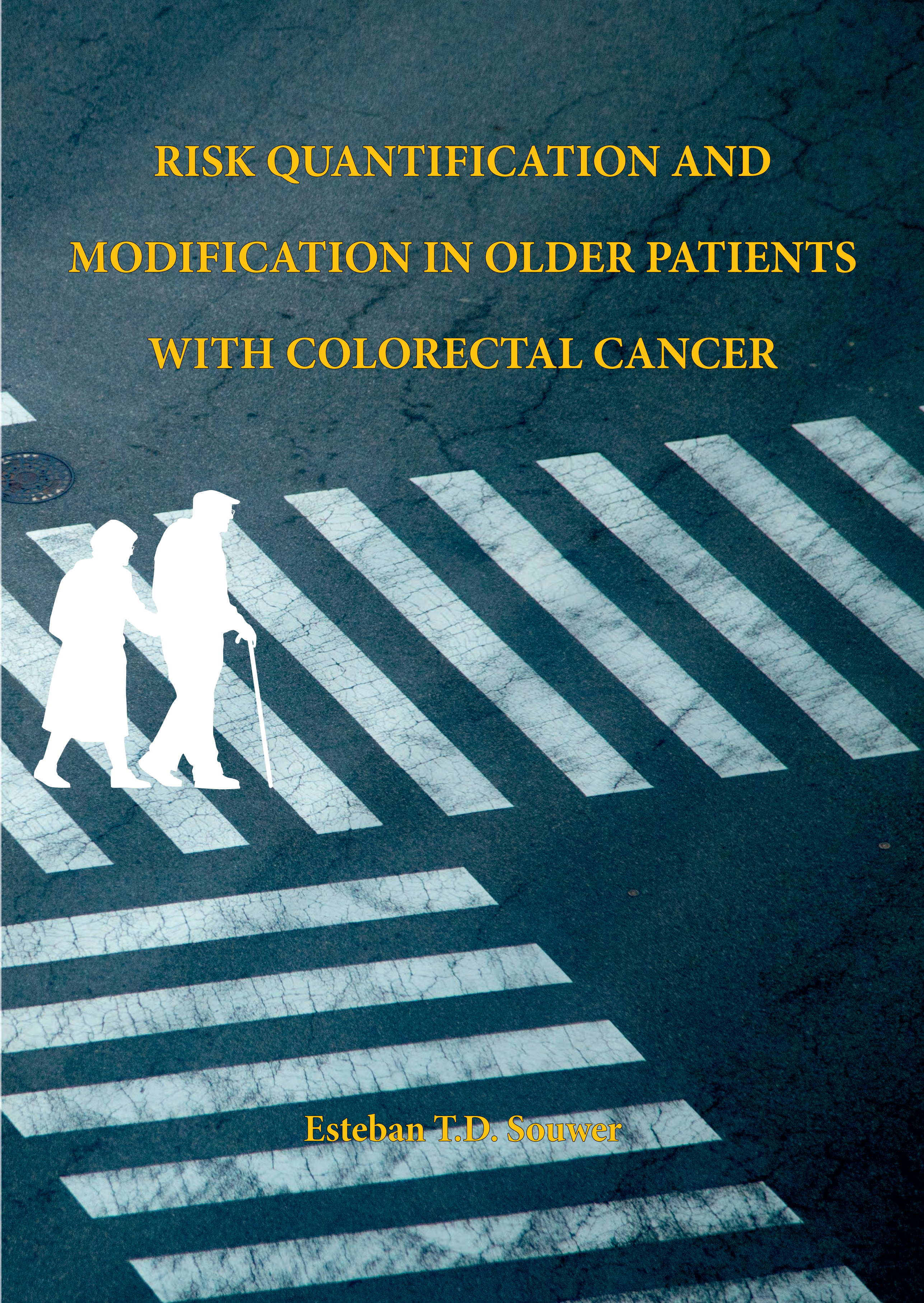
Risk quantification and modification in older patients with colorectal cancer

Souwer, E.T.D.

Author: Souwer, E.T.D.
Title: Risk quantification and modification in older patients with colorectal cancer
Issue Date: 2020-11-12

RISK QUANTIFICATION AND MODIFICATION IN OLDER PATIENTS WITH COLORECTAL CANCER



Esteban T.D. Souwer

Risk quantification and modification in older patients with colorectal cancer

Esteban Thomas Daniël Souwer

Colophon

Cover design, lay-out: Ferdinand van Nispen, *my*-thesis.nl
Printing: GVO drukkers en vormgevers, Ede The Netherlands

ISBN/EAN: 978-94-6332-691-9

Printing of this thesis was financially supported by: Uitgeverij Jaap, Pfizer, Chipsoft, Norgine Pharma, Servier Nederland, Erbe Nederland en Hagaziekenhuis

Risk quantification and modification in older patients with colorectal cancer

Proefschift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 12 november 2020
klokke 10:00 uur

door

Esteban Thomas Daniël Souwer
geboren te Zevenaar
in 1985

Promotor:
Prof. dr. J.E.A. Portielje

Co-promotores:
Dr. F. van den Bos
Dr. J.W.T. Dekker

Leden promotiecommissie
Prof. dr. A.J. Gelderblom
Prof. dr. H.J.T. Rutten (Catharina Ziekenhuis, Eindhoven)
Prof. dr. M. Koopman (Universitair Medisch Centrum Utrecht, Utrecht)

Table of contents

Chapter 1

General introduction and thesis outline

Colorectal cancer (CRC) is the second most common cancer worldwide. In the Netherlands, the number of newly diagnosed patients is around 15,000 per year, with more than 50% of these patients being 70 years and older.[1] In the decades to come, the number of older patients with colorectal cancer is expected to increase due to unfavourable lifestyle changes, increased life-expectancy and early detection programs.[2] The mainstay of curative treatment for stage I-III involves surgical resection.[3] But with advancing age, there is an increased risk for adverse outcomes of surgery such as postoperative complications, readmission or even death.[4-6] In addition, surgery may have a prolonged impact on older patients,[7] including decreased physical functioning[8] and quality of life.[9-11] In individual patients, these adverse outcomes may outweigh the possible benefits of surgery, such as symptom relief or cancer survival.

Selecting the appropriate cancer treatment for older patients is challenging. Scientific evidence is lacking because older patients, especially frail older patients, are underrepresented in clinical trials.[12,13] Hence, in clinical practice, there is often uncertainty what the best cancer treatment is for an individual patient. In CRC care, this is demonstrated by the considerable treatment variation with respect to radiotherapy and surgery for rectal cancer patients and adjuvant chemotherapy for patients with stage III colon cancer.[14,15]

Traditionally, treatment decisions have depended on age, ASA (American Society of Anesthesiologists) score or the physical performance scale (PS). However, these criteria do not capture the heterogeneity of health and physical performance of older patients.[16] Fortunately, there is a growing number of studies that have investigated risk factors and methods that can direct cancer treatment decisions in older patients. In addition, pre- and perioperative interventions that are aimed to improve outcomes of older patients have become available or are already implemented into standard CRC care.

Quantifying the risk for adverse outcomes

In older patients, undernutrition,[17] cognitive impairment, polypharmacy,[18-20] reduced mobility and impaired physical performance[21,22] have been identified as important risk factors for increased risk of postoperative complications, chemotoxicity and lower overall survival after cancer treatment. Low physical performance and functional dependency are also associated with increased care needs after hospitalisation and readmission.[23-25,26] In addition, patients with preoperative impairment in activities of daily living (ADL) are at increased risk of further functional decline after CRC surgery.[27] Also, skeletal muscle mass and density (related to sarcopenia, physical functioning and functional decline) showed associations with postoperative complications, extended hospital stay[28-33] and chemotoxicity.[34] Although, skeletal muscle mass and density as prognostic factors have not been studied in older colorectal cancer patients.

It is important to realise that impaired physical performance, comorbidity, undernutrition, and cognitive impairments are regularly missed during oncological workup,[35] resulting in an incorrect assessment of performance status.[36] Therefore, for individual risk assessment in older patients, Comprehensive Geriatric Assessment (CGA) has been advocated because it captures the considerable heterogeneity in health and functional ability of older patients. CGA can estimate the patient's physical and cognitive reserves that are needed to tolerate cancer treatment and it can reduce the risk of under- and overtreatment.[37] CGA has been shown to change the treatment decision in up to 40% of older cancer patients, especially those receiving chemotherapy.[38]

When CGA is not available, prognostic information for individual patients may be obtained from a Geriatric Assessment (GA)[39] or even geriatric screening tools (such as ISAR-HP[40] and G8[41]) as outcomes of these screening are associated with treatment tolerance, overall survival and functional decline in haematological malignancies, head and neck cancer and lung cancer.[42-44] Risk-prediction models may also be used to support treatment decisions because they can an estimate of individual treatment outcomes.

Prediction models need to be applicable, relevant and accurate for their intended use.[45] Providing accurate prognostic information to older CRC patients concerning possible risk and benefits of treatment improves the likelihood that treatment decisions are consistent with individual needs, values, and preferences. Multiple risk prediction models are available for the prediction of morbidity and mortality after CRC surgery.[46-51] However, it is unclear whether these prediction models are applicable and accurate for older, especially frail, patients. Ideally, prognostic information should include not only adverse events but also functional outcomes and quality of life after treatment, as this information is especially relevant to older patients. Providing prognostic information can also be used to identify high-risk populations to indicate interventions aimed at improving surgical outcomes.

Risk modification

In CRC care, perioperative interventions such as Enhanced Recovery After Surgery (ERAS) and laparoscopic surgery, have been shown to be beneficial to older patients.[52,53] Several studies have addressed the effects of prehabilitation before surgery aimed to increase resilience[54,55] and early discharge to a rehabilitation centre aimed to reduce the adverse effects of a hospital stay.[56] In the majority of younger patients, prehabilitation before CRC surgery positively influenced physical performance,[55,57-59] but the impact on postoperative complications was absent.[60] Also, in patients scheduled for thoracic surgery, prehabilitation has shown to reduce complication rates and shorten hospital stay.[61] However, prehabilitation studies in older CRC patients are scarce and results are inconsistent.[58] There is also a lack of studies that investigated optimal patient selection for prehabilitation. However, information collected from a (C)GA might be of aid.

In patients planned for cancer treatment, CGA can be used to direct non-oncological interventions including nutritional, social and psychological support, and medication optimisation. Such non-oncological interventions are proposed in up to 70% of patients referred for CGA. Therefore, geriatric screening and assessment are recommended as part of standard oncological workup.[62] Thus far, the usefulness of oncogeriatric care and interventions on outcomes of CRC surgery including mortality, complications, quality of life and physical functioning is not clear.

Aim and thesis outline

This thesis aims to investigate which older patients with CRC are at risk of poor surgical outcomes. Existing prediction tools are explored and evaluated, and predictive patient characteristics are studied in a real life cohort (**Part I**). In addition, interventions are studied designed to modify the risk for poor surgical outcomes in older patients with CRC and quality of life and functional performance after CRC treatment, outcomes that are especially relevant to older patients, are studied (**Part II**).

Part I. risk quantification

In **Chapter 2,** a systematic review method is used to discuss existing prediction models and risk groups for adverse outcomes of colorectal surgery. Also, the different predictors and outcomes of these models are evaluated for their applicability to older patients.

In **Chapter 3**, the predictive value of the G8 and ISAR-HP screening tools are studied with regard to postoperative complications and 1-year mortality after colorectal cancer surgery in older patients. In **Chapter 4**, skeletal muscle mass and density are studied for their prognostic value for adverse events after CRC surgery. A comprehensive multicentre database containing demographic and geriatric data of 550 consecutive older patients provided the data for **Chapter 5.** In this chapter, we investigated the prognostic value of geriatric predictors based on the data of Chapters 2 to 5, a new preoperative prediction model for severe complications is presented in **Chapter 6.**

Part II. risk modification

In **Chapter 7**, the effect of a prehabilitation and rehabilitation program for older patients on 1-year mortality and complications, is studied. In **Chapter 8**, Health-Related Quality of Life (HRQoL) in the first postoperative year is investigated in older patients with colorectal cancer treated in a geriatric care pathway. Differences between patients with and without geriatric deficits are studied. **Chapter 9** describes the effect of CGA on treatment decisions for older patients with colorectal cancer. Following a summary in **Chapter 10**, the main findings and future perspectives are discussed in **Chapter 11**.

References

1. *Netherlands Cancer Registry (NKR).* Retrieved from www.cijfersoverkanker.nl: [Accessed 01 June 2018].
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut.* 2017;66(4):683-91.
3. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandala M, Cervantes A, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2013;24 Suppl 6(suppl_6):vi64-72.
4. Dekker JW, Gooiker GA, Bastiaannet E, van den Broek CB, van der Geest LG, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. *European Journal of Surgical Oncology.* 2014;40(11):1481-7.
5. Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: A systematic review. *Journal of Geriatric Oncology.* 2016;7(6):479-91.
6. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Annals of Surgical Oncology.* 2012;19(8):2428-34.
7. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Annals of Surgical Oncology.* 2011;18(6):1533-9.
8. Hamaker ME, Prins MC, Schiphorst AH, van Tuyl SA, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. *Journal of Geriatric Oncology.* 2015;6(2):153-64.
9. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. *Annals of Surgery.* 2014;259(5):916-23.
10. Di Cristofaro L, Ruffolo C, Pinto E, Massa M, Antoniutti M, Cagol M, et al. Complications after surgery for colorectal cancer affect quality of life and surgeon-patient relationship. *Colorectal Disease.* 2014;16(12):O407-19.
11. Stucky CC, Pockaj BA, Novotny PJ, Sloan JA, Sargent DJ, O'Connell MJ, et al. Long-term follow-up and individual item analysis of quality of life assessments related to laparoscopic-assisted colectomy in the COST trial 93-46-53 (INT 0146). *Annals of Surgical Oncology.* 2011;18(9):2422-31.
12. Hamaker ME, Stauder R, van Munster BC. Exclusion of older patients from ongoing clinical trials for hematological malignancies: an evaluation of the National Institutes of Health Clinical Trial Registry. *Oncologist.* 2014;19(10):1069-75.
13. Schulkes KJ, Nguyen C, van den Bos F, van Elden LJ, Hamaker ME. Selection of Patients in Ongoing Clinical Trials on Lung Cancer. *Lung.* 2016.
14. Claassen YHM, Vermeer NCA, Iversen LH, van Eycken E, Guren MG, Mroczkowski P, et al. Treatment and survival of rectal cancer patients over the age of 80 years: a EURECCA international comparison. *British Journal of Cancer.* 2018;119(4):517-22.
15. Vermeer NCA, Claassen YHM, Derks MGM, Iversen LH, van Eycken E, Guren MG, et al. Treatment and Survival of Patients with Colon Cancer Aged 80 Years and Older: A EURECCA International Comparison. *Oncologist.* 2018;23(8):982-90.
16. Kim SW, Han HS, Jung HW, Kim KI, Hwang DW, Kang SB, et al. Multidimensional frailty score for the prediction of postoperative mortality risk. *JAMA Surg.* 2014;149(7):633-40.
17. Kwag S-J, Kim J-G, Kang W-K, Lee J-K, Oh S-T. The nutritional risk is a independent factor for postoperative morbidity in surgery for colorectal cancer. *Annals of Surgical Treatment and Research.* 2014;86(4):206-11.
18. Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, Johns S, et al. Prevalence and factors associated with polypharmacy in older people with cancer. *Supportive Care in Cancer.* 2014;22(7):1727-34.
19. Maggiore RJ, Dale W, Gross CP, Feng T, Tew WP, Mohile SG, et al. Polypharmacy and Potentially Inappropriate Medication Use in Older Adults with Cancer Undergoing Chemotherapy: Effect on Chemotherapy-Related Toxicity and Hospitalization During Treatment. 2014;62(8):1505-12.
20. Nightingale G, Hajjar E, Guo K, Komura S, Urnoski E, Sendecki J, et al. A pharmacist-led medication assessment used to determine a more precise estimation of the prevalence of complementary and alternative medication (CAM) use among ambulatory senior adults with cancer. *Journal of Geriatric Oncology.* 2015;6(5):411-7.

21. Cohen ME, Bilimoria KY, Ko CY, Hall BL. Development of an American College of Surgeons National Surgery Quality Improvement Program: Morbidity and Mortality Risk Calculator for Colorectal Surgery. *Journal of the American College of Surgeons.* 2009;208(6):1009-16.
22. Kiran RP, Attaluri V, Hammel J, Church J. A novel nomogram accurately quantifies the risk of mortality in elderly patients undergoing colorectal surgery. *Annals of Surgery.* 2013;257(5):905-8.
23. Hoogerduijn JG, de Rooij SE, Grobbee DE, Schuurmans MJ. Predicting functional decline in older patients undergoing cardiac surgery. *Age and Ageing.* 2014;43(2):218-21.
24. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. *JAMA.* 2011;305(1):50-8.
25. Mahoney JE, Sager MA, Jalaluddin M. Use of an ambulation assistive device predicts functional decline associated with hospitalization. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 1999;54(2):M83-8.
26. Dent E, Chapman I, Howell S, Piantadosi C, Visvanathan R. Frailty and functional decline indices predict poor outcomes in hospitalised older people. *Age and Ageing.* 2014;43(4):477-84.
27. Finlayson E, Zhao S, Boscardin WJ, Fries BE, Landefeld CS, Dudley RA. Functional status after colon cancer surgery in elderly nursing home residents. *Journal of the American Geriatrics Society.* 2012;60(5):967-73.
28. Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB.* 2011;13(7):439-46.
29. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *British Journal of Cancer.* 2012;107(6):931-6.
30. Sabel MS, Terjimanian M, Conlon AS, Griffith KA, Morris AM, Mulholland MW, et al. Analytic morphometric assessment of patients undergoing colectomy for colon cancer. *Journal of Surgical Oncology.* 2013;108(3):169-75.
31. Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewe KW, Hoofwijk AG, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Annals of Surgery.* 2015;261(2):345-52.
32. Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, et al. Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer. *International Journal of Colorectal Disease.* 2016;31(6):1117-24.
33. Jones KI, Doleman B, Scott S, Lund JN, Williams JP. Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. *Colorectal Disease.* 2015;17(1):O20-6.
34. Jung HW, Kim JW, Kim JY, Kim SW, Yang HK, Lee JW, et al. Effect of muscle mass on toxicity and survival in patients with colon cancer undergoing adjuvant chemotherapy. *Supportive Care in Cancer.* 2015;23(3):687-94.
35. Hamaker ME, Prins MC, Stauder R. The relevance of a geriatric assessment for elderly patients with a haematological malignancy--a systematic review. *Leukemia Research.* 2014;38(3):275-83.
36. Jolly TA, Deal AM, Nyrop KA, Williams GR, Pergolotti M, Wood WA, et al. Geriatric assessment-identified deficits in older cancer patients with normal performance status. *Oncologist.* 2015;20(4):379-85.
37. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer. *Journal of Clinical Oncology.* 2014;32(24):2595-603.
38. Hamaker ME, Schiphorst AH, ten Bokkel Huinink D, Schaar C, van Munster BC. The effect of a geriatric evaluation on treatment decisions for older cancer patients--a systematic review. *Acta Oncologica.* 2014;53(3):289-96.
39. Huisman MG, Kok M, de Bock GH, van Leeuwen BL. Delivering tailored surgery to older cancer patients: Preoperative geriatric assessment domains and screening tools - A systematic review of systematic reviews. *European Journal of Surgical Oncology.* 2016.
40. Hoogerduijn JG, Buurman BM, Korevaar JC, Grobbee DE, de Rooij SE, Schuurmans MJ. The prediction of functional decline in older hospitalised patients. *Age and Ageing.* 2012;41(3):381-7.
41. Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Annals of Oncology.* 2012;23(8):2166-72.
42. Pottel L, Lycke M, Boterberg T, Pottel H, Goethals L, Duprez F, et al. G-8 indicates overall and quality-adjusted survival in older head and neck cancer patients treated with curative radiochemotherapy. *BMC Cancer.* 2015;15:875.

43. Schulkes KJG, Souwer ETD, van Elden LJR, Codrington H, van der Sar-van der Brugge S, Lammers JJ, et al. Prognostic Value of Geriatric 8 and Identification of Seniors at Risk for Hospitalized Patients Screening Tools for Patients With Lung Cancer. *Clinical Lung Cancer.* 2017;18(6):660-6 e1.
44. Hamaker ME, Mitrovic M, Stauder R. The G8 screening tool detects relevant geriatric impairments and predicts survival in elderly patients with a haematological malignancy. *Annals of Hematology.* 2014;93(6):1031-40.
45. Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Medicine.* 2014;11(10):e1001744.
46. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *British Journal of Surgery.* 1991;78(3):355-60.
47. Richards CH, Leitch EF, Anderson JH, McKee RF, McMillan DC, Horgan PG. The revised ACPGBI model is a simple and accurate predictor of operative mortality after potentially curative resection of colorectal cancer. *Annals of Surgical Oncology.* 2011;18(13):3680-5.
48. Slim K, Panis Y, Alves A, Kwiatkowski F, Mathieu P, Mantion G. Predicting postoperative mortality in patients undergoing colorectal surgery. *World Journal of Surgery.* 2006;30(1):100-6.
49. Tekkis PP, Prytherch DR, Kocher HM, Senapati A, Poloniecki JD, Stamatakis JD, et al. Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM). *British Journal of Surgery.* 2004;91(9):1174-82.
50. van der Sluis FJ, Espin E, Vallribera F, de Bock GH, Hoekstra HJ, van Leeuwen BL, et al. Predicting postoperative mortality after colorectal surgery: a novel clinical model. *Colorectal Disease.* 2014;16(8):631-9.
51. Dekker JW, Liefers GJ, de Mol van Otterloo JC, Putter H, Tollenaar RA. Predicting the risk of anastomotic leakage in left-sided colorectal surgery using a colon leakage score. *Journal of Surgical Research.* 2011;166(1):e27-34.
52. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. *Colorectal Disease.* 2014;16(12):947-56.
53. Gietelink L, Wouters MW, Bemelman WA, Dekker JW, Tollenaar RA, Tanis PJ. Reduced 30-Day Mortality After Laparoscopic Colorectal Cancer Surgery: A Population Based Study From the Dutch Surgical Colorectal Audit (DSCA). *Annals of Surgery.* 2016;264(1):135-40.
54. Topp R, Ditmyer M, King K, Doherty K, Hornyak J, 3rd. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. *AACN Clinical Issues.* 2002;13(2):263-76.
55. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology.* 2014;121(5):937-47.
56. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. *World Journal of Surgery.* 2014;38(6):1531-41.
57. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surgical Endoscopy.* 2013;27(4):1072-82.
58. Dronkers JJ, Lamberts H, Reutelingsperger IM, Naber RH, Dronkers-Landman CM, Veldman A, et al. Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. *Clinical Rehabilitation.* 2010;24(7):614-22.
59. West MA, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *British Journal of Anaesthesia.* 2015;114(2):244-51.
60. Moran J, Guinan E, McCormick P, Larkin J, Mockler D, Hussey J, et al. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: A systematic review and meta-analysis. *Surgery.* 2016;160(5):1189-201.
61. Hulzebos EH, Smit Y, Helders PP, van Meeteren NL. Preoperative physical therapy for elective cardiac surgery patients. *Cochrane Database of Systematic Reviews.* 2012;11:Cd010118.
62. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. *Annals of Oncology.* 2015;26(3):463-76.

Part I.

Risk quantification

Chapter 2

Risk prediction models for postoperative outcomes of colorectal cancer surgery in the older population - a systematic review

Journal of Geriatric Oncology 2020;S1879-4068(19)30412-6 (epub)

E.T.D. Souwer
E. Bastiaannet
E.W. Steyerberg
J.W.T. Dekker
F. van den Bos
J.E.A. Portielje

Abstract

Background: An increasing number of patients with Colorectal Cancer (CRC) is 65 years or older. We aimed to systematically review existing clinical prediction models for postoperative outcomes of CRC surgery, study their performance in older patients and assess their potential for preoperative decision making.

Methods: A systematic search in Pubmed and Embase for original studies of clinical prediction models for outcomes of in colorectal surgery. Bias and relevance for preoperative decision making with older patients were assessed using the CHARMS guidelines.

Results: 26 prediction models from 25 publications were included. The average age of included patients ranged from 61 to 76. Two models were exclusively developed for patients of 65 and older. Common outcomes were mortality (n=10), anastomotic leakage (n=7) and surgical site infections (n=3). No prediction models for quality of life or physical functioning were identified. Age, gender and ASA score were common predictors; 12 studies included intraoperative predictors. For the majority of the models, bias for model development and performance was considered moderate to high.

Conclusions: Prediction models are available that address mortality and surgical complications after colorectal surgery. Most models suffer from methodological limitations, and their performance for older patients is uncertain. Models that contain peri-operative predictors are of limited use for preoperative decision making. Future research should address the predictive value of geriatric characteristics to improve the performance of prediction models for older patients.

Abbreviations

ACPGBI	The Association of Coloproctology of Great Britain and Ireland
ACS	The American College of Surgeons
AFC	the *French* Association for *Surgery*
BH 2012	Barwon Health 2012 model
CCF	Cleveland Clinic Foundation
CLS	Colon leakage score
COLA score	Contamination, Obesity, laparotomy and ASA Grade score
CR	Colorectal
CR-BHOM	Colorectal The Biochemistry and Haematology Outcome Model
CRC	Colorectal Cancer
CrOSS	Colorectal preOperative Surgical Score
IRCS score	Identification of Risk in Colorectal Surgery score
I-score	Ileus Score
JSCCR	Japanese Society for Colon and Rectal Cancer
LARS	the Low Anterior Resection Syndrome
NNIS	the National Nosocomial Infections Surveillance (Japan)
N-RIC	NNIS - risk index category
NSQIP	N*ational Surgical Quality Improvement Program*
POSSUM	The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity
PROCOLE	Prognostic Colorectal Leakage

Introduction

Older patients make up the majority of new patients with colorectal cancer, and for this heterogeneous population, risks and benefits of treatment must be weighted at an individual level.[1-4] Prediction models can be used to facilitate this process and estimate the outcomes of treatment. Morbidity and mortality are important outcomes to discuss when deciding upon cancer treatment, but for older patients with cancer quality of life and retaining functional independence are also important outcomes.[5]

The aim of this systematic review was to study existing clinical prediction models that were developed to predict postoperative outcomes of colorectal cancer surgery. Quality and accuracy of the prediction models in older patients were studied. Furthermore, their usefulness for preoperative decision making in older patients was evaluated.

Methods

Search strategy and article selection

This systematic review is reported following the recommendations set forth by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[6] A literature search was performed on 1 November 2018, in both the electronic databases Pubmed and Embase. The search contained the following key elements: "colorectal", "surgery" and "prediction" or "risk model" or "nomogram". No limits in age, language or publication date were included in the search. The full search strategies are shown in Appendix A.

Inclusion criteria for prediction modelling studies were as follows; the study's main goals included the development of a prediction model for postoperative outcomes of colorectal surgery. The final prediction model included more than one variable, and the model's performance was reported as an Area Under the Curve (AUC) or C-statistic/index. It was mandatory that pre- or intraoperative predictors were included in the published prediction model. Studies examining the validity of a prediction model outside the development population (the study population on which the prediction model was developed), without calibration or model update, were not eligible for inclusion in this review. Neither were reviews, editorials and conference abstracts.

Predefined outcomes of interest were any postoperative morbidity (for example, complications, readmission, hospital stay, functional and quality of life outcomes) and postoperative mortality up to 12 months.

All titles and abstracts of the studies retrieved by the search were addressed by two reviewers (ETDS and EB), to determine which studies warranted further examination. Articles in other languages then English, German, French or Dutch were excluded.

The following studies were excluded based on title and abstract: treatment options other than colorectal surgery, no original research, non-human studies, only a subgroup of patients (e.g. only lung metastasis or liver metastasis), the inclusion of postoperative variables in the final model or the outcome of interest was not postoperative morbidity of mortality. All potentially relevant articles were subsequently screened as full text by two authors (ETDS and EB). In the case a model update was published, the updated model was included in the review, but study information of the original study model was used when applicable. Furthermore, references of included publications were cross-referenced to retrieve any additional relevant citations. Finally, only studies that had a score chart or nomogram published or online/offline calculator made available were eligible for data-extraction.

Data extraction and quality assessment

The CHecklist for critical Appraisal and data extraction for Systematic Reviews of prediction Modelling Studies (CHARMS) was used for data extraction.[7] For each included study, the following data were independently extracted by two investigators (ETDS, EB): Study date, data ssource (cohort, case-case control, randomised trial or registry data), study population (age, gender, tumour stage and type of surgery), outcome of interest, number of outcome events reported, predictors included in the final model. The final model's performance was assessed based on its discrimination (AUC of the c-statistic/index, sensitivity and specificity to calculate a Likelihood Ratio) and calibration (accuracy of the predicted risk versus the observed risk, and reported by Hosmer-Lemeshow (H-L) test value, Observed/expected ratio or calibration plot). For all studies, we searched for external validation studies in the Pubmed and Embase databases.

Clinical predictors were classified into demographic-, comorbidity- (including American Society of Anesthesiologists Classification (ASA) score, Body Mass Index (BMI)) biochemical- (electrolytes and albumin), geriatric- (falls, functional dependency, independency (i) Activities of Daily Living (ADL), cognition) and non-geriatric predictors (all others, including weight loss).

Quality assessment

The methodological quality of each study was independently assessed by two reviewers (ETDS, EB). The CHARMS checklist was also used to evaluate the risk of bias and applicability concerns. Applicability refers to the extent to which the prediction model is useful for older colorectal cancer.[7] The intended use is for preoperative shared decision making with older patients. Therefore, predictors need to be available preoperatively. In Appendix A and B, the criteria for quality assessment and applicability are described. These criteria were adapted from a systematic review of asthma prediction models by Smit et al.[8] We defined a prediction tool representative for the average older patient with colorectal cancer, when at least 30% of the study population was 65 years or older. In European countries and the USA, more than half of all patients with colorectal cancer are 65 years or older.[9] In case of a model update; the model development studies were reviewed to assess the method of predictor selection.

Data synthesis and analysis

We describe study characteristics and the outcomes of interest, the predictors of each model and the model's performance. Furthermore, the quality (bias and applicability) of the prediction model studies was described.

Results

Study characteristics

The literature search identified 2885 citations (1899 from Medline and 1100 from Embase), of which 992 were duplicates. Details on the search and final study selection are shown in Figure 1. After exclusion of 2957 publications, 25 publications with 26 prediction models were included in this review.[10-34] Cross-referencing yielded no additional results. The characteristics of 26 prediction models (Shen et al. reported two models)[34] are summarised in Table 1. Four publications were adaptions of earlier published prediction models.[35-38]

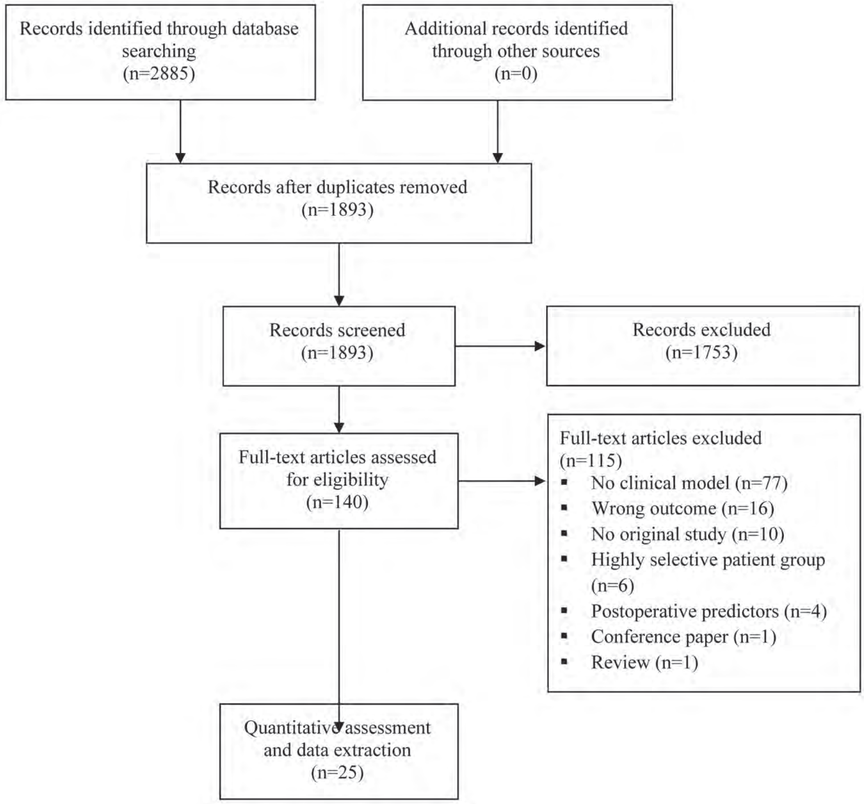


Figure 1 PRISMA flow diagram

Publication years ranged from 2003 to 2018; seven studies originated from the United States (USA), four from the United Kingdom (UK) including one collaboration with Denmark and three from China. Other countries were Australia, Bosnia Herzegovina, France, Japan, the Netherlands, Spain and Switzerland. There was some heterogeneity between the study cohorts and related interventions; patient cohorts included patients with colorectal cancer and patients with colorectal surgery (including those with noncancer indications). The most frequently studied intervention was resectional colorectal surgery; in the study of

Dekker et al.[15] the studied intervention was left-sided colorectal surgery and in the studies of Hu et al.[22], Battersby et al.[31] and Hoshino et al.[33] only rectal surgery was studied. The study populations for the 25 studies originated from single centres (13), multicentre studies (5) and registry data or administrative data (7). In the majority of the studies (19 out of the 25) data were collected prospectively. Two prediction model studies used a meta-analysis to select predictors for the final model instead of a primary database.[15,27]

Patients and outcomes

The number of patients that were included ranged from 119 to 23,5407. Average age ranged from 61 to 76. Two models were exclusively developed for patients of 65 and over.[29,34]

Of the 26 models, ten models studied mortality as an outcome and seven anastomotic leakages (Table 1). Two models with mortality as an outcome were also developed to predict major complications or major morbidity.[13,14] Deep organ space infections, wound disruptions, stroke, renal failure and sepsis were considered major complications and anastomotic leakage, abscess, bleeding or postoperative bowel obstruction as major morbidity in these studies. No models focused on quality of life or postoperative functional dependency.

Predictors

For model development, predictors were mostly selected based on their statistical significance (with $p<.10$ or $p<.05$) with a corresponding weight (OR), before constructing the final model.[10-14,16-26,28-30,32-34] For three models, the choice of predictors depended exclusively on the research of the literature or clinical experience.[15,27,31] The median number of predictors included was 6 (range 4-22). In Table 2A-C, predictors in the different prediction models are depicted, categorised by outcome (mortality, anastomotic leakage and "other outcomes") which include all other surgical complications including ileus, post-acute care discharge, cardiac events and readmission.

Age, ASA score, tumour stage, operative urgency, and albumin were more common predictors for mortality and anastomotic leakage. Six models included parameters such as weight loss[12,29,31] and functional status or dependency.[13,18,26] Thirteen out of 26 prediction models included intraoperative predictors such as laparoscopic surgery, surgical extent, peritoneal contamination, distance of the anastomosis, duration of surgery , and intraoperative complications such as blood loss.[10,15,17,19,21,22,24,25,28-31,34] The proportion of studies that included intraoperative predictors were higher in models with anastomotic leakage as an outcome (5 out of 7)[15,19,21,22,29] and the "other outcomes" summarised in Table 2C.[17,24,28,30,34] In contrast, only one model for postoperative mortality included intraoperative predictors in their final model.[10]

Applicability concerns

Shown in Table 3, are the applicability concerns for participant selection, predictors and outcomes for the different studies where they are judged based on their applicability for preoperative shared decision making with older patients. Applicability concerns related to the population were raised for the studies of Pasic et al.[19] and Rojas.[27] These studies did not describe their study population in more detail or did not include > 30% older patients.

Table 1 Characteristics of the 25 Selected Prediction Modelling Studies

Author	Cohort years	Model "name"	Outcomes	type of surgery	Single or multicentre or /data source	Pro/retro-spective	Tu-mour stages	No. of pa-tients	Mean age (range)	Patients > 65[a] of >70[b]
Tekkis et al. [10] UK	1993-2001	CR-POSSUM	In-hospital mortality	CR surgery (37.2% CRC)	Multicentre (n=15)	Pro	I-IV	6883	NR	37%[b]
Fazio et al. [11] USA	1976-2002	CCF-CRM	30-day mortality	CRC surgery	Single Centre	Pro	I-IV	5053	Median 66 (18-98)	50%[a]
Slim et al. [12] France	2002	AFC Index	In-hospital mortality	CR surgery (CRC 70%)	Multicentre (n=81)	Pro	NR	1421	NR	46%[a]
Cohen et al. [13] USA	2005-2007	ACS-NSQIP	1. 30-day mortality 2. 30-day overall and severe morbidity	CR surgery (49% CRC)	ACS-NSQIP database	Pro	I-IV	28863/ 3037 (V)	Mean 61.8 (SD 15.9)	NR
Farooq et al. [14] UK	2001-2007	CR-BHOM	1. 30-day mortality 2. Major morbidity	CRC surgery	Single Centre	Pro	NR	704	Median 74 (24-98)	NR
Dekker et al. [15] The Netherlands	2005-2006	CLS	Anastomotic Leakage	Left-sided CRC	Single Centre	Meta-analysis	NR	121	Median 66 (25-93)	NR
Richards et al. [16] UK	1997-2007	Revised ACPGBI	30-day mortality	Curative CRC surgery	Single Centre	Pro	I-III	423	NR	67%[a]
Gervaz et al. [17] Switzerland	2008-2010	COLA-score	1. SSI – superficial 2. SSI - deep	CR surgery	Multicentre (n=24)	Pro	NA	543	NR	NR
Kiran et al. [18] USA	2005-2007	Elderly ACS-NSQIP	30-day mortality	CR surgery (% CRC NR)	ACS-NSQIP database	Pro	I-IV	235407	Non-elderly 52.8 Elderly (70+)78.4	35%[b]
Pasic et al. [19] Bosnia and Herzegovina	2009-2011	-	Anastomotic leakage	CR surgery	Single Centre	Retro	NR	119	Mean 62 (33-87)	NR
Van der Sluis et al. [20] The Netherlands	1990-2011	IRCS	In-hospital mortality	CRC surgery	Single Centre	Pro	I-IV	2856	NR	49%[b]
Frasson et al. [21] Spain	2011-2012	Anastomoticleak.com	Anastomotic leakage	CRC surgery	Multicentre (n=52)	Pro	I-IV	3193	Median (63-79)	NR

Hu et al. [22] China	2010-2014	-	Anastomotic leakage	Laparoscopic Rectal cancer surgery	Single Centre	Pro	I-IV	1968	Mean 61 (27-83)	NR
Kong et al. [23] Australia	2008-2010	CrOSS	In-hospital mortality	CRC surgery	Single Centre	Pro	I-IV	894	NR	50%[b]
Vather et al. [24] Australia	2012-2014	I-score	Prolonged postoperative ileus	CR surgery (28% CRC)	Single Centre	Pro	NR	351	Mean 67 (SD 23)	NR
Watanabe et al. [25] Japan	2005-2010	N-RIC derived study model	SSI	CR surgery (88% CRC)	Single Centre	Retro	I-IV	538	65.5 (20-98)	NR
Murray et al. [26] USA	2006-2012	Preop ACS-NSQIP	30-day mortality	Elective CRC surgery	ACS-NSQIP database	Pro	I-IV	59.968	Median 67 (IQR 56-77)	NR
Rojas-Machando et al. [27] Spain	2003-2010	PROCOLE	Anastomotic leakage	CRC surgery	Single	Retro	I-III	123	NR	NR
Bailey et al. [28] USA	2009-2010	-	Post-acute care discharge	CRC surgery without postoperative complications	NY and California database	Pro	I-IV	32942	NR	NR
Rencuzogullari et al. [29] USA	2012-2014	ACS-NSQIP	Anastomotic leakage	65+ CRC surgery	ACS-NSQIP database	Pro	I-III	10392	Mean 74.9 (SD 7.1)	All
Zang et al. [30] China	2007-2012	-	Major Perioperative Cardiac Events	CRC surgery	Single Centre	Retro	I-IV	1899	NR	NR
Battersby et al. [31] UK/ Denmark	2009-2014	POLARS Score	LARS (EORTC) score	Elective rectal surgery (PME/ TME)	Multicentre	Retro	I-IV	1401	Mean 64.9 (29-92)	NR
Fieber et al. [32] USA	2008-2011	-	Multiple admissions within the year after CRC surgery	Elective CRC surgery	SID and SPARCS database	Pro	I-IV	14780	Median 69 (IQR 58-77)	47[b]
Hoshino et al. [33] Japan	2010-2013	JSCCR	Anastomotic leakage	Rectal surgery (LAR < 10 cm	JSCCR database	Pro	I-IV	936	Mean/ Median NR	29%[b]
Shen et al. [34] China	1998-2013	SCSECC SSISECC	Surgical complications SSI	65+ CRC surgery	Single Centre	Retro	I-IV	1008	Median 74 (65-99)	49% *75+*

Pro/retro pro- or retrospectively collected data; SD, standard deviation; IQR, interquartile range; PME, partial mesorectal excision; TME, total mesorectal excision

2

Table 2A Predictors for mortality

		Predictors							
Author	**Outcome**	Age	Gender	Tumour stage[1]	Comorbidity	Geriatric predictors	Biochemical predictors	Operative urgency (or mode of admission)	"Other predictors"
Tekkis et al. [10]	In-hospital mortality	√	-	√	CHD, Respiratory status	-	Hemoglobin, WBC, Sodium, Potassium, Urea,	√	ECG, Blood Pressure, Pulse, GCS, No of. procedures, Blood loss, Peritoneal Soiling
Fazio et al. [11]	30-day mortality	√	-	√	ASA score	-	Hematocrit	√	CR resection
Slim et al. [12]	90-day mortality	√	-	-	Neurological deficit			√	Weight loss
Cohen et al. [13]	1. 30-day mortality 2. 30-day overall morbidity 3. 30-day severe morbidity	√	-	√	COPD, Dyspnea BMI	Functional dependency	Creatinine, Albumin, PT time	√	Sepsis, Indication for surgery, Surgical extent, Wound Class
Farooq et al. [14]	1. 30-day mortality 2. Major morbidity	√	-	-	-	-	Urea, Sodium, Albumin	√	
Richards et al. [16]	30-day mortality	√	-	√	ASA score	-		√	Operative procedure[2]
Kiran et al. [18]	30-day mortality	√	-	√	ASA score, Renal failure or dialysis	Functional dependency	Albumin	√	
Van der Sluis et al. [20]	In-hospital mortality	√	-	√	CHD, Pulmonary failure	-		√	-
Kong et al. [23]	In-hospital mortality	√	-	-	CHD	-	Albumin	√	-
Murray et al. [26]	30-day mortality	√	-	√	ASA score, Renal failure, Ascites, CHD	Functional dependency	Albumin	-	-

√ Predictor included, - Predictor not included. BMI, body mass index, [1] Disseminated cancer or actual tumour stage; GCS, Glasgow Coma Scale; PT time, partial thromboplastin time;
WBC, white blood cell count; [2]Type of surgery; CR, colorectal; CHD, congestive heart disease including signs of heart failure.

Table 2B Predictors for anastomotic leakage

Author	Outcome	Predictors							
		Age	Gender	Tumour stage[1]	Comorbidity	Geriatric predictors	Biochemical predictors	Operative urgency (or mode of admission)	"Other predictors"
Dekker et al. [15]	Anastomotic leakage	√	√	-	BMI	-		√	Intoxication, Neoadjuvant therapy, Distance of anastomosis, Blood Loss, Additional procedures, Duration of surgery
Pasic et al. [19]	Anastomotic leakage		-	-	ASA score	-		-	Rectal tumours, Duration of surgery, Blood transfusion
Frasson et al. [21]	Anastomotic leakage	-	√	-	Oral Anticoagulants BMI	-		-	Intraoperative complication, Serum protein, Hospital size (No of beds)
Hu et al. [22]	Anastomotic leakage	-	√	-	Diabetes	-		-	Distance of anastomosis, Blood Loss
Rojas-Machando et al. [27]	Anastomotic leakage	-	√	-	ASA score, Diabetes, CV Disease, Respiratory Disease, Renal Disease, Hepatic Disease, Steroid use	-	Haemoglobin, WBC, Albumin,	√	Intoxications, Neoadjuvant treatment, Concurrent presented pathologies, Additional surgery, Mechanical anastomosis
Rencuzogullari et al. [29]	Anastomotic leakage	- [a]	√	-	ASA score, Diabetes, COPD Steroid use			√	Weight loss, Open Wound/ Wound infection, Duration of surgery
Hoshino et al. [33]	Anastomotic leakage	-	√	-	-	-	Albumin	-	Tumour location, Tumour diameter, Additional surgery

√ predictor included, - predictor not included. BMI, body mass index, [1] Stage IV (disseminated) cancer or actual tumour stage; WBC, white blood cell count; [2]Typ of surgery (colectomy, ostomy ect); CHF, congestive heart disease including signs of heart failure. [i]ntoxication include alcohol abuses and smoking. [a]Model development for patients of age ≥65.

