Colorectal cancer treatment in an ageing world

Technical advances, treatment decisions and multidisciplinary care

Anandi H.W. Schiphorst

Colorectal cancer treatment in an ageing world
Technical advances, treatment decisions and multidisciplinary care

Thesis, Faculty of Medicine, University Utrecht, the Netherlands,
with a summary in Dutch
Proefschrift, Medische faculteit, Universiteit Utrecht,
met een samenvatting in het Nederlands

ISBN/EAN: 978-90-393-6270-9

Financial support for this thesis was kindly provided by: Aart Huisman Stichting, Maatschap chirurgen Diakonessenhuis, Maatschap interne geneeskunde/MDL/klinische geriatrie Diakonessenhuis, ABNAMRO, Boehringer Ingelheim, Chipsoft, Coloplast, Covidien, Dansac, Diakademie Diakonessenhuis, Erbe, Excen, iMove Medical, Medireva, Olympus Nederland BV, Quincunx, Roche, Takeda, Welland.

Cover: Still reading by Pedro Ribeiro Simões
Layout: Naomi G.H.M. Schiphorst
Print: Gildeprint, the Netherlands

Colorectal cancer treatment in an ageing world

Technical advances, treatment decisions and multidisciplinary care

Behandeling van colorectaal carcinoom in een verouderende wereld
Technische ontwikkelingen, behandelkeuzes en multidisciplinaire zorg
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 19 februari 2015 des middags te 2.30 uur

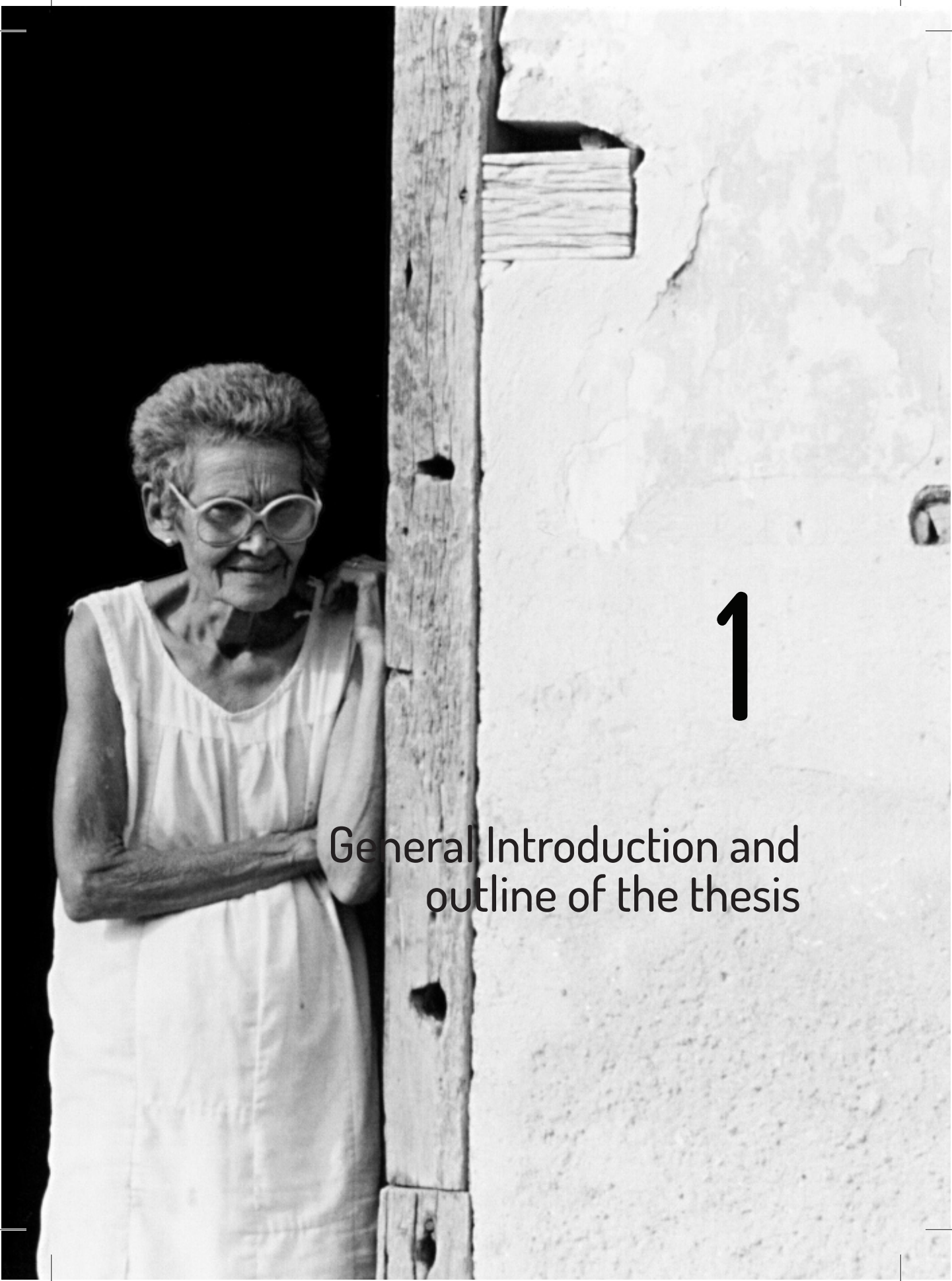
door

Anandi Hendrica Wilhelmina Schiphorst
geboren op 23 mei 1980 te Heerlen

Promotor:	Prof.dr. I.H.M. Borel Rinkes
Copromotoren:	Dr. A. Pronk
	Dr. M.E. Hamaker

Voor mijn ouders

photo: Old Woman by Chris Goldberg



1

General Introduction and outline of the thesis

Background

Colorectal cancer is currently the third most common malignancy in the Netherlands and its incidence has almost doubled in the last twenty years (Figure 1).[1] Concurrent with the rise in global life expectancy and ageing of the population, the number of older patients with newly diagnosed colorectal cancer has increased greatly in the last decade. These elderly patients currently account for the majority of patients presenting with colorectal malignancies.[1]

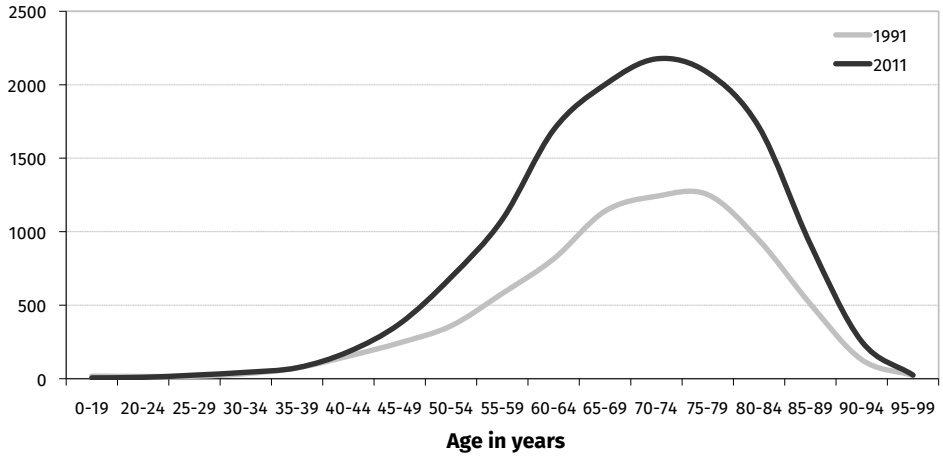


Figure 1. Incidence of colorectal cancer in the Netherlands, www.cijfersoverkanker.nl.[1]

Surgery remains the cornerstone of therapy for colorectal cancer but it comes with a considerable risk of treatment-related morbidity and mortality, especially in elderly patients who are more prone to adverse events following colorectal resection.[2] When complications occur, these patients fare significantly worse and suffer from excess mortality-rates throughout the first year after surgery.[3,4] Only once they live through the first postoperative year, does cancer-specific survival become equal for younger and elderly patients.[4]

Over the past decades, colorectal treatment modalities have made an enormous leap in technological development. Minimally invasive surgery has gained wide acceptance in a variety of indications for abdominal surgery and appears to result

in pain reduction, decreased blood loss and faster recovery.[5-7] However, to date, it is unclear if older patients will benefit as much as younger patients from technical advances in the treatment of colorectal cancer.
The paucity of evidence for the effectiveness of (surgical) therapy in elderly colorectal cancer patients, leaves questions regarding their optimal treatment strategy unanswered. Guidelines on colorectal cancer are based on studies that have generally excluded elderly and those with comorbidities.[8,9] Moreover, ageing is an individual process that comes with a wide variety of health issues, functional impairments, loss of physical reserves and geriatric conditions.[10] As a result, treatment recommendations for younger, fit patients cannot automatically be extrapolated to the heterogeneous elderly population. Therefore, the decisions on optimal management for the growing number of elderly colorectal cancer patients can pose significant challenges to cancer specialists. Collaboration with geriatricians is increasingly being sought to optimise the decision-making process. However, such initiatives are complicated by the lack of elderly-specific data from clinical trials or even observational cohort studies on which to base such decisions.

Aim and outline of the thesis

The aim of this thesis was to study the current technological advances in the surgical treatment of colorectal cancer, to assess whether the benefits of these developments are applicable to the elderly population, and to evaluate decision making and multidisciplinary care for the most vulnerable colorectal cancer patients. The thesis comprises three parts.

In **Part I**, technical advances in the surgical management of colorectal malignancies and pre-malignant adenomas are explored. In **Chapter 2** the results of a comparative cohort study between laparoscopic and conventional surgery for low rectal cancer are presented. **Chapter 3** describes the functional outcome of transanal minimally invasive surgery (TAMIS) for rectal adenomas. In **Chapter 4**, a review of randomised clinical trials comparing laparoscopic surgery for colorectal cancer with conventional surgery is presented in which the incidence of non-surgical (especially cardio-pulmonary) complications in short-term results is analysed.

Part II focuses on decision-making for elderly patients with colorectal cancer. This requires knowledge on the current practice of care and outcome of treatment, in

addition to insights on whether the best available evidence for treatment options in colorectal cancer are applicable to the elderly population. **Chapter 5** addresses current care for elderly patients with low rectal cancer. Delivered treatment modalities in different age groups are compared to guidelines on rectal cancer standard at that time and outcome of surgical treatment in elderly is compared to results in younger patients. In **Chapter 6**, the survival following laparoscopic and conventional surgery for colorectal cancer in the Netherlands between 2008 and 2011 is presented for both younger and elderly patients. **Chapter 7** focuses on the applicability of data from randomised trials on laparoscopic colorectal surgery for elderly patients and their representation in these trials.

In **Part III**, multidisciplinary care with geriatric expertise for elderly cancer patients is evaluated. In **Chapter 8**, a literature review on the effect of geriatric assessments on decision-making in oncologic care is presented. **Chapter 9** describes the results of a national survey of cancer specialists and geriatricians on their use of geriatric evaluations for elderly cancer patients and their opinions on the possible improvements as well as obstacles hindering the implementation of a geriatric oncology programme. The outcome of a consecutive series of geriatric consultations for elderly cancer patients is outlined in **Chapter 10**.

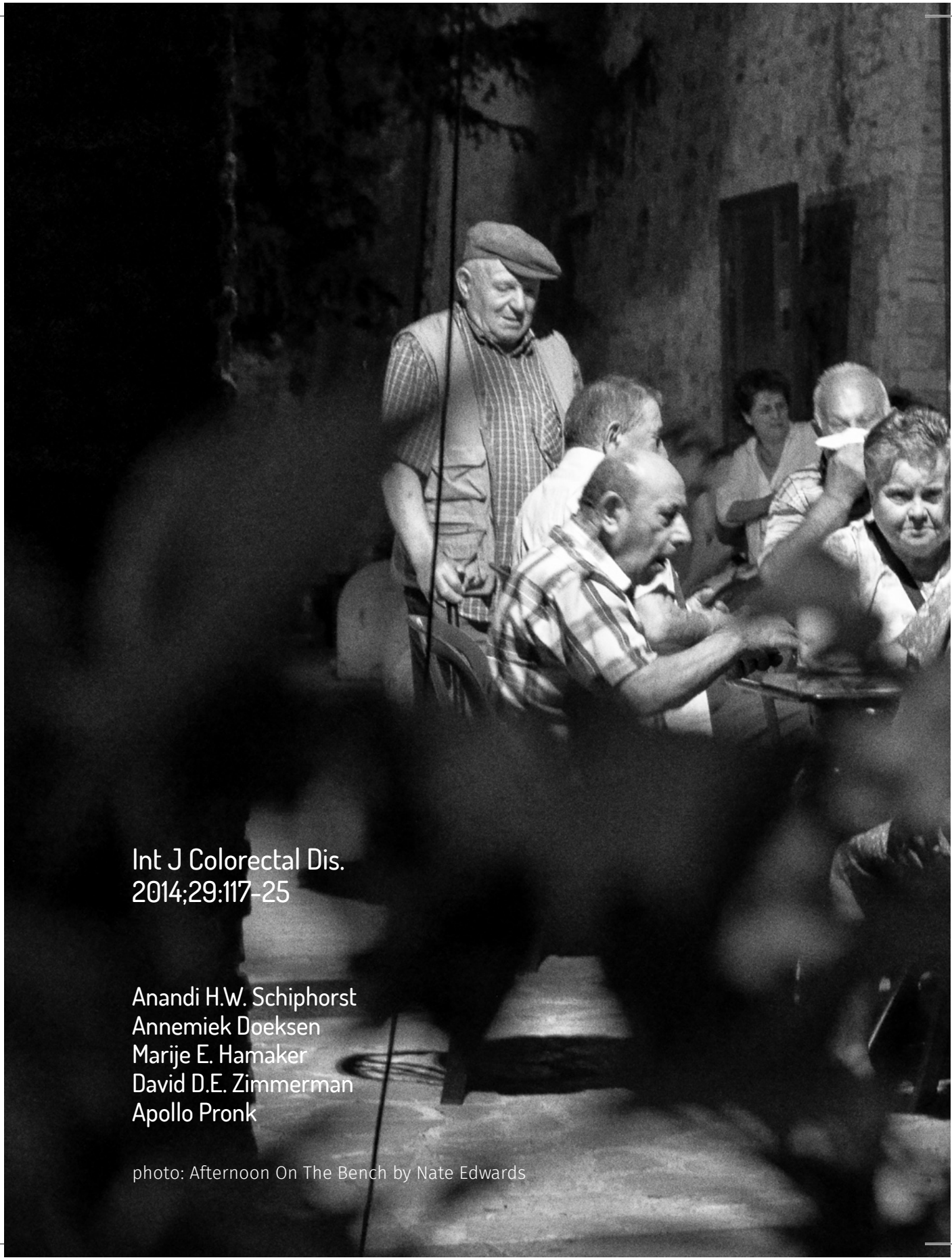
Finally, **Part IV** of this thesis summarises the main findings of the research done, discusses where we stand in the care for elderly colorectal cancer patients and addresses future perspectives.

References

1. www.cijfersoverkanker.nl.
2. Colorectal Cancer Collaborative Group. Surgery for colorectal cancer in elderly patients: a systematic review. Lancet 2000;356:968-74.
3. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, Tollenaar RA, Liefers GJ. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. Ann Surg Oncol 2012;19:2428-34.
4. 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. Ann Surg Oncol 2011;18:1533-9.
5. Schwenk W, Haase O, Neudecker J, Muller JM. Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev 2005:CD003145.
6. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy AM. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-84.
7. van der Pas MH, Haglind E, Cuesta MA, Furst A, Lacy AM, Hop WC, Bonjer HJ. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-8.
8. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, Housman MG, Escarce JJ. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21:1383-9.
9. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Oncol 2005;23:3112-24.
10. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, Mor V, Monfardini S, Repetto L, Sorbye L, Topinkova E. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005; 55:241-52.

Part I

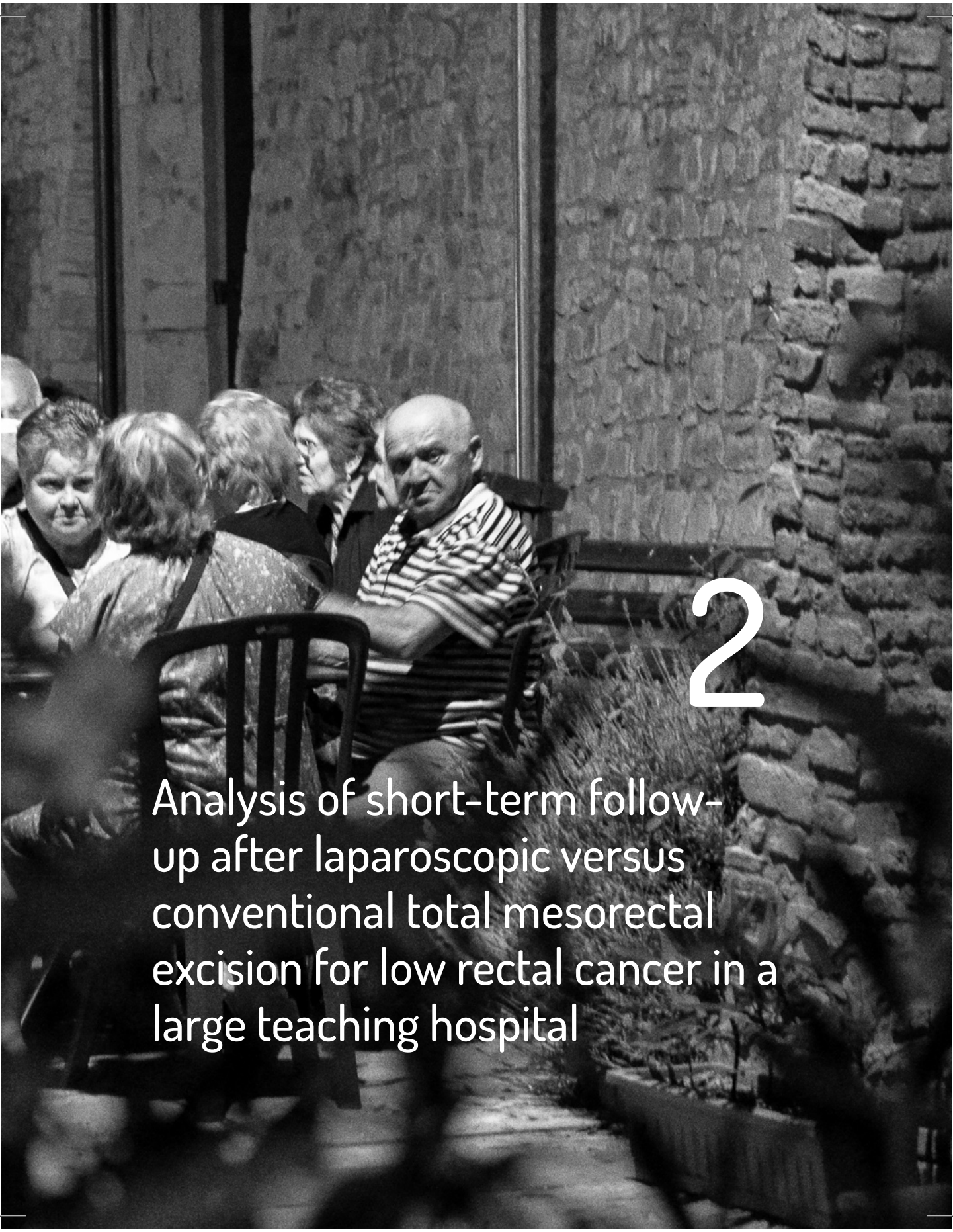
Technical advances in colorectal cancer surgery



Int J Colorectal Dis.
2014;29:117-25

Anandi H.W. Schiphorst
Annemiek Doeksen
Marije E. Hamaker
David D.E. Zimmerman
Apollo Pronk

photo: Afternoon On The Bench by Nate Edwards



2

Analysis of short-term follow-up after laparoscopic versus conventional total mesorectal excision for low rectal cancer in a large teaching hospital

Abstract

Background

Laparoscopic resection for low rectal cancer remains controversial and large randomised studies on oncologic outcome are lacking. The objective of this study was to analyse the short-term results of laparoscopic resection versus conventional total mesorectal excision (TME) for low rectal cancer (≤10cm from the anal verge).

Methods

The institutional colorectal surgery-database was reviewed and 166 consecutive patients operated for low rectal cancer between 2006 and 2011 were included in this analysis which focuses on the first 18 months of follow-up.

Results

Eighty patients underwent conventional TME whereas 86 patients underwent laparoscopic TME. Patient characteristics were comparable between groups. Conversion rate was 17%. Laparoscopic rectal resection resulted in significantly less blood loss (200ml versus 475 ml, $p<0.001$) and a 3 days shorter hospital stay (median 7 versus 10 days, $p=0.06$). Oncologic results from resected specimens were comparable, although significantly more lymph nodes were harvested in laparoscopic resections (median 13 versus 11, $p=0.005$). Disease-free survival after curative resection was better in the laparoscopic group ($p=0.04$), but this was no longer significant after correction for potential confounders.

Conclusion

In this analysis of laparoscopic versus conventional TME for low rectal cancer, laparoscopic surgery provides less blood loss and a shorter hospital stay while median operation time was similar. More lymph nodes were harvested in laparoscopic resection and a trend towards better disease-free survival was noticed.

Introduction

Laparoscopic resections are performed with increasing frequency for the treatment of colonic cancer. Benefits of laparoscopic surgery have been extensively described, such as shorter length of hospital stay, pain reduction, decreased intra-operative blood-loss, shorter duration of postoperative ileus, earlier return to functionality, while oncologic results are similar to a conventional surgical approach.[1-5] For rectal cancer, there is less evidence on outcomes after laparoscopic resections. Several cohort studies and one small randomised clinical trial have shown that laparoscopic resection in rectal cancer is safe.[6-9] However, there are few randomised clinical trials that find similar disease-free survival and local recurrence rates comparing laparoscopic Total Mesorectal Excision (TME) with conventional TME.[10] Long-term data from large randomised trials such as the COLOR II trial are awaited.[11, 12]
Laparoscopic rectal resection can be challenging, is shown to have a high morbidity rate[13] and a long learning curve. One concern is a higher rate of circumferential resection margin (CRM) positivity for tumours in the lower rectum,[14-18] due to poor visibility and exposure in the pelvis, and a relatively thin mesorectal envelope in the distal rectum. Furthermore. the current available stapler devices can be inadequate to perform an adequate distal resection, especially in the narrow male pelvis. Fibrosis caused by chemoradiation or radiotherapy can cause further difficulties in laparoscopic surgery, especially as tactile feedback is limited. Therefore, laparoscopic TME is still controversial. On the other hand, laparoscopy could provide a superior (magnified) view of the pelvic structures and may therefore aid in complex resections of distal tumours as well as improved identification of the anatomy in the narrow pelvis.
In this study we analysed the short-term results of laparoscopic versus conventional TME for tumours in the distal rectum in a consecutive series of patients operated at a large teaching hospital in the Netherlands.

Materials and Methods

Design

Data from patients undergoing resection for rectal cancer in the distal rectum (≤10 cm from the anal verge) were collected in a prospective colorectal surgery-database. In the present study we reviewed this database for short-term surgical and oncologic outcomes comparing laparoscopic versus conventional resection of low rectal cancer. This study was approved by the local research and review committee. All patients consented to undergo either conventional or laparoscopic rectal resection.

Patients

From July 2006 to January 2012, consecutive patients undergoing conventional or laparoscopic rectal resection for rectal cancer in the lower rectum (≤10 cm from the anal verge, measured by digital rectal examination, rigid or flexible rectoscopy, flexible colonoscopy or radiographically), were included.
Patients who underwent a rectal resection for benign or premalignant disease were excluded from this study.

Standardised procedure

All patients underwent a standardised procedure according to the Dutch Guidelines[19] and a multimodal rehabilitation program. The clinical work-up consisted of a total colonoscopy, computed tomography (CT) of the abdomen, rectal magnetic resonance imaging (MRI) and chest X-ray.
All patients were considered in a multidisciplinary team for neoadjuvant therapy. Data on neoadjuvant treatment were routinely recorded in the database. Neoadjuvant therapy was not offered to patients with severe comorbidity and patients who underwent an emergency procedure. For patients with a clinical stage T4 and or/N2 status, neoadjuvant therapy consisted of chemoradiation (capecitabine 825 mg/m2 twice daily and 25 radiotherapy fractions of 2 Gray); all others were offered preoperative radiotherapy of 5 times 5 Gray. Surgery was planned within 10 days after completion of radiotherapy or 5-6 weeks after completion of chemoradiation therapy.
The surgical strategy (laparoscopic TME versus open TME) was decided by either a certified colorectal surgeon or by a general surgeon enrolled in a coloproctology fellowship. All patients were assessed and optimised preoperatively where applicable by an anaesthesiologist for perioperative risks. Bowel preparation and perioperative antibiotic prophylaxis were given routinely.

All resections were performed according to the TME principles[20, 21] by or supervised by two specialised colorectal surgeons, skilled in laparoscopic colorectal surgery. If required for whatever reason, surgery could be converted from a laparoscopic to a conventional approach. A temporary deviating ostomy was placed at the surgeon's discretion.
Resection was considered curative when no distant metastasis were present and resection margins were tumour negative. Patients less than 80 years of age with node-positivity and/or patients with a stage T4 tumour as well as angiolymphatic invasion were offered a consultation with an oncologist to discuss the need for postoperative adjuvant chemotherapy. Data on type of adjuvant treatment were routinely recorded in the colorectal database.
Standard follow-up consisted of regular out-patient visits at 3-month intervals for the first year and 6 months intervals thereafter. The follow-up included physical exams and carcinoembryonic antigen (CEA) assay at each visit, chest X-ray and hepatic ultrasonography yearly. One year after surgery, a colonoscopy was routinely performed.

