successfully completed chemoradiotherapy.[117] While literature is controversial, SCRT seems associated with reduced toxicity. The preliminary results of the randomised NACRE study (NCT02551237) showed that all patients above 75 years old completed SCRT, while 14% did not complete chemoradiotherapy.[118] The number of serious adverse events (13 vs. 7 events) was also higher in patients treated with chemoradiotherapy.[118] A randomised trial by Bujko et al. reported less acute toxicity in patients treated with SCRT when compared to chemoradiotherapy (3.2% vs. 18.2%), while late toxicity was comparable (7.1% vs. 10.1%).[119] Similar results were observed in a later meta-analysis.[120]

When tolerated, chemoradiotherapy seems to be the most effective treatment for achieving local control in patients unable to undergo TME surgery.[4,6] SCRT has a shorter treatment duration and seems to result in lower toxicity, which may be preferable in frail or comorbid patients unfit for chemoradiotherapy or for whom treatment compliance might be a potential issue.

Outcomes of other EBRT schedules (e.g., 13 × 3 Gy) on local control rates are scarce and unexplored. In the Lyon R90-01 trial, 29% of patients with cT2–T3 rectal cancer who were treated with 13 × 3 Gy EBRT achieved a complete or near-complete response after a waiting interval of 6–8 weeks.[121] These alternative schedules are currently under investigation, mostly in combination with dose escalating endoluminal radiotherapeutic boosts.[42,122]

Dose escalation of radiotherapy

Radiotherapeutic dose-response analyses have showed that tumour responses can be improved by increasing the radiotherapy dose.[94] An earlier analysis by Appelt et al. showed that 72 Gy was needed to achieve a major tumour response in 50% of cT3–T4 rectal tumours.[94] Increased radiotherapy doses can be delivered by endoluminal radiotherapeutic modalities, such as contact X-ray brachytherapy (CXB) or high-dose rate endorectal brachytherapy (HDR-BT). Endoluminal radiotherapy has the ability to deliver high doses of radiotherapy directly to the tumour with a rapid dose fall-off, thus sparing normal surrounding tissue. If technically eligible, definitive dose escalations of radiotherapy are an attractive modality in elderly and frail patients unable to undergo TME surgery to maximise local control. These endoluminal interventions are only available in selected centres and should be surveilled by dedicated multidisciplinary teams.

Contact X-ray brachytherapy

The use of CXB is mainly described as a beneficial dose-escalating modality in patients unable to undergo surgery. Sun Myint et al. and Gérard et al. have described the use of CXB in rectal cancer patients as monotherapy (in early and small tumours), as an additional boost to EBRT, or as adjuvant treatment after local excision.[97,123–125]

CXB as an additional boost to EBRT has been explored in multiple studies. In the Lyon R96-02 trial, a significant improvement in clinical complete response rates (24% vs. 2%) and pathological complete and near-complete response rates (57% vs. 34%) were observed in patients treated with an additional CXB boost after EBRT (13 × 3 Gy) when compared to EBRT (13 × 3 Gy) alone.[122] A multicentre phase II study by Gérard et al. showed that EBRT combined with a CXB boost resulted in complete and near-complete response rates of 95% in cT2–T3 rectal cancer.[40] Another study by the same group described complete and near-complete response rates after CXB and EBRT of 33–88%.[126] In a cohort described by Sun Myint et al., patients unsuitable for or refusing surgery achieved a complete response in 64–72%, of which 86–87% were sustained after a median follow-up of 2.5–2.7 years.[39,123] An additional 21–23% of patients with a clinical incomplete response had pathological complete responses after resection.[39,123] A recent study by Custers et al. reported on local control rates in older and inoperable rectal cancer patients who were treated with CXB after different schedules of radiotherapy (79%) or local excision (21%).[41] The study showed that local control was achieved in 13 out of 19 (68.4%) patients, while 9 out of 19 (47.4%) patients had a clinical complete response.[41] The 1-year local progression-free survival was 78%, while the overall 1-year survival was 100%.[41] The quality of life was only slightly impaired and successfully returned to baseline after 6 months.[41] These results suggest that, if technically possible, CXB is an effective option in the elderly and frail to improve local control. Most studies were not randomised and did not include locally advanced tumours. The currently ongoing randomised OPERA trial (NCT02505750) and the OPAXX study will likely give more insights in the value of CXB in more advanced rectal tumours.[127]

The reported toxicity rates of CXB are relatively low.[39,123,128] In the Lyon R96-02 trial, early and late grade III toxicity involved 9% and 11% of patients, respectively.[40] According to other studies, toxicity mostly included rectal bleeding. Grade I-III rectal bleeding occurred in 24–40% of patients, while grade III bleeding was described in <5%.[39,125] Rectal ulceration was described in 30% of patients, which was most often asymptomatic and usually healed within 3–6 months.[39,125] Functional outcomes after CXB are reported to be relatively good, with 65% of patients having no LARS complaints.[40,129]

High-dose rate endorectal brachytherapy

An alternative endoluminal dose-escalating modality to improve local control is HDR-BT.[130] Vuong et al. showed that a preoperative HDR-BT boost resulted in improved tumour response rates.[131] The study reported pT0N0-1 rates of 32%, while an additional 38% of patients only had small microscopic residual disease.[131] The beneficial effects of HDR-BT on the tumour response has been investigated in multiple other studies. In the phase I HERBERT study, 38 patients (median age of 83 years) were treated with 13 × 3 Gy EBRT followed by HDR-BT (3 fractions of 5–8 Gy).[42] A clinical tumour response was observed in 29 out of 33 patients (87.9%), of which 20 patients achieved a complete response (60.6%).[42] The 1-year local progression-free survival was 64% and the 1-year overall survival was 82%.[42] Overall grade 3/4 toxicity were observed in 33% and 4%, while acute and late grade 2/3 proctitis were observed in 81.6% and 88% of patients.[42] The authors concluded that HDR-BT provided good tumour responses, but had a considerable risk for toxicity in the elderly and frail. In a study by Garant et al., elderly patients (median age of 82 years) with mainly cT2–T3 tumours achieved a clinical complete response in 86.2% after 40 Gy of EBRT (in 16 fractions) followed by HDR-BT (3 fractions of 10 Gy).[132] The 2-year local control rate was 71.5%.[132] In a randomised study by Jakobsen et al., cT3–T4 rectal cancer patients were treated with chemoradiotherapy followed by HDR-BT (2 fractions of 5 Gy), which resulted in a complete or near-complete response rate of 44%.[133] Toxicity mostly included diarrhea, skin problems and proctitis, but was comparable to those treated with chemoradiotherapy alone.[133] Appelt et al. described that 40 out of 51 (78.4%) patients with cT1–3ab rectal cancer achieved a complete response after chemoradiotherapy followed by a 5 Gy boost of HDR-BT, with 2-year local control rates of 58%.[134] These patients had relatively good functional outcomes, as 69% of patients did not report faecal incontinence.[134] Based on these results, HDR-BT may be a useful modality to improve tumour response and optimise local control. Currently, the randomised HERBERT-II study (Netherlands Trial Register: NL7795) is investigating the additional effect of HDR-BT (3 × 7 Gy) after EBRT (13 × 3 Gy) in elderly and frail patients unable to undergo surgery.

Local excision

Early rectal cancer can be treated with local excision with relatively low risks for morbidity and mortality, and relatively good functional outcomes.[4,135] Over the years, the indication for local excision has been broadened. However, long-term results reported local recurrence rates after a primary local excision of pT2 tumours up to 37%.[136] In the CARTS-study, patients with cT1-3N0 rectal cancer underwent chemoradiotherapy followed by local excision in case of residual ycT0-2N0 disease.[43] The study reported successful organ-preservation in 64% of patients with residual ycT0-2N0 disease, and in 55% of all patients that started with chemoradiotherapy.[43] A meta-analysis that investigated chemoradiotherapy followed by local excision in cT2–T3 rectal cancer showed adequate local control rates, with no recurrences in patients with a pathological complete response, while the recurrence rates were 2%, 7%, and 12% in patients with ypT1, ypT2, and ypT3 disease, respectively.[137] Additionally, several other studies reported comparable local control rates after local excision in patients after chemoradiotherapy.[137–139] However, local excision preceded by neoadjuvant treatment seems to result in an increased risk for wound infections, wound dehiscence and severe functional bowel complaints.[138,140,141] In the long-term follow-up of the CARTS-study, major LARS was observed in 50% of patients.[140] Local excision may be reasonable to treat small residual disease after chemoradiotherapy or SCRT in the elderly and frail unable to undergo completion TME surgery.[142] Nevertheless, selecting the patients that benefit most seems challenging. The outcomes in locally advanced rectal cancer are unknown. More insights will probably be gained by the currently ongoing OPAXX study, which randomises patients with more advanced rectal cancer and a near complete response between CXB and the extension of the waiting interval followed by a local excision.[127]

RESPONSE EVALUATION AND FOLLOW-UP

Response evaluation

Since the primary aim in treating elderly and frail rectal cancer patients unable to undergo TME surgery is to achieve local control of disease, response evaluation could be relevant to consider additional local treatment options, such as endoluminal radiotherapy or local excision. Earlier studies by Maas et al., showed that digital rectal examination, magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI), and endoscopy is the most accurate combination to evaluate tumour response.[143] MRI-DWI is a suitable imaging technique to identify good responders, with high positive predictive values up to 91% for tumour downstaging and downsizing confined to the rectal wall.[144] MRI-DWI seems to be able to identify potential candidates for additional endoluminal radiotherapy or local excision. In these patients, an endoscopy performed by a dedicated gastroenterologist can further characterise the tumour. The endoscopy is preferably performed in the presence of a dedicated surgical oncologist and radiation oncologist to identify the eligibility for local treatment options.

The current standard between the end of radiotherapy and response evaluation is 6–8 weeks, which is also considered as a beneficial period to select patients for additional local treatment options. It has been shown that the tumour response increases over time. Earlier studies have reported ongoing tumour responses up to 22–26 weeks after finishing EBRT.[145–147] In some cases, it might, consequently, be necessary to lengthen the interval before considering additional local treatment modalities to allow further tumour shrinkage. In these patients, a re-assessment of the tumour response at a later interval may be relevant.

In elderly and frail patients who are unable to undergo TME surgery, response evaluations should not be performed routinely, but should be adapted to the individual patient, treatment goals, and the relevance for considering additional treatment options.

Follow-up

The follow-up of elderly and frail patients unable to undergo TME surgery should be tailored and patient-centred. The follow-up will probably have different goals than clinicians are used to in the follow-up of young and fit patients. Especially in those in whom relapsing disease would have no clinical consequences, the oncological benefits of the follow-up are negligible. However, the follow-up in elderly and frail patients should be considered as an important period to monitor the patient's health status and prevent functional decline. Clinicians should realise that, although the treatment might have finished, the care for these patients never stops.

Many patients experience a decline in their level of independence after intensive treatment.[27–30] Yet, while most patients are able to return to baseline levels within 3–6 months, they face a long-term risk for functional decline.[27–30] The follow-up in these patients should aim at preventing functional decline and loss of independence, and at monitoring the consequences of treatment or tumour progression. A personalised follow-up plan is required, considering the benefits of the early detection of relapsing disease or functional decline, versus the burden of follow-up.