Table 2C Predictors for surgical site infections (SSI) and other outcomes

Author	Outcome	Predictors							
		Age	Gender	Tumour stage[1]	Comorbidity	Geriatric predictors	Biochemical predictors	Operative urgency (or mode of admission)	"Other predictors"
Gervaz et al. [17]	1. SSI – superficial 2. SSI - deep	-	-	-	ASA score, Obesity	-	-	-	Contamination class, Laparotomy
Vather et al. [24]	Prolonged postoperative ileus	-	√	-	-	-	Albumin,	-	Open Surgery, Operation difficulty, Wound Size, RBC transfusion
Watanabe et al. [25]	SSI	-		-	ASA score	-	-	-	Wound Classification, Duration of surgery, Laparoscopic surgery
Bailey et al. [28]	Post-acute care discharge	√	√	-	No. comorbid conditions	-	-	√	Open surgery, New Ostomy, ≥1 admission in the previous year
Zhang et al. [30]	Major Perioperative Cardiac Events	√		-	Kidney Disease, Coronary Artery Disease, CHD	-	Hematocrit, Albumin	-	Intoxication (smoking), Blood Pressure, RBC transfusion
Battersby et al. [31]	LARS (EORTC) score	√	√	T-stage	-		-	√	Weight loss, TME Ostomy, Neoadjuvant Radiotherapy
Fieber et al. [32]	Multiple admissions within the year after CRC surgery	-		-	Elixhauser index	-	-	√	No of admission in the previous year, Primary Payer Health Insurance
Shen et al. [34]	Surgical Complications	- [a]		-	-	-	-	-	Bowel obstruction, Laparoscopic Surgery, Blood Loss, Classification of the incision, Intraoperative low body temperature
Shen et al. [34]	SSI	- [a]		-	BMI	-	C reactive protein, Electrolyte Imbalance	-	Bowel Obstruction, Thickness subcutaneous fat, Laparoscopic surgery, Blood Loss, Classification of the incision, Intraoperative low body temperature, faecal contamination

√ Predictor included, - predictor not included. BMI, body mass index; CHD, congestive heart disease; RBC, red blood cell;
[a] Model development for patients of age ≥ 65.

All the outcomes were considered relevant for older patients, all the non-mortality outcomes such as anastomotic leakage, surgical complications, LARS symptoms, multiple admission (health care usage) could result in delayed recovery and decrease in HRQoL. That also included surgical site infections. Due to the inclusion of intraoperative predictors, there were applicability concerns for preoperative decision making for thirteen studies.[10,15,17,19,21,22,24,25,28-31,34] The CR-POSSUM model for postoperative mortality [10] includes a peri-operative collected physiological score that cannot be calculated preoperatively. Inclusion of predictors such as intraoperative blood loss and duration of surgery,[15,19,25,29,30,34] intraoperative complications,[21] the distance of the anastomosis to the anal verge[15,22] limits the applicability for preoperative decision making.

Table 3 Applicability concern based on the CHARM checklist

	Applicability Concern		
	Participant selection	Predictors	Outcome
Mortality			
Tekkis et al. [10]	L	M	L
Fazio et al. [11]	L	L	L
Slim et al. [12]	L	L	L
Cohen et al. [13]	L	L	L
Farooq et al. [14]	L	L	L
Richards et al. [16]	L	L	L
Kiran et al. [18]	L	L	L
Van der Sluis et al. [20]	L	L	L
Kong et al. [23]	L	L	L
Murray et al. [26]	L	L	L
Anastomotic leakage			
Dekker et al. [15]	L	M	L
Pasic et al. [19]	M	M	L
Frasson et al. [21]	L	M	L
Hu et al. [22]	L	M	L
Rojas-Machando et al. [27]	H	L	L
Rencuzogullari et al. [29]	L	M	L
Hoshino et al. [33]	L	L	L
Other outcomes			
Gervaz et al. [17]	L	M	L
Vather et al. [24]	L	M	L
Watanabe et al. [25]	L	L	L
Bailey et al. [28]	L	L	L
Zhang et al. [30]	L	M	L
Battersby et al. [31]	L	L	L
Fieber et al. [32]	L	L	L
Shen et al. [34]	L	M	L

CHARMS; checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Model Studies. Criteria listed in the Appendix B.
L, low concern; M, moderate concern; H, high concern

Technical analysis and performance

Tables 4A-C shows the technical analysis and performance of all model. For mortality (Table 4A), the reported discrimination (AUC) of the models during model development ranged from 0.73 to 0.91. However, eight studies did not report confidence intervals.[11-14,16,18,23,26] The internal validation methods that were reported were random-split,[10,11,18,26] cross-validation,[13] two studies reported external validation.[16,20]

Additional external validation studies were found for the following models: CR-POSSUM,[39-42] CCF-CRM,[43] AFC Index,[44] CR-BHOM,[41] revised ACPGBI,[45] and IRCS.[42] Discrimination ranged from 0.56-0.89. However, calibration was considered poor except for the CR-BHOM and AFC model. Calibration could not be judged for the ACS-NSQIP model[13]. The performance of the CR-POSSUM[10] and CR-BHOM[14] models in a cohort of 991 Portuguese octogenarians were AUC 0.74 and 0.65, and poor and good calibration, respectively.[41]

For the anastomotic leakage models (Table 4B), discriminaton of the models ranged from 0.63 to 0.95 (in the development cohort). Discrimination in the development phase did not apply to the studies of Dekker et al.[15] and Rojas-Machado et al.[27] because of their meta-analysis approach for model development. Remarkably, the study of Pasic et al. reported an AUC of 1.0 (validation) without a confidence interval in a small study population of 40 patients.[19] Additional external validation studies were found for the CLS,[27,46] anastomoticleak.com,[46] and ACS-NSQIP anastomotic leakage model.[46] In these studies, AUC ranged from 0.58-0.80. Calibration could not be judged for the ACS-NSQIP anastomotic leakage model and JSCCR model.

For the "other" outcomes, the methodological and model performance analysis is shown in Table 4C. Of note, the discriminatory performance of the COLA-score model varied across the countries France, England and Switzerland (AUC 0.60-0.64), with poor calibration in all three cohorts.

Online calculators can be found for the CR-POSSUM[10], ACS-SNQIP[13,26,29] and ACPGBI models.[16] Other modes of presentation were a formula, chart or nomogram.

Table 4A Model performance and risk of bias for “mortality” prediction models

	Development			Validation				Presentation	Risk of bias				
Author	Events (n)	Predictors (n)	Discr. AUC	Type	Ref.	Discr. AUC	Calibr.		Participant Selection	Outcome	Predictor	Attrition	Analysis
Tekkis et al. [10]	387	18	0.90	External	39 40 41 42	0.78 0.74 0.74 0.65	O:E 0.75 O:E 1.25 H-L p<0.01 O:E 1.11	FOR-MULA	M	L	L	M	M
Fazio et al. [11]	116	6	0.80	External	43	0.81	H-L p=0.03	CHART	M	M	L	M	M
Slim et al. [12]	48	4	0.82	External	44	0.89	H-L p=0.37	CHART	L	L	L	M	M
Cohen et al. [13]	1126 7014 3290	15 15 15	0.91 0.68 0.72	Internal	-	0.91 0.68 0.73	NR	ONLINE[2]	M	L	L	L	M
Farooq et al. [1]4	50 80	5 5	0.81 0.70	External	41	0.56	O:E 1.0	FOR-MULA	M	L	L	H	M
Richards et al. [16]	153	5	0.73	External	45	0.83	H-L p<0.01	FOR-MULA	L	L	L	M	M
Kiran et al. [18]	817	7	NR	Internal	-	0.89	Plot	NOMO-GRAM	M	L	L	M	M
Van der Sluis et al. [20]	146	5	0.83	External[1]	 42	0.83 0.74	H-L p=0.51 H-L p<0.01	FOR-MULA	M	L	L	L	M
Kong et al. [23]	24	4	0.81	External[1]	-	0.85	H-L p=0.2	FOR-MULA	L	L	L	H	M
Murray et al. [26]	1080	8	0.82	Internal	-	0.83	H-L p=0.63 Plot	CHART	L	L	L	M	M

Calibr, Calibration; Discr. Discrimination; H-L: Hosmer-Lemeshow Chi-square X^2 (p-value); O:E expected/observed ratio, NR, not reported.
AUC Area Under the Curve with (95% CI) 95% Confidence Interval; NR, not reported; [1]External validation published together with internal validation.
Mode of presentation: [2] ONLINE, online calculator; Risk of bias: L, low risk; M, moderate; H, high risk.

Table 4B Model Performance and Risk of Bias for "Anastomotic leakage" Prediction Models

	Development			Validation				Presentation	Risk of bias				
Author	Events (n)	Predictors (n)	Discr. AUC	Type	Ref	Discr. AUC	Calibr.		Participant Selection	Outcome	Predictor	Attrition	Analysis
Dekker et al. [15]	10	11	0.95	External	27 46	0.65 0.80	NR	CHART	L	M	M	H	M
Pasic et al. [19]	14	4	NR	External[1]		1.0	NR	CHART	M	M	M	H	H
Frasson et al. [21]	277	6	0.63	External	46	0.73	NR	NOMO-GRAM[2]	L	L	L	M	M
Hu et al. [22]	63	4	NR	None	-			CHART	L	L	L	H	M
Rojas-Machando et al. [27]	31	23	0.82	None	-			CHART	M	M	M	L	M
Rencuzogullari et al. [2]9	332	9	0.65	External[1]	46	NR 0.58	O:E 1.1 NR	NOMO-GRAM	M	L	L	L	M
Hoshino et al. [33]	149	5	0.72	Internal		0.72	Plot	NOMO-GRAM	L	L	L	M	M

Calibr, Calibration; Discr. Discrimination; H-L: Hosmer-Lemeshow Chi-square X^2 (p-value); O:E expected/observed ratio. NA, not applicable; NR, not reported; CI, 95% Confidence Interval;

NR, not reported; [1]External validation published together with internal validation; Mode of presentation: [2] Including an online calculator.

Table 4C Model performance and risk of bias for "Other Outcomes" prediction models

	Development			Validation				Presentation	Risk of bias				
Author	Events	Predictor	Discr. AUC	Type	Ref.	Discr. AUC	Calibr.		Participant Selection	Outcome	Predictor	Attrition	Analysis
Gervaz et al . [17]	387	4	0.70	External	60	0.64 0.60	"poor"	CHART	L	L	H	H	M
Vather et al. [24]	116	6	0.68	None	-	-	NR	CHART	L	L	L	M	M
Watanabe et al. [25]	48	4	0.83	None	-	-		CHART	L	L	L	M	M
Bailey et al. [28]	1126 7014 3290	7	0.73	Internal	-	0.83	NR ("well")	CHART	M	L	L	M	M
Zhang et al. [30]	56	9	0.92	None	-	-	plot	NOMO-GRAM	L	M	M	M	M
Battersby et al. [31]	NA	6	0.62	External[1]	-	0.63	plot	CHART[2]	L	M	M	M	M
Fieber et al. [32]	1143	4	0.64	External[1]	-	0.63	O:E 1.0	CHART	M	L	L	H	M
Shen et al. [34] *(SCSECC)*	118	5	NR	Internal	-	0.74	H-L p=0.81	FOR-MULA	M	L	M	H	M
Shen et al. [34] *(SSISEC)*	72	10	0.80	Internal	-	0.82	H-L p=0.93	NOMO-GRAM	M	L	M	H	M

Discr. Discrimination; Calibr. Calibration. H-L: Hosmer-Lemeshow, O:E expected/observed ratio. Chi-square X^2 (p-value); NR, not reported; CI, 95% Confidence Interval; NR, not reported; [1]External validation published together with internal validation
Mode of presentation: [2]Including an online calculator; Risk of bias: L, low risk; M, moderate risk; H, high risk.

Critical appraisal

Also shown in Tables 4A-C is the quality assessment of the studies. The risk for bias can be subdivided into selection bias (participant selection and sample attrition), information bias (predictor and outcome assessment concerns) and analysis concerns.

Selection bias

The risk of selection bias for the prediction models studied was rated moderate to high; eight studies rated 'high' for risk of selection bias. In two studies, participant selection was unclear.[19,27] For these studies and five others that did not report loss of follow up, there were high attrition concerns.[14,16,17,20,31] In only four prediction model studies, there was no loss of follow-up.[13,20,21,29]

Information bias

In the majority of the studies, the risk of information bias related to the outcome was considered low. Three studies[15,19,27] did not use data-driven predictor selection, but predictor selection was based on a meta-analysis or Delphi Round. In the studies that did not have mortality as an outcome, the risk was higher due to the unclear measurement of the outcome, lack of blinding or non-standardised timing of the outcome.

Analysis bias

Lastly, for the risk related to the analysis, all studies were rated 'moderate' to 'high'. In the majority of the studies, the number of missing values was not reported, and predictors were included not independent of the p-value. Other concerns were related to the small sample sizes for estimation of the predictor effect; the event/ predictor ratio being less than ten events per predictor in seven studies[19,22,23,27,30,34]

In 6 out of the 25 studies, internal or external validation was not performed or reported.[14,15,22,24,25,27] Therefore assessment of potential overfitting and optimism could not be assessed.

Discussion

We identified 26 prediction models out of 25 studies for postoperative outcomes of colorectal surgery; ten models studied mortality as an outcome and seven anastomotic leakages. Other outcomes were surgical complications, gastrointestinal problems (including prolonged ileus), perioperative cardiac events, readmissions, and discharge not to home. The average age of included patients ranged from 61 to 76. Two models were exclusively developed for patients of 65 and older. We found no models with quality of life or functional dependency as an outcome. Age, gender and ASA score were common predictors. Twelve studies included intraoperative predictors, such as surgical extent, the distance of the anastomosis, duration of surgery, and intraoperative complications, including both models for older patients, which limits their use for preoperative decision making.[29,34]

There were methodological concerns relating to sample in size (28%), missing external validation (42%) and not reporting on calibration (28%). Information bias and analysis bias was considered moderate to high in 22 studies (88%). In external validation studies, discrimination and calibration were more likely to be worse compared to the original study. Based on the applicability and methodological concerns, no useful model for older patients was identified that could be used for preoperative shared decision making.

For older patients risks and benefits of treatment must be weighted at an individual level. Identification of high-risk patients enables the initiation of geriatric interventions such as prehabilitation[47] that could reduce the risk. In older medical oncology patients, a Geriatric Assessment (GA) has been shown to reveal previously unknown medical issues that are associated with poor outcomes of treatment,[48,49] including surgical oncology.[50] Potential predictors of surgical outcomes in older patients are comorbidity, functional dependency [13,18,26], falls and cognitive impairments.[51] Introduction of such predictors in existing prediction tools may improve a prediction model's performance for older patients.

Methodological concerns affect clinical applicability and generalizability of prediction models. Especially in small datasets, the effect of included predictors may be overestimated.[15,19,23,34] Hence, alternative methods are available for the selection process of candidate predictors to reduce this risk of overestimation. These include selecting candidate predictors based on meta-analysis or literature[15,27], or more modern techniques such as least absolute shrinkage and selection operator (LASSO).[31,52] These methods still need a sufficient sample size to provide reliable estimations.

Concerns in generalisability exist, when data-driven models are not internally or externally validate.[22,24,25,27,30] Furthermore, a split-sample validation does not assess the external validity of a model in the development study.[10,11,18,26,32,34] For more recently published models, it was more easy to judge bias and applicability, because these were more often reported in line with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD)[53]. That does not disqualify the validity of the earlier developed models, however it hampers the formal assessment of the quality and performance and applicability for older patients as used by the CHARMS checklist.

This review summarised the information available on the included predictors and performance of the different models. By selecting 25 studies out of almost 1900 publications, it is unlikely that we missed any unknown prediction models, which adds to the strength of this review. The assessment of the risk of bias aids in the critical appraisal of a prediction model for clinical practice. Albeit, the various prediction models did not prove to be specifically useful for older CRC patients.

There are some limitations to our review. First, we focused on clinical prediction models, excluding studies only describing logistic models without further analysis of their model performance. Second, with 25 studies included in this review, we decided not to assess the individual predictors on their association with the outcomes. Therefore, no information is provided on the weight of predictors, although the CHARMS checklist suggests providing these details.[7] For these details as well as for the definition of outcomes such as anastomotic leakage and severe morbidity were refer to the individual studies.

Recommendations for future research

For prediction model development and validation studies, sample size should be sufficient to reliably estimate a model's performance. Furthermore, for prognostic research, calibration measures (reliability of the prediction for the different risk groups) within external validation studies have more importance then discrimination (who is at risk and who is not)[54] because only reliable individual risks predictions can be used to make treatment decisions.

Also, a model may require periodic updating because of changes in the population under interest.[55] Outcomes of colorectal surgery have improved due to care innovations such as auditing, ERAS (including laparoscopic surgery),[56] neoadjuvant treatment and wait-and-see policies for rectal cancer (after complete remission after radiotherapy) and liberal use of defunctioning colostomy.[57] Furthermore, a decrease in 30-day and one-year mortality after CRC surgery occurred in the past decades.[58,59]

Lastly, transparent reporting of future prediction model studies can improve by systematically using the TRIPOD guidelines.[53]

Conclusion

Many prediction models are available that address mortality and surgical complications after colorectal surgery, but not for prediction of quality of life or functional decline. Most of these models were not developed for older patients and include only a limited number of risk factors specific to older patients. Half of the included prediction models included peri-operative predictors, which limit their use for preoperative decision making. Future research should address geriatric characteristics to improve prediction models for preoperative decision making with older patients.

Acknowledgements

We thank Dr. N. van der Werf, Walaeus Medical Library of Leiden University Medical Centre, for her expertise in developing an appropriate search strategy for this review.

References

1. Hamaker ME, Prins MC, Schiphorst AH, van Tuyl SA, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. *Journal of Geriatric Oncology.* 2015;6(2):153-64.
2. Dekker JW, Gooiker GA, Bastiaannet E, van den Broek CB, van der Geest LG, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. *European Journal of Surgical Oncology.* 2014;40(11):1481-7.
3. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Annals of Surgical Oncology.* 2012;19(8):2428-34.
4. Kolfschoten NE, Wouters MW, Gooiker GA, Eddes EH, Kievit J, Tollenaar RA, et al. Nonelective colon cancer resections in elderly patients: results from the dutch surgical colorectal audit. *Digestive Surgery.* 2012;29(5):412-9.
5. Corner J, Wright D, Hopkinson J, Gunaratnam Y, McDonald JW, Foster C. The research priorities of patients attending UK cancer treatment centres: findings from a modified nominal group study. *British Journal of Cancer.* 2007;96(6):875-81.
6. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine.* 2009;6(7):e1000097.
7. Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Medicine.* 2014;11(10):e1001744.
8. Smit HA, Pinart M, Anto JM, Keil T, Bousquet J, Carlsen KH, et al. Childhood asthma prediction models: a systematic review. *Lancet Respir Med.* 2015;3(12):973-84.
9. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. *CA: A Cancer Journal for Clinicians.* 2017;67(3):177-93.
10. Tekkis PP, Prytherch DR, Kocher HM, Senapati A, Poloniecki JD, Stamatakis JD, et al. Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM). *British Journal of Surgery.* 2004;91(9):1174-82.
11. Fazio VW, Tekkis PP, Remzi F, Lavery IC. Assessment of operative risk in colorectal cancer surgery: the Cleveland Clinic Foundation colorectal cancer model. *Diseases of the Colon and Rectum.* 2004;47(12):2015-24.
12. Slim K, Panis Y, Alves A, Kwiatkowski F, Mathieu P, Mantion G. Predicting postoperative mortality in patients undergoing colorectal surgery. *World Journal of Surgery.* 2006;30(1):100-6.
13. Cohen ME, Bilimoria KY, Ko CY, Hall BL. Development of an American College of Surgeons National Surgery Quality Improvement Program: Morbidity and Mortality Risk Calculator for Colorectal Surgery. *Journal of the American College of Surgeons.* 2009;208(6):1009-16.
14. Farooq N, Patterson AJ, Walsh SR, Prytherch DR, Justin TA, Tang TY. Predicting outcome following colorectal cancer surgery using a colorectal biochemical and haematological outcome model (Colorectal BHOM). *Colorectal Disease.* 2011;13(11):1237-41.
15. Dekker JW, Liefers GJ, de Mol van Otterloo JC, Putter H, Tollenaar RA. Predicting the risk of anastomotic leakage in left-sided colorectal surgery using a colon leakage score. *Journal of Surgical Research.* 2011;166(1):e27-34.
16. Richards CH, Leitch EF, Anderson JH, McKee RF, McMillan DC, Horgan PG. The revised ACPGBI model is a simple and accurate predictor of operative mortality after potentially curative resection of colorectal cancer. *Annals of Surgical Oncology.* 2011;18(13):3680-5.
17. Gervaz P, Bandiera-Clerc C, Buchs NC, Eisenring MC, Troillet N, Perneger T, et al. Scoring system to predict the risk of surgical-site infection after colorectal resection. *British Journal of Surgery.* 2012;99(4):589-95.
18. Kiran RP, Attaluri V, Hammel J, Church J. A novel nomogram accurately quantifies the risk of mortality in elderly patients undergoing colorectal surgery. *Annals of Surgery.* 2013;257(5):905-8.
19. Pasic F, Salkic NN. Predictive score for anastomotic leakage after elective colorectal cancer surgery: a decision making tool for choice of protective measures. *Surgical Endoscopy.* 2013;27(10):3877-82.
20. van der Sluis FJ, Espin E, Vallribera F, de Bock GH, Hoekstra HJ, van Leeuwen BL, et al. Predicting postoperative mortality after colorectal surgery: a novel clinical model. *Colorectal Disease.* 2014;16(8):631-9.

21. Frasson M, Flor-Lorente B, Rodriguez JLR, Granero-Castro P, Hervas D, Alvarez Rico MA, et al. Risk factors for anastomotic leak after colon resection for cancer: Multivariate analysis and nomogram from a multicentric, prospective, national study with 3193 patients. *Annals of Surgery.* 2015;262(2):321-30.
22. Hu X, Cheng Y. A Clinical Parameters-Based Model Predicts Anastomotic Leakage After a Laparoscopic Total Mesorectal Excision: A Large Study With Data From China. *Medicine (Baltimore).* 2015;94(26):e1003.
23. Kong CH, Guest GD, Stupart DA, Faragher IG, Chan ST, Watters DA. Colorectal preOperative Surgical Score (CrOSS) for mortality in major colorectal surgery. *ANZ Journal of Surgery.* 2015;85(6):403-7.
24. Vather R, Josephson R, Jaung R, Robertson J, Bissett I. Development of a risk stratification system for the occurrence of prolonged postoperative ileus after colorectal surgery: A prospective risk factor analysis. *Surgery (United States).* 2015;157(4):764-73.
25. Watanabe M, Suzuki H, Nomura S, Hanawa H, Chihara N, Mizutani S, et al. Performance Assessment of the Risk Index Category for Surgical Site Infection after Colorectal Surgery. *Surgical Infections.* 2015;16(1):84-9.
26. Murray AC, Mauro C, Rein J, Kiran RP. 30-day mortality after elective colorectal surgery can reasonably be predicted. *Techniques in Coloproctology.* 2016;20(8):567-76.
27. Rojas-Machado SA, Romero-Simo M, Arroyo A, Rojas-Machado A, Lopez J, Calpena R. Prediction of anastomotic leak in colorectal cancer surgery based on a new prognostic index PROCOLE (prognostic colorectal leakage) developed from the meta-analysis of observational studies of risk factors. *International Journal of Colorectal Disease.* 2016;31(2):197-210.
28. Bailey EA, Hoffman RL, Wirtalla C, Karakousis G, Kelz RR. Development and validation of a prediction model for patients discharged to post-acute care after colorectal cancer surgery. *Surgery.* 2017;161(4):1049-57.
29. Rencuzogullari A, Benlice C, Valente M, Abbas MA, Remzi FH, Gorgun E. Predictors of Anastomotic Leak in Elderly Patients After Colectomy: Nomogram-Based Assessment From the American College of Surgeons National Surgical Quality Program Procedure-Targeted Cohort. *Diseases of the Colon and Rectum.* 2017;60(5):527-36.
30. Zhang J, Xiao Y, Yang D, Zhuang X, Wang L, Gao X, et al. Development of a new risk nomogram of perioperative major adverse cardiac events for Chinese patients undergoing colorectal carcinoma surgery. *International Journal of Colorectal Disease.* 2017;32(8):1157-64.
31. Battersby NJ, Bouliotis G, Emmertsen KJ, Juul T, Glynne-Jones R, Branagan G, et al. Development and external validation of a nomogram and online tool to predict bowel dysfunction following restorative rectal cancer resection: the POLARS score. *Gut.* 2018;67(4):688-96.
32. Fieber JH, Sharoky CE, Collier KT, Hoffman RL, Wirtalla C, Kelz RR, et al. A preoperative prediction model for risk of multiple admissions after colon cancer surgery. *Journal of Surgical Research.* 2018;231:380-6.
33. Hoshino N, Hida K, Sakai Y, Osada S, Idani H, Sato T, et al. Nomogram for predicting anastomotic leakage after low anterior resection for rectal cancer. *International Journal of Colorectal Disease.* 2018;33(4):411-8.
34. Shen Z, Lin Y, Ye Y, Jiang K, Xie Q, Gao Z, et al. The development and validation of a novel model for predicting surgical complications in colorectal cancer of elderly patients: Results from 1008 cases. *European Journal of Surgical Oncology.* 2018;44(4):490-5.
35. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *British Journal of Surgery.* 1991;78(3):355-60.
36. Tekkis PP, Poloniecki JD, Thompson MR, Stamatakis JD. Operative mortality in colorectal cancer: prospective national study. *Bmj.* 2003;327(7425):1196-201.
37. Longo WE, Virgo KS, Johnson FE, Oprian CA, Vernava AM, Wade TP, et al. Risk factors for morbidity and mortality after colectomy for colon cancer. *Diseases of the Colon and Rectum.* 2000;43(1):83-91.
38. Ragg JL, Watters DA, Guest GD. Preoperative risk stratification for mortality and major morbidity in major colorectal surgery. *Diseases of the Colon and Rectum.* 2009;52(7):1296-303.
39. Ramkumar T, Ng V, Fowler L, Farouk R. A comparison of POSSUM, P-POSSUM and colorectal POSSUM for the prediction of postoperative mortality in patients undergoing colorectal resection. *Diseases of the Colon and Rectum.* 2006;49(3):330-5.
40. Bromage SJ, Cunliffe WJ. Validation of the CR-POSSUM risk-adjusted scoring system for major colorectal cancer surgery in a single center. *Diseases of the Colon and Rectum.* 2007;50(2):192-6.

41. Gomes A, Rocha R, Marinho R, Sousa M, Pignatelli N, Carneiro C, et al. Colorectal surgical mortality and morbidity in elderly patients: comparison of POSSUM, P-POSSUM, CR-POSSUM, and CR-BHOM. *International Journal of Colorectal Disease*. 2015;30(2):173-9.
42. Bare M, Alcantara MJ, Gil MJ, Collera P, Pont M, Escobar A, et al. Validity of the CR-POSSUM model in surgery for colorectal cancer in Spain (CCR-CARESS study) and comparison with other models to predict operative mortality. *BMC Health Services Research*. 2018;18(1):49.
43. Dogrul AB, Kilic YA, Celebi AE, Celik S, Dumlu GE, Cetinkaya E, et al. External validation of Cleveland Clinic Foundation colorectal cancer model in a University Clinic in terms of predicting operative mortality. *Techniques in Coloproctology*. 2010;14(1):9-12.
44. Alves A, Panis Y, Mantion G, Slim K, Kwiatkowski F, Vicaut E. The AFC score: validation of a 4-item predicting score of postoperative mortality after colorectal resection for cancer or diverticulitis: results of a prospective multicenter study in 1049 patients. *Annals of Surgery*. 2007;246(1):91-6.
45. Degett TH, Roikjaer O, Iversen LH, Gogenur I. A model predicting operative mortality in the UK has only limited value in Denmark. *International Journal of Colorectal Disease*. 2018;33(2):141-7.
46. Sammour T, Cohen L, Karunatillake AI, Lewis M, Lawrence MJ, Hunter A, et al. Validation of an online risk calculator for the prediction of anastomotic leak after colon cancer surgery and preliminary exploration of artificial intelligence-based analytics. *Techniques in Coloproctology*. 2017;21(11):869-77.
47. Barberan-Garcia A, Ubre M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. *Annals of Surgery*. 2018;267(1):50-6.
48. Audisio RA, Pope D, Ramesh HS, Gennari R, van Leeuwen BL, West C, et al. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. *Critical Reviews in Oncology/Hematology*. 2008;65(2):156-63.
49. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. *Journal of Clinical Oncology*. 1998;16(4):1582-7.
50. Feng MA, McMillan DT, Crowell K, Muss H, Nielsen ME, Smith AB. Geriatric assessment in surgical oncology: a systematic review. *Journal of Surgical Research*. 2015;193(1):265-72.
51. Souwer ETD, Hultink D, Bastiaannet E, Hamaker ME, Schiphorst A, Pronk A, et al. The Prognostic Value of a Geriatric Risk Score for Older Patients with Colorectal Cancer. *Annals of Surgical Oncology*. 2018.
52. Tibshirani R. Regression Shrinkage and Selection via the Lasso. *Journal of the Royal Statistical Society Series B (Methodological)*. 1996;58(1):267-88.
53. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Annals of Internal Medicine*. 2015;162(1):55-63.
54. Collins GS, de Groot JA, Dutton S, Omar O, Shanyinde M, Tajar A, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC Medical Research Methodology*. 2014;14:40.
55. Minne L, Eslami S, de Keizer N, de Jonge E, de Rooij SE, Abu-Hanna A. Effect of changes over time in the performance of a customized SAPS-II model on the quality of care assessment. *Intensive Care Medicine*. 2012;38(1):40-6.
56. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. *Colorectal Disease*. 2014;16(12):947-56.
57. Snijders HS, van den Broek CB, Wouters MW, Meershoek-Klein Kranenbarg E, Wiggers T, Rutten H, et al. An increasing use of defunctioning stomas after low anterior resection for rectal cancer. Is this the way to go? *Eur J Surg Oncol*. 2013;39(7):715-20.
58. Breugom AJ, Bastiaannet E, Dekker JWT, Wouters M, van de Velde CJH, Liefers GJ. Decrease in 30-day and one-year mortality over time in patients aged >/=75 years with stage I-III colon cancer: A population-based study. *European Journal of Surgical Oncology*. 2018;44(12):1889-93.
59. Bos A, Kortbeek D, van Erning FN, Zimmerman DDE, Lemmens V, Dekker JWT, et al. Postoperative mortality in elderly patients with colorectal cancer: The impact of age, time-trends and competing risks of dying. *European Journal of Surgical Oncology*. 2019.
60. Grant R, Aupee M, Buchs NC, Cooper K, Eisenring MC, Lamagni T, et al. Performance of surgical site infection risk prediction models in colorectal surgery: external validity assessment from three European national surveillance networks. *Infection Control and Hospital Epidemiology*. 2019:1-8.

Appendix A Full search Pubmed and Embase

Pubmed

(”Colon”[majr] OR ”Colon”[ti] OR ”colonic”[ti] OR ”colorectal”[ti] OR ”Rectum”[majr] OR ”Rectum”[ti] OR ”rectal”[ti] OR ”large bowel”[ti] OR lower gastro*[ti]) AND (”Colorectal Surgery”[majr] OR ”General Surgery”[majr] OR ”surgery”[ti] OR ”surgical”[ti] OR ”Colectomy”[majr] OR ”Colectomy”[ti] OR ”Colectomies”[ti] OR resect*[ti] OR dissect*[ti] OR ”Anastomosis, Surgical”[Majr:NoExp] OR ”anastomosis”[ti] OR ”anastomoses”[ti] OR ”anastomotic”[ti] OR ”Surgical Stomas”[majr] OR ”stoma”[ti] OR ”stomas”[ti] OR ”Ostomy”[Majr:NoExp] OR ”Ostomy”[ti] OR ”ostomies”[ti] OR ”Enterostomy”[majr] OR ”Enterostomy”[ti] OR ”Enterostomies”[ti] OR ”Colostomy”[ti] OR ”Colostomies”[ti] OR ”Ileostomy”[ti] OR ”Ileostomies”[ti]) AND (”Decision Support Techniques”[Mesh] OR ”Nomograms”[Mesh] OR nomogram*[tw] OR ((model*[tw] OR calculat*[tw]) AND (predict*[tw] OR ”Risk”[Mesh] OR ”risk”[tw] OR ”risks”[tw]))) NOT (”animals”[mesh] NOT ”humans”[mesh])

Embase

(exp *colon/ OR ”Colon”.ti. OR ”colonic”.ti. OR ”colorectal”.ti. OR exp *rectum/ OR ”Rectum”.ti. OR ”rectal”.ti. OR ”large bowel”.ti. OR lower gastro*.ti.) AND (exp *colorectal surgery/ OR *general surgery/ OR ”surgery”.ti. OR ”surgical”.ti. OR exp *colon resection/ OR ”Colectomy”.ti. OR ”Colectomies”.ti. OR resect*.ti. OR dissect*.ti. OR exp *anastomosis/ OR ”anastomosis”.ti. OR ”anastomoses”.ti. OR ”anastomotic”.ti. OR *stoma/ OR *colon stoma/ OR *ileostoma/ OR ”stoma”.ti. OR ”stomas”.ti. OR *ostomy/ or *enterostomy/ OR ”Ostomy”.ti. OR ”ostomies”.ti. OR ”Enterostomy”.ti. OR ”Enterostomies”.ti. OR ”Colostomy”.ti. OR ”Colostomies”.ti. OR ”Ileostomy”.ti. OR ”Ileostomies”.ti.) AND (exp decision support system/ OR nomogram/ OR nomogram*.ti,ab. OR ((model*.ti,ab. OR calculat*.ti,ab.) AND (predict*.ti,ab. OR risk/ OR mortality risk/ OR patient risk/ OR risk factor/ OR ”risk”.ti,ab. OR ”risks”.ti,ab.))) NOT conference abstract.pt. NOT (animal/ NOT human/)

Appendix B Criteria for scoring of risk of bias based on the CHARMS checklist

Potential Bias	Risk of bias		Items to be considered for potential bias
Participant selection	L	Low risk if	- selection bias was unlikely, - study avoided inappropriate inclusions or exclusions, - in- and exclusion criteria were adequately described - participants were enrolled at a similar presentation of their disease - differences were accounted for by including appropriate predictors in the analysis
Selective inclusion	M	Moderate risk if	- not satisfying one of the above OR - no adequate description of the recruitment of the study sample - no adequate description of the sample for key predictors
	H	High risk if	if both items were not adequately described
Predictor assessment	**Risk of bias**		
	L	Low risk if	- predictor definitions were the same for all participants - predictor measurement was blinded to outcome data - all predictors were available at the time the model is intended to be used - predictors were measured with valid and reproducible methods such that misclassification was limited and if - predictors were assessed in a similar way for all study participants
Treatment predictors; do the modify outcome and were they handled appropriately	M	Moderate risk if	one of the criteria was not satisfied
	H	High risk if	if method for assessment of outcome was not adequately described
Outcome assessment	**Risk of bias**		
	L	Low risk if	- the outcome was pre-specified and - measured with sufficient validity and reproducibility and - measured in a similar way for all study participants and - if the outcome was assessed independently from the assessment of predictors Note: for easy to obtain predictors such as gender, it is not possible to assess outcome independent of predictor information
	M	Moderate risk if	one of the criteria was not satisfied
	H	High risk if	the assessment of outcome was not adequately described
Attrition	**Risk of bias**		
	L	Low risk if	there was no loss-to-follow-up - there were no important differences on key characteristics between included participants and those who were lost-to-follow-up or missing
	M	Moderate risk if	- loss-to-follow-up was lower than 20% and - there were no important differences on key characteristics between included participants and those who were lost-to-follow-up or missing OR: - loss-to-follow-up was higher than 20% but missing data and loss-to-follow-up were imputed adequately or there were no important differences on key characteristics between included participants and those who were lost-to-follow-up or missing

	H	High risk if	- loss-to-follow-up was higher than 20% and/or - there were important differences on key characteristics between included participants and those who were lost-to-follow-up or missing or -loss-to-follow-up was not described
Analysis (including? time interval between predictor and outcome was reasonable, part of eligibility)	**Risk of bias**		
	L	Low risk if	- relevant aspects of analysis were described allowing to judge the quality of the analysis to be adequate - # outcome events per candidate predictor reasonable - missing data handled appropriately or no differences - predictors included independent of p-value - overfitting and optimism accounted for - weights assigned according to the regression coefficient - calibration and discrimination assessed - recalibrated or described that it was not needed
	M	Moderate risk if	- relevant aspects of analysis were described allowing to judge the quality of the analysis to be adequate and part or none of the model evaluation items were reported
	H	High risk if	not satisfying any of the aspects under low risk of bias

Applicability concert	**Applicability concern**		**Items to be considered for applicability concern**
Participant selection	**L**	Low if	Truly representative of an average elderly patient with colorectal cancer And > 30% older patients (65) were included
	M	Moderate if	Somewhat representative of the average older patient with colorectal cancer
	H	High if	Not representative of the average older patient with colorectal cancer OR no clear definition
Predictor	**Applicability concern**		
	L	Low risk if	- Predictors are available for older patients with colorectal cancer and - All Predictors are ***preoperatively*** assessed
	M	Moderate if	One of the above criteria was not met
	H	High if	Both criteria were not met
Outcome	**Applicability concern**		
	L	Low if	- Outcome applicable to older patients with colorectal cancer - Outcomes discussed could change a treatment decision
	M	Moderate if	If one of the above criteria was not met
	H	High if	None of the criteria was met

Chapter 3

Risk stratification for surgical outcomes in older colorectal cancer patients using ISAR-HP and G8 screening tools

Journal of Geriatric Oncology 2018;9(2):110-114

E.T.D. Souwer
N.M. Verweij
F. van den Bos
E. Bastiaannet
R.M.E. Slangen
W.H. Steup
M.E. Hamaker
J.E.A. Portielje

Abstract

Background: Older patients are at risk for adverse outcomes after surgical treatment of cancer. Identifying patients at risk could affect treatment decisions and prevent functional decline. Screening tools are available to select patients for Geriatric Assessment. Until now, their predictive value for adverse outcomes in older colorectal cancer patients has not been investigated.

Objective: To study the predictive value of the Geriatric 8(G8) and Identification of Seniors at Risk for Hospitalized Patients (ISAR-HP) screening tools for adverse outcomes after elective colorectal surgery in patients older than 70 years. Primary outcomes were 30-day complication rates; secondary outcomes were the length of hospital stay and six-month mortality.

Patients and methods: Multicentre cohort study from two hospitals in the Netherlands. Frail was defined as a G8≤14 and/or ISAR-HP ≥2. Odds Ratio (OR) is given with 95% CI.

Results: Overall, 139 patients (52%) out of 268 patients were included; 32 patients (23%) were ISAR-HP-frail, 70 (50%) were G8-frail, 20 were frail on both screening tools. Median age was 77.7 years. ISAR-HP frail patients were at risk for 30-day complications OR 2.4 (CI 1.1-5.4, p= 0.03), readmission OR 3.4 (1.1-11.0), cardiopulmonary complications OR 5.9 (1.6-22.6), longer hospital stay (10.3 versus 8.9 days) and six-month mortality OR 4.9 (1.1-23.4). When ISAR-HP and G8 were combined OR increased for readmission, 30-day and six-month mortality. G8 alone had no predictive value.

Conclusions: ISAR-HP-frail patients are at risk for adverse outcomes after colorectal surgery. ISAR-HP combined with G8, has the strongest predictive value for complications and mortality.

Introduction

In the Netherlands, more than 13,000 patients are diagnosed with colorectal cancer every year.[1] Colorectal cancer is predominantly a disease of the elderly as 60% of patients are over 70 years of age at time of diagnosis and the number of older patients in the next two decades is expected to increase by another 40%.[2]
Older patients are a heterogeneous group with a great variety in comorbidity, physiological reserves, geriatric impairments and functionality.[3,4] As a result of these differences, benefit from treatment can differ and the elderly are at risk for adverse health outcomes after major stressors like emergency department visits, hospitalization, cancer and its treatment.[5,6] Selecting optimal treatment for older patients is challenging as age, cognitive functioning, physical functioning and comorbidities are related to adverse outcomes and death.[7-10] The International Society of Geriatric Oncology (SIOG) recommends assessment of patient's physiological reserve using a geriatric assessment (GA).[11] A GA can detect health issues and functional problems that are often missed in a regular oncological workup while they are associated with poor oncological outcomes.[12] With an increasing number of older patients diagnosed with cancer, screening methods have been developed to identify those at risk for adverse health outcomes and who may benefit from a comprehensive geriatric evaluation and interventions. At present, several screening methods are proposed in the SIOG guideline to select patients for subsequent GA.[13] The screening questionnaire Geriatric 8 (G8) proved to have the highest sensitivity compared to the TRST 1+, GFI and VES-13 screening tools[14] Unfortunately, specificity and positive predictive value of the G8 are low, resulting in high numbers of unnecessary GA and low predictive value for outcomes. Therefore, a GA is still considered the golden standard for identifying frail patients and predicting adverse outcomes.[14]

In 2012 the Identification of Seniors At Risk-Hospitalized Patients (ISAR-HP) was developed to select patients that are at risk for functional decline both during and after hospital admission.[15] It was validated in adults ≥65 years of age.[15,16]

From 2015 onward hospitals in the Netherlands are required by The Dutch Health Care Inspectorate to screen older colorectal cancer patients for vulnerability (patients with urgent or emergency surgery are excluded). Both the G8 and the ISAR-HP may be used for this purpose.[17]

The objective of this study was to assess the predictive value of the G8 and ISAR-HP for adverse outcomes after colorectal cancer surgery in elderly patients aged 70 years and older with stage I-III colorectal cancer. Outcomes of interest were postoperative complications, rates of readmissions, early death (30-days) and six-month mortality. Analysis of the best performing screening tool would give insight into patient's characteristics that are associated with these adverse outcomes.

Patients and methods

Study design

We conducted a cohort study using a prospectively collected database and electronic hospital records. Data was collected from two teaching hospitals in the Netherlands: the Hagaziekenhuis in The Hague and the Diakonessenhuis in Utrecht. The prospectively collected database consisted of data from the Dutch Surgical Colorectal Audit (DSCA) that is also used for quality purposes and collects data from all Dutch patients who had surgery for colorectal carcinoma.[18]

Patient selection

We identified all patients aged >70 years, who had surgical treatment for colorectal cancer between May 1st 2014 and August 1st 2016. Patients with non-elective surgery, Transanal Endoscopic Microsurgery (TEM), metastatic disease (stage IV) and patients with synchronous cancer were excluded. The primary outcomes of interest were 30-day complication rates, readmission rates and 30-day mortality. Secondary outcomes were the length of hospital stay and six-month mortality

Frailty assessment

In both hospitals, the ISAR-HP and G8 frailty screening questionnaires were part of the workup for older patients with the diagnosis of colorectal cancer. Both screening tools were performed by qualified nurses as part of the diagnostic workup prior to surgery. The G8 questionnaire consists of eight items with a total score ranging from zero to seventeen. It contains questions about food intake, weight loss, mobility, self-evaluation of health status, neuropsychological problems, body mass index (BMI), polypharmacy and age.[19] Patients with a score of >14 were regarded as 'fit' (G8-fit). Patients with a score of ≤ 14 were regarded as potentially 'frail' (G8–frail). The ISAR-HP consists of four questions about the need for assistance in instrumental activities of daily living (iADL), travelling, use of a walking device and about education. Scores range from 0 to 2 points with a maximum total score of 5. Patients with a score of <2 were regarded as 'fit' (ISAR-HP-fit), Appendix A. A cut-off score of ≥2 is defined as abnormal; these patients were regarded as potentially 'frail' (ISAR-HP-frail), Appendix B.

Data collection

Data retrieved from the DSCA database included the following patient information: age, Body Mass Index (BMI; kg/m^2), Charlson Comorbidity Index (CCI),[10] American Society of Anaesthesiologist (ASA) score,[20] tumour location, preoperative tumour complications, tumour stage (TNM 5th edition), (neo) adjuvant treatment (radiotherapy/chemoradiation or chemotherapy) and type of resection (classified as open or laparoscopic resection). Moreover, surgical and non-surgical complications are defined as complications within 30 days of surgery. Surgical complications that needed reintervention are being registered separately and include anastomotic leakage. Non-surgical complications are registered as 1) cardiac, 2) pulmonary, 3) neurological, 4) thrombo-embolic, 5) infectious and 6) 'other' complications that occurred after surgery. A patient having 2 pulmonary and 2 infectious complications post surgery is registered as 1 pulmonary complication and 1 infectious complication. Additionally all re-interventions, length of hospital stay, 30-day readmissions and 30-day mortality are entered. Data entry in this database is done by a qualified data-entry manager or nurse.

From electronic hospital records, the following data was extracted from the day of admission prior to surgery: Katz Index of Independence in Activities of Daily Living (Katz-6)[21] with a cut-off ≥2 considered as activities of daily living dependent, the use of a walking device, reported falls within the 6 months before surgery, impaired malnutrition screening scores from the Short Nutritional Assessment Questionnaire (SNAQ; cut-off ≥2)[22] or Malnutrition Universal Screening Tool (MUST; cut-off ≥1),[23] self-reported cognitive impairment.

In addition a delirium was registered as complication separately when it was recorded in the electronic hospital record as such by the treating or consulting physician. When applicable, the cause of death was also extracted. Trough a linkage with the Municipal Personal Records Database, the exact date of death was retrieved and six-month mortality (182-days) was calculated from the date of surgery to time of death. Follow-up of all patients was at least 183 days. The regional ethics committee and institutional review board of both hospitals approved this study.