Data collection and outcomes

Data were collected by an independent observer using an electronic database. The following data were included: age, sex, comorbidity (using the American Society of Anaesthesiologists (ASA)-score and Charlson comorbidity index,[22] BMI, polypharmacy (patient using 5 or more medications), history of abdominal surgery, distance of rectal tumour from the anal verge, type of neoadjuvant treatment, surgical treatment data (type of surgery, duration of operation, blood loss, conversion, type of anastomosis, requirement of ostomies, intra-operative complications), postoperative data (number of ICU-days, hospital stay, number of blood transfusions needed, complications, re-interventions, re-admissions and mortality), oncologic data (tumour stage, type of neoadjuvant treatment, pathologic specimen data, form of adjuvant treatment), and follow-up. Conversions were classified as early (occurring within 30 minutes from start of the operation) or late. Postoperative complications were categorised as major or minor according to the classification by Bakx et al.[23]

Statistical analysis

Data were analysed by the intention-to-treat-principle. Statistical analysis was performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) for windows. Statistical significance was defined as $p<0.05$. For comparisons between surgical procedure groups, the Chi-square test was used for nominal and ordinal variables. The Anova test was used for continuous variables. To compare overall and disease-free survival

within 18 months of follow-up, Kaplan– Meier survival curves were assessed using a log-rank analysis. To determine which baseline characteristics and outcome parameters were associated with mortality in the 18 months following curative rectal resection, a Cox regression analysis was performed. For each variable, the Cox proportional hazards assumption was tested using the log-minus-log plot. Accordingly, a univariate Cox-regression analysis was performed to determine which factors were associated with mortality in the 18 months following curative rectal resection. Factors with a p-value ≤ 0.20 were subsequently included in the multivariate analysis. A backward selection procedure was applied, accepting a p-value of $p<0.05$. A similar procedure was followed for disease-free survival.

Results

Patient population

From July 2006 to January 2012, 166 resections for rectal cancer in the distal rectum (≤10 cm from the anal verge) were performed. There were 100 men (60%) with median age of patients was 68 (37-91) years. The laparoscopic group (LAPTME) consisted of 86 (52%) patients, and the conventional group (CONTME) consisted of 80 (48%) patients. Patient characteristics are displayed in Table 1.
Fifteen patients (9%) had synchronous metastatic disease and in nine cases (5%) a deviating colostomy was placed prior to neoadjuvant treatment and rectal surgery because of intestinal obstruction. In addition, 136 (82%) of patients received neoadjuvant treatment: 78 (47%) patients received radiation therapy prior to surgery and 58 (35%) received chemoradiation therapy.
Fifty patients (30%) had a history of prior abdominal surgery, two of which due to colon cancer. Seventeen patients (10%) were scored as ASA-score of 3-4, the remainder were ASA 1-2 patients. The mean Charlson comorbidity index score was 0.5 and nine patients (5%) scored 3 or more.

Surgical and oncologic outcome

In 106 (64%) patients a low anterior resection was performed (LAPTME 56/86 - 65%; CONTME 50/80 - 63%) while in the remaining patients an abdominoperineal resection was performed. Of the 106 with a low anterior resection, 41 patients (40%) received a permanent colostomy (LAPTME 20/56 - 36%; CONTME 21/50 - 42%), while the remaining 60 patients underwent resection with performance of an anastomosis, with or without a protective ostomy.

	Laparoscopic TME (n=86)	Conventional TME (n=80)	P
Male	53 (62)	47 (59)	n.s.
Median age (range)	68yrs (37-91)	68yrs (39-88)	n.s.
Median distance to anal verge (range)	5cm (1-10)	5cm (1-10)	n.s.
Year of surgery			
2006-2008	16 (22)	57 (78)	<0.001
2009-2011	70 (75)	23 (25)	
Previous abdominal surgery	22 (26)	28 (35)	n.s.
ASA 3-4	7 (8)	10 (13)	n.s.
Mean Charlson comorbidity index[22] (range)	0.5 (0-4)	0.5 (0-4)	n.s.
Charlson comorbidity index ≥ 2	11 (13)	7 (9)	n.s.
Median BMI (range)	25 (16-40)	25 (18-39)	n.s.
Neoadjuvant short-course RT	44 (51)	34 (43)	n.s.
Neoadjuvant CHRT	26 (30)	32 (40)	n.s.
Adjuvant CHT	26 (30)	18 (23)	n.s.
Pathological tumour stage according to Dukes classification			
- A: T1-2, N0, M0	22 (26)	16 (20)	n.s.
- B: T3-4, N0, M0	17 (20)	23 (29)	n.s.
- C: T1-4, N1-2, M0	36 (42)	30 (38)	n.s.
- D: T1-4, N1-2, M1	6 (7)	9 (11)	n.s.
Complete remission after CHRT	6 (7)	3 (4)	n.s.

Table 1. Patient characteristics

TME: Total Mesorectal Excision; ASA: American Society of Anaesthesiologists; BMI: Body Mass Index; RT: radiotherapy, CHRT: chemoradiation therapy; CHT: chemotherapy; n.s.: not significant
All values in parentheses are percentages unless stated otherwise.

During the study period the proportion of rectal resections performed laparoscopically increased significantly. In the first half of the study period 22% of all rectal resections were laparoscopic compared to 75% in the second half (p<0.001). In the laparoscopic TME group 15 of 86 procedures (17%) were converted to conventional resection. In five cases conversion was deemed necessary because of tumour-related causes. In three cases this was because of tumour fixation and inability to dissect without tactile feedback. The other two conversions were because

	Laparoscopic TME (n=86)	Conventional TME (n=80)	P
APR	30 (35)	30 (38)	
LAR	56 (65)	50 (63)	
Median operation time in minutes (range)	146 (74-233)	130 (63-236)	0.06
Median blood loss in ml (range)	200 (0-2500)	457 (0-3000)	<0.001
Number of patients requiring blood transfusions (range)	10 (12%)	21 (26%)	0.02
Protective ostomy in patients undergoing LAR	32/56 (57%)	24/50 (48%)	0.35
Number of patients with postoperative complication[a]	23 (27%)	30 (38%)	0.14
Major complications[b]	10 (12%)	12 (15%)	0.52
• Anastomotic leakage leading to			
• reoperation	3	1	
• fistula	1	2	
• Postoperative haemorrhage (ST)	2	1	
• Intra-abdominal abscess (ST)	0	0	
• Mortality (30-day)	1	2	
• Sepsis/MOF	1	4	
• Pulmonary embolism	0	0	
• Myocardial infarction	0	0	
• Long-term fecal incontinence	0	0	
• Perineal wound dehiscence/abscess (ST)	2	1	
• Small bowel obstruction (ST)	3	2	
Minor complications[b]	13 (15%)	18 (23%)	0.22
• Perineal wound dehiscence (conservative)	1	3	
• Complication of colostomy	4	2	
• Complication of protective ostomy	0	0	
• Intra-abdominal abscess[c]	4	3	
• Small bowel obstruction (conservative)	0	6	0.01
• Abdominal wound infection	1	4	
• Urinary tract infection	1	1	
• Urinary retention	2	4	
• Pneumonia	1	3	
• Deep venous thrombosis	0	0	
Re-operation	12 (14%)	10 (13%)	0.78
Other re-intervention	1	4	0.15
Median hospital stay in days (range)	7 (3-141)	10 (3-93)	0.06
Median number of days on ICU	2 (0-6)	2 (0-48)	0.11
Re-admission	10 (12%)	11 (14%)	0.68

Table 2. Operative outcome

TME: Total Mesorectal Excision; APR: abdominoperineal resection; LAR: low anterior resection; ST: surgical treatment; MOF: Multi Organ Failure; ICU: Intensive Care Unit

[a] A patient could have had more than one complication.

[b] Complications were categorised as described by Bakx et al.[23]

[c] Leading to percutaneous drainage or conservative treatment

of tumour size and inability to get an adequate overview of the pelvis with a bulky tumour. All tumour-related conversions were late conversions. Five conversions were due to adhesions after prior abdominal surgery (four early conversions, one late). In three patients retracting was difficult due to obesity (all early conversions). In two late conversions overview was difficult due to fibrosis after chemotherapy, and because of a narrow pelvis.

Blood loss was significantly lower after LAPTME as compared to CONTME (median 200ml versus 457ml, p<0.001) as was the number of patients requiring blood transfusion (LAPTME 10 (12%); CONTME 21 (26%), p=0.016, Table 2). Median operation time was not significantly different between the two groups (146 minutes versus 130 minutes, p=0.06).

Median duration of hospital-stay was seven days (range 3-141) after LAPTME versus ten days (range 3-93) after CONTME (p=0.06, Table 2). Fifty-three patients (32%) experienced post-operative complications (LAPTME 23/86 - 27% versus CONTME 30/80 - 38%, p=0.14). According to the classification by Bakx et al[23], ten of 86 LAPTME patients and twelve of 80 CONTME patients experienced major complications (p=0.52). Of these, a total of 7 patients (4%) had an anastomotic leakage (LAPTME 4/86 – 5% versus CONTME 3/80 – 4%, p=0.77) leading to reoperation or fistula. All other complications were minor. In the LAPTME group conservatively treated postoperative adynamic ileus was significantly lower as compared to CONTME (nil versus six patients, p=0.01). Small bowel obstruction leading to operative intervention occurred in three LAPTME patients versus two CONTME. One trocar herniation occurred after LAPTME requiring re-intervention. Occurrence of complications was associated with longer duration of admission (median 7 days versus 11, p<0.001), more ICU-days (0-48 days versus 0-4 days, p=0.001), and higher number of patients requiring blood transfusion (16/53 (30%) versus 15/113 (13%), p=0.009).

In the first month after surgery, one of the 86 laparoscopic TME patients died (due to multi-organ failure after anastomotic leakage) and two of the 80 patients in the conventional TME group (both due to pneumoseptic complications) (p=0.52). Resection was considered curative in 143 patients (86%; LAPTME 76/86 (88%) versus. CONTME 67/80 (84%) p=0.39). The pathology results showed an overall tumour positive CRM (≤1 mm) in nine cases (5%); five patients after LAPTME and four patients after CONTME (Table 3, p=0.82). Two of these patients had synchronous metastasis and in three cases a macroscopic irradical (R2) resection was performed (one patient underwent laparoscopic resection and the other two conventional rectal resection). The median number of resected lymph nodes was significantly higher after laparoscopic surgery: 13 (range 1-25) after LAPTME versus 11 (range 0-31)

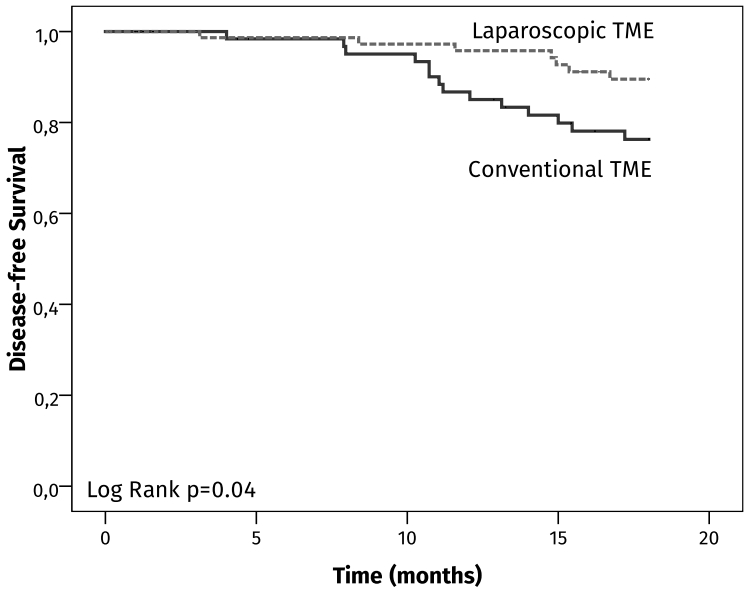
after CONTME (p=0.005).
Oncologic outcome in the 18 months following resection is displayed in Table 3. In the LAPTME group, seven patients (9%) developed recurrent disease after curative resection: one patient had local tumour recurrence, five patients had distant metastasis and one patient had both. After 18 months, two patients died from recurrent disease despite curative resection. By comparison, in the CONTME group, 21% of patients experienced disease recurrence after curative resection: one patient was diagnosed with a local recurrence, eleven patients developed distant metastasis and two patients had both. Of these patients, two died from tumour-related causes within 18 months.
As demonstrated by Figure 1a, there was an overall trend towards less disease recurrence after laparoscopic surgery (log-rank p=0.04) but this association was no longer significant after correcting for potential confounders (Table 4). Similarly, there was a trend toward improved overall survival in the laparoscopic TME group (Figure 1b, log rank p=0.16) but in the multivariable analysis, only age (hazard ratio 1.11, 95% confidence interval 1.04-1.18, p=0.002) was independently associated with overall survival (Table 5).

	Laparoscopic TME (n=86)	Conventional TME (n=80)	P
Curative resection	76 (88%)	67 (84%)	n.s.
Median CRM in mm (range)	10 (0-35)	10 (0-20)	n.s.
Tumour positive CRM	5	4	n.s.
Median number of LNN (range)	13 (1-25)	11 (0-31)	0.005
Local tumour recurrence after curative resection	2	3	n.s.
Distant metastasis after curative resection	6 (8%)	13 (19%)	0.04
Overall cancer related mortality	5	9	n.s.

Table 3. Oncologic outcome in 18 months follow-up

CRM: circumferential resection margin; LNN: lymph nodes; TME: Total Mesorectal Excision; n.s.: not significant

a.



b.

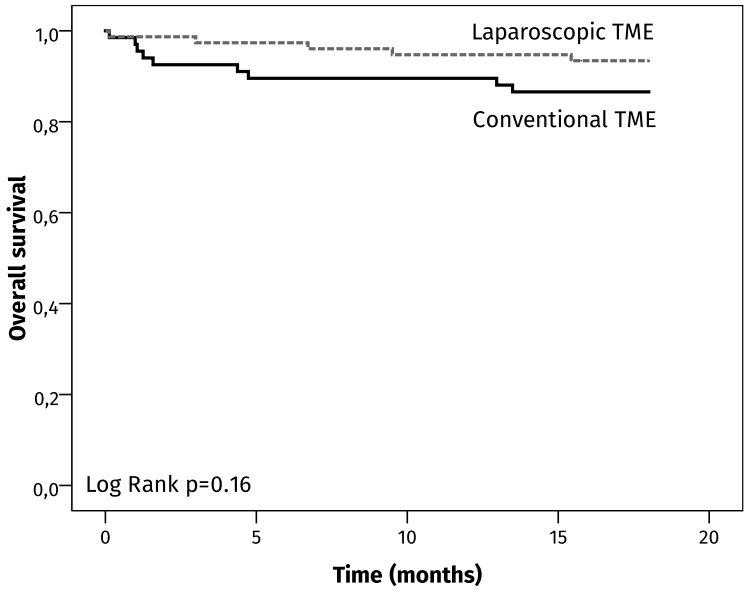


Figure 1. Kaplan-Meier curve of disease-free survival (a) and overall survival (b) in 18 months follow-up after curative resection

TME: Total Mesorectal Excision.

Factor	Univariate			Multivariable		
	HR	95% Confidence Interval	P*	HR	95% Confidence Interval	P*
Age	1.01	0.97-1.04	0.77	-		
Sex	1.36	0.53-3.51	0.52	-		
ASA 3-4	0.50	0.07-3.72	0.50	-		
Charlson Comorbidity Index[22]	0.98	0.62-1.54	0.92	-		
Polypharmacy	1.10	0.42-2.83	0.85			
BMI	0.92	0.81-1.05	0.22			
Neoadjuvant therapy	0.97	0.57-1.65	0.90			
Year of surgery	0.95	0.74-1.22	0.68			
Laparoscopic resection	0.64	0.26-1.59	0.34	-		
LAR/APR	0.57	0.24-1.35	**0.19**	0.57	0.24-1.35	0.20
Surgeon	1.69	0.72-3.99	0.23			
Dukes tumour stage	1.11	0.61-2.04	0.73			
Number of lymph nodes resected	0.98	0.90-1.06	0.60			
Adjuvant therapy	1.47	0.57-3.81	0.43			
Complications	1.22	0.52-2.90	0.65			

Table 4. Cox-regression analysis of factors associated with disease recurrence within 18 months after curative rectal resection

ASA: American Society of Anaesthesiologists; BMI: Body Mass Index; LAR: Low Anterior Resection; APR: Abdominoperineal resection; HR: Hazard Ratio.
* Variables with a p-value ≤0.20 (printed in bold font) were included in the multivariable analyses, as were potential confounders such as age, sex, ASA classification, Charlson comorbidity index and surgical approach (laparoscopic versus conventional resection).

Discussion

In this cohort study of consecutive patients who underwent total mesorectal resection for distal rectal cancer (≤10cm of the anal verge) we analysed short-term surgical and oncologic results of a laparoscopic versus conventional approach. Operation time was 16 minutes longer in laparoscopic resections (p=0.06) and significantly less blood loss and need for blood transfusions were seen. LAPTME led to 3 days reduction in hospital stay, although this was not statistically significant, possibly due to group size. There was a trend towards less complications in the laparoscopic group, mainly caused by a significant reduction in the incidence of postoperative ileus. Oncologic adequacy of resection was similar between groups but we found a significantly higher percentage of lymph nodes harvested after laparoscopic rectal resection. Although there was a trend towards better 18 month disease-free and overall survival in favour of laparoscopic resection for low rectal cancer, this association was no longer significant after correction for potential confounders.

Previous studies have shown beneficial effects of laparoscopic rectal resection on short-term outcome, but few have focused on tumours of the distal 2/3 of the rectum. This group of patients receives more neoadjuvant treatment, causing post (chemo)radiation effects. Anatomic coning of the pelvis can make laparoscopic surgery for the distal rectum challenging. Furthermore, a current topic of debate concerns the limitations in the laparoscopic stapling devices for adequate oncologic distal resections.

This analysis demonstrates that laparoscopic resection for low rectal cancer is feasible and safe. These findings are supported by previous studies which have demonstrated a reduction in the incidence of postoperative ileus and less intraoperative blood loss with laparoscopic surgery[1,10,12] as well as comparable incidence of a tumour positive CRM with either surgical approach.[24-26] The latter is important since oncologic clearance is a strong predictor for curation, tumour recurrence and ultimately survival. Results from other studies also demonstrated a higher number of harvested lymph nodes in laparoscopic resections compared to conventional rectal resection.[10,27]

There are other potential benefits from laparoscopic surgery. A smaller surgical trauma will decrease immunologic response and preserves postoperative immunologic defences.[28,29] This may lead to not only a lower incidence of infections but also fewer local recurrences and/or distant metastasis, as these defence mechanisms are thought to be of importance in preventing tumour spread.[30-32]

Factor	Univariate			Multivariable		
	HR	95% Confidence Interval	P*	HR	95% Confidence Interval	P*
Age	1.08	1.03-1.14	**0.005**	1.11	1.04-1.18	0.002
Sex	0.95	0.33-2.74	0.92	-		
ASA 3-4	3.94	1.23-12.58	**0.02**	-		
Charlson Comorbidity Index[22]	1.17	0.69-1.98	0.57	-		
Polypharmacy	1.54	0.48-4.90	0.47			
BMI	0.93	0.80-1.09	0.37			
Neoadjuvant therapy	0.75	0.36-1.56	0.44			
Year of surgery	0.88	0.65-1.19	0.88			
Laparoscopic resection	0.47	0.16-1.39	**0.17**	0.37	0.11-1.24	0.11
LAR/APR	1.0	0.33-2.97	0.99			
Surgeon	1.86	0.62-5.54	0.27			
Dukes tumour stage	0.94	0.49-1.80	0.85			
Number of lymph nodes resected	1.03	0.93-1.14	0.58			
Adjuvant therapy	0.72	0.20-2.59	0.62			
Complications	3.03	1.05-8.75	**0.04**	2.72	0.89-8.31	0.08

Table 5. Cox-regression analysis of factors associated with mortality within 18 months after curative rectal resection

ASA: American Society of Anaesthesiologists; BMI: Body Mass Index; LAR: Low Anterior Resection; APR: Abdominoperineal resection; HR: Hazard ratio.
* Variables with a p-value ≤0.20 (printed in bold font) were included in the multivariable analyses, as were potential confounders such as age, sex, ASA classification and Charlson comorbidity index

Furthermore, in laparoscopy tissue handling tends to be more subtle, with less surgical manipulation, further decreasing the spreading of tumour cells.[33]
Since the introduction of laparoscopic rectal surgery in our hospital, an increasing percentage of our patients underwent laparoscopic resection (11% in 2006, 80% in 2010). This is probably due to improved laparoscopic skills of the surgeons during the study period. Expected adhesions are becoming less important in the decision to start laparoscopically. Conversion rate in our study was 17%. Only in five patients TME could not be completed laparoscopic due to tumour-related reasons. This rate is comparable or lower to rates reported in the literature.[1,12,34] The number of patients with anastomotic leakage is relatively low in our series. Reports in literature of anastomotic leakage after laparoscopic rectal resection are varying from 3-13%.[1,6,12,35-37]

Some have advocated that firing multiple intracorporeal staples across the rectum during laparoscopy may lead to a higher incidence of anastomotic leakage.[10,37-40] In the present study, these articulated laparoscopic stapling devices have also been used. The low rate of (clinical) anastomotic leakage may be due to the high amount of protective ostomies used in our patient population. This however resembles a patient population with cancer in the distal 2/3 of the rectum and a high percentage of neoadjuvant treatment, making the decision for placing protective ostomies more common.[8,37]

This study has some limitations. The decision between a laparoscopic and conventional approach was left to the surgeon's discretion. The motivation behind this decision was not recorded in the database, thus leaving some uncertainty on the reason for allocation to one group or the other. This may have introduced the possible confounding by indication. However, we explored differences between the laparoscopic versus conventional group and found no differences in baseline characteristics. Another potential limitation is that the patient population was heterogeneous, containing all ages and stages of disease. However, this has also resulted in a real-life patient population, thus providing an overview of what actually happens in daily practice.

Conclusion

This analysis of short-term results of laparoscopic versus conventional TME for low rectal cancer demonstrates that laparoscopic surgery is feasible and safe, resulting in similar oncologic outcomes with less blood loss, a trend towards less post-operative complications and shorter duration of hospital stay. Further randomised studies are needed to attribute to the body of evidence of equivalence or even superiority of laparoscopic resections compared to conventional resections for distal rectal cancer.

References

1. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005;365:1718-26.
2. Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy A, Bonjer HJ. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol 2009;10:44-52.
3. Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer J. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. Cancer Treat Rev 2008;34:498-504.
4. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy AM. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-84.
5. McKay GD, Morgan MJ, Wong SK, Gatenby AH, Fulham SB, Ahmed KW, Toh JW, Hanna M, Hitos K. Improved short-term outcomes of laparoscopic versus open resection for colon and rectal cancer in an area health service: a multicenter study. Dis Colon Rectum 2011;55:42-50.
6. Barlehner E, Benhidjeb T, Anders S, Schicke B. Laparoscopic resection for rectal cancer: outcomes in 194 patients and review of the literature. Surg Endosc 2005;19:757-66.
7. Ng KH, Ng DC, Cheung HY, Wong JC, Yau KK, Chung CC, Li MK. Laparoscopic resection for rectal cancers: lessons learned from 579 cases. Ann Surg 2009;249:82-6.
8. Seshadri RA, Srinivasan A, Tapkire R, Swaminathan R. Laparoscopic versus open surgery for rectal cancer after neoadjuvant chemoradiation: a matched case-control study of short-term outcomes. Surg Endosc 2011;26:154-61.
9. Leroy J, Jamali F, Forbes L, Smith M, Rubino F, Mutter D, Marescaux J. Laparoscopic total mesorectal excision (TME) for rectal cancer surgery: long-term outcomes. Surg Endosc 2004;18:281-9.
10. Lujan J, Valero G, Hernandez Q, Sanchez A, Frutos MD, Parrilla P. Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer. Br J Surg 2009;96:982-9.
11. Buunen M, Bonjer HJ, Hop WC, et al. COLOR II. A randomized clinical trial comparing laparoscopic and open surgery for rectal cancer. Dan Med Bull 2009;56:89-91.
12. van der Pas MH, Haglind E, Cuesta MA, Furst A, Lacy AM, Hop WC, Bonjer HJ. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-8.
13. Shearer R, Gale M, Aly OE, Aly EH. Have early post-operative complications from laparoscopic rectal cancer surgery improved over the past 20 years? Colorectal Dis 2013.
14. Guren MG, Eriksen MT, Wiig JN, Carlsen E, Nesbakken A, Sigurdsson HK, Wibe A, Tveit KM. Quality of life and functional outcome following anterior or abdominoperineal resection for rectal cancer. Eur J Surg Oncol 2005;31:735-42.