Apart from the treating physician, the general practitioner has a crucial role during the follow-up of these patients. A study showed that most patients preferred contacting the general practitioner to discuss problems related to nutrition, physical condition, and fatigue, which are common contributors to the onset and progression of functional decline.[148] On the other hand, patients were inclined to discuss disease-specific complaints with their treating physician.[148] Hence, effective communication and alignment of care between the treating physician and the general practitioner is required. This has been supported by a Dutch study among 140 older colorectal cancer patients (≥70 years). The study showed that a standardised transmission of communication between the treating physician and the general practitioner, combined with regular follow-up by the general practitioner resulted in improved health, reduced frailty, and increased quality of life.[149] This supports that elderly and frail patients require close monitoring after treatment to detect early signs of functional decline. Promising shared-care models between the general practitioner, the geriatrician, and the treating physician have been described to improve outcomes during and after treatment.[149–151]

A geriatric assessment is not only valuable to personalise treatment, but also to tailor follow-up with targeted interventions.[53] In a randomised study, in which elderly patients (mean age 82.5 years) underwent follow-up based on a geriatric assessment, reduced 3-year mortality rates and higher patient satisfaction were observed.[152] Rehabilitation programmes improve treatment-induced functional decline and long-term side effects caused by chemotherapy and radiotherapy (e.g., fatigue, reduced physical condition, weight changes and cognitive deterioration), resulting in improved quality of life.[153–155] This may help patients to improve their health status, return to their baseline level of functioning, and prevent functional decline.

MULTIDISCIPLINARY CLINICAL CARE PATHWAY

A practical suggestion of a multidisciplinary care pathway

Based on a literature review, the authors of this study have successfully implemented a multidisciplinary care pathway in the Catharina Hospital (Eindhoven, The Netherlands) for elderly and frail rectal cancer patients unable to undergo TME surgery. The clinical care pathway was developed in close collaboration with an advisory board of rectal cancer patients to improve personalised care within the multidisciplinary clinical care pathway.

All rectal cancer patients considered frail by the treating physician enter the clinical care pathway. First of all, the patient is discussed and the diagnostic work-up is evaluated by the multidisciplinary team. The expertise of the multidisciplinary team treating these patients is ensured by the attendance of a dedicated surgical oncologist, medical oncologist, radiation oncologist, and a geriatrician, all with special interest on the non-operative management of elderly and frail rectal cancer patients.

After the multidisciplinary team meeting, the patient is admitted in day care and evaluated by the members of the multidisciplinary team. In some cases, the anaesthesiologist is also part of the multidisciplinary team to assess the tolerability of surgery and anaesthesia, if applicable. After each individual physician has assessed and informed the patient about the benefits and risks of the treatment options, a second multidisciplinary team meeting is organised. The patient's health status, preferences, and treatment goals are discussed by the concerning physicians. The outcomes of the comprehensive geriatric assessment have a central role within the multidisciplinary discussion. The multidisciplinary team conscientiously composes a personalised non-operative treatment advice, aiming to provide local control of disease, prevent the onset of debilitating symptoms, prolong survival, and maintain functional independence and quality of life. The personalised treatment advice may vary from an intensive trajectory of systemic therapy, followed by chemoradiotherapy, and endoluminal brachytherapy in fairly fit patients who refuse surgery, to short-course radiotherapy schedules or no treatment at all in the frailest patients. The treatment advice, including the benefits and risks, is communicated with the patient and their relatives, who are actively involved in the decision-making process. After the treating physician and the patient have weighed the benefits and risks, a definitive treatment plan is proposed.

After treatment has finished, response evaluation and follow-up are adapted to the individual patient, treatment goals, and the relevance for considering additional treatment options. Figure 1 presents a flowchart of the multidisciplinary clinical care pathway.

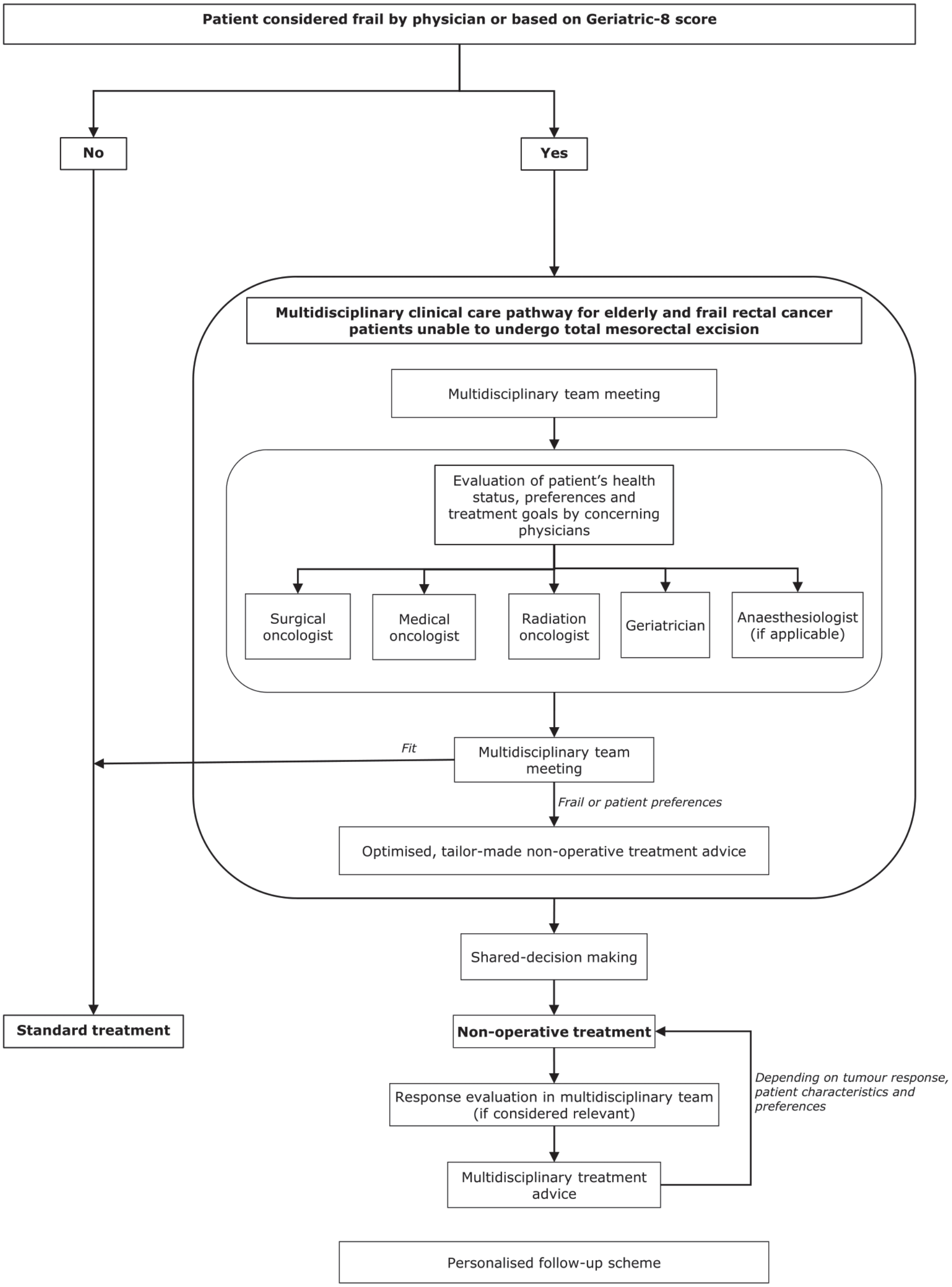

Figure 1. Flowchart of the multidisciplinary clinical care pathway for elderly and frail rectal cancer patients that has been successfully implemented by the authors of the study.

Future perspectives

Limited knowledge is available on the outcomes of the non-operative management of elderly and frail rectal cancer patients. The lack of data impedes counselling patients with a doubtful health status or unwillingness to undergo TME surgery. Clinicians are unable to provide adequate information about short-term and long-term outcomes. Prospective studies evaluating the treatment and outcomes of elderly and frail patients unable to undergo TME surgery are warranted to improve the decision-making process.

The authors of the present study have initiated a currently ongoing single-centre prospective observational cohort study, named the RESORT study (A Prospective Registry of the Non-Invasive Multimodality Treatment in Inoperable Rectal Cancer Patients: Evaluating the Current Treatment Strategies in Rectal Cancer Patients Unable to Undergo TME Surgery). The aim of the study is to evaluate the decision-making process, the treatment, and the outcomes of elderly and frail rectal cancer patients unable to undergo TME surgery. Patients unable to undergo TME surgery and treated in the multidisciplinary clinical care pathway in the Catharina Hospital are eligible for inclusion. After informed consent is obtained, the study prospectively collects data during a follow-up of 3 years. The data collection includes information regarding patient characteristics, diagnosis, treatment, local control of disease, survival, quality of life, and functional outcomes (Table 2).

Table 2. Overview of the variables for data collection in the RESORT-study.

Variable group	Variables	
Patient characteristics	Age Sex Weight, length, BMI Living situation	Medical history ECOG Performance status Comorbidities
Primary diagnosis	Clinical complaints Tumour location Tumour size	TNM stage Histology
Geriatric assessment	Geriatric scoring tools (e.g. Katz-ADL, Lawton and Brody-IADL, MNA-SF, 6-CIT, Mini-Cog, 4-Meter Gait Speed) Clinical Frailty Score Treatment goals and preferences	
Multidisciplinary evaluation	Considerations of the multidisciplinary team	Treatment advice
Treatment	Treatment modalities Treatment schedules	Compliance rates Adverse effects/complications
Response evaluation	Tumour response Tumour characteristics	Multidisciplinary advice on response evaluation
Follow-up	Clinical complaints Local control rates Relapsing disease (local/distant)	Survival outcomes Date of death (if applicable) Cause of death (if applicable)
Quality of life and functional outcomes[2]	EORTC[1] QLQ-C30 EORTC QLQ-CR29 EQ-5D-5L	Katz-ADL Lawton and Brody IADL

[1]EORTC, European Organisation for Research and Treatment of Cancer

[2]At baseline and after 6 months, 12 months, 24 months, and 36 months after finishing treatment)

CONCLUSION

In elderly and frail rectal cancer patients unable to undergo TME surgery, non-operative treatment strategies may offer a viable alternative, aiming to obtain local control of the primary tumour. Elderly and frail patients often prioritise quality of life and maintaining independence over oncological outcomes. The challenge in treating the elderly and frail is to maximise the effectiveness of treatment by optimising the balance between the probability for maximal local control, the patient's preferences, and the burden of treatment. Personalisation of care is of utmost importance and requires a patient-centred approach, in which the patient is actively involved. A comprehensive geriatric assessment is considered as a crucial element and should have a central role in the multidisciplinary discussion. Response evaluation and follow-up should be adapted to the individual patient, treatment goals, and clinical relevance as well.