Statistical analysis

Patients were classified as 'screened' if a G8 and/or ISAR-HP screening was performed prior to surgery. We performed descriptive analysis of patient's characteristics for both screened and non-screened patients and for the best performing screening tool. Normally distributed variables are presented as a mean with standard deviation (SD) and for non-normal distributed as a median with the interquartile range (IQR, 25^{th}-75^{th} percentile). The chi-square test (χ^2) was used to compare ordinal variables and the Mann-Whitney U test or unpaired t-test for continues variables. Odds ratio (OR) was used as a measure for the association between ISAR-HP and G8 screening tool and primary and secondary outcomes. An OR is expressed with a 95% confidence interval. A p-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 268 patients aged >70 years, with colorectal cancer were identified. After exclusion of patients with emergency surgery (n=37), Transanal Endoscopic Microsurgery (n=4), stage IV disease (n=7) and synchronous cancer at time of diagnosis (n=6), a total of 214 patients were included. Of the latter, 139 patients (65%) were screened prior to surgery. From two out of these 139 patients, only an ISAR-HP screening was available.

Seventy-nine patients (57%) had a partial or hemicolectomy, 55 (40%) a low-anterior resection, three patients (2%) had an abdominoperineal resection and two patients (1%) a subtotal colectomy.

Baseline characteristics all screened patients are depicted in Table 1. Median age of screened patients was 77.7 years (IQR 75.0-82.8), 29% of patients were classified as ASA III or IV and 35% had a CCI score ≥2. Analysis of the non-screened patients of the total cohort showed no significant differences between screened and non-screened patients other than a slightly higher age (77.7 years versus 75.5 years p= 0.01), a more frequent a history of falls (p= 0.02) and more cognitive impairment (p= 0.02). Please see Appendix C for a more detailed comparison between screened en non-screened patients.

Frailty assessment

Sixty-eight (50%) were classified as frail based on G8 (G8-frail), and 32 (23%) based on ISAR-HP (ISAR-HP-frail), 48 patients (35%) who were classified as frail on G8 were classified as non-frail on the ISAR-HP. Eleven patients (8%) who were classified as frail on the ISAR-HP were non-frail according to the G8 screening tool. Twenty patients (15%) were classified as frail on both the G8 and ISAR-HP.
ISAR-HP-frail patients were significantly older (79.8 versus 76.3) had more comorbidities (50% versus 31%), were more ADL dependent (25% versus 4%), they used more often a walking device (63% versus 4%) and reported more falls in the six months prior to surgery (23% versus 4%). There was no significant difference between the number of frail patients (on one or both screening tools) receiving neoadjuvant radiotherapy or adjuvant chemotherapy compared to non-frail patients.

Primary and secondary outcomes

Fifty-one patients (37%) had one or more postoperative complications within 30 days of surgery; twenty-four patients had one or more surgical complications; this required an intervention in ten patients. Anastomotic leakage was reported in seven patients (5%). Twenty-six patients (19%) had a non-surgical complication: ten cardiopulmonary, two neurological, ten infectious and 20 'other' events were registered. Seven patients (5%) a delirium and thirteen patients (9%) were readmitted within 30-days of surgery. Analysis of the 20 'other' events showed that nine consisted of postoperative urinary retention, six were an ileus with recovery after conservative treatment, two were acute renal failure, one non-specific abdominal pain, one anxiety episode requiring psychiatric medication and one a hypocalcaemia.

Table 1 Characteristics of all screened patients

	Screened	
	n=139	
Geriatric characteristics		
Median age (IQR)	77.7	(75.0-82.8)
Female gender (%)	63	(45)
Body Mass Index kg/M2 (SD)	26.2	(4.0)
Charlson Comorbidity Index score ≥2 (%)	49	(35)
ADL dependent[a] (%)	12	(9)
The use of a walking device (%)	24	(17)
Reported falls < 6 months (%)	11	(8)
Risk of malnutrition (%)	36	(26)
Self-reported cognitive impairment (%)	9	(7)
Polyfarmacy (≥5 medications) (%)	35	(49)
Tumour characteristics and treatment		
Tumour location (%)		
Colon	114	(82)
Rectum	25	(18)
Tumour stage AJCC (%)		
I	33	(24)
II	57	(41)
III	49	(35)
Surgical approach (%)		
Laparoscopic	105	(76)
Open	33	(24)
ASA score (%)		
I-II	98	(71)
III-IV	41	(29)
Primary anastomosis (%)	117	(84)
(Neo)adjuvant therapy (%)		
Radiotherapy[b]	10	(7)
Chemoradiation[b]	8	(6)
Chemotherapy[c]	21	(15)

Baseline characteristics are presented with interquartile range (IQR) or standard deviation (SD). Frequencies with percentage (%)
[a]ADL, Activities of Daily Living. Dependent; Katz ADL ≥2
[b]Rectal cancer patients, [c]colon cancer patients

Table 2 Postoperative outcome of patients stratified by screening method

	ISAR-HP-frail	ISAR-HP-fit			G8-frail	G8-fit			Frail[a]	Non-Frail		
Outcome	*n*=32	*n*=107	OR (95%CI)	*p*-value	*n*=68	*n*=69	OR (95%CI)	*p*-value	*n*= 20	*n*=117	OR (95%CI)	*p*-value
Patients with a 30-day complication (%)	17 (53)	34 (32)	2.4 (1.1-5.4)	0.03	24 (35)	22 (32)	1.2 (0.6-2.4)	0.7	10 (50)	36 (31)	2.1 (0.9-5.9)	0.09
Patients a surgical complication (%)	9 (28)	16 (15)	2.3 (0.9-5.9)	0.09	10 (15)	14 (20)	0.7 (0.3-1.6)	0.4	4 (20)	20 (17)	1.2 (0.3-4.0)	0.8
Anastomotic leakage (%)	2 (6)	5 (5)	1.4 (0.3-7.6)	0.7	5 (7)	2 (3)	2.7 (0.5-14.2)	0.2	1 (5)	6 (5)	1.0 (0.1-8.5)	0.9
Patients a non-surgical complication (%)	8 (25)	18 (17)	1.6 (0.6-4.2)	0.3	16 (24)	10 (15)	1.8 (0.8-4.3)	0.2	6 (30)	20 (17)	2.1 (0.7-6.1)	0.2
Cardiopulmonary complications	6 (19)	4 (4)	5.9 (1.6-22.6)	0.01	5 (7)	4 (6)	1.3 (0.3-5.0)	0.7	4 (20)	5 (4)	5.6 (1.4-23)	0.03
Delirium (%)	3 (9)	4 (4)	2.7 (0.6-12.9)	0.2	4 (6)	3 (4)	1.4 (0.3-6.4)	0.7	1(5)	6 (5)	0.9 (0.1-8.5)	0.9
Readmission < 30 days (%)	6 (19)	7 (6)	3.4 (1.1-11.0)	0.03	8 (12)	4 (6)	2.2 (0.6-7.6)	0.2	5 (25)	7 (6)	5.4 (1.5-18.6)	0.01
30-day mortality (%)	3 (9)	3 (3)	3.6 (0.7-18.7)	0.1	3 (4)	3 (4)	1.0 (0.2-5.2)	1.0	3 (15)	3 (3)	6.7 (1.3-36.0)	0.01
Mean lenght of hospital stay (SD)	10.3 (6.0)	8.9 (9.4)		0.01	8.3 (7.0)	9.0 (6.7)		0.9	8.6 (4.2)	8.7 (7.1)		0.9
6-month mortality (%)	4 (13)	3 (3)	4.9 (1.1-23.4)	0.04	4 (6)	3 (4)	1.4 (0.3-6.4)	0.7	4 (20)	3 (3)	9.5 (1.9-47.4)	0.001

Frequencies are with percentage (%). Continuous variables with standard deviation (SD). [a]Patient both ISAR-HP-frail and G8-frail

3

Table 2 shows primary and secondary outcomes for frail versus non-frail patients depending on the ISAR-HP, the G8 and both screening tools combined. The G8 had no predictive value for the primary outcomes. However ISAR-HP-frail patients had a 2.4 times (95% CI 1.1-5.4) higher odds for complications with more cardiopulmonary complication 19% versus 4% (OR 5.9, 95% CI 1.6-22.6) with higher rates of readmissions within 30 days after discharge: 19% versus 6% in the non-frail OR 3.4 (95% CI 1.1-11.0). Combining the two screening tools resulted in predictive value for readmissions OR 5.4 (95% CI 1.5-18.6) and 6.7 times increased odds for 30-day mortality (95% CI 1.3-36.0). ISAR HP had no predictive value for anastomotic leakage, delirium or 'other' complications.

For the secondary outcomes, ISAR-HP-frail patients were significantly at risk for a longer length of hospital stay (10.3 versus 8.9 days in non-frail patients, p = 0.01) and a total of seven patients (5%) died within six months of follow-up. Five of these (71%) died due to complications after surgery. One patient with a history of cardiac failure developed postoperative cardiac and respiratory failure and declined further treatment. No cause of death was retrieved for one patient. ISAR-HP frail patients had a 4.9 (95 % CI 1.1-24.1) higher odds for dying within six months of surgery. Patients who were frail on both ISAR-HP and G8 had a 9.5 (95% CI 1.9-47.4) higher odds for six months mortality compared to non-frail patients. The G8 alone was not associated with any of the secondary outcomes.

Subgroup analysis

Subgroup analysis of all 214 patients (screened and non-screened) found that patients with a CCI score ≥2 were at risk for 1 or more complications (surgical and non-surgical) after surgery with an OR of 2.1 (95% CI 1.1-3.9) when corrected for the potential confounders: age, gender, ASA score and tumour stage. We found no association of co-morbidities or ASA score with the risk of readmission, 30-day or six-months mortality.

Discussion

This cohort study using a prospectively collected database investigated the predictive value of G8 and ISAR-HP questionnaires for adverse outcomes after surgery in older colorectal cancer patients in two teaching hospitals in the Netherlands. The results show that ISAR-HP frail patients were at increased risk for 30-day complications, risk for readmission after surgery and had a significantly longer length of hospital stay and an increased risk for six-month mortality. Combining the ISAR-HP with the G8 screening tool resulted in an even higher predictive value: patients being frail on both screening tools had 20% more complications, 19% more readmissions and 6-times increased odds for 30-day mortality. Moreover, they had 9-times increased odds for six-month mortality compared to non-frail patients. No association was observed between the G8 and outcome.

The ISAR-HP screening is an easy to use 4 question tool which can be performed by nurses. It was developed in the Netherlands to identify acutely hospitalised patients at risk for functional decline and readmission.[15,16] In addition, a recent study showed that the ISAR-HP had moderate sensitivity (83%) and specificity (77%) for frailty in a population of older patients with end-stage renal disease.[24] This is the first study of the ISAR-HP screening tool in colorectal cancer patients, and this study confirms its predictive value for readmission. Subgroup analysis showed that comorbidity alone did not predict mortality, which underlines the importance of other geriatric information.

The G8 was developed as a frailty screening tool for predicting the presence of impairments on a comprehensive geriatric assessment and was not intended to be a prognostic tool. Among all frailty screenings tools, G8 demonstrated the highest sensitivity for frailty.[14] The lack of specificity of the G8 for frailty could explain the lack of association between a positive screening outcome and postoperative morbidity and mortality.

The prediction of adverse outcomes and identifying those patients at risk is important for several reasons. First, risk stratification helps clinicians to counsel their patients in the selection of the most appropriate treatment strategy and gives opportunities to discuss advanced care planning when treatment is withheld. Second, it yields opportunities for postoperative care planning, such as early-rehabilitation and/or fast-track surgery.[25] In our hospital's surgical strategies are currently not influenced by the result of the screening tools. However, patients identified as frail in the screening systems had a full geriatric intake to guide geriatric interventions and long term care needs and to initiate peri- and postoperative guidance.

This study has some limitations. First, only 61% of all elective surgical colorectal cancer patients received a geriatric screening. Comparison of baseline characteristics yielded no indication of selection bias, but the risk of confounding by indication may exist. Second, unfortunately, we do not have data on functional outcomes, which especially in an older population, are important outcomes after cancer treatment. Third, older patients with non-elective, acute colorectal surgery had no frailty screening and hence could not be included in the study, while risk stratification, preoperative optimisation and advanced care planning may be especially important for this category of patients.[26] Moreover, the number of primary events was too low to perform multivariable analysis to correct for standard confounders or assess the impact of (neo)adjuvant therapy on outcomes. As this was a cohort analysis of available data, we did not perform an official sample size calculation.

Despite these limitations, one may use ISAR-HP with or without G8 to gain insight into the risk for adverse outcomes, thereby providing valuable information for shared decision making. It can also be used to adjust treatment plans in this heterogeneous group of patients.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *European Journal of Cancer.* 2013;49(6):1374-403.
2. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA: A Cancer Journal for Clinicians.* 2014;64(2):104-17.
3. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hebert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. *Lancet.* 1999;353(9148):205-6.
4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2001;56(3):M146-56.
5. Deschodt M, Wellens NI, Braes T, De Vuyst A, Boonen S, Flamaing J, et al. Prediction of functional decline in older hospitalized patients: a comparative multicenter study of three screening tools. *Aging Clinical and Experimental Research.* 2011;23(5-6):421-6.
6. McCusker J, Bellavance F, Cardin S, Trepanier S, Verdon J, Ardman O. Detection of older people at increased risk of adverse health outcomes after an emergency visit: the ISAR screening tool. *Journal of the American Geriatrics Society.* 1999;47(10):1229-37.
7. Robinson TN, Wu DS, Pointer LF, Dunn CL, Moss M. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. *Journal of the American College of Surgeons.* 2012;215(1):12-7; discussion 7-8.
8. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Annals of Surgical Oncology.* 2012;19(8):2428-34.
9. Robinson TN, Wu DS, Sauaia A, Dunn CL, Stevens-Lapsley JE, Moss M, et al. Slower walking speed forecasts increased postoperative morbidity and 1-year mortality across surgical specialties. *Annals of Surgery.* 2013;258(4):582-8; discussion 8-90.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases.* 1987;40(5):373-83.
11. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Critical Reviews in Oncology/Hematology.* 2005;55(3):241-52.
12. Decoster L, Vanacker L, Kenis C, Prenen H, Van Cutsem E, Van Der Auwera J, et al. Relevance of Geriatric Assessment in Older Patients With Colorectal Cancer. *Clinical Colorectal Cancer.* 2017;16(3):e221-e9.
13. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendationsdagger. *Annals of Oncology.* 2015;26(2):288-300.
14. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncology.* 2012;13(10):e437-44.
15. Hoogerduijn JG, Buurman BM, Korevaar JC, Grobbee DE, de Rooij SE, Schuurmans MJ. The prediction of functional decline in older hospitalised patients. *Age and Ageing.* 2012;41(3):381-7.
16. Hoogerduijn JG, de Rooij SE, Grobbee DE, Schuurmans MJ. Predicting functional decline in older patients undergoing cardiac surgery. *Age and Ageing.* 2014;43(2):218-21.
17. The Dutch Health Care Inspectorate I. Basic set quality indicators hospitals. *Download from: https://www.igz.nl.* 2015.
18. Van Leersum N, Snijders H, Henneman D, Kolfschoten N, Gooiker G, Ten Berge M, et al. The Dutch surgical colorectal audit. *European Journal of Surgical Oncology.* 2013;39(10):1063-70.
19. Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol.* 2012;23(8):2166-72.

20. Dripps RD, Lamont A, Eckenhoff JE. The role of anesthesia in surgical mortality. *JAMA*. 1961;178:261-6.
21. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: The index of adl: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185(12):914-9.
22. Wilson MM, Thomas DR, Rubenstein LZ, Chibnall JT, Anderson S, Baxi A, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *American Journal of Clinical Nutrition*. 2005;82(5):1074-81.
23. Stratton RJ, Hackston A, Longmore D, Dixon R, Price S, Stroud M, et al. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. *British Journal of Nutrition*. 2004;92(5):799-808.
24. van Munster BC, Drost D, Kalf A, Vogtlander NP. Discriminative value of frailty screening instruments in end-stage renal disease. *Clin Kidney J*. 2016;9(4):606-10.
25. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. *World Journal of Surgery*. 2014;38(6):1531-41.
26. Dekker JW, Gooiker GA, Bastiaannet E, van den Broek CB, van der Geest LG, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. *European Journal of Surgical Oncology*. 2014;40(11):1481-7.

Appendix A Geriatric-8 (G8) screening tool

Items	Possible responses (score)
1. Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = Severe decrease in food intake 1 = Moderate decrease in food intake 2 = No decrease in food intake
2. Weight loss during the last 3 months?	0 = Weight loss >3 kg 1 = Does not know 2 = Weight loss between 1 and 3 kg 3 = No weight loss
3. Mobility?	0 = Bed or chair bound 1 = Able to get out of bed/chair but does not go out 2 = Goes out
4. Neuropsychological problems?	0 = Severe dementia or depression 1 = Mild dementia 2 = No psychological problems
5. Body mass index (BMI)? (weight in kilograms) / (height in square metres)	0 = BMI <19 1 = BMI 19 to <21 2 = BMI 21 to <23 3 = BMI ≥23
6. Takes more than three prescription drugs per day?	0 = Yes 1 = No
7. In comparison with other people of the same age, how does the patient consider their health status?	0.0 = Not as good 0.5 = Does not know 1.0 = As good 2.0 = Better
8. Age	0 = >85 1 = 80–85 2 = <80
Total score 0–17	Cut-off ≤ 14: potentially frail

The G8 Screening questionnaire. BMI, Body mass index. Adapted from Bellera et al.[19]

Appendix B Identification of seniors at risk for hospitalized patients (ISAR-HP) screening tool

Items	Possible responses (score)
1. Before hospital admission, did you need assistance for IADL (e.g. assistance in housekeeping, preparing meals, shopping, etc.) on a regular basis?	0 = No 1 = Yes
2. Do you use a walking device (e.g. a cane, walking frame, crutches, etc.)?	0 = No 2 = Yes
3. Do you need assistance for travelling?	0 = No 1 = Yes
4. Did you continue education after age 14?	0 = No 1 = Yes
Total score 0-5	Cut-off ≥ 2: potentially frail

The ISAR-HP Screening questionnaire. IADL, instrumental activities of Daily Life. Adapted from Hoogerduijn et al.[16]

Appendix C Characteristics of screened and non-screened patients

	Screened	Non-screened	
	n=139	*n*=74	*p*-value
Geriatric characteristics			
Median Age (IQR)	77.7 (75.0-82.8)	75.5 (72.3-79.7)	0.01
Female gender (%)	63 (45)	32 (43)	0.7
Body Mass Index kg/M^2 (SD)	26.2 (4.0)	25.2 (4.6)	0.1
Charlson Comorbidity Index score ≥2 (%)	49 (35)	29 (40)	0.4
ADL dependent[a] (%)	12 (9)	11 (15)	0.2
The use of a walking device (%)	24 (17)	14 (19)	0.7
Reported falls < 6 months (%)	11 (8)	14 (19)	0.02
Risk of malnutrition (%)	36 (26)	20 (27)	0.9
Self-reported cognitive impairment (%)	9 (7)	12 (16)	0.02
Polyfarmacy (≥5 medications) (%)	49 (35)	24 (32)	0.7
Tumour characteristics and treatment			
Tumour location (%)			0.7
Colon	114 (82)	59 (80)	
Rectum	25 (18)	15 (20)	
Tumour stage AJCC (%)			0.1
I	33 (24)	25 (34)	
II	57 (41)	33 (44)	
III	49 (35)	16 (22)	
Surgical approach (%)			0.2
Laparoscopic	105 (76)	50 (68)	
Open	33 (24)	24 (32)	
ASA score (%)			0.4
I-II	98 (71)	48 (65)	
III-IV	41 (29)	26 (35)	
Primary anastomosis (%)	117 (84)	62 (84)	0.8
(Neo)adjuvant therapy (%)			0.1
Radiotherapy[b]	10 (7)	11 (15)	
Chemoradiation[b]	8 (6)	1 (1)	
Chemotherapy[c]	21 (15)	13 (18)	

Baseline characteristics are presented with Interquartile range (IQR) or Standard Deviation (SD) Frequencies with percentage (%). [a]ADL, Activities of Daily Living. Dependent; Katz ADL ≥2
[b]rectal cancer patients, [c]colon cancer patients

Chapter 4

The prognostic value of a geriatric risk score for older patients with colorectal cancer

Annals of Surgical Oncology 2019;26(1):71-78

E.T.D. Souwer
D. Hultink
E. Bastiaannet
M.E. Hamaker
A. Schiphorst
A. Pronk
J.M. van der Bol
W.H. Steup
J.W.T. Dekker
J.E.A. Portielje
F. van den Bos

Abstract

Introduction: VMS is a Dutch risk assessment tool for hospitalised older adults that includes a short evaluation of four geriatric domains: risk for delirium, risk for undernutrition, risk for physical impairments, and fall risk. We investigated whether the information derived from this tool has prognostic value for outcomes of colorectal cancer (CRC) surgery.

Patients and methods: All consecutive patients over age 70 years who underwent elective CRC surgery in three Dutch hospitals (2014-2016) were studied. The presence of risk was scored prior to surgery and per geriatric domain as either 0 (risk absent) or 1 (risk present). The total number of geriatric risk factors was summed. The primary outcome was long-term survival. Secondary outcomes were postoperative complications, including delirium. Cox proportional hazards models were used to evaluate the sumscore and risk factors associated with overall survival (OS).

Results: Five hundred fifty patients were included. Median age was 76.5 years and median follow-up was 870 days. Patients with intermediate (1-2) or high (3-4) sumscore were independently associated with lower overall survival: intermediate sumscore HR 1.9 (95% Confidence Interval (CI) 1.1-3.5; $p=0.03$) and high sumscore HR 8.7 (95% CI 4.0-19.2; $p<0.001$), respectively. Sumscores were also associated with postoperative complications (intermediate sumscore OR 1.8; 95% CI 1.2-2.7 and high sumscore OR 2.4; 95% CI 1.02-5.5).

Conclusions: This easy-to-use geriatric sumscore has strong associations with long term outcome and morbidity after CRC surgery. This information may be included in risk models for morbidity and mortality and can be used in shared decision making.

Introduction

In Europe, colorectal cancer is the second most common cancer in women and the third most common in men.[1] Colorectal cancer is an age-related disease; over 50% of all newly diagnosed patients are 70 years or older.[2] Older patients represent a heterogeneous population due to differences in comorbidity, functional capacity and presence of geriatric impairments. These impairments can lead to decreased physiological reserves and diminished resistance to stressors and increase the risk of adverse outcomes of treatment.[3] Not only do older patients have a four-fold higher risk of adverse postoperative outcomes[4], but they are also more likely to experience a postoperative decline in physical function resulting in functional dependency and decreased quality of life.[5]

Geriatric assessment (GA) can be used to detect previous unaddressed problems in older patients. Information derived from GA can be used to discuss treatment options and improve functional status, and possibly survival.[6] However prognostic information for patients with geriatric impairments is scarce, and currently available risk prediction tools for electively operated colorectal cancer patients do not include geriatric parameters.[7-9] Therefore more prognostic information is required for the challenging process of shared decision making in older patients.

In The Netherlands for all older hospitalised patients over 70 years, standard care at admission includes a short evaluation of four important geriatric domains: risk for undernutrition, physical impairment, risk for delirium and fall risk, independently of whether GA is performed. This screening tool was implemented nationwide in 2012 as part of a National Patient Safety Program (VMS) after studying adverse events and potentially preventable deaths in Dutch hospitals and to direct geriatric interventions. Although VMS does not replace a GA, this easy-to-use and well-implemented geriatric tool could provide useful prognostic information, as it is also performed for all patients prior to elective surgery.

In this study we investigated whether a cumulative risk score composed of undernutrition, physical impairment, risk for delirium, and fall risk has prognostic value for survival and complications independently of age and American Society of Anesthesiologists (ASA) score in a large cohort of older electively operated colorectal cancer patients.

Patients and methods

Study population

All patients aged 70 years or older with surgical treatment for colorectal cancer between 1 January 2014 and 31 December 2016 in three teaching hospitals in The Netherlands (Hagaziekenhuis in The Hague, Diakonessenhuis in Utrecht, and the Reinier de Graaf Gasthuis in Delft) were included in this cohort study. Patients with acute or urgent surgery, transanal endoscopic microsurgery (TEM), stage IV colorectal carcinoma, or a synchronous second malignancy were excluded.

The primary outcome for this study was overall survival. Secondary outcomes were postoperative complications (surgical, cardiopulmonary, delirium, and other complications), readmission within 30 days and (temporary) discharge to a rehabilitation centre or nursing home.

Data collection

Preoperative patient characteristics and surgical outcome parameters were retrieved from the prospectively collected Dutch Colorectal Audit (DCRA). We complemented this with data from electronic medical records (EMR) for geriatric parameters. Follow-up on survival status was available until 1 February 2018 through a linkage with the Municipal Personal Records Database.

From the DCRA we retrieved the following data: age, gender, ASA score, comorbidity and oncological data (i.e. tumor type, tumor location, and staging), surgical approach (open or laparoscopic), type of surgery (acute, urgent or elective), postoperative complications, hospital stay, readmissions within 30 days, and 30-day mortality. The Charlson comorbidity index (CCI)[10] was calculated for all patients. Postoperative complications registered in this audit were subdivided into surgical complications, cardiopulmonary complications and other complications. Any complication refers to the number of patients with one or more complications. When two or more surgical complications occurred, the most severe surgical complication was registered. Surgical complications included wound infections, bleeding, ileus and complications that needed intervention (including anastomotic leaks). Cardiopulmonary complications consisted of pulmonary complications (pneumonia, atelectasis, pulmonary embolism, pulmonary insufficiency or other pulmonary complications) and cardiac complications (myocardial infarction, heart failure, arrhythmia, angina pectoris, cardiac arrest, or other cardiac complications).

Other complications consisted of infectious complications, thromboembolic complications, and complications defined as "other"in the DCRA.

Presence of delirium after surgery and destination after discharge (to home or an extended care facility) could not be retrieved from the DCRA and was also extracted from the EMR. Delirium was defined as present when (1) the occurrence was documented in a patient's medical record by a geriatrician or treating physician, (2) haloperidol was prescribed during hospital stay or (3) Delirium Observation Screening Scale[11] ≥3 in three consecutive moments was recorded in the medical record.

Geriatric parameters (used in VMS)

In the participating hospitals, the risk for undernutrition (or at risk of becoming undernourished), physical impairment, the risk of delirium and fall risk were assessed preoperatively by nursing staff with the screening questionnaires. The full 13-item list of the four questionnaires is presented in Appendix A.

Risk for undernutrition was assessed using either the Short Nutritional Assessment Questionnaire (SNAQ)[12] or Malnutrition Universal Screening Tool (MUST).[13] Increased risk for undernutrition was defined as SNAQ score ≥3 or MUST score ≥2. Functional impairment was assessed with the six-item Katz- activities of daily living (ADL)[14] consisting of questions regarding bathing, dressing, using the toilet, eating, transferring from bed to chair and if they used incontinence materials. An impaired score was defined as Katz- ADL score ≥2. Fall risk consisted of one question and was either present or absent. Risk for delirium was assessed using three yes or no questions scoring 1 or 0. Score ≥1 was considered as an increased risk. We kept the cutoff value of 1 for the delirium score as suggested by the national guidelines, as Heim at al. earlier showed its independent association with increased care, worse ADL functioning, and short-term mortality in an unselected group of older hospitalised patients.[15]

For this study, we composed a cumulative risk score of the VMS, by summing the total number of impairments. All individual domains were included, independent of whether the individual domain was significantly associated with an outcome. Low risk score was defined as a sumscore of 0, an intermediate risk as sumscore of 1 or 2 and a high risk sumscore of 3 or 4.

In all three hospitals, geriatric information was registered in the EMR prior to surgery for the majority of patients on the day of admission, except for malnutrition, where screening is done shortly after the decision for surgery is made. The information from the VMS does not alter the primary therapeutic plan but is used to guide supportive measures after surgery. For patients with impairments in the individual domains of falls and ADL dependency, this is postoperative mobilisation with physiotherapy. For patients who have undernutrition, dietary support is advised and in case of increased risk for delirium, postoperative monitoring using Delirium Observation Screening Scale[11] is advised.

Statistical analysis

We used descriptive analysis expressing normally distributed variables as mean with standard deviation (SD) and nonnormally distributed variables as median with interquartile range (IQR). Frequencies are presented as number and percentage. A chi-squared test was used to compare proportions between the three risk groups.

To assess the prognostic value of the three risk scores on overall survival (OS), a multivariate Cox proportional hazards model was used to estimate hazard ratios (HRs) with corresponding 95% confidence interval (CI). To assess the association between risk factors and postoperative outcomes, multivariate logistic regression models were used to calculate odds ratios (ORs) with corresponding 95% CI. Age, male gender, and tumor stage were considered potential confounders and were added to a multivariate model in addition to ASA score. All analyses were performed using SPSS version 24.0 (SPSS, Inc., Chicago, IL), p-values < 0.05 were considered statistically significant.

Results

A total of 707 patients aged 70 years or older were identified. After excluding 157 patients based on the predefined criteria, 550 patients were included in the analysis of whom 293 (53%) were men.

The median age was 76.5 years (IQR 74.3-82.1 years). Median follow-up was 870 days, and 60 deaths (11%) were registered. Table 1 presents the demographic characteristics and geriatric parameters. Most patients had laparoscopic surgery (n=436; 79%). Thirty-five patients (6%) had KatzADL score of 2 or higher, and at least one fall in the past 6 months was reported by 76 patients (14%) prior to surgery. For 27 patients (5%), the fall history was unknown. Undernutrition was present in 127 patients (23%), and 106 patients (19%) were at risk for delirium. A total of 303 patients (55%) had low risk sumscore, 220 patients (40%) had intermediate risk sumscore, and 27 patients (5%) had a high risk sumscore.

Primary outcome

Twenty-five patients (5%) died within 6 months after surgery, and 31 patients (6%) died within 1 year. Figure 1 presents the survival analysis is shown for all three risk groups. Patients with intermediate risk sumscore (HR 1.9; 95% CI 1.1-3.5; p=0.03) and high risk sum score, (HR 8.7; 95% CI 4.0-19.2; p<0.001) had significantly lower overall survival. At end of follow-up, 13% (n=29) in the intermediate risk group and 44% (n=12) in the high risk group had died compared with 6% (n=19) in the low risk group.

When analysing the individual domains separately and corrected for age, gender, tumour stage and ASA score, we found that impaired functionality (Katz ≥2), fall risk, and risk for delirium were all associated with overall survival with HR of 4.7 (95% CI 2.5-8.8), 2.6 (95% CI 1.4-4.6) and 2.1 (95% CI 2.0-6.0), respectively. Risk for undernutrition was not independently associated with overall survival (Table 2).

Table 1 Patient characteristics at baseline

	Total patients	
	n=550	
Median (IQR) age (years)	76.5	(74.3-82.1)
Gender		
Male	293	(53)
Female	257	(47)
ASA score		
III-IV	172	(31)
CCI ≥2	211	(38)
Tumour location		
Colon	432	(79)
Rectum	118	(21)
Surgical approach		
Laparoscopic	436	(79)
Tumour stage		
I	167	(30)
II	214	(39)
III	169	(31)
Geriatric characteristics		
Katz ADL ≥2	35	(6)
Fall risk	76	(14)
Risk for undernutrition	106	(19)
Risk for delirium	119	(22)

Values expressed as number (%). Median age with Interquartile Range (IQR). ASA (American Society of Anesthesiologists) CCI (Charlson Comorbidity Index)

Table 2 Survival analysis for the individual geriatric domains

	HR (95% CI)	*p*-value
Katz ADL ≥2	4.7 (2.5-8.8)	<0.001
Fall Risk	2.6 (1.4-4.6)	0.002
Risk for Malnutrition	1.5 (0.8-2.7)	0.2
Risk for Delirium	3.5 (2.0-6.0)	<0.001

Mutivariable model include: age, gender, tumour stage, and ASA score

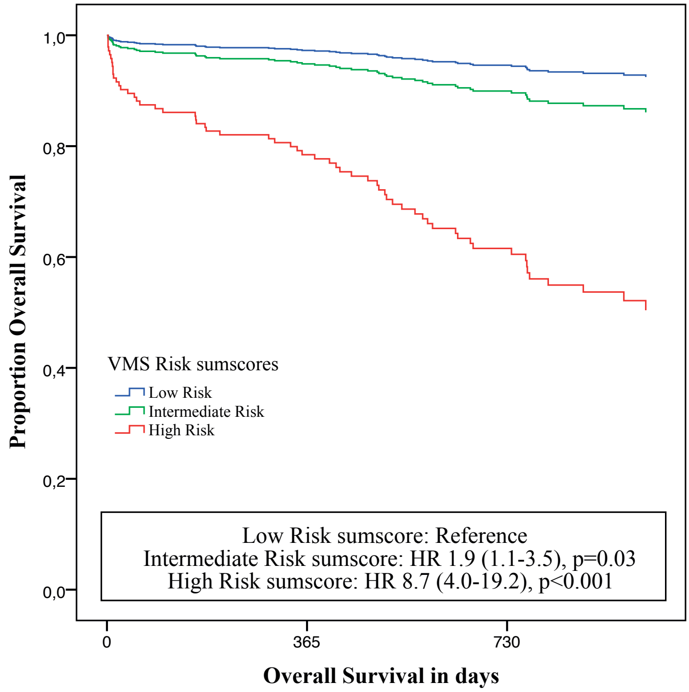


Figure 1 Overall survival stratified by the VMS risk sumscores

Secondary outcomes

One hundred ninety-one patients (35%) had one or more complications: 16% had surgical complications (n=87), 9% cardiopulmonary complications (n=48) and 6% suffered from delirium (n=34). Mean length of stay was 8.7 days (±7.0 days standard deviation, SD). Forty-eight patients (9%) were readmitted within 30 days after discharge, and 98 patients (18%) were discharged to a nursing home or rehabilitation centre. The complication rate (any complication) -was 28.7% in the low risk group, 40.9% in the intermediate risk score group and 51.9% in the high risk group (Appendix B).

In the multivariate model, intermediate risk sumscore (OR 1.8;(95% CI 1.2-2.7, p=0.003) and high risk sumscore (OR 2.4; (95% CI 1.0-5.5, p=0.04) were both associated with complications. Intermediate risk score was also independently associated with delirium (OR 2.9; 95% CI 1.3-6.4, p=0.009) and discharge not to home (OR 2.7; 95% CI 1.6-4.5, p<0.001). We could not find an independent association between the risk sumscore and surgical complications, cardiopulmonary complications, or readmission.

Analysis of the individual domains of the risk scores showed that Katz ADL score ≥2 (OR 3.5; 95% CI 1.6-7.3) and risk for delirium (OR 1.4; 95% CI 1.0-1.9) were independently associated with complications. Katz ADL ≥2 was also independently associated with discharge not to home (OR 2.9; 95% CI 1.4-6.3) and readmission (OR 2.9; 95% CI 1.4-6.3). Risk for delirium was independently associated with delirium (OR 2.1; 95% CI 1.4-3.1), discharge not to home (OR 1.8; 95% CI 1.3-2.6) and readmissions (OR 1.7; 95% CI 1.2-2.5). We found no associations between undernutrition or falls and any of the secondary outcomes.

Because undernutrition was not associated with survival or complications, we assessed these outcomes using a risk score where we omitted undernutrition. The results can be found in Appendix C. The HR for OS increased for score 1 (HR 2.5; 95% CI 1.4-4.6), 2 (HR 4.7; 95% CI 2.2-10.4) and 3 (HR 15.1; 95% CI 6.1-37.4). A score of 1 was associated with any complication (OR 1.8; 95% CI 1.2-2.9), the other scores were not. Mixed results were seen for the other outcomes.

Discussion

A risk sumscore that reflects the cumulative risk of four geriatric domains (delirium, undernutrition, falls and physical impairment) in older colorectal cancer patients was shown to be highly prognostic for mortality and morbidity after colorectal cancer surgery. In this study, patients with high risk sumscore had greatly increased hazard for mortality and complications independently of age and ASA score. Almost half of patients with high risk sumscore died within 3 years after surgery.

This study shows that this easy-to-use and well-implemented tool, which is aimed to direct geriatric care interventions, can also provide insight into individual risks of morbidity and mortality after colorectal cancer surgery in older patients and hence provide opportunities to discuss outcomes of treatment and shared decision making.

Two prior studies have been performed on the VMS geriatric domains. Heim et al. included more than 800 acute or electively hospitalised patients and showed that impairment in three or more domains was strongly associated with functional decline, death, and high healthcare demand up to 3 months after hospitalization. The separate domains in that study did not satisfactorily predict the incidence of these adverse outcomes, as found in the current study for the risk for undernutrition.[15] In addition, this adapted risk score of Heim, where patients aged 70–80 years are considered at risk when positive on three or more of the four VMS domains, appeared not useful for this study. Only 12 out of 356 patients (5%) under 80 years old in our study would be identified as at risk, missing important prognostic information for the majority of patients, most likely caused by differences between the populations of these two studies.

Similar to Heim et al. and in a similar population, Oud et al. found an incremental risk for 6-month mortality when more domains were impaired.[16] The results of the current study confirm these results for patients admitted for elective colorectal cancer surgery and show a sustained mortality risk beyond the first year.

As stated above, we found no association between risk for undernutrition and survival and complications even though undernutrition is an acknowledged risk factor for complications in abdominal surgery.[17-19] This may be related to the tools used to detect undernutrition. Multiple screening tools have been proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN).[20] However, all proposed tools differ in sensitivity and positive predictive value for adverse outcome, and the SNAQ and MUST screening tools show somewhat worse performance in this field compared with the more comprehensive NRS 2002.[21] In addition, two categories of patients with high risk both for undernutrition and complications and death, were excluded from the present analysis: stage IV colorectal cancer patients and patients with acute or emergency indications for surgery. Of note, when undernutrition was omitted from the risk score, the HR for OS increased for survival, but the risk scores were no longer prognostic for any complication, possibly due to a modifying effect of undernutrition on the other domains.

For delirium, several preoperative risk factors have been reported, including advanced age, cognitive impairment, earlier delirium, and functional dependency.[22] In this study, there was no objective assessment of cognitive function. Although the three-item delirium risk assessment has not yet been validated, it is promising that these three questions were also associated with postoperative delirium. When interested in cognitive function, other tools, such as an MMSE,[23] would be appropriate.

Strengths of our study include its multicentre design, respectable sample size and the completeness of data. This study also has several limitations. First, we chose to include only patients with elective surgery. This may be a missed opportunity to obtain additional prognostic information and improve treatment decisions for patients in the emergency setting, who are especially at risk for complications and mortality.[24,25] Second, patients were selected from the surgical audit, hence a decision to operate had been made. This introduced a possible selection bias, with patients highly dependent on care not being included in our analysis. The inability to report on preoperative instrumental ADL functioning (iADL) and iADL/ADL functioning as outcome is another limitation. It can be argued that, in addition to survival and complications, maintaining independence is a very relevant outcome after cancer surgery for older patients.[26] Furthermore, the magnitude of the impact of preoperative impairments on adverse postoperative outcomes, might have weakened given the intervention attached to the risk scores. Lastly, we note that this tool could be used to discuss outcomes of treatment and shared decision making but does not replace a GA.

The older colorectal cancer population is growing, thus it is important to identify patients at risk of unfavourable outcomes. In addition, the colorectal cancer screening programs that have been introduced in recent years will increase the number of older patients with low stages of disease for whom surgical risk and cancer risk must be carefully weighed. Colorectal cancer surgery is now considered generally safe in older patients,[27] with decreasing mortality rates over the past decades, but morbidity and mortality rates are still higher compared with the younger population.[28] As the risk assessment tools used in our study have already been successfully introduced in many Dutch hospitals, the cumulative risk sumscore can provide valuable information, which can be used in shared decision making with patients regarding their prognosis and treatment.

Conclusions

A geriatric sumscore that reflects an individual's risk for delirium, undernutrition, falls, and physical impairment has strong predictive value for morbidity and mortality after colorectal cancer surgery in older patients. This information can be used in shared decision making and may be included in risk models for morbidity and mortality in older colorectal cancer patients.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *European Journal of Cancer.* 2013;49(6):1374-403.
2. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA: A Cancer Journal for Clinicians.* 2014;64(2):104-17.
3. Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: A systematic review. *Journal of Geriatric Oncology.* 2016.
4. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncology.* 2012;13(10):e437-44.
5. Hamaker ME, Prins MC, Schiphorst AH, van Tuyl SA, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. *Journal of Geriatric Oncology.* 2015;6(2):153-64.
6. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer. *Journal of Clinical Oncology.* 2014;32(24):2595-603.
7. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *British Journal of Surgery.* 1991;78(3):355-60.
8. Tekkis PP, Prytherch DR, Kocher HM, Senapati A, Poloniecki JD, Stamatakis JD, et al. Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM). *British Journal of Surgery.* 2004;91(9):1174-82.
9. Hippisley-Cox J, Coupland C. Development and validation of risk prediction equations to estimate survival in patients with colorectal cancer: cohort study. *BMJ.* 2017;357.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases.* 1987;40(5):373-83.
11. Scheffer AC, van Munster BC, Schuurmans MJ, de Rooij SE. Assessing severity of delirium by the Delirium Observation Screening Scale. *International Journal of Geriatric Psychiatry.* 2011;26(3):284-91.
12. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren MA. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ). *Clinical Nutrition.* 2005;24(1):75-82.
13. Cawood AL, Elia M, Sharp SK, Stratton RJ. Malnutrition self-screening by using MUST in hospital outpatients: validity, reliability, and ease of use. *American Journal of Clinical Nutrition.* 2012;96(5):1000-7.
14. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: The index of adl: a standardized measure of biological and psychosocial function. *JAMA.* 1963;185(12):914-9.
15. Heim N, van Fenema EM, Weverling-Rijnsburger AW, Tuijl JP, Jue P, Oleksik AM, et al. Optimal screening for increased risk for adverse outcomes in hospitalised older adults. *Age and Ageing.* 2015;44(2):239-44.
16. Oud FM, de Rooij SE, Schuurman T, Duijvelaar KM, van Munster BC. [Predictive value of the VMS theme 'Frail elderly': delirium, falling and mortality in elderly hospital patients]. *Nederlands Tijdschrift voor Geneeskunde.* 2015;159:A8491.
17. Schwegler I, von Holzen A, Gutzwiller JP, Schlumpf R, Muhlebach S, Stanga Z. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. *British Journal of Surgery.* 2010;97(1):92-7.
18. Kwag S-J, Kim J-G, Kang W-K, Lee J-K, Oh S-T. The nutritional risk is a independent factor for postoperative morbidity in surgery for colorectal cancer. *Annals of Surgical Treatment and Research.* 2014;86(4):206-11.
19. Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. *JAMA Surg.* 2013;148(1):65-71.

20. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clinical Nutrition.* 2017;36(1):11-48.

21. Leistra E, Langius JA, Evers AM, van Bokhorst-de van der Schueren MA, Visser M, de Vet HC, et al. Validity of nutritional screening with MUST and SNAQ in hospital outpatients. *European Journal of Clinical Nutrition.* 2013;67(7):738-42.

22. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis. *Age and Ageing.* 2014;43(3):326-33.

23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research.* 1975;12(3):189-98.

24. Dekker JW, Gooiker GA, Bastiaannet E, van den Broek CB, van der Geest LG, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. *European Journal of Surgical Oncology.* 2014;40(11):1481-7.

25. McArdle CS, Hole DJ. Emergency presentation of colorectal cancer is associated with poor 5-year survival. *British Journal of Surgery.* 2004;91(5):605-9.

26. Wilson MK, Karakasis K, Oza AM. Outcomes and endpoints in trials of cancer treatment: the past, present, and future. *Lancet Oncology.* 2015;16(1):e32-42.

27. Gietelink L, Wouters MW, Bemelman WA, Dekker JW, Tollenaar RA, Tanis PJ. Reduced 30-Day Mortality After Laparoscopic Colorectal Cancer Surgery: A Population Based Study From the Dutch Surgical Colorectal Audit (DSCA). *Annals of Surgery.* 2016;264(1):135-40.

28. Dutch Institute for Clinical Auditing. Jaarverlag 2015. download available from: https://dica.nl/jaarrapportage-20152016.

Appendix A VMS questionnaires

Risk for delirium

1. Do you have cognitive problems?
2. Did you need help with self-care in the past 24 hours?
3. Have you experienced an episode of confusion or delirium before?

Fall risk

1. Did you fall at least once in the last 6 months?

Yes: increased risk for further functional decline

Risk for undernutrition

SNAQ

1. Did you lose weight unintentionally?
   - ≥6kg in the past 6 months(3)
   - ≥3kg in the last month (2)
2. Did you have a reduced appetite last month? (1)
3. Did you take nutritional drinks or did you use a feeding pump last month? (1)

2 points: medium risk : observe intake
≥3 points: high-risk: consult dietician

MUST

1. Calculate body mass index
   - >20(0)
   - 18.5-20 (1)
   - <18.5 (2)
2. Weight loss score in past 3-6 months
   - 5%(0)
   - 5-10% (1)
   - >10% (2)
3. Acute illness and likely to be no nutritional intake for >5 days (2)

1 point: observe intake
≥2 points high-risk: consult dietician

Katz-ADL 6

1. Do you need help with bathing?
2. Do you need help with dressing?
3. Do you need help with using the toilet?
4. Do you need help with eating?
5. Do you need help with a transfer from bed to chair?
6. Do you use incontinence materials?