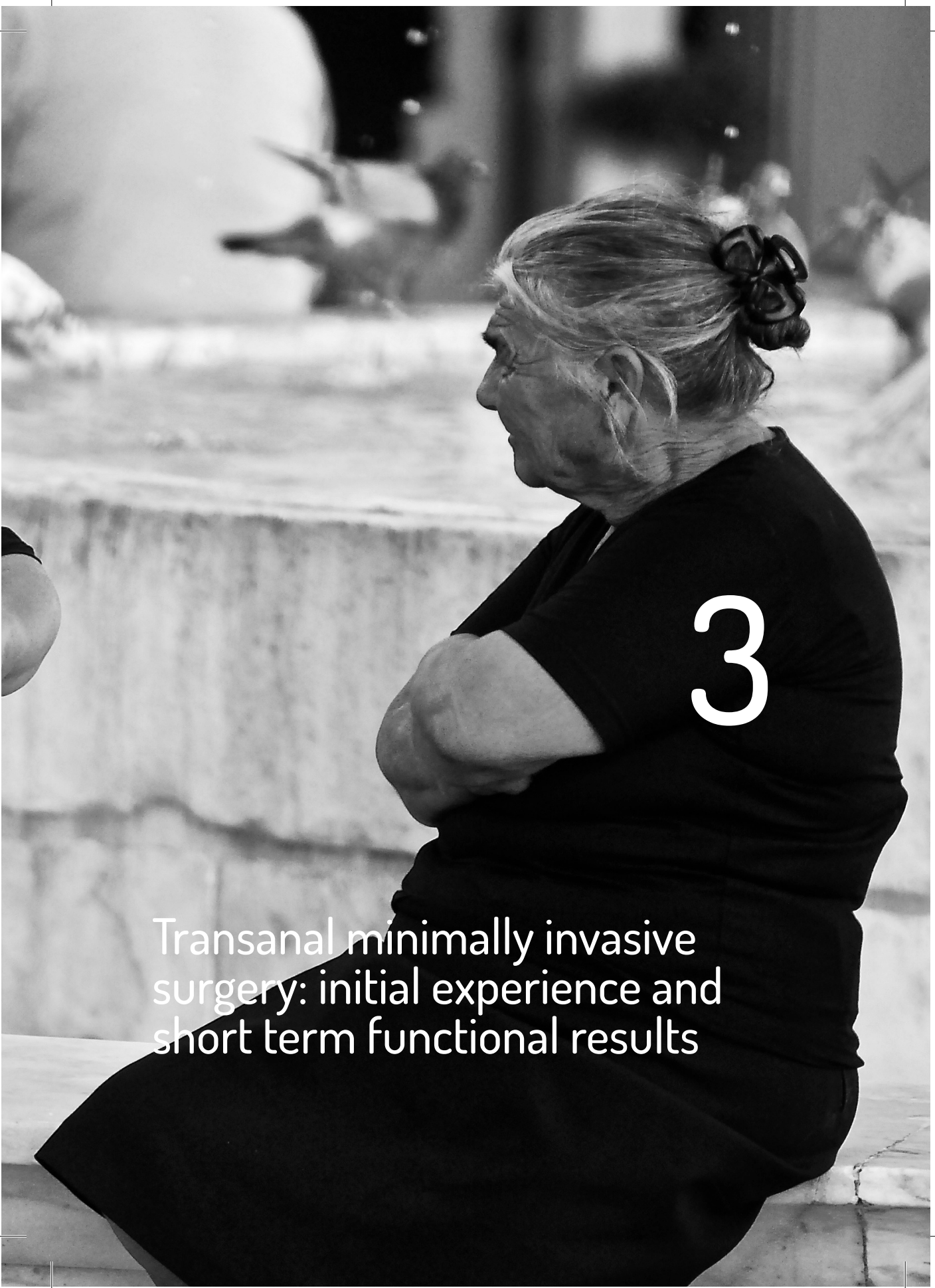
15. Marr R, Birbeck K, Garvican J, Macklin CP, Tiffin NJ, Parsons WJ, Dixon MF, Mapstone NP, Sebag-Montefiore D, Scott N, Johnston D, Sagar P, Finan P, Quirke P. The modern abdominoperineal excision: the next challenge after total mesorectal excision. Ann Surg 2005;242:74-82.
16. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26:303-12.
17. West NP, Finan PJ, Anderin C, Lindholm J, Holm T, Quirke P. Evidence of the oncologic superiority of cylindrical abdominoperineal excision for low rectal cancer. J Clin Oncol 2008;26:3517-22.
18. Wibe A, Syse A, Andersen E, Tretli S, Myrvold HE, Soreide O. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection. Dis Colon Rectum 2004;47:48-58.
19. Huibers CJ, de Roos MA, Ong KH. The effect of the introduction of the ERAS protocol in laparoscopic total mesorectal excision for rectal cancer. Int J Colorectal Dis;27:751-7.
20. Heald RJ. Total mesorectal excision. The new European gold standard. G Chir 1998;19:253-5.
21. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-46.
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
23. Bakx R, Emous M, Legemate DA, Machado M, Zoetmulder FA, van Tets WF, Bemelman WA, Slors JF, van Lanschot JJ. Categorization of major and minor complications in the treatment of patients with resectable rectal cancer using short-term pre-operative radiotherapy and total mesorectal excision: a Delphi round. Colorectal Dis 2006;8:302-8.
24. Anderson C, Uman G, Pigazzi A. Oncologic outcomes of laparoscopic surgery for rectal cancer: a systematic review and meta-analysis of the literature. Eur J Surg Oncol 2008;34:1135-42.
25. Breukink SO, Grond AJ, Pierie JP, Hoff C, Wiggers T, Meijerink WJ. Laparoscopic vs open total mesorectal excision for rectal cancer: an evaluation of the mesorectum's macroscopic quality. Surg Endosc 2005;19:307-10.
26. Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, Lim SB, Lee TG, Kim DY, Kim JS, Chang HJ, Lee HS, Kim SY, Jung KH, Hong YS, Kim JH, Sohn DK, Kim DH, Oh JH. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. Lancet Oncol 2010;11:637-45.
27. Lelong B, Bege T, Esterni B, Guiramand J, Turrini O, Moutardier V, Magnin V, Monges G, Pernoud N, Blache JL, Giovannini M, Delpero JR. Short-term outcome after laparoscopic or open restorative mesorectal excision for rectal cancer: a comparative cohort study. Dis Colon Rectum 2007;50:176-83.
28. Veenhof AA, Vlug MS, van der Pas MH, Sietses C, van der Peet DL, de Lange-de Klerk ES, Bonjer HJ, Bemelman WA, Cuesta MA. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. Ann Surg 2012;255:216-21.
29. Wang G, Jiang Z, Zhao K, Li G, Liu F, Pan H, Li J. Immunologic response after laparoscopic

colon cancer operation within an enhanced recovery program. J Gastrointest Surg 2012;16:1379-88.
30. Novitsky YW, Litwin DE, Callery MP. The net immunologic advantage of laparoscopic surgery. Surg Endosc 2004;18:1411-9.
31. Sietses C, Beelen RH, Meijer S, Cuesta MA. Immunological consequences of laparoscopic surgery, speculations on the cause and clinical implications. Langenbecks Arch Surg 1999;384:250-8.
32. Wichmann MW, Huttl TP, Winter H, Spelsberg F, Angele MK, Heiss MM, Jauch KW. Immunological effects of laparoscopic vs open colorectal surgery: a prospective clinical study. Arch Surg 2005;140:692-7.
33. Wind J, Tuynman JB, Tibbe AG, Swennenhuis JF, Richel DJ, van Berge Henegouwen MI, Bemelman WA. Circulating tumour cells during laparoscopic and open surgery for primary colonic cancer in portal and peripheral blood. Eur J Surg Oncol 2009;35:942-50.
34. Aziz O, Constantinides V, Tekkis PP, Athanasiou T, Purkayastha S, Paraskeva P, Darzi AW, Heriot AG. Laparoscopic versus open surgery for rectal cancer: a meta-analysis. Ann Surg Oncol 2006;13:413-24.
35. Akiyoshi T, Kuroyanagi H, Oya M, Konishi T, Fukuda M, Fujimoto Y, Ueno M, Miyata S, Yamaguchi T. Factors affecting the difficulty of laparoscopic total mesorectal excision with double stapling technique anastomosis for low rectal cancer. Surgery 2009;146:483-9.
36. Laurent C, Leblanc F, Wutrich P, Scheffler M, Rullier E. Laparoscopic versus open surgery for rectal cancer: long-term oncologic results. Ann Surg 2009;250:54-61.
37. Milsom JW, de Oliveira O, Jr., Trencheva KI, Pandey S, Lee SW, Sonoda T. Long-term outcomes of patients undergoing curative laparoscopic surgery for mid and low rectal cancer. Dis Colon Rectum 2009;52:1215-22.
38. Brannigan AE, De Buck S, Suetens P, Penninckx F, D'Hoore A. Intracorporeal rectal stapling following laparoscopic total mesorectal excision: overcoming a challenge. Surg Endosc 2006;20:952-5.
39. Brescia A, Mari FS, Favi F, Milillo A, Nigri G, Dall'oglio A, Pancaldi A, Masoni L. Laparoscopic lower anterior rectal resection using a curved stapler: original technique and preliminary experience. Am Surg 2013;79:253-6.
40. Mari FS, Gasparrini M, Nigri G, Berardi G, Laracca GG, Flora B, Pancaldi A, Brescia A. Can a curved stapler made for open surgery be useful in laparoscopic lower rectal resections? Technique and experience of a single centre. Surgeon 2013;11 Suppl 1:S23-6.

Dis Colon Rectum.
2014;57:927-32

Anandi H.W. Schiphorst
Barbara S. Langenhoff
John Maring
Apollo Pronk
David D.E. Zimmerman

photo: Exchanging some facts by Pedro Ribeiro Simões



3

Transanal minimally invasive surgery: initial experience and short term functional results

Abstract

Background

Currently, the preferred method for local excision of rectal polyps is Transanal Endoscopic Microsurgery (TEM), avoiding rectal resection. Transanal minimally invasive surgery (TAMIS) is a relatively new technique utilising a disposable port in combination with conventional laparoscopic instruments. This method is less expensive and relatively easy to learn as well as available. Despite wide adoption of TAMIS, to date only few series on implementation and use of this technique are reported and detailed information its the effect on fecal continence is not available. The objective of this study was to prospectively assess the functional outcome after TAMIS using Rockwood's Fecal Incontinence Severity Index (FISI) pre- and postoperatively.

Methods

A prospective cohort study was conducted in a large teaching hospital in the Netherlands. All consecutive patients undergoing transanal minimally invasive surgery were entered in a prospective database. Pre- and postoperative FISI scores were compared. Main outcome measures were postoperative surgical and functional results.

Results

Between October 2011 and September 2013, 37 patients underwent TAMIS. Short-term morbidity-rate was 14% and positive resection margins were reported in 6 cases (16%). Overall, there was a significant decline in pre- and postoperative FISI scores (p=0.02), indicating an improvement in anorectal function after TAMIS for patients with impaired preoperative continence. Seventeen patients (49%) had impaired continence before TAMIS (mean FISI 21). Continence improved in fifteen (88%) of these patients after surgery; no change was observed in one patient (6%) and continence further decreased in another. Additionally, eighteen patients (51%) had normal preoperative continence (FISI=0), of which 83% had no change in functionality and continence decreased in three.

Conclusion

Short term functional results of TAMIS for rectal polyps are excellent and comparable to results using the TEM-equipment. More research on outcome after TAMIS is needed to assess morbidity-rates and oncologic clearance.

Introduction

Currently, the preferred method for local resection of rectal polyps is transanal endoscopic microsurgery (TEM). With this technique a full thickness local excision of T1 rectal cancers, large polyps and neuroendocrine tumours can be safely performed and radical rectal surgery in form of total mesorectal excision (TME) can be avoided. However, the specialised instruments for TEM are expensive and the technique has a long learning curve.[1,2]

It is hypothesised that due to prolonged dilatation of the anorectal sphincter with the introduction of a 4cm wide operating rectoscope during TEM, sphincter function might be at risk.[3,4] However, no clinically significant postoperative fecal incontinence has been reported.[5,6]

Transanal minimally invasive surgery (TAMIS) is a relatively new technique utilising a disposable flexible port in combination with conventional laparoscopic instruments for local excision of rectal polyps.[7,8] The start-up costs for this method are less compared to the TEM equipment, although there are ongoing costs per case for flexible ports. However, it has to be noted that the cost per case due to disposable insufflation equipment used for TEM is similar to the costs of most disposable flexible ports. The technique of TAMIS is advocated to be more easy to learn9 and since no specialised insufflator or operating rectoscope is needed, it is more readily available. Further, this procedure could be performed under spinal anaesthesia.10 Another major advantage is that all procedures can be performed in supine position rather than positioning depending on tumour location as with TEM, thus saving theatre time. Although some studies report that no sphincter lesion is noted after TAMIS,[7,10] to date literature on the functional outcome of TAMIS is lacking. The aim of this analysis was to study the feasibility of TAMIS and prospectively assess the functional results of TAMIS using Rockwood's Fecal Incontinence Severity Index (FISI) pre- and postoperatively.[11]

Patients and methods

All consecutive patients eligible for elective transanal surgery at the TweeSteden and St. Elisabeth Hospitals in Tilburg, the Netherlands, were included in a prospective database for quality control purposes. Informed consent was obtained from all patients and the study was approved by the institutional ethics committee. Criteria for eligibility in the present analysis were comprised of sessile rectal adenomas with any degree of dysplasia, cT1-carcinomas or more invasive tumours in patients unsuitable for rectal resection. All patients were assessed preoperatively with rectal digital examination, flexible colonoscopy, tumour biopsy and rigid rectoscopy; the latter to determine height and location of the lesion. In case of invasive carcinomas, or lesions larger than 30mm, patients were also staged preoperatively with pelvic magnetic resonance imaging (MRI). Preoperatively, endoanal sonography was performed to exclude deep invasion (>T1) in all patients. The FISI detailed questionnaire was completed by the treating physician together with the patient during the first preoperative consultation. The Fecal Incontinence Severity Index is based on a type x frequency matrix.[11] The matrix includes four types of leakage commonly found in the fecal incontinent population: gas, mucus, liquid and solid stool and five frequencies: one to three times per month, once per week, twice per week, once per day, and twice per day. The FISI questionnaire was developed using both colon and rectal surgeons and patient input for the specification of the weighting scores. FISI scores range from 0 (total continence) to 61 (complete incontinence to solid stool on a daily basis). The cumulative of the validated weighting scores (based on patients' rating of severity) was used. Postoperatively, the FISI questionnaire was completed again at 3, 6, 9 and 12 months. Preoperative FISI scores were compared to postoperative scores, using the first postoperative measurement. Follow-up routinely consisted of 3 month physical examination and rigid rectoscopy, supplemented by polyp screening as described by national guidelines. In case of T1 invasive carcinomas, follow-up also included annual pelvic MRI.

Surgical procedure

TAMIS was performed or supervised by one colorectal surgeon (D.Z.), trained in TEM and laparoscopic surgery. All patients underwent standard bowel preparation using a phosphate enema, in the morning before surgery. For antibiotic prophylaxis, patients received 2.2 grams of amoxicillin-clavulanic acid and all patients received a urinary catheter during surgery which was removed on the first postoperative

day. The TAMIS procedure was performed in lithothomy position using the single incision laparoscopic surgery (SILS™)-port (Covidien, Mansfield, MA, USA) or single-site laparoscopic (SSL™) access system (Ethicon Endo-Surgery, Cincinnati, OH, USA). Pneumorectum was established with a pressure of 8mmHg. High-definition laparoscopic optics were used with 30° camera lenses and standard laparoscopic instruments as well as a laparoscopic ultrasonic dissection device. In all cases a full thickness rectal wall excision was performed. The rectal wall defect was closed using a V-loc™ barbed absorbable suture (Covidien) at the surgeon's discretion. Patients received standard postoperative care and were discharged at the earliest on the first postoperative day.

Data collection

The following data were prospectively collected and maintained: patient demographics, details on preoperative diagnostic examinations, surgical details, histopathological results, per-operative complications, postoperative complications (defined as postoperative haemorrhage requiring readmission, re-intervention or transfusion, abscesses and/or fistulae, urinary tract infections, mortality), hospital stay, readmissions, pre- and postoperative FISI scores and follow-up data (local recurrences and long-term morbidity).

Statistical analysis

Descriptive statistics were used for describing the study population (demographic and clinical characteristics). Statistical analysis was performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) for windows. Statistical significance was defined as $p<0.05$. Changes of FISI score pre- and postoperatively within the study population were evaluated using the nonparametric Wilcoxon signed-ranks test. To determine which factors were associated with improvement or decline in pre- and postoperative FISI scores, a univariate linear regression analysis was performed using operation time, distance from dentate line, closure of the rectal defect and specimen size as independent variables.

Results

Between October 2011 and September 2013, 37 consecutive patients underwent TAMIS and were included in the present analysis. Patient characteristics are depicted in Table 1. Median age was 71 years (34-91), nineteen patients (51%) were female and median distance of lesions from the dentate line was 7cm (0-19).
TAMIS was completed in 36 patients. Conversion to laparoscopic anterior resection was performed in one patient due to a large rectal defect with pneumoperitoneum. A second defect with pneumoperitoneum was successfully closed using TAMIS. Median operation time was 64 minutes (range 17-211 minutes, Table 2). In seven cases (19%) a 'hybrid technique' was used, in which case the most distal part of the excision was performed transanally using a Scott retractor (Lone Star Retractor System, Lone Star Medical Products, TX, USA). In all of these cases, the rectal lesion was located within 4cm of the anal verge. The rectal defect was closed in 27 cases (73%). Closure was deemed unnecessary in eight cases, in one patient impossible due to the defect's size and the other patient had pneumoperitoneum and subsequent conversion to laparoscopic resection.

	n=37
Male	18 (49%)
Median age in years (range)	71 (34-91)
Median distance from dentate line (range)	7 cm (0-19)
Patients with preoperative functional impairment*	17 (49%)
Mean preoperative FISI score (range)**	21 (4-40)

Table 1. Patient characteristics

FISI: Fecal Incontinence Severity Index
* FISI scores were available in 35 patients
** For patients with preoperative impairment

Histopathology

A median surface of 18 cm2 was resected (4.5-56 cm^2, Table 2). The histopathological results of resected specimens showed adenoma in twenty-three cases (62%), carcinoma in situ in seven patients (19%) and invasive carcinoma in six (16%). In one patient no residual tumour was found after earlier endoscopic resection of a carcinoma in situ. Of the six patients with invasive carcinomas, one received palliative TAMIS for a T3 tumour; one patient with a T2 tumour underwent

	n=37
Median operation time (range)	64 min (17-211)
Hybrid technique	7 (19%)
Defect closure	27 (73%)
Median hospital stay (range)	1 day (1-23)
Conversion	1 (3%)
Peroperative complications	2 (5%)
• Rectal perforation	2
Postoperative complications	3 (8%)
• Haemorrhage	2
• Abscess	1
Long-term morbidity	3 (8%)
• Local recurrence	2
• Rectal stricture	1
Readmissions	3 (8%)
Histopathological results	
• Adenoma	23 (62%)
• Carcinoma in situ	7 (19%)
• Invasive adenocarcinoma	6 (16%)
• T1	4
• T2-3	2
Median size of resection (range)	18 cm^2 (4.5-56)
Positive margins R1/Rx	6/2

Table 2. Operative results

FISI: Fecal Incontinence Severity Index
* FISI scores were available in 35 patients
** For patients with preoperative impairment

subsequent laparoscopic TME. Others were T1 carcinomas. No patients received neoadjuvant treatment prior to TAMIS. There were no fragmented excisions.
Six specimens (16%) showed microscopically positive margins and in two cases uncertainty on margin completeness remained after histopathological examination. Of resections with positive margins, two were carcinoma in situ, others were adenomas. These patients received no additional surgery but were observed closely.

Postoperative course

Patients were discharged after a median of one day (1-23 days) and three patients were readmitted. Postoperative complications occurred in three patients (8%): two patients were readmitted for postoperative haemorrhage and treated successfully with conservative treatment and no blood transfusion in both; one patient suffered from a pelvic abscess leading to fistula and reoperation. The abscess was drained and the perineal fistula that formed healed spontaneously.

Functional results

The FISI scores were available for 35 patients, which were subsequently included in the following analysis. Overall, the observed differences in mean FISI scores pre- and post TAMIS showed a significant decline (10 pre-TAMIS (range 0-40) vs. 5 post-TAMIS (range 0-20), p=0.01, Figure 1). Preoperatively, eighteen patients (51%) had a normal continence (FISI=0), three of these patients developed postoperative soiling, which was no longer apparent in two patients after 6 months (Figure 2). Seventeen patients (49%) had decreased continence before surgery with a mean FISI score of 21 (4-40). Continence improved in fifteen of these patients (88%) after surgery; no change was observed in one patient (6%) and continence further decreased in one (6%). Postoperative FISI scores were significantly lower in patients with impaired preoperative continence (21 preoperatively vs. 9 postoperatively, p=0.001), indicating a significant improvement in anorectal function after TAMIS for patients with impaired preoperative continence. In the univariate linear regression analysis, no independent variables were significantly associated with improvement or decline of pre- and postoperative FISI score.

Follow-up

Median follow-up was 11 months (3-19 months). One patient developed a rectal stenosis four months after TAMIS with rectal defect closure, which was successfully treated with endoscopic dilatation. During the follow-up period, two patients (5%) developed recurrent disease. One patient had recurrent carcinoma in situ nine months after microscopic complete excision with TAMIS of a T1 carcinoma. The other patient presented with a second recurrent adenoma eight months after TAMIS with positive microscopic margins. The initial excision was done elsewhere using TEM. Both patients were successfully re-operated using TAMIS.

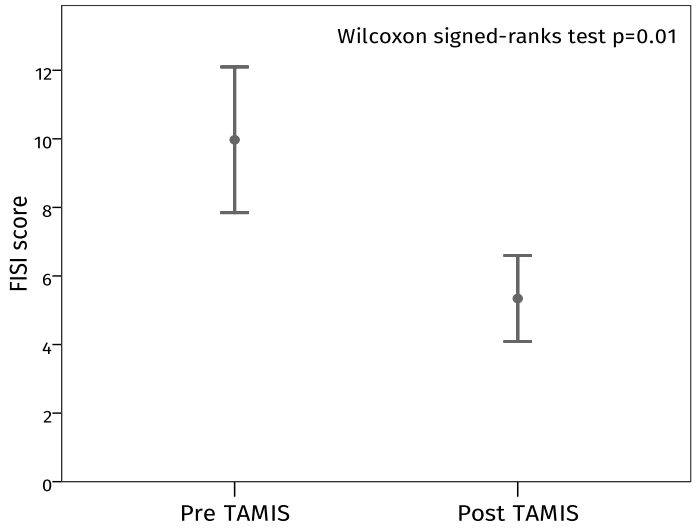


Figure 1. Overall pre- and postoperative FISI score

Values are mean (±SEM). Higher FISI scores indicate worse anorectal functioning. FISI scores range from 0 (total continence) to 61 (complete incontinence to solid stool on a daily basis).

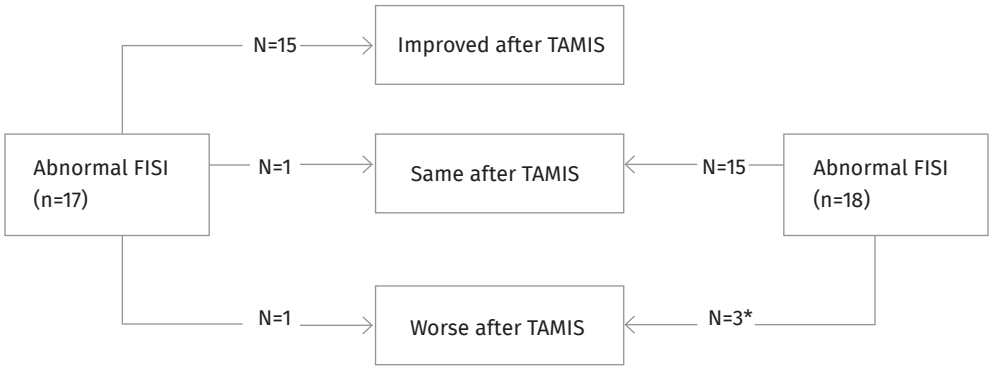


Figure 2. Functional outcome after TAMIS

* FISI score normalised after 6 months in two patients
TAMIS: Transanal minimally invasive surgery
FISI: Fecal Incontinence Severity Index

Discussion

In this analysis of 37 patients we studied the feasibility of TAMIS and its influence on anorectal functioning. We showed the technique is feasible with a median operation time of 64 minutes and low morbidity rates. Lesions up to 56cm^2 can be resected using TAMIS and short term functional results show a significant improvement of continence in 88% of patients with pre-existent impaired anorectal function (p=0.001).

With the introduction of TEM as a minimally invasive procedure for excision of rectal lesions in the 1980's by Buess in Germany,[12] a safe and effective alternative for radical resections of rectal adenomas and T1N0 adenocarcinomas has been introduced, although for T1 carcinomas a higher incidence of local recurrence is reported as compared to TME.[13] Local resections with TEM also appear to be superior in terms of functional results, as postoperative morbidity from sphincter-preserving TME surgery, such as anterior resection syndrome and defecation disorders, are avoided.[14,15]

The use of single port surgical access techniques has been adopted in laparoscopic surgery and more recently in transanal surgery as an alternative to TEM.[7,8] Advantages are the lower costs of the disposable ports, 360° visibility and the use of standard laparoscopic instruments which may also lead to a more readily available use. Even though favourable functional results have been reported after TEM,[5,16,17] conceptually, the use of flexible ports in comparison to the rigid TEM apparatus might lead to less damage on the anal sphincter complex during surgery since these ports are more malleable and might allow for a better fit within the anal canal. However, the movements of the portal could be more extreme compared to TEM and might damage the sphincter complex. To date, literature reports on the use of TAMIS are promising,[7,9] but no studies specifically addressed functional outcome following TAMIS. In the present series, we show that in the majority of patients with pre-existent impairment of anorectal function, functional outcome after TAMIS is significantly improved. Additionally, in 83% of patients without pre-operative impairment, functionality remained unaffected by TAMIS. The postoperative impairment of fecal continence in the minority of our patients was limited and temporarily in 50% of the cases. No manometric studies or sonographic assessments of the anal sphincter were performed as clinical significance of these investigations remains uncertain.[4,18]

Our results are fully comparable with reports on functional outcome after TEM.[5,19] Doornebosch et al. reported deterioration of FISI scores in 15% of patients after TEM

and improvement in 51%.[5,19] Fenech et al. also described a higher preoperative FISI score in patients with large villous adenomas which led to an overall improvement of fecal continence in 38.5% of patients.[16] These improvements may be due to the fact that rectal lesions and subsequent mucous production attribute to symptoms of fecal incontinence which disappear once the lesion is excised. Furthermore, the presence of a large rectal mass may induce a continuous internal anal sphincter reflex, leading to a decreased anorectal function. This may explain the high number of patients with preoperative impairment in our study. Additionally, Doornebosch et al. stated that the location of neoplasms within the rectum may influence functional outcome.[5] We found no variables that were significantly associated with difference in pre- and postoperative FISI score. This might however be due to limited sample size. The margin positivity rate in our cohort is higher as reported in previous TAMIS series.[7,9] However, results are similar to earlier large reports on conventional TEM resection.[1,21] Furthermore, in the second half of this study, the resected specimen was pinned down after surgery to facilitate pathology examination and margin positivity rates declined from 21% to 11%. Also, these results may reflect a learning curve effect of both surgeon and pathologist. Finally, it has to be noted that despite meticulous follow-up, only 2 local recurrences were encountered, of which margin positivity was reported in only one case.

As this is a new technique in our centre, other results may have also been subject to a learning curve effect. However, the limited sample size of our study population precludes adequate analysis of learning curve effects and more research will be needed to conclude if this affects surgical outcome, oncologic clearance and recurrence rate after TAMIS.