Although an increasing number of elderly and frail patients are treated non-operatively, limited knowledge is available on the optimal non-operative management of this patient group. Elderly and frail patients unable to undergo TME surgery should be treated in specific clinical care pathways by dedicated multidisciplinary teams with expertise on the non-operative management of these patients. Based on the literature review, we provided a practical suggestion of a successfully implemented clinical care pathway, in which patients are assessed and discussed multidisciplinary to personalise treatment. Future studies regarding the treatment and outcomes of the elderly and frail unable to undergo TME surgery are needed to improve decision making. The authors of this study have initiated a currently ongoing prospective observational cohort study (RESORT study) to investigate the outcomes of a multimodal and patient-centred non-operative treatment approach for elderly and frail rectal cancer patients unable to undergo TME surgery. The study will provide important data regarding the decision-making process, treatment, and outcomes.

This narrative review provides a robust literature review and a practical suggestion for a multidisciplinary clinical care pathway in order to assist rectal cancer experts in improving and personalising the care for elderly and frail rectal cancer patients.

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PART III

Summary, general discussion,
future perspectives,
and impact paragraph

CHAPTER 12

Summary, general discussion, and future perspectives

SUMMARY

The aims of this thesis were: I) to gain insights into the treatment outcomes of elderly patients with colorectal cancer, in order to improve patient selection and counselling, and thereby, improve shared decision-making; II) to explore improvements in the care for elderly patients with colorectal cancer. The introduction (**chapter 1)** provided an overview of the available evidence and current status with regard to the aims of the thesis.

Part I: Treatment outcomes of elderly patients with colorectal cancer

Chapter 2 evaluated whether the postoperative outcomes of elderly patients (≥75 years) with colorectal cancer have improved over the years, and compared the outcomes in elderly patients to those of younger patients (<75 years) in a single-centre, retrospective cohort. Among 1037 colon cancer and 981 rectal cancer patients, the 30-day and 90-day mortality rates of elderly patients improved from 5.8% and 9.1%, respectively, in the period 2006–2012, to 1.2% and 4.6%, respectively, in the period 2013–2017. In addition, the 1-year relative survival rates in the elderly improved from 88.4% in the period 2006–2012 to 94.3% in the period 2013–2017. In the most recent time period, the 30-day and 90-day mortality rates, and the 1-year relative survival rates were no longer different in elderly when compared to younger patients.

Chapter 3 evaluated the developments in postoperative outcomes in a single-centre, retrospective cohort of elderly patients (≥75 years) with clinical T4 rectal cancer (cT4RC) and locally recurrent rectal cancer (LRRC) over time, and compared the outcomes in the elderly to those of younger patients (<75 years). Elderly patients suffered more often from postoperative complications when compared to younger patients (cT4RC: 76.4% vs. 61.7%, $p = 0.02$; LRRC: 96.2% vs. 77.1%, $p = 0.001$), mostly due to non-surgical complications. The 30-day mortality rate of elderly patients improved over time and was no longer significantly different between both age groups in the most recent time period (2012–2017) (cT4RC: 3.1% in ≥75 years vs. 1.5% in <75 years, $p = 0.46$; LRRC: 0.0% in ≥75 years vs. 1.4% in <75 years, $p > 0.99$). However, the 90-day (cT4RC: 9.4% in ≥75 years vs. 2.1% in <75 years, $p = 0.06$; LRRC: 9.1% in ≥75 years vs. 2.2% in <75 years, $p = 0.09$) and 1-year (cT4RC: 28.1% in ≥75 years vs. 6.2% in <75 years, $p = 0.001$; LRRC: 27.3% in ≥75 years vs. 13.8% in <75 years, $p = 0.06$) mortality rates were still worse in the elderly population. About one in four elderly with cT4RC and LRRC died in the first postoperative year, mostly due to treatment-induced or other non-cancer related causes after the period of hospitalisation. On the contrary, relapsing disease was the main cause of death in younger patients.

Chapter 4 evaluated the prevalence of functional bowel complaints and the impact on quality of life in elderly patients (≥70 years) after colorectal cancer surgery in a large, regional, multicentre cohort study. The LARS score was used to assess functional bowel complaints, and the EORTC QLQ-C30 and QLQ-CR29 were used to assess quality of life. Elderly patients reported major LARS in 40.6% after rectal cancer surgery and in 22.2% after colon cancer surgery, while younger patients (<70 years) reported major LARS in 57.3% after rectal cancer surgery (p = 0.001) and in 20.4% after colon cancer surgery (p = 0.41). Patients who suffered from major LARS reported significantly worse quality of life outcomes on almost all domains of the EORTC QLQ-C30 and EORTC QLQ-CR29.

Chapter 5 investigated the diverting ostomy-related outcomes in elderly patients (≥70 years) with more advanced rectal cancer in a single-centre, retrospective cohort. The majority (91.5%) of elderly patients with rectal cancer underwent primary or secondary ostomy creation. A total of 72.5% underwent diverting ostomy reversal after a median time of 3.2 (IQR 2.3–5.0) months. Non-reversal was mostly related to relapsing disease. Ostomy reversal was associated with no or minor complications in 84.0% of patients (95%-CI 75.3–90.6%). During follow-up, 15.0% of patients underwent ostomy recreation. The ostomy-free survival was 69.5% (95%-CI 61.6–76.6%) at 1 year after primary surgery, and 65.8% (95%-CI 57.8–73.2%) after the median follow-up of 3.8 years.

Part II: Towards improved care in elderly patients with colorectal cancer

Chapter 6 comprised of an overview of the developments that have been made over the years to improve the care of elderly patients with colorectal cancer, and which elements require additional attention when treating the elderly. Several developments in the treatment of elderly patients have probably contributed to the improved outcomes, including the implementation of minimal invasive surgery, improved perioperative care and enhanced recovery protocols, increased expertise due to colorectal differentiation, and high-volume care. When treating the elderly, attention should be paid for adequate staging protocols, frailty screening and assessment, preoperative optimisation of the patient's health status, a standardised evaluation by a multidisciplinary team including a geriatrician, and specific protocols to deal with problems like acute bowel obstruction.

Chapter 7 investigated the postoperative outcomes of a single-centre, retrospective cohort of elderly patients (≥70 years) with colorectal cancer who were screened positive for frailty, and evaluated the changes in treatment after frailty screening and geriatric assessment. A total of 43.5% of patients were screened positive for frailty (G8 ≤14) by the Geriatric-8 (G8) score. In those with a G8 ≤14 who underwent geriatric assessment, frailty and intermediate frailty were observed in 28.6% and 50.0%, respectively. Based on geriatric assessment, the oncological treatment plan was altered to a less intensive regimen in 8.9% of patients due to frailty, and to a more intensive regimen in 1.8%. Surgery was performed in 87.8% of patients with G8 ≤14 and 96.9% of patients with G8 >14 (p = 0.03). The overall postoperative complication (46.2% vs. 47.3%, p = 0.89) and Clavien-Dindo ≥III (13.8% vs. 18.3%, p = 0.46) rates did not differ between patients with G8 ≤14 and G8 >14. Postoperative delirium occurred in 7.7% of patients with G8 ≤14 and 1.1% of patients with G8 >14 (p = 0.08). No differences were observed between patients with G8 ≤14 and G8 >14 with regard to 30-day mortality rates (1.1% vs. 1.5%, p >0.99), and 1-year and 2-year overall survival rates (log-rank, p = 0.26).

Chapter 8 presented a prospective, regional, multicentre cohort study to investigate the outcomes of continuous wound infusion (CWI) of local analgesics in a strictly adhered to enhanced recovery protocol after colorectal cancer surgery. Within the already existing ERAS protocols, the use of CWI was implemented in VieCuri Medical Centre since May 2019 and in the Catharina Hospital since March 2020. On the day of surgery, 61.5% (95%-CI 52.6–69.9%) of patients treated with CWI used opioids postoperatively, which decreased to 21.5% (95%-CI 14.8–29.6%), 20.8% (95%-CI 14.2–28.8%), and 13.8% (95%-CI 8.4–21.0%) on postoperative day 1, 2, and 3, respectively. The median pain scores were <4 on all postoperative days. A postoperative delirium was observed in 0.8% of patients. The median time until the first passage of stool was 1.0 (IQR 1.0–2.0) day and the median length of hospital stay was 3.0 (IQR 2.0–5.0) days.

Chapter 9 presented an evaluation of the implementation of the colorectal ERAS protocol in a single-centre, retrospective cohort of rectal cancer patients who underwent TME surgery. In addition, ERAS related outcomes and compliance were compared between rectal cancer patients who underwent TME surgery, and LARC and LRRC patients who underwent beyond TME surgery. Specific modifications that are warranted to suit the complexity and needs of patients who undergo beyond TME surgery for LARC and LRRC were identified. In rectal cancer patients who underwent TME surgery, the mean overall compliance to ERAS improved from 54.7% before ERAS implementation, to 85.6% after ERAS implementation (p < 0.001). This resulted in significantly shorter median times until the first passage of stool (2.0 vs. 1.0 days, $p = 0.04$) and discharge (4.0 vs. 3.0 days, $p < 0.001$), without compromising postoperative complications (52.1% vs. 37.3%, $p = 0.077$). In patients with LARC and LRRC who underwent beyond TME surgery, compliance to ERAS was significantly less when compared to the TME group before and after ERAS implementation (44.4% vs. 54.7% vs. 85.6%, $p < 0.001$), in particular for the postoperative period (25.4% vs. 42.5% vs. 75.4%, $p < 0.001$). In addition, longer median times until passage of stool (3.0 days) and discharge (9.0 days), and increased major postoperative complication rates (40.0% in bTME vs. 21.9% in pre-ERAS TME vs. 12.2% in post-ERAS TME, $p < 0.001$) were observed in the beyond TME group. Based on compliance rates and outcomes in LARC and LRRC patients, a tailored, multimodal ERAS protocol with specific modifications is warranted for LARC and LRRC patients undergoing beyond TME surgery, which is currently being developed in the Catharina Hospital Eindhoven.

Chapter 10 presented a literature overview on the Dutch perspectives and recent developments of organ preservation in the treatment of rectal cancer. Due to the promising outcomes in recent studies, there is a growing interest in organ preserving treatment approaches among both patients and clinicians. Currently, several ongoing studies investigate the value of different organ preserving treatment modalities to further improve tumour responses and increase the chance for successful organ preservation in early and advanced rectal cancer cases. Contact X-ray brachytherapy (CXB) is a promising treatment modality, and seems especially relevant for elderly and frail patients unable or refusing to undergo TME surgery.

Chapter 11 discussed a multidisciplinary treatment approach to personalise the non-operative management of elderly and frail patients unable to undergo TME surgery. Patients unable to undergo TME surgery are at risk of undertreatment. Advancements in non-operative treatment modalities (e.g. systemic chemotherapy, (chemo)radiotherapy, endoluminal radiotherapy, and local excision) may provide alternative treatment options if surgery is not possible, aiming for optimal local control of the primary tumour. Due to the complexity of treating the elderly and frail, dedicated multidisciplinary clinical care pathways are warranted to personalise the non-operative management of these patients. This chapter also provided a short overview of the currently ongoing RESORT study, a prospective observational cohort study. The RESORT study aims to gain insights into the decision-making, treatment, and outcomes of elderly and frail rectal cancer patients who are unable to undergo surgery.

GENERAL DISCUSSION

The elderly population is a heterogeneous group, consisting of patients with a health status varying between fit and frail. Shared-decision making is a central element when treating the elderly. Increased knowledge on the challenges and outcomes of different treatment modalities is required to adequately select and counsel patients, and to personalise treatment. In this thesis, challenges in the treatment of colorectal cancer in the elderly have been evaluated with regard to patient selection and patient counselling, perioperative care, and the non-operative management of rectal cancer.