Appendix B Complications and outcomes stratified based on the risk sumscore

	Low risk		**Intermediate risk**		**High risk**		
	Sumscore 0		Sumscore 1-2		Sumscore 3-4		
	n=303		n=220		n=27		*p*-value
Any complication	87	(29)	90	(41)	14	(52)	0.002
Any surgical complication	43	(14)	41	(19)	4	(15)	0.4
Need for reintervention	22	(7)	26	(12)	2	(7)	0.5
Anastomotic leakeage	7	(2)	14	(6)	1	(4)	0.07
Non-surgical complication	44	(15)	49	(22)	10	(37)	0.004
Cardiopulmonary complication	20	(7)	22	(10)	6	(22)	0.02
Delirium	11	(4)	20	(9)	3	(11)	0.02
Discharge not to home	31	(10)	59	(27)	8	(30)	<0.001
Readmission	21	(7)	23	(10)	4	(15)	0.2
30-day mortality	6	(2)	3	(1)	5	(19)	<0.001
6-month mortality	10	(3)	8	(4)	7	(26)	<0.001
1-year mortality	11	(4)	13	(6)	7	(26)	<0.001

Values are expressed in numbers (%), *p*-value for the difference between groups.

Appendix C Multivariate analysis postoperative outcomes for risk score with and without malnutrition

Outcome	Overall survival	Any complication	Any surgical complication	Non-surgical complication	Cardiopulmonary complications	Delirium	Discharge not to home	Readmission <30 days
Risk sumscore including undernutrition								
Score 0		*reference*	*reference*	*reference*	*reference*	*reference*	*reference*	*reference*
Score 1-2	**1.9 (1.1-3.5)**	**1.8 (1.2-2.7)**	1.5 (0.9-2.5)	1.3 (0.8-2.2)	1.4 (0.7-2.7)	**2.9 (1.3-6.4)**	**2.7 (1.6-4.5)**	1.7 (0.9-3.0)
Score 3-4	**8.7 (4.0-19.2)**	**2.4 (1.0-5.5)**	1.0 (0.3-3.3)	**3.1 (1.2-7.7)**	2.2 (0.7-6.9)	2.5 (0.6-10.4)	2.5 (0.9-6.9)	2.1 (0.6-7.0)
Risk sumscore without undernutrition								
Score 0	*reference*	*reference*	*reference*	*reference*	*reference*	*reference*	*reference*	*reference*
Score 1	**2.5 (1.4-4.6)**	**1.8 (1.2-2.9)**	**1.9 (1.1-3.3)**	1.3 (0.8-2.3)	1.8 (0.9-3.7)	**4.0 (1.8-8.9)**	**2.7 (1.5-4.6)**	**2.1 (1.1-4.3)**
Score 2	**4.7 (2.2-10.4)**	2.1 (1.0-4.2)	0.9 (0.3-2.6)	**2.6 (1.2-5.6)**	1.8 (0.6-5.2)	1.9 (0.5-7.5)	**3.7 (1.6-8.5)**	1.6 (0.5-5.0)
Score 3	**15.1 (6.1-37.4)**	3.2 (1.0-10.8)	1.8 (0.5-7.5)	2.6 (0.8-8.8)	3.6 (0.9-13.9)	6.2 (1.4-27.9)	3.3 (0.9-12.0)	3.4 (0.8-14.5)

Values are expressed as indicated in OR with (95% Confidence Interval). Significant values ($p<0.05$) are presented in bold. Mutivariate model include: age, gender, tumour stage, and ASA score

Chapter 5

Physical performance has a strong association with poor surgical outcome in older patients with colorectal cancer

European Journal of Surgical Oncology 2020;46(3):462-469

E.T.D. Souwer
S.I. Moos
C.J. van Rooden
A.Y. Bijlsma
E. Bastiaannet
W. H. Steup
J.W.T. Dekker
M. Fiocco
F. van den Bos
J.E.A. Portielje

Abstract

Background: Low lumbar skeletal muscle mass and density have been associated with adverse outcomes in different populations with colorectal cancer (CRC). We aimed to determine whether skeletal muscle mass, density, and physical performance are associated with postoperative complications and overall survival (OS) in older CRC patients.

Patients and methods: We analysed consecutive patients (≥70 years) undergoing elective surgery for non-metastatic CRC (stage I-III). Lumbar skeletal muscle mass and muscle density were measured using abdominal CT-images obtained prior to surgery. Low skeletal muscle mass and low muscle density were defined using commonly used thresholds and by gender-specific quartiles (Q). The preoperative use of a mobility aid served as a marker for physical performance. Cox regression proportional hazard models were used to investigate the association between the independent variables and OS.

Results: 174 Patients were included (mean age 78.0), with median follow-up 2.6 years. 36 Patients (21%) used a mobility aid preoperatively. Low muscle density (Q1 vs Q4) and not muscle mass was associated with worse postoperative outcomes, including severe complications ($p<0.05$). Use of a mobility aid was associated with more complications, including severe complications (39% vs 17%, $p=0.004$) and OS (HR 2.65, CI 1.29-5.44, $p=0.01$). However, patients with mobility aid use and low skeletal muscle mass had worse OS (HR 5.68, $p=0.003$).

Conclusions: Low skeletal muscle density and not muscle mass was associated with more complications after colorectal surgery in older patients. Physical performance has the strongest association for poor surgical outcomes and should be investigated when measuring skeletal muscle mass and density.

Introduction

Colorectal cancer (CRC) is predominantly an illness of older patients, with more than 50% of all new patients aged 70 years or older.[1] In this heterogeneous group of older patients, there is a need for markers associated with outcome to guide individual decision making for the treatment of CRC.

In relatively younger colorectal cancer patients (mean age 58-71) low skeletal muscle mass and muscle density have been associated with postoperative complications and longer hospital stay after cancer surgery[2-7] and increased risk of chemotoxicity.[8] Therefore, skeletal muscle mass or muscle density has the potential to predict adverse outcomes and possibly guide individual patient-centred decision making.

It remains unclear whether low skeletal muscle mass and muscle density are associated with poor surgical outcome in older patients. Previous studies were performed in groups with heterogeneous age and stage composition hindering interpretation of the observed associations between skeletal muscle mass and quality and outcomes for older patients. Furthermore, it is important to assess physical performance when assessing skeletal muscle mass.[5,9] This is supported by the recently updated guidelines of the European Working Group on Sarcopenia in Older People (EWGSOP).[10]

This study aimed to investigate the association between skeletal muscle mass and density and physical performance with postoperative complications as well as Overal Survival (OS) in older patients undergoing elective surgery for non-metastatic CRC.

Patients and methods

Study population

All consecutive patients aged ≥ 70 years with colorectal surgery between January 1st 2014 and December 30th 2016 from a large teaching hospital in the Netherlands (Hagaziekenhuis) were identified from the prospectively collected Dutch Colorectal Audit database (DCRA).[11] This hospital provides geriatric-oncological care for all patients of 70 years and over, with geriatric screening and subsequent geriatric assessment in case of possible frailty. The Enhanced Recovery After Surgery (ERAS) guidelines[12] were part of standard care for all surgical patients.

Patients with abdominal CT imaging as part of preoperative staging prior to colorectal surgery were eligible for inclusion. Exclusion criteria were acute surgery, transanal endoscopic microsurgery (TEM), stage IV CRC or synchronous cancer at the time of diagnosis.

This study was approved by the local Medical Ethical Review Board Zuidwest-Holland, the Netherlands. A waiver for informed consent was granted.

Data collection

The DCRA provided the demographic data as well as pre- and postoperative outcome data on all surgically treated patients. We retrieved the following demographic data: gender, age, height and length, American Society of Anesthesiologists physical status classification (ASA score), Charlson comorbidity index (CCI)[13], Body Mass Index, tumour location and pathological tumour stage (according to AJCC, 7th edition). Also, preoperative information on Activities of Daily Living (Katz ADL questionnaire)[14] and any preoperative use of a mobility aid (the use of a cane, crutches, a walking frame and wheelchair) were collected from the electronic medical records (EMRs). Preoperative use of a mobility aid was assessed by a single yes or no question. All parameters were all registered as part of standard preoperative care. Complications were defined as in-and-out of hospital morbidity within 30-days of surgery.

In the DCRA, the number of complications refers to the number of patients with one or more complications. Surgical complications included wound infections, ileus and complications that needed (surgical) intervention (including anastomotic leaks). Cardiopulmonary complications consisted of pulmonary complications (pneumonia, atelectasis, pulmonary embolism, pulmonary insufficiency or other pulmonary complications) and cardiac complications (myocardial infarction, heart failure, arrhythmia, angina pectoris, cardiac arrest or other cardiac complications). Details concerning the length of hospital stay, ICU-admission, 30-day readmissions and 30-day mortality and data on adjuvant treatment were also retrieved. Also, discharge status (to home or an extended care facility) was retrieved from the EMRs.

Severe complications were defined as complications leading to an ICU admission (more than two days), the need for a (surgical) reintervention, a prolonged hospital stay (more than 14 days), or postoperative mortality. This definition is consistent with previous publications in which data from the DSCA were analysed.[15] Date of death was retrieved through a linkage with the Municipal Personal Records Database. Follow-up of all patients was at least one year.

Skeletal muscle mass and density assessment

Computerised tomography (CT) was used to assess skeletal muscle mass and density (or muscle attenuation) as a proxy of muscle quality.[16] Low muscle density reflects changes in skeletal muscle composition that occur with increased fat infiltration into skeletal muscle[17] and has been associated with low physical performance in previous well-functioning older men and women.[18] Picture Archiving and Communication System (PACS) radiological software were used to identify and extract preoperative contrast-enhanced CT-images. CT-image analysis software SliceOmatic version 4.3 (Tomovision, Montreal, Quebec, Canada) was used for assessment of skeletal muscle mass and muscle density. Skeletal muscle mass was evaluated on a single slice at the L3 level using Hounsfield Unit (HU) thresholds of–29 to 150 for skeletal muscle.[19] Muscles measured at this level were the psoas, paraspinal, transverse abdominal, external oblique, internal oblique and rectus abdominis muscle. The sum of skeletal cross-sectional muscle areas was normalised for stature (m^2)[20] and is reported as cm^2/m^2. Skeletal muscle density is expressed as the mean of the HU of the skeletal muscle mass measured at L3.

All images were analysed by a trained investigator. To confirm the reliability of measurements, 25% (n=52) of all images were randomly selected and analysed by a trained second analyst (i.e. radiologist). Cohen's kappa statistic was used to test interrater reliability.

Low skeletal muscle mass and low muscle density

Low skeletal muscle mass and muscle density were defined using two different methods. The first method was based on thresholds published by Martin et al.[21] These thresholds were developed in a mixed cohort of cancer patients (40% CRC patients, mean age 65) accounting for gender and BMI differences. For skeletal muscle mass thresholds were: men BMI < 25 kg/m^2 skeletal muscle mass$< 43 cm^2/m^2$, men BMI≥ 25 kg/m^2 skeletal muscle mass < 53 cm^2/m^2, women independent of

BMI skeletal muscle mass < 41 cm^2/m^2. For low skeletal muscle density, body mass index (BMI) specific thresholds were used independently of gender: BMI< 25 kg/m^2 HU< 41 and BMI ≥25 kg/m^2 HU < 33.

Secondly, we determined the sex-specific quartiles for skeletal muscle mass and density in our cohort. Patients were stratified into quartiles to allow comparison between the four groups and to compare patients with the lowest quartile of skeletal muscle mass and density with those with the highest skeletal muscle mass and density.

Physical performance

The preoperative use of a mobility aid was used as a marker of physical performance. Subgroup analysis was intended for patients with low muscle mass and low muscle density that also used a mobility aid preoperatively. Only patients with a Katz ADL score of ≥2 was considered functionally dependent.

Statistical analysis

OS was calculated from the day of surgery until death (all possible causes) or last follow-up. Continuous variables are reported mean with standard deviation (SD) and categorical variables with numbers and percentages. The Mann–Whitney U test or X^2 test were used to compare groups. OS was depicted through the Kaplan–Meier method. To assess the association between skeletal muscle mass, skeletal muscle density and physical performance with postoperative outcomes, logistic regression models were used to estimate Odds Ratios (ORs) with their corresponding 95% Confidence Interval (CI). To study the effect of these variables on OS, univariable and multivariable Cox-proportional hazards model was used to estimate hazard ratios (HRs) with their corresponding 95% CI.

The following confounders were considered: age, gender, BMI (for skeletal muscle mass and density only)[21] and tumour stage (for OS analysis). Comorbidity was considered a confounder for physical performance and outcomes.[22] A sensitivity analysis was performed on colon cancer patients only and this did not change our findings. Therefore, analyses were performed on all patients.

For assessing the additional effect of physical performance in patients with a low muscle mass and low muscle density, the interaction between muscle mass/

muscle density and physical performance was tested, and subgroup analysis was performed in case of a significant interaction.

A p-value < .05 was considered statistically significant. All analyses were performed using SPSS version 24.0 (SPSS, Inc., Chicago, IL).

Results

Study population

Between 1 January 2014 and 31 December 2016 a total of 228 patients aged 70 years and older who were operated for non-metastatic colorectal cancer and 174 (76%) met our inclusion criteria. Forty-nine patients were excluded based on the predefined criteria (acute surgery n=36, stage IV disease n=7, synchronous other cancer n=6) and five patients were excluded because the transversal CT-images were not suitable for secondary analyses. An interobserver correlation coefficient of 0.94 was reached between two observers based on analysis of 52 CT-images. Median follow-up was 954 days (2.6 years) and a total of 34 deaths were registered.

Baseline characteristics

Mean age was 78.0 years (SD 5.1), 60 patients (34%) were 80 years or older; age was equally distributed among sexes (Table 1). In 27 patients (16%) the tumour was detected as part of the national screening program, 143 (82%) had colon cancer and 31 (18%) rectal cancer. Laparoscopic surgery was performed in 114 patients (66%).

Prior to surgery, 36 patients (21%) used a mobility aid preoperatively, and nine (5%) were ADL dependent. Of the 36 patients with preoperative use of a mobility aid, six (17%) were also ADL dependent. One hundred forty-two patients (82%) had low skeletal muscle mass and 152 (87%) patients had low muscle density based on previously described definitions by Martin et al.[21]

The gender-specific quartiles (Qs) for skeletal muscle mass were Q1 men: < 39.84 cm^2/m^2, women: <32.68 cm^2/m^2; Q2 men: 39.84-44.83 cm^2/m^2, women: 32.68-34.95; Q3 men: 44.83-48.86 cm^2/m^2, women: 34.95-37.61 cm^2/m^2; Q4 men: >48.86 cm^2/m^2, women: >37.61 cm^2/m^2. The gender-specific quartiles for skeletal muscle density were Q1 men: <23.21 HU, women: <20.08 HU; Q2 men: 23.21-30.26 HU, women: 20.08-25.42 HU; Q3 men: 30.26-33.18 HU, women: 25.42-31.22 HU; Q4 men: >33.18 HU, women: >31.22 HU. Baseline characteristics with stratification based on preoperative use of a mobility aid can be found in Appendix A.

Table 1 Baseline characteristics

	Skeletal Muscle Mass (quartiles)										
	All patients		Q1		Q2		Q3		Q4		*p*
Total number of patients (n)	174		43		45		43		43		
Mean age (SD)	78.0	5.1	78.4	(5.1)	77.7	(5.3)	79	(4.9)	77	(4.9)	0.2
Gender (%)											
Male	89	(51)	22	(51)	23	(51)	22	(51)	22	(51)	0.9
Female	85	(49)	21	(49)	22	(49)	21	(49)	21	(49)	
BMI[a] kg/m^2											
BMI < 25	79	(45)	27	(63)	23	(51)	15	(35)	14	(33)	0.02
BMI ≥ 25	95	(55)	16	(37)	22	(49)	28	(65)	29	(67)	
Comorbidity (%)											
Cardiac Comorbidity	9	(5)	18	(42)	17	(38)	17	(40)	19	(44)	0.6
CCI[b] score ≥2	70	(40)	17	(40)	20	(44)	16	(37)	17	(40)	0.8
Tumour location (%)											
Colon	143	(82)	40	(93)	31	(69)	40	(93)	32	(74)	
Rectum	31	(18)	3	(7)	13	(29)	4	(9)	11	(26)	0.01
Tumour stage (%)											
I	50	(29)	7	(16)	13	(29)	12	(28)	18	(42)	0.3
II	66	(38)	19	(44)	17	(38)	16	(37)	14	(33)	
III	58	(33)	17	(40)	14	(31)	16	(37)	11	(26)	
ASA score (%)											
III or IV	48	(28)	17	(40)	7	(16)	12	(28)	12	(28)	0.1
(Neo)adjuvant treatment											
Neoadjuvant chemoradiation	9	(5)	0		6	(13)	1	(2)	2	(5)	0.2
Adjuvant chemotherapy	28	(16)	5	(12)	10	(22)	7	(16)	6	(14)	
Type of surgery											
Laparoscopic	114	(66)	29	(67)	28	(62)	27	(63)	30	(70)	0.8
Open	60	(34)	14	(33)	16	(36)	17	(40)	13	(30)	0.8
Functional parameters											
Use of a mobility aid[c]											
Yes	36	(21)	9	(21)	4	(9)	11	(26)	12	(28)	0.1
No	136	(79)	33	(79)	40	(91)	32	(74)	31	(72)	
ADL Dependency (Katz ≥2)											
Yes	9	(5)	3	(7)	1	(2)	2	(5)	3	(7)	0.7
No	165	(95)	40	(93)	43	(96)	42	(98)	40	(93)	

Table 1 continued

			Skeletal Muscle Mass (quartiles)								
	All patients		Q1		Q2		Q3		Q4		*p*
Body composition											
Mean Skeletal Muscle Mass (SD)[d]											
For men	44.1	(8.0)									
For women	35.9	(5.1)									
Mean Muscle Density (SD)[e]											
For men	28.9	(8.0)									
For women	25.8	(8.5)									
Low Skeletal Muscle Mass[f]	142	(82)	43	(100)	42	(93)	40	(93)	17	(40)	<0.001
Low Skeletal Muscle Density[f]	152	(87)	41	(95)	39	(87)	40	(93)	32	(74)	0.02

Mean with (SD) or frequency with percentage (%), Quartiles are sex-specific quartiles. Lowest (Q1) to highest (Q4). [a]BMI, body mass index; [b]CCI, Charlson Comorbidity Index; [c]2 missing values; [d]Skeletal Muscle Mass in cm^2/m^2. [e]Muscle Density in HU; [f]Based on thresholds published by Martin et al.[21]

5

Low skeletal muscle mass and low muscle density

In Table 2A and 2B, surgical outcomes are stratified based on the gender-specific quartiles of skeletal muscle mass and muscle density. Patient with the lowest versus the highest quartile of skeletal muscle density had significantly more complications (49% versus 28%, p=0.046), including more pulmonary complications (14% versus 2%, p=0.049) and more severe complications (28% versus 7%, p=0.01). For all postoperative outcomes, multivariable regression models were constructed with skeletal muscle mass and density included in a p-for-trend analysis. Except for cardiac complications, we found no statistically significant associations between higher quartiles of skeletal muscle mass or density and postoperative complications. There was also no significant association between skeletal muscle mass (HR 1.25, 95% CI 0.92-1.70, p=0.2) and skeletal muscle density (HR 0.74, 95% CI 0.54-1.10, p=0.06) and OS in the univariable model. Table 3 shows the multivariable models for OS. Including skeletal muscle mass and density as continuous variables in the multivariable model, did not yield different results (HR 1.02, 95% CI 0.97-1.07 and HR 0.96, 95% CI 0.92-1.01, respectively).

Physical performance

Patients that used a mobility aid preoperatively, had more complications that needed re-intervention (25% versus 7%, p= 0.003), more pulmonary complications (17% versus 4%, p=0.005) and more severe complications (39% versus 17%, p=0.004) including a higher 30-day mortality (17% versus 3%, p=0.002) and 1-year mortality (25% versus 6%, p=0.001). These associations were confirmed in the multivariable analysis (Table 4).

Table 2A Outcomes with stratification based on the gender-specific quartiles of skeletal muscle mass

	Skeletal Muscle Mass										Q1 vs Q4	Unadjusted OR		*p-for-trend*	Adjusted OR[a]		*p-for-trend*
	All patients		Q1 (%)		Q2 (%)		Q3 (%)		Q4 (%)		*p*	(95% CI)			(95% CI)		
Total *n*	174		43		44		44		43								
Any complication	68	(39)	13	(30)	18	(41)	18	(41)	19	(44)	0.2	1.19	(0.91-1.57)	0.2	1.17	(0.87-1.57)	0.3
Any Surgical complication	39	(22)	7	(16)	7	(16)	10	(23)	15	(35)	0.048	1.49	(1.04-2.02)	0.03	1.31	(0.92-1.88)	0.1
Need for reintervention	19	(11)	5	(12)	4	(9)	4	(9)	6	(14)	0.7	1.07	(0.70-1.65)	0.7	1.02	(0.64-1.65)	0.9
Anastomotic leakage	11	(6)	2	(5)	4	(9)	4	(9)	1	(2)	0.6	0.89	(0.51-1.54)	0.5	0.9	(0.48-1.69)	0.9
Pulmonary complication	12	(7)	3	(7)	3	(7)	4	(9)	2	(5)	0.6	0.93	(0.55-1.58)	0.9	0.82	(0.50-1.48)	0.5
Cardiac complication	11	(6)	6	(14)	2	(5)	1	(2)	2	(5)	0.1	0.58	(0.31-1.07)	0.08	0.44	(0.22-0.90)	0.02
Severe complication	38	(22)	10	(23)	9	(20)	9	(20)	10	(23)	1.0	1.0	(0.72-1.38)	1	0.97	(0.68-1.38)	0.9
Discharge not to home	22	(13)	6	(14)	5	(11)	4	(9)	7	(16)	0.8	1.04	(0.70-1.56)	0.8	1.13	(0.71-1.78)	0.6
Readmission	18	(10)	2	(5)	4	(9)	4	(9)	8	(19)	0.04	1.61	(1.00-2.58)	0.05	1.58	(0.97-2.58)	0.07
30-day mortality	10	(6)	2	(5)	2	(5)	3	(7)	3	(7)	0.6	1.19	(0.67-2.12)	0.6	1.09	(0.58-2.06)	0.8
1-year mortality	17	(10)	4	(9)	3	(7)	6	(14)	4	(9)	1.0	1.08	(0.69-1.70)	0.8	1.05	(0.65-1.72)	0.8

Gender-specific quartiles. Percentage (%). Odds Ratio's (ORs) with 95% Confidence Interval (CI)

[a]Logistic regression model included Skeletal Muscle Mass (gender-specific quartiles), age (years) and BMI (m2/kg)

Table 2B Outcomes with Stratification based on the gender-specific quartiles of skeletal muscle density

	Skeletal Muscle Density										Q1 vs Q4 p	Unadjusted OR (95% CI)		p-for-trend	Adjusted OR[a] (95% CI)		p-for-trend
	All patients		Q1 (%)		Q2 (%)		Q3 (%)		Q4 (%)								
Total n	174		43		45		43		43								
Any complication	68	(39)	21	(49)	17	(38)	18	(42)	12	(28)	0.046	0.78	(0.59-1.03)	0.08	0.83	(0.61-1.12)	0.2
Any Surgical complication	39	(22)	11	(26)	9	(20)	14	(33)	5	(12)	0.1	0.81	(0.52-1.25)	0.3	1.01	(0.71-1.44)	0.9
Need for reintervention	19	(11)	5	(12)	6	(13)	6	(14)	2	(5)	0.2	1.32	(0.74-2.32)	0.3	0.95	(0.59-1.54)	0.8
Anastomotic leakage	11	(6)	3	(7)	4	(9)	3	(7)	1	(2)	0.3	0.76	(0.43-1.34)	0.3	0.90	(0.48-1.70)	0.8
Pulmonary complication	12	(7)	6	(14)	3	(7)	2	(5)	1	(2)	0.049	0.53	(0.29-0.98)	0.04	0.87	(0.31-1.12)	0.1
Cardiac complication	11	(6)	7	(16)	2	(4)	1	(2)	1	(2)	0.03	0.42	(0.20-0.85)	0.02	0.47	(0.22-0.99)	0.048
Severe complication	38	(22)	12	(28)	10	(22)	13	(30)	3	(7)	0.01	0.72	(0.52-1.01)	0.06	0.79	(0.55-1.13)	0.2
Discharge not to home	22	(13)	7	(16)	4	(9)	9	(21)	2	(5)	0.1	0.81	(0.54-1.22)	0.3	0.91	(0.57-1.43)	0.7
Readmission	18	(10)	3	(7)	5	(11)	6	(14)	4	(9)	0.7	1.11	(0.72-1.73)	0.6	1.12	(0.69-1.81)	0.7
30-day mortality	10	(6)	4	(9)	3	(7)	2	(5)	1	(2)	0.2	0.64	(0.35-1.19)	0.6	0.75	(0.39-1.46)	0.7
1-year mortality	17	(10)	6	(14)	6	(13)	3	(7)	2	(5)	0.1	0.67	(0.41-1.07)	0.1	0.70	(0.42-1.18)	0.2

Gender-specific quartiles. Percentage (%). Odds Ratio's (ORs) with 95% Confidence Interval (CI)

Table 3 Multivariable Cox-regression models for overall survival

	Overall Survival n=34		
	Adjusted HR (95% CI)		*p*
Skeletal Muscle Mass, quartile	1.15	(0.82-1.61)	0.4
Age, years	1.01	(0.94-1.08)	0.8
BMI, kg/m2	1.08	(0.99-1.16)	0.09
Tumour Stage	1.15	(0.75-1.74)	0.53

Model A. Skeletal Muscle Mass. 95% Confidence Interval (CI)

	Overall Survival n=34		
	Adjusted HR (95% CI)		*p*
Skeletal Muscle Density, quartile	0.81	(0.57-1.13)	0.2
Age, years	1.00	(0.93-1.07)	0.9
BMI, kg/m2	1.06	(0.99-1.15)	0.1
Tumour Stage	1.1	(0.72-1.68)	0.7

Model B. Skeletal Muscle Density. 95% Confidence Interval (CI)

	Overall Survival n=34		
	Adjusted HR (95% CI)		*p*
Use of a mobility aid			
No	1		
Yes	2.65	(1.29-5.44)	0.01
Age, years	1	(0.93-1.07)	0.9
Gender			
Female	1		
Male	1.57	(0.78-3.19)	0.2
Tumour stage	1.08	(0.70-1.66)	0.7

Model C. Use of a mobility Aid. 95% Confidence Interval (CI)

Table 4 Surgical Outcomes with Stratification based on preoperative use of a mobility aid

			Use of a Mobility Aid					Unadjusted OR			Adjusted OR[a]		
			yes (%)		no (%)		p	(95% CI)		p	(95% CI)		p
Total *n**	172*		36		136								
Any complication	66	(38)	18	(50)	49	(36)	0.1	1.78	(0.80-3.85)	0.2	1.62	(0.72-3.40)	0.2
Any Surgical complication	39	(23)	11	(31)	28	(21)	0.2	1.7	(0.65-3.64)	0.3	1.88	(0.76-4.49)	0.2
Need for reintervention	19	(11)	9	(25)	10	(7)	0.003	4.2	(1.28-10.4)	0.02	3.83	(1.27-11.6)	0.02
Anastomotic leakage	11	(6)	5	(14)	6	(4)	0.04	3.5	(0.65-10.0)	0.2	3.60	(0.79-16.4)	0.1
Pulmonary complication	12	(7)	6	(17)	5	(4)	0.005	5.24	(1.32-17.4)	0.02	4.21	(1.09-16.3)	0.04
Cardiac complication	11	(6)	4	(11)	7	(5)	0.2	2.3	(0.41-6.82)	0.5	1.28	(0.31-5.21)	0.4
Severe complication	36	(21)	14	(39)	23	(17)	0.004	3.13	(1.19-6.57)	0.02	2.95	(1.21-7.20)	0.02
Discharge not to home	13	(8)	7	(5)	6	(19)	0.009	4.32	(1.06-17.2)	0.04	3.53	(0.88-14.2)	0.08
Readmission	18	(10)	5	(14)	13	(10)	0.5	1.52	(0.61-6.31)	0.3	1.60	(0.49-5.24)	0.4
30-day mortality	10	(6)	6	(17)	4	(3)	0.002	6.6	(1.51-25.2)	0.01	6.10	(1.39-26.7)	0.01
1-year mortality	17	(10)	9	(25)	8	(6)	0.001	5.33	(1.78-16.0)	0.003	5.30	(1.67-16.9)	0.01

Percentage (%). * 2 missing. Odds Ratio (OR) with 95% Confidence Interval (CI)

[a]Logistic Regression model included use of a mobility aid, age (years), gender and comorbidity (*n*)

Mobility aid use was also associated with worse OS in the univariable analysis (HR 2.57, 95% CI 1.26-5.51, p=0.01; Appendix B shows the Kaplan Meier Curve) and multivariable analysis that included age, gender and tumour stage (HR 2.65, 95% CI 1.29-5.44, p=0.01). When comorbidity was included in the multivariable model for OS, the preoperative use of a mobility aid was still associated with worse OS (HR 2.62, 95% CI 1.22-5.63, p=0.013).

Low skeletal muscle mass and physical performance

Due to the relatively small group of patients, we performed subgroup analysis for OS based on the sex-specific median of skeletal muscle mass instead of sex-specific quartiles. There was a borderline significant interaction between mobility aid use and skeletal muscle mass (p=0.05) and no interaction between mobility aid use and skeletal muscle density (p=0.14). Stratified analysis showed that patients with a skeletal muscle mass below the median in combination with preoperative use of mobility aid had worse OS (HR 5.68, 95% CI 1.79-18.02, p=0.003). In patients with a skeletal muscle mass above the median, the use of a mobility aid was not associated with OS (HR 1.38, 95% CI 0.55-3.43, p=0.5).

Discussion

In a cohort of older patients (≥ 70 years of age), undergoing surgical treatment for CRC, the preoperative use of a mobility aid as derivative of "physical performance" was associated with higher morbidity and mortality. Skeletal muscle mass and density were not associated with OS, and only muscle density had weak associations with postoperative complications when the lowest and highest quartiles were compared. The importance of the assessment of physical performance when assessing skeletal muscle mass and density in older patients was further shown as patients with the lowest skeletal muscle mass in combination with preoperative use of a mobility aid had worse OS.

Our study suggests that a single radiological measurement of muscle mass and density has insufficient potential to be used for risk stratification in the majority of older colorectal patients and physical performance measures such as the use of a mobility aid, Timed Up and Go (TUG)[23,24] or gait speed,[9] would be of more importance. Although we did not assess the association between low skeletal muscle mass in combination with decreased physical performance and postoperative complications, earlier studies in CRC patients showed associations with increased risk of sepsis and severe complications.[9, 5]

That muscle mass was unrelated to postoperative complications is in line with a study in older Asian CRC patients (>65 years)[25] and a recent study in older Dutch CRC patients.[26] In addition, our study findings correlate with previous findings that muscle density is more strongly associated with surgical outcome compared to skeletal muscle mass.[6,24,25] Studies investigating the association between low skeletal muscle mass and density and OS are inconsistent. Van Vught et al. also found no association.[27] However, an association was reported by studies that included younger and older patients, including those with metastatic disease[2-4,7,28] or only open surgery.[6]

The lack of association found in our cohort between skeletal muscle mass and outcomes compared to the studies mentioned above could have several explanations. Our study population consisted of only older patients and patients with elective surgery for stage I-III disease in contrast to the before-mentioned studies. In this group, low skeletal muscle mass can be assumed to be part of the chronological ageing process and less likely as a result of secondary causes such as cancer. Also, this selection resulted in less variety in skeletal muscle mass and density, limiting its discriminative power. We used sex-specific quartiles for skeletal muscle mass and density in our cohort to overcome this problem. Another explanation is that in studies of patients with advanced disease, skeletal muscle mass may have declined due to the presence of metastasis. Moreover, skeletal muscle mass measurements are only normalised for stature. As a consequence, low skeletal muscle mass is underestimated in overweight patients and overestimated in underweight patients. Patients with preserved adipose tissue despite decreased muscle mass (sarcopenic obesity), may represent a separate risk group.[6,29,30] Hence, with muscle density, the amount of fat infiltration is accounted for, and this may explain the importance of skeletal muscle density over skeletal muscle mass.

In non-metastatic CRC patients, physical performance measures such as preoperative use of a mobility aid alone, are unlikely to change a surgical treatment plan. However, as a predictor in risk models for outcomes of CRC surgery, mobility aid use might be useful.[31,32] In addition, low physical performance could serve as an important target for interventions such as prehabilitation for improving outcomes.[33]

There are some limitations to our study. First, the incidence of severe complications such as anastomotic leakage was low. By stratifying patients based in quartiles, the number of events in each outcome of interest was further reduced. Second, we did not have data on the number of patients that were considered unsuitable for surgery, which may have induced a selection bias.

Despite these limitations, we think that our results are representative. Strengths of this study are that a relatively large older cohort of patients was included, with prospectively collected data with standardised quality. The low interrater variability indicates that our skeletal muscle mass and muscle density analysis is robust.

To increase clinical applicability of muscle mass and density measurements for older cancer patients, larger cohort studies are needed that also include measurement of muscle strength and physical performance, in accordance with the updated guidelines on sarcopenia.[10] Also, the use of a mobility aid as derivative of physical performance and other frailty parameters included in a geriatric assessment, such as cognitive functioning, are also of interest in association with poor surgical outcome.

Conclusion

Low skeletal muscle density and not muscle mass might be associated with more complications after colorectal surgery in older patients with non-metastatic cancer. Physical performance has the strongest association for poor surgical outcome, including OS and should be investigated when measuring skeletal muscle mass and density.

References

1. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA: A Cancer Journal for Clinicians.* 2014;64(2):104-17.
2. Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB.* 2011;13(7):439-46.
3. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *British Journal of Cancer.* 2012;107(6):931-6.
4. Sabel MS, Terjimanian M, Conlon AS, Griffith KA, Morris AM, Mulholland MW, et al. Analytic morphometric assessment of patients undergoing colectomy for colon cancer. *Journal of Surgical Oncology.* 2013;108(3):169-75.
5. Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewe KW, Hoofwijk AG, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Annals of Surgery.* 2015;261(2):345-52.
6. Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, et al. Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer. *International Journal of Colorectal Disease.* 2016;31(6):1117-24.
7. Jones KI, Doleman B, Scott S, Lund JN, Williams JP. Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. *Colorectal Disease.* 2015;17(1):O20-6.
8. Jung HW, Kim JW, Kim JY, Kim SW, Yang HK, Lee JW, et al. Effect of muscle mass on toxicity and survival in patients with colon cancer undergoing adjuvant chemotherapy. *Supportive Care in Cancer.* 2015;23(3):687-94.
9. Huang DD, Wang SL, Zhuang CL, Zheng BS, Lu JX, Chen FF, et al. Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. *Colorectal Disease.* 2015;17(11):O256-64.
10. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing.* 2018.
11. Van Leersum N, Snijders H, Henneman D, Kolfschoten N, Gooiker G, Ten Berge M, et al. The Dutch surgical colorectal audit. *European Journal of Surgical Oncology.* 2013;39(10):1063-70.
12. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. *World Journal of Surgery.* 2014;38(6):1531-41.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases.* 1987;40(5):373-83.
14. Katz S, Akpom CA. 12. Index of ADL. *Medical Care.* 1976;14(5 Suppl):116-8.
15. Henneman D, Ten Berge MG, Snijders HS, van Leersum NJ, Fiocco M, Wiggers T, et al. Safety of elective colorectal cancer surgery: non-surgical complications and colectomies are targets for quality improvement. *Journal of Surgical Oncology.* 2014;109(6):567-73.
16. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Applied Physiology, Nutrition, and Metabolism Physiologie Appliquée, Nutrition et Métabolisme.* 2008;33(5):997-1006.
17. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta Physiologica (Oxford, England).* 2014;210(3):489-97.
18. Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2005;60(3):324-33.

19. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *Journal of Applied Physiology.* 1998;85(1):115-22.

20. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *American Journal of Epidemiology.* 1998;147(8):755-63.

21. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *Journal of Clinical Oncology.* 2013;31(12):1539-47.

22. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev.* 2011;10(4):430-9.

23. Huisman MG, van Leeuwen BL, Ugolini G, Montroni I, Spiliotis J, Stabilini C, et al. "Timed Up & Go": a screening tool for predicting 30-day morbidity in onco-geriatric surgical patients? A multicenter cohort study. *PloS One.* 2014;9(1):e86863.

24. Schmidt M, Eckardt R, Altmeppen S, Wernecke KD, Spies C. Functional impairment prior to major non-cardiac surgery is associated with mortality within one year in elderly patients with gastrointestinal, gynaecological and urogenital cancer: A prospective observational cohort study. *Journal of Geriatric Oncology.* 2018;9(1):53-9.

25. Miyamoto Y, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, Kurashige J, et al. Sarcopenia is a Negative Prognostic Factor After Curative Resection of Colorectal Cancer. *Annals of Surgical Oncology.* 2015;22(8):2663-8.

26. Mosk CA, J LAvV, de Jonge H, Witjes CD, Buettner S, Ijzermans JN, et al. Low skeletal muscle mass as a risk factor for postoperative delirium in elderly patients undergoing colorectal cancer surgery. *Clinical Interventions in Aging.* 2018;13:2097-106.

27. van Vugt JLA, Coebergh van den Braak RRJ, Lalmahomed ZS, Vrijland WW, Dekker JWT, Zimmerman DDE, et al. Impact of low skeletal muscle mass and density on short and long-term outcome after resection of stage I-III colorectal cancer. *European Journal of Surgical Oncology.* 2018;44(9):1354-60.

28. Malietzis G, Currie AC, Athanasiou T, Johns N, Anyamene N, Glynne-Jones R, et al. Influence of body composition profile on outcomes following colorectal cancer surgery. *British Journal of Surgery.* 2016;103(5):572-80.

29. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncology.* 2008;9(7):629-35.

30. Lodewick TM, van Nijnatten TJA, van Dam RM, van Mierlo K, Dello SAWG, Neumann UP, et al. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? *HPB.* 2015;17(5):438-46.

31. Berian JR, Zhou L, Hornor MA, Russell MM, Cohen ME, Finlayson E, et al. Optimizing Surgical Quality Datasets to Care for Older Adults: Lessons from the American College of Surgeons NSQIP Geriatric Surgery Pilot. *Journal of the American College of Surgeons.* 2017;225(6):702-12.e1.

32. Mahoney JE, Sager MA, Jalaluddin M. Use of an ambulation assistive device predicts functional decline associated with hospitalization. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 1999;54(2):M83-8.

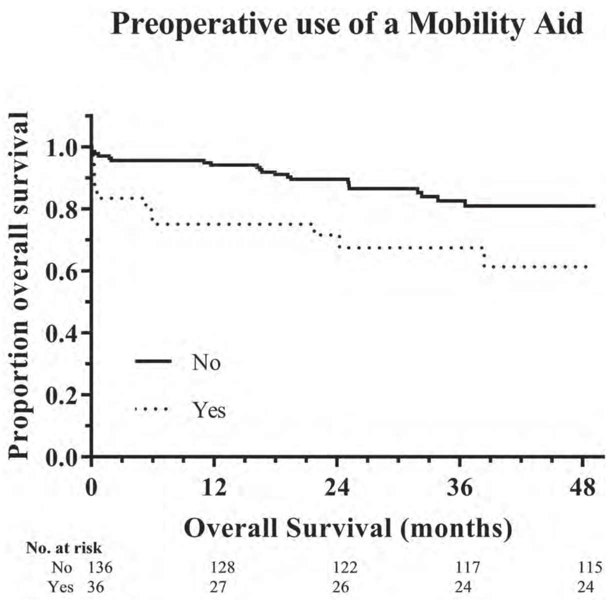
33. Bruns ER, van den Heuvel B, Buskens CJ, van Duijvendijk P, Festen S, Wassenaar EB, et al. The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. *Colorectal Disease.* 2016;18(8):O267-77.

Appendix A Baseline characteristics with stratification based on preoperative use of a mobility aid

	All patients		Use of mobility aid		No use of mobility aid		*p*
Total number of patients (n)	174		36		136		
Mean age (SD)	78.0	5.1	80	(5.3)	77.5	(4.9)	0.01
Gender (%)							
Male	89	(51)	16	(44)	72	(53)	0.36
Female	85	(49)	20	(56)	64	(47)	
BMI[a] kg/m^2							
BMI < 25	79	(45)	10	(28)	68	(50)	0.02
BMI ≥ 25	95	(55)	26	(72)	68	(50)	
Comorbidity (%)							
Cardiac Comorbidity	9	(5)	11	(31)	19	(14)	0.02
CCI[b] score ≥2	70	(40)	21	(58)	49	(36)	0.02
Tumour location (%)							
Colon	143	(82)	32	(89)	109	(80)	0.2
Rectum	31	(18)	4	(11)	27	(20)	
Tumour stage (%)							
I	50	(29)	11	(31)	39	(29)	0.7
II	66	(38)	15	(42)	50	(37)	
III	58	(33)	10	(28)	47	(35)	
ASA score (%)							
III or IV	48	(28)	15	(42)	33	(24)	0.04
(Neo)adjuvant treatment							
Neoadjuvant chemoradiation	9	(5)	0		9	(7)	0.4
Adjuvant chemotherapy	28	(16)	2	(6)	35	(26)	0.06
Type of surgery							
Laparoscopic	114	(66)	21	(58)	92	(68)	0.3
Open	60	(34)	15	(42)	44	(32)	
Functional parameters							
ADL Dependency (Katz ≥2)							
Yes	9	(5)	6	(17)	3	(2)	0.001
No	165	(95)	30	(83)	133	(98)	
Body composition							
Mean Skeletal Muscle Mass[c] (SD)							
For men	44.1	(8.0)	46.3	(7.9)	43.6	(8.0)	0.3
For women	35.9	(5.1)	37.2	(6.2)	35.5	(4.8)	0.2
Mean Muscle Density (SD)[d]							
For men	28.9	(8.0)	24.9	(7.2)	29.7	(7.9)	0.03
For women	25.8	(8.5)	23.0	(10.1)	26.7	(7.8)	0.09

Mean with (SD) or frequency with percentage (%). [a]BMI, body mass index; [b]CCI, Charlson Comorbidity Index;,[c]Skeletal Muscle Mass in cm^2/m^2. [d]Muscle Density in HU

5



Appendix B Kaplan Meier Survival analysis for preoperative use of a mobility aid

Chapter 6

A prediction model for severe complications after elective colorectal cancer surgery in patients of 70 years and older

Submitted

E.T.D. Souwer
E. Bastiaannet
E.W. Steyerberg
J.W.T. Dekker
W.H. Steup
M.E. Hamaker
D.J.A. Sonneveld
T.A. Burghgraef
F. van den Bos
J.E.A. Portielje

Abstract

Background: Older patients have an increased risk of morbidity and mortality after colorectal cancer (CRC) surgery. Existing CRC surgical prediction models have not incorporated geriatric predictors, limiting applicability for preoperative decision making.

The objective was to develop and internally validate a predictive model based on preoperative predictors, including geriatric characteristics, for severe postoperative complications after elective surgery for stage I-III CRC in patients ≥70 years.

Patients and methods: Prospectively collected database containing 1088 consecutive patients from five Dutch hospitals (2014-2017) with 171 severe complications (16%). Potential predictors included demographics, comorbidity, tumour location, Activities of Daily Living (ADL), history of falls, malnutrition, risk factors for delirium, use of a mobility aid and polypharmacy. The LASSO (least absolute shrinkage and selection operator) method was used for predictor selection and prediction model building. Internal validation was done using bootstrapping.

Results: A geriatric model that included gender, previous DVT or Pulmonary Embolism, COPD/Asthma/Emphysema, rectal cancer, the use of a mobility aid, ADL assistance, previous delirium and polypharmacy showed satisfactory discrimination AUC 0.69 95% CI 0.73-0.64 and optimism corrected (AUC 0.65). Based on these predictors, the 8-item Colorectal Geriatric Model (GerCRC) was developed.

Conclusion: The GerCRC is the first prediction model specifically developed for older patients planned for CRC surgery. Combining tumour and patient-specific predictors, including geriatric predictors, improve outcome prediction in the heterogeneous older population. After external validation, this risk model has the potential to be used for preoperative (shared) decision making.

Background

Older patients make up the majority of newly diagnosed patients with colorectal cancer (CRC)[1] and for this heterogeneous population, risks and benefits of treatment must be weighted at an individual level.[2-5] Prediction models can be used to facilitate decision-making and estimate outcomes of treatment such as surgery-related morbidity and mortality. Especially severe complications are of interest, because they hinder the postoperative course and impact postoperative functioning and quality of life of older patients.[6-8]

For older patients with CRC potential predictors for these outcomes include physical performance measures,[9-11] falls and cognitive impairments.[12,13] However, in currently available prediction models, there is a focus on cancer- and surgery-related predictors. At the same time, the inclusion of perioperative predictors in many models limits their use for preoperative decision making.[14-16]

We have previously shown that most available CRC prediction models have a moderate to high risk of bias, especially in older adults.[17] That also applies to the three surgical risk prediction models for prediction of severe complications; The Physiology and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM),[14] Colorectal Biochemical and Hematological Outcome Model (CR-BHOM)[18] and The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP).[10,19] Predictors related to geriatric characteristics might improve a prediction model's performance for older CRC patients.[20,21]

This study aimed to develop and internally validate a prognostic preoperative clinical model for severe postoperative complications after elective surgery for stage I-III CRC, intended to support shared decision making with older patients. We hereto analyzed data from a large population-based cohort of patients ≥70 years.