One potential disadvantage of TAMIS might be the use of the disposable port for lesions in the upper rectum. As introduction of the port is only limited, lesions located higher from the dentate line might be unable to reach. Median distance from the dentate line was 7cm in our population and no difficulties were encountered in TAMIS for more proximal lesions. However, in one patient, a conversion to laparoscopic anterior resection occurred due to inability to close a peritoneal defect. Possibly, closure of this defect would have been possible if regular TEM equipment were available.[20,21]

A limitation of the present analysis is the lack of quality of life measurements in addition to assessment of anorectal functioning, since this would depict patients' perspectives and may attribute to clinical significance. However, the FISI questionnaire used in our study is an easy to use validated instrument, utilising patient input to weigh type and severity of fecal incontinence. Furthermore, it has been shown to have an excellent correlation with quality-of-life measures (lifestyle,

restriction, depression, and embarrassment).[22] In the past years this questionnaire has proven to be a highly sensitive measuring tool which enables assessment of functional recovery (or deterioration) over time.[22]

Conclusion

TAMIS for rectal lesions is feasible and short term functional results are excellent and comparable to results after TEM. More research on TAMIS is needed to draw definitive conclusions on safety and oncologic clearance. However, the present series is encouraging and offers no barriers to continue utilising this promising technique. Future studies on functional outcome should focus on long term functionality and quality of life measurements.

References

1. Barendse RM, Dijkgraaf MG, Rolf UR, et al. Colorectal surgeons' learning curve of transanal endoscopic microsurgery. Surg Endosc 2013;27:3591-602.
2. Maslekar S, Pillinger SH, Sharma A, Taylor A, Monson JR. Cost analysis of transanal endoscopic microsurgery for rectal tumours. Colorectal Dis 2007;9:229-34.
3. Dafnis G, Pahlman L, Raab Y, Gustafsson UM, Graf W. Transanal endoscopic microsurgery: clinical and functional results. Colorectal Dis 2004;6:336-42.
4. Herman RM, Richter P, Walega P, Popiela T. Anorectal sphincter function and rectal barostat study in patients following transanal endoscopic microsurgery. Int J Colorectal Dis 2001;16:370-6.
5. Doornebosch PG, Gosselink MP, Neijenhuis PA, Schouten WR, Tollenaar RA, de Graaf EJ. Impact of transanal endoscopic microsurgery on functional outcome and quality of life. Int J Colorectal Dis 2008;23:709-13.
6. Planting A, Phang PT, Raval MJ, Brown CJ. Transanal endoscopic microsurgery: impact on fecal incontinence and quality of life. Can J Surg 2013;56:243-8.
7. Albert MR, Atallah SB, deBeche-Adams TC, Izfar S, Larach SW. Transanal minimally invasive surgery (TAMIS) for local excision of benign neoplasms and early-stage rectal cancer: efficacy and outcomes in the first 50 patients. Dis Colon Rectum 2013;56:301-7.
8. Atallah S, Albert M, Larach S. Transanal minimally invasive surgery: a giant leap forward. Surg Endosc 2010;24:2200-5.
9. Barendse RM, Doornebosch PG, Bemelman WA, Fockens P, Dekker E, de Graaf EJ. Transanal employment of single access ports is feasible for rectal surgery. Ann Surg 2012;256:1030-3.
10. Lee TG, Lee SJ. Transanal single-port microsurgery for rectal tumors: minimal invasive surgery under spinal anesthesia. Surg Endosc 2014;28:271-80.
11. Rockwood TH, Church JM, Fleshman JW, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. Dis Colon Rectum 1999;42:1525-32.
12. Buess G, Kipfmuller K, Hack D, Grussner R, Heintz A, Junginger T. Technique of transanal endoscopic microsurgery. Surg Endosc 1988;2:71-5.
13. De Graaf EJ, Doornebosch PG, Tollenaar RA, et al. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. Eur J Surg Oncol 2009;35:1280-5.
14. Doornebosch PG, Tollenaar RA, Gosselink MP, et al. Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer. Colorectal Dis 2007;9:553-8.
15. Emmertsen KJ, Laurberg S. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. Br J Surg 2013;100:1377-87.
16. Fenech DS, Takahashi T, Liu M, et al. Function and quality of life after transanal excision of rectal polyps and cancers. Dis Colon Rectum 2007;50:598-603.
17. 1Wang HS, Lin JK, Yang SH, Jiang JK, Chen WS, Lin TC. Prospective study of the functional results of transanal endoscopic microsurgery. Hepatogastroenterology 2003;50:1376-80.
18. Kennedy ML, Lubowski DZ, King DW.

Transanal endoscopic microsurgery excision: is anorectal function compromised?
Dis Colon Rectum 2002;45:601-4.

19. Barendse RM, Oors JM, de Graaf EJ, et al. The effect of endoscopic mucosal resection and transanal endoscopic microsurgery on anorectal function.
Colorectal Dis 2013;15:e534-41.
20. Rimonda R, Arezzo A, Arolfo S, Salvai A, Morino M. TransAnal Minimally Invasive Surgery (TAMIS) with SILS port versus Transanal Endoscopic Microsurgery (TEM): a comparative experimental study.
Surg Endosc 2013;27:3762-8.
21. de Graaf EJ, Doornebosch PG, Tetteroo GW, Geldof H, Hop WC. Transanal endoscopic microsurgery is feasible for adenomas throughout the entire rectum: a prospective study. Dis Colon Rectum 2009;52:1107-13.
22. Cavanaugh M, Hyman N, Osler T. Fecal incontinence severity index after fistulotomy: a predictor of quality of life.
Dis Colon Rectum 2002;45:349-53.

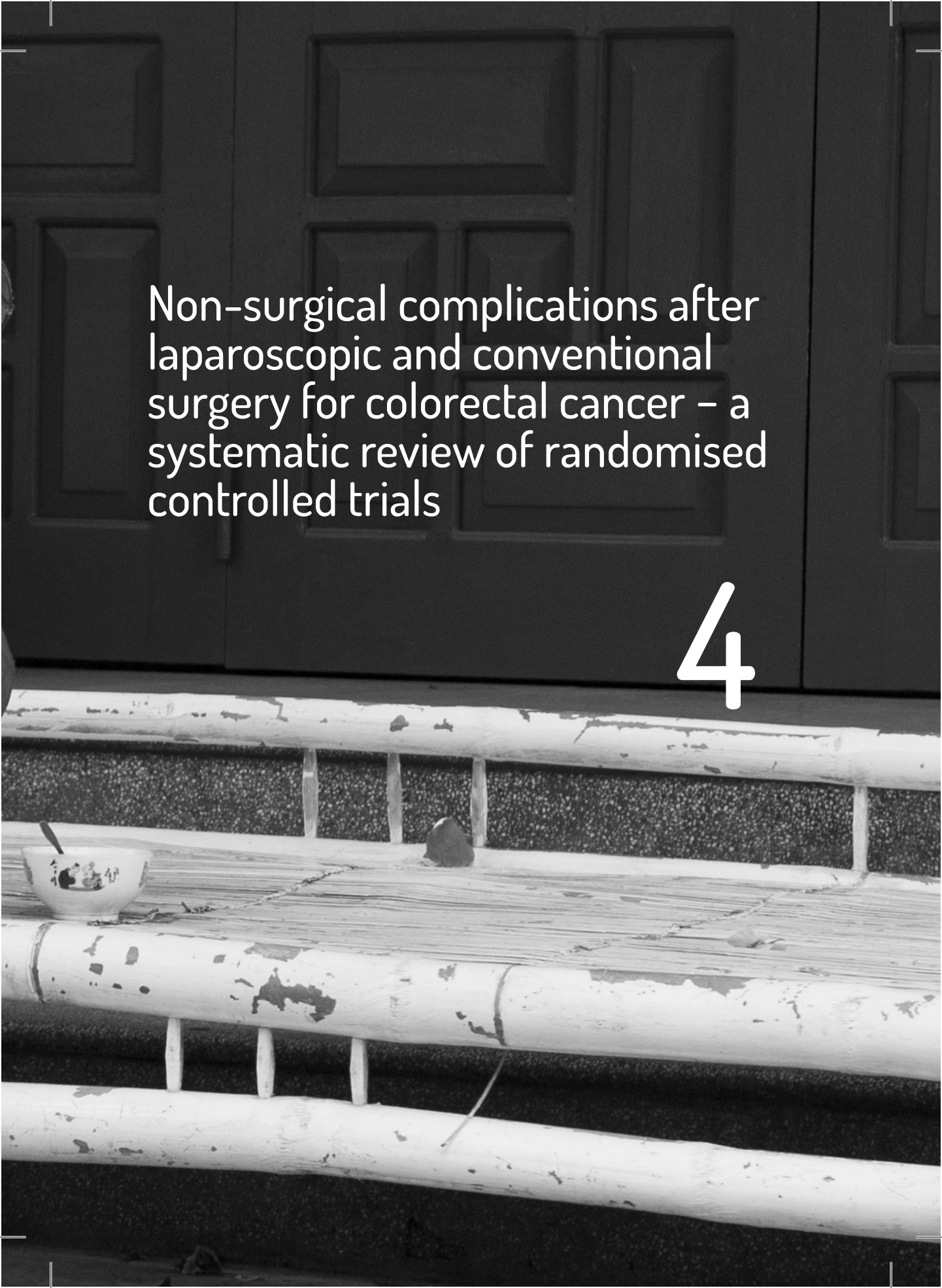
Submitted

Anandi H.W. Schiphorst
Norbert M. Verweij
Apollo Pronk
Inne H.M. Borel Rinkes
Marije E. Hamaker

photo: Delgada by Martin Garrido

Non-surgical complications after laparoscopic and conventional surgery for colorectal cancer – a systematic review of randomised controlled trials

4



Abstract

Background

Morbidity rates in colorectal cancer surgery are high. Cardiac and pulmonary complications account for a large part of postoperative mortality, especially in the growing number of elderly colorectal cancer patients. This review studies the effect of laparoscopic surgery for colorectal cancer on short term non-surgical morbidity.

Methods

A literature search was conducted in Medline and Embase to identify randomised trials on laparoscopic compared to conventional colorectal surgery with reported cardiac or pulmonary complications.

Results

The search retrieved 3302 articles, of which 18 studies were included with a total of 6153 patients. Eight trials (44%) studied colon cancer patients, seven trials (39%) included only rectal cancer patients and three studies (17%) included both. Overall reported incidence of postoperative cardiac complications was low for both laparoscopic and conventional colorectal resection (median 2%, range 0-7%). In the pooled analysis, there was a trend towards fewer cardiac adverse events following laparoscopic surgery (OR 0.66, 95% CI 0.41-1.06, p=0.08), and this effect was most marked for laparoscopic colectomy (OR 0.28, 95% CI 0.11-0.71, p=0.007). Incidence of postoperative pulmonary complications ranged from 0-11% (median 2%) and no benefit on pulmonary complications was found for laparoscopic surgery, although a possible trend was seen in favour of laparoscopic colectomy (OR 0.78, 95% CI 0.53-1.13, p=0.19). Overall morbidity rates varied from 11% to 69% with a median of 33%. Mortality rates were generally low (median 2%).

Conclusion

One-third of patients in trials on conventional versus laparoscopic colorectal surgery suffer from postoperative morbidity. For laparoscopic colectomies, significantly less cardiac complications occurred compared with conventional surgery. However, it is unclear whether these results from clinical trials can be extrapolated to the heterogeneous real-life population of colorectal cancer patients.

Introduction

With the global rise in life expectancy and the increasing incidence of colorectal cancer, more elderly patients are diagnosed with this disease.[1] As surgery remains the cornerstone of curative therapy, the number of older patients presented for colorectal resection is increasing rapidly. Elderly patients are at a higher risk of postoperative morbidity,[2, 3] and suffer from increased excess mortality rates throughout the first year after colorectal surgery.[4] Recent population-based data suggest that this vulnerable patient population can benefit from the use of less invasive surgical approaches.[5]

Since its introduction in the 90's,[6] laparoscopic surgery has gained wide acceptance for resection of malignancies in the colon,[7] although debate on the optimal surgical strategy for rectal cancers remains.[8, 9] The short-term benefits of laparoscopic surgery, such as less pain, reduced blood loss, shorter hospitalisation and faster recovery have been described in a myriad of publications.[9-11] Another potential benefit of laparoscopic surgery may be a reduction of cardio-pulmonary morbidity,[12] resulting from a decrease in blood loss and stress response with minimally invasive techniques and from reduced postoperative pain. Cardiac and pulmonary complications are associated with a considerable increase in mortality and health care costs,[12-16] and have been advocated as a target for quality improvement in elective colorectal surgery.[17]

Since most studies on laparoscopic surgery for colorectal cancer have focused on surgical or oncologic outcome, it is unclear if laparoscopic surgery leads to a reduction of cardiac and pulmonary morbidity. Therefore, we set out to investigate the incidence of non-surgical complications in randomised trials on laparoscopic resections for colorectal cancer and to assess whether possible benefits of less invasive surgery on non-surgical complications are similar for older and younger patients.

Methods

We aimed to identify randomised clinical trials comparing laparoscopic with conventional colorectal surgery. The primary outcome measure for this systematic review was the incidence of cardiac and pulmonary complications in short-term follow-up (occurring during hospital stay or within 30 days after surgery). Cardiac complications were defined as myocardial infarction, heart failure, arrhythmia, angina pectoris, cardiac arrest or other cardiac complications. Pulmonary complications could consist of pneumonia, atelectasis, pulmonary embolism, pulmonary insufficiency or other pulmonary complications. Secondary endpoints were overall morbidity, mortality and other non-surgical (general) complications.

Search strategy and article selection

The following search was performed on December 13th 2013, in both Medline and Embase: ((clinical AND (trial OR study)) OR (randomi* AND trial)) AND (((laparoscopy[MeSH Major Topic]) OR (laparoscop*[tiab] OR (minimal* AND invasive))) AND (((((“Neoplasms"[Mesh]) OR (neoplasm*[tiab] OR cancer*[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR oncolog*[tiab] OR malignan*[tiab]))) AND (colorectal OR colon OR rectal OR rectum)) OR ("Colorectal Neoplasms"[Mesh]))). MeSH refers to medical subheading; tiab refers to title and abstract. No limits in age, language or publication date were applied.
The titles and abstracts of all studies retrieved by the search were assessed by one reviewer (AS) to determine which warranted further examination. All potentially relevant articles were subsequently screened as full text by two authors (AS and NV). Non-randomised studies were excluded, as were animal-studies, non-original reports, abstracts for conference meetings and non-English papers. In addition, studies on other cancer types or benign disease and those that did not compare laparoscopic to conventional surgery were excluded. Trials were only included if an intention-to-treat analysis was done or could be performed based on the presented data. Finally, specific publications from subgroup analysis of elderly patients were included. If only an abstract was available, an effort was made to find the final report of the study by searching Embase and Medline using the names of the first, second and/or final author as well as key words from the title. References of included publications were cross-referenced to retrieve any additional relevant citations.

Data extraction

Data regarding study design and results for each eligible study were independently

extracted by two investigators (AS and NV), using a predefined electronic data extraction form. Items that were extracted were: in- and exclusion criteria (including upper age limits and cardio-pulmonary restrictions), study demographics, study population (age, American Association of Anaesthesiologists (ASA)-score, location of tumours, TNM staging), number of patients receiving allocated treatment, conversion rate, complications occurring in the first 30 days after surgery: cardiac and pulmonary complications, overall morbidity (the overall number of patients suffering one or more postoperative adverse events), other non-surgical complications (categorised as renal, urogenital, neuropsychological, vascular and other) and perioperative mortality (occurring during hospital stay or within 30 days after surgery). For each type of complication, the reported number of events was extracted, meaning that one patient could have experienced several complications. In addition, study results specific to elderly patients were extracted whenever available.

Quality assessment

The methodological quality of each of the studies was independently assessed by two reviewers (AS, NV), using a 9-item list adopted from the Cochrane guidelines for methodological assessment of randomised trials[18] and the guidelines for critical appraisal of randomised controlled trials supplied by the Oxford Centre for Evidence Based Medicine.[19] Details can be found in Appendix 1. Disagreement among the reviewers was discussed during a consensus meeting and in case of persisting disagreement the assistance of a third reviewer (MH) was enlisted.

Data synthesis and analysis

We summarised the study results to describe our main outcomes of interest. Data on cardiac and pulmonary complications as well as mortality rates were pooled using the Review Manager software.[20] Where data were not supplied, the study was excluded from analysis for that outcome. When possible, separate data regarding colonic and rectal resections are presented. The I2 statistic and Cochran Q Chi2 test were used to assess heterogeneity between studies and statistical heterogeneity was defined as $I2>30\%$ and $p\leq0.05$. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using a fixed-effects model (Mantel-Haenszel method) when statistical heterogeneity was absent.
For other outcomes, performing a formal meta-analysis was deemed inappropriate due to heterogeneity of trials and differences in definitions of morbidity between studies; therefore, only summarised results are presented.

Results

Literature search

A total of 3302 articles were retrieved with the literature search (Medline 1237, Embase 2065). After exclusion of 610 duplicates, and 2672 for other reasons (Figure 1), 20 articles on 18 studies were included in the present analysis.[9, 11, 13, 21-37] Cross-referencing yielded no additional results.

Study characteristics

Trial characteristics of included studies are depicted in Table 1. Studies were carried out between 1993 and 2010. The pooled data comprised of 6153 patients and there were six multi-centre trials.[9, 11, 13, 24, 27, 32] The median sample size was 212 (range 28-1082) and most studies used a one-to-one randomisation design. Two studies published separate analyses for elderly patients.[36, 37]

No upper age limits were used. Two trial protocols defined cardiac or pulmonary restrictions in their exclusion criteria.[13, 22] Reported median or mean age varied from 56 years to 72 years. Comorbidity was addressed by eleven studies (61%), most of which only reported on the distribution of ASA-scores in their study population. The percentage of included patients with ASA-scores ≥3 ranged from 7%-38% (Table 1). Eight studies (44%) included only patients with tumours located in the colon, seven trials (39%) focused on rectal cancer patients and three studies (17%) included both, of which one trial specifically mentioned outcome per tumour location. Eight trials (44%) included patients with stage 4 disease. Seventeen studies (94%) described their conversion percentage and these ranged from 0% to 45%, with a median of 12% (Table 1).

Quality assessment

Overall quality assessment is depicted in Figure 2; details per study can be found in Appendix 2. Risk of bias in random sequence generation and allocation concealment was generally low. One trial randomised after initial diagnostic laparoscopy to assess the feasibility of laparoscopic resection,[32] while other trials randomised patients prior to surgery. No studies stated blinding of their patients, surgeons or other personnel. There was a significant risk of detection bias, as blinding of outcome assessment was reported in only one trial while four trials supplied insufficient data. Risk of attrition bias was low in all included studies. Primary endpoints were defined in 89% of trials and 61% of included studies described an adequate power calculation (three trials reported not achieving their initial inclusion). Baseline

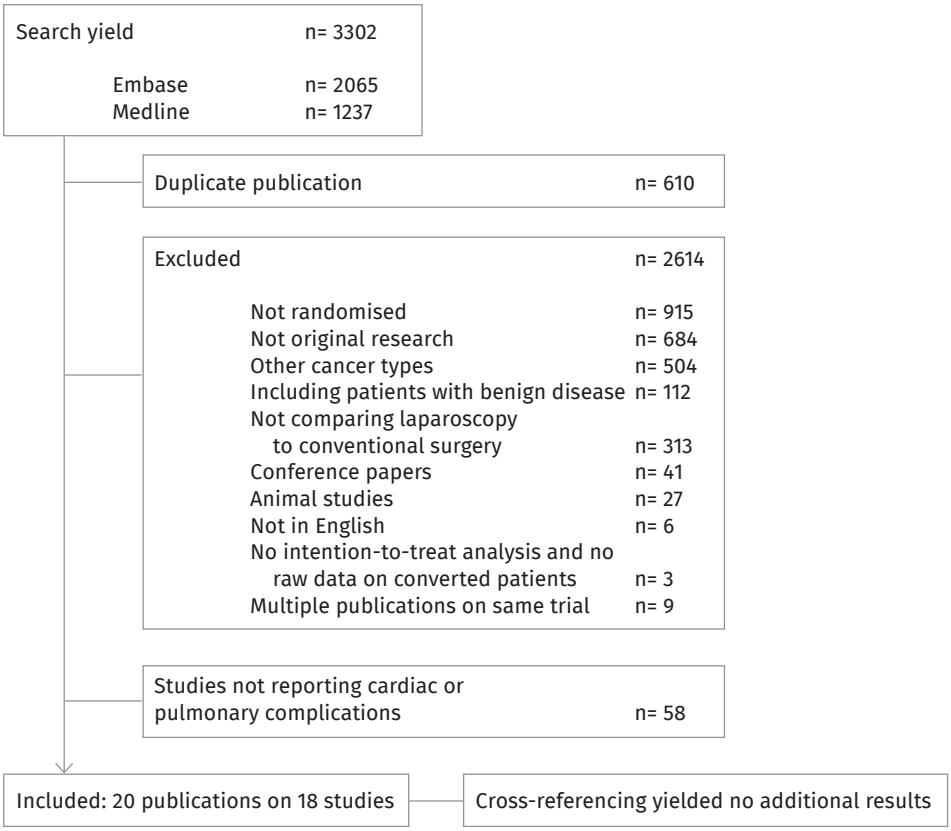


Figure 1. Search results and trial selection

group comparison was considered adequate in ten trials (56%); in two, baseline characteristics were significantly different between groups (a significantly higher age of patients treated with laparoscopy in one study and more advanced disease in the laparoscopic group in another study). The remaining six reports supplied insufficient data on comorbidity to determine the adequacy of group comparability. Intention-to-treat analyses were reported by sixteen trials (89%). Two trials provided a separate analysis for converted patients,[23, 25] and these data were re-classified for our primary outcome.

Cardiac complications

Data regarding cardiac complications were available from ten trials (Table 2), reporting on a total of 3773 patients. Overall incidence of postoperative cardiac complications was low for both laparoscopic and conventional colorectal resection, ranging from 0% to 7% with a median of 2%. None of the individual studies found significant differences in the incidence of cardiac complications. In the pooled analysis, there was a trend towards fewer cardiac adverse events following laparoscopic resection of colorectal malignancies as compared to conventional resection (odds ratio (OR) 0.66, 95% confidence interval (CI) 0.41-1.06, p=0.08, Figure 3a). The benefit of laparoscopic surgery was most marked for colectomies (OR 0.28, 95% CI 0.11-0.71, p=0.01, Figure 3b), while for rectal resections there was no apparent difference in postoperative cardiac morbidity (OR for laparoscopy 0.85, 95% CI 0.41-1.71, p=0.65, Figure 3c). Although there was no statistical heterogeneity, (I2=0% and p=0.54, Figure 3), there was generally insufficient data regarding the precise definitions of cardiac complications to ascertain the absence of methodological heterogeneity.

Pulmonary complications

Pulmonary complication rates were addressed in all studies. Median reported incidence of pulmonary complications was 2% (range 0%-11%, Table 2), and no individual studies demonstrated significant differences in pulmonary morbidity rate between treatment groups. The pooled analysis showed no difference in the occurrence of pulmonary complications between laparoscopic and conventional surgery (OR 0.94, 95% CI 0.71-1.24, p=0.67, Figure 4a), although there was a possible trend towards lower pulmonary morbidity when focussing on colon cancer only (OR for laparoscopy 0.78, 95% CI 0.53-1.13, p=0.19, Figure 4b). In rectal cancer resection, no benefit for laparoscopic surgery was observed (OR 1.19, 95% CI 0.74-1.90, p=0.47, Figure 4c). Notably, as for cardiac complications, no statistical heterogeneity was observed (I2= 4%, p=0.41, Figure 4a), but methodological heterogeneity could not be excluded.