Patient selection

Patient selection is the key to optimise the treatment and outcomes of elderly patients. Although the treatment of elderly colorectal cancer patients is multidisciplinary, surgery is still considered to be the cornerstone of the curative treatment. However, colorectal cancer resections have their drawbacks. Previous studies have reported increased rates of morbidity and mortality in the elderly.[1,2] As a result, clinicians are often reluctant to offer elderly patients curative and guideline-based treatment regimens, enlarging the risk of undertreatment.[3–5] Nevertheless, the earlier reported outcomes no longer reflect the actual daily practice.[6,7] In accordance to other recent studies, the findings of **chapter 2** demonstrated significant improvements in the 30-day and 90-day mortality rates, and the one-year relative survival rates of older colorectal cancer patients.[8–10] Over the years, the postoperative survival gap between elderly and younger patients has been faded, and elderly patients considered fit for surgery benefit as much from curative treatment as younger patients.[8] Elderly patients should not be withheld curative treatment based on age or comorbidities alone. This was supported by a recent Dutch population-based study, which demonstrated that elderly patients considered eligible for curative treatment clearly benefitted from guideline-based treatment regimens.[5]

In contrast to non-advanced colorectal cancer, the treatment of more advanced rectal cancer often consists of intensive neoadjuvant treatment regimens, followed by extended multivisceral resections. As a result, the treatment of locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) is associated with high rates of morbidity and mortality, in particular in the elderly.[1,11,12] Although **chapter 3** presented that the 30-day mortality rates in elderly patients with cT4 rectal cancer (cT4RC) and LRRC have improved over time, the 90-day and 1-year mortality rates continued to be worse when compared to younger patients. About one in four elderly patients with cT4RC and LRRC died in the first postoperative year, mostly in the period after hospitalisation due to treatment-induced deterioration or non-cancer related causes, rather than disease recurrence. It has been hypothesised that the impact of intensive neoadjuvant treatment, extended multivisceral surgery, and hospitalisation may exceed the capacity of homeostatic mechanisms, inducing a gradual decline in the patient's health status.[13] Although these mechanisms are mainly expected in more frail patients, these may explain the increased morbidity and mortality observed in elderly patients with cT4RC and LRRC. A recent population-based study among colorectal cancer patients treated between 2007–2016 in four Northern-European countries supported the finding that excess mortality in the elderly increased in more advanced disease stages.[14] However, no time-trend analyses were performed to investigate whether improvements have occurred over the years.[14] The worse outcomes in elderly patients with more advanced disease stages underline the importance of finding a good balance between undertreatment and overtreatment, emphasising the need for adequate patient selection. Special attention and care is needed in the treatment of elderly patients, and individual differences in health status and preferences need to be assessed multidisciplinary. Programmes to optimise the patient's health status, frailty assessment, and referral to expert centres may be of added value to obtain optimal treatment.[5]

The key elements that should be considered to deliver personalised care in the elderly are functional outcomes, quality of life, and maintaining independence.[15–17] Elderly patients need to be informed well about the decisions that can be made. After colorectal surgery, poor functional outcomes are frequently observed, which may impair quality of life. After rectal cancer surgery, urogenital dysfunction is reported in 30-60% of patients, whereas about 40% of patients develop severe functional bowel complaints.[18,19] More recent studies showed that functional bowel complaints also occurred after colon cancer surgery in about 20% of patients.[20,21] The results of **chapter 4** indicate that elderly patients are not at increased risk to develop severe functional bowel complaints after colorectal cancer surgery when compared to younger patients. Yet, almost half of elderly rectal cancer and one in five elderly colon cancer patients developed major LARS, which severely impaired quality of life. Elderly patients, in particular those with rectal cancer, should be informed about the substantial risk and impact of functional bowel complaints when the benefits and risks of a restorative versus a non-restorative procedure are weighed. Risk stratification tools, such as the POLARS score, may be beneficial during decision-making to identify patients at risk and set the right expectations.[22]

The risk of anastomotic leakage and ostomy-related outcomes should also be considered. Anastomotic leakages are observed in 8-20% of patients after colorectal surgery and may have devastating consequences.[23–25] In the elderly, an anastomotic leakage is associated with mortality rates up to 30%.[23,25] While the value of a diverting ostomy on preventing the absolute risk of an anastomotic leakage is still unclear, a diverting ostomy seems to reduce the morbidity if an anastomotic leakage occurs.[26,27] Nevertheless, a diverting ostomy also has its disadvantages. There is a risk of ostomy-related complications, such as high-output ostomy, ostomy prolapse, and parastomal herniation.[28,29] In addition, there is a risk of non-reversal, leading to an unintended permanent diverting ostomy.[7,30–32] A more selective strategy, aiming to perform primary diversion merely in those who benefit most from it, is often suggested.[32,33] A diverting ostomy may therefore be beneficial in elderly patients with more advanced rectal cancer who prefer a restorative procedure after neoadjuvant treatment.[23,25] The study in **chapter 5** reported a diverting ostomy reversal rate of 72.5% in the elderly, which was almost comparable to the reversal rates in patients of all ages in other studies.[34,35] Nevertheless, in addition to the risk of non-reversal, 15% of patients underwent ostomy recreation over time, resulting in approximately one third of patients who ended up with an ostomy during follow-up. On an individual basis, the risk and morbidity of anastomotic leakage, functional bowel complaints, the need for a secondary procedure for ostomy reversal, the potential burden of non-reversal, and the risk of ostomy recreation should be balanced against a non-restorative procedure.

Frailty screening and assessment have an important role in the treatment of elderly patients.[36,37] Frailty is associated with increased postoperative complications, dependency, hospitalisation, institutionalisation, reduced quality of life, and worse survival.[13,38] By a comprehensive evaluation of multiple domains, the comprehensive geriatric assessment (CGA) can help to stratify patients at risk of poor recovery, and apply strategies to optimise the patient's health status.[39] The CGA can also clarify the patient's preferences and treatment goals. Since a CGA is time-consuming, frailty screening is often performed. Frailty screening helps to identify patients at risk of frailty and is important in both the elective and emergent setting. In addition, it provides important information on modifiable risk factors (e.g. nutritional status, functional status, comorbidities) that can be addressed with targeted preoperative interventions.[37] There is growing evidence that identifying patients at risk of poor recovery, and applying adequate preoperative strategies to optimise the patient's health status can improve the outcomes of geriatric patients.[40,41]

Rather than age or comorbidities, the decision-making should be driven on frailty, patient preferences, and treatment goals.[42] If no frailty is suspected, elderly patients should be offered standard treatment. If patients are screened positive for frailty, there might be an increased risk of poor postoperative recovery, and a CGA should be considered. Earlier studies have shown that patients screened positive for frailty were at increased risk of postoperative complications and one-year mortality.[43–46] However, the findings of **chapter 7** indicated that, within current clinical practice, elderly patients screened positive for frailty can safely undergo surgery if deemed eligible, without increased morbidity and mortality. Nevertheless, it is beyond dispute that extra attention is needed when selecting and treating these patients. The geriatrician is an indispensable member to include in the multidisciplinary team. In a recent Dutch study, the implementation of a multidisciplinary onco-geriatric approach for frail patients improved patient selection and prehabilitation, and resulted in comparable postoperative outcomes between frail and non-frail patients.[47] Close alignment of care and effective communication between the geriatrician, the surgeon, and the rest of the multidisciplinary team is crucial to optimise decision-making and perioperative care. A select group of the most frail patients are still at high risks of poor outcomes, even after they would follow multidisciplinary programmes to optimise health, treatment, and outcomes. It is crucial to identify patients who are unable to undergo surgery, and in whom a multidisciplinary onco-geriatric approach may support a personalised non-operative treatment regimen.

Perioperative care

In addition to better patient selection and more attention to optimise the patient's preoperative health status, the use of minimal invasive techniques and the introduction of Enhanced Recovery After Surgery (ERAS) protocols have probably contributed strongly to the improved outcomes.[48,49] ERAS protocols aim to optimise elements in the perioperative care, varying from improved anaesthesiological protocols and optimal fluid management, to multimodal pain management, early mobilisation, and early oral intake.[50] The feasibility of ERAS protocols in elderly patients has been endorsed increasingly in literature.[51,52] Although ERAS protocols have been followed for a longer period of time, the Catharina Hospital initiated a dedicated implementation programme in 2020 to improve and maintain adherence to ERAS protocols. The results of **chapter 8** and **chapter 9** underline that a multidisciplinary programme to increase the adherence to ERAS results in beneficial postoperative outcomes, even in the elderly.[48] Nevertheless, strict adherence might be more difficult in the more vulnerable elderly, especially if frailty, polypharmacy, or multimorbidity is present. In these patients, ERAS protocols could be adjusted on an individual basis (e.g. more liberal fluid management, guidance of physiotherapist to support early mobilisation).[53] Including a geriatrician in the multidisciplinary team may help to suit the perioperative care to the needs of more frail patients.[53,54] In a recent study, geriatric co-management was associated with better postoperative outcomes and reduced 90-day mortality.[55] Although increased overall adherence to the ERAS protocol is key, minimal invasive surgery, multimodal pain management, and limited opioid use seem to have a strong impact on recovery.[56] Additional efforts to optimise these elements may therefore contribute to better outcomes. Minimal invasive surgery should be the first choice in elderly patients, in particular in those at risk of frailty, unless contra-indicated.[57] The implementation of continuous wound infusion (CWI) of local analgesics seems promising to optimise multimodal pain management and limit opioid consumption. As a result, the use of CWI was standardly implemented within the ERAS protocols in the VieCuri Medical Centre since May 2019 and in the Catharina Hospital since March 2020. CWI seems associated with low opioid consumption, adequate pain control, and enhanced recovery when used within ERAS protocols (**chapter 8**).[58] Since the elderly are most prone for opioid-related side effects, they seem to benefit greatly from opioid-sparing techniques.[59,60]

Although ERAS protocols will probably benefit patients with LARC and LRRC who require beyond TME surgery as well, they are part of another subgroup in whom adherence to ERAS protocols seems challenging. The study in **chapter 9** showed that LARC and LRRC patients who underwent beyond TME surgery are a different category of patients when compared to rectal cancer patients who underwent TME surgery in terms of tumour characteristics, neoadjuvant treatment, surgery, perioperative care, morbidity, and postoperative recovery. As a result, compliance rates to the current ERAS protocol for colorectal cancer are low, underlining that the current colorectal ERAS protocol is not directly applicable nor feasible in patients who undergo beyond TME surgery. In an effort to improve the outcomes of LARC and LRRC patients, specific modifications in the pre-admission, pre-operative, intra-operative, and post-operative phase of the ERAS protocol are warranted to suit the complexity and needs of these patients. These modifications include specific multimodal pain management protocols to minimise opioid consumption and stimulate early recovery, protocols on resection-site drainage, urinary drainage, and nasogastric tube placement, and schedules to stimulate early oral intake and mobilisation. Currently, the protocol is being developed and implemented in the Catharina Hospital Eindhoven. After implementation, a feasibility study will be performed to investigate the implementation and outcomes in a small group of patients in order to identify whether further modifications are required. Since **chapter 3** revealed that the elderly in particular faced high rates of morbidity and mortality after surgery for cT4RC and LRRC, the implementation of a strictly adhered to ERAS protocol might probably favour the outcomes of elderly patients with LARC and LRRC. In addition, since the elderly mainly died in the period after hospitalisation due to treatment-induced and non-cancer related causes, more attention should be paid towards preventing functional decline after discharge. Rehabilitation programmes and adapted follow-up schedules with the co-management of the geriatrician seem promising.[55,61–63]