Patients and methods

Data and Participants

This study is reported in accordance with the recommendations set forth by The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Initiative.[22] This study was approved by the medical ethical review board of Southwest Holland, The Netherlands. A waiver for informed consent was granted due to the retrospective of this study.

Five Dutch Hospitals provided data for this study. Patient demographic data, as well as outcome data, were retrieved from the Dutch ColoRectal Audit (DCRA) between January 2014 and December 2017. The DCRA is a national mandatory surgical database contains pre-, peri- and postoperative surgical and outcome data on all operated CRC patients in the Netherlands as part of a national quality improvement project. From the Electronic Hospital Records (EHRs), Geriatric Data were retrieved that were registered as part of standard preoperative care.

Patients who were 70 years or older on the day of surgery were identified from the DCRA. All consecutive patients are prospectively enrolled in this database by qualified staff.[23] Eligible for inclusion were patients with elective surgery for stage I-III CRC. Exclusion criteria were synchronous cancer at diagnosis, non-elective or Transanal endoscopic microsurgery (TEMS).

The Enhanced Recovery After Surgery (ERAS) guidelines[24] were part of standard care. Other standard care measures and interventions during the study period were the detection of undernutrition and dietary support when needed, post-operative physiotherapy in case of functional dependency (Activities of Daily Living, ADL) and early detection of delirium in high-risk patients.

Outcome

A complication was defined as in-and-out of hospital morbidity (of any kind) within 30-days of surgery. A severe complication was defined as a complication leading to ICU admission (more than two days), a reintervention (surgical or radiological), prolonged hospital stay (more than 14 days), or postoperative mortality. This is consistent with previous publications in which outcome data from the DCRA were analysed.[25]

Predictors

A systematic review of prediction models for adverse outcomes of CRC was used to identify commonly used predictors in younger and older patients.[17] Candidate predictors that were available from the DCRA database included demographic information (age, gender, body mass index (BMI)), tumour stage and location, ASA (American Society of Anesthesiologists) score and comorbidity. Comorbidity included previous abdominal surgery, cardiac comorbidity (including arrhythmias, myocardial infarction, cardiac surgery and cardiomyopathy), pulmonary comorbidity (COPD/Asthma/Emphysema and other), and previous thrombo-embolic such as Pulmonary Embolism (PE) or Deep Venous Thrombosis (DVT). From the comorbidity data, a Charlson Comorbidity Index (CCI) was calculated.[26]

From the EMR the following preoperative additional candidate predictors were extracted: undernutrition (or at risk of becoming undernourished), functional impairment, the use of a mobility aid (the use of a cane, crutches, a walking frame or wheelchair), the risk of delirium and falls in the past six months. Risk for undernutrition was assessed with either the SNAQ[27] or MUST[28] screening tool. Functional impairment was assessed with the six-item Katz ADL[29] consisting of questions regarding bathing, dressing, using the toilet, eating, transferring from bed to chair and the use of incontinence materials. Risk for delirium was assessed using three yes or no questions concerning previous delirium during hospitalization, self-reported need for ADL assistance (in the past 24 hours) and self-reported cognitive impairment. Polypharmacy (using five or more prescribed medications) was based on preoperative medication/prescriptive data from the EMR. All predictors from the EMR had been registered at the day of hospital admission or in the weeks before surgery (up to 6 weeks).

Statistical analysis

Data were inspected for missing variables. Missing predictor data were estimated in a regression model using all other predictor variables and outcomes as independent variables. Missing data on candidate predictors were subsequently imputed with a single imputation technique and used for final predictor selection and model development.

Baseline characteristics were reported as means with standard deviation (SD) or as frequencies and percentages. Before imputation, candidate predictors were related to the outcome using univariable logistic regression analysis to estimate Odds Ratio (OR) with corresponding 95% Confidence Interval (CI) and p-value.

To investigate the added value of a geriatric predictors, two models were created. A "demographic model" included only preoperative demographic predictors, comorbidity, tumour location and stage, and ASA score. For a "geriatric" model, the geriatric predictors from the EMR were added to all candidate predictors from the demographic model.

The questions of the Katz ADL, self-reported need for ADL assistance, previous delirium and self-reported cognitive impairments (classified as a risk for delirium) were added as a categorical predictor on an individual level and dichotomised (Katz ADL ≥2 and risk for delirium ≥1). Because of expected co-linearity between Katz ADL questions and the self-reported need for ADL assistance, either the Katz ADL or self-reported ADL assistance were used as candidate predictors.

In both the demographic and geriatric model, the final model selection was obtained using the Least Absolute Shrinkage and Selection Operator (LASSO) method. LASSO applies a penalty on the absolute value of the regression coefficients, such that some are set to zero whereas others are shrunk towards smaller (absolute) values. Variables that are shrunk to zero are omitted from the model. The goal of this process is to minimize the prediction error. Compared to backward selection, the addition of shrinkage may improve model performance by avoiding overfitting and miscalibration.[30]

The validity of both models was tested by performing bootstrap validation with 500 replications and optimism correction. The discriminative predictive performance of the models was demonstrated with the Area Under the Curve (AUC). For the optimism corrected model, no valid 95% CI can be calculated. The final shrunk coefficients from the LASSO were used to generate a score chart which is intended as a clinical tool. The shrunk β coefficients from the geriatric model were rounded for selection in the simplified clinical tool. Predictors with a β of less than 0.1 were therefore not selected for the clinical tool to increase the robustness of the model.[30] At least 1 point was given to each predictor included. Subsequent risk groups were created based on at least 70 observations in each risk category.

Imputation, LASSO shrinkage and bootstrap validation were analysed with R (Version 3.5.2) using "mice", "rms", "glmnet" packages. All other analyses were performed using SPSS version 23.0 (SPSS, Inc., Chicago, IL).

Results

Participants

The total cohort consisted of 1366 older patients who underwent colorectal resection between January 2014 and December 2017 (Figure 1). From one hospital, data was only available from January 2014 until December 2015 because of a change in EHR registration. There were no missing demographic data (Table 1). The number of complete cases was 977 (89.8%), 87 cases (8%) had one missing candidate predictor, 24 (2%) had 2 or more missing candidate predictors. Mean age was 77.7 (SD 5.2), there were 498 (46%) females, 270 (25%) patients with rectal cancer and 354 (33%) had an ASA score of III or IV.

Model development

There were 171 patients (16%) with one or more severe complications recorded; 51 patients were admitted to the ICU for more than two days, 26 of whom had a reintervention. A total of 121 patients (including 29 ICU patients) had a hospital stay of > 14 days; 30-day mortality was 1.7% (n=19). The distribution of severe complications is available in Appendix A.

Unadjusted associations between each candidate predictor and severe complications are shown in Table 1 and Appendix B. For the demographic model development, with only demographic candidate predictors, the final predictors were age, gender, COPD/Asthma/Emphysema, previous PE or DVT, ASA score and tumour location. The AUC of the demographic model was 0.65 (95% CI 0.62-0.70), which was corrected to AUC 0.62 after internal validation.

The discriminatory performance of the preoperative model improved to 0.69 (95% CI 64-0.73) when the geriatric predictors delirium, cognitive impairments, ADL assistance, the use of mobility aid, and polypharmacy were included. The optimism corrected AUC was 0.65. Table 2 shows the regression coefficients of the demographic and geriatric models.

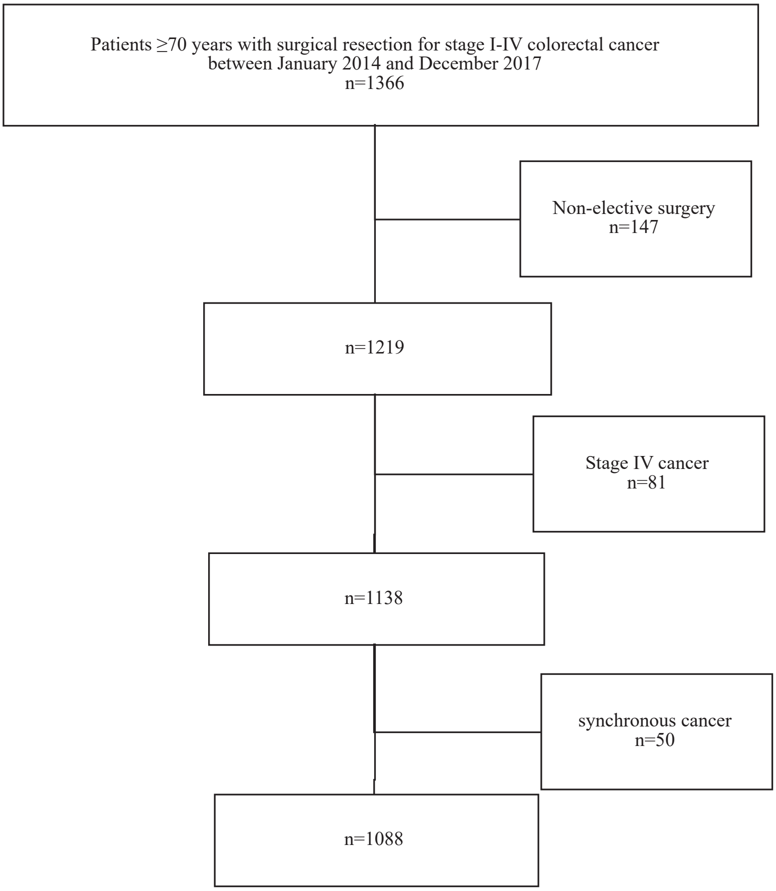


Figure 1 Patient selection

Table 1 Baseline characteristics and univariable associations with severe complications

	No patients =1088							**Odds Ratio (95% CI)**		
	missing	all		Severe complication						
Predictors				yes		no				*p*-value
Demografics										
Age. Years (mean. SD)	-	77.67	(5.2)	78.5	(5.2)	77.51	(5.1)	1.038	(1.01-1.07)	0.017
Age Categories										
70-74	-	383	(35)	47	(12)	336	(88)		*reference*	
75-79	-	353	(32)	62	(18)	291	(82)	1.52	(1.01-2.30)	0.044
80-84	-	241	(22)	40	(17)	201	(83)	1.42	(0.90-2.25)	0.13
85+	-	111	(10)	22	(20)	89	(80)	1.77	(1.01-3.09)	0.045
Gender	-									
Females	-	498	(46)	60	(12)	439	(88)		*reference*	
Males	-	590	(54)	111	(19)	479	(81)	1.69	(1.2-2.38)	0.002
BMI. kg/m2 (mean. SD)	-	26.48	11.4	26.8	(4.4)	26.4	(12.3)	1	(0.99-1.01)	0.71
BMI Categories										
<25 kg/m^2	-	464	(43)	62	(13)	402	(87)		*reference*	
25-30 kg/m^2	-	467	(43)	81	(17)	386	(83)	1.36	(0.95-1.95)	0.09
>30 kg/m^2	-	157	(14)	28	(18)	129	(82)	1.41	(0.86-2.29)	0.17
Comorbidity										
History of Abdominal Surgery	-	460	(42)	75	(16)	385	(84)	1.08	(0.78-1.50)	0.65
Cardic Comorbidity	-	401	(37)	74	(18)	327	(82)	1.38	(0.99-1.92)	0.06
COPD/ Asthma/ Emphysema	-	110	(10)	30	(27)	80	(73)	2.27	(1.41-3.51)	0.001
Previous PE or DVT[a]	-	52	(5)	15	(29)	37	(71)	2.56	(1.25-4.44)	0.008
Charlon Comorbidity Index (median. range)		1	(0-2)	1	(0-8)	1	(0-7)	1.27	(1.03-1.56)	0.022
Comorbidity CCI ≥ 2	-	392	(36)	76	(19)	318	(81)	1.49	(1.07-2.07)	0.02
ASA Score (mean. SD)		2.3	(0.6)	2.4	(0.7)	2.2	(0.6)	1.61	(1.24-2.07)	<0.001
I-II	-	734	(67)	97	(13)	637	(87)		*reference*	
III-IV	-	354	(33)	74	(21)	280	(79)	1.74	(1.24-2.42)	0.001

Tumour Location										
Colon	-	818	(75)	120	(15)	698	(85)		*reference*	
Rectum	-	270	(25)	51	(19)	219	(81)	1.35	(0.94-1.94)	0.099
Tumour stage										
I	-	336	(31)	54	(16)	282	(84)		*reference*	
II	-	411	(38)	63	(15)	348	(85)	0.95	(0.64-1.04)	0.78
III	-	341	(31)	54	(16)	287	(84)	0.98	(0.65-1.48)	0.93
Surgical Approach										
Laparoscopic	-	877	(81)	119	(14)	758	(86)		*reference*	
Open	-	211	(19)	52	(25)	159	(75)	2.08	(1.44-3.01)	<0.001
Geriatic										
Katz ADL (mean. SD)	15	0.3	(0.8)	0.5	(1.3)	0.2	(0.7)	1.38	(1.18-1.61)	<0.001
score ≥2		65	(6)	22	(34)	43	(66)	2.97	(1.73-5.11)	<0.001
Reported Falls	76	129	(12)	24	(19)	105	(81)	1.19	(0.74-1.92)	0.47
Risk for Malnutrition	12	215	(20)	37	(17)	156	(73)	1.35	(0.90-2.02)	0.1
Risk for Delirium (mean. SD)	18	0.3	(0.6)	0.5	(0.8)	0.2	(0.6)	1.69	(1.34-2.12)	<0.001
Delirium Score ≥1		210	(19)	56	(27)	154	(73)	2.38	(1.65-3.42)	<0.001
Medication Use (mean. SD)	18	4	(0-17)	5	(0-17)	4	(0-16)	1.1	(1.05-1.56)	<0.001
Polypharmacy (No. ≥5)		490	(45)	103	(21)	387	(79)	2.18	(1.55-3.07)	<0.001
Preoperative Use of a Mobility Aid	21	191	(18)	51	(27)	116	(61)	2.39	(1.64-3.47)	<0.001

Mean with Standard Deviation (SD). median with (range) and frequencies with percentage (%).
Odds Ratio's with 95% Confidence Interval (CI). [a] PE, pulmonary Embolism; DVT, Deep Venous Thrombosis

When the predictors Katz ADL (instead of self-reported ADL assistance) and risk for delirium (score ≥1) were included as candidate predictors in the geriatric model, this yielded an AUC of 0.69 (95% CI 0.65-0.73) after internal validation and 0.65 in the optimism corrected model. Judged by its clinical applicability, we used the first model (with self-reported ADL assistance) for further risk score development.

Clinical Prediction Model

For the development of a clinically useful prediction model and tool, the regression coefficients from the geriatric model were used to develop the Geriatric Colorectal Cancer Model (GerCRC). After rounding, age (every 10 years, b=0.04), ASA score (b=0.02) and self-reported cognitive impairment (b=0.09) were omitted due to their marginal effect (b<0.1).

Based on the weight of the regression coefficients, all predictors were given 2 points except for tumour location (1 point) and the (self-reported) need for ADL assistance (1 point). In the simplified model, a total of 14 points can be obtained (Table 3A). The number of patients with a score of 0 or 1 was 171 (16%) and 46 (4%), respectively. The maximum score obtained by patients in our study was 11 (n=3), of whom two (67%) had a severe complication.

After grouping patients with a score of 0-1 and 7 or higher, Table 3B shows the corresponding predicted proportion of complications with corresponding sensitivity and specificity. At a score of 5, the difference between predicted risk and observed risk was 6% (19% versus 13%), at a score of 7 this was 14% (31% versus 45%, respectively).

Table 2 Model development and multivariable regression coefficients after shrinkage

	Demographic Model	**Geriatric Model**
Predictors	Beta[a]	Beta[a]
Cohort Model Estimates		
Intercept	-6.64	-2.64
Age (for every 10 years)	0.14	0.04
Male gender	0.26	0.32
BMI, kg/m2	-	-
History of abdominal surgery	-	-
Cardiac comorbidity	-	-
COPD/ASTMA/Emfysema	0.27	0.34
Previous PE or DVT[b]	0.37	0.35
ASA score	0.2	0.02
Rectal tumour	0.03	0.12
Tumour stage	*	-
Reported falls	*	-
Risk for malnutrition	*	-
Previous delirium	*	0.33
Self-reported cognitive impairment	*	0.09
Self-reported need for ADL assistance	*	0.16
Mobility aid	*	0.43
Polypharmacy (≥5)	*	0.35
Mode performance (AUC)		
Model after bootstrapping	0.648	0.687
Optimism corrected model	0.623	0.650

[a] Regression coefficient after shrinkage using LASSO method
- candidate predictor was not selected after shrinkage
* candidate predictor was not used in model development
[b] PE, Pulmonary Embolism; DVT, Deep Venous Thrombosis

Table 3A Score chart geriatric colorectal (GerCRC) model

Characteristic	Scores
Male gender	2
COPD/Asthma/Emphysema	2
Previous PE or DVT[a]	2
Rectal cancer	1
Mobility Aid	2
Previous delirium	2
Need for ADL assistance	1
Polypharmacy	2
Total Score (add all)	
Probability of developing a severe complication (Table 3B).	%

[a] PE. pulmonary Embolism; DVT. Deep Venous Thrombosis

Table 3B Probability of severe complications after CRC surgery in relation to the sum score from *Table 3A*

Score from table 3A	events/No. Cases	Predicted	Sensitivity[a]	Specificity[a]	+ LR[b]	- LR[b]
0-1	18/217	10%	1	0	1	-
2	28/293	13%	0.89	0.22	1.14	0.49
3	20/139	14%	0.73	0.51	1.48	0.53
4	37/198	17%	0.61	0.64	1.69	0.61
5	11/86	19%	0.40	0.81	2.11	0.74
6	23/80	23%	0.33	0.89	3.12	0.75
7-or higher	34/75	31%	0.20	0.96	4.45	0.84

[a] Sensitivity and Specificity based on the development cohort
[b] LR. Likelihood ratio. + positive . - negative

Discussion

This study set out to establish what factors are associated with severe postoperative complications after CRC surgery in order to develop a preoperative clinical prediction model for older patients. Based on tumour and preoperative registry and geriatric data of 1088 patients, the use of a mobility aid, risk factor for delirium, and polypharmacy were identified as strong and important predictors for severe complications after surgery for CRC. Adding geriatric predictors to demographic and tumour related predictors improved the model's prognostic accuracy for older patients. With a AUC of 0.65 after optimism correction stronger predictions are needed for better discrimination.

Gender, COPD/Asthma/emphysema, previous PE or DVT, rectal cancer, previous delirium, self-reported need for ADL assistance and polypharmacy were selected as predictors to develop the GerCRC clinical prediction model. Gender, rectal cancer and severe comorbidity are well-known predictors for poor outcomes of colorectal surgery, also in older patients.[25] We recently showed strong associations between ADL and postoperative complications[21] in line with other studies in older CRC and non-CRC patients.[31-33] A recent geriatric pilot of the ACS-NSQIP among orthopedic and vascular surgery patients, also identified physical functioning, the use of a mobility aid preoperatively, and cognitive functioning as important predictors for 20 of the 25 outcomes measured.[20] For polypharmacy and postoperative outcomes, results have been conflicting.[34]

In contrast to other prediction models for mortality, anastomotic leakage or surgical site infections,[9,11,15,35,36] in our study age and ASA score had no additional predictive value. This is in accordance with a study among older patients with CRC referred for GA.[33] Several explanations can be put forward. First, because our study population was limited to older patients, the age distribution is smaller and therefore less likely to be discriminative. Possibly, in our model, calendar age (and possibly ASA score) were replaced by measures of age related problems such as cognitive functioning, functional performance and comorbidity. Second, in the Netherlands, national guidelines recommend geriatric screening of older patients planned for CRC surgery to identify high-risk surgical patients and guide interventions or adapt treatment plans. This means our study population could be somewhat selected, as we have no information on the non-surgically treated older patients in our cohort.

After interval validation, the expected discrimination of our model was 0.65. Because we aimed to develop a model that can be used in preoperative decision-making, we did not include predictors such as the surgical technique (laparoscopic surgery or not) or perioperative complications, were not included. Also, high-risk patients such as a patient with metastatic disease or acute surgery were not included[4] When these predictors and patients were added, the GerCRC model performance improved (data not shown). When our GerCRC model will be externally validated, more focus will be on the calibration of the different risk groups to judge the performance and clinical usefulness of this model.[37]

A head-to-head comparison with the POSSUM,[14] CR-BHOM[18] and ACS-NSQIP original and recently published universal model[10,19] is with caution because differences in the definition of severe complications, the use of perioperative predictors and the lack of external validation. The GerCRC model is the only model that uses a prolonged length of hospital stay in the definition of a severe complication, accounting for a possible negative impact of a prolonged hospital stay on physical functioning and quality of life. The use of perioperative predictors in the other models limits preoperative decision making.

External validation for all models (including the GerCRC model) has not been performed or was shown to be somewhat disappointing for older patients. The POSSUM was shown to overpredict complication and mortality risk. A recent evaluation of the performance of the POSSUM in 1380 UK patients (with surgery between 2008-2013) confirmed its poor discriminatory performance for severe complications (AUC 0.51).[38] The discriminatory performance for prediction morbidity in 204 Portuguese octogenarians, was 0.65 for the POSSUM and 0.66 for the CR-BHOM model with poor calibration.[39] The original ACS-NSQIP surgical risk model was not specifically developed for colorectal cancer surgery and also the accuracy of the universal ACS-NSQIP model for severe complications or its performance for outcomes in older CRC patients has not been published. The accuracy of the universal ACS-SNQIP model for severe complications in 200 older gynecologic oncology patients undergoing laparatomie (2009-2013), was only 0.62also with poor calibration.[40] To account for possible heterogeneity between cohorts[30] external validation of the proposed prediction models is required; also changes in the healthcare setting and geographic differences are reasons for periodic updating and recalibration.[41] This applies to the ACS-NSQIP model that had not been validated outside the USA, as well as for the GerCRC model. More detailed comparison of the preoperative GerCRC, CR-BHOM and ACS-NSQIP models are shown in Appendix C.

Strengths of our study are the reasonable sample size of high-quality prospectively collected data, the inclusion of geriatric predictors, and statistical techniques to take into account possible optimism. Limitations of our study are our model development with a relatively low number of index events. Only 16% of the patients experienced a severe complication. With 19 candidate predictors, the 10:1 ratio was exceeded, that is advocated to decrease the risk of selecting noise predictors.[42] However, no previous unknown predictors were selected. We further note that self-reported physical function can be overestimated in some older patients.[43]

Providing accurate prognostic information to older CRC patients concerning possible risk and benefits of their surgical treatment is important because of several reasons. Prediction tools enable discussing risks of adverse treatment outcomes with potential negative effect on quality of life and physical functioning,[44] and improves the likelihood that treatment decisions are consistent with their needs, values and preferences. Furthermore, they can direct alternative treatment options when available and last, when high risk populations can be identified, interventions aimed to improve surgical outcomes may become feasible. The GerCRC model has therefore good potential to be used for preoperative decision making, providing better and more accurate estimates of the risk of surgery.

Possible future research could focus on whether predictors such as physical functioning and pulmonary comorbidity such as COPD/ Asthma/Emphysema are amendable for preoperative interventions such as prehabilitation,[45] pulmonary optimisation,[46] and geriatric co-management[47] to improve outcomes.

Conclusions

The GerCRC is the first prediction model specifically developed for older patients planned for CRC surgery. Combining tumour and geriatric predictors in the GerCRC model modestly improves performance in the heterogeneous older population. After external validation, this risk model could serve as a basis for preoperative decision making.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA: A Cancer Journal for Clinicians.* 2016;66(1):7-30.
2. Hamaker ME, Prins MC, Schiphorst AH, van Tuyl SA, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. *Journal of Geriatric Oncology.* 2015;6(2):153-64.
3. Dekker JW, Gooiker GA, Bastiaannet E, van den Broek CB, van der Geest LG, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. *European Journal of Surgical Oncology.* 2014;40(11):1481-7.
4. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Annals of Surgical Oncology.* 2012;19(8):2428-34.
5. Kolfschoten NE, Wouters MW, Gooiker GA, Eddes EH, Kievit J, Tollenaar RA, et al. Nonelective colon cancer resections in elderly patients: results from the dutch surgical colorectal audit. *Digestive Surgery.* 2012;29(5):412-9.
6. Gonzalez-Saenz de Tejada M, Bilbao A, Bare M, Briones E, Sarasqueta C, Quintana JM, et al. Association of social support, functional status, and psychological variables with changes in health-related quality of life outcomes in patients with colorectal cancer. *Psycho-Oncology.* 2016;25(8):891-7.
7. Couwenberg AM, de Beer FSA, Intven MPW, Burbach JPM, Smits AB, Consten ECJ, et al. The impact of postoperative complications on health-related quality of life in older patients with rectal cancer; a prospective cohort study. *Journal of Geriatric Oncology.* 2017.
8. van Abbema D, van Vuuren A, van den Berkmortel F, van den Akker M, Deckx L, Buntinx F, et al. Functional status decline in older patients with breast and colorectal cancer after cancer treatment: A prospective cohort study. *Journal of Geriatric Oncology.*
9. Murray AC, Mauro C, Rein J, Kiran RP. 30-day mortality after elective colorectal surgery can reasonably be predicted. *Techniques in Coloproctology.* 2016;20(8):567-76.
10. Cohen ME, Bilimoria KY, Ko CY, Hall BL. Development of an American College of Surgeons National Surgery Quality Improvement Program: Morbidity and Mortality Risk Calculator for Colorectal Surgery. *Journal of the American College of Surgeons.* 2009;208(6):1009-16.
11. Kiran RP, Attaluri V, Hammel J, Church J. A novel nomogram accurately quantifies the risk of mortality in elderly patients undergoing colorectal surgery. *Annals of Surgery.* 2013;257(5):905-8.
12. Souwer ETD, Verweij NM, van den Bos F, Bastiaannet E, Slangen RME, Steup WH, et al. Risk stratification for surgical outcomes in older colorectal cancer patients using ISAR-HP and G8 screening tools. *Journal of Geriatric Oncology.* 2018;9(2):110-4.
13. Souwer ETD, Hultink D, Bastiaannet E, Hamaker ME, Schiphorst A, Pronk A, et al. The Prognostic Value of a Geriatric Risk Score for Older Patients with Colorectal Cancer. *Annals of Surgical Oncology.* 2018.
14. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *British Journal of Surgery.* 1991;78(3):355-60.
15. Richards CH, Leitch EF, Anderson JH, McKee RF, McMillan DC, Horgan PG. The revised ACPGBI model is a simple and accurate predictor of operative mortality after potentially curative resection of colorectal cancer. *Annals of Surgical Oncology.* 2011;18(13):3680-5.
16. Tekkis PP, Prytherch DR, Kocher HM, Senapati A, Poloniecki JD, Stamatakis JD, et al. Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM). *British Journal of Surgery.* 2004;91(9):1174-82.
17. Souwer ET, Bastiaannet E, Steyerberg EW, Dekker JWT, Van den Bos F, Portielje JE. Risk prediction models for postoperative outcomes of colorectal cancer surgery in the older population - a systematic review. *Journal of Geriatric Oncology.* 2020;accepted january 2020.
18. Breugom AJ, Bastiaannet E, Dekker JWT, Wouters M, van de Velde CJH, Liefers GJ. Decrease in 30-day and one-year mortality over time in patients aged >/=75 years with stage I-III colon cancer: A population-based study. *European Journal of Surgical Oncology.* 2018;44(12):1889-93.

19. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *Journal of the American College of Surgeons.* 2013;217(5):833-42.e1-3.
20. Berian JR, Zhou L, Hornor MA, Russell MM, Cohen ME, Finlayson E, et al. Optimizing Surgical Quality Datasets to Care for Older Adults: Lessons from the American College of Surgeons NSQIP Geriatric Surgery Pilot. *Journal of the American College of Surgeons.* 2017;225(6):702-12.e1.
21. Souwer ETD, Hultink D, Bastiaannet E, Hamaker ME, Schiphorst A, Pronk A, et al. The Prognostic Value of a Geriatric Risk Score for Older Patients with Colorectal Cancer. *Annals of Surgical Oncology.* 2019;26(1):71-8.
22. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Annals of Internal Medicine.* 2015;162(1):55-63.
23. Van Leersum N, Snijders H, Henneman D, Kolfschoten N, Gooiker G, Ten Berge M, et al. The Dutch surgical colorectal audit. *European Journal of Surgical Oncology.* 2013;39(10):1063-70.
24. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. *World Journal of Surgery.* 2014;38(6):1531-41.
25. Henneman D, Snijders HS, Fiocco M, van Leersum NJ, Kolfschoten NE, Wiggers T, et al. Hospital variation in failure to rescue after colorectal cancer surgery: results of the Dutch Surgical Colorectal Audit. *Annals of Surgical Oncology.* 2013;20(7):2117-23.
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases.* 1987;40(5):373-83.
27. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren MA. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ). *Clinical Nutrition.* 2005;24(1):75-82.
28. Cawood AL, Elia M, Sharp SK, Stratton RJ. Malnutrition self-screening by using MUST in hospital outpatients: validity, reliability, and ease of use. *American Journal of Clinical Nutrition.* 2012;96(5):1000-7.
29. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: The index of adl: a standardized measure of biological and psychosocial function. *JAMA.* 1963;185(12):914-9.
30. Steyerberg EW. *Clinical prediction models: a practical approach to development, validation, and updating.* Springer Science & Business Media; 2008.
31. Boakye D, Rillmann B, Walter V, Jansen L, Hoffmeister M, Brenner H. Impact of comorbidity and frailty on prognosis in colorectal cancer patients: A systematic review and meta-analysis. *Cancer Treatment Reviews.* 2018;64:30-9.
32. Hoogerduijn JG, Buurman BM, Korevaar JC, Grobbee DE, de Rooij SE, Schuurmans MJ. The prediction of functional decline in older hospitalised patients. *Age and Ageing.* 2012;41(3):381-7.
33. Kristjansson SR, Jordhoy MS, Nesbakken A, Skovlund E, Bakka A, Johannessen HO, et al. Which elements of a comprehensive geriatric assessment (CGA) predict post-operative complications and early mortality after colorectal cancer surgery? *Journal of Geriatric Oncology.* 2010;1(2):57-65.
34. Huisman MG, Kok M, de Bock GH, van Leeuwen BL. Delivering tailored surgery to older cancer patients: Preoperative geriatric assessment domains and screening tools - A systematic review of systematic reviews. *European Journal of Surgical Oncology.* 2016.
35. Rencuzogullari A, Benlice C, Valente M, Abbas MA, Remzi FH, Gorgun E. Predictors of Anastomotic Leak in Elderly Patients After Colectomy: Nomogram-Based Assessment From the American College of Surgeons National Surgical Quality Program Procedure-Targeted Cohort. *Diseases of the Colon and Rectum.* 2017;60(5):527-36.
36. Rojas-Machado SA, Romero-Simo M, Arroyo A, Rojas-Machado A, Lopez J, Calpena R. Prediction of anastomotic leak in colorectal cancer surgery based on a new prognostic index PROCOLE (prognostic colorectal leakage) developed from the meta-analysis of observational studies of risk factors. *International Journal of Colorectal Disease.* 2016;31(2):197-210.
37. Collins GS, de Groot JA, Dutton S, Omar O, Shanyinde M, Tajar A, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC Medical Research Methodology.* 2014;14:40.

38. Bagnall NM, Pring ET, Malietzis G, Athanasiou T, Faiz OD, Kennedy RH, et al. Perioperative risk prediction in the era of enhanced recovery: a comparison of POSSUM, ACPGBI, and E-PASS scoring systems in major surgical procedures of the colorectal surgeon. *International Journal of Colorectal Disease.* 2018;33(11):1627-34.

39. Gomes A, Rocha R, Marinho R, Sousa M, Pignatelli N, Carneiro C, et al. Colorectal surgical mortality and morbidity in elderly patients: comparison of POSSUM, P-POSSUM, CR-POSSUM, and CR-BHOM. *International Journal of Colorectal Disease.* 2015;30(2):173-9.

40. Shaker S, Rivard C, Nahum R, Vogel RI, Teoh D. The American College of Surgeon's surgical risk calculator's ability to predict disposition in older gynecologic oncology patients undergoing laparotomy. *Journal of Geriatric Oncology.* 2019;10(4):618-22.

41. Minne L, Eslami S, de Keizer N, de Jonge E, de Rooij SE, Abu-Hanna A. Effect of changes over time in the performance of a customized SAPS-II model on the quality of care assessment. *Intensive Care Medicine.* 2012;38(1):40-6.

42. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Annals of Internal Medicine.* 2015;162(1):W1-73.

43. Herbolsheimer F, Riepe MW, Peter R. Cognitive function and the agreement between self-reported and accelerometer-accessed physical activity. *BMC Geriatrics.* 2018;18(1):56.

44. Corner J, Wright D, Hopkinson J, Gunaratnam Y, McDonald JW, Foster C. The research priorities of patients attending UK cancer treatment centres: findings from a modified nominal group study. *British Journal of Cancer.* 2007;96(6):875-81.

45. Barberan-Garcia A, Ubre M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. *Annals of Surgery.* 2017.

46. Bare M, Monton C, Mora L, Redondo M, Pont M, Escobar A, et al. COPD is a clear risk factor for increased use of resources and adverse outcomes in patients undergoing intervention for colorectal cancer: a nationwide study in Spain. *International Journal of Chronic Obstructive Pulmonary Disease.* 2017;12:1233-41.

47. Van Grootven B, Flamaing J, Dierckx de Casterle B, Dubois C, Fagard K, Herregods MC, et al. Effectiveness of in-hospital geriatric co-management: a systematic review and meta-analysis. *Age and Ageing.* 2017;46(6):903-10.

48. Farooq N, Patterson AJ, Walsh SR, Prytherch DR, Justin TA, Tang TY. Predicting outcome following colorectal cancer surgery using a colorectal biochemical and haematological outcome model (Colorectal BHOM). *Colorectal Disease.* 2011;13(11):1237-41.

Appendix A Specification of one or more severe complications

	Total	(%)	Re-intervention	ICU > 2 days	LOS >14 days	30-day mortality
Reintervention	100	(9)	x	26	58	10
ICU admission > 2 days	51	(5)	26	x	29	6
Length of hospital stay (LOS) > 14 days	124	(11)	58	29	x	1
30-day mortality	19	(2)	10	6	1	x
1 or more severe complications (total)	171	(16)	100	44	114	19

Frequencies with percentage (%). ICU, Intensive Care Unit; LOS, length of hospital stay
Some patients had more than one complication. including ICU admittance for > 2 days with a reintervention of a total hospital stay of > 14 days

Appendix B Geriatric predictors of severe complications

	Patients (n=1088)				Severe complications (n=171)						
Predictor	Missings	(%)	No.	(SD/%)	Yes (%)		No. (%)		OR	(95% CI)	*p*-value
Individual Questions											
Katz ADL											
Dressing	15	(1)	63	(6)	20	(32)	43	(68)	2.67	(1.53-4.66)	0.001
Bathing	16	(1)	74	(7)	20	(27)	54	(73)	2.09	(1.22-3.60)	0.007
Incontinence	20	(2)	96	(9)	23	(24)	73	(76)	1.77	(1.07-2.92)	0.026
Transfer	17	(2)	19	(2)	11	(58)	8	(42)	7.6	(2.10-27.49)	0.002
Eating	19	(2)	12	(1)	5	(42)	7	(58)	3.89	(1.22-12.40)	0.02
Toilet	15	(1)	25	(2)	10	(40)	15	(60)	3.7	(1.63-8.38)	0.002
Delirium		()									
Previous delirium	41	(4)	57	(5)	18	(32)	39	(68)	2.63	(1.46-4.71)	0.001
Self-reported cognitive impairment	18	(2)	145	(13)	36	(25)	109	(75)	1.95	(1.28-2.96)	0.002
Need for ADL assistance	29	(3)	80	(7)	24	(30)	56	(70)	2.47	(1.48-4.10)	0.001

Mean with Standard Deviation (SD) and frequencies with percentage (%)
Odds ratio (OR)s with 95% Confidence Interval (CI)

6

Appendix C Comparison of three preoperative risk prediction models

Model Name	GerCRC	ACS-NSQIP Universal Model	CR-BHOM
Year	2019	2013 [19]	2011 [48]
Population	CRC surgery (Mean age 77)	CR surgery (Mean age 61)	CRC surgery (Mean age 74)
Definition Severe Complications	Any complication leading to death, ICU admission > 2 days, reintervention, or an hospital stay > 14 days	Deep wound infection, wound disruption, CVA, MI, Cardic Arrest, PE, Ventilator Dependence, AKI, major bleeding, sepsis	Anastomic leakage, abscess, bleeding or bowel obstruction (not including mortality)
No Predictors	8	15	5
Preditors	Gender, COPD/Asthma/ Emphysema, Previous PE or DVT, Rectal Cancer, Mobility Aid, previous delirium, Need for ADL assistance, polypharmacy	Age, Tumour Stage, COPD, Dyspnoea, BMI, Functional Dependency, Creatinine, albumin, PT time, sepsis, Operative Urgency, Disseminated Cancer, Indication for surgery, Surgical Extent, Wound class	Age, Urea, Sodium, Albumin, Operative Urgency
Development AUC	0.69 (0.65#)	0.72	0.70
External AUC	none	none	0.66*
External calibration	none	none	Poor-fit*

Optimism corrected model
**observational study across 182 octogenarians with malignant-and non-malignant indications for Colorectal Surgery*

Complications defined as Clavian-Dindo Classification Grade II or higher
PE. pulmonary embolism; DVT. Deep Venous Thrombosis; CVA. Cerebral Vascular Accident; BMI. Body Mass Index; PT. Prothrombin Time; AKI. Acute Kidney Injury; MI. Myocardial Infarction

Part II.

Risk modification

Chapter 7

Comprehensive multidisciplinary care program for elderly colorectal cancer patients: ”from prehabilitation to independence”

European Journal of Surgical Oncology 2018;44(12):1894-1900

E.T.D. Souwer
E. Bastiaannet
S. de Bruijn
A.J. Breugom
F. van den Bos
J.E.A. Portielje
J.W.T. Dekker

Abstract

Background: We implemented a multidisciplinary pre- and rehabilitation program for elderly patients (≥75 years of age) in a single centre consisting of prehabilitation, laparoscopic surgery and early rehabilitation with the intention to lower 1-year overall mortality.

Patients and methods: In this study, we compared all patients that underwent elective surgery for stage I-III colorectal cancer before and during development and after implementation of the program (2010-2011, 2012-2013 and 2014-2015). The primary endpoint was 1-year overall mortality, the secondary endpoint was 30-day postoperative outcome.

Results: Eighty-six consecutive patients were included in the study cohort and compared to 63 patients from 2010-2011 and 75 patients from 2012-2013. Patient characteristics were comparable; median age in the study cohort was 80.6. Seventy-three patients (85%) participated in the program, 54 (63%) of whom followed a prehabilitation program, 46 (53%) of whom were discharged to a rehabilitation center. Laparoscopic surgery increased over the years, from 70% to 83% in the study cohort. There was a trend in lower 1-year overall mortality: 11% versus 3% (p=0.08). There was a significant reduction in cardiac complications and the number of patients with a prolonged length of stay ($p<0.01$).

Conclusions: Multidisciplinary care for elderly colorectal cancer patients that includes prehabilitation and rehabilitation is feasible and may contribute to lower complications and reduced length of stay. This study did not show a clear benefit of implementing a comprehensive care program, including both prehabilitation and rehabilitation. Dedicated multidisciplinary care seems the key attributor to favourable outcomes of CRC surgery in elderly patients.

Abbreviations

CCI	Charlson Comorbidity Index
(I)ADL	(Instrumental) Activities of Daily Living
CRC	Colorectal Cancer
SIOG	International Society of Geriatric Oncology
DCRA	Dutch ColoRectal Audit

Introduction

Colorectal cancer is an age-related disease, disproportionally affecting older patients with an expected increase of 52% in the next two decades.[1,2] While survival for all cancer types increases, improvement of cancer outcome has been relatively limited in older patients.[3] Comorbidity, social and cognitive functioning, nutritional status and physical performance level contribute to daily functioning and patient's resilience to withstand or adapt to stressors. As surgery is a major stressor, this also explains why elderly have a fourfold increase in major postoperative complications.[4] Comorbidity, functional dependency and older age are associated with early postoperative mortality.[5] Surgery also seems to have a prolonged impact on elderly patients, as early postoperative mortality highly underestimates 1-year mortality in these patients.[6,7] Besides this prolonged risk of mortality, elderly patients experience a decline in self-care capacity up to 60% in the first year after surgery.[8] Preventing functional decline and optimizing patient's preoperative condition are possible strategies to increase treatment outcomes and increase patients' chance of retaining independence. Earlier studies focused on improving physical performance using exercise training were only moderately successful and did not improve self-reported performance but dealt with low adherence.[9]

Conceptually there are three ways to limit the impact of colorectal cancer (CRC) surgery in elderly patients. First, through prehabilitation, by optimising functional capacity prior to surgery using exercise training, nutritional support and optimising comorbidity resulting in increased resilience.[10,11] Second, by limiting the impact of surgery through minimally invasive and enhanced recovery strategies reducing perioperative stress response, tissue injury and metabolic response[12,13] potentially resulting in fewer complications and less postoperative pain. Third, by means of early discharge to a rehabilitation centre, thereby countering the negative effects of hospital stay i.e. low daily activity and reducing the risk for hospital-acquired infections. With rehabilitation, we try to restore preoperative levels of functioning, thereby limiting the susceptibility to other illnesses and to restore a patient's quality of life.

With this concept in mind, a multimodality care program for elderly colorectal cancer patients was initiated in a teaching hospital in the western part of the

Netherlands that dealt with all three aspects. Starting in 2012, a multidisciplinary Delphi round with multiple iterations was used to develop this multimodality approach which consisted of dedicated care, geriatric counselling, nutritional support, exercise training, laparoscopic surgery and early discharge to a rehabilitation facility when patients were not able to return home before day 6 after surgery (Appendix A).

In January 2014, this comprehensive multidisciplinary care program for colorectal cancer patients of 75 and older was implemented as standard practice. We hypothesised that this program could reduce mortality rates by half and also reduce complication rates.

In Europe and the Netherlands in particular, several prehabilitation and rehabilitation programs are currently initiated. However, there is a paucity of research in this field. To this day, we mostly rely on expert opinion on what elements to include in a pre- and rehabilitation program for elderly patients. This stresses the need for more clinical evidence.

This study aims to assess the usefulness of our multimodality care program for elderly CRC patients operated with curative intent. For comparison, we used two historic control cohorts of consecutive older patients operated in the same centre in the previous 4 years, before (2010-2011) and during (2012-2013) the development of the program. The primary endpoint of this study was 1-year overall mortality. Secondary endpoints were postoperative complication rates, readmission rates and 30-day mortality.

Patients and methods

Study population

All consecutive older patients aged 75 years who underwent surgical resection for CRC between 1 January 2010 and 31 December 2015 were included in our analysis. Patients from the first two years after the start of our comprehensive multidisciplinary care program (2014-2015) were compared to all consecutive older patients from before (2010-2011) and during (2012-2013) the development of our program. We choose historical cohorts from the same centre to minimalise demographic as well as institutional variation. To minimise the risk for confounding by indication, we excluded patients with stage IV disease, synchronous cancer at the time of diagnosis, or non-elective surgery from all three cohorts from our analysis.

Comprehensive multidisciplinary care program

From January 1st 2014 onwards, patients aged 75 years and older, referred for elective colorectal surgery to the department of colorectal surgery at Reinier de Graaf Hospital, were informed about our multidisciplinary care program.

Our team consisted of dedicated health-care professionals focused on improving care for elderly patients. All surgeons were experienced colorectal surgeons with more than 200 laparoscopic colorectal resections performed per surgeon before the start of this program.

A more detailed overview of our program is shown in Appendix A. In short, a preoperative assessment of patients was done by the treating surgeon and dedicated nurses, which also included geriatric screening[14,15] and a subsequent geriatric assessment when indicated. Patinets with cardiac or pulmonary comorbidity were referred for cardiopulmonary optimisation prior to surgery. All patients were referred to a dietician for a full nutritional assessment,[16] with subsequent nutrition support with a targeted intake of protein of 1.2-1.5grams/kg/day.[17,18] A Short Nutritional Assessment Questionnaire (SNAQ) questionnaire (cut-off ≥2)[19] was performed for all patients.

As part of standard care, a surgical oncology nurse practitioner was assigned as case manager that ensured meeting patients individual needs. This also included cognitive and emotional guidance, both pre- and post-operatively, with referral to more specialised care when needed.[20] Radiological workup was according to the Dutch national guidelines on CRC[21] and all patients were discussed in a multidisciplinary oncology team (MDT).

Timing of surgery was at least 6 weeks after diagnosis to allow preoperative physical training. The training program consisted of resistance training as well as endurance training and two sessions a week were intended for 4-6 weeks. All training sessions were supervised by a local physiotherapist, and each session was

30-45 minutes. Also, instructions for home-exercises and breathing exercises were given.

Patients extremely fit, or patients with obstructing tumour were not deemed eligible for preoperative physical training, but could however participate in the postoperative program of rehabilitation.

The Enhanced Recovery After Surgery (ERAS) guidelines[22] were implemented in 2008 as part of standard care for all surgical patients. At the day of admission prior to surgery, a standardised preoperative geriatric interview was performed by nurses. Laparoscopic surgery was the technique of choice unless previous surgical history or patient's condition prevented its safe application.