Right-hand page: Table 1. Characteristics of included studies

Lap: Laparoscopic surgery group; Open: Open surgery group; ASA: American Association of Anaesthesiologists; USA: United States of America

[a] Data presented as reported in articles in mean (SD) or median (range);

[b] Only median ASA-score reported;

[c] Outcome reported separately for colon and rectal cancers;

[d] Converted patients were analysed separately;

Study					Study population									Outcome reported		
Name of trial or author	Year of publication	Sample size	Country	Randomisation period	Tumour location	Tumour stage	Conversion rate	No. of patients		Mean or median age in years[a]		Patients with ASA-score ≥3		Cardiac morbidity	Pulmonary morbidity	Subgroup analysis of elderly patients
								Lap	Open	Lap	Open	Lap	Open			
ALCCaS[24, 36]	2008 2010	592	AU, NZ	1998-2005	C	I-III	15%	294	298	71.1 (±10.4)	69.4 (±11.4)	28%	27%		x	x
Araujo[21]	2003	28	BR	1997-2000	R	I-III	0%	13	15	59.1 (31-75)	56.4 (24-78)	-	-		x	
Braga[22]	2007	168	IT	2000-2003	R	I-IV	7%	83	85	62.8 (±12.6)	65.3 (±10.3)	b	b	x	x	
CLASSICC[13]	2005	794	UK	1996-2002	CR[c]	I-IV	29%	526	268	69 (±11)	69 (±12)	12%	13%		x	
COLOR[11]	2005	1082	FI, FR, DE, IT, NL, ES, SE	1997-2003	C	I-III	17%	536	546	71 (27-92)	71 (31-95)	15%	19%	x	x	
COLOR II[9]	2013	1044	BE, CA, DK, DE, NL, ES, KR, SE	2004-2010	R	I-III	17%	699	345	66.8 (±10.5)	65.8 (±10.9)	19%	18%	x	x	
Curet[23]	2000	43	USA	1993-1995	C	I-IV	28%[d]	25	18	65.6 (45-83)	69.2 (49-82)	-	-	x	x	
Kaiser[25]	2004	48	USA	1995-2001	C	I-III	45%[d]	28	20	59 (41-83)	60.5 (42-80)	-	-	x	x	
Lacy[26, 37]	2002 2000	219	ES	1993-1998	C	I-III	-	111	108	68 (±12)	71 (±11)	-	-		x	x
LAPKON II[32]	2009	472	DE	1998-2004	CR	I-III	11%	250	222	66.8 (±10.1)	66.4 (±11.1)	27%	27%	x	x	
Leung[27]	2004	403	HK	1993-2002	CR	I-IV	23%	203	200	67.1 (±11.7)	66.5 (±12.3)	-	-	x	x	
Li[28]	2012	145	HK	1996-2005	C	I-IV	15%	71	74	68 (±11.3)	68 (±13.3)	25%	16%	x	x	
Liang JT[29]	2007	269	TW	2000-2004	C	I-III	3%	135	143	64.4 (±9.4)	64.2 (±12.0)	7%	10%	x	x	
Liang X[30]	2011	343	CN	2004-2008	R	I-III	1%	169	174	57.3 (±14.1)	57.4 (±13.1)	-	-		x	
Lujan[31]	2009	204	ES	2002-2007	R	I-IV	8%	101	103	67.8 (±12.9)	66.0 (±9.9)	34%	35%		x	
Ng[34]	2008	99	HK	1994-2005	R	I-IV	10%	51	48	63.7 (±11.8)	63.5 (±12.6)	-	-	x	x	
Ng[33]	2014	80	HK	2001-2007	R	I-IV	8%	40	40	60.2 (±11.3)	62.1 (±12.6)	-	-		x	
Pascual[35]	2011	120	ES	2004-2008	C	I-III	12%	60	60	68.5 (±5.4)	71.5 (±5.1)	38%	38%		x	

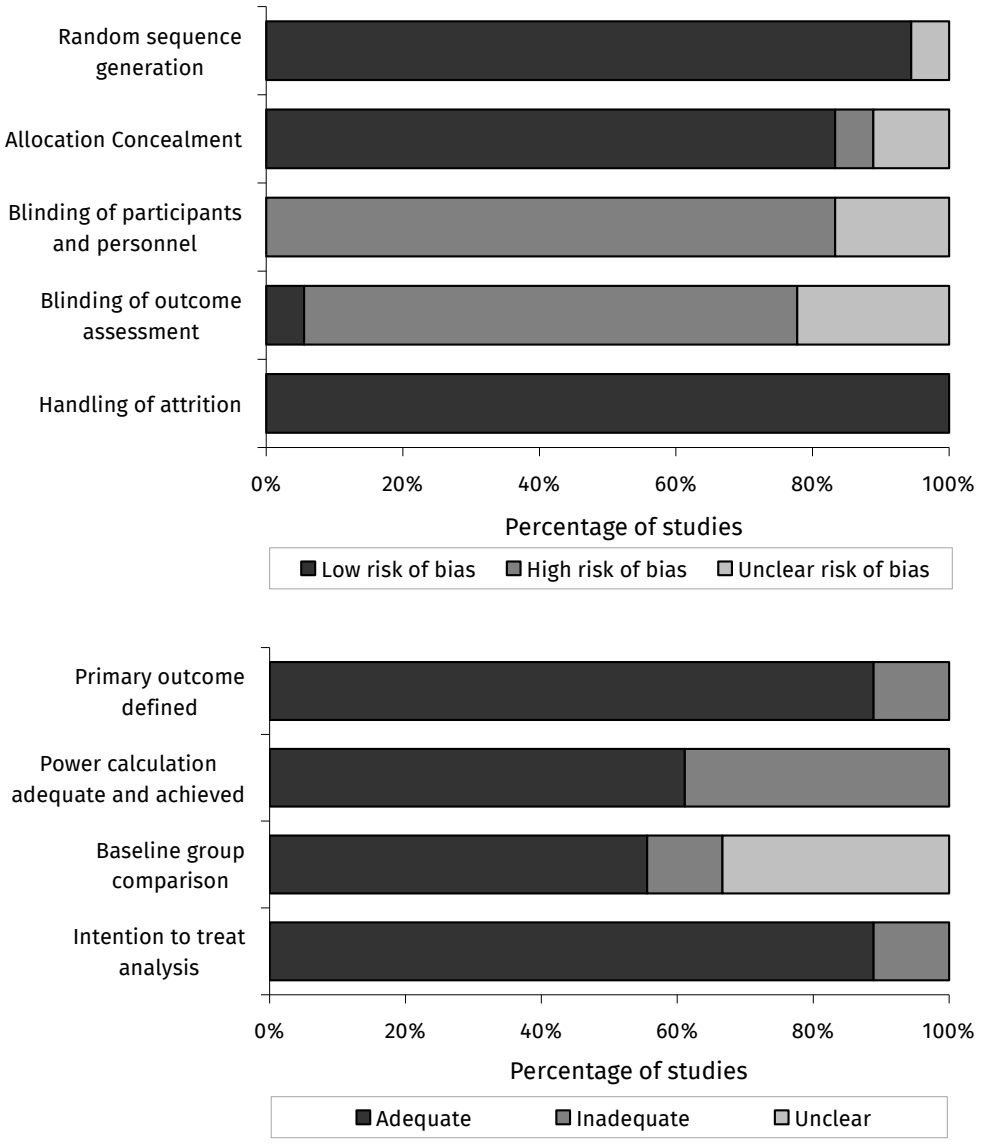


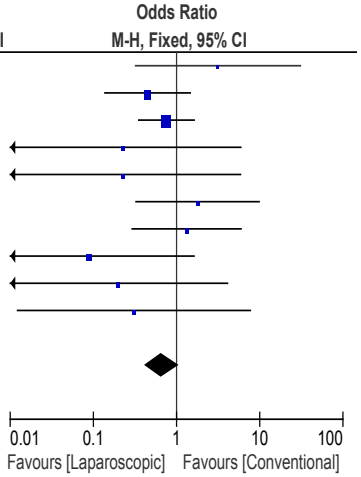
Figure 2. Quality assessment

Quality was assessed using a 9-item list, details of which can be found in Appendix 1.
Full quality assessment for individual studies is depicted in Appendix 2.

a.

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Conventional Events	Conventional Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Braga	3	83	1	85	2.3%	3.15 [0.32, 30.91]
COLOR	4	536	9	546	21.1%	0.45 [0.14, 1.47]
COLOR II	17	699	11	345	34.2%	0.76 [0.35, 1.63]
Curet	0	25	1	18	4.0%	0.23 [0.01, 5.95]
Kaiser	0	28	1	20	4.1%	0.23 [0.01, 5.89]
LAPKON II	4	250	2	222	5.0%	1.79 [0.32, 9.86]
Leung	4	203	3	200	7.1%	1.32 [0.29, 5.97]
Li	0	71	5	74	12.7%	0.09 [0.00, 1.63]
Liang JT	0	135	2	134	6.0%	0.20 [0.01, 4.11]
Ng 2008	0	51	1	48	3.6%	0.31 [0.01, 7.73]
Total (95% CI)		**2081**		**1692**	**100.0%**	**0.66 [0.41, 1.06]**
Total events	32		36			

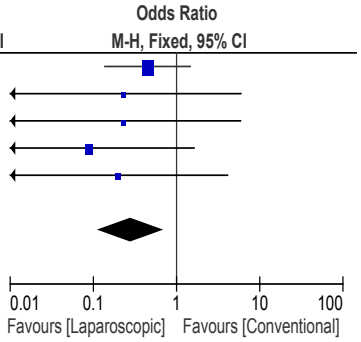
Heterogeneity: Chi² = 7.93, df = 9 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)



b.

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Conventional Events	Conventional Total	Weight	Odds Ratio M-H, Fixed, 95% CI
COLOR	4	536	9	546	44.0%	0.45 [0.14, 1.47]
Curet	0	25	1	18	8.5%	0.23 [0.01, 5.95]
Kaiser	0	28	1	20	8.5%	0.23 [0.01, 5.89]
Li	0	71	5	74	26.6%	0.09 [0.00, 1.63]
Liang JT	0	135	2	134	12.4%	0.20 [0.01, 4.11]
Total (95% CI)		**795**		**792**	**100.0%**	**0.28 [0.11, 0.71]**
Total events	4		18			

Heterogeneity: Chi² = 1.28, df = 4 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)



c.

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Conventional Events	Conventional Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Braga	3	83	1	85	5.7%	3.15 [0.32, 30.91]
COLOR II	17	699	11	345	85.3%	0.76 [0.35, 1.63]
Ng 2008	0	51	1	48	9.1%	0.31 [0.01, 7.73]
Total (95% CI)		**833**		**478**	**100.0%**	**0.85 [0.42, 1.71]**
Total events	20		13			

Heterogeneity: Chi² = 1.73, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)

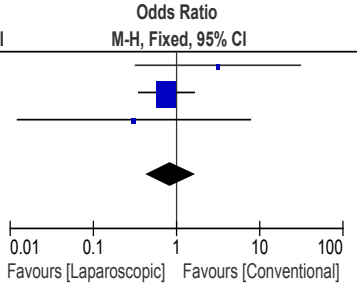
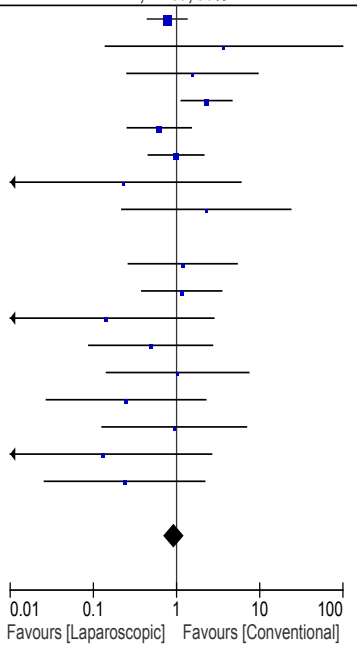


Figure 3. Forest plots for cardiac morbidity for (a) all studies, (b) studies on colon cancer and (c) rectal cancer.

a.

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Conventional Events	Conventional Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ALCCaS	25	294	32	298	28.1%	0.77 [0.45, 1.34]
Araujo	1	13	0	15	0.4%	3.72 [0.14, 99.48]
Braga	3	83	2	85	1.8%	1.56 [0.25, 9.56]
CLASSICC	43	526	10	268	11.7%	2.30 [1.14, 4.65]
COLOR	8	536	13	546	12.3%	0.62 [0.26, 1.51]
COLOR II	20	699	10	345	12.6%	0.99 [0.46, 2.13]
Curet	0	25	1	18	1.6%	0.23 [0.01, 5.95]
Kaiser	3	28	1	20	1.0%	2.28 [0.22, 23.68]
Lacy	0	111	0	108		Not estimable
LAPKON II	4	250	3	222	3.0%	1.19 [0.26, 5.36]
Leung	7	203	6	200	5.6%	1.15 [0.38, 3.50]
Li	0	71	3	74	3.3%	0.14 [0.01, 2.82]
Liang JT	2	135	4	134	3.8%	0.49 [0.09, 2.71]
Liang X	2	169	2	174	1.9%	1.03 [0.14, 7.40]
Lujan	1	101	4	103	3.8%	0.25 [0.03, 2.25]
Ng 2008	2	51	2	48	1.9%	0.94 [0.13, 6.94]
Ng 2014	0	40	3	40	3.3%	0.13 [0.01, 2.65]
Pascual	1	60	4	60	3.8%	0.24 [0.03, 2.19]
Total (95% CI)		**3395**		**2758**	**100.0%**	**0.94 [0.71, 1.24]**
Total events	122		100			

Heterogeneity: Chi² = 16.61, df = 16 (P = 0.41); I² = 4%
Test for overall effect: Z = 0.43 (P = 0.67)



b.

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Conventional Events	Conventional Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ALCCaS	25	294	32	298	46.9%	0.77 [0.45, 1.34]
Classicc - Colon	18	273	5	140	10.0%	1.91 [0.69, 5.25]
COLOR	8	536	13	546	20.5%	0.62 [0.26, 1.51]
Curet	0	25	1	18	2.7%	0.23 [0.01, 5.95]
Kaiser	3	28	1	20	1.7%	2.28 [0.22, 23.68]
Lacy	0	111	0	108		Not estimable
Li	0	71	3	74	5.5%	0.14 [0.01, 2.82]
Liang JT	2	135	4	134	6.4%	0.49 [0.09, 2.71]
Pascual	1	60	4	60	6.3%	0.24 [0.03, 2.19]
Total (95% CI)		**1533**		**1398**	**100.0%**	**0.78 [0.53, 1.13]**
Total events	57		63			

Heterogeneity: Chi² = 7.23, df = 7 (P = 0.41); I² = 3%
Test for overall effect: Z = 1.31 (P = 0.19)

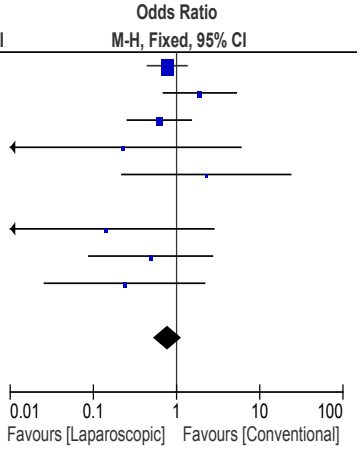
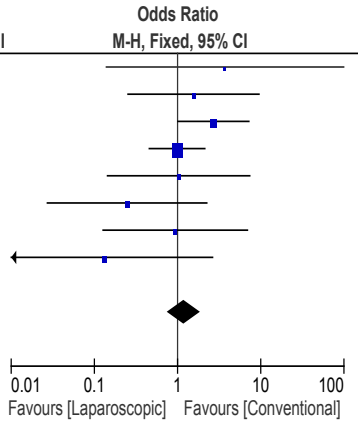


Figure 4. Forest plots for pulmonary morbidity for (a) all studies, (b) studies on colon cancer and (c, right-hand page) rectal cancer.

c.

Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Conventional Events	Conventional Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Araujo	1	13	0	15	1.3%	3.72 [0.14, 99.48]
Braga	3	83	2	85	5.8%	1.56 [0.25, 9.56]
Classicc - rectum	25	253	5	128	18.3%	2.70 [1.01, 7.22]
COLOR II	20	699	10	345	39.9%	0.99 [0.46, 2.13]
Liang X	2	169	2	174	6.0%	1.03 [0.14, 7.40]
Lujan	1	101	4	103	12.0%	0.25 [0.03, 2.25]
Ng 2008	2	51	2	48	6.1%	0.94 [0.13, 6.94]
Ng 2014	0	40	3	40	10.6%	0.13 [0.01, 2.65]
Total (95% CI)		**1409**		**938**	**100.0%**	**1.19 [0.74, 1.90]**
Total events	54		28			

Heterogeneity: Chi² = 7.51, df = 7 (P = 0.38); I² = 7%
Test for overall effect: Z = 0.72 (P = 0.47)



Outcome	Number of studies addressing outcome (n=18)	References	Median reported incidence		Range in reported incidence	
			Lap	Open	Lap	Open
Cardiac complications	10	9, 11, 22, 23, 25, 27-29, 32, 34	1%	2%	0-4%	1-7%
Pulmonary complications	18	9, 11, 13, 21-35	2%	4%	0-11%	0-11%
Overall morbidity	16	9, 11, 13, 21-24, 26-29, 31-35	31%	33%	11-69%	20-55%
Mortality	16	9, 11, 13, 21-24, 26-28, 30-35	1%	2%	0-4%	0-5%
Urogenital complications	16	11, 21-35	5%	5%	1-35%	0-35%
Neuropsychological complications	6	27-29, 32-34	1%	2%	0-1%	0-4%
Vascular complications	8	13, 23, 27-30, 32, 34	1%	2%	0-3%	0-6%
Renal complications	4	26, 28, 32, 33	1%	1%	0-2%	0-1%
Other non-surgical complications	11	9, 11, 22, 24, 26-28, 31-34	3%	2%	0-35%	1-44%

Table 2. Reported outcome

Lap: Laparoscopic surgery group; Open: Open surgery group

Overall morbidity and mortality

Mortality rates were available from sixteen studies and median mortality rate was 1% (range 0-5%, Table 2). Pooled rates were comparable between laparoscopic and conventional surgery (1.7% for laparoscopic surgery versus 1.8% for conventional surgery, p=0.3). Cause of death was rarely reported, although one study mentioned cardio-respiratory failure as the main cause of death (47% of fatalities).[13]
The overall number of patients suffering one or more adverse events in short term follow-up after surgery for colorectal cancer was reported by sixteen studies (Table 2). Median overall morbidity rate was 33%, but with a wide range from 11% to 69%. Morbidity rates for colonic resections were lower compared to rectal resections (median 26% versus 40%). Three studies demonstrated a significant reduction in overall morbidity rates following laparoscopic colorectal surgery.[26, 33, 35] When comparing all studies, overall morbidity rates following laparoscopic surgery were only marginally lower than after conventional surgery (median 31% versus 33%). Due to inconsistency in definitions, a formal meta-analysis of overall morbidity was considered not feasible.

Other non-surgical complications

The reporting of non-surgical complications was highly variable between studies and only two studies specifically defined postoperative surgical and non-surgical morbidity.[24, 32] Of remaining non-surgical complications (Table 2), urogenital complications were most frequently addressed and had the highest median incidence, albeit with a wide range (0% to 43%). As with overall morbidity, the lack of consistency in addressing other non-surgical complications precluded meaningful comparisons between laparoscopic and conventional colorectal surgery.

Non surgical complications in elderly patients

Two trials performed a subgroup analysis of patients aged ≥70 years.[36, 37] Both showed a significant reduction in overall morbidity following laparoscopic colectomy in the elderly patients, while this difference was not seen in younger patients. One study, which included 326 patients aged ≥70 years, reported an overall morbidity of 51% following conventional colectomy compared with 37% after laparoscopic resection (p=0.02).[36] The other, reporting on 126 older patients, found that the overall complication rate was more than three times reduced in laparoscopic colectomy (10% compared with 31% after conventional surgery, p=0.004).[37]
All other studies provided insufficient data on the outcome of surgery in elderly patients.

Discussion

In this systematic review of cardiac and pulmonary complications in randomised controlled trials comparing laparoscopic with conventional colorectal cancer surgery, we found that there was great variation in the reporting of complications, and that adverse events were rarely well-defined. However, pooled analyses revealed significantly fewer cardiac adverse events following laparoscopic colectomy, with a possible trend toward fewer pulmonary complications, but no benefit for laparoscopic rectal surgery. Reported overall morbidity rates accumulated to over two-thirds of patients and although mortality was generally low, cause of death was rarely addressed.

This analysis has some limitations. First, definitions and classifications of outcome measures and complications are not consistent between trials, leading to (methodological) heterogeneity and possibly, an underestimation of postoperative complications. This heterogeneity precluded the execution of a formal meta-analysis for all endpoints; however, we were able to pool the data on postoperative cardiac and pulmonary complications to provide an overview of the most relevant data. Second, the available published data were subject to a risk of detection bias since blinding was rarely reported and this may consequently have affected the overall quality of evidence. Finally, comorbidity of the study population was poorly addressed and adequacy of baseline group comparability could not be determined in all studies. However, since all included trials were randomised and there were no real concerns regarding the randomisation process of the included studies, selection bias appears unlikely.

Laparoscopic surgery has gained great popularity for colectomies, although there is an ongoing debate on the optimal surgical resection of rectal cancers.[8, 9] Despite recent technologic advances and increased surgeon experience in minimally invasive techniques, a significant improvement in the postoperative complication rate for colorectal surgery is still lacking.[2, 3, 8, 38] Non-surgical morbidity has been identified as a potential target for further improvements.[12, 17] Although no useful comparisons could be made for some non-surgical adverse events, our systematic review demonstrates a decrease in cardiac morbidity following laparoscopic surgery for colon cancer.

There are several possible explanations. First, laparoscopy leads to a decrease in intra-operative blood loss and transfusion rate, as demonstrated by many studies.[9-11, 32, 39] Blood loss may result in hypotension and hypoperfusion, resulting in cardiac injury. Second, minimally invasive surgery is associated with a reduced

physiological stress response[40] and coagulation pathways are activated to a lower degree in laparoscopic procedures as compared to conventional surgery,[41] leading to favourable outcome. Additionally, it is suggested that laparoscopic surgery results in a reduction of postoperative pain and some studies have suggested that this would subsequently result in a decreased incidence of pulmonary complications.[12, 42, 43] However, this effect of laparoscopic surgery on pulmonary morbidity was limited in our analysis.

Interestingly, for rectal cancer resections, no benefit of laparoscopic surgery on cardio-pulmonary complications was found. One reason could be that rectal surgery is generally more extensive and associated with an inherently higher overall morbidity rate.[8, 9] Furthermore, studies have demonstrated that operative duration is associated with an increased risk of cardiopulmonary complications.[42, 44] Since the duration of total mesorectal excision is generally more prolonged when compared to colectomy and laparoscopic techniques prolong the duration of surgery even further,[9, 11] the benefits of laparoscopic surgery may be less apparent for rectal cancer.

Cardiac and pulmonary complications following colorectal surgery are most common in older patients.[2, 3] A recent review comparing laparoscopic with conventional colorectal surgery in the elderly patients demonstrated a lower incidence of postoperative chest infections and cardiac complications after laparoscopy.[45] However, the quality of the studies included in that review was limited, as the data were mostly observational and thus affected by selection bias and confounding by indication.[46] Although the burden of colorectal cancer is mainly carried by the elderly, high quality evidence regarding the benefits of laparoscopic colorectal surgery in this patient group is limited, as these patients are frequently excluded from randomised trials.[47, 48] In our review, only 22% of trials reported a mean or median age of included patients over 70 years of age (Table 1). Subsequently, it is unclear if the trial population of these studies is representative for all patients. Moreover, only two trials performed a subgroup analysis of elderly patients (aged ≥70 years). Both demonstrated a significant decrease in overall morbidity rates for the elderly patients that underwent laparoscopic colectomy, more so than in younger patients. This supports the findings of earlier research by our group that it is the elderly who may benefit most from minimally invasive surgery.[5] However, there was insufficient data to draw conclusions on the effect of laparoscopy on the incidence of cardiac or pulmonary complications for the elderly patients.

Overall, it remains unclear if the results of this systematic review can be extrapolated to all patients in daily practice, especially those patients prone to cardiac and pulmonary adverse events. It appears that the use of laparoscopic

techniques in colorectal surgery only provides marginal benefits in terms of reducing cardio-pulmonary and other non-surgical complications. Despite the technique used, anticipation for postoperative morbidity remains essential. This requires accurate pre-surgical assessment and tailoring of care. In addition, several studies demonstrate that some form of 'prehabiliation' with preoperative cardiopulmonary exercise may improve physical fitness and reduce postoperative morbidity.[49, 50] However, it remains to be determined whether these interventions will indeed provide the much needed improvement of outcome after colorectal surgery.

Conclusion

In conclusion, in this systematic review we have demonstrated fewer cardiac adverse events and a trend towards fewer pulmonary complications following laparoscopic colectomy, although for rectal cancer, this reduction was not seen. As classification of adverse events was unsatisfactory, these results must be interpreted with caution. Methodological quality of future research should improve; studies should report on comorbidity of included patients as well as provide clear definitions of their outcome measures and morbidity. Overall morbidity rates for colorectal surgery remain high and tailoring of care will be needed for individual patients when deciding on surgical intervention. This will be helped by performing subgroup analyses for the more vulnerable patient populations and we therefore recommend that this be a standard component of future clinical trials.

References

1. www.cijfersoverkanker.nl.
2. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol 2008;9:494-501.
3. Colorectal Cancer Collaborative Group. Surgery for colorectal cancer in elderly patients: a systematic review. Lancet 2000;356:968-74.
4. 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. Ann Surg Oncol 2011;18:1533-9.
5. Hamaker ME. Improved survival for older patients undergoing surgery for colorectal cancer between 2008 and 2011. Int J Colorectal Dis. 2014;29:1231-6
6. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc 1991;1:144-50.
7. http://dsca.clinicalaudit.nl.
8. Shearer R, Gale M, Aly OE, Aly EH. Have early post-operative complications from laparoscopic rectal cancer surgery improved over the past 20 years? Colorectal Dis 2013.
9. van der Pas MH, Haglind E, Cuesta MA, Furst A, Lacy AM, Hop WC, Bonjer HJ. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-8.
10. Schwenk W, Haase O, Neudecker J, Muller JM. Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev 2005:CD003145.
11. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy AM. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-84.
12. Mamidanna R, Burns EM, Bottle A, Aylin P, Stonell C, Hanna GB, Faiz O. Reduced risk of medical morbidity and mortality in patients selected for laparoscopic colorectal resection in England: a population-based study. Arch Surg 2012;147:219-27.
13. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005;365:1718-26.
14. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005;242:326-41; discussion 41-3.
15. Webb S, Rubinfeld I, Velanovich V, Horst HM, Reickert C. Using National Surgical Quality Improvement Program (NSQIP) data for risk adjustment to compare Clavien 4 and 5 complications in open and laparoscopic colectomy. Surg Endosc 2012;26:732-7.
16. Henneman D, Snijders HS, Fiocco M, van Leersum NJ, Kolfschoten NE, Wiggers T, Wouters MW, Tollenaar RA. Hospital variation in failure to rescue after colorectal cancer surgery: results of the Dutch Surgical Colorectal Audit. Ann Surg Oncol;20:2117-23.
17. Henneman D, Ten Berge MG, Snijders HS,

van Leersum NJ, Fiocco M, Wiggers T, Tollenaar RA, Wouters MW. Safety of elective colorectal cancer surgery: non-surgical complications and colectomies are targets for quality improvement. J Surg Oncol 2014;109:567-73.

18. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.Available from www.cochrane-handbook.org.
19. http://www.cebm.net/index.aspx?o=1157.
20. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
21. Araujo SE, da Silva eSousa AH, Jr., de Campos FG, Habr-Gama A, Dumarco RB, Caravatto PP, Nahas SC, da Silva J, Kiss DR, Gama-Rodrigues JJ. Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial. Rev Hosp Clin Fac Med Sao Paulo 2003;58:133-40.
22. Braga M, Frasson M, Vignali A, Zuliani W, Capretti G, Di Carlo V. Laparoscopic resection in rectal cancer patients: outcome and cost-benefit analysis. Dis Colon Rectum 2007;50:464-71.
23. Curet MJ, Putrakul K, Pitcher DE, Josloff RK, Zucker KA. Laparoscopically assisted colon resection for colon carcinoma: perioperative results and long-term outcome. Surg Endosc 2000;14:1062-6.
24. Hewett PJ, Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Rieger NA, Smith JS, Solomon MJ, Stephens JH, Stevenson AR. Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. Ann Surg 2008;248:728-38.
25. Kaiser AM, Kang JC, Chan LS, Vukasin P, Beart RW, Jr. Laparoscopic-assisted vs. open colectomy for colon cancer: a prospective randomized trial. J Laparoendosc Adv Surg Tech A 2004;14:329-34.
26. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-9.
27. Leung KL, Kwok SP, Lam SC, Lee JF, Yiu RY, Ng SS, Lai PB, Lau WY. Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. Lancet 2004;363:1187-92.
28. Li JC, Leung KL, Ng SS, Liu SY, Lee JF, Hon SS. Laparoscopic-assisted versus open resection of right-sided colonic cancer--a prospective randomized controlled trial. Int J Colorectal Dis 2012;27:95-102.
29. Liang JT, Huang KC, Lai HS, Lee PH, Jeng YM. Oncologic results of laparoscopic versus conventional open surgery for stage II or III left-sided colon cancers: a randomized controlled trial. Ann Surg Oncol 2007;14:109-17.
30. Liang X, Hou S, Liu H, Li Y, Jiang B, Bai W, Li G, Wang W, Feng Y, Guo J. Effectiveness and safety of laparoscopic resection versus open surgery in patients with rectal cancer: a randomized, controlled trial from China. J Laparoendosc Adv Surg Tech A 2011;21:381-5.
31. Lujan J, Valero G, Hernandez Q, Sanchez A, Frutos MD, Parrilla P. Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer. Br J Surg 2009;96:982-9.
32. Neudecker J, Klein F, Bittner R, Carus T, Stroux A, Schwenk W. Short-term outcomes from a prospective randomized trial comparing laparoscopic and open surgery for colorectal cancer. Br J Surg 2009;96:1458-67.

33. Ng SS, Lee JF, Yiu RY, Li JC, Hon SS, Mak TW, Ngo DK, Leung WW, Leung KL. Laparoscopic-assisted versus open total mesorectal excision with anal sphincter preservation for mid and low rectal cancer: a prospective, randomized trial. Surg Endosc 2014;28:297-306.
34. Ng SS, Leung KL, Lee JF, Yiu RY, Li JC, Teoh AY, Leung WW. Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. Ann Surg Oncol 2008;15:2418-25.
35. Pascual M, Alonso S, Pares D, Courtier R, Gil MJ, Grande L, Pera M. Randomized clinical trial comparing inflammatory and angiogenic response after open versus laparoscopic curative resection for colonic cancer. Br J Surg 2011;98:50-9.
36. Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Hewett PJ, Rieger NA, Smith JS, Solomon MJ, Stevenson AR. Australasian Laparoscopic Colon Cancer Study shows that elderly patients may benefit from lower postoperative complication rates following laparoscopic versus open resection. Br J Surg 2010;97:86-91.
37. Delgado S, Lacy AM, Garcia Valdecasas JC, Balague C, Pera M, Salvador L, Momblan D, Visa J. Could age be an indication for laparoscopic colectomy in colorectal cancer? Surg Endosc 2000;14:22-6.
38. 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. Ann Surg 2014;259:916-23.
39. Tjandra JJ, Chan MK. Systematic review on the short-term outcome of laparoscopic resection for colon and rectosigmoid cancer. Colorectal Dis 2006;8:375-88.
40. Pappas-Gogos G, Tellis C, Lasithiotakis K, Tselepis AD, Tsimogiannis K, Tsimoyiannis E, Chalkiadakis G, Chrysos E. Oxidative stress markers in laparoscopic versus open colectomy for cancer: a double-blind randomized study. Surg Endosc 2013;27:2357-65.
41. Tsiminikakis N, Chouillard E, Tsigris C, Diamantis T, Bongiorni C, Ekonomou C, Antoniou C, Bramis I. Fibrinolytic and coagulation pathways after laparoscopic and open surgery: a prospective randomized trial. Surg Endosc 2009;23:2762-9.
42. Owen RM, Perez SD, Lytle N, Patel A, Davis SS, Lin E, Sweeney JF. Impact of operative duration on postoperative pulmonary complications in laparoscopic versus open colectomy. Surg Endosc 2013;27:3555-63.
43. Bottger TC, Hermeneit S, Muller M, Terzic A, Rodehorst A, Elad L, Schamberger M. Modifiable surgical and anesthesiologic risk factors for the development of cardiac and pulmonary complications after laparoscopic colorectal surgery. Surg Endosc 2009;23:2016-25.
44. Bailey MB, Davenport DL, Vargas HD, Evers BM, McKenzie SP. Longer operative time: deterioration of clinical outcomes of laparoscopic colectomy versus open colectomy. Dis Colon Rectum 2014;57:616-22.
45. Grailey K, Markar SR, Karthikesalingam A, Aboud R, Ziprin P, Faiz O. Laparoscopic versus open colorectal resection in the elderly population. Surg Endosc 2013;27:19-30.
46. Walker AM. Confounding by indication. Epidemiology 1996;7:335-6.
47. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061-7.

48. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, Housman MG, Escarce JJ. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21:1383-9.
49. Pouwels S, Stokmans RA, Willigendael EM, Nienhuijs SW, Rosman C, van Ramshorst B, Teijink JA. Preoperative exercise therapy for elective major abdominal surgery: a systematic review. Int J Surg 2014;12:134-40.
50. O'Doherty AF, West M, Jack S, Grocott MP. Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. Br J Anaesth 2013;110:679-89.

	Low risk of bias	High risk of bias	Unclear risk of bias
Random treatment allocation	- Method for sequence generation process stated and considered truly at random (e.g. referring to a random number table, using a computer random number generator, shuffling cards or envelopes;	- Sequence generated by inadequate process (e.g. odd or even date of birth, sequence generated by some rule based on date (or day) of admission	- Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
Allocation concealment	- Central allocation (including telephone, web-based and pharmacy-controlled randomisation); - Sequentially numbered, opaque, sealed envelopes.	- Using an open random allocation schedule (e.g. a list of random numbers); - Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); - Any other explicitly unconcealed procedure.	- Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Blinding of participants and personnel	-No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; - Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.	- No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; - Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement is likely to be influenced by lack of blinding.	- Insufficient information to permit judgement of 'Low risk' or 'High risk'; - The study did not address this outcome.
Blinding of outcome assessment	- No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; - Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.	- No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; - Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement is likely to be influenced by lack of blinding.	- Insufficient information to permit judgement of 'Low risk' or 'High risk'; - The study did not address this outcome.
Handling of attrition	- Loss to follow-up less than 5% for short-term results - Reasons for missing outcome data unlikely to be related to true outcome - Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;	- Loss to follow-up more than 5% for short-term results - Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;	- Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk'; - The study did not address this outcome.
	Adequate	Inadequate	Unclear
Power calculation	- Adequate if stated to have been undertaken and achieved	- No sample size calculation is provided or if the study did not achieve the initial inclusion.	
Primary outcome	- Adequate if defined explicitly or used in sample size calculation	- No primary outcome is defined	
Baseline group comparison	- Adequate if groups were comparable for age, comorbidity (defined by ASA-score or other scoring method) and tumour stage	- Significant differences in patient demographics (age, comorbidity and tumour stage) were observed	- Insufficient information to permit judgement of 'adequate' or 'inadequate' - The study did not address this outcome.
Intention-to-treat analysis	- Adequate if described and converted patients were analysed in the laparoscopic study-group	- Inadequate if 'as-treated' analysis was done	

Name of study or author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Handling of attrition	Primary outcome defined	Power calculation adequate and achieved	Baseline group comparison adequate	Intention to treat analysis
ALCCaS	+	+	-	-	+	+	+	-	+
Araujo	?	?	-	?	+	-	-	?	+
Braga	+	+	-	-	+	+	+	+	+
COLOR	+	+	-	-	+	+	+	+	+
COLOR II	+	+	-	-	+	+	+	+	+
CLASSICC	+	+	-	-	+	+	-	+	+
Curet	+	?	?	?	+	-	-	?	-
Kaiser	+	-	?	?	+	+	-	-	-
Lacy	+	+	?	?	+	+	+	?	+
LAPKON II	+	+	-	-	+	+	-	+	+
Leung	+	+	-	-	+	+	+	?	+
Li	+	+	-	-	+	+	+	+	+
Liang JT	+	+	-	-	+	+	+	+	+
Liang X	+	+	-	+	+	+	-	?	+
Lujan	+	+	-	-	+	+	+	+	+
Ng 2014	+	+	-	-	+	+	-	+	+
Ng 2008	+	+	-	-	+	+	+	?	+
Pascual	+	+	-	-	+	+	+	+	+

Appendix 2. Quality assessment for individual studies

Quality was assessed using a 9-item list, details of which can be found in Appendix 1.

Left-hand page: Appendix 1. Items for assessment of methodological quality of included studies

This 9-item list was adopted from the Cochrane guidelines for methodological assessment of randomised trials[18] and the guidelines for critical appraisal of randomised controlled trials supplied by the Oxford Centre for Evidence Based Medicine.[19]

Part II

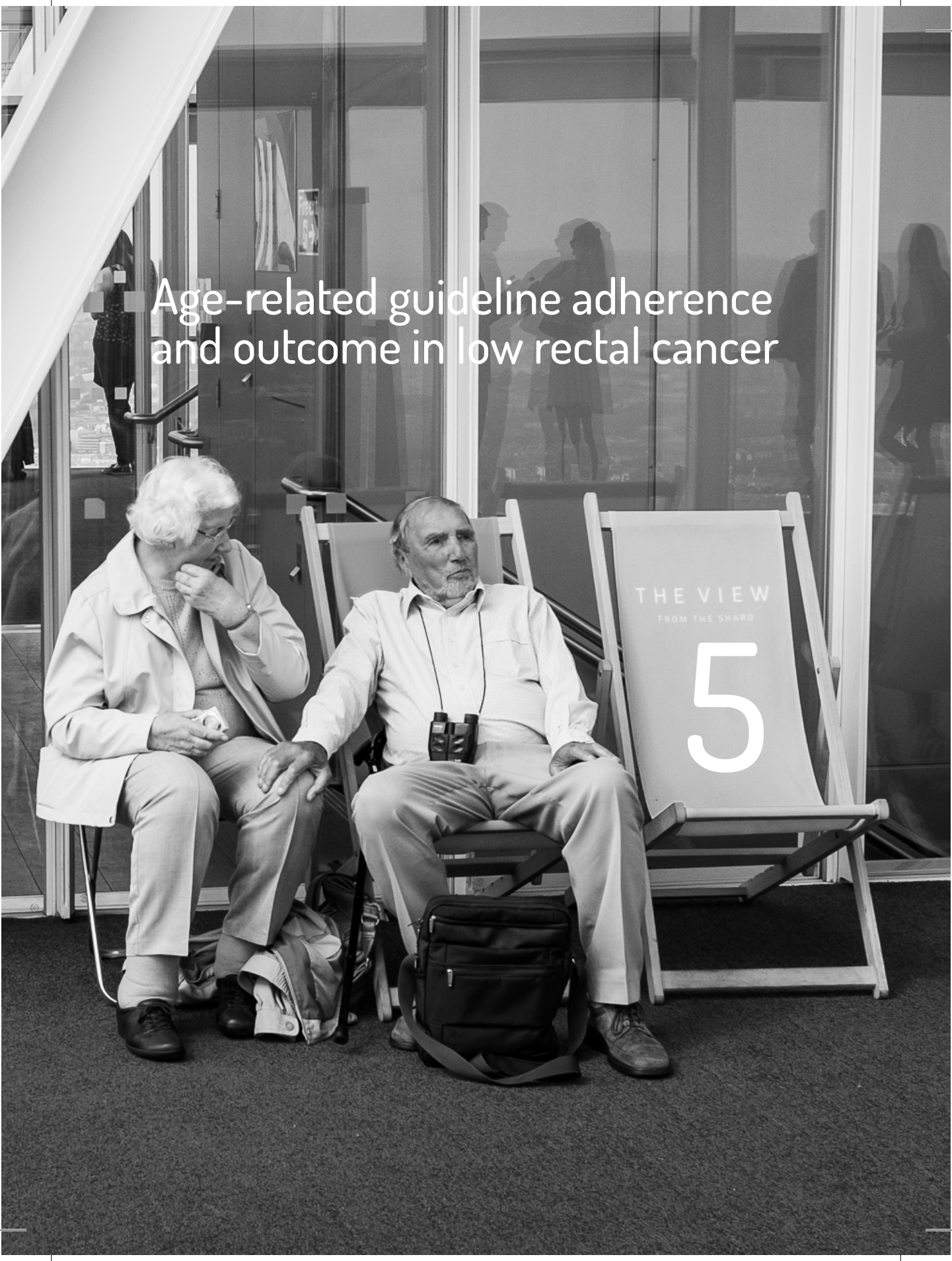
Age-related treatment decisions in colorectal cancer

Dis Colon Rectum.
2014;57:967-75

Anandi H.W. Schiphorst
Norbert M. Verweij
Apollo Pronk
Marije E. Hamaker

photo: Shared Picnic by «davemc»

Age-related guideline adherence and outcome in low rectal cancer



Abstract

Background

Care for elderly patients with low rectal cancer can pose dilemmas as radical TME surgery comes with high morbidity- and mortality rates.
Objective: To analyse the treatment of patients with low rectal cancer, comparing treatment choices, guideline-adherence and outcomes for elderly (≥75 years) with younger patients (<75 years).

Methods

This study was performed at a high volume teaching hospital. Patients with newly diagnosed rectal cancer (≤10 cm from the anal verge) were retrieved from the hospital's pathology database and data from surgically treated patients from the hospital's prospective colorectal surgery database. Charts were reviewed for reasons for non-adherence to treatment guidelines. Delivered treatment modalities for stage I-III rectal cancer patients were compared with treatment advised by national guidelines and reasons stated by the treating physician for non-adherence to guidelines were subsequently collected. Main outcome measures were treatment decisions, guideline adherence and outcome of surgical treatment were main outcome parameters.

Results

Of 218 included patients, 75 (34%) were aged ≥75 years. Guideline-adherence for all treatment modalities in stage I-III rectal cancer was significantly lower in elderly patients (62% versus 87% aged <75 years $p<0.001$) and age was the primary reason mentioned for withholding treatment. Palliative anticancer treatment for stage 4 disease was also initiated significantly less frequently in elderly patients (60% versus 97%, $p=0.002$). Overall rates of treatment complications after TME were similar for both patient groups ($p=0.71$), but the impact of complications on survival was much greater for elderly patients ($p=0.002$).

Conclusion

Guideline-adherence for all treatment modalities in stage I-III rectal cancer declines significantly with increasing age. Future research should focus on strategies of treatment tailored to the patient's health status rather than chronological age.

Introduction

Colorectal cancer is one of the most common cancers worldwide and ranks third in the incidence of all cancers in the Netherlands. The occurrence increases with age, with 54% being 70 years or older.[1] Rectal cancer comprises more than 30% of all colorectal cancer,[1] and its treatment is essentially different from malignancies in the upper colon. It has a poorer prognosis due to the high incidence of local recurrences and distant metastasis.[2,3]

Surgical treatment for cancer in the distal 10 centimetres of the rectum focuses on diminishing the chances of local recurrence by preoperative radiotherapy (in higher tumour stages combined with chemotherapy) followed by total mesorectal excision (TME).[4,5] Due to the anatomical coning of the pelvis and possible tumour involvement of the pelvic wall, rectal surgery is challenging. It carries a high morbidity rate,[6,7] despite recent developments such as minimally invasive surgery, advanced laparoscopic techniques and even robot-assisted surgery.[8,9] On the other hand, multimodal recovery programs after surgery have been introduced successfully, making return to functionality faster and reducing the morbidity caused by surgery.[10,11]

In the care for elderly patients with low rectal cancer, physicians are faced with dilemmas on how to proceed with treatment. As ageing is an individual process with increasing variety in comorbid disease, physical reserve, disability and geriatric conditions, treatment recommendations for fit, younger patients cannot automatically be extrapolated to older patients.[12,13] For older patients, treatment with high morbidity rates is disputed and neoadjuvant treatment is shown to increase the risk of complications.[14] Further, elderly with adverse events are at increased risk of worse survival.[15,16] Even palliative treatment for rectal cancer can be demanding, carrying its own morbidity rates,[17] and deviating ostomies to prevent obstruction still require surgery and may result in care dependence. However, omission of such treatment can lead to serious cancer-related complications. With increasing age, the choice to operate and curate or to palliate will be increasingly dependent on comorbidity, overall physical condition and patient's wishes.

Although some data is available on outcome of surgical treatment of rectal cancer in elderly,[18-23] adequate interpretation of these data also requires knowledge about the untreated elderly population. Trials on rectal cancer treatment do not show real-life outcomes as elderly and those with comorbidity are often excluded,[24,25] and details on treatment decisions are often not reported. National guidelines on rectal cancer are based on studies in which elderly are generally underrepresented and guidelines

specifically focusing on elderly are lacking.
To date, literature on palliative or curative treatment choices for rectal cancer in elderly patients is scarce. Therefore, we set out to investigate the treatment of patients with low rectal cancer, comparing treatment choices, guideline-adherence and outcomes for elderly (≥75 years) with younger patients (<75 years).

Methods

This study was performed at the Diakonessenhuis in Utrecht, a large teaching hospital in the Netherlands. All patients with newly diagnosed rectal cancer between July 2006 and December 2011 were retrieved from the hospital's pathology database. Only patients with cancer of the distal two-thirds of the rectum (≤10 cm from the anal verge, measured by digital rectal examination, rigid or flexible rectoscopy, flexible colonoscopy or radiographically) were included. Data from surgically treated patients were retrieved from the hospital's prospective colorectal surgery database. For non-operated patients the medical charts were reviewed. Patients who underwent surgery in other hospitals were excluded from the analysis.
The following data were collected: age at diagnosis, sex, comorbidity (using the American Society of Anaesthesiologists (ASA)-score and Charlson comorbidity index)[26] body mass index (BMI), polypharmacy (defined as the use of ≥5 medications), prior history of abdominal surgery and distance of tumour from the anal verge.
For surgically treated patients, data extraction also included type of neo-adjuvant treatment (if any), surgical treatment data (type of surgery, surgical approach, duration of operation, blood loss, type of anastomosis, requirement of ostomies, intra-operative complications), postoperative data (number of ICU-days, duration of hospital stay, number of blood transfusions received, complications, re-interventions, re-admissions and mortality), oncologic data (tumour stage, type of adjuvant treatment, pathologic specimen data), and follow-up data. For non-surgically treated patients details concerning tumour stage, palliative chemotherapy and/or radiotherapy and follow-up were collected.
Treatment for patients with stage I-III rectal cancer was divided into three groups: patients who underwent intended curative resection, patients who received palliative treatment and patients who received no cancer treatment at all.
Intended curative resection was defined as patients with stage I-III rectal cancer who underwent (laparoscopic or conventional) TME or local resection by transanal endoscopic microsurgery (TEM), the latter only if given to patients with low risk T1 carcinomas without (neo)adjuvant treatment.

Delivered treatment modalities for stage I-III rectal cancer patients were compared with treatment advised by national guidelines for the treatment of rectal cancer.[27] A summary of these treatment guidelines is presented in Appendix 1. Briefly, neoadjuvant treatment followed by TME surgery is advised in all patients except low risk cT1N0 tumours in which case local resection with TEM is recommended. There are no clear recommendations regarding adjuvant treatment.
For patients not receiving the standard treatment, reasons stated by the treating physician for non-adherence to guidelines were subsequently collected from the charts; these were classified as age, comorbidity, patient's request, cognitive decline, poor general condition, tumour characteristics or unclear.
Treatment for patients with stage IV rectal cancer was divided into two groups: palliative treatment and no treatment at all. Dutch treatment guidelines on stage IV rectal cancer are not stringent (Appendix 1). Guideline adherence for these patients was therefore not determined.
Follow-up data were retrieved from the charts and mortality was determined using the Municipal Data Registry.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) for windows. Statistical significance was defined as $p<0.05$. For comparisons between groups, the chi-square test was used for nominal and ordinal variables; the anova test was used for continuous variables. Overall survival was assessed using Kaplan-Meier plots with a log-rank analysis. To determine which baseline characteristics and outcome parameters were associated with mortality for stage I-III rectal cancer in 18 months follow-up, a Cox regression analysis was performed. For each variable, the Cox proportional hazards assumption was tested using a log-minus-log plot. Factors with clinical significance or $p\leq0.20$ were subsequently included in a multivariable analysis. A backward selection procedure was applied, accepting a p-value of <0.05.

Results

Between July 2006 and December 2011, 221 patients were diagnosed with low rectal cancer at the Diakonessenhuis. After exclusion of three patients who underwent surgery at other hospitals, 218 patients were included in this study.
Patient characteristics are reported in Table 1. Median age was 70 years (range 37-95 years); 60% were men. There were 29 patients (13%) with an ASA score of 3 or 4. Median distance between the tumour and the anal verge was 5cm (0-10cm). Forty-one patients were diagnosed with stage IV rectal cancer (19%).
Of all patients, 75 (34%) were aged 75 years or older (Table 1). The elderly patients group consisted of significantly more women (65% versus 33%, p=0.002), more patients with an ASA-score of 3 or 4 (25% versus 7%, p<0.001) and a higher incidence of polypharmacy (31% versus 18%, p=0.03). The median Charlson comorbidity index was also higher in the elderly patients (1 versus 0, p=0.05), with borderline significance. Older and younger patients did not differ in tumour stage at presentation (p=0.13).

Treatment choices

Figure 1 shows the treatment choices for all patients. Overall, 166 patients were treated with curative intent, 43 received palliative treatment and in nine patients, no treatment was given.
When comparing treatment for older and younger patients, significantly less elderly with stage I-III disease were treated with curative intent (83% in older patients versus 100% of younger patients, p<0.001). If treated with curative intent, elderly received neoadjuvant treatment as often as younger patients (73% versus 86% of younger patients, p=0.14, Table 1). However, elderly received significantly more short-course radiotherapy and less chemoradiation therapy (59% versus 42% in younger patients, p=0.04 and 13% versus 40%, p<0.001 respectively).
A total of 41 patients had stage IV rectal cancer (31 patients aged <75 yrs (76%) and 10 patients aged ≥75 yrs (24%). Of these, the elderly patients received significantly less palliative treatment (60% versus 97%, p=0.002). An additional seven patients had stage I-III rectal cancer and received only palliative (not curative) treatment, all of which were elderly. Thus, a total of 43 patients received some form of palliative treatment (30 younger and 13 elderly patients, Figure 1). Palliative surgery was received by equal number of patients between age groups (77% aged <75 years versus 62% aged ≥75 years, p=0.31) but was generally less extensive in the elderly (13% received palliative TME in elderly versus 61% in younger patients, p=0.001). The

	Total n=218	<75 n=143	≥75 n=75	P
Male	130 (60%)	96 (67%)	34 (45%)	0.002
Median age (range)	70 (37-95)	62 (37-74)	81 (75-95)	
<55y	31 (14%)	31 (22%)		
55-64	53 (24%)	53 (37%)		
65-74	59 (27%)	59 (41%)		
75-84	53 (24%)		53 (71%)	
≥85	22 (10%)		22 (29%)	
Median distance to anal verge (range)	5 (0-10)	5 (0-10)	5 (0-10)	0.80
ASA 3-4	29 (13%)	10 (7%)	19 (25%)	<0.001
Median Charlson comorbidity index[26] (range)	0 (0-7)	0 (0-7)	1 (0-7)	0.05
Polypharmacy	48 (22%)	25 (18%)	23 (31%)	0.03
Median BMI (range)	25 (16-40)	25 (16-40)	24 (17-35)	0.08
Pathological tumour stage according to Dukes classification				
- A: T1-2, N0, M0	55 (25%)	39 (27%)	16 (21%)	
- B: T3-4, N0, M0	43 (20%)	29 (20%)	14 (19%)	
- C: T1-4, N1-2, M0	70 (32%)	44 (31%)	26 (35%)	
- D: T1-4, N1-2, M1	41 (19%)	31 (22%)	10 (13%)	0.13
- Unknown	9 (4%)	0	9 (12%)	<0.001
Intended curative resection	166 (76%)	112 (78%)	54 (72%)	0.30
Neoadjuvant treatment*	131 (79%)	92 (82%)	39 (72%)	0.14
RTx	79 (48%)	47 (42%)	32 (59%)	0.04
CHRTx	52 (31%)	45 (40%)	7 (13%)	<0.001

Table 1. Patient characteristics

* For patients treated with curative intent
ASA: American Society of Anaesthesiologists; BMI: Body Mass Index; RTx: radiotherapy; CHRTx: chemoradiation therapy

elderly received significantly more palliative radiotherapy (62% versus 23%, p=0.02) and significantly less palliative chemotherapy (31% versus 73%, p=0.009). Nine patients received no treatment at all, eight of which (89%) were aged 75 years or older (Figure 1).

Guideline adherence

Of 177 patients with stage I-III rectal cancer, 137 (77%) were treated in accordance with guidelines, with a significant decline with age (87% aged <75 years versus 62% aged ≥75 years, p<0.001). Guideline adherence per age group and for different treatment modalities in patients with stage I-III disease is presented in Figure 2. Neoadjuvant treatment declined significantly with increasing age (86% aged <75 years versus 60% aged ≥75 years, p<0.001). Twenty percent of patients aged 85 years and older received neoadjuvant treatment in accordance with guidelines, compared to 96% of patients aged <55 years (p<0.001). Surgery was received by over 90% of patients up to 84 years of age and declined to 60% in patients aged 85 years and older (p<0.001). Adjuvant chemotherapy treatment also decreased steadily with increasing age (77% aged <75 years versus 15% aged ≥75 years, p<0.001).
Reasons for non-adherence to neoadjuvant treatment guidelines in younger patients (n=15/42) were comorbidity (n=1), patient refusal (n=2), tumour characteristics (n=6) and in 6 six cases reasons for non-adherence could not be retrieved (Table 2). Age was the primary reason mentioned for withholding treatment in older patients both for neoadjuvant therapy (n=7) as for surgery (n=3). Other reasons were cognitive decline (n=2), patient's request (n=3) and poor general health (n=1). Comorbidity was not stated as a reason to withhold neoadjuvant treatment. In five cases reasons for non-adherence to guidelines could not be retrieved from the patient's charts.