Non-operative management

After the introduction of the wait-and-see (W&S) approach in rectal cancer patients with a clinical complete response, numerous studies have shown the benefits of a W&S approach as a surrogate for surgery.[64,65] The beneficial oncological and functional outcomes have increased the interest for non-operative treatment regimens among patients and clinicians.[66–68] An increasing amount of patients explicitly ask for organ preservation, in an effort to avoid surgery. Over the recent years, multiple studies have investigated organ preserving treatment regimens in early and advanced rectal cancer (**chapter 10**). The TREC and STAR-TREC study have investigated the feasibility of radiotherapy-based treatment strategies in early rectal cancer, with the goal of organ preservation, and compared it to primary resection.[69,70] Beneficial outcomes regarding organ preservation and quality of life were reported.[69,71] Other recent studies have explored modalities to increase the chance for successful organ preservation by escalating radiotherapy doses or local excisional procedures.[72–74] Contact X-ray brachytherapy (CXB) is considered a feasible endoluminal modality to escalate the radiotherapy dose directly on the tumour, and can be used as primary treatment or to treat small residual tumours after (chemo) radiotherapy.[75,76] The developments in treatment modalities have increased the non-operative toolbox. However, the challenge remains to identify which patients are suitable candidates for organ preservation and which patients benefit most from surgery. In addition to patients who prefer organ preservation, there is also a subgroup of patients who are too frail to undergo surgery. These patients are at risk of undertreatment, resulting in undesirable outcomes (e.g. debilitating symptoms due to tumour progression, impaired quality of life, and poor survival).[77–80] Non-operative treatment modalities may provide an alternative. Rather than aiming for a palliative treatment when tumour-related complaints arise, a non-operative treatment approach may be more beneficial, in an effort to prevent the onset of debilitating symptoms by obtaining local control of the primary tumour. The treatment of this heterogeneous and frail population poses a difficult challenge for clinicians. The care for these patients is therefore best organised in dedicated multidisciplinary teams with expertise on the non-operative management of elderly and frail patients (**chapter 11**). Obviously, the geriatrician has a central role in the multidisciplinary team to evaluate the patient's health status, preferences, and treatment goals. Since October 2021, a dedicated multidisciplinary clinical care pathway has been initiated in the Catharina Hospital to personalise the non-operative treatment for elderly and frail patients who are unable or refuse to undergo surgery. In this care pathway, elderly and frail patients are comprehensively evaluated by the multidisciplinary team. The multidisciplinary team then composes a personalised treatment advice, based on the patient's health status, preferences, and treatment goals. In order to gain insights into the decision-making, treatment, and outcomes of this complex patient population, a prospective, observational cohort study (RESORT study) has been initiated.

FUTURE PERSPECTIVES

To further personalise the treatment of elderly patients with colorectal cancer, efforts are needed to improve patient selection, minimise morbidity and mortality, and explore non-operative treatment options. The ultimate goal in the treatment of elderly patients with colorectal cancer would be that each patient is treated with the most optimal treatment regimen, thereby eliminating overtreatment and undertreatment. In the ideal scenario, elderly patients are treated in dedicated multidisciplinary care pathways with special expertise on the treatment of colorectal cancer in the elderly. Frailty screening should be a standard element in the elective and emergent setting. Patients should be counselled on the different treatment options that are available, which include treatment options that aim for curation on the one hand, and treatment options that aim to minimise toxicity or morbidity, and maintain quality of life and functional independence on the other. With the patient as the centre of the decision-making process, treatment decisions should be driven by frailty status, patient's preferences, and treatment goals.

A promising step to improve patient selection would be that clinicians are able to predict the influence of treatment on oncological and functional outcomes, thereby stratifying which patient benefits most from which treatment. Validated clinical parameters to predict outcomes in the elderly are warranted. Other parameters, such as serum biomarkers or physical activity tests, have recently been identified and may be useful to characterise the patient's biological age, and determine the presence of frailty or subclinical comorbid diseases.[13] However, the prognostic value of these novel factors within the clinical setting still needs to be clarified.[13] The currently ongoing Triage in Elderly Needing Treatment (TENT) study is a Dutch, multicentre, prospective cohort study to identify the value of different conventional clinical parameters and novel biomarkers to predict treatment outcomes.[81]

The patient's preferences and treatment goals should be considered as the core of shared decision-making. Adequate knowledge on functional outcomes and quality of life is necessary, which can guide decision-making and set the patient's expectations. More prospective studies, such as the Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery (GOSAFE) study, to investigate functional recovery and quality of life after colorectal cancer treatment are needed.[82] Validated scoring tools should be developed to predict the influence of treatment on morbidity, mortality, functional recovery, and quality of life.[22,82–84]

Another important step to improve the care for the elderly is to further optimise perioperative care. The implementation and optimisation of ERAS seems beneficial to reduce the impact of treatment.[48] Since increasing adherence is strongly associated with better outcomes, each hospital treating patients with colorectal cancer should be encouraged to further implement and maintain ERAS protocols. Particularly the elderly may benefit from a further reduction of opioid consumption.[56,85] Currently, some studies have reported on the potential benefits of opioid-free anaesthesia protocols.[85] However, further research to these protocols are required. In addition, studies to investigate the effectiveness of ERAS protocols in subgroups of patients are needed, e.g. in patients with LARC and LRRC. The ERAS protocol that is currently being developed and implemented in the Catharina Hospital to suit the needs of LARC and LRRC patients who undergo beyond TME surgery (**chapter 9**) will be investigated in a prospective setting. If the ERAS protocol effectively improves the outcomes of this complex subgroup of patients, the next step would be to disseminate the protocol across other hospitals. Future studies should also focus on extending ERAS protocols to the preoperative and postoperative period. Preoperatively, predicting and modifying risk factors (e.g. sarcopenia, myosteatosis) may be considered as key goals of ERAS, in particularly in elderly and frail patients. Prehabilitation programmes could be implemented as part of ERAS to attenuate deficits in the patient's health status.[86] However, since it is still unclear which elements should be part of the most optimal prehabilitation programme, more focus on personalised programmes with targeted interventions might be beneficial.[87] In the postoperative phase, efforts should be made to maintain the patient's functional status and quality of life. Elderly might benefit from a close alignment between the involved physicians, such as the general practitioner, the geriatrician, and the surgeon. Promising shared-care models have been described and may be part of an entire multidisciplinary clinical care pathway.[47,62,88] However, further research is required.

Another promising development is the growing tendency towards the non-operative management of rectal cancer. As mentioned in **chapter 10**, several studies are currently investigating the value of different organ preserving modalities. In particular in patients in whom surgery might result in undesirable risks of morbidity or mortality, or those who explicitly ask for organ preservation, these treatment strategies hold great promise. The promising results support a further exploration of non-operative approaches. Studies to investigate dose escalation of radiotherapy, e.g. by an external boost or by endoluminal radiotherapy, seem promising.[75,89] The OPERA trial (NCT02505750) investigated the role of contact X-ray brachytherapy as an endoluminal boost to external beam radiotherapy in patients with cT2-3ab rectal cancer. Although the definitive results are awaited, the preliminary results showed a 90% complete response rate and 3-year successful organ preservation rates of 81% in patients treated with an additional boost of contact X-ray brachytherapy.[74] Local excisional techniques form an alternative to treat small residual disease after (chemo)radiotherapy, which is currently being investigated and compared with contact X-brachytherapy in the OPAXX study.[90,91] The currently ongoing STAR-TREC phase III study will provide valuable insights into the organ preserving treatment of early rectal cancer.[70] Moreover, this study will obtain data on the effectiveness of chemoradiotherapy versus short-course radiotherapy to achieve organ preservation, which may provide important insights for the decision-making in the elderly. Future studies are warranted to investigate the effectivity and tolerability of different non-operative treatment approaches specifically in the elderly and frail. Studies, such as the HERBERT-II study and the RESORT study (**chapter 11**), will provide important data on the treatment and outcomes in elderly and frail patients if surgery is not possible.[92]

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CHAPTER 13

Impact paragraph

This thesis focused on the treatment of elderly patients with colorectal cancer. Over half of patients with colorectal cancer are 70 years or older at the time of diagnosis. Elderly patients suffer more often from comorbidities, physical impairments, dependency in activities of daily living, or frailty when compared to younger patients. This may challenge the treatment of colorectal cancer in this specific population.

The standard treatment of colon cancer consists of a surgical resection, while in stage III colon cancer, surgery may be followed by adjuvant (i.e. after surgery) chemotherapy. The current standard to treat early stage rectal cancer consists of surgery. Although, improvements in the non-operative treatment of early stage rectal cancer are currently being made. More advanced rectal cancer is treated with neoadjuvant radiotherapy (i.e. before surgery), followed by a surgical resection of the rectum. In case of locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC), the tumour often extends the rectal wall and involves surrounding pelvic structures (e.g. bladder or reproductive organs). In LARC and LRRC, intensive treatment regimens are often required to downsize the tumour before surgery. Neoadjuvant therapy for LARC standardly consists of chemoradiotherapy (i.e. radiotherapy combined with oral chemotherapy). The surgical procedure for LARC and LRRC often comprises of an extended surgical resection with removal of the affected organs in the pelvis (i.e. resection of rectum, bladder, reproductive organs).

The surgical treatment of colorectal cancer is associated with a risk of complications. In addition, it may affect bowel, bladder, and sexual function. Since earlier studies have reported that elderly patients are at increased risk of postoperative complications and mortality, it has been believed that elderly patients could not withstand intensive treatment. This has resulted in a concern for overtreatment, and, thereby, a reluctance to offer elderly patients guideline-based treatment. However, due to improvements in the care and outcomes of elderly patients, it may be unnecessary to deny elderly patients an optimal curative treatment nowadays. This illustrates that there is much to gain in improving the care for elderly patients with colorectal cancer. Therefore, the main objective of this thesis was to gain insights into the treatment and outcomes of elderly patients with colorectal cancer, in an effort to further improve and personalise treatment. Challenges and improvements regarding patient selection, perioperative treatment, and non-operative management were identified and addressed.

In this thesis, we concluded that the postoperative outcomes of elderly patients with colorectal cancer have improved over the years. Elderly patients who are eligible for surgery can withstand curative treatment, and no longer have an increased risk of postoperative complications or mortality. This underlines that elderly patients should not be deprived of optimal treatment, based on age or comorbidities alone. However, we found that there are still some areas of concern. Although perioperative care have improved, elderly patients with LARC and LRRC still face high postoperative mortality rates. In particular in these patients, further improvements in patient selection and perioperative care are warranted.