At day 6, the postoperative discharge was planned to a rehabilitation facility for as long as necessary to become self-supporting at home. When patients were self-supporting before day 6, they went home. Rehabilitation care included a local program of physical training, dietary support and cognitive and emotional guidance. Short-postoperative follow-up after discharge was individualised when patients were in a rehabilitation centre. Our program was initiated as standard of care. However, patients could decide not to participate.

For this study, patients were considered to participate in our comprehensive multidisciplinary care program when preoperative prehabilitation and or rehabilitation was initiated.

Data collection

Patient demographic data, as well as outcome data, were retrieved from the Dutch ColoRectal Audit (DCRA) and Electronic Hospital Records (EMR). The DCRA contains pre-, peri- and postoperative surgical outcome data on all operated CRC patients in the Netherlands as part of a national quality improvement project. All patients are prospectively enrolled in this database and data entry is done by a qualified data-entry manager or nurse. Detailed information on this initiative was published elsewhere.[23]

Demographic information included ASA score, comorbidity from which a Charlson Comorbidity Index (CCI) score[24] was calculated and tumour stage (according to AJCC 5th edition). Postoperative information also included data on length of hospital stay, readmission (within 30 days) and adjuvant chemotherapy.

Postoperative complications (any complication) were subdivided into any surgical complication (e.g., wound infection, bleeding, abscess, anastomotic leakage, ileus and readmission) and non-surgical complications (including cardiac complications). Postoperative mortality was defined as death within 30 days of resection. Severe complications were defined as complications leading to ICU admission (longer than 2 days), to a reintervention, to a prolonged hospital stay of more than 14 days, or to postoperative mortality. This is consistent with previous publications in which data from the DSCA were analyzed.[25] Both severe complications, as well as a hospital stay of more than 14 days, were used as a proxy of the severity of a complication or the inappropriate use of a hospital bed when no complication was registered.[26,27] One-year mortality was calculated using data from the Municipal Personal Records Database.

From medical records, the cause of death and the standardised geriatric interview data were collected. The standardised geriatric interview data was only available from 2014 onward. The interview questions concerned the abilities to perform basic daily activities (ADL) from which a Katz ADL 6 core (cut-off ≥2) was constructed.[28] Other data included the use of a walking device, reported falls in the past 6 months and the self-report of cognitive impairment. Patients using 5 or more medications on a daily bases were identified as having polypharmacy.

Statistical analysis

We performed descriptive analysis, expressing normally distributed variables as mean with standard deviation (SD) or nonnormal distributed variables as median with interquartile range (IQR). Frequencies are presented with numbers and percentage. Baseline variables of the three groups were compared using the one-way analysis of variance (ANOVA) or the chi-squared test (X^2). Outcomes of the 2014-2015 cohort were analysed using a logistic regression analysis with 2010-2011 or 2012-2013 as reference group or Fisher-exact test when logistic regression was not deemed suitable because of less than five events in one group. Odds ratios (ORs) are given with a 95% Confidence Interval (CI). A p-value ≤ .05 was considered statistically significant. All analyses were performed using SPSS version 24.0 (SPSS, Inc., Chicago, IL).

Results

Eighty-six patients were treated in 2014-2015 after implementation of the comprehensive multidisciplinary care program and were defined as our study cohort. The two control cohorts consisted of 63 patients in 2010-2011 and 75 patients in 2012-2014.

Baseline characteristics of patients in the three cohorts did not differ and are presented in Table 1. There was no significant difference in the distribution of patients with ASA score III or IV or patients with CCI score ≥2 (p=0.2) nor with congestive heart failure prior to surgery. The majority of patients had a tumour located in the colon. There was no difference in tumour stage (p=0.2). Preoperative geriatric evaluation was performed in 95% of patients in the study cohort, 34 patients (40%) had geriatric consultation. Nine patients (10%) were functional dependent with a KATZ score ≥2, seventeen patients (20%) reported falls within the past 6 months before surgery, 32 patients (37%) used a walking device, 18 patients (21%) reported cognitive impairment, 23 patients (27%) were at risk for malnutrition and in 40 patients (47%) polypharmacy was detected. Six patients (10%) in 2010-2011, seven patients (9%) in 2012-2013 and eleven patients (13%) in the study cohort received adjuvant chemotherapy (p=0.5).

Comprehensive multidisciplinary care program

Seventy-three out of the 86 patients (85%) followed the whole multimodality program or only the preoperative prehabilitation or postoperative rehabilitation part. Reasons for patients not to participate were: the patient was not interested (n=4), the patient was estimated fit (n=3), the patient was not informed (n=2). Four patients were not deemed eligible for the prehabilitation program because of an obstructing tumour (n=3) and M. Alzheimer (n=1).

Fifty-four patients (63%) patients followed the complete prehabilitation program, including prehabilitation at home or in an out-patient facility. One patient (1%) initially participated in the prehabilitation program but during the first three weeks developed bowel obstruction with subsequent non-elective surgery. A laparoscopic approach was used in 71 patients (83%). There was no difference in preoperative complications or surgical approach between the study and the control cohorts (Table 2).

During the first two years of the program, 49 patients (57%) were discharged to a rehabilitation centre (46 of whom participated in the program); nine patients (10%) continued physical therapy at home after discharge, and 26 patients (30%) had a fast recovery and were discharged to their home without additional support.

Table 1 Baseline characteristics for all cohorts

	2010-2011		2012-2013		2014-2015		
	n=63		n=75		n=86		*p*-value
Median age (IQR)	81.4	(7.3)	79.7	(5.0)	80.6	(6.2)	0.5
Gender (%)							0.9
Male	33	(52)	38	(51)	42	(49)	
Female	30	(48)	37	(49)	44	(51)	
BMI kg/M2 (SD)	25.3	(5.2)	26.8	(4.6)	26.0	(3.8)	0.2
ASA score (%)							0.9
I	3	(5)	3	(4)	4	(5)	
II	35	(56)	42	(56)	48	(56)	
III	24	(38)	29	(39)	33	(38)	
IV	1	(2)	1	(1)	1	(1)	
Any comorbidity (%)							0.2
CCI score 0	16	(25)	12	(16)	27	(31)	
CCI score 1	23	(37)	25	(33)	26	(30)	
CCI score ≥2	24	(38)	38	(51)	33	(38)	
Number of patients with CHD	3	(5)	3	(4)	5	(6)	0.9
Tumour location (%)							0.5
Colon	47	(75)	56	(75)	60	(70)	
Rectum	16	(25)	19	(25)	26	(30)	
Tumour stage AJCC (%)							0.2
I	17	(27)	21	(28)	32	(37)	
II	25	(40)	21	(28)	29	(34)	
III	21	(33)	33	(44)	25	(29)	
Katz ADL ≥ 2	-		-		9	(10)	
Reported falls < 6 months	-		-		17	(20)	
Use of a walking device	-		-		32	(37)	
Self reported cognitive impairment	-		-		18	(21)	
SNAQ ≥ 2	-		-		23	(27)	
Polypharmacy (≥5 medications)	-		-		40	(47)	

2010-2011 and 2012-2013, control cohort; 2014-2015, study cohort, IQR, interquartile range; %, percentage; SD, standard deviation; CCI, Charlson Comorbidity Index CHD: congestive heart disease

Table 2 Preoperative interventions, preoperative complications and surgical approach

	2010-2011		2012-2013		2014-2015		
	n=63		n=75		n=86		*p*-value
Prehabilitation (%)							
None	-		-		32	(37) [a]	
Local	-		-		25	(29)	
Out-patiënt in a Rehabilitation center	-		-		24	(28)	
In-patiënt in a Rehabilitation center	-		-		5	(6)	
Geriatric Consultation (%)	-		-		34	(40)	
Dietitian Consultation (%)	-		-		74	(86)	
Preoperative Treatment (%)	-		-				0.9
Radiotherapy	8	(13)	12	(16)	13	(15)	
Chemoradiation	4	(6)	2	(3)	2	(2)	
Diverting Stomy	1	(2)	0		1	(1)	
Peroperative Ileus (%)	1	(2)	1	(1)	4	(5)	
Surgical Approach (%)							0.8
Laparoscopic	44	(70)	63	(84)	71	(83)	
Open	19	(30)	12	(16)	15	(17)	
Primary Anastomosis (%)	49	(78)	55	(73)	62	(72)	0.8

2010-2011 and 2012-2013, control cohort; 2014-2015, study cohort, IQR, interquartile range; %, percentage; SD, standard deviation. [a]Including 13 patients that did not participate in the program

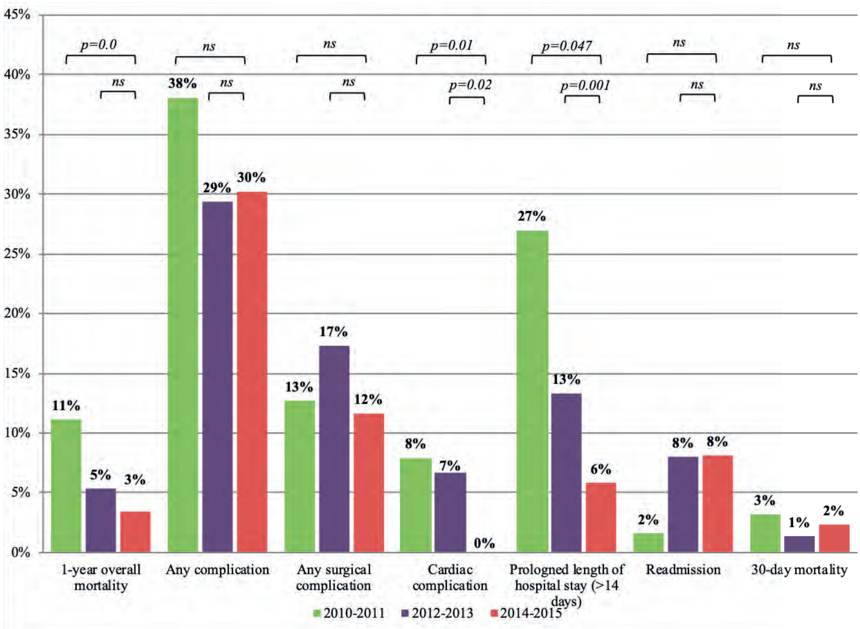
Primary and secondary outcomes

In Figure 1, primary and secondary outcomes for the three cohorts are shown. One year mortality was in 11% (n=7) in 2010-2011, 5 % (n=4) in 2012-2013 and 3% (n=3) in 2014-2015. Compared to 2010-2011, this improvement did not reach statistical significance (OR 0.3 95% CI 0.1-1.2, p=0.08). In the study cohort, two patients died within 30 days of surgery due to surgical complications. Notably, one of the early postoperative deaths was considered a medical calamity due to stapler failure and was reported to the Dutch Inspection for Health. The full overview of causes of death in both the study cohort as well as the control cohorts can be found in Appendix B.

Concerning secondary outcomes, the number of patients with any complications after surgery decreased from 38 % (n=24) in 2010-2011 to 29% (n=22) in 2012-2013 and 30% (n=26) in 2014-2015. The number of surgical complications did not differ between the three cohorts, although a slight increase was seen in 2012-2013 (13% to 17%). There was a significant decrease of 8% in cardiac complications, from 8% in 2010-2011 (n=5) to none in 2014-2015 (Fisher-exact test, p=0.01) and no difference in pulmonary complications (p=0.3). The number of patients with a severe complication decreases from 32% (n=20) in 2010-2011 to 17% (n=13) in

2012-2013 and 16% (n=14) in 2014-2015 (2010-2011 vs 2014-2015; OR 0.4 (95% CI 0.2-0.9, p=0.03). The number of patients with a prolonged length of hospital stay i.e. more than 14 days decreased from 27% (n=17) in 2010-2011 to 13% (n=10) in 2012-2013 and 6% (n=5) in 2014-2015 (OR 0.1, 95% CI 0.01-0.97, p=0.047 and OR 0.2, 95% CI 0.1-0.5, p=0.001), with readmission rates of 3% (n=2), 8 % (n=6) and 8% (n=7) respectively. Thirty-day mortality was 3% (n=2), 1% (n=1) and 2% (n=2). Multivariate logistic analysis was not deemed suitable because of the low number of events in each cohort.

Figure 1 Outcomes for the control cohorts (2010-2011 and 2012-2013) and the study cohort (2014-2015)



Discussion

A comprehensive multidisciplinary care program was implemented in a single teaching hospital as a quality program aimed to improve the outcome of surgery for all elderly colorectal cancer patients. In this study, we assessed the merits of this program by comparing a cohort of patients operated after the introduction of the program with two historical cohorts. Contrary to what we expected, we could not demonstrate a clear improvement in 1-year mortality after the start of the program. What we noticed, however, was that improvements in outcomes already started during the development of our program. This could imply that dedicated multidisciplinary care was the main driver of the improved outcomes for our elderly CRC patients and that the actual program did not add to that significantly. However, a further decrease in cardiac complications and a lower number of patients with a prolonged length of stay was seen after implementation of the complete program, which could be regarded a merit of the program.

To our knowledge, this is the first study to assess the usefulness of a comprehensive multidisciplinary care program for older colorectal cancer patients that included both prehabilitation and rehabilitation. There are however multiple studies that investigated these components separately, most of them in a much younger population. These studies found that prehabilitation positively influenced functional capacity,[11,29-31] only one study showing a benefit on morbidity[32] as was also shown in a meta-analysis.[33] Other studies of rehabilitation and fast-track surgery in elderly patients demonstrated a shortened length of stay without increasing readmission rates.[22] Further comparison with other studies is difficult as the inclusion of older, more high-risk patients in these studies was low or even absent.[33] However, one publication showed a promising effect of a prehabilitation program for older ASA III-IV patients and elective abdominal surgery with a reduction of complications of 20%.[32] Despite 51% of patients having significant comorbidity in our study, our mortality rates from 2012 onwards could be considered low.[6,34]

Our study did not show the clear benefit we had expected from a comprehensive multidisciplinary care program. Several possible explanations can be put forward, which are interconnected to its strengths and limitations. Already in 2012, we started our multidisciplinary Delphi rounds to develop a comprehensive multidisciplinary care program for elderly CRC patients in our hospital. The increased focus on elderly CRC patients is likely to have improved treatment outcomes in a way similar to the so-called Hawthorne effect.[35] During the development of the program, clinicians were probably more aware of the specific problems, and demands of elderly CRC patients and other caregivers such as dieticians and physiotherapists were more regularly involved. That could explain why there was a dramatic decrease in 1-year mortality in our most recent controls

(2012-2013). These controls fared much better than expected from previous research.[34] For reference, in the Dutch ColoRectal Audit (DCRA) data, a gradual improvement is seen over the years in outcomes, i.e. less postoperative mortality, but no dramatic change between 2010-2011 and 2012-2013.[36]

Due to the small numbers of index events i.e. postoperative deaths, chance (such as a calamity with stapling) could have had a disproportionate impact on the results. This may have masked a positive effect of implementing the program. It could be argued that a weakness of our study is that prehabilitation and rehabilitation were not standardised for all patients in our program. In our opinion, the choice to allow for limited tailoring to a patient's needs within our protocol ensures its applicability to daily practice. A fit elderly patient actively playing sports will be difficult to motivate for prehabilitation he or she is unlikely to benefit from. Likewise, an elderly patient that recovers very fast after surgery and can return home on day five is not going to benefit from staying in a rehabilitation facility. On the other end of the spectrum, very frail patients can be limited by their comorbidity to participate in an exercise program. These are the main reasons that not all patients in this study participated in all aspects of the program. Therefore we believe that prehabilitation and rehabilitation should both be facilitated in a comprehensive care program for elderly patients. This is in contrast to the suggestion that research should focus on preoperative interventions following research in younger counterparts.[11,37]

One of the problems in dealing with elderly patients is that there is no ultimate test to select patients. Age alone is not a predictor of outcome,[38] but it could be regarded as a key determinant for the progressive functional inadequacy of physiological systems that leads to an impaired physical capacity to overcome stressors. Therefore in our program, we chose age 75 and up as a cut-off.

Philosophically there are two opposing ways to go about with research in this field. First, we could focus on the individual patient and completely individualise prehabilitation, rehabilitation and treatment. As a consequence, it will be very difficult to reach scientific evidence about what we are doing exactly. The other way would be to succumb every patient to a strict protocol, but as discussed earlier it would be difficult to include all patients; in the absence of reliable prognosticators to make a proper selection of patients. Therefore, we chose all consecutive patients aged 75 and up as our cohort, but left some room for personalised prehabilitation and rehabilitation fitting the clinical setting of daily practice. Thus making our program applicable, usable and reproducible.

An important question that remains is whether complications and mortality are the most relevant outcome parameters. Maybe for elderly patients self-sustainability, mobility and overall quality of life should be paramount.[39] Future studies should put more focus on these topics and should also overcome the lack of consensus to what elements to include in a prehabilitation program[33] and the problem of low adherence to the training protocol which was earlier reported to range from 16-97%.[9]

Conclusion

We hypothesised that a comprehensive multidisciplinary care program would be beneficial for elderly patients by boosting perioperative resilience, preventing decline and thereby getting them back to their preoperative level of functioning as soon as possible.

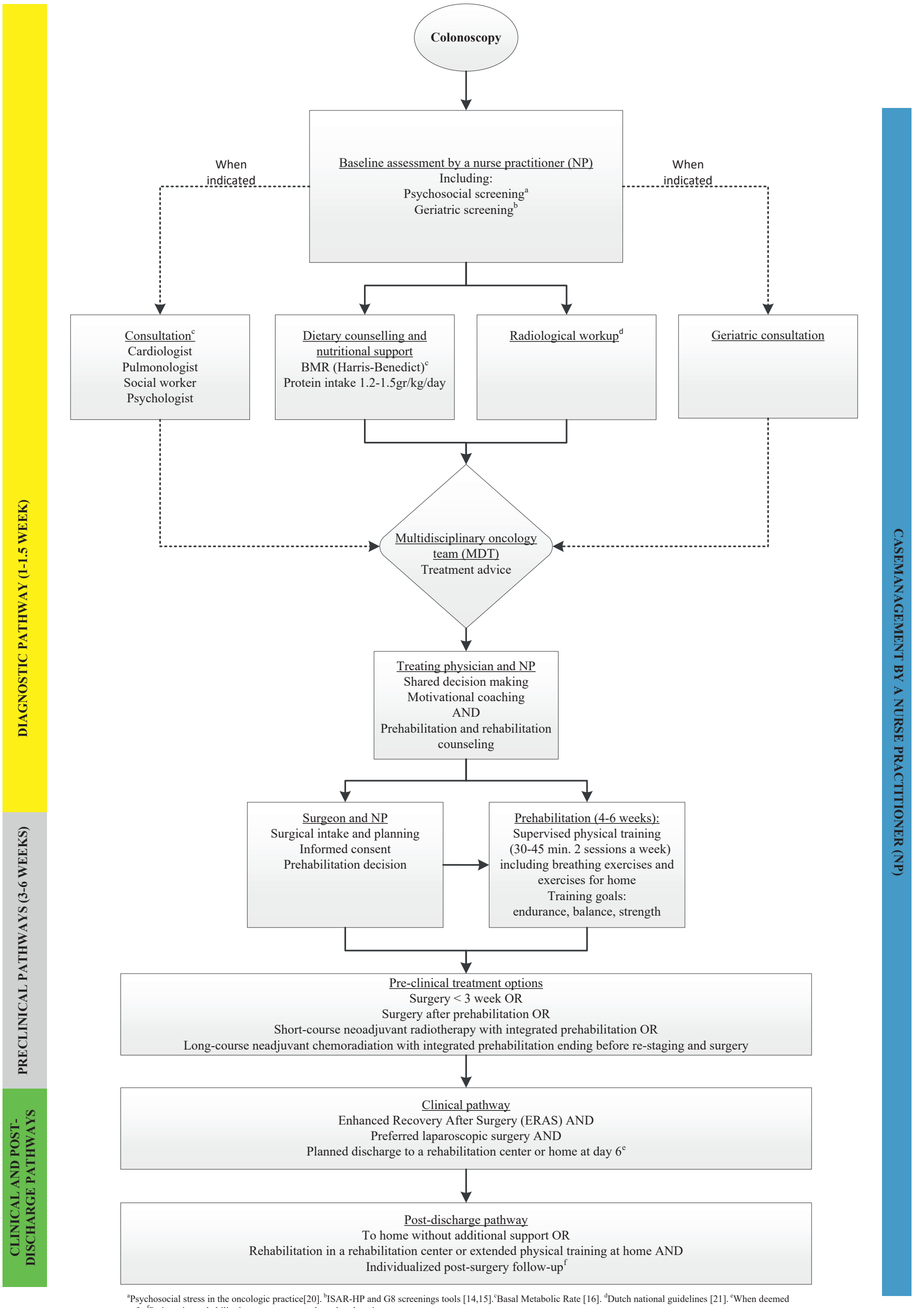
In this study, we were not able to demonstrate a clear effect on perioperative complications and 1-year mortality after the implementation of our program. However, the use of two control cohorts allowed for a better insight into what drives improvement here. The fact that a significant improvement in outcome already occurred during the development of the program seems to imply that focused and dedicated multidisciplinary care is the essential element of favourable outcomes of CRC surgery in elderly patients and there lies the benefit of starting such a program.

References

1. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *Journal of Clinical Oncology.* 2009;27(17):2758-65.
2. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA: A Cancer Journal for Clinicians.* 2014;64(2):104-17.
3. Berrino F, Verdecchia A, Lutz JM, Lombardo C, Micheli A, Capocaccia R. Comparative cancer survival information in Europe. *European Journal of Cancer.* 2009;45(6):901-8.
4. Tan KY, Kawamura YJ, Tokomitsu A, Tang T. Assessment for frailty is useful for predicting morbidity in elderly patients undergoing colorectal cancer resection whose comorbidities are already optimized. *American Journal of Surgery.* 2012;204(2):139-43.
5. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Annals of Surgical Oncology.* 2012;19(8):2428-34.
6. van Gestel YR, Lemmens VE, de Hingh IH, Steevens J, Rutten HJ, Nieuwenhuijzen GA, et al. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. *Annals of Surgical Oncology.* 2013;20(2):371-80.
7. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Annals of Surgical Oncology.* 2011;18(6):1533-9.
8. Hamaker ME, Prins MC, Schiphorst AH, van Tuyl SA, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. *Journal of Geriatric Oncology.* 2015;6(2):153-64.
9. Bruns ER, van den Heuvel B, Buskens CJ, van Duijvendijk P, Festen S, Wassenaar EB, et al. The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. *Colorectal Disease.* 2016.
10. Topp R, Ditmyer M, King K, Doherty K, Hornyak J, 3rd. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. *AACN Clinical Issues.* 2002;13(2):263-76.
11. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology.* 2014;121(5):937-47.
12. Ren L, Zhu D, Wei Y, Pan X, Liang L, Xu J, et al. Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial. *World Journal of Surgery.* 2012;36(2):407-14.
13. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). *Annals of Surgery.* 2011;254(6):868-75.
14. Hoogerduijn JG, de Rooij SE, Grobbee DE, Schuurmans MJ. Predicting functional decline in older patients undergoing cardiac surgery. *Age and Ageing.* 2014;43(2):218-21.
15. Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Annals of Oncology.* 2012;23(8):2166-72.
16. Harris JA, Benedict FG. A Biometric Study of Human Basal Metabolism. *Proceedings of the National Academy of Sciences of the United States of America.* 1918;4(12):370-3.
17. Wolfe RR, Miller SL, Miller KB. Optimal protein intake in the elderly. *Clinical Nutrition.* 2008;27(5):675-84.
18. Jeevanandam M, Lowry SF, Horowitz GD, Legaspi A, Brennan MF. Influence of increasing dietary intake on whole body protein kinetics in normal man. *Clinical Nutrition.* 1986;5(1):41-8.
19. Wilson MM, Thomas DR, Rubenstein LZ, Chibnall JT, Anderson S, Baxi A, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *American Journal of Clinical Nutrition.* 2005;82(5):1074-81.
20. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE. Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. *Cancer.* 2008;113(4):870-8.

21. Dutch National Guidelines on colorectal cancer, version 3.0. [Accessed 01 June 2018]; 2014.
22. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. *World Journal of Surgery.* 2014;38(6):1531-41.
23. Van Leersum N, Snijders H, Henneman D, Kolfschoten N, Gooiker G, Ten Berge M, et al. The Dutch surgical colorectal audit. *European Journal of Surgical Oncology.* 2013;39(10):1063-70.
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases.* 1987;40(5):373-83.
25. Henneman D, Ten Berge MG, Snijders HS, van Leersum NJ, Fiocco M, Wiggers T, et al. Safety of elective colorectal cancer surgery: non-surgical complications and colectomies are targets for quality improvement. *Journal of Surgical Oncology.* 2014;109(6):567-73.
26. Dekker JW, Gooiker GA, van der Geest LG, Kolfschoten NE, Struikmans H, Putter H, et al. Use of different comorbidity scores for risk-adjustment in the evaluation of quality of colorectal cancer surgery: does it matter? *European Journal of Surgical Oncology.* 2012;38(11):1071-8.
27. Poelemeijer YQM, Lijftogt N, Detering R, Fiocco M, Tollenaar RAEM, Wouters MWJM. Obesity as a determinant of perioperative and postoperative outcome in patients following colorectal cancer surgery: A population-based study (2009–2016). *European Journal of Surgical Oncology.* 2018.
28. Katz S, Akpom CA. 12. Index of ADL. *Medical Care.* 1976;14(5 Suppl):116-8.
29. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surgical Endoscopy.* 2013;27(4):1072-82.
30. Dronkers JJ, Lamberts H, Reutelingsperger IM, Naber RH, Dronkers-Landman CM, Veldman A, et al. Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. *Clinical Rehabilitation.* 2010;24(7):614-22.
31. West MA, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *British Journal of Anaesthesia.* 2015;114(2):244-51.
32. Barberan-Garcia A, Ubre M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. *Annals of Surgery.* 2017.
33. Moran J, Guinan E, McCormick P, Larkin J, Mockler D, Hussey J, et al. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: A systematic review and meta-analysis. *Surgery.* 2016;160(5):1189-201.
34. Dekker JW, Gooiker GA, Bastiaannet E, van den Broek CB, van der Geest LG, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. *European Journal of Surgical Oncology.* 2014;40(11):1481-7.
35. Parsons HM. What Happened at Hawthorne? *Science.* 1974;183(4128):922-32.
36. Dutch Institute for Clinical Auditing. Jaarverlag 2015. download available from: https://dica.nl/jaarrapportage-20152016
37. Carli F, Gillis C, Scheede-Bergdahl C. Promoting a culture of prehabilitation for the surgical cancer patient. *Acta Oncologica.* 2017:1-6.
38. Makela JT, Kiviniemi H, Laitinen S. Survival after operations for colorectal cancer in patients aged 75 years or over. *European Journal of Surgery.* 2000;166(6):473-9.
39. Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG, Luciani A, et al. End Points and Trial Design in Geriatric Oncology Research: A Joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology Position Article. *Journal of Clinical Oncology.* 2013;31(29):3711-8.

Appendix A Comprehensive multidisciplinary care program



[a]Psychosocial stress in the oncologic practice[20]. [b]ISAR-HP and G8 screenings tools [14,15]. [c]Basal Metabolic Rate [16]. [d]Dutch national guidelines [21]. [e]When deemed safe. [f]Patients in a rehabilitation center were evaluated on location.

Appendix B Cause of death in the first postoperative year

	2010-2011		2012-2013		2014-2015	
	n=7		n=4		n=3	
Surgery related	2	(29)	1	(25)	2	(67)
Tumour related	1	(14)	2	(50)	0	
Other	1	(14)	0		0	
Unknown	3	(43)	1	(25)	1	(33)

Number with frequencies (%)

Chapter 8

The impact of colorectal surgery on health-related quality of life in older functionally dependent patients with cancer– A longitudinal follow-up study

Journal of Geriatric Oncology 2019;10(5):724-732

E.T.D. Souwer
S. Oerlemans
L.V. van de Poll-Franse
F.N. van Erning
F. van den Bos
J.S. Schuijtemaker
F.W.P.J van den Berkmortel
D. ten Bokkel Huinink
M.E. Hamaker
J.W.T. Dekker
C.A. Wientjes
J.E.A. Portielje
H.A.A. Maas

Abstract

Background: Older patients who are functionally compromised or frail may be at risk for loss of quality of life (QoL) after colorectal cancer (CRC) surgery. We prospectively studied health-related QoL (HRQoL) and its association with functional dependency on multiple time points before and after CRC surgery.

Patients and methods: Included were patients aged 70 years and older who underwent elective CRC surgery between 2014 and 2015 in combination with an oncogeriatric care path. HRQoL (EORTC QLQ-C30 and CR38) and activities of daily living (ADL, Barthel Index) were measured at four time-points; prior to (T0) and at 3 (T3), 6 (T6), and 12 (T12) months after surgery. Functional dependency was defined as a Barthel Index <19. Using mixed-model regression analysis associations between dependency, time and HRQoL outcomes were tested and corrected for confounders.

Results: Response rate was 67% (n=106) to two or more questionnaires; 26 (25%) patients were functionally dependent. Overall, functionally independent patients experienced a higher HRQoL than dependent patients. Compared to T0, significant and clinically relevant improvements in HRQoL after surgery were observed in functionally dependent patients: better role functioning, a higher global health, a higher summary score, less fatigue and less gastrointestinal problems (p<0.05). In functional independent patients, we observed no clinically relevant change in HRQoL.

Conclusions: Colorectal surgery embedded in geriatric-oncological care has a positive impact on HRQoL in older functionally dependent patients with cancer. Moderate functional dependency should not be considered a generic reason for withholding surgical treatment. Information derived from this study could be used in shared decision making.

Introduction

In 2016, > 15,000 patients were diagnosed with colorectal cancer (CRC) in the Netherlands, and > 50% of these patients were aged 70 years or older.[1] For most patients, surgical resection is the treatment of choice.[2] However, with increasing age, older patients are at increased risk for adverse outcomes of treatment such as complications, readmission or death.[3-5] The risk of adverse outcomes of surgery is influenced by comorbidity, impaired physical functioning and cognitive impairments, all more prevalent among older patients with CRC.[6-8]

Besides classical endpoints of oncological trials such as survival and complication rates[9], functional, social and emotional issues have high priorities to older patients[10] Health-related quality of life (HRQoL) and retaining independence are therefore relevant outcomes in older patients with cancer[11] and are ideally discussed in addition to survival and complications when decisions are made about cancer treatment.

Complications[12-14] as well as receiving chemotherapy and older age itself[15,16] are associated with lower HRQoL after surgery. Still, HRQoL is expected to differ among older patients especially in patients with functional dependency, knowing that functional dependency is related to frailty and is also an important determinant for adverse outcomes of surgery.[17] Therefore, preoperative and postoperative HRQoL outcome information with stratification based on functional dependency is likely to be useful for shared decision making. In this process, HRQoL outcome information should also include a longer postoperative follow-up, as the impact of surgery for older patients extends to the first postoperative year.[18] Based on earlier literature we would still expect a negative impact of CRC surgery on HRQoL in functionally dependent patients. Studies that investigated the impact of surgery on HRQoL and physical functioning are limited or showed mixed results.[19-21] In the majority of these studies, important information on preoperative functioning and baseline HRQoL was lacking.

This study aims to investigate HRQoL at multiple time points before and after colorectal surgery and the association with functional dependency, time and HRQoL in older patients with CRC in the first year after surgery.

Patients and methods

Population and setting

Data from Elder-1, a multicentre project designed to improve geriatric-oncological care for older patients with CRC, was used to perform this study. The Elder-1 was a longitudinal follow-up study on HRQoL and physical functioning, before and 3, 6 and 12 months after surgery. Furthermore, the project included a geriatric-oncological educational program and an online-tool for nurses. These were designed to identify frail patients and suggest early therapeutic interventions such as dietary support based on undernutrition screening and advising physiotherapy pre-and postoperatively for patients with recent falls or functional dependency. In addition, it was advised to identify polypharmacy, inadequate social support and perform cognitive and depression screening (Mini-Mental State Exam[22] and geriatric depression scale[23]) with the advice of additional evaluation when indicated.

In participating hospitals, laparoscopic surgery was the preferred operating technique[24] and peri- and postoperative care followed the Enhanced Recovery After Surgery (ERAS)[25] guidelines.

From January 2014 to December 2015, patients were included from six Dutch hospitals. Ethical approval for this study was obtained from the Medical Ethics Committee Southwest Holland.

For the current study, all patients who were 70 years or older with elective surgery for CRC were included in the analysis. Exclusion criteria were carcinoma in situ, synchronous metastases or a synchronous other primary cancer or non-surgical treatment only.

Data collection

Before surgical treatment (T0), patients were asked to complete self-administered questionnaires about HRQoL and activities of daily living (ADL). Supplementary questions were added to these validated questionnaires to include social-demographic information such as marital status and current living situation (alone or with others).

HRQoL was also completed at 3 (T3), 6 (T6), and 12 (T12) months after surgery. No ADL questionnaires were sent to patients at 6 months. Patients that did not complete a previous set of questionnaires were not invited for the sequential set. Patients that did not complete at least one set of questionnaires after T0 were excluded from the analysis.

Tumour and surgery-specific data were retrieved from the Netherlands Cancer Registry (NCR). This registry supplied demographic information including tumour characteristics (tumour stage and tumour location), surgical (open or laparoscopic surgery, whether or not with an ostomy) and medical treatment including neo- and adjuvant treatment.

From the NCR, we also retrieved demographic data of all non-participants (≥70 years) with surgical treatment in the same study period (2014-2015) from the participating study centres.

Health-related quality of life

HRQoL was assessed with the Dutch version of the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Core-30 (C-30) and EORTC QLQ-Colorectal-38 (CR-38).

The cancer-specific EORTC QLQ-C30 consists of 30 items belonging to five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), three symptom scales (fatigue, pain and nausea and vomiting), six single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and a global health item.[26]

A summary score of the QLQ-C30 was calculated that averages all functioning and symptom scores except financial problems and the global health scale and has been shown to have equal or even superior responsiveness to the underlying QLQ-C30 scale scores.[27]

The EORTC QLQ-CR38 consists of four functional scales (body image, sexual functioning and enjoyment, and future perspective), and eight symptoms scales (gastrointestinal and micturition problems, chemotherapy side effects, defecation problems, ostomy-related problems, weight loss, and male and female sexual problems).[28]

For both the QLQ-C30 and the QLQ-C38, answer categories range from one (‘not at all’) to four (‘very much’) expect for global health which ranges from 0 (‘very poor) to 7 (‘excellent’). All scales are linearly transformed according to the guidelines of the EORTC to reach a scale range of 0 to 100. A higher score on the functional scales, the global health item and summary score implies better HRQoL, whereas higher scores on symptom scales represent higher symptom burden.

We compared patients on four QLQ-C30 functioning scales (physical functioning, role functioning, emotional functioning, cognitive functioning), two QLQ-C30 symptom scales (fatigue and pain), the global health scale, the summary score and four QLQ-CR38 scales (body image, future perspective, gastrointestinal problems and weight loss). These more general outcomes were chosen based on clinical grounds. This also reduced the risk of type I errors introduced by multiple testing.

Functional assessment

For functional assessment, we used the ADL Barthel Index. It consists of 10 questions with 2 to 4 answer options, with each option scoring 0 to 3 points, and a maximum overall score of 20.[29,30] For this study we stratified patients based on this index and considered patients fully functionally ‘independent’ with a Barthel Index of 19 or higher following the definition of the Stroke Unit Trialists’ Collaboration.[31] Patients with a score lower than 19 were considered functionally ‘dependent’.

Statistical analyses

Following the EORTC guidelines, in case of missing items within a scale, the scale score was calculated by using only those items for which values were available provided that at least half of the items in the scale were completed. Likewise, at least 50% of the questions of the Barthel Index were needed to calculate a score.

Sociodemographic and clinical characteristics are presented with mean and standard deviation (SD) for normally distributed continuous variables and median with interquartile range (IQR) for non-normally distributed variables. Sociodemographic and clinical characteristics were compared using the two sided X^2 or *t*-test.

All scores were compared using two-way Analysis of Variance (ANCOVA). Predefined confounders were age, gender, tumour stage, patients living alone (patients not living together with spouse or partner), open surgery (yes or no) and postoperative treatment with chemotherapy (yes or no).

Linear mixed-effect models (i.e. covariance pattern model with unstructured error covariance matrix and maximum likelihood estimation)[32] were used to study the course of HRQoL, functioning and symptom scales over time. This technique uses data efficiently by also including incomplete cases in the analyses. As a result, bias is limited and statistical power is preserved. Dependency status (analysed as a categorical time-invariant predictor: dependent versus independent), time (analysed as categorical predictor with four levels (i.e. four time points)) and confounders as collected from baseline (analysed as time-invariant predictors) were entered in the regression equation as independent variables. The interaction of dependency status and time was tested separately and when these interactions were significantly associated with the individual functioning and symptom scales, stratified analyses were performed per dependency status (i.e. independent and dependent).

The clinical relevance of the differences in HRQoL QLQ-C30 outcomes between functionally independent and dependent patients were estimated using the consensus-based guidelines of Cocks et al.[33] Changes over time within a group were separately evaluated on clinical relevance.[34] Both guidelines were developed to aid the interpretation of differences in HRQoL scores between groups and the interpretation of change scores over time. Differences in mean scores were categorized into trivial, small, medium or large depending on the scale. Using the global health scale as an example, a difference between two groups of 0-4 would be categorized as trivial, 4-10 as small, 10-15 as medium and >15 as large. For interpreting differences in QLQ-C38 outcomes, Norman's rule of thumb was used, where a threshold of half an SD was regarded as a clinically relevant difference.[35] All analyses were performed using SAS 9.4 (SAS, Cary, NC, USA). A p-value of < 0.05 was considered statistically significant.

Results

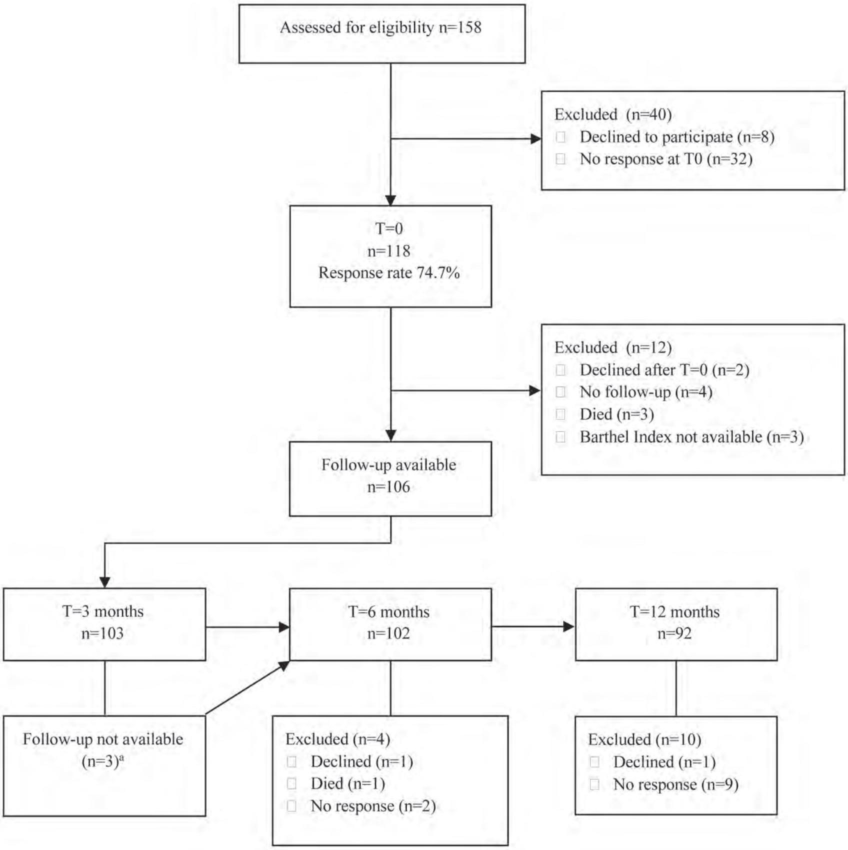
Baseline characteristics

A total of 158 patients met our inclusion criteria. The response rate to the baseline questionnaires was 74.7% (118 out of 158). For 106 patients (67%) at least one follow-up questionnaire was available and these were included for further analysis (Figure 1). Between included patients and non-responders (n=32) there was a small difference in mean age (76.4 vs 78.7, p=0.046), but no difference in gender, tumour stage, functional dependency or adjuvant treatment (p>0.05, Appendix A). Similar results were seen when demographic characteristics of the study cohort (n=106) were compared to the whole population of older patients with CRC treated in the participating centres during the study period (Appendix B).

Missing values on individual's scores of the HRQoL scales ranged from 0 to 4%. Most commonly missing data were on the scales of emotional functioning, cognitive functioning, weight loss and fatigue. Based on the Barthel Index at baseline, 80 patients (75%) were regarded as functionally independent (Barthel Index ≥19) and 26 (25%) as functionally dependent (Barthel Index <19).

Baseline characteristics are depicted in Table 1. Mean age of all patients was 76.4. Differences between functionally dependent and independent were seen in gender (p=0.02), open-surgery (p=0.02) and the number of ostomies (p=0.003)

Figure 1 Flow diagram of patients available for longitudinal analysis



[a] Follow-up was available at T=6 for 3 but not at T=3 for three patients

8

Table 1 Demographic and baseline characteristics of patients stratified based on functional dependency

	All		Independent		Dependent		
	n=106		n=80		n=26		p-value[a]
Mean Age (SD)	(76.4)	(4)	76. 3	(4)	77.0	(4)	0.4
70-74	35	(33)	27	(34)	8	(31)	
75-79	47	(44)	37	(46)	10	(38)	
80-84	18	(17)	11	(14)	7	(27)	
85+	6	(6)	5	(6)	1	(4)	
Gender (%)							0.02
Male	57	(54)	48	(60)	9	(35)	
Female	49	(46)	32	(40)	17	(65)	
Barthel Index Score							
20	72	(68)	72	(90)	-		
19	8	(7)	8	(10)	-		
18	18	(17)	-		18	(69)	
17	2	(2)	-		2	(8)	
≤16	6	(6)	-		6	(23)	
Current living situation[†]							0.1
Alone	33	(31)	22	(28)	11	(42)	
With Others	67	(63)	55	(69)	12	(46)	
Nursing Home	4	(4)	2	(3)	2	(8)	
Tumour Location (%)							0.8
Colon	71	(67)	53	(66)	18	(69)	
Rectum	35	(33)	27	(34)	8	(31)	
Tumour Stage AJCC (%)							<0.001
I	29	(27)	25	(31)	4	(15)	
II	35	(33)	24	(30)	11	(42)	
III	38	(36)	28	(35)	10	(39)	
IV	4	(4)	3	(4)	1	(4)	
Type of Surgery							0.02
Laparoscopic Surgery	78	(74)	61	(76)	17	(65)	
Open	28	(26)	19	(24)	9	(35)	
Surgical Procedure							0.4
(Hemi) Colectomy	69	(65)	51	(64)	18	(69)	
Low Anterior Resection	30	(28)	24	(30)	6	(23)	
Abdominoperineal Resection	7	(7)	5	(6)	2	(8)	
Ostomy Surgery	28	(26)	18	(23)	10	(38)	0.003
Neoadjuvant or Adjuvant Therapy							0.7
Radiotherapy	10	(9)	8	(10)	2	(8)	
Chemoradiation	13	(12)	10	(13)	3	(12)	
Chemotherapy	15	(14)	11	(14)	4	(15)	

Mean are given with standard deviation (SD). Frequencies with percentage (%). Patients were considered ADL dependent with a Barthel Index below 19

[a]p-value between independent and dependent patients. †2 missing

Baseline HRQoL

Tables 2A and 2B show the baseline and uncorrected differences in HRQoL scores between functionally independent and dependent patients. Functionally dependent patients reported lower physical functioning, role functioning, global health and more symptoms such as fatigue and pain (all p<0.001). The HRQoL summary score was, on average, 17 points lower for functionally dependent patients compared to functionally independent patients (68.9 versus 86.4, p<0.001). The clinical relevance of the majority these differences in baseline scores can be classified as medium to large.

Table 2A Baseline QLQ-C30 scores with stratification based on functional dependency

	Independent n=80		Dependent n=26			Relevance[a]
QLQ-C30	*mean*	*(SD)*	*mean*	*(SD)*	*p-value*	
Physical Functioning	81.6	(28)	62.4	(28)	<0.001	medium
Role Functioning	80.0	(37)	55.8	(37)	<0.001	medium
Emotional Functioning	84.8	(16)	78.1	(16)	0.1	none
Cognitive Functioning	89.6	(18)	84.7	(18)	0.2	none
Fatigue	28.5	(35)	51.3	(35)	<0.001	large
Pain	14.2	(35)	34.0	(35)	0.001	large
Global Health	76.5	(20)	61.5	(20)	<0.001	large
summary score	86.4	(12)	68.9	(18)	<0.001	large

Numbers as mean values with corresponding (SD). [a]Interpretation of clinical relevance based on Cocks et al.[33]

8

Table 2B Baseline QLQ-CR38 scores with stratification based on functional dependency

	Independent n=80		Dependent n=26			Relevance[b]
QLQ-CR38	*mean*	*(SD)*	*mean*	*(SD)*	*p-value*	
Future Perspective	70.8	(23)	60.3	(28)	0.06	none
Gastointestinal Problems	16.5	(14)	26.7	(16)	0.003	relevant
Weight Loss	18.6	(24)	33.3	(35)	0.02	relevant

Numbers as mean values with corresponding (SD). [b]Interpretation of clinical relevance based on Norman's rule of thumb[35]

HRQoL over time for dependent and independent patients

The observed mean scores of the HRQoL domains over time for functionally dependent and independent patients are depicted in figures 2A and 2B.