Outcome of TME surgery

A total of 174 patients underwent (curative or palliative) TME, of which 53 (30%) were aged ≥75 years. Although an equal proportion of procedures was started laparoscopically (50% aged <75 years versus 51% aged ≥75 years, p=0.9 – Table 3), conversion rate was significantly higher in the elderly (33% versus 10% in younger patients, p=0.008). Overall complication rate was similar between groups, but significantly more pulmonary complications occurred in the elderly (8% versus none in the younger, p=0.002). The proportion of patients requiring postoperative admission to the Intensive Care Unit was significantly higher in the elderly (47% versus 26% of younger patients, p=0.005) as was the proportion of patients requiring blood transfusion (30% versus 13% respectively, p=0.008), even though median peroperative blood loss was not different between groups. Younger patients

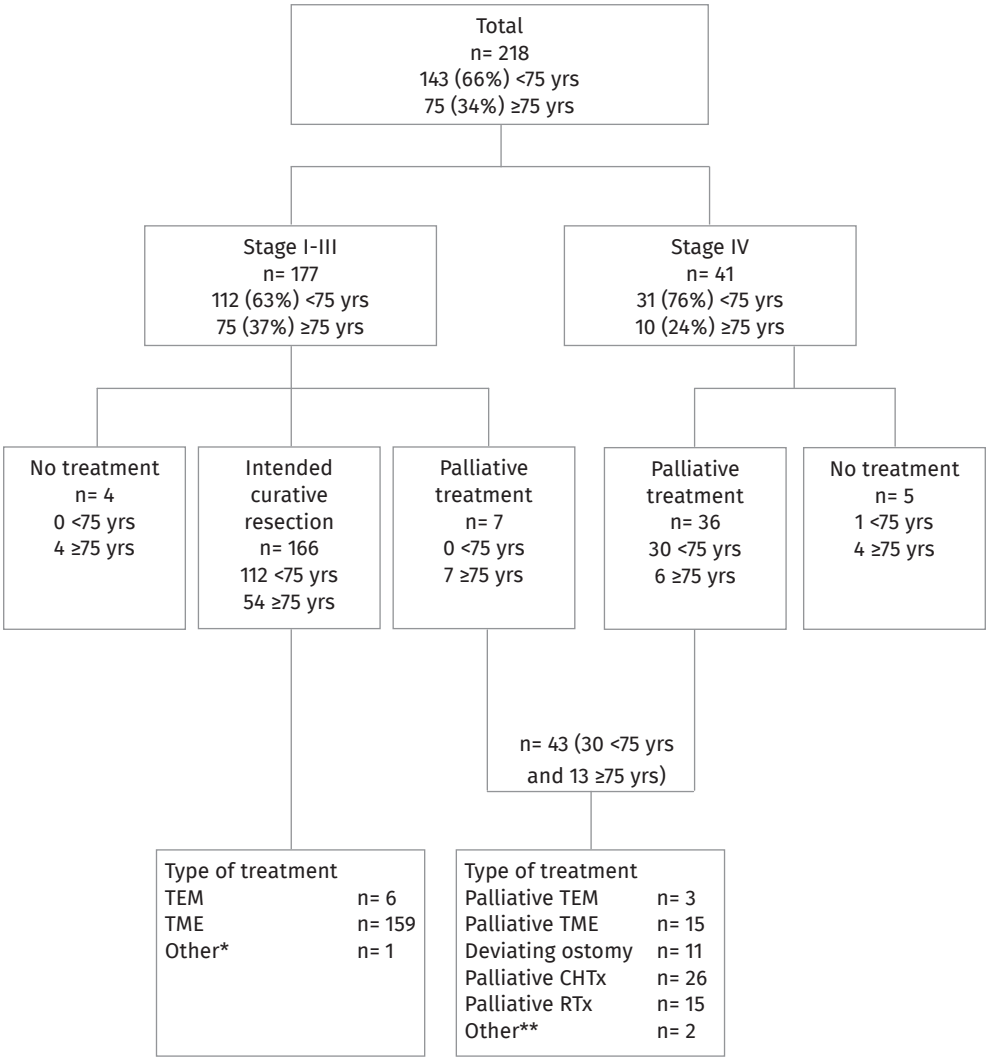


Figure 1. Flow chart of treatment choices in stage I-III and stage IV rectal cancer

TEM: Transanal Endoscopic Microsurgery; TME: Total Mesorectal Excision; CHTx: Chemotherapy; RTx: radiotherapy.

* One patient died during neoadjuvant chemotherapy

** Two patients underwent palliative radio frequent ablation (RFA) of liver metastases

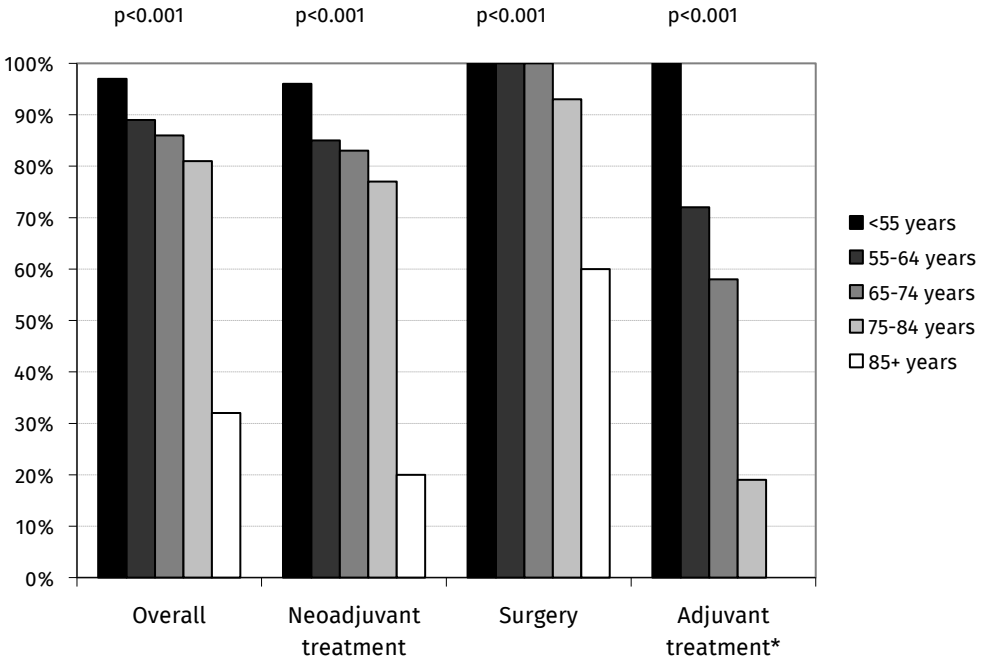


Figure 2. Proportion of stage I-III rectal cancer patients treated in accordance with guidelines per age group

* For adjuvant treatment, no stringent guidelines are provided; therefore, proportion of patients receiving adjuvant treatment after surgical therapy is depicted.

	Number of patients not treated in accordance with guidelines	Overall	Neo-adjuvant treatment	Surgery
		n=15	n=15	n=0
Younger (<75 years) n=112	Reason stated			
	• age		0	
	• comorbidity		1	
	• patient refusal		2	
	• cognitive decline		0	
	• poor general health		0	
	• tumour characteristics		6	
	• unclear		6	
		n=25	n=14	n=11
Elderly (≥75 years) n=65	Reason stated			
	• age	10	7	3
	• comorbidity	1	0	1
	• patient refusal	3	1	2
	• cognitive decline	2	0	2
	• poor general health	1	0	1
	• tumour characteristics	3	3	0
	• unclear	5	3	2

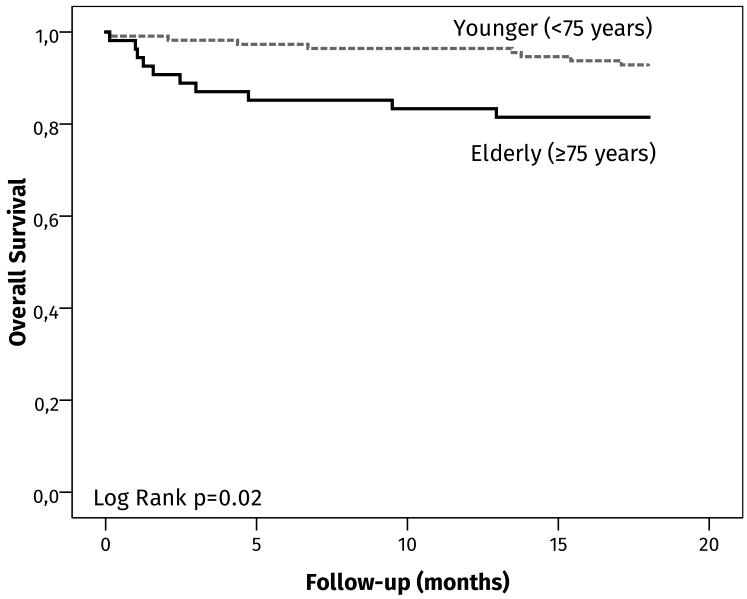
Table 2. Reason stated in clinical charts for non-adherence to guidelines in patients with stage I-III rectal cancer.

	<75 n=121	≥75 n=53	P
Surgery started laparoscopic	60 (50%)	27 (51%)	0.87
Conversion to conventional TME	6/60 (10%)	9/27 (33%)	**0.008**
APR/LAR	45/76	16/37	0.37
Median blood loss in ml (range)	300 (0-3000)	400 (0-1500)	0.67
Number of patients requiring blood transfusions	16 (13%)	16 (30%)	**0.008**
Number of patients with postoperative complications*	40 (33%)	16 (30%)	0.71
- Anastomotic leakage	6 (8%)	1 (3%)	0.28
- Pulmonary complications	0	4 (8%)	**0.002**
Re-operation	15 (12%)	7 (13%)	0.88
Other re-intervention	4 (3%)	1 (2%)	0.61
Median hospital stay in days (range)	7 (3-141)	10 (3-93)	0.12
Number of patients with ICU admittance	31 (26%)	25 (47%)	**0.005**
Re-admission	22 (18%)	1 (2%)	**0.003**
30-day mortality	1 (1%)	2 (4%)	0.17

Table 3. Operative outcome after TME surgery

* A patient could have had more than one complication
TME: Total Mesorectal Excision, APR: Abdominoperineal Resection; LAR: Low Anterior Resection; ICU: Intensive Care Unit

a.



b.

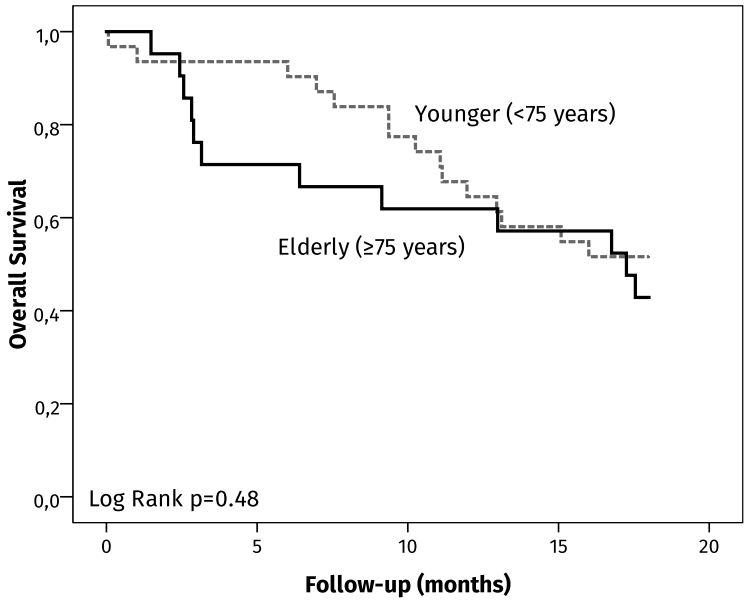


Figure 3. Kaplan-Meier curves of overall survival in 18 months follow-up for patients after intended curative resection (a) and patients not undergoing intended curative resection (b).

required significantly more readmissions (18% versus 2% in older patients, p=0.003). Thirty-day mortality did not differ between groups. No differences were seen in postoperative complication rate in both younger and elderly patients with or without neoadjuvant treatment.

Survival

As demonstrated by Figure 3a, overall survival in 18 months follow-up after intended curative resection was significantly better in younger patients (93% versus 82%, log rank p=0.02). For patients without intended curative resection initial survival was worse for the elderly, but after 13 months this difference was no longer noticeable (Figure 3b). If complications occurred after TME, the relative risk of dying within 6 months after surgery almost tripled for elderly patients (5.8 versus 2.0 for younger patients, p=0.002).

To determine baseline factors associated with mortality in 18 months follow-up in patients with stage I-III rectal cancer, univariate and multivariable analysis were performed (Table 4). In the univariate analysis age, Dukes tumour stage, intended curative resection and the occurrence of complications were associated with mortality in 18 months follow-up. In the multivariable analysis, complications after TME surgery were the prime predictor of survival in 18 months follow-up (hazard ratio (HR) 1.41, 95% confidence interval (CI) 1.15-1.73, p=0.001). Other factors associated with survival were age (HR1.85, 95%CI 1.18-2.91, p=0.007) and intended curative resection (HR 0.14, 95%CI 0.02-0.82, p=0.03).

Factor	Univariate			Multivariable		
	HR	95% Confidence Interval	P*	HR	95% Confidence Interval	P*
Age in 10 year groups	2.23	1.48-3.36	**<0.001**	1.85	1.18-2.91	**0.007**
Sex	1.19	0.51-2.74	0.69	-		
ASA 3-4	2.34	0.92-5.94	**0.07**	-		
Polypharmacy	1.44	0.59-3.49	0.42			
Dukes tumour stage	1.75	1.23-2.49	**0.002**	-		
Intended curative resection	0.21	0.08-0.58	**0.002**	0.14	0.02-0.82	**0.03**
Neoadjuvant therapy	1.01	0.33-3.05	0.99			
Laparoscopic resection	0.66	0.38-1.16	**0.15**	-		
Complications	1.30	1.17-1.44	**<0.001**	1.41	1.15-1.73	**0.001**
Adjuvant therapy	0.66	0.19-2.30	0.52			

Table 4. Cox-regression analysis of factors associated with mortality within 18 months in patients with stage I-III rectal cancer

ASA: American Society of Anaesthesiologists; HR: Hazard ratio;
* Variables with a p-value ≤0.20 (printed in bold font) were included in the multivariable analyses, as were potential confounders such as age.

Discussion

In this study of treatment decisions for low rectal cancer for 218 patients, we analysed differences in treatment choices and outcome of treatment between younger (<75 years) and elderly (≥75 years) patients. We found that guideline-adherence for all treatment modalities in stage I-III rectal cancer was significantly lower in elderly patients (62% versus 87% in younger patients), with age being the primary reason mentioned in patients' charts for withholding treatment. Palliative treatment was also initiated less frequently in the elderly patients. Although the overall rate of surgical complications was similar in both age groups, survival after complications from TME surgery was significantly worse in elderly patients.

Low rectal cancer has multiple treatment modalities, the cornerstone of which is radical surgery according to TME principles, which carries a high complication rate.[4,7,28] Treatment choices can be complex, especially for the elderly, which form a heterogeneous group of patients from fit to frail and with a variance of comorbidities. These factors may negatively affect outcomes of neo-adjuvant treatment and surgery[14,15,23] but are generally not incorporated in treatment guidelines.[24,25] Furthermore, elderly are more prone to adverse sequelae of treatment-related complications, such as functional decline, care-dependency, and death.[15,29] For example, in our study the overall complication rate for older and younger patients was similar, but when postoperative complications did occur, survival for older patients was much worse. Although older patients may also benefit from recent developments, such as enhanced recovery programs and laparoscopic rectal resections,[30,31] it remains to be seen if elderly will benefit as much as younger patients have.

Most experts agree that chronological age itself is not sufficient grounds for withholding cancer treatment;[19,32] as it is not possible to judge if a patient is fit for radical rectal cancer treatment merely by looking at a patient's date of birth. However, multiple studies have demonstrated that treatment decisions in elderly cancer patients are still largely based on age.[33-36] This could be due to the fact that treatment guidelines generally do not discriminate between younger or older cancer patients and are based on trials from which elderly were often excluded. [24,25] Thus, tailoring of care is needed and for this reason, some form of geriatric evaluation is increasingly being incorporated in oncologic care.[12,37-39] A geriatric evaluation can help identify previously unrecognised health issues which have been demonstrated to be associated with prognosis and treatment-related complications and can provide guidance in balancing the risks and benefits of treatment.[39] However, without

further research optimal stratification of older patients will remain elusive. Such studies should not only incorporate a geriatric evaluation but also those outcome measures most relevant to older patients in their treatment decisions, such as care dependence and quality of life.

This study has some limitations. First, data on outcome of other treatment modalities such as chemotherapy and radiotherapy are lacking in our analysis as these were insufficiently available from patient's charts. Second, comorbidity was analysed using the ASA-score and Charlson comorbidity score. These scores only provide a global assessment of a patient's comorbidity but do not take the severity of that comorbidity into account. Although useful multimorbidity scales are available,[40] these need to be filled out prospectively. Furthermore, details on socio-economic or functional status were not available but may have attributed to treatment decision making and guideline adherence. Finally, our study population is relatively small with only 218 patients. However, they represent a real-life population of patients diagnosed with low rectal cancer. Therefore, our analysis provides worthwhile insights in day-to-day decision-making that cannot be obtained from clinical trials or studies based on cancer registry databases.

Conclusion

Guideline adherence for all treatment modalities in stage I-III rectal cancer declines significantly with increasing age. Survival in 6 months after complications from TME surgery is worse in patients aged ≥75. Geriatric assessment might lead to better, individualised treatment approaches for low rectal cancer in older patients.

References

1. www.cijfersoverkanker.nl. Accessed December 1st, 2013
2. van der Pool AE, de Wilt JH, Lalmahomed ZS, Eggermont AM, Ijzermans JN, Verhoef C. Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases. Br J Surg. 2010;97:383-90.
3. Yeo HL, Paty PB. Management of recurrent rectal cancer: Practical insights in planning and surgical intervention. J Surg Oncol. 2014;109:47-52
4. Kapiteijn E, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345:638-46.
5. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg. 1998;133:894-9.
6. Shearer R, Gale M, Aly OE, Aly EH. Have early post-operative complications from laparoscopic rectal cancer surgery improved over the past 20 years? Colorectal Dis. 2013;15:1211-26.
7. Schiphorst AH, Doeksen A, Hamaker ME, Zimmerman DD, Pronk A. Short-term follow-up after laparoscopic versus conventional total mesorectal excision for low rectal cancer in a large teaching hospital. Int J Colorectal Dis. 2014;29:117-25.
8. Breukink S, Pierie J, Wiggers T. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev. 2006:CD005200.
9. Collinson FJ, Jayne DG, Pigazzi A, et al. An international, multicentre, prospective, randomised, controlled, unblinded, parallel-group trial of robotic-assisted versus standard laparoscopic surgery for the curative treatment of rectal cancer. Int J Colorectal Dis. 2011;27:233-41.
10. Huibers CJ, de Roos MA, Ong KH. The effect of the introduction of the ERAS protocol in laparoscopic total mesorectal excision for rectal cancer. Int J Colorectal Dis. 2012;27:751-7.
11. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. Cochrane Database Syst Rev. 2001:CD007635.
12. Extermann M, Aapro M, Bernabei R, 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). Crit Rev Oncol Hematol. 2005;55:241-52.
13. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341:2061-7.
14. Maas HA, Lemmens VE, Nijhuis PH, de Hingh IH, Koning CC, Janssen-Heijnen ML. Benefits and drawbacks of short-course preoperative radiotherapy in rectal cancer patients aged 75 years and older. Eur J Surg Oncol. 2013;39:1087-93.
15. Shahir MA, Lemmens VE, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. Eur J Cancer. 2006;42:3015-21.
16. 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. Ann Surg Oncol. 2011;18:1533-9.
17. Cameron MG, Kersten C, Vistad I, Fossa S, Guren MG. Palliative pelvic radiotherapy of symptomatic incurable rectal cancer - a systematic review. Acta Oncol. 2014;53:164-73
18. Akiyoshi T, Kuroyanagi H, Oya M, et al. Short-term outcomes of laparoscopic rectal surgery for primary rectal cancer in elderly patients: is it safe and beneficial? J Gastrointest Surg. 2009;13:1614-8.
19. Manceau G, Karoui M, Werner A, Mortensen NJ, Hannoun L. Comparative outcomes of rectal cancer surgery between elderly and non-elderly patients: a systematic review. Lancet Oncol. 2013;13:e525-36.
20. Chang GJ, Skibber JM, Feig BW, Rodriguez-Bigas M. Are we undertreating rectal cancer in the elderly? An epidemiologic study. Ann Surg. 2007;246:215-21.
21. Endreseth BH, Romundstad P, Myrvold HE, Bjerkeset T, Wibe A. Rectal cancer treatment of the elderly. Colorectal Dis. 2006;8:471-9.
22. Jung B, Pahlman L, Johansson R, Nilsson E. Rectal cancer treatment and outcome in the elderly: an audit based on the Swedish Rectal Cancer Registry 1995-2004. BMC Cancer. 2009;9:68.
23. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol. 2008;9:494-501.
24. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol. 2003;21:1383-9.
25. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Oncol. 2005;23:3112-24.
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
27. www.oncoline.nl/rectumcarcinoom. Accessed December 1st, 2013.
28. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol. 2013;14:210-8.
29. Lemmens VE, Janssen-Heijnen ML, Verheij CD, Houterman S, Repelaer van Driel OJ, Coebergh JW. Co-morbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. Br J Surg. 2005;92:615-23.
30. Kuhry E, Schwenk WF, Gaupset R, Romild U, Bonjer HJ. Long-term results of laparoscopic colorectal cancer resection. Cochrane Database Syst Rev. 2008:CD003432.
31. Jayne DG, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ. Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. Br J Surg. 2010;97:1638-45.
32. Barrier A, Ferro L, Houry S, Lacaine F, Huguier M. Rectal cancer surgery in patients more than 80 years of age. Am J Surg. 2003;185:54-7.
33. Damhuis RA, Wereldsma JC, Wiggers T. The influence of age on resection rates and postoperative mortality in 6457 patients with colorectal cancer. Int J Colorectal Dis. 1996;11:45-8.
34. Mahoney T, Kuo YH, Topilow A, Davis JM. Stage III colon cancers: why adjuvant chemotherapy is not offered to elderly patients. Arch Surg. 2000;135:182-5.

35. Potosky AL, Harlan LC, Kaplan RS, Johnson KA, Lynch CF. Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. J Clin Oncol. 2002;20:1192-202.
36. Schrag D, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. J Natl Cancer Inst. 2001;93:850-7.
37. Decoster L, Kenis C, Van Puyvelde K, et al. The influence of clinical assessment (including age) and geriatric assessment on treatment decisions in older patients with cancer. J Geriatr Oncol. 2013;4:235-41.
38. Kenis C, Bron D, Libert Y, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. Ann Oncol. 2013;24:1306-12.
39. 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 Oncol. 2014;53:289-96.
40. Wedding U, Roehrig B, Klippstein A, Steiner P, Schaeffer T, Pientka L, Hoffken K. Comorbidity in patients with cancer: prevalence and severity measured by cumulative illness rating scale. Crit Rev Oncol Hematol. 2007;61:269-76.

Clinical stage	Neoadjuvant treatment	Surgical treatment	Adjuvant treatment
I (Dukes A) cT1-2N0M0			
T1 (low risk)*	none	Local resection (TEM)	none
T1 (high risk)*	Short course RT**	TME	none
T2	Short course RT	TME	none
II (Dukes B) cT3-4N0M0			
T3	Short course RT	TME	none
T4	Chemoradiation therapy***	TME	no clear recommendation
III (Dukes C) cTxN1-2M0			
N1	Short course RT	TME	no clear recommendation
N2	Chemoradiation therapy	TME	no clear recommendation
IV (Dukes D) cTxNxM1	Multiple treatment options depending on resectability and patient preferences		

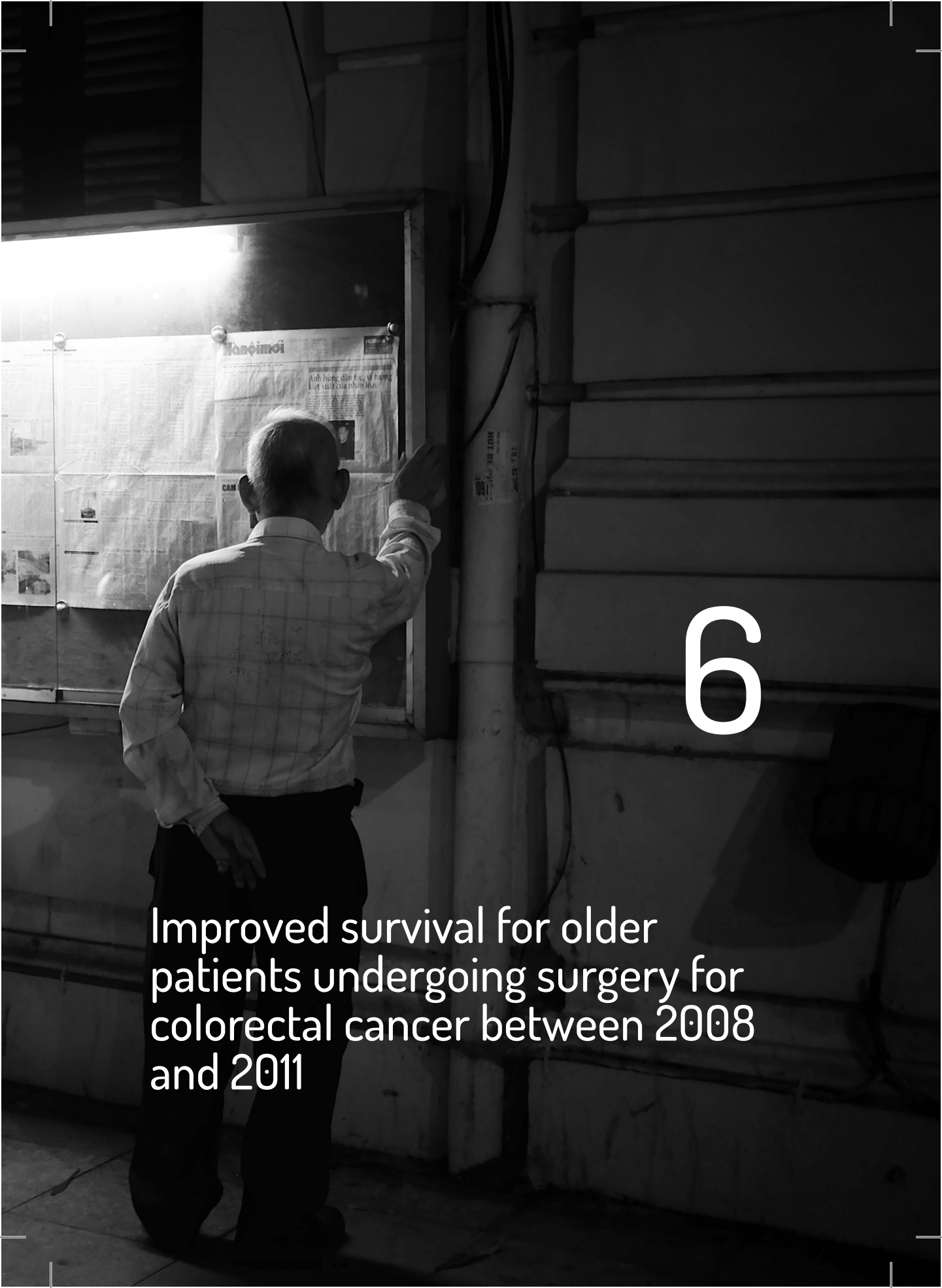
Appendix 1. Summary of Dutch guidelines for the treatment of rectal cancer according to clinical tumour stage

* Low risk: G1/2L0V0 tumours: good or moderate degree of tumour differentiation, no lymphatic or venous invasion. High risk: T1 carcinoma with stage >G1/2L0V0.
** Short course radiotherapy: 5x5Gy
*** Chemoradiation therapy: 25x2Gy in combination with capecitabine 825 mg/m2
TEM: Transanal Endoscopic Microsurgery; RT: radiotherapy; TME: Total Mesorectal Excision;
Full guidelines for treatment of rectal cancer in the Netherlands can be found online.[27]

Int J Colorectal Dis.
2014;29:1231-6

Marije E. Hamaker
Anandi H.W. Schiphorst
Norbert M. Verweij
Apollo Pronk

photo: Untitled by Konrad Lembcke



6

Improved survival for older patients undergoing surgery for colorectal cancer between 2008 and 2011

Abstract

Introduction

Older colorectal cancer patients have a higher risk of postoperative complications and the impact of adverse events on survival is also significantly higher. Innovations like laparoscopic surgery which improve short-term outcome for older patients can also benefit their overall prognosis. We set out to analyse the impact of an increased utilisation of laparoscopic surgery for colorectal cancer in the Netherlands on overall survival.