An important part of shared-decision making is adequate patient counselling, which also contributes to better patient selection. Patients should be informed about the treatment options, risks, and consequences. We observed that elderly patients were not at an increased risk to develop functional bowel complaints after colorectal surgery when compared to younger patients. However, we found that half of elderly patients with rectal cancer and one in five with colon cancer developed severe functional bowel complaints after surgery that profoundly impaired their quality of life. Furthermore, we observed that the diverting ostomy reversal rates in elderly patients with more advanced rectal cancer were relatively high and comparable to other studies among younger patients. Nevertheless, one in four did not reverse their diverting ostomy, whereas ostomy recreation was performed in about 15%. These studies underlined that the treatment of colorectal cancer also affects quality of life and functional outcomes. Although many aspects may influence these outcomes, this thesis showed that functional bowel complaints and ostomy-related outcomes should be considered as an essential part of the decision-making process, especially when balancing a restorative procedure versus a non-restorative procedure.

The findings of the first part of this thesis have changed our view on the role of age and comorbidities on the treatment of elderly patients. The outcomes of the first part of this thesis may benefit clinicians during patient selection, counselling, and decision-making. Clinicians should be encouraged to incorporate these aspects and outcomes when different treatment options are balanced and discussed. In addition, these outcomes may benefit elderly patients themselves, since they support the improvements in care and may provide them with insights to optimise shared-decision making, and weigh the benefits and risks of different treatment options. The outcomes have also resulted in novel research questions and efforts to further improve and personalise the treatment and outcomes of elderly patients. These include improvements in patient selection, perioperative care, and whether prehabilitation and rehabilitation programmes will benefit the outcomes of the elderly. Some of these efforts and novel research questions were investigated in the second part of this thesis.

In the second part of this thesis, we investigated which elements required additional attention in the treatment of elderly patients with colorectal cancer. We found that frailty screening and assessment may provide important insights to improve patient selection and outcomes in elderly patients, in particularly in the more frail. The study in **chapter 7**, unveiling the changes in treatment after frailty screening and assessment, as well as the favourable postoperative outcomes of elderly patients at risk of frailty nowadays, was selected for an oral presentation at the 2022 European Society of Surgical Oncology (ESSO) conference in Bordeaux. More importantly, the outcomes have resulted in a closer alignment of care between the geriatrician and the rest of the multidisciplinary team in our hospital. In particular when treating patients with a doubtful health status or those who clearly suffer from frailty, geriatric co-management has become standard in our hospital.

We also investigated whether and how the perioperative care of elderly patients could be improved. We found that the implementation of continuous wound infusion (CWI) of local analgesics (i.e. continuous infusion of pain-reducing agents that act locally on the surgical wound by a small wound catheter) as part of the postoperative pain management in patients that were treated within enhanced recovery protocols (i.e. perioperative protocol to optimise all elements during treatment to improve the recovery after surgery and reduce the risk of complications) resulted in beneficial outcomes. Patients used low amounts of opioids and quickly recovered after surgery, while adequate pain control was maintained. Not only the elderly patient will greatly benefit from reduced opioid consumption, but all patients will. Based on the outcomes of the study and the clinical advantages that were observed, CWI has become standard of care after colorectal surgery in both hospitals that participated in the study in **chapter 8**. Hopefully, the outcomes of the study can support the transition of CWI to become standard of care in more centres. Thereby, our study may contribute to further improvements in the postoperative recovery of patients after colorectal surgery. Furthermore, we identified the need for a modified enhanced recovery protocol with specific elements to improve perioperative care for patients after more extensive surgery for LARC and LRRC (**chapter 9**). Based on the identified elements that needed specific adaptations for LARC and LRRC patients, a perioperative protocol is being developed and implemented in the Catharina Hospital. Hopefully, this will benefit the outcomes of patients after undergoing major rectal cancer surgery.

The non-operative management of rectal cancer has gained interest over the recent years, which may be especially beneficial for elderly patients who refuse surgery or who are unable to undergo surgery, e.g. due to frailty. The beneficial outcomes that were observed have resulted in the set-up of a Papillon facility (i.e. contact X-ray brachytherapy, which is a technique in which radiotherapy is directly administered to the tumour in the rectum) in our hospital to complete the spectrum of non-operative treatment strategies. Since the non-operative treatment of elderly and frail patients requires a multidisciplinary onco-geriatric approach to personalise treatment, we have implemented a dedicated multidisciplinary clinical care pathway for the treatment of elderly and frail rectal cancer patients unable or refusing to undergo surgery. The multidisciplinary team consists of a surgical oncologist, radiation oncologist, medical oncologist, geriatrician, and, if applicable, an anaesthesiologist. By implementing the multidisciplinary onco-geriatric pathway, we have aimed to improve patient selection, align care between different medical specialties, and optimise the treatment and follow-up of elderly patients. Likely, this will further improve decision-making, in an effort to better meet the needs, and, thereby, improve the outcomes of elderly patients with colorectal cancer.

Since the optimal treatment and outcomes of patients unable to undergo surgery are unknown, we have initiated a single centre, prospective observational cohort study, the RESORT study. Due to the observational character, the study will also provide insights into the decision-making process. Hopefully, the insights of the RESORT study with regard to decision-making, treatment, and outcomes will contribute to improved patient selection and counselling of patients with a doubtful physical condition or willingness to undergo surgery. Thereby, the RESORT study may serve clinicians who are often confronted with elderly and frail rectal cancer patients who are unable to undergo surgery.

The outcomes of this thesis have changed our view on the treatment of elderly patients with colorectal cancer. The studies in this thesis have shown that the majority of elderly patients can be treated safely with standard approaches. However, we found that additional attention may be needed in those undergoing major surgery or those at risk of frailty to optimise their health status or to personalise treatment. In addition, this thesis provides insights on the non-operative treatment of elderly patients unable or refusing surgery. Based on the findings of this thesis, several important changes have been made in the current care for these patients in our hospital. For example the implementation of multidisciplinary onco-geriatric treatment pathways to improve patient selection, the improved perioperative care protocols, and the exploration of personalised non-operative treatment strategies. This thesis will also stimulate follow-up studies to further improve the care for elderly patients with colorectal cancer.

In this thesis, studies were included that could benefit several people that are involved in the treatment of elderly patients. Apart from patients and surgeons, the results of the studies in this thesis provide relevant data and knowledge that is applicable for the decision-making of all members of the multidisciplinary team. In addition, from a societal point of view, the results of this thesis show that delivering appropriate care to elderly patients is beneficial. Most elderly patients benefit as much from adequate treatment as younger patients. Therefore, this thesis underlines that efforts should be made to achieve optimal treatment in the elderly.

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CHAPTER 14

Nederlandse samenvatting

Dit proefschrift heeft als doel: I) meer inzichten te krijgen in de behandeluitkomsten van oudere patiënten met een colorectaal carcinoom, om zo de selectie en voorlichting van patiënten te verbeteren en de gezamenlijke besluitvorming te optimaliseren; II) de behandeling van oudere patiënten met een colorectaal carcinoom te verbeteren. De introductie (**hoofdstuk 1**) geeft een overzicht van de huidige beschikbare literatuur en het huidige wetenschappelijke bewijs in de behandeling van het colorectaal carcinoom.

Deel I: De behandeluitkomsten van oudere patiënten met een colorectaal carcinoom

In **hoofdstuk 2** wordt in een single-center, retrospectief cohort onderzocht of de postoperatieve uitkomsten van oudere patiënten (≥75 jaar) met een colorectaal carcinoom over de jaren zijn verbeterd. In dit onderzoek worden de postoperatieve uitkomsten bij oudere patiënten vergeleken met de postoperatieve uitkomsten van jongere patiënten (<75 jaar). In het onderzoek werden 1037 patiënten met een coloncarcinoom en 981 patiënten met een rectumcarcinoom onderzocht. De 30-dagen mortaliteit bij patiënten ≥75 jaar verbeterde van 5.8% in de periode 2006–2012 naar 1.2% in de periode 2013–2017. De 90-dagen mortaliteit verbeterde van 9.1% in de periode 2006–2012 naar 4.6% in de periode 2013–2017. De 1-jaars relatieve overleving bij oudere patiënten verbeterde van 88.4% in de periode 2006–2012 naar 94.3% in de periode 2013–2017. In de meest recente tijdsperiode waren de 30-dagen mortaliteit, 90-dagen mortaliteit en 1-jaars relatieve overleving niet langer statistisch significant verschillend tussen oudere en jongere patiënten.

In **hoofdstuk 3** worden de postoperatieve uitkomsten van een single-center, retrospectief cohort van oudere patiënten (≥75 jaar) met een klinisch T4 (cT4) rectumcarcinoom of lokaal recidief rectumcarcinoom (LRRC) in verschillende tijdsperiodes geëvalueerd en worden deze uitkomsten vergeleken met die van jongere patiënten (<75 jaar). Bij oudere patiënten traden vaker postoperatieve complicaties op dan bij jongere patiënten (cT4: 76.4% vs. 61.7%, $p = 0.02$ en LRRC: 96.2% vs. 77.1%, $p = 0.001$). Dit betrof met name niet-chirurgische complicaties. De 30-dagen mortaliteit bij oudere patiënten verbeterde over de tijd en was in de periode 2012–2017 vergelijkbaar tussen beide leeftijdsgroepen (cT4: 3.1% bij ≥75 jaar vs. 1.5% bij <75 jaar, $p = 0.46$ en LRRC: 0.0% bij ≥75 jaar vs. 1.4% bij <75 jaar, $p > 0.99$). Echter, de 90-dagen mortaliteit (cT4: 9.4% bij ≥75 jaar vs. 2.1% bij <75 jaar, $p = 0.06$ en LRRC: 9.1% bij ≥75 jaar vs. 2.2% bij <75 jaar, $p = 0.09$) en de 1-jaars mortaliteit (cT4: 28.1% bij ≥75 jaar vs. 6.2% bij <75 jaar, $p = 0.001$ en LRRC: 27.3% bij ≥75 jaar vs. 13.8% bij <75 jaar, $p = 0.06$) verbeterde niet bij oudere patiënten en bleef statistisch significant slechter ten opzichte van jongere patiënten. Ongeveer 1 op de 4 oudere patiënten met een cT4 rectumcarcinoom of LRRC overleed in het eerste postoperatieve jaar, met name ten gevolge van door behandeling geïnduceerde doodsoorzaken of niet-kanker gerelateerde doodsoorzaken. Daarentegen was bij jongere patiënten recidief ziekte de belangrijkste doodsoorzaak.

In **hoofdstuk 4** wordt de prevalentie van functionele darmklachten en de impact hiervan op de kwaliteit van leven onderzocht bij oudere patiënten (≥70 jaar) na een operatieve ingreep voor een colorectaal carcinoom in een groot, regionaal, multicentrisch cohort. De Low Anterior Resection Syndrome (LARS) score werd gebruikt om de mate van functionele darmklachten te bepalen. De EORTC QLQ-C30 en EORTC QLQ-CR29 vragenlijsten werden gebruikt om de kwaliteit van leven te beoordelen. Major LARS werd door 40.6% van de oudere patiënten gerapporteerd na een operatieve ingreep voor een rectumcarcinoom en door 22.2% na een operatieve ingreep voor een coloncarcinoom. Bij de jongere patiënten (<70 jaar) werd major LARS gerapporteerd door 57.3% van de patiënten na een operatieve ingreep voor een rectumcarcinoom ($p = 0.001$) en door 20.4% van de patiënten na een operatieve ingreep voor een coloncarcinoom ($p = 0.41$). Patiënten met major LARS rapporteerden een significant slechtere kwaliteit van leven op vrijwel alle domeinen van de EORTC QLQ-C30 en de EORTC QLQ-CR29 vragenlijsten.