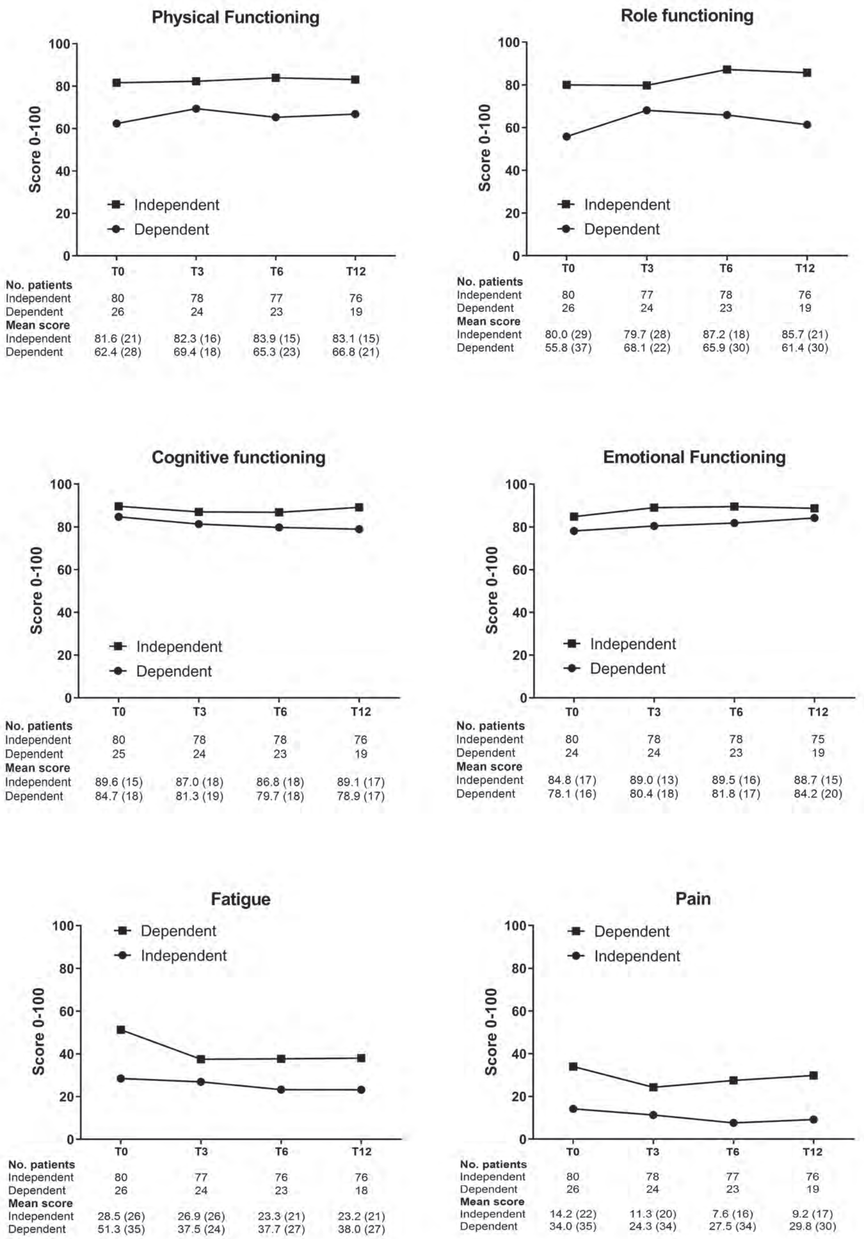
Over the course of one year, functionally dependent patients persistently reported lower role functioning (b=-16.40; 95% CI -24.74 to -8.06), lower global health (b=-7.0; 95% CI -13.6 to -0.3, p=0.04) and more fatigue (b=11.3; 95% CI 1.5 to 21.5), more pain (b=15.5; 95% CI 7.0 to 23.9), more gastrointestinal problems (b=7.0; 95% CI 1.8 to 12.2) and more weight loss (b=8.4; 95% CI 2.8 to 13.9) compared to functionally independent patients. This was also reflected in a lower summary score for functionally dependent patients (b=-8.0 95% CI -12.8 to -3.1).

Figures 2A and 2B illustrate that mean scores for role functioning, emotional functioning, fatigue, pain, global health, the HRQoL summary score, gastrointestinal problems and weight loss improved over time for functionally dependent patients and not for functionally independent patients. This was also reflected in the statistic interaction between time and dependency status (p<0.05), indicating that HRQoL significantly changes over time, but these changes differ between functionally dependent and independent patients.

After correction for confounders the improvement in functionally dependent patients was significant and clinically relevant at T3 compared to T0 for fatigue (b=-13.9; 95% CI -27.9 to 0.0) and for the HRQoL summary score (b=12.0; 95% CI 3.3 to 20.7). At T6 compared to T0 significant improvements (p<0.05) were observed in role functioning (b=17.1; 95% CI 1.4 to 32.7), fatigue (b=-18.6; 95% CI -31.0 to -6.2), gastrointestinal problems (-9.8; 95% CI -15.8 to -3.8), global health (b=13.7; 95% CI 3.0 to 24.3) and the HRQoL summary score (b=12.7, 95% CI 4.3 to 21.2). At T12 (versus T0) these improvements were only statistically significant and clinical relevant for weight loss (b=-18.8; 95% CI -34.9 to -2.7) and gastrointestinal problems (b=-10.4; 95% CI -20.0 to -0.7, p=0.04) and no longer for the other functioning and symptom scales.

In functionally independent patients, at T3 emotional functioning significantly improved (b=4.2 95% CI 0.6-7.8) although this difference was not clinically relevant. At T6 compared to T0 improvements were observed in emotional functioning (b=4.9 95% CI 1.3-8.6), pain (b=-7.1 95% CI -12.8 to -1.3), weight loss (b=-14.0 95% CI -20.4 to -7.5) and gastrointestinal problems (b=-4.2, 95% CI -7.2 to -1.3). At T12 (versus T0) the improvements in emotional functioning (b=4.7, 95% CI 0.9 to 8.5), weight loss (b=-12.5, 95% CI -18.9 to -6.1) and gastrointestinal problems (b=-3.3, 95% CI -6.4 to -0.2) remained significant but not for pain (p=0.08). The temporality improvement in the pain score and the improvement in weight loss could be regarded as clinically relevant, all other improvements had trivial or no clinical relevance.

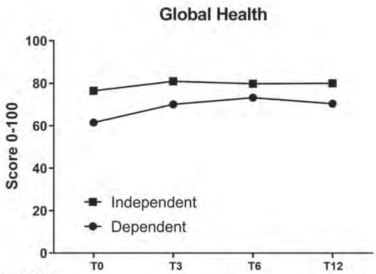
Figure 2A Longitudinal health related quality of life (HRQoL)



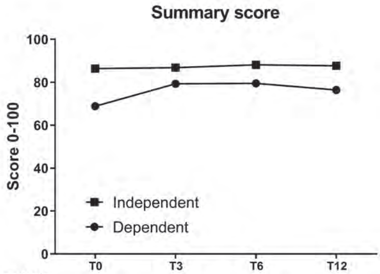
Scores are mean with (SD). For the symptom scales higher scores mean more symptoms

8

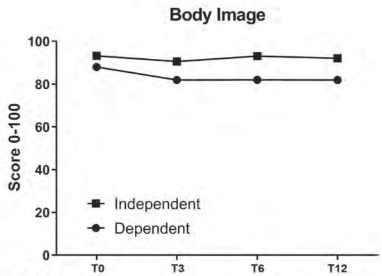
Figure 2B Longitudinal Health-Related Quality of Life (HRQoL)



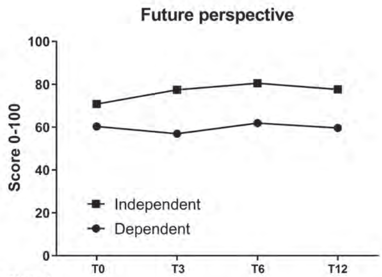
	T0	T3	T6	T12
No. patients				
Independent	80	78	78	76
Dependent	26	24	23	20
Mean score				
Independent	76.5 (17)	80.9 (15)	79.8 (15)	80.3 (13)
Dependent	61.5 (20)	70.1 (18)	73.3 (23)	70.4 (22)



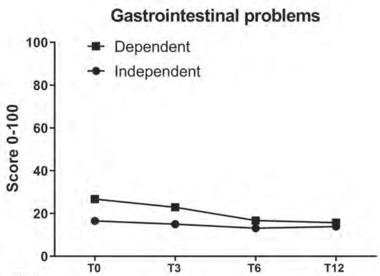
	T0	T3	T6	T12
No. patients				
Independent	77	75	72	72
Dependent	23	22	21	17
Mean score				
Independent	86.4 (12)	86.8 (12)	88.1 (10)	88.7 (10)
Dependent	68.9 (18)	79.3 (12)	79.5 (17)	76.4 (18)



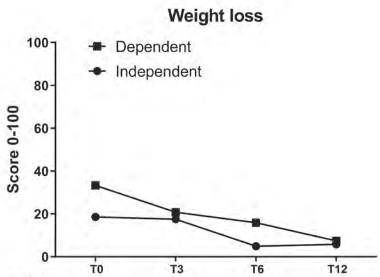
	T0	T3	T6	T12
No. patients				
Independent	79	76	77	75
Dependent	24	24	21	19
Mean score				
Independent	93.2 (12)	90.6 (16)	93.1 (15)	92.1 (14)
Dependent	88.0 (23)	81.9 (28)	82.0 (25)	81.9 (22)



	T0	T3	T6	T12
No. patients				
Independent	80	78	77	76
Dependent	26	24	21	19
Mean score				
Independent	70.8 (23)	77.4 (23)	80.5 (21)	77.6 (21)
Dependent	60.3 (28)	56.9 (30)	61.9 (29)	59.6 (29)



	T0	T3	T6	T12
No. patients				
Independent	79	78	76	74
Dependent	26	23	20	17
Mean score				
Independent	16.5 (14)	15.0 (12)	13.1 (11)	13.9 (14)
Dependent	26.7 (16)	22.9 (11)	16.7 (13)	15.7 (18)



	T0	T3	T6	T12
No. patients				
Independent	79	78	75	75
Dependent	26	24	21	18
Mean score				
Independent	18.6 (24)	17.5 (27)	4.9 (12)	5.8 (14)
Dependent	33.3 (35)	20.8 (26)	15.9 (27)	7.4 (18)

Scores are mean with (SD). For the symptom scales higher scores mean more symptoms

Discussion

In this study, we observed clinically relevant improvement in the majority of the HRQoL domains for functionally dependent patients with improvements in global health and a decrease in pain, fatigue, and gastrointestinal problems. For the functionally independent patients, global health remained stable with only clinically relevant improvement in weight loss. The expected negative impact of surgery on HRQoL in functionally dependent patients was not seen, despite the lower overall quality of life before surgery between functionally dependent and independent patients.

Only three earlier studies focused (partly) on functionally dependent[36,37] or frail patients with CRC.[19] One study among a group of 86 older patients (mean age 70) undergoing CRC surgery reported that poorer physical functioning was borderline associated (p=0.058) with lower quality of life both prior to surgery and at 5-8 months follow-up.[36] Another study reported an improvement in quality of life (measured with the EuroQol-5D) in older patients with CRC or gastric cancer (>75 years) 6 months after surgery. However, patients were not stratified based on geriatric or functional dependency.[37] Our study is in line with these studies and also confirms the findings of a study that showed an improvement in HRQoL at 3 months follow-up in frail patients but no improvement at 12-28 months follow-up.[19]

8

In our study, 10% of the functionally independent patients and 12% of the functionally dependent patients had at least 1 point decrease in their Barthel Index after surgery (data not shown). These numbers are similar or even lower compared to other studies (7-31%).[19,36,37] The reported decrease in physical function in these studies and our study are also lower than the studies included in an earlier review, where up to 60% decrease in perceived physical functioning was described.[38] This discrepancy might be explained by improved CRC care in recent years: multiple efforts have been undertaken to improve surgical care, including improvement in peri-operative care (such as Enhanced Recovery After Surgery (ERAS)[39] and laparoscopic surgery)[40], better patient selection, and the introduction of geriatric-oncological additional care. These improvements in surgical care and the decrease in surgical complications and mortality in the past decade[41] may have resulted in fewer patients with functional decline.

Our observed improvements in multiple domains of HRQoL including symptom scales after surgery could be related to the reduction of symptoms after surgery (i.e. therapeutic effect). An alternative explanation might be the 'response shift phenomenon', i.e. the reframing of the perception of their health over time, resulting in the reporting of improved HRQoL.[42,43] Last, the majority of our patients were treated in hospitals were oncogeriatric care is extendedly integrated into the pre-, peri-, and postoperative care processes and this may influence the effect of surgery on physical functioning and quality of life.[44]

It is unlikely that the postoperative improvement in HRQoL was caused by loss of follow-up as the majority of these patients were not found to be the ones with the lowest scores at baseline. That improvements in the majority of the HRQoL scales were not significant at T12 for dependent patients, may have been caused by the lower number of respondents at this time point or that patients return to their original level of HRQoL indicating only a temporarily improvement.

Strengths of our study are the longitudinal follow-up of a cohort of older patients, with baseline assessment before surgery and a high response rate at follow-up (78%-87%). We reported on multiple time points showing a trajectory of HRQoL and using linear mixed-models we corrected for possible confounders resulting in more robust findings.

There are some limitations in our study that need to be addressed. First, we chose functional dependency as an indicator of possible frailty. However, frailty encompasses multiple domains, including cognitive and social functioning. The impairments in other geriatric domains may have further influenced HRQoL. Second, in our study patients had a Barthel Index score of 15 or higher, hence, patients that were highly dependent on care (score < 10) were not included, and neither were patients with acute surgery. Third, we cannot exclude the possibility that patients who did not respond or were not included in our study exhibited better or worse HRQoL, which would limit the generalizability of our results. Lastly, the interval between the HRQoL questionnaires was 3 months, and may not have captured the nadir of postoperative decline in HRQoL as was seen in earlier trials.[14,45,46]

Our results suggest that one point difference in the Barthel Index can discriminate between groups of older patients that experience a difference in HRQoL before and after surgery. It underlines the importance of functional dependency in the investigation of HRQoL in older patients. Furthermore, we already know that age is not a useful selection tool for oncologic treatment and in older patients, other geriatric factors should be taken into account in the process of shared decision making.[47] We add to this field that mild to moderate functional dependency, although a low baseline quality of life suggests otherwise, should not be considered a generic reason for withholding surgical treatment to older patients with CRC. Whether oncogeriatric care itself limits the impact of surgery or even improves HRQoL, should be further investigated.

Conclusions

Our study showed that in older functional dependent patients with CRC, colorectal surgery embedded in oncogeriatric care has a positive impact on HRQoL. Functionally dependent patients with CRC who survived the first three months after surgery reported significantly and clinically relevant better HRQoL compared to before surgery, although dependency persisted. This is important information that has to be taken into account in the decision-making process of older patients with CRC.

References

1. *Netherlands Cancer Registry.* Retrieved from www.cijfersoverkanker.nl.
2. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandala M, Cervantes A, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2013;24 Suppl 6(suppl_6):vi64-72.
3. Dekker JW, Gooiker GA, Bastiaannet E, van den Broek CB, van der Geest LG, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. *European Journal of Surgical Oncology.* 2014;40(11):1481-7.
4. Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: A systematic review. *Journal of Geriatric Oncology.* 2016;7(6):479-91.
5. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Annals of Surgical Oncology.* 2012;19(8):2428-34.
6. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hebert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. *Lancet.* 1999;353(9148):205-6.
7. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2001;56(3):M146-56.
8. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. *Journal of the American College of Surgeons.* 2010;210(6):901-8.
9. Wilson MK, Collyar D, Chingos DT, Friedlander M, Ho TW, Karakasis K, et al. Outcomes and endpoints in cancer trials: bridging the divide. *Lancet Oncology.* 2015;16(1):e43-52.
10. Corner J, Wright D, Hopkinson J, Gunaratnam Y, McDonald JW, Foster C. The research priorities of patients attending UK cancer treatment centres: findings from a modified nominal group study. *British Journal of Cancer.* 2007;96(6):875-81.
11. Mohile SG, Hurria A, Cohen HJ, Rowland JH, Leach CR, Arora NK, et al. Improving the quality of survivorship for older adults with cancer. *Cancer.* 2016;122(16):2459-568.
12. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. *Annals of Surgery.* 2014;259(5):916-23.
13. Di Cristofaro L, Ruffolo C, Pinto E, Massa M, Antoniutti M, Cagol M, et al. Complications after surgery for colorectal cancer affect quality of life and surgeon-patient relationship. *Colorectal Disease.* 2014;16(12):O407-19.
14. Stucky CC, Pockaj BA, Novotny PJ, Sloan JA, Sargent DJ, O'Connell MJ, et al. Long-term follow-up and individual item analysis of quality of life assessments related to laparoscopic-assisted colectomy in the COST trial 93-46-53 (INT 0146). *Annals of Surgical Oncology.* 2011;18(9):2422-31.
15. Hung HC, Chien TW, Tsay SL, Hang HM, Liang SY. Patient and clinical variables account for changes in health- related quality of life and symptom burden as treatment outcomes in colorectal cancer: a longitudinal study. *Asian Pacific Journal of Cancer Prevention.* 2013;14(3):1905-9.
16. Scarpa M, Di Cristofaro L, Cortinovis M, Pinto E, Massa M, Alfieri R, et al. Minimally invasive surgery for colorectal cancer: quality of life and satisfaction with care in elderly patients. *Surgical Endoscopy.* 2013;27(8):2911-20.
17. Kristjansson SR, Jordhøy MS, Nesbakken A, Skovlund E, Bakka A, Johannessen H-O, et al. Which elements of a comprehensive geriatric assessment (CGA) predict post-operative complications and early mortality after colorectal cancer surgery? *Journal of Geriatric Oncology.* 2010;1(2):57-65.
18. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Annals of Surgical Oncology.* 2011;18(6):1533-9.
19. Ronning B, Wyller TB, Nesbakken A, Skovlund E, Jordhoy MS, Bakka A, et al. Quality of life in older and frail patients after surgery for colorectal cancer-A follow-up study. *Journal of Geriatric Oncology.* 2016;7(3):195-200.

20. Orsini RG, Thong MS, van de Poll-Franse LV, Slooter GD, Nieuwenhuijzen GA, Rutten HJ, et al. Quality of life of older rectal cancer patients is not impaired by a permanent stoma. *European Journal of Surgical Oncology.* 2013;39(2):164-70.

21. Traa MJ, Orsini RG, Den Oudsten BL, De Vries J, Roukema JA, Bosman SJ, et al. Measuring the health-related quality of life and sexual functioning of patients with rectal cancer: does type of treatment matter? *International Journal of Cancer.* 2014;134(4):979-87.

22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research.* 1975;12(3):189-98.

23. D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders. I: The acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. *Family Practice.* 1994;11(3):260-6.

24. Gietelink L, Wouters MW, Bemelman WA, Dekker JW, Tollenaar RA, Tanis PJ. Reduced 30-Day Mortality After Laparoscopic Colorectal Cancer Surgery: A Population Based Study From the Dutch Surgical Colorectal Audit (DSCA). *Annals of Surgery.* 2016;264(1):135-40.

25. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. *World Journal of Surgery.* 2014;38(6):1531-41.

26. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute.* 1993;85(5):365-76.

27. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *Journal of Clinical Epidemiology.* 2016;69:79-88.

28. Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. *European Journal of Cancer.* 1999;35(2):238-47.

29. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *International Disability Studies.* 1988;10(2):61-3.

30. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Maryland State Medical Journal.* 1965;14:61-5.

31. Stroke Unit Trialists C. Organised inpatient (stroke unit) care for stroke. *Cochrane Database of Systematic Reviews.* 2013(9):CD000197.

32. Hedeker DR, Gibbons RD. In: *Longitudinal data analysis.* Hoboken, New Jersey, USA: Wiley; 2006.

33. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Journal of Clinical Oncology.* 2011;29(1):89-96.

34. Cocks K, King MT, Velikova G, de Castro G, Jr., Martyn St-James M, Fayers PM, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *European Journal of Cancer.* 2012;48(11):1713-21.

35. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Medical Care.* 2003;41(5):582-92.

36. Ulander K, Jeppsson B, Grahn G. Quality of life and independence in activities of daily living preoperatively and at follow-up in patients with colorectal cancer. *Supportive Care in Cancer.* 1997;5(5):402-9.

37. Amemiya T, Oda K, Ando M, Kawamura T, Kitagawa Y, Okawa Y, et al. Activities of daily living and quality of life of elderly patients after elective surgery for gastric and colorectal cancers. *Annals of Surgery.* 2007;246(2):222-8.

38. Hamaker ME, Prins MC, Schiphorst AH, van Tuyl SA, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. *Journal of Geriatric Oncology.* 2015;6(2):153-64.

39. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. *Colorectal Disease.* 2014;16(12):947-56.

40. Cerdan Santacruz C, Frasson M, Flor-Lorente B, Ramos Rodriguez JL, Trallero Anoro M, Millan Scheiding M, et al. Laparoscopy may decrease morbidity and length of stay after elective colon cancer resection, especially in frail patients: results from an observational real-life study. *Surgical Endoscopy.* 2017;31(12):5032-42.

41. Breugom AJ, Bastiaannet E, Dekker JWT, Wouters MWJM, van de Velde CJH, Liefers GJ. Decrease in 30-day and one-year mortality over time in patients aged ≥75 years with stage I–III colon cancer: A population-based study. *European Journal of Surgical Oncology.* 2018;44(12):1889-93.

42. Padilla GV, Grant MM, Lipsett J, Anderson PR, Rhiner M, Bogen C. Health quality of life and colorectal cancer. *Cancer.* 1992;70(5 Suppl):1450-6.

43. Bernhard J, Hurny C, Maibach R, Herrmann R, Laffer U. Quality of life as subjective experience: reframing of perception in patients with colon cancer undergoing radical resection with or without adjuvant chemotherapy. Swiss Group for Clinical Cancer Research (SAKK). *Annals of Oncology.* 1999;10(7):775-82.

44. Hansen DG, Larsen PV, Holm LV, Rottmann N, Bergholdt SH, Sondergaard J. Association between unmet needs and quality of life of cancer patients: a population-based study. *Acta Oncologica.* 2013;52(2):391-9.

45. Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *Journal of Clinical Oncology.* 2007;25(21):3061-8.

46. Andersson J, Angenete E, Gellerstedt M, Angeras U, Jess P, Rosenberg J, et al. Health-related quality of life after laparoscopic and open surgery for rectal cancer in a randomized trial. *British Journal of Surgery.* 2013;100(7):941-9.

47. Hamaker ME, Te Molder M, Thielen N, van Munster BC, Schiphorst AH, van Huis LH. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients - A systematic review. *Journal of Geriatric Oncology.* 2018;9(5):430-40.

Appendix A Baseline characteristics of responders and non-responders (T0)

	Responders		Non-responders		
	n=106		n=32		p-value
Mean Age (SD)	76.4	(4)	78.7	(6)	0.046
Gender (%)					0.8
Male	57	(54)	18	(56)	
Female	49	(46)	14	(44)	
Functionally Dependent					
Barthel Index < 19 or Katz ADL ≥ 2[a]	26	(25)	7	(24)	0.7
Tumour location					0.06
Colon	71	(67)	27	(84)	
Rectum	35	(33)	5	(16)	
Tumour stage AJCC[b]					0.4
Stage I-II	64	(60)	13	(41)	
Stage III	38	(36)	12	(38)	
Stage IV	4	(4)	2	(6)	
Neoadjuvant or adjuvant therapy					
Chemoradiation/ radiotherapy	23	(22)	2	(6)	0.047
Adjuvant chemotherapy	15	(14)	3	(9)	0.5

[a]Information based on 106 responders and 29 non-responders
[b]Information on tumour stage of 5 patients was missing

Appendix B Baseline characteristics of the study cohort and all patients from the participating centres from the same period (2014-2015)

	Study cohort n=106		All patients[a] 2014-2015 n=923	
	Independent n=80	Dependent n=26		p-value[b]
Mean age (SD)	76.3 (4.0)	77.0 (4.0)	77.8 (5)	0.04
Gender				0.08
Male	48 (60)	9 (35)	496 (54)	
Female	32 (40)	17 (65)	427 (46)	
Tumour location				0.01
Colon	53 (66)	18 (69)	738 (80)	
Rectum	27 (34)	8 (31)	185 (20)	
Tumour stage AJCC				0.3
Stage I-II	49 (61)	15 (58)	527 (57)	
Stage III	28 (35)	10 (38)	301 (33)	
Stage IV	3 (4)	1 (4)	95 (10)	
Neoadjuvant or adjuvant therapy				
Neo-adjuvant chemoradiation/radiotherapy	18 (23)	5 (19)	107 (12)	0.02
Adjuvant chemotherapy	11 (14)	4 (15)	149 (16)	0.9
Ostomy	18 (23)	10 (38)	245 (27)	0.3

[a]All surgically treated patients for colorectal cancer (≥70 years) in the participating centres between 2014-2015. Data from the Dutch Cancer Registry (NKR). [b]Between the three groups. Frequencies are shown with percentage (%) or mean with SD

Chapter 9

The effect of a geriatric evaluation on treatment decisions for older patients with colorectal cancer

International Journal of Colorectal Disease 2017;32(11):1625-1629

E.T.D. Souwer
N.M. Verweij
A.H.W. Schiphorst
H.A.A. Maas
J.E.A. Portielje
A. Pronk
F. van den Bos
M.E. Hamaker

Abstract

Background: Treating elderly colorectal cancer patients can be challenging. It is very important to carefully weigh the risks and benefits of potential treatments in individual patients. This treatment decision making can be guided by geriatric consultation. We aimed to assess the effect of a geriatric evaluation on treatment decisions for older patients with colorectal cancer.

Patients and methods: Colorectal cancer patients who were referred for a geriatric consultation between 2013 and 2015 in three Dutch teaching hospitals were included in a prospective database. The outcome of geriatric assessment, non-oncological interventions and geriatricians' treatment recommendations were evaluated.

Results: The total number of included referrals was 168. The median age was 81 years (range 60-94). Most patients (71%) had colon cancer, and 49% had tumour stage III disease. The reason for geriatric consultation was uncertainty regarding the optimal oncologic treatment in 139 patients (83%). Overall, 93% of patients suffered from geriatric impairments, non-oncological interventions that followed after geriatric consultation was mostly aimed at malnutrition. The geriatrician recommended the 'more intensive treatment' option in 69% and the 'less intensive treatment' option in 31% of which 63% 'supportive care only'.

Conclusion: Geriatric consultation can be useful in treatment decision making in elderly patients with colorectal cancer. It may lead to changes in the treatment plan for individual cases and may result in an additional optimisation of patient's health status prior to treatment.

Introduction

Treating elderly colorectal cancer patients can be challenging. These patients have higher rates of post-treatment morbidity and (excess) mortality.[1,2] In addition, they are also at risk for functional decline after treatment, with reported rates of more than 60% in the elderly.[3] Therefore, it is very important to carefully weigh the risks and benefits of potential treatments. Given the heterogeneity within the older adult population, age itself is not a useful selection tool for oncologic treatment, and patients should be managed according to their individual health status.[4] Recent research has focused on using geriatric assessments to provide a more comprehensive overview of an older patient's overall health status across multiple domains such as physical, psychosocial and functional status.[5,6]

This study aimed to assess the relevance of geriatric consultations (including a comprehensive geriatric assessment) in decision making for older patients with colorectal cancer and to assess if it leads to an altered treatment of these patients.

Patients and methods

This study was performed at three teaching hospitals in the Netherlands. Patients were included between 2013 and 2015 from the Diakonessenhuis Hospital in Utrecht, the Hagaziekenhuis in The Hague and the Elisabeth-Tweesteden Hospital in Tilburg. Consecutive colorectal cancer patients who were referred for a geriatric consultation were included. Patients were selected for geriatric consultation by the referring physician (surgeon, medical oncologist, gastroenterologist) or within a multidisciplinary oncology team (MDT) meeting to obtain a recommendation regarding the treatment or for optimisation of patient's health prior to the treatment. Patients were seen by a geriatrician in the outpatient clinic or during hospital stay.

The geriatric consultations were performed by three geriatricians trained in geriatric oncology (MH, HM and FB). These assessments consisted of an evaluation of the patient's medical history, polypharmacy (the use of ≥5 medications), cognitive impairments, mood disorders, nutritional status, physical impairments, social network and care needs. Interventions for each of these domains were initiated if necessary or possible to optimise health status. Advanced care planning (post-treatment) could be discussed with the patient as well as patient's expectations and priorities considering treatment options.

In general, the colorectal cancer treatment options were formulated before geriatric consultation; this could be the standard treatment according to guidelines or an adjusted treatment based on clinical judgement of the patient's health status. Often, the cancer specialist suggested two options and asked the geriatrician's input regarding which to choose. After the consultation, the geriatrician could subsequently agree with one of these options or recommend another alternative.

The geriatrician's recommendations were discussed during MDT meetings or directly between the geriatrician and patient's cancer specialist, after which a definitive treatment plan was formulated. Geriatric follow-up was initiated when indicated.

Data analysis

The primary outcome was to assess the effect of a geriatric evaluation on treatment decisions for older patients with colorectal cancer. Secondary analyses included the prevalence of geriatric impairments and the effect of geriatric evaluation on non-oncological interventions.

We collected the following data: age, sex, Charlson comorbidity index,[7] medication use, tumour location (colon or rectum), tumour stage, treatment setting (palliative or curative) and suggested treatment (surgery (with/without (neo)adjuvant therapy), chemotherapy and/or radiotherapy, supportive care). Data from the geriatric evaluation included the presence of geriatric impairments, non-oncological interventions, suggestions regarding treatment choices and any additional yield of the consultation regarding advanced care planning, clarifying patient's priorities and expectations regarding the treatment. Treatment decisions following geriatric consultation were classified as 'more intensive treatment' if the geriatrician recommended the treatment which is the more intensive of the suggested treatments (e.g. extensive surgery instead of (palliative) chemotherapy; normal-dose chemotherapy instead of low-dose chemotherapy or treatment). Suggestions were classified as 'less intensive treatment' if the less intensive treatment option was recommended by the geriatrician (e.g. low-dose chemotherapy instead of normal-dose chemotherapy or (extensive) surgical treatment) or if no oncologic treatment was recommended ('supportive care only').

Statistical analysis

The statistical program IBM SPSS for Windows, version 23.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses. For comparisons between groups, the Chi-square test was used for nominal and ordinal variables, the Anova test for continuous variables. A p-value of <0.05 was considered statistically significant.

Results

The total number of included referrals was 168. Of these, 76 patients (45%) were from the Diakonessenhuis hospital, 62 (37%) from the Hagaziekenhuis and 30 patients (18%) from the Elisabeth-Tweesteden hospital. The median age was 81 years (range 60-94) and 51% were male (Table 1). A total of 45% had a Charlson comorbidity index of ≥2 and 69% used five or more medications. The majority of patients (71%) were diagnosed with colon cancer, the other 29% had rectal cancer. Almost half of the patients had stage III disease.

Geriatric consultations

The reason for geriatric consultation was uncertainty regarding the optimal oncologic treatment in 139 patients (83%). The remainder (17%) already had a final treatment plan: they were referred for optimisation prior to the oncological treatment. Most patients were referred by a gastroenterologist (59%) or a colorectal surgeon (33%). The majority (85%) was seen in the out-patient clinic.

Overall, 93% of patients had one or more geriatric impairments. Most common impairments were polypharmacy (57%), impaired mobility (38%) and comorbidity (38%, Table 2). Non-oncological interventions that followed after geriatric consultation were mostly aimed at malnutrition, social network, psychological and cognitive disorders.

Advanced care planning considerations were mentioned in the charts of 55 patients (33%). Clarification of patient's priorities was required for 43 patients (26%) and erroneous treatment expectations were corrected in 40 patients (24%).

Table 1 Patient demographics

	Total (n=168)
Male (%)	86 (51%)
Median age in years (range)	81 (60-94)
Number of patients with charlson Comorbidity Index ≥ 2 (%)	75 (45%)
Polypharmacy (use of ≥5 medications) (%)	115 (69%)
Tumour location (%)	
colon	118 (71%)
rectum	49 (29%)
Tumour stage (%)	
I	13 (9%)
II	30 (21%)
III	70 (49%)
IV	31 (22%)

Treatment decisions

Of the 139 cases that had a geriatric consultation because of uncertainty regarding the treatment plan, the geriatrician recommended the 'more intensive treatment' option in 96 cases (69%) and the 'less intensive treatment' option in 43 cases (31%, Figure 1). Of the latter, 'supportive care only' was recommended in 27 cases (63%), 50% of these patients had stage IV cancer.

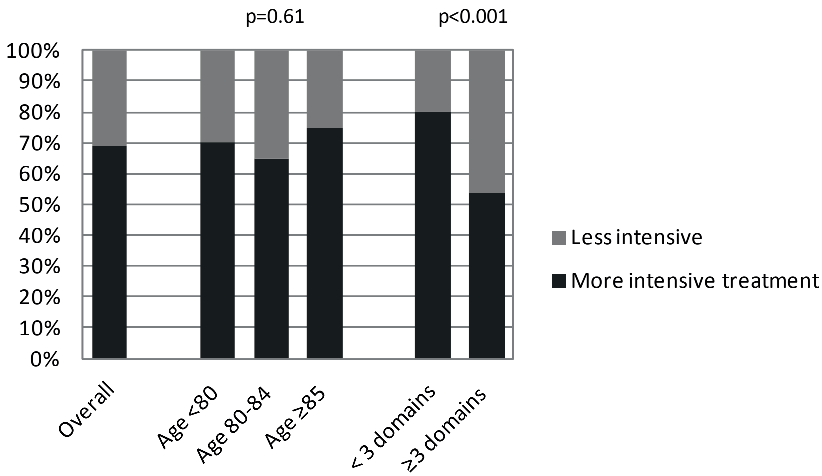
For 45 of the 139 patients (32%) the recommendation differed from the treatment plan of the referring specialist. The alternative plan suggested by the geriatrician for these 45 patients, was accepted for 34 patients (76%) while for 9 patients (20%), the initial plan was maintained. The remaining two (4%) patients opted out of treatment themselves. Treatment suggestions following geriatric consultation were not different between the age groups <80 years, 80-84 years and ≥85 years (p=0.61). For patients with ≥3 impaired geriatric domains, 'more intensive treatment' was recommended significantly less often while 'less intensive treatment' was recommended more often (in 54% and 46% respectively in patients with ≥3 domains compared to 80% and 20% respectively of those with <3 domains, p=0.001).

Table 2 Geriatric assessment outcome: prevalence of geriatric impairment and suggestions for non-oncological interventions

	Geriatric Impairment	Resulting in Non-Oncological Interventions
(i)ADL[a]	70 (42%)	4 (6%)
Cognitive	46 (27%)	9 (20%)
Polypharmacy	96 (57%)	13 (14%)
Comorbidity	63 (38%)	5 (8%)
Social network	28 (17%)	6 (21%)
Malnutrition	54 (32%)	29 (54%)
Psychological	19 (11%)	8 (42%)
Mobility	63 (38%)	9 (14%)

[a](Instrumental) Activities of Daily Living

Figure 1 Treatment suggestions following geriatric consultation



Discussion

In this analysis of 168 patients who underwent geriatric consultation because of colorectal cancer, we found that these consultations can be useful in guiding the process of decision making and also focus on the optimisation of a patient's health status. Moreover, treatment plans changed in individual cases after the geriatrician's evaluation; most of the time (76%) these suggestions were adopted by the referring physician. Suggestions for 'more intensive treatment' options were significantly reduced in patients with multiple geriatric domain limitations. Non-oncological interventions that followed after geriatric consultation were mostly aimed at malnutrition, social network, psychological and cognitive disorders.

The number of older colorectal cancer patients has increased in recent years en is expected to rise even further in decades to come.[8] These patients often present with co-existing health issues and functional or cognitive decline.[9] Especially in these frail patients, colorectal surgery comes with high morbidity-rates.[1] Moreover, survival is greatly affected by the outcome of surgery, mainly in the first postoperative year.[2] Therefore, optimal decision making is of the utmost priority for this heterogeneous patient group. Our study shows, similar to other studies,[10,11] that a geriatric consultation can be helpful in this challenging task.

Untreated colorectal cancer can lead to serious cancer-related complications. One could decide to choose for 'less intensive treatment' which does not always mean that there will be no treatment. For example, instead of an extensive surgical colorectal resection, one could perform minimal surgery only such as the placement of an (diverting) ostomy to palliate obstruction complaints. Elderly do not experience more limitations or psychosocial impact due to this ostomy compared to younger ostomy carriers.[12] In such cases, these 'less intensive treatment' options may prevent the high postoperative complication rates (reported in up to 41%) and postoperative 30-day mortality rates of 10% in patients ≥85 years old undergoing colorectal cancer resection.[1] This might be an option in some individual cases for whom 'the more intensive treatment' is not desirable. Another way to reduce the treatment intensity, is by offering a patient monotherapy instead of combination chemotherapy. The expected oncologic effect might not be as good as in normal (protocolised) dose chemotherapy, but one can expect treatment-related toxicity to be less pronounced.[13,14]

Similar to what we have seen in our cohort, previous research has shown that the geriatric consultations can result in non-oncologic interventions in up to 70% of patients.[15] These interventions are aimed at improving patient's health status before treatment, which could be particularly pertinent because patients with comorbidity are more prone to develop post-treatment morbidity or mortality[1,16] The effectiveness of these interventions is still not very clear. A recent study that enrolled 60 cancer patients aged 70 years or older showed that geriatric assessment guided multidisciplinary interventions increased quality of life and decreased functional decline after treatment.[17] Another prospective randomised controlled trial which will determine the effect of these interventions to reduce hospitalisation and toxicity in older cancer patients receiving chemotherapy, is currently ongoing.[18]

This study has several limitations. First, we collected data from three different hospitals. Although all of the geriatricians who examined the patients are well-trained and experienced in geriatric oncology, consultations were not protocolised and therefore, there might be some differences in their execution and the interpretation of the results. While this may affect homogeneity, it is also a reflection of actual clinical practice. Second, the presented data represent a selected patient group, for which the primary cancer specialist or multidisciplinary team deemed a geriatric consultation as desirable or necessary. Therefore, these patients are not representative of all older colorectal cancer patients and the results of this study should be extrapolated with some caution.

Despite these limitations, this study demonstrates that geriatric assessment impacts oncologic treatment decision-making in older colorectal cancer patients. In the future, case managers (e.g. specialised geriatric oncology nurses) could aid the multidisciplinary decision-making process by collecting information about patient's health status, wishes and priorities and treatment possibilities. Subsequently, older cancer patients with uncertainty regarding their ability to tolerate treatment or regarding the optimal oncologic treatment plan should be referred to specialists, who are experienced in geriatric oncology, for geriatric consultation to receive a thorough assessment which can help in formulating an individualised plan for the cancer treatment as well as optimising their overall health status.

Conclusion

Geriatric consultation can be useful in treatment decision making in elderly patients with colorectal cancer. It may lead to changes in the treatment plan for individual cases. Additionally, it may optimise patient's health status prior to treatment.

References

1. Verweij NM, Schiphorst AH, Maas HA, Zimmerman DD, van den Bos F, Pronk A, et al. Colorectal Cancer Resections in the Oldest Old Between 2011 and 2012 in The Netherlands. *Annals of Surgical Oncology.* 2016;23(6):1875-82.
2. Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Annals of Surgical Oncology.* 2011;18(6):1533-9.
3. Hamaker ME, Prins MC, Schiphorst AH, van Tuyl SA, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. *Journal of Geriatric Oncology.* 2015;6(2):153-64.
4. Hamaker ME, Prins MC, Stauder R. The relevance of a geriatric assessment for elderly patients with a haematological malignancy--a systematic review. *Leukemia Research.* 2014;38(3):275-83.
5. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer. *Journal of Clinical Oncology.* 2014;32(24):2595-603.
6. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Critical Reviews in Oncology/Hematology.* 2005;55(3):241-52.
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases.* 1987;40(5):373-83.
8. *Netherlands Cancer Registry (NKR).* Retrieved from www.cijfersoverkanker.nl: [Accessed 01 June 2018].
9. Verweij NM, Schiphorst AH, Pronk A, van den Bos F, Hamaker ME. Physical performance measures for predicting outcome in cancer patients: a systematic review. *Acta Oncologica.* 2016;55(12):1386-91.
10. Brunello A, Fontana A, Zafferri V, Panza F, Fiduccia P, Basso U, et al. Development of an oncological-multidimensional prognostic index (Onco-MPI) for mortality prediction in older cancer patients. *Journal of Cancer Research and Clinical Oncology.* 2016;142(5):1069-77.
11. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *Journal of Clinical Oncology.* 2007;25(14):1824-31.
12. Verweij NM, Hamaker ME, Zimmerman DD, van Loon YT, van den Bos F, Pronk A, et al. The impact of an ostomy on older colorectal cancer patients: a cross-sectional survey. *International Journal of Colorectal Disease.* 2017;32(1):89-94.
13. Lai P, Sud S, Zhang T, Asmis T, Wheatley-Price P. Palliative chemotherapy in advanced colorectal cancer patients 80 years of age and older. *Current Oncology (Toronto, Ont).* 2016;23(3):144-53.
14. Reynolds J, Chamberland-Tremblay A, Herrington JD, Munoz Maldonado Y, Wong L. High- versus low-dose leucovorin in the modified FOLFOX6 regimen for first-line treatment of metastatic colorectal cancer. *Journal of Oncology Pharmacy Practice.* 2017;23(3):173-8.
15. Hamaker ME, Schiphorst AH, ten Bokkel Huinink D, Schaar C, van Munster BC. The effect of a geriatric evaluation on treatment decisions for older cancer patients--a systematic review. *Acta Oncologica.* 2014;53(3):289-96.
16. Verweij NM, Schiphorst A, Pronk A, Hamaker MJWJoCS. Conventional and laparoscopic colon resections in the elderly. 2015;5(2):3.
17. Puts MTE, Sattar S, Kulik M, MacDonald ME, McWatters K, Lee K, et al. A randomized phase II trial of geriatric assessment and management for older cancer patients. *Supportive Care in Cancer.* 2018;26(1):109-17.
18. Li D, Kelly C, Trent M, Fakih M, Koczywas M, Cristea M, et al. A randomized controlled trial of geriatric assessment guided multidisciplinary interventions: the first year experience. *Journal of Geriatric Oncology.* 2016;Abstract SIOG Conference:S91.

Part III.

Summary, general discussion and future perspectives

Chapter 10

Summary

This thesis has aimed to investigate which older patients with colorectal cancer (CRC) are at risk of poor surgical outcomes by exploring existing prediction tools and study patient characteristics that could quantify risk and identify patients at a high risk of adverse outcomes (**Part I**). In addition, interventions were studied designed to modify surgical risk in older patients with CRC and elderly specific outcomes were studied. Finally, the impact of Geriatric Assessment (GA) on treatment decisions in CRC was studied (**Part II**).

Part I. Risk quantification

Risk prediction models have been developed to provide prognostic information and support treatment decisions. In **Chapter 2,** existing risk prediction models for adverse outcomes of CRC surgery were systematically reviewed and usefulness and accuracy were assessed to enable preoperative prediction in older patients. A relatively large number of prediction models have been developed, the oldest dating back to 2004. Of 26 models identified, ten predicted mortality and seven anastomotic leakage. None of the models was developed to estimate outcomes for the highly heterogeneous older population nor did these models address outcomes such as quality of life or functional decline. The inclusion of peri-operative predictors limits the use of several models for preoperative decision making. Some models needed further validation because they carried a relatively high risk of bias. Others needed updates because operative risk factors and quality of care may have changed over time, thus affecting a model's accuracy.

In **Chapter 3**, we assessed the Identification of Seniors at Risk for Hospitalised Patients (ISAR-HP) and Geriatric 8 (G8) screening tools for their prognostic value for postoperative complications and mortality in a real-life CRC population over the age of 70 years. Patients screened "at risk of frailty" with the ISAR-HP were at increased risk for 30-day complications including cardiopulmonary complications, readmission and six-month mortality. In contrast, patients identified as "at risk of frailty" with the G8 screening tool, did not have a higher risk of poor surgical outcomes However, patients that were at risk of frailty with both screening tools had the highest risk of complications. Therefore, ISAR-HP and G8 combined had the strongest predictive value for complications and mortality.

10

In **Chapter 4**, functional dependency, previous falls, undernutrition and risk of delirium were investigated for their prognostic value for 30-day morbidity and overall survival (OS) after elective CRC surgery. Using a population-based multi-centre database, we assessed these preoperatively collected geriatric characteristics as predictors for poor surgical outcomes. ADL dependency, experiencing at least one fall in the last 6 months, and being at risk of delirium were associated with a higher likelihood of overall mortality, even after adjustment for age, gender, tumour stage, and American Society of Anesthesiologists (ASA) Physical Status classification. We showed that compared to low-risk patients, high-risk patients (> 2 out of 4 impairments) had more postoperative complications and worse OS; almost 50% of these patients died within three years of surgery. These geriatric predictors also showed associations with the need for additional care after surgery. We have suggested that these geriatric predictors could be useful in a prediction model designed specifically for older patients.

In **Chapter 5** we studied skeletal muscle mass and density as a prognostic factor for poor outcomes of CRC surgery. In an observational study among patients with non-metastatic CRC, lumbar skeletal muscle mass and density were measured from a single CT-image. We found very little prognostic value in lumbar skeletal muscle mass and density. Previously published cut-off values for radiologically assessed low skeletal muscle mass and density did not apply to older patients and did not discriminate between patients at risk and not at risk. These conclusions were not altered when skeletal muscle mass and density were analysed by gender-specific quartiles or as a linear measure. We have shown that physical functioning reflected by the use of a mobility aid has better potential as a predictor for complications and survival then a single CT-measurement of muscle mass or muscle density. Radiologically assessed muscle mass cannot be used as a prognostic marker for outcomes of CRC surgery unless age, gender and BMI specific cut-off points become available.

In **Chapter 6,** a preoperative geriatric risk prediction model is presented for severe complications after elective surgery, developed in 1088 patients with stages I-III CRC. Strong predictors were rectal cancer, gender, a history of COPD or Emphysema, a history of thromboembolic events (Deep Venous Thrombosis or Pulmonary Embolism), functional dependency, the use of a mobility aid, a previous delirium and polypharmacy. Age alone was no longer a predictor in this cohort. High-risk patients had up to 30% predicted risk for severe complications. Estimated discrimination of our model was AUC 0.65 by using the LASSO regression analysis method. Internal validation contributed to the reliability of the model, but external validation including assessment of calibration is warranted before further use of this model to guide preoperative counselling and possible allocation of interventions.

Part II. Risk modification

In **Chapter 7,** we have shown that it was feasible to implement a prehabilitation and rehabilitation program for patients aged 75 years and older and that such a program may contribute to lower complications and reduces length of hospital stay. No clear benefit was shown for other postoperative outcomes. Dedicated multidisciplinary care seems the key attributor to favorable outcomes of CRC surgery in elderly patients.

The topic of **Chapter 8** has been Health-Related Quality of Life (HRQoL) and functional dependency after CRC surgery among patients treated in an oncogeriatric care setting. A longitudinal follow-up study was designed for older CRC patients, with baseline and follow-up questionnaires (at 3, 6 and 12 months). Older patients with mild to moderate functional dependency (Barthel Index < 19) were shown to have a lower baseline quality of life compared to functionally independent patients before surgery including more symptoms (fatigue and pain) and lower perceived global health. During 1-year of follow-up, mean scores on the function and symptom scores improved in functionally dependent patients and remained at the preoperative level for functionally independent patients. Therefore, CRC surgery embedded in a geriatric-oncological care model may have a positive impact on HRQoL in older functionally dependent cancer patients.

Chapter 9 addresses the effect of a Comprehensive Geriatric Assessment (CGA) on treatment decisions. Older patients with stage I-IV CRC referred for geriatric consultation between 2013-2015 were included. In 93% of patients, one or more geriatric impairments were found. A “more intensive treatment” option was recommended in 69% of patients and in 31% a “less intensive treatment” option. CGA can lead to changes in the treatment plan for individual cases, also in older CRC patients.

Chapter 11

General discussion and future perspectives

Selecting the appropriate cancer treatment for older patients with cancer remains challenging.

Personalised treatment recommendations require the evaluation of patient-, disease- and treatment characteristics in combination with individual patient's needs, values, and preferences to weigh gain and burden of treatment and disease. Ideally, more personalised outcome information regarding the risk of postoperative complications and mortality, but also regarding postoperative physical functioning and quality of life is available to support treatment advice.

Part I of this thesis addresses methods to quantify the risk of postoperative complications for older patients with non-metastatic CRC cancer. We have incorporated our findings into a new prediction model for severe complications of surgery. In **Part II** of this thesis, we have studied interventions designed to modify the risk for poor surgical outcomes in this patient group.

In this chapter, implications for future research (prognostic research, body composition research and prehabilitation research) and clinical practice (pre- and postoperative care) are discussed, and an adapted care pathway for older non-metastatic CRC patients is proposed.

Implications for future research

Prognostic Research

Prognostic research can provide tools for personalised outcome information. However, the implementation of these tools in clinical practice, requires critical evaluation. To this purpose, future prediction model studies should systematically use the TRIPOD guidelines to allow critical assessment of a model's applicability, bias performance. For performance assessment, discrimination as well as calibration measures need to be reported, and external validation should be available before considering implementation into clinical practice.[1]

Using these guidelines, we concluded that most prediction models are not useful for older patients with CRC (Chapter 2). Good discrimination does not always mean there is proper calibration. As shown in Chapter 2, many prediction models for outcomes of CRC surgery, have acceptable discrimination but unsatisfactory calibration. As a consequence, the use of poorly calibrated models that overestimate individual risks could lead to worse outcomes compared to not using a prediction model.[2] Moreover, many prediction models showed unsatisfactory performance in validation studies (Chapter 2). In addition, prediction models for outcomes of CRC need a periodic update owing to possible changes of the population and certain changes in therapy.[3] This applies to surgical CRC prediction models, because of the many efforts made to improve outcomes of colorectal cancer surgery for patients (i.e. auditing, ERAS including laparoscopic surgery, neoadjuvant treatment and wait-and-see for rectal cancer and selective use of defunctioning stoma).[4,5] For the GerCRC model from Chapter 6, we initiated validation including evaluation of its calibration, and this will be completed in 2020.

With regard to the field of surgical oncology, we have shown that gender, comorbidity, physical functioning (need for ADL assistance and use of a mobility aid), cognitive functioning (previous delirium) and tumour location are useful predictors for postoperative complications and have incorporated this in the GerCRC model. The GerCRC model underlines the importance of taking geriatric- predictors into account when conducting prognostic research in the field of surgical oncology. It is possible that the discriminatory value of the GerCRC model could be enhanced with other geriatric parameters or physical performance measures such as the need for help with Instrumental Activities of Daily Living (IADL) or physical performance measures such as walking speed or grip strength. A planned validation study will demonstrate whether further improvement of the performance of the GerCRC model is needed. Hence this would require fewer patients (and events) to investigate.[6] As highlighted in Chapter 2, the geriatric screening tool G8 alone is not useful as a prognostic tool for complications of CRC surgery.

Body composition research

Previously published cut-off values for radiologically assessed low skeletal muscle mass and density do not apply to older patients. We have shown that physical functioning reflected by the use of a mobility aid has better potential as a predictor for complications and survival then a single CT-measurement of muscle mass or muscle density. The big challenge for body composition research is determining interpersonal variation and pathological loss of muscle mass and quality[7] and thereby also determining age, gender and BMI specific cut-off points. Also, further standardisation of assessment methods and terminology could advance this field.[8] For now, research should focus on these challenges and clinicians should rely on clinical measures such as physical functioning to provide prognostic information to older patients.

Health-related quality of life research

For older patients, retaining independence and health-related quality of life (HRQoL) are important outcomes of treatment and are ideally discussed when deciding upon cancer treatment.[9,10] Although patients with mild to moderate functional dependency had a worse quality of life before CRC surgery, improvement in global health (QL), as well as on several functioning and symptom scales, were seen up to 6 months after surgery (Chapter 8). The observed improvement in quality of life after surgery could be related to the therapeutic effect of surgery or the effect of the oncogeriatric care they received. However, some older patients experience a persistent decrease in physical performance and lower HRQoL after CRC surgery. In our study cohort, this was around 10% of all patients (Chapter 8). Longitudinal QoL studies thus provide valuable information for patients and healthcare givers. Therefore future research in CRC could shift its focus from standard outcome measures such as complications and mortality to more patient-centred goals such as quality of life and postoperative physical functioning.

Standard measurement of pre- and postoperative physical functioning helps to determine which older patients lack resilience and do not recover to their preoperative level of functioning. In 256 older breast cancer patients receiving chemotherapy, 42% of patients experienced some form of functional decline; but almost 50% recovered after 12 months. Identifying the non-resilient patients and determining risk factors for non-resilience would be an advancement in the field of CRC care. This would also provide targets for interventions that could reduce the negative impact of CRC treatment for these patients.

Prehabilitation research

Improving a patient's resilience before surgery using prehabilitation has gained interest in cancer surgery to improve outcomes and has been investigated in Chapter 7. At present, there is still no consensus on which elements to include in a prehabilitation program. Most prehabilitation programs included strength and endurance training combined with sufficient dietary intake (proteins).[11] However, due to the considerable heterogeneity of the prehabilitation programs and the heterogeneity of patients under scrutiny, sound interpretation of the study results is difficult.[11] In addition, the impact of prehabilitation on outcomes such as quality of life is scarce or even absent, and this needs further investigation. Prehabilitation as a preventive strategy for delirium in older frail patients is of interest and was recently investigated, however evidence is still limited.[12]

One of the largest challenges for prehabilitation research is who to select for such a program. Better patient selection for prehabilitation is needed, because of the limited effect shown in a non-selective population.[11,13] However, there are no optimal selection methods yet. Patient selection based on age (≥75 years) and patient motivation, was not shown to significantly improve outcomes (Chapter 7). However, selection based on ASA score III-IV (severe systemic disease or life-threatening disease) of patients scheduled for major abdominal surgery (50% CRC surgery) and allocated prehabilitation resulted in 20% fewer complications in comparison to standard treatment.[14]

However, we showed that ASA score alone is not the best selection method for older patients (Chapter 4, 6), and more patients might benefit from prehabilitation when better selection criteria are used. A trial is underway for a 4-week training program with selection based on the Clinical Frailty Scale.[15,16] However, the clinical frailty score does not take into account important prognostic factors such as tumour characteristics or comorbidity,[17,18] limiting its use for a large number of patient. Therefore, the GerCRC model, which also uses tumour and comorbidity, might serve as a possible instrument to select patients for prehabilitation (after validation). Ideally, a Net Benefit (NB) of the prediction model is calculated that compares prediction model based treatment with default policies of ‘’treat none” or ‘’treat all”.[6]

Implications for clinical practice

Since 2014, a (Comprehensive) Geriatric Assessment of high-risk patients with CRC has been mandatory in the Netherlands.[19] This is in addition to the standard evaluation of the four geriatric domains: undernutrition, physical impairment, fall risk, and risk for delirium that are part of the nationwide implemented Dutch National Patient Safety Program ("veiligheid management systeem" or "VMS")[20] and the national guideline for detection of undernutrition for all patients with CRC. These efforts to improve (postoperative) outcomes of CRC patients also coincide with ERAS.

Where Geriatric Assessment (GA) is used to identify patients at risk of geriatric deficits, a comprehensive GA (CGA) can confirm or negate the presence of geriatric impairments, and subsequently direct interventions aimed at improving outcomes, the discussion of treatment goals and treatment preferences to improve quality of life, and improving treatment adherence.[21,22] Interventions initiated by the VMS program include a comprehensive nutritional evaluation of high-risk patients, physiotherapy in case of ADL dependence of previous falls, and postoperative delirium prevention in high-risk patients.[20] Where geriatric screening and assessment are usually performed before treatment decisions are made, in current clinical practice the VMS is assessed on the day of hospital admission. Concurrently, the Enhanced recovery after surgery (ERAS) guideline also has been implemented in many Dutch hospitals. To illustrate the current clinical practice, Figure 1 shows a care pathway for older CRC patients used in multiple Dutch Hospitals.

Preoperative colorectal cancer care

Disadvantages of the current clinical practice with geriatric screening and assessment, VMS and preoperative care components of ERAS, are the overlap of these methods with respect to detection of (geriatric) deficits and introduction of interventions. Additionally, timing of screening and interventions (including CGA) can be optimised. The resources needed for a CGA are still scarce in many hospitals, or even non-existing. In current practice, screening tools are used to select patients for CGA, but especially for the G8, the low specific results in an unnecessary referral for CGA. In addition, patients with only an impairment of single geriatric domains might be managed accordingly, without the need for a CGA. A CGA is then preserved for high-risk patients who may benefit the most (multiple geriatric impairments) or patients with metastatic disease where alternative therapy or even best-supportive care is considered.

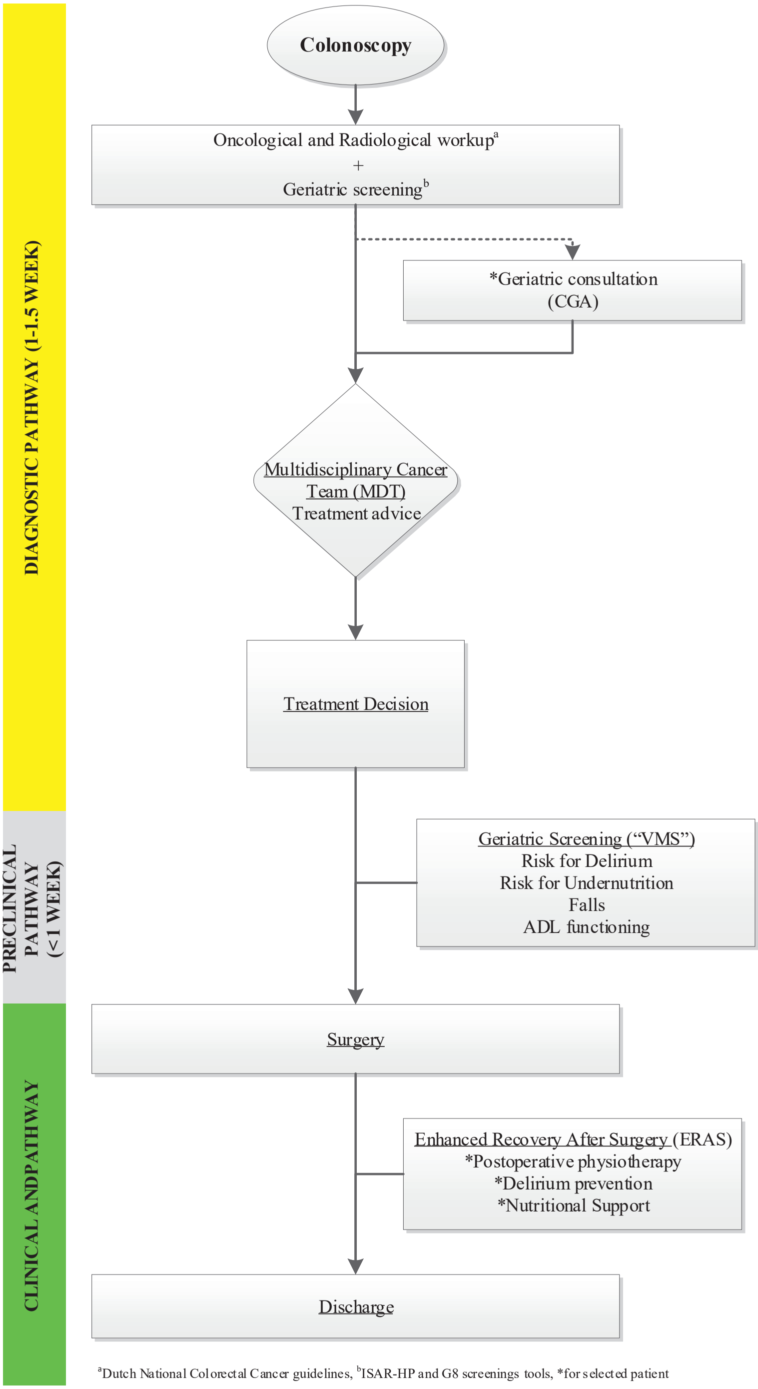


Figure 1 An example of a care pathway for older patients (≥70 years) with CRC, that includes geriatric screening and assessment and vms

Within a care pathway for older patients with CRC, a risk model could replace current geriatric screening and CGA assessment for most patients. However, there are two major additions to such a care pathway: the risk for delirium should be assessed preoperatively because of the association of delirium with postoperative complications (Chapter 3) including a longer hospital stay, in-hospital mortality23 and reduced OS,24 and the strong evidence that (non-pharmacological) multicomponent delirium prevention is useful for hospitalised patients.25 Furthermore, because of the association between undernutrition and mortality,26 preoperative nutritional status should be assessed as soon as possible after CRC diagnosis to maximise the efficacy of nutritional interventions. Screening of undernutrition on the day of surgery then becomes obsolete. Moreover, pulmonary optimisation can be achieved for patients that smoke by advocating smoking cessation. Hence, smoking cessation for even four weeks before surgery can reduce the risk of wound-healing complications.27

Information from a risk model should then be presented during the MDT meeting. Theoretically, the advantage of using prognostic information during an MDT, is that it creates awareness among healthcare professionals of the risks of surgical treatment. The prognostic information can also be used in the decision-making process later on. Figure 2 depicts an example of a possible care pathway where our findings and suggestions are incorporated.

Postoperative colorectal cancer care

In addition to preoperative interventions, we should also give more attention to postoperative interventions that also might improve outcomes of CRC surgery. Reduction of postoperative immobilisation using ERAS and postoperative physiotherapy are well established and have shown to be useful for reducing complications and length of hospital stay.[28-30] However, we do not advocate the implementation of prearranged rehabilitation into standard care for CRC; in contrast to the rehabilitation program from Chapter 7. The recent advancements in CRC care have likely contributed to the further shortening of the length of hospital stay and a reduction in complications, limiting the necessity of such a program.[31] However, postoperative delirium preventive measures and early mobilisation can be initiated after screening (VMS) by the treating physician. In high-risk older patients, a multidisciplinary approach with geriatric co-management might be an additional strategy of further reducing postoperative complications (including delirium) and shortening the length of hospital stay of hospital stay.[32]

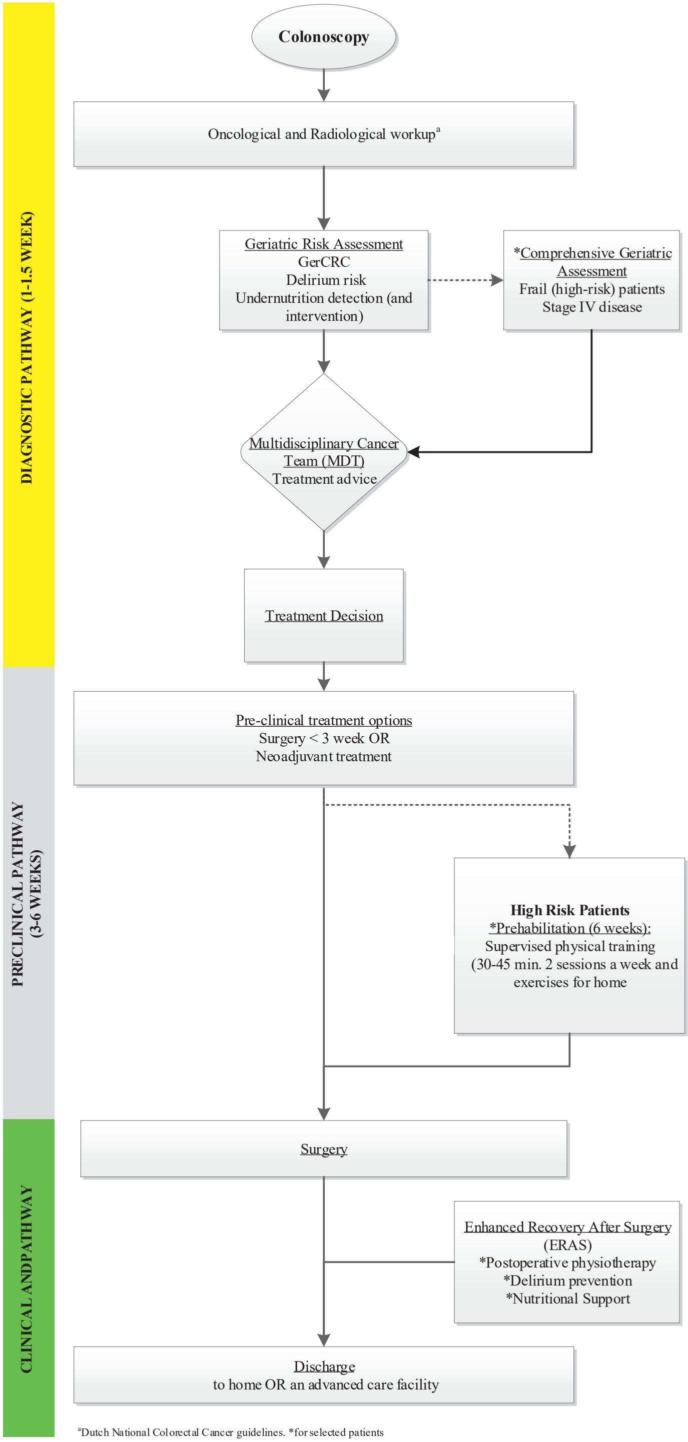


Figure 2 Concept care pathway for patients ≥70 years with colorectal cancer

A final suggestion for improving pre-and postoperative care for older patients is concerning the role of the Dutch ColoRectal Audit (DCRA) in this process. Audit date from the DCRA has been an important data source for research and has itself shown to be useful for quality improvement and reducing health care cost.[33,34] Therefore, we also propose that the DCRA from now on should include pre- and postoperative geriatric parameters, including physical functioning, to provide more opportunities for research. As more than 50% of patients in this registry is ≥ 70 years, it seems time to adopt initiatives such as the American College of Surgeons (ACS) geriatric audit pilot where standard preoperative geriatric data were collected for all older patients in this database.[35]

Conclusion

Improved risk assessment for older CRC is possible when demographics, tumour and geriatric predictors are combined. Directing interventions for high-risk patients could ultimately lead to improved outcomes, including quality of life and functionality.

References

1. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Annals of Internal Medicine.* 2015;162(1):55-63.
2. Collins GS, de Groot JA, Dutton S, Omar O, Shanyinde M, Tajar A, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC Medical Research Methodology.* 2014;14:40.
3. Minne L, Eslami S, de Keizer N, de Jonge E, de Rooij SE, Abu-Hanna A. Effect of changes over time in the performance of a customized SAPS-II model on the quality of care assessment. *Intensive Care Medicine.* 2012;38(1):40-6.
4. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. *Colorectal Disease.* 2014;16(12):947-56.
5. Snijders HS, van den Broek CB, Wouters MW, Meershoek-Klein Kranenbarg E, Wiggers T, Rutten H, et al. An increasing use of defunctioning stomas after low anterior resection for rectal cancer. Is this the way to go? *Eur J Surg Oncol.* 2013;39(7):715-20.
6. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating.* Springer International Publishing; 2019.
7. Metter EJ, Conwit R, Tobin J, Fozard JL. Age-Associated Loss of Power and Strength in the Upper Extremities in Women and Men. *The Journals of Gerontology: Series A.* 1997;52A(5):B267-B76.
8. Williams GR, Rier HN, McDonald A, Shachar SS. Sarcopenia & aging in cancer. *Journal of Geriatric Oncology.* 2019;10(3):374-7.
9. Corner J, Wright D, Hopkinson J, Gunaratnam Y, McDonald JW, Foster C. The research priorities of patients attending UK cancer treatment centres: findings from a modified nominal group study. *British Journal of Cancer.* 2007;96(6):875-81.
10. Mohile SG, Hurria A, Cohen HJ, Rowland JH, Leach CR, Arora NK, et al. Improving the quality of survivorship for older adults with cancer. *Cancer.* 2016;122(16):2459-568.
11. Bruns ER, van den Heuvel B, Buskens CJ, van Duijvendijk P, Festen S, Wassenaar EB, et al. The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. *Colorectal Disease.* 2016.
12. Janssen TL, Mosk CA, van Hoof-de Lepper CCHA, Wielders D, Seerden TCJ, Steyerberg EW, et al. A multicomponent prehabilitation pathway to reduce the incidence of delirium in elderly patients in need of major abdominal surgery: study protocol for a before-and-after study. *BMC Geriatrics.* 2019;19(1):87.
13. O'Doherty AF, West M, Jack S, Grocott MP. Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. *British Journal of Anaesthesia.* 2013;110(5):679-89.
14. Barberan-Garcia A, Ubre M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. *Annals of Surgery.* 2017.
15. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal.* 2005;173(5):489-95.
16. McIsaac D, Saunders C, Hladkowicz E, Bryson G, J Forster A, Gagne S, et al. PREHAB study: A protocol for a prospective randomised clinical trial of exercise therapy for people living with frailty having cancer surgery. *BMJ Open.* 2018;8:e022057.
17. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Annals of Surgical Oncology.* 2012;19(8):2428-34.
18. Dekker JW, Gooiker GA, van der Geest LG, Kolfschoten NE, Struikmans H, Putter H, et al. Use of different comorbidity scores for risk-adjustment in the evaluation of quality of colorectal cancer surgery: does it matter? *European Journal of Surgical Oncology.* 2012;38(11):1071-8.

19. Nederlandse Vereniging voor Klinische Geriatrie. Behandeling kwetsbare ouderen bij chirurgie.2016; https://richtlijnendatabase.nl/richtlijn/behandeling_kwetsbare_ouderen_bij_chirurgie/colorectaal_carcinoom_preoperatieve_traject.html#tab-content-general.
20. de Rooij SE, Emmelot-Vonk MH, Evers A. *Kwetsbare ouderen.* VMS Veiligheidsprogramma; 2009.
21. van de Pol MH, Fluit CR, Lagro J, Slaats YH, Olde Rikkert MG, Lagro-Janssen AL. Expert and patient consensus on a dynamic model for shared decision-making in frail older patients. *Patient Education and Counseling.* 2016;99(6):1069-77.
22. Corre R, Greillier L, Le Caer H, Audigier-Valette C, Baize N, Berard H, et al. Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study. *Journal of Clinical Oncology.* 2016;34(13):1476-83.
23. van der Sluis FJ, Buisman PL, Meerdink M, Aan de Stegge WB, van Etten B, de Bock GH, et al. Risk factors for postoperative delirium after colorectal operation. *Surgery.* 2017;161(3):704-11.
24. Breugom AJ, van Dongen DT, Bastiaannet E, Dekker FW, van der Geest LG, Liefers GJ, et al. Association Between the Most Frequent Complications After Surgery for Stage I-III Colon Cancer and Short-Term Survival, Long-Term Survival, and Recurrences. *Annals of Surgical Oncology.* 2016;23(9):2858-65.
25. Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database of Systematic Reviews.* 2016;3:Cd005563.
26. Ramjaun A, Nassif MO, Krotneva S, Huang AR, Meguerditchian AN. Improved targeting of cancer care for older patients: a systematic review of the utility of comprehensive geriatric assessment. *Journal of Geriatric Oncology.* 2013;4(3):271-81.
27. Wong J, Lam DP, Abrishami A, Chan MTV, Chung F. Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie.* 2012;59(3):268-79.
28. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. *Cochrane Database of Systematic Reviews.* 2011(2):Cd007635.
29. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. *Clinical Nutrition.* 2010;29(4):434-40.
30. Zhuang CL, Ye XZ, Zhang XD, Chen BC, Yu Z. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: a meta-analysis of randomized controlled trials. *Diseases of the Colon and Rectum.* 2013;56(5):667-78.
31. Dutch Institute for Clinical Auditing. Jaarverlag 2015. download available from: https://dica.nl/jaarrapportage-20152016;
32. Van Grootven B, Flamaing J, Dierckx de Casterle B, Dubois C, Fagard K, Herregods MC, et al. Effectiveness of in-hospital geriatric co-management: a systematic review and meta-analysis. *Age and Ageing.* 2017;46(6):903-10.
33. de Neree Tot Babberich MPM, Detering R, Dekker JWT, Elferink MA, Tollenaar R, Wouters M, et al. Achievements in colorectal cancer care during 8 years of auditing in The Netherlands. *European Journal of Surgical Oncology.* 2018;44(9):1361-70.
34. Govaert JA, van Bommel AC, van Dijk WA, van Leersum NJ, Tollenaar RA, Wouters MW. Reducing healthcare costs facilitated by surgical auditing: a systematic review. *World Journal of Surgery.* 2015;39(7):1672-80.
35. Berian JR, Zhou L, Hornor MA, Russell MM, Cohen ME, Finlayson E, et al. Optimizing Surgical Quality Datasets to Care for Older Adults: Lessons from the American College of Surgeons NSQIP Geriatric Surgery Pilot. *Journal of the American College of Surgeons.* 2017;225(6):702-12.e1.

Appendices

Author affiliations

E. Bastiaannet	Department of Surgery, Leiden University Medical Centre, Leiden Department of Medical Oncology, Leiden University Medical Centre, Leiden
A.Y. Bijlsma	Department of Geriatric Medicine, University Medical Centre Utrecht, Utrecht
A.J. Breugom	Department of Pulmonary Medicine, Leiden University Medical Center, Leiden
T.A. Burghgraef	Department of Surgery, Meander Medisch Centrum, Amersfoort
S. de Bruin	Department of Surgery, Reinier de Graaf Gasthuis, Delft
J.W.T. Dekker	Department of Surgery, Reinier de Graaf Gasthuis, Delft
F. Erning	Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht
M. Fiocco	Department of Biomedical Sciences, Leiden University Medical Centre, Leiden Mathematical Institute, Leiden University, Leiden
M.E. Hamaker	Department of Geriatric Medicine, Diakonessenhuis, Utrecht-Zeist
D. Hultink	Department of Internal Medicine, Hagaziekenhuis, The Hague
H.A.A. Maas	Department of Geriatric Medicine, Elisabeth-Tweesteden Ziekenhuis, Tilburg
S.I. Moos	Department of Radiology, Hagaziekenhuis, The Hague
S. Oerlemans	Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht
J.E.A. Portielje	Department of Medical Oncology, Leiden University Medical Centre, Leiden

A. Pronk	Department of Surgery, Diakonessenhuis, Utrecht-Zeist
A. Schiphorst	Department of Surgery, Diakonessenhuis, Utrecht-Zeist
J.S. Schuijtemaker	Department of Geriatric Medicine, Dijklander Ziekenhuis, Hoorn
R.M.E. Slangen	Department of Gastroenterology, Hagaziekenhuis, The Hague
D.J.A. Sonneveld	Department of Surgery, Waterlandziekenhuis, Hoorn
W.H. Steup	Department of Surgery, Hagaziekenhuis, The Hague
E.W. Steyerberg	Department of Medical Statistics, Leiden University Medical Centre, Leiden
D. ten Bokkel Huinink	Department of Internal Medicine, Diakonessenhuis, Utrecht-Zeist
L.V. van de Poll-Franse	Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht Center of Research on Psychology in Somatic diseases, Department of Medical en Clinical Psychology, Tilburg University, Tilburg Division of Psychosocial Research and Epidemiology, the Netherlands Cancer Institute (NKI), Amsterdam
F.W.P. van den Berkmortel	Department of Internal Medicine, Zuyderland Medisch Centrum, Geleen-Heerlen
F. van den Bos	Department of Geriatric Medicine, Leiden University Medical Center, Leiden
J.M. van der Bol	Department of Geriatric Medicine, Reinier de Graaf Gasthuis, Delft
C.J. van Rooden	Department of Radiology, Hagaziekenhuis, The Hague
N.M. Verweij	Department of Radiology, Amsterdam University Medical Centre, Amsterdam
C.A. Wientjes	Department of Gastroenterology, OLVG, Amsterdam

Nederlandse samenvatting

Darmkanker is met name een ziekte van de oudere patiënt en voor de grootste groep patiënten is chirurgie de aangewezen behandeling. Echter, oudere patiënten hebben meer risico op complicaties, waardoor zij mogelijk minder goed herstellen van een operatie. In deel 1 van dit proefschrift wordt bestudeerd welke ouderdomskenmerken een verhoogd complicatie risico geven, om zo voor oudere patiënten een betere risico-inschatting te kunnen maken. In Nederland zijn er verschillende initiatieven geweest om het operatief risico te verkleinen voor oudere patiënten. In deel 2 van dit proefschrift worden de resultaten van een preoperatief trainingsprogramma beschreven welke tot doel had het postoperatief herstel van oudere patiënten te versnellen en het aantal complicaties te beperken. Daarnaast wordt de kwaliteit van leven van oudere patiënten die behandeld zijn in een oncologisch-geriatrisch zorgpad bestudeerd evenals de invloed van een CGA (Comprehensive Geriatric Assessment) op behandelbeslissingen.

Deel I. Risico inschatting

Risicomodellen kunnen worden gebruikt om een risico-inschatting te maken van een behandeling voor een individuele patiënt. In **hoofdstuk 2** worden bestaande risicomodellen voor complicaties van chirurgische behandeling systematisch beoordeeld op bruikbaarheid en nauwkeurigheid voor de oudere patiënt. Daarbij wordt ook gekeken of deze modellen voldoende bruikbaar zijn om preoperatieve besluitvorming te ondersteunen.

Er bleken in totaal 26 risicomodellen te zijn ontwikkeld, echter waren een deel van deze risicomodellen gedateerd of kon de betrouwbaarheid door gebrek aan validatie niet goed worden ingeschat. In een deel van de risicomodellen werden risicofactoren gebruikt die pas tijdens of na een operatie bekend worden, waardoor deze modellen niet bruikbaar zijn voor preoperatieve besluitvorming. Door deze beperkingen concludeerden wij dat de bruikbaarheid en nauwkeurigheid van de huidige modellen voor ouderen beperkt is. In slechts een klein aantal modellen werd gebruik gemaakt van verouderingskenmerken. Door verouderingskenmerken op te nemen in preoperatieve risicomodellen voor oudere darmkankerpatiënten vallen deze modellen wellicht te verbeteren.

In **hoofdstuk 3** worden de geriatrische screeningsinstrumenten ISAR-HP en G8 beoordeeld op hun prognostische waarde voor postoperatieve complicaties. De ISAR-HP en G8 worden nu al standaard gebruikt om patiënten te screenen die mogelijk profijt kunnen hebben van verdere geriatrische evaluatie (CGA). Patiënten die met de ISAR-HP als mogelijk “kwetsbaar” werden aangemerkt, bleken ook daadwerkelijk meer postoperatieve complicaties te hebben, waaronder ook meer heropnames na een operatie en een hogere sterftekans. Daarentegen hadden patiënten die met de G8-screeningtool werden geïdentificeerd als mogelijk “kwetsbaar”, niet méér kans op complicaties. Patiënten die door beide screeningsinstrumenten geïdentificeerd werden als “kwetsbaar” hadden echter het hoogste risico op complicaties. Daarmee is zowel de ISAR-HP als de ISAR-HP gecombineerd met de G8 bruikbaar om een preoperatieve risico-inschatting te maken.

De ziekenhuisopname na operatie is voor kwetsbare oudere patiënten ook risicovol vanwege hun verhoogde kans op ondervoeding, delier of vallen. Als onderdeel van het VMS Veiligheidsprogramma worden in Nederlandse ziekenhuis daarom standaard geriatrische gegevens verzameld met als doel vroege herkenning en het voorkomen van deze onbedoelde schade en daarmee het verbeteren van de uitkomsten na een ziekenhuisopname. Onderwerp van **hoofdstuk 4** was of deze standaard preoperatief verzamelde geriatrische informatie ook risicofactoren zijn voor postoperatieve complicaties en vroegtijdig overlijden na een darmkanker operatie. Patiënten met één of meer van deze risicofactoren hadden hoger risico op postoperatieve complicaties en bijna 50% van de patiënten met drie of meer risicofactoren was na drie jaar niet meer in leven. Deze geriatrische onderdelen van de VMS Veiligheidsprogramma bieden dus relevante prognostische informatie en zijn mogelijk bruikbaar voor een preoperatief risicomodel.

In patiënten met onder andere uitgezaaide darmkanker was eerder gebleken dat ook spiermassa en spierdichtheid (als maat voor spier kwaliteit) risicofactoren zijn voor het krijgen van een postoperatieve complicatie. **Hoofdstuk 5** onderzoekt daarom of spiermassa en spierdichtheid ook voorspellers zijn voor slechte uitkomsten bij oudere darmkanker patiënten met niet-uitgezaaide darmkanker. Het blijkt echter dat spiermassa en spierdichtheid welke op een CT-scan is gemeten, weinig voorspellende waarde heeft voor deze groep oudere patiënten en daarom nu niet bruikbaar is voor de klinische praktijk. Wij zagen dat het preoperatief gebruik van functionele hulpmiddelen, zoals een wandelstok, echter meer potentie heeft als voorspeller voor complicaties.

In **hoofdstuk 6** wordt een nieuw geriatrisch risicomodel gepresenteerd voor ernstige postoperatieve complicaties welke is gebaseerd op de eerdere bevindingen uit voorgaande hoofdstukken. Sterke preoperatieve voorspellers in dit model zijn de locatie van de tumor, geslacht, een voorgeschiedenis van COPD of emfyseem, een voorgeschiedenis van trombose, functionele afhankelijkheid, het gebruik van een loophulpmiddel, een verhoogd risico op een delier en polyfarmacie (het gebruik van 5 of méér medicijnen). Patiënten met meerdere risicofactoren hebben meer dan 30% kans op een ernstige complicatie. Dit is bijna 20% meer dan patiënten zonder een van deze risicofactoren. Externe validatie van dit model is echter nog wel noodzakelijk voordat dit model kan worden gebruikt in de klinische praktijk.

Deel II. Interventies

Hoofdstuk 7 laat zien dat het haalbaar is om een trainings- en rehabilitatie-programma te implementeren in een zorgpad voor oudere patiënten. Een dergelijk zorgpad draagt mogelijk bij aan het verder verminderen van het aantal complicaties en het verkorten van de opnameduur. Welke patiënten hier het meest van profiteren moet echter nog verder worden onderzocht.

In **hoofdstuk 8** beschrijft de kwaliteit van leven (HRQoL) in relatie tot functionele zelfstandigheid van oudere darmkanker patiënten die werden behandeld in een oncologisch-geriatrisch zorgpad. In een longitudinale studie werden meerdere “kwaliteit van leven” vragenlijsten afgenomen bij oudere patiënten, zowel voor start van chirurgische behandeling als na afloop (3, 6 en 12 maanden). Minder zelfstandigheid voor de operatie kan gepaard gaan met een slechtere kwaliteit van leven en met meer klachten zoals vermoeidheid en pijn. Echter, bij deze groep minder zelfstandige patiënten, verbeterde de gemiddelde kwaliteit van leven na operatie duidelijk. Op basis van deze resultaten concludeerden wij dat darmkanker chirurgie bij oudere patiënten, als onderdeel van een oncologisch-geriatrisch zorgpad, een positieve invloed heeft op kwaliteit van leven van oudere darmkanker patiënten.

Hoofdstuk 9 beschrijft het effect van een CGA op behandelbeslissingen van oudere kankerpatiënten. Bij 93% van de in deze studie geïncludeerde patiënten werden één of meer geriatrische afwijkingen gevonden en in de meerderheid van patiënten werden hiervoor aanvullende behandelsuggesties gedaan. In 32% van de patiënten verschilde het behandeladvies van dat van de verwijzend specialist, maar in de meerderheid van de gevallen werd dit advies wel opgevolgd. Wij concludeerden dat volledige geriatrische evaluatie, ook bij oudere darmkanker patiënten, kan leiden tot wijzigingen in het behandelplan.

Conclusie

Omdat geriatrische kenmerken voorspellend zijn voor postoperatieve uitkomsten, vragen goed geïnformeerde behandelbeslissingen om geriatrische kennis. Preoperatieve interventies in een oncologisch-geriatrisch zorgpad kunnen mogelijk bijdragen aan een beter postoperatief herstel, mits er een goede selectie van deze patiënten plaatsvindt.

List of publications

Snijders BMG, Emmelot-Vonk MH, <u>Souwer ETD</u>, Kaasjager HAH, van den Bos F. Prognostic value of screening instrument based on the Dutch national VMS guidelines for older patients in the emergency department. *European Geriatric Medicine*. 2020. Sep 1. Online ahead of print

<u>Souwer ETD</u>, Bastiaannet E, Steyerberg EW, Dekker JT, van den Bos F, Portielje JEA. Risk prediction models for postoperative outcomes of colorectal cancer surgery in the older population - a systematic review. *Journal of Geriatric Oncology*. 2020 May 12:S1879-4068(19)30412-6. Online ahead of print

<u>Souwer ETD</u>, Moos SI, van Rooden CJ, et al. Physical performance has a strong association with poor surgical outcome in older patients with colorectal cancer. *European Journal of Surgical Oncology*. 2020;46(3):462-469.

<u>Souwer ETD</u>, Oerlemans S, van de Poll-Franse LV, van Erning FN, van den Bos F, Schuijtemaker JS, et al. The impact of colorectal surgery on health-related quality of life in older functionally dependent patients with cancer - A longitudinal follow-up study. *Journal of Geriatric Oncology*. 2019;10(5):724-32.

<u>Souwer ETD</u>, Hultink D, Bastiaannet E, Hamaker ME, Schiphorst A, Pronk A, et al. The Prognostic Value of a Geriatric Risk Score for Older Patients with Colorectal Cancer. *Annals of Surgical Oncology*. 2019;26(1):71-8.

<u>Souwer ETD</u>, Verweij NM, van den Bos F, Bastiaannet E, Slangen RME, Steup WH, et al. Risk stratification for surgical outcomes in older colorectal cancer patients using ISAR-HP and G8 screening tools. *Journal of Geriatric Oncology*. 2018;9(2):110-4.

<u>Souwer ETD</u>, Bastiaannet E, de Bruijn S, Breugom AJ, van den Bos F, Portielje JEA, et al. Comprehensive multidisciplinary care program for elderly colorectal cancer patients: "From prehabilitation to independence". *European Journal of Surgical Oncology*. 2018;44(12):1894-900.

A

Verweij NM, Souwer ETD, Schiphorst AHW, Maas HA, Portielje JEA, Pronk A, et al. The effect of a geriatric evaluation on treatment decisions for older patients with colorectal cancer. *International Journal of Colorectal Disease*. 2017;32(11):1625-9.

Schulkes KJG, Souwer ETD, van Elden LJR, Codrington H, van der Sar-van der Brugge S, Lammers JJ, et al. Prognostic Value of Geriatric 8 and Identification of Seniors at Risk for Hospitalized Patients Screening Tools for Patients With Lung Cancer. *Clinical Lung Cancer*. 2017;18(6):660-6 e1.

Schulkes KJ, Souwer ETD, Hamaker ME, Codrington H, van der Sar-van der Brugge S, Lammers JJ, et al. The Effect of A Geriatric Assessment on Treatment Decisions for Patients with Lung Cancer. *Lung*. 2017;195(2):225-31.

Blaauw J, Souwer ETD, Coffeng SM, Smit AJ, van Doormaal JJ, Faas MM, et al. Follow up of intima-media thickness after severe early-onset preeclampsia. *Acta Obstetricia et Gynecologica Scandinavica*. 2014;93(12):1309-16.

Souwer ETD, Blaauw J, Coffeng SM, Smit AJ, Van Doormaal JJ, Faas MM, et al. Decreased arterial elasticity in formerly early-onset preeclamptic women. *Acta Obstetricia et Gynecologica Scandinavica.* 2011;90(7):797-801.

Coffeng SM, Blaauw J, Souwer ETD, Rakhorst G, Smit AJ, Graaff R, et al. Skin autofluorescence as marker of tissue advanced glycation end-products accumulation in formerly preeclamptic women. *Hypertension in Pregnancy*. 2011;30(2):231-42.

Curriculum Vitae

Esteban Thomas Daniël Souwer was born on 3 May 1985 in Zevenaar and has two younger siblings. In 2003, Daniël graduated from het Nieuwe Lyceum in Bilthoven and started his medical school at Rijksuniversiteit Groningen. During his study, he became interested in medical education and research. During medical school he fulfilled several student assessor positions. Between 2010 and August 2013, he worked as a non-training resident at the Intensive Care Unit of Haaglanden Medisch Centrum The Hague and the Emergency Department of Vlietland Ziekenhuis. In September 2013, he started his residency Internal Medicine at Hagaziekenhuis in The Hague under supervision of dr. van Aken. In September 2016, he started working on his PhD thesis within the field of geriatric oncology under the supervision of prof. dr. J.E.A. Portielje, dr. F. van den Bos and dr. J.W.T. Dekker. The results of his studies were presented at several national and international conferences. During his residency and PhD, he was chair of the resident committee of Hagaziekenhuis and chair of the Young Network of Samenwerkende Topklinische opleidingsZiekenhuizen (STZ). Currently, Daniël lives in Haarlem and resumed his residency Internal Medicine at the Leiden University Medical Center under supervision of prof. de Fijter. His fellowship medical oncology will commence in January 2021.

Dankwoord

Prof. dr. Portielje en dr. van den Bos, beste Johanneke en Frederiek, jullie zijn onmisbaar geweest in mijn ontwikkeling als wetenschapper en medisch professional. Zeer veel dank voor jullie begeleiding, vertrouwen, geduld en scherpzinnigheid.

Dr. Dekker, beste Jan Willem, dank voor de prettige samenwerking en jouw chirurgische begeleiding.

Dr. Bastiaannet, beste Esther, jij maakte ons onderzoeksteam compleet. Dank voor al je hulp en de fijne samenwerking tot nu toe.

Dit proefschrift was ook niet tot stand gekomen zonder de begeleiding, hulp, steun en bevlogenheid van medeauteurs, kamergenoten, mede-wetenschappers en wetenschapsondersteuners, IKNL (onderzoekers), de afdeling dagbehandeling en het wetenschapsbureau van het Hagaziekenhuis, de afdeling Medische Oncologie van het LUMC, (oud) collega's, Ferrand en Marijke op ten Noort, familie en vrienden.

Samen maakt altijd meer. D^2

A