In **hoofdstuk 5** worden de uitkomsten gerelateerd aan het aanleggen van een deviërend stoma onderzocht bij een single-center, retrospectief cohort van oudere patiënten (≥70 jaar) met een rectumcarcinoom. Bij de meerderheid (91.5%) van de oudere patiënten werd een primair of secundair stoma aangelegd. Het deviërend stoma werd bij 72.5% van de oudere patiënten succesvol opgeheven binnen 18 maanden na het aanleggen van het stoma. De mediane tijd tot het opheffen van het deviërend stoma was 3.2 (IQR 2.3–5.0) maanden. Het niet-opheffen van het deviërend stoma was meestal het gevolg van recidief ziekte. In 84.0% (95%-BI 75.3–90.6%) van de patiënten traden geen of niet-ernstige complicaties op na het opheffen van het deviërend stoma. Gedurende de follow-up werd bij 15.0% van de patiënten opnieuw een stoma aangelegd. De stomavrije overleving op 1 jaar na de primaire operatie was 69.5% (95%-BI 61.6–76.6%). Na de mediane follow-up van 3.8 jaar was de stomavrije overleving 65.8% (95%-BI 57.8–73.2%).

Deel II: Richting een betere behandeling van oudere patiënten met een colorectaal carcinoom

In **hoofdstuk 6** wordt een overzicht gegeven van de ontwikkelingen die over de jaren hebben plaatsgevonden ten aanzien van de perioperatieve zorg voor oudere patiënten met een colorectaal carcinoom. Daarnaast wordt beschreven welke elementen in de perioperatieve zorg van oudere patiënten met een colorectaal carcinoom om extra aandacht vragen. Verschillende ontwikkelingen in de behandeling van oudere patiënten hebben bijgedragen aan de verbetering van de postoperatieve uitkomsten, waaronder de implementatie van minimaal invasieve chirurgie, verbeterde patiëntselectie, perioperatieve zorg en de implementatie van Enhanced Recovery After Surgery (ERAS) protocollen, toename van expertise door colorectale differentiatie en hoog-volume zorg. Bij de behandeling van oudere patiënten met een colorectaal carcinoom moet extra aandacht worden verleend aan adequate stadiëring, de screening en het onderzoek naar kwetsbaarheid en de preoperatieve optimalisatie van de gezondheidsstatus. Een uitgebreide evaluatie van iedere casus door een multidisciplinair team, inclusief een geriater, is essentieel. Daarnaast moet er aandacht zijn voor specifieke protocollen omtrent de behandeling van mogelijke problemen die kunnen ontstaan gedurende de behandeling, zoals het optreden van acute darmobstructie.

In **hoofdstuk 7** worden de postoperatieve uitkomsten onderzocht van een single-center, retrospectief cohort van oudere patiënten (≥70 jaar) met een colorectaal carcinoom die positief zijn gescreend op kwetsbaarheid. Daarnaast worden de veranderingen in de behandeling ten gevolge van de screening op kwetsbaarheid en het volledige geriatrische onderzoek geëvalueerd. Van de oudere patiënten met een colorectaal carcinoom werd 43.5% positief gescreend op kwetsbaarheid (G8 ≤14) middels de Geriatric-8 (G8) score. Van de patiënten die een volledig geriatrisch onderzoek ondergingen, werd 28.6% geclassificeerd als kwetsbaar en 50.0% als intermediair kwetsbaar. Ten gevolge van het volledige geriatrisch onderzoek werd het oncologisch behandelplan in 8.9% van de patiënten veranderd naar een minder intensief behandelplan en in 1.8% naar een meer intensief behandelplan. Een chirurgische behandeling werd verricht bij 87.8% van de patiënten met een G8 ≤14 en bij 96.9% van de patiënten met een G8 >14 (p = 0.03). Postoperatieve complicaties (46.2% vs. 47.3%, p = 0.89) en het aantal Clavien-Dindo ≥III complicaties (13.8% vs. 18.3%, p = 0.46) was vergelijkbaar tussen patiënten met een G8 ≤14 en G8 >14. Een postoperatief delier trad op bij 7.7% van de patiënten met een G8 ≤14 en bij 1.1% van de patiënten met een G8 >14 (p = 0.08). De 30-dagen mortaliteit (1.1% vs. 1.5%, p > 0.99) en de absolute 1-jaars en 2-jaarsoverleving waren vergelijkbaar tussen beide groepen (log-rank, p = 0.26).

In **hoofdstuk 8** worden in een prospectief, regionaal, multicentrische cohortstudie de uitkomsten van continue wondinfusie (CWI) van lokale analgetica als onderdeel van de multimodale pijnstilling binnen een strikt nageleefd ERAS protocol na een operatieve ingreep voor een colorectaal carcinoom geëvalueerd. Binnen de al bestaande multimodale pijnstillingsprotocollen werd in mei 2019 in het VieCuri Medisch Centrum (Venlo) en in maart 2020 in het Catharina Ziekenhuis (Eindhoven) het gebruik van CWI geïmplementeerd. Op de dag van de operatie gebruikte 61.5% (95%-BI 52.6–69.9%) van de patiënten die met CWI werd behandeld postoperatief opiaten. Op postoperatief dag 1, 2 en 3 nam het percentage patiënten dat opiaten gebruikte af naar 21.5% (95%-BI 14.8–29.6%), 20.8% (95%-BI 14.2–28.8%) en 13.8% (95%-BI 8.4–21.0%), respectievelijk. De mediane pijnscores waren <4 op alle postoperatieve dagen. Postoperatief was er bij 0.8% van de patiënten sprake van een delier. De mediane tijd tot het op gang komen van de ontlasting was 1.0 (IQR 1.0–2.0) dag. De mediane opnameduur was 3.0 (IQR 2.0–5.0) dagen.

In **hoofdstuk 9** werd de implementatie van het colorectale ERAS protocol geëvalueerd in een single-center, retrospectief cohort van patiënten met een rectumcarcinoom die een totale mesorectale excisie (TME) procedure ondergingen. Tevens werden ERAS-gerelateerde uitkomsten en de mate van naleving van het ERAS protocol vergeleken tussen patiënten met een rectumcarcinoom die een TME ondergingen en patiënten met een lokaal gevorderd rectumcarcinoom of LRRC die een beyond TME ondergingen. Bij patiënten met een rectumcarcinoom die een TME procedure ondergingen verbeterde de naleving van het ERAS protocol van 54.7% vóór de implementatie van ERAS naar 85.6% na de implementatie ($p < 0.001$). Dit resulteerde in een significante kortere mediane tijd tot het op gang komen van de ontlasting (2.0 vs. 1.0 dagen, $p = 0.04$) en tot ontslag uit het ziekenhuis (4.0 vs. 3.0 dagen, $p < 0.001$), zonder dat een toename van postoperatieve complicaties werd gezien (52.1% vs. 37.3%, $p = 0.077$). In patiënten met een lokaal gevorderd rectumcarcinoom of LRRC die een beyond TME ondergingen was de naleving van het ERAS protocol statistisch significant lager ten opzichte van patiënten die een TME ondergingen vóór en na de implementatie van ERAS (44.4% vs. 54.7% vs. 85.6%, $p < 0.001$). Dit verschil was het sterkst aanwezig in de postoperatieve periode (25.4% vs. 42.5% vs. 75.4%, $p < 0.001$). De mediane tijd tot het op gang komen van de ontlasting (3.0 dagen) en tot ontslag uit het ziekenhuis (9.0 dagen) was langer bij patiënten die een beyond TME ondergingen. Bovendien werden er meer ernstige postoperatieve complicaties (40.0% in beyond TME vs. 21.9% in pre-ERAS TME vs. 12.2% in post-ERAS TME, $p < 0.001$) geobserveerd bij patiënten die een beyond TME procedure ondergingen. Gebaseerd op deze uitkomsten is een ERAS protocol dat zich specifiek richt op patiënten met een lokaal gevorderd rectumcarcinoom of LRRC die een beyond TME ondergaan van belang. Op dit moment wordt er in het Catharina Ziekenhuis een dergelijk gespecificeerd ERAS protocol ontwikkeld.

Hoofdstuk 10 geeft een overzicht van de Nederlandse perspectieven en de huidige ontwikkelingen ten aanzien van de orgaansparende behandeling van het rectumcarcinoom. Vanwege de veelbelovende uitkomsten in recente studies is er onder patiënten en artsen in toenemende mate interesse in orgaansparende behandelopties. Op dit moment worden er meerdere studies verricht naar de waarde van verschillende orgaansparende behandelmodaliteiten om de tumorrespons en daarmee de kans op succesvolle orgaansparing te vergroten bij zowel vroege als meer gevorderde rectumcarcinomen. Contact X-ray brachytherapie (CXB) is een veelbelovende orgaansparende behandelmodaliteit die onder meer bij oudere en kwetsbare patiënten van meerwaarde zou kunnen zijn.

Hoofdstuk 11 beschrijft een multidisciplinaire benadering om de niet-operatieve behandeling van oudere en kwetsbare patiënten met een rectumcarcinoom die een TME procedure niet kunnen of willen ondergaan, te personaliseren. Patiënten die een TME procedure niet kunnen of willen ondergaan lopen het risico om onderbehandeld te worden. Verbeteringen in niet-operatieve behandelmodaliteiten (bv. systemische chemotherapie, (chemo)radiotherapie, endoluminale radiotherapie en lokale excisie) kunnen een alternatief bieden als chirurgie niet mogelijk is, met als doel om optimale lokale controle van de primaire tumor te bereiken. Vanwege de complexiteit van de behandeling van deze oudere en kwetsbare patiëntengroep is een multidisciplinair zorgpad van essentieel belang om de niet-operatieve behandeling zo optimaal mogelijk te personaliseren. Dit hoofdstuk beschrijft daarnaast een kort overzicht van de op dit moment lopende RESORT studie, een prospectieve, observationele cohortstudie. De RESORT studie heeft als doel om inzichten te verkrijgen in de besluitvorming, de behandeling en de uitkomsten van oudere en kwetsbare patiënten met een rectumcarcinoom die een operatieve ingreep niet kunnen of willen ondergaan.

APPENDICES

List of publications

Curriculum vitae

Dankwoord

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A

CURRICULUM VITAE

Stijn Henricus Johannes Ketelaers was born on May 2, 1997 in Nederweert, The Netherlands. After graduating from secondary school (VWO) at Philips van Horne (Weert, the Netherlands) in 2015, he started studying Medicine at Maastricht University. After finishing his Bachelor's degree (cum laude) in 2018, he started as a student-researcher at the Department of Surgery in the Catharina Hospital (Eindhoven, the Netherlands) under the supervision of prof. dr. Harm Rutten, which resulted in a PhD track. During his Master's degree (clinical rotations), he followed an elective internship at the Department of Paediatric Surgery at Maastricht University Medical Centre+ (Maastricht, the Netherlands). During his clinical rotations, his interest in surgery further grew, which resulted in a senior scientific and clinical internship at the Department of Surgery in the Catharina Hospital.

After obtaining his medical degree (cum laude) in 2021, he started as a formal PhD candidate at the Department of Surgery in the Catharina Hospital under the supervision of prof. dr. H.J.T. Rutten, dr. J.W.A. Burger, dr. J.G. Bloemen, and dr. R.G. Orsini, which resulted in this thesis. The results of some chapters of this thesis have been presented at national (*GROW Science Day at Maastricht (2019, 2021), NVvH Chirurgendagen at Veldhoven (2023)*) and international meetings (*European Society of Surgical Oncology in Lisbon (2021) and Bordeaux (2022)*). After one year of fulltime research, Stijn continued his medical career as a resident not in training (ANIOS) at the Intensive Care Unit in the Catharina Hospital since September 2022. From April 2023, he started as a resident not in training (ANIOS) at the Department of Surgery in the Catharina Hospital.

DANKWOORD

Dit proefschrift had niet tot stand kunnen komen zonder de hulp en steun van velen. Enkele personen wil ik in het bijzonder bedanken.

Ten eerste dank aan alle patiënten die hebben deelgenomen aan de verschillende onderzoeken. Jullie hebben een waardevolle bijdrage geleverd aan het verkrijgen van nieuwe inzichten die de behandeling van het colorectaal carcinoom hopelijk verder kunnen verbeteren.

Geachte promotor, prof. dr. Rutten, beste **Harm**, bedankt dat je me als jonge student de kans gaf om onderzoek te doen. Vanaf de eerste dag ben je enorm betrokken geweest en kreeg ik het volste vertrouwen, waarbij er altijd ruimte was om met eigen ideeën aan de slag te gaan. Bedankt voor alle tijd en energie die je in de begeleiding van mijn promotie hebt gestoken. Je enorme kennis, ervaring en passie voor wetenschappelijk onderzoek en patiëntenzorg zijn indrukwekkend en inspirerend. Ik hoop dat je van je welverdiende pensioen aan het genieten bent, maar ik ben blij dat je nog altijd bij het onderzoek betrokken bent!

Geachte copromotor, dr. Burger, beste **Pim**. Bedankt voor de fijne begeleiding en het vertrouwen dat je in me hebt. Ondanks een drukke agenda, staat de deur van je kantoor altijd open voor overleg of een moment om te brainstormen. Je scherpe en overzichtelijke blik en het vermogen om de vinger altijd op de juiste plek te leggen, gaven vaak heldere nieuwe inzichten aan manuscripten. Je enorme drive en je organisatorische vermogen om het onderzoek binnen onze groep naar een steeds hoger niveau te tillen, zijn bewonderenswaardig. Ik ben dankbaar en trots dat we onze samenwerking voort kunnen zetten en kijk ernaar uit om nog veel van je te leren!

Geachte copromotor, dr. Bloemen, beste **Johanne**. Je toewijding om de dagelijkse praktijk te verbeteren hebben tal van onderzoeksideeën in dit proefschrift (en daarbuiten) voortgebracht: van het evalueren van de geriatrische screening tot de implementatie van nieuwe elementen in het ERAS protocol. Het is indrukwekkend om te zien hoe de dagelijkse patiëntenzorg hiervan heeft geprofiteerd. Onze samenwerking is altijd heel fijn geweest en ik wil je bedanken voor je interesse, nauwe betrokkenheid en vertrouwen. Bovendien herinnerde je me er altijd aan om de successen tijdens mijn promotie te vieren! Ik ben blij dat onze samenwerking nog niet ophoudt en dat ik nog veel van je mag leren!

Geachte copromotor, dr. Orsini, beste **Ricardo**. Als ik jou niet toevallig als beoordelaar van de onderwijspoli had getroffen in mijn derde jaar geneeskunde, was dit proefschrift er wellicht nooit geweest. Jij haalde me als jonge student van Maastricht naar Eindhoven om onderzoek te komen doen bij de colorectale chirurgie. Op je vrije avonden leerde je me de kneepjes van de statistiek en het schrijven van een wetenschappelijk artikel. Ik wil je bedanken voor de hoeveelheid tijd en energie die je vanaf het begin hebt geïnvesteerd om van mij een volwaardig onderzoeker te maken.

Geachte leden van de beoordelingscommissie, **prof. dr. Stassen**, **prof. dr. Marijnen**, **prof. dr. Janssen – Heijnen en dr. Maas**, hartelijk dank voor het beoordelen van mijn proefschrift. Verder ook veel dank aan de overige leden van de oppositie.

Alle co-auteurs van de artikelen in dit proefschrift wil ik bedanken voor hun belangrijke bijdrage en de fijne samenwerking. In het bijzonder **dr. Grard Nieuwenhuijzen**, veel dank voor de uitzonderlijk snelle en scherpe feedback, en de prettige samenwerking bij vrijwel al mijn manuscripten in dit proefschrift. **Dr. Jip Tolenaar**, bedankt voor de fijne samenwerking en je belangrijke bijdrage aan meerdere manuscripten. Je enthousiasme is altijd bevorderlijk geweest voor het opzetten van projecten en de afronding van manuscripten. Verder in het bijzonder dank aan **Joost Nederend, Geert-Jan Creemers, Irene van Hellemond, Jeltsje Cnossen, An-Sofie Verrijssen, Heike Peulen, Anne Jacobs en Harm Scholten** voor jullie betrokkenheid en flexibiliteit bij het opzetten van het multidisciplinaire zorgpad voor kwetsbare patiënten en jullie multidisciplinaire inbreng als co-auteur of in de researchmeetings.

Het researchteam en de verpleegkundig specialisten van de Chirurgie en de oncologiepoli in het Catharina Ziekenhuis. In het bijzonder **Loes, Nikky, Mariëlle en Nikki** voor de vele taken die jullie op je hebben genomen ten aanzien van het opzetten en organiseren van onderzoek, het multidisciplinaire zorgpad voor kwetsbare patiënten en het includeren van patiënten. Tevens extra veel dank aan **Jennifer Demelinne**. Als projectcoördinator van het TZO-project was je voor ons als onderzoekers goud waard! We konden altijd bij je terecht voor alle vragen of organisatorische zaken.

Alle chirurgen en fellows van de afdeling Chirurgie in het Catharina Ziekenhuis. Bedankt voor de mogelijkheid die jullie hebben geboden om in jullie kliniek onderzoek uit te voeren. Verder wil ik jullie bedanken voor de prettige manier van samenwerken en de ervaring die ik bij jullie op mag doen als arts-assistent. Ik kan me geen betere plek bedenken om mijn carrière te mogen beginnen. **Alle arts-assistenten van de Chirurgie in het Catharina Ziekenhuis**: ik wil jullie bedanken dat ik onderdeel mag zijn van deze collegiale groep arts-assistenten. In deze korte tijd heb ik al enorm veel van jullie geleerd.

Alle intensivisten, collega arts-assistenten en physician assistants van de Intensive Care in het Catharina Ziekenhuis. Dankzij jullie fijne manier van begeleiding en samenwerking voelde mijn eerste stappen als jonge dokter in het ziekenhuis direct vertrouwd en heb ik een brede klinische basis mogen leggen. Bedankt voor alle leerzame momenten!

Alle collega-onderzoekers van de rectumchirurgie van het Catharina Ziekenhuis: **Stefi, Kim, Floor, Eva, Dennis, Liën, Davy, Evi en Barbara.** Veel dank voor de fijne samenwerking. In het bijzonder **Stefi, Kim en Floor** voor onze gezamenlijke tijd in het 'Hoofdkwartier'. Naast dat het altijd heel gezellig was en koffiepauzes regelmatig een vast onderdeel van de dag vormden, waren we een enorme productiemachine en wisten we altijd precies waar we elkaar konden aanvullen en helpen.

Dank aan alle onderzoekers van de Chirurgie op de 'zolder', in het bijzonder de huidige lichting: **Anouk, Friso, Mark, Tessa, Teun, Thijs en Vincent**. Hoewel steeds spaarzamer sinds de verhuizing van de rectumonderzoekers naar het 'Hoofdkwartier', waren de feestlunches en gezamenlijke uitjes altijd iets om naar uit te kijken. Uiteraard ook veel dank aan de arts-onderzoekers van de Chirurgie die de huidige lichting voorgingen.

Dit proefschrift was er nooit gekomen zonder de steun en betrokkenheid van mijn vrienden en familie.

Mannen van Licentiatus Medicinae (**Bob, Jarno, Luuk, Ruud en Sem**). Bedankt voor de mooie studiejaren in Maastricht, maar zeker ook voor de onvergetelijke weekenden in Leuven, Gent, Durbuy en andere Belgische steden waar we zijn neergestreken! Het is mooi om te zien hoe ieder van ons aan zijn eigen weg timmert. Veel succes in jullie carrières en op naar nog vele mooie weekenden!

Beste **Rutger**, **Luc, Manon, Miloe en Fabiënne**, bedankt voor onze bijna dagelijkse eet- en borrelavonden in Maastricht tijdens onze eerste jaren van de studie. Deze waren meer een vast onderdeel van onze agenda's dan dat ze afgesproken moesten worden!

Beste **Sjors, Wouter, Teun en Tim.** We zijn sinds de middelbare school al beste vrienden en hebben al veel avonturen samen mee mogen maken. Ondanks dat ieder zijn eigen weg is gegaan en we op verschillende plekken wonen, weten we nog regelmatig tijd in onze agenda vrij te maken. Het bijna wekelijkse groepsapp-berichtje 'Wie heeft zin om dit weekend wat te doen?' is eigenlijk iets wat sinds de aanmaak van de groepsapp (16 november 2012) niet is veranderd! Bedankt voor jullie betrokkenheid!

Mijn paranimfen, **Rutger Slegers en Ivo de Bruin**, jullie zijn fantastische vrienden en het is een eer om jullie aan mijn zijde te hebben. Bedankt voor jullie oprechte interesse en betrokkenheid!

Lieve **oma**, je bent altijd enorm trots op wat ik doe en je hebt een uitzonderlijke interesse in mijn studie, werk en onderzoek. Bedankt!

Lieve **Amina, Nadia en Sarah**, ik heb me altijd gelukkig geprezen met jullie als 'bonus/stief'-familie. Bedankt dat jullie me altijd hebben gestimuleerd en geholpen om de juiste keuzes te maken en mezelf te ontwikkelen!

Lieve **Maud**, als mijn oudere zus heb ik van jongs af aan alles bij je kunnen afkijken. Ondanks dat we elkaar niet altijd even vaak zien, hebben we altijd veel lol en weet ik dat ik altijd op je kan bouwen. Bedankt voor alles!

Lieve **pap en mam**, jullie hebben vanaf jongs af aan laten zien dat hard werken loont en je de mooie momenten moet vieren. Ik ben trots dat jullie mijn ouders zijn. Bedankt voor jullie onnavolgbare betrokkenheid en onvoorwaardelijke steun om het beste uit mezelf te halen.

Lieve **Demi**, met jou voelt het iedere dag als een feest! Je bent altijd jezelf, en je vrolijkheid en onuitputbare energie zijn enorm aanstekelijk. Samen genieten we van alle hoogtepunten die we beleven en elke stap die we zetten. Ik ben ontzettend blij met jou en kijk uit naar de mooie momenten die we samen gaan beleven. Ik hou van je!