Methods

All patients diagnosed with stage I-III colorectal cancer in the Netherlands between 2008 and 2011 were selected from the Netherlands Cancer Registry. Changes in perioperative mortality, three-month mortality and one-year mortality rates were analysed using year of diagnosis as an instrumental variable.

Results

Over 33,000 patients were included in the analyses. Data on surgical approach were not precisely known for 2008 and 2009; in 2010 36.6% of definitive surgical procedures were performed laparoscopically, and in 2011 45.9%. A laparoscopic approach was used less frequently in the patients aged ≥75 years (in 2011, 40.3% versus 49.2% of younger patients; $p<0.001$). Between 2008 and 2011, perioperative mortality decreased from 2.0% to 1.5% ($p=0.02$), three-month mortality from 4.8% to 3.9% ($p=0.01$) and one-year mortality from 9.6% to 8.3% ($p<0.001$). The absolute risk reduction was greatest for patients aged ≥75 years, reaching 2.1% for one-year mortality.

Conclusion

Between 2008 and 2011, the utilisation of a laparoscopic approach increased significantly, resulting in reduced mortality rates, particularly for the elderly. Therefore, a laparoscopic approach should be used whenever possible, which may allow for further improvement of outcomes.

Introduction

Over the past ten years, the incidence of colorectal cancer in the Netherlands has risen by 43%. It is currently the second most common malignancy in both men and women and 12% of cancer-related deaths can be attributed to this disease.[1] Over one-third of newly diagnosed patients are older than 75 years of age and with the imminent ageing of western societies, the number of older colorectal cancer patients is expected to increase greatly over the coming decades.[2] This will present a significant challenge to cancer specialists, as many questions still remain regarding the optimal treatment for this heterogeneous patient population.

Previous studies have demonstrated that age is a significant risk factor for death after curative surgery for colorectal cancer.[3] Not only are older patients at a higher risk of postoperative complications but the impact of such adverse events on survival is also markedly higher.[4] Furthermore, elderly patients demonstrate an excess mortality rate throughout the first year following surgery, suggesting a prolonged negative impact of treatment.[5] However, when they have survived the first year, older patients have a cancer-related survival rate that is similar to that of younger patients.[5]

This may mean that innovations that improve short-term outcome for older patients can significantly benefit their overall prognosis. One such innovation is the use of laparoscopic surgical techniques, which appear to be associated with less postoperative pain, better pulmonary function, reduced occurrence of ileus and shorter hospital stay with similar oncologic outcomes.[6,7] Although exact numbers for the earlier years are not known, the proportion of colorectal cancer surgeries performed using a laparoscopic approach in the Netherlands has increased steadily, reaching 46% in 2011 - one of the highest rates in the world.[8]

In this study, we set out to analyse the impact that this increased utilisation of laparoscopic surgery for colorectal cancer in the Netherlands has had on overall survival for older and younger patients.

Methods

In this population-based analysis, patients diagnosed with colorectal cancer between 2008 and 2011 were selected from the Netherlands Cancer Registry. This registry contains information of all newly diagnosed malignancies in the Netherlands. Patients are detected through the central pathology database. Trained personnel obtain patient, tumour and treatment characteristics directly from the patient charts, fully independent from the surgical oncology team. Follow-up status is available through linkage of the Cancer Registry data with municipal population registries.

All patients with stage I-III colorectal cancer were included. Stage was determined according to the pathological Tumour-Node-Metastasis (TNM)-stage in the year of diagnosis. If pathological stage was missing, clinical stage was used. Treatment was categorised as no treatment, non-surgical treatment only, limited resection (for example, only local excision) and extensive surgery. The most extensive surgery was used for the analyses. Surgical approach (laparoscopic vs. conventional) was only available for 2010 and 2011. Extensive surgery was subdivided in hemicolectomy, sigmoid resection, Hartmann procedure, low anterior resection and abdominoperineal resection. Patients with multifocal tumours or undergoing multisegmental resections, including (sub)total colectomies, were excluded, as were patients undergoing emergency surgical procedures. For patients undergoing extensive surgery, data on neo-adjuvant and adjuvant treatment was also extracted from the cancer registry.

Patients were followed until December 31st, 2012.

Given the nature of this study, no approval from the Medical Ethics Board was elicited.

Statistical analyses

All analyses were performed in SPSS Statistics version 21.0. A p-value smaller than 0.05 was considered as statistically significant. For comparisons between groups, the chi-square test was used for nominal and ordinal variables; the Anova test was used for continuous variables.

Perioperative mortality, three-month mortality and one-year mortality rates for patients undergoing extensive surgery were analysed. Perioperative mortality was defined as death within 30 days of surgery. In addition, one-year excess mortality rates were calculated using the following formula: ((observed number of deaths in the first year – expected number of deaths in the first year in the general

population)/number of patients). The expected number of deaths was calculated using national life tables.[2]

As a straightforward comparison of a laparoscopic approach with conventional surgery was not possible due to the fact that registration of surgical approach was incomplete for 2008 and 2009, we chose to use the year of diagnosis as an instrumental variable. An instrumental variable is a factor that is associated with treatment allocation but is unrelated to the outcome.[9] To assess changes in overall survival due to the introduction of laparoscopic surgery, we therefore performed a multivariable Cox logistic regression analysis using year of diagnosis, age, stage of disease, and location of tumour (colon or rectum).

	All patients n=33254	<75 years n=20437	≥75 years n=12817	P
Tumour location				<0.001
Colon	69.9%	65.6%	76.8%	
Rectum	30.1%	34.4%	23.2%	
Tumour stage				<0.001
Stage I	27.5%	28.6%	25.8%	
Stage II	37.8%	34.9%	42.4%	
Stage III	34.7%	36.4%	31.8%	
Neo-adjuvant treatment (rectal cancers only)				<0.001
None	33.5%	27.9%	46.7%	
Radiotherapy	43.2%	42.8%	44.0%	
Chemoradiation	23.4%	29.3%	9.3%	
Treatment				<0.001
No treatment	1.1%	0.4%	2.3%	
Non-surgical treatment only	2.7%	1.9%	3.8%	
Limited surgery only	9.4%	9.9%	8.6%	
Extensive surgery	86.8%	87.7%	85.2%	
Type of extensive surgery				<0.001
Hemicolectomy	45.5%	39.7%	55.0%	
Sigmoid resection	18.6%	19.5%	17.1%	
Hartmann procedure	5.4%	4.3%	7.2%	
Low anterior resection	21.0%	25.2%	14.1%	
Abdominoperineal resection	9.5%	11.3%	6.6%	
Surgical approach in 2011				<0.001
Conventional	54.1%	50.8%	59.7%	
Laparoscopic	45.9%	49.2%	40.3%	
Adjuvant chemotherapy	17.7%	24.8%	6.4%	<0.001

Table 1. Baseline characteristics and treatment choices for all patients and per age group

Results

Baseline characteristics

Between 2008 and 2011, 35698 patients were diagnosed with stage I-III colorectal cancer in the Netherlands. After exclusion of 2444 patients (7%) due to multifocal tumours or multisegmental resections, 33254 patients were included in our analysis. Baseline characteristics for these patients can be found in Table 1. Approximately 30% of malignancies were located in the rectum and 70% in the colon. Stage I disease was diagnosed in 27.5% of patients, stage II in 37.8% and stage III in 34.7%. Overall, 1.1.% of patients did not receive any treatment and 2.7% received non-surgical treatment only while 86.8% of patients underwent extensive surgery. Hemicolectomies were most frequent (45.5%) followed by low anterior resections (21.0%) and sigmoid resections (18.6%).

Mean age of patients was 70.0 years (standard deviation 11.4 years) and 39% was older than 75 years of age (Table 1). Older patients more frequently received no treatment (2.3% compared to 0.4% of younger patients) or non-surgical treatment only (3.8% compared to 1.9%) and were slightly less likely to undergo extensive surgery (85.2% compared to 87.7% of younger patients; $p<0.001$). When surgery was performed, a laparoscopic approach was used less frequently than in younger patients (in 2011, 40.3% versus 49.2% respectively; $p<0.001$). In addition, elderly patients received significantly less neo-adjuvant treatment, particularly chemoradiation for rectal tumours (9.3% versus 29.3% of younger patients; $p<0.001$) and less adjuvant chemotherapy for both colon and rectal tumours (6.4% versus 24.8% of younger patients; $p<0.001$).

Table 2 shows a comparison of patient, tumour and treatment characteristics in the four years of this analysis. There were slightly more stage I tumours in 2011 compared to 2008 (29.0% vs. 26.3% respectively) and slightly less abdominoperineal resections (8.8% in 2011 vs. 10.3% in 2008). Data on surgical approach are not known exactly for 2008 and 2009; in 2010 36.6% of definitive surgical procedures were performed laparoscopically, and in 2011 45.9%.

Survival

Survival analyses were performed for patients undergoing extensive surgical procedures. Using the data from 2010 and 2011, a direct comparison of surgical approach revealed that at all three end-points, laparoscopy was associated with better outcomes: perioperative mortality was reduced from 2.5% to 0.7% ($p<0.001$), three-month mortality from 5.6% to 2.5% ($p<0.001$) and one-year mortality from

	2008	2009	2010	2011	P
Mean age (standard deviation)	70.0 (11.3)	69.9 (11.3)	70.2 (11.3)	69.9 (11.5)	0.27
Tumour location					0.94
Colon	70.0%	70.0%	69.9%	69.6%	
Rectum	30.0%	30.0%	30.1%	30.4%	
Tumour stage					<0.001
Stage I	26.3%	26.3%	28.7%	29.0%	
Stage II	38.6%	34.5%	37.3%	35.7%	
Stage III	35.1%	34.2%	34.1%	35.3%	
Treatment					<0.001
No treatment	1.0%	0.8%	1.3%	1.4%	
Non-surgical treatment only	2.3%	2.6%	2.9%	2.9%	
Limited surgery only	10.3%	9.3%	9.5%	8.4%	
Extensive surgery	86.4%	87.2%	86.3%	87.3%	
Type of extensive surgery					<0.001
Hemicolectomy	45.4%	45.3%	45.6%	45.8%	
Sigmoid resection	18.8%	18.7%	18.0%	18.7%	
Hartmann procedure	5.5%	5.1%	5.8%	5.3%	
Low anterior resection	20.2%	21.0%	21.3%	21.5%	
Abdominoperineal resection	10.1%	9.9%	9.3%	8.8%	
Surgical approach	*	*			<0.001
Conventional			63.4%	54.1%	
Laparoscopic			36.6%	45.9%	
Conversions from laparoscopic to conventional approach	*	*	19.3%	17.2%	0.16

Table 2. Tumour characteristics and treatment choices per year of diagnosis

* no exact data available for 2008 and 2009. Based on data from the Dutch Surgical Colorectal Audit, the percentage of laparoscopically operated patients was at least 25% in 2009.[10]

11.6% to 5.6% (p<0.001). Conversion from laparoscopy to a conventional approach resulted in an increased mortality at all end-points compared to surgeries completed laparoscopically, but this risk was not higher than those surgeries started with a conventional approach (perioperative mortality after conversion 1.1%, three-month 4.1% and one year 8.2%). While these results may be affected by a selection bias, analyses using year of diagnosis as an instrumental variable also revealed a significant and incremental decrease in mortality rates (Figure 1): perioperative mortality decreased from 2.0% to 1.5% (p=0.02), three-month mortality from 4.8% to 3.9% (p=0.01) and one-year mortality from 9.6% to 8.3% (p<0.001). In addition, for each type of surgical procedure, a reduction in mortality was seen at every end-point when comparing 2011 with 2008 (Table 3), although not always sufficiently to achieve statistical significance. After correcting for age, stage and tumour localisation, later year of diagnosis remained associated with a significantly lower risk of death in the first year (hazard ratio 0.86, 95% confidence interval 0.77-0.96; p=0.01).
When differences in expected mortality in the general population were taken into account, the relative risk reduction for older and younger patients were similar (21% and 20% respectively, Table 4). However, the benefit in terms of absolute risk reduction was greatest for patients aged 75 years of age and older: 0.8% for perioperative mortality, 1.7% for three-month mortality and 2.1% for one-year mortality.

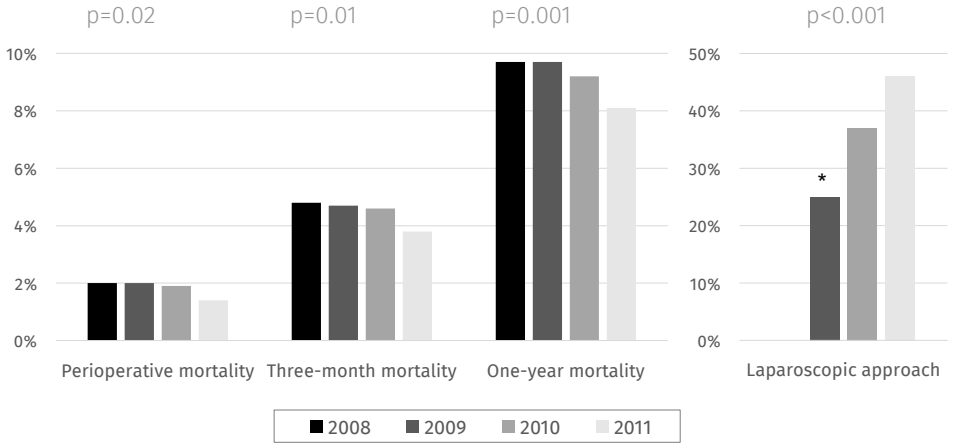


Figure 1. Perioperative, three-month and one-year mortality per year of diagnosis for patients undergoing extensive surgery

* no exact data available for 2008 and 2009. Based on data from the Dutch Surgical Colorectal Audit, the percentage of laparoscopically operated patients was at least 25% in 2009.[10]

	Reduction in perioperative mortality	Reduction in three-month mortality	Reduction in one-year mortality
Hemicolectomy	0.8%*	0.9%	1.1%
Sigmoid resection	0.2%	0.7%*	2.3%*
Hartmann procedure	0.8%	0.2%	0.4%
Low anterior resection	0%	0.6%	1.3%
Abdominoperineal resection	0.4%	0.3%	1.9%

Table 3. Absolute reduction in mortality between 2008 and 2011, per type of surgical procedure

* $p<0.05$

A. <75 years	2008	2011	p-value	Absolute risk reduction	Relative risk reduction
Perioperative mortality	0.8%	0.6%	0.17	0.2%	25%
Three-month mortality	2.1%	1.8%	0.21	0.3%	14%
One-year mortality	5.1%	4.3%	0.06	0.8%	16%
Excess one-year mortality	4.0%	3.2%		0.8%	20%

B. 75+ years	2008	2011	p-value	Absolute risk reduction	Relative risk reduction
Perioperative mortality	3.9%	3.1%	0.11	0.8%	21%
Three-month mortality	9.3%	7.6%	**0.03**	1.7%	16%
One-year mortality	17.1%	15.0%	**0.04**	2.1%	12%
Excess one-year mortality	10.8%	8.5%		2.3%	21%

Table 4. Mortality rates per age group in 2008 and 2011, for patients undergoing extensive surgery

Discussion

In this population-based study, we found that a laparoscopic approach is increasingly being utilised in colorectal surgery. This has resulted in a significant reduction in perioperative, three-month and one-year mortality rates. Elderly patients appear to benefit most in terms of absolute reduction in mortality risk, reaching up to 2.1% one year after surgery. Despite this, a laparoscopic approach is used less frequently for older patients than for younger patients, suggesting that additional reductions may be possible.

This study has some limitations. Primarily, we could only make use of the data as collected in the Netherlands Cancer Registry database. Although registration of surgical approach was initiated in 2008, comparison with other data sources, primarily the data of the Dutch Surgical Colorectal Audit,[8,10] revealed that registration of this parameter was incomplete in the first two years. However, using year of diagnosis as an instrumental variable, we were no longer dependent on the exact proportion of laparoscopic surgeries.

This method also enabled us to demonstrate that the change in mortality was not merely the result of confounding by indication; this type of confounding is the result of the fact that choice of surgical approach does not occur at random. For instance, data from the Dutch Surgical Colorectal Audit revealed significant differences in case-mix between patients undergoing laparoscopic versus conventional surgery, with patients treated with laparoscopy being significantly younger, with lower stage of disease and less comorbidity.[11] Other variations may exist, regarding factors not routinely recorded and which can thus not be corrected for. As a result, a direct comparison of outcome between these two surgical approaches in non-randomised studies could suggest benefit that in actual fact is not due to the approach but instead to differences in the a priori risk of poor outcome. However, this issue does not apply when using an instrumental variable.

Previous studies demonstrated that over the years survival for younger and middle-aged colorectal cancer improved but elderly patients did not reap similar benefits from improved cancer treatments.[12,13] This could in part be due to the fact that older patients are more likely to die of causes other than the active cancer, as demonstrated by the markedly larger gap between one-year mortality and one-year excess mortality in the elderly (Table 4). Another explanation could be that while older and younger patients experience similar rates of surgical complications, the rate of postoperative pulmonary and cardiovascular complications is much higher in the elderly.[14] These adverse events are a significant factor contributing to the excess mortality in this age group[4] and will

not significantly be diminished with improved cancer-specific treatments.
However, our study reveals that over the past few years, the survival gap between older and younger patients is beginning to decrease: the difference in one-year excess mortality rate between both age groups was 6.8% in 2008, and 5.3% in 2011, representing a reduction of 22%. This could be the result of the increased use of a laparoscopic surgical approach. Studies have demonstrated that such minimally invasive techniques result in much less extensive post-surgical stress and an attenuated acute phase response.[15-17] While not altering cancer-specific outcomes,[6,7] the limited trauma on the body could limit the occurrence of non-surgical complications. This could be most beneficial to the elderly, as there is an exponential rise of cardiovascular and pulmonary adverse events with increasing age.[14]
The proportion of older patients operated laparoscopically is lagging: in 2011, 40.3% compared to 49.2% of younger patients. This could in part be due to the fact that older patients are known to present with a later stage of disease and more often have had previous abdominal surgery, which may have affected choice of surgical approach. However, it is possible that further improvement in outcome may be achievable with a further increase in the utilisation of laparoscopic surgery, in particular in the elderly. Some studies have found that conversion from laparoscopy to open surgery resulted in higher complication rates.[18,19] However, this could for a large part be explained by confounding by indication, particularly when conversion is compared only to those surgeries completed laparoscopically,[19] as it is clear that perioperative complications are an important reason for choosing to convert. In our study, conversion from laparoscopy to a conventional approach did not result in a poorer outcome than surgeries started conventionally. This suggests that it may be beneficial to begin more procedures laparoscopically rather than taking the preoperative decision that this approach will not be feasible. Although this will probably result in a higher rate of conversions, it is also likely to result in an overall increase in surgeries completed with laparoscopy which may further improve in perioperative and longer-term outcomes. However, future research will be needed to test this hypothesis and the implications of a further increase of laparoscopy on short-term surgical outcomes.

Conclusion

A laparoscopic approach is increasingly utilised in colorectal surgery, resulting in a significant reduction in perioperative, three-month and one-year mortality rates, particularly for the elderly. Therefore, using a laparoscopic approach whenever possible may allow for further improvement of outcomes.

References

1. www.cijfersoverkanker.nl.
2. www.cbs.nl.
3. Gooiker GA, Dekker JW, Bastiaannet E et al. Risk Factors for Excess Mortality in the First Year After Curative Surgery for Colorectal Cancer. Ann Surg Oncol. 2012 Aug;19(8):2428-34
4. Shahir MA, Lemmens VE, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. Eur J Cancer 2006;42:3015-3021.
5. 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. Ann Surg Oncol 2011;18:1533-1539.
6. Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer J. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. Cancer Treat Rev 2008;34:498-504.
7. Schwenk W, Haase O, Neudecker J, Muller JM. Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev 2005;CD003145.
8. Dutch Surgical Colorectal Audit. DSCA yearly report 2011. dsca.clinicalaudit.nl
9. Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004;363:1728-1731.
10. Dutch Surgical Colorectal Audit. DSCA yearly report 2009. dsca.clinicalaudit.nl
11. Kolfschoten NE, van Leersum NJ, Gooiker GA et al. Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals. Ann Surg 2013;257:916-921.
12. Elferink MA, van Steenbergen LN, Krijnen P et al. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989-2006. Eur J Cancer 2010;46:1421-1429.
13. van den Broek CB, Dekker JW, Bastiaannet E et al. The survival gap between middle-aged and elderly colon cancer patients. Time trends in treatment and survival. Eur J Surg Oncol 2011;37:904-912.
14. Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. Lancet 2000;356:968-974.
15. Wichmann MW, Huttl TP, Winter H et al. Immunological effects of laparoscopic vs open colorectal surgery: a prospective clinical study. Arch Surg 2005;140:692-697.
16. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. Lancet 2003;362:1921-1928.
17. Biffl WL, Moore EE, Moore FA, Peterson VM. Interleukin-6 in the injured patient. Marker of injury or mediator of inflammation? Ann Surg 1996;224:647-664.
18. Guillou PJ, Quirke P, Thorpe H et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005;365:1718-1726.
19. Marusch F, Gastinger I, Schneider C et al. Importance of conversion for results obtained with laparoscopic colorectal surgery. Dis Colon Rectum 2001;44:207-214.

Colorectal Dis.
2014;16:976-985

Anandi H.W. Schiphorst
Apollo Pronk
Inne H.M. Borel Rinkes
Marije E. Hamaker

photo: Afternoon Read by Leon Fishman

7

Representation of the elderly in trials on laparoscopic surgery for colorectal cancer

Abstract

Introduction

While the majority of colorectal cancer patients are elderly, data regarding the optimal surgical treatment for elderly are scarce and mostly observational. Benefits of laparoscopic surgery might be most advantageous to the heterogeneous elderly population. However, it is unclear if elderly have participated sufficiently in trials on laparoscopic colorectal surgery. The objective of this analysis was to study the characteristics of these trials and to assess if elderly have been able to participate and if so, were they sufficiently accrued.

Methods

A search was conducted of the NIH clinical trial registry and the ISRCTN register for randomised trials on laparoscopic surgery for colorectal cancer. Trial characteristics and outcome measures were extracted from the registry website and supplemented with published results, if available.

Results

Of 52 included trial protocols, the majority did not formulate any restrictions regarding cardiac or pulmonary functioning (77% and 79% respectively), and more than half had no restrictions regarding ASA-score. 44% of trials excluded elderly based on age, comorbidity or organ function. When an upper age limit was used, half of these studies had no restrictions regarding organ function, indicating that chronologic age rather than physical condition was the reason for exclusion. In 86% of published trials, the average age of participants was <70 years, and no details concerning concurrent disease were reported.

Conclusion

Participation of elderly in trials on laparoscopic surgery for colorectal cancer has lagged behind. To enhance representativity in future trials, protocol criteria should be selected critically, allowing for accrual of the elderly population.

Introduction

Colorectal cancer is one of the most common cancers worldwide and ranks third in the incidence of all cancers in the Netherlands.[1] It is predominantly a disease of the elderly as in 2011 54% of newly diagnosed colorectal cancer patients were over 70 years of age.[1] With the imminent rise in life-expectancy, questions regarding optimal treatment for older colorectal cancer patients are becoming increasingly urgent. As the elderly form a heterogeneous patient population with a wide variety in health issues, physical reserve, geriatric conditions and disability,[2] treatment recommendations for younger and fit patients cannot automatically be extrapolated to the elderly population. For example, elderly are more prone to adverse events following treatment for colorectal cancer and, as demonstrated by previous studies, the impact of postoperative complications on survival is significantly increased.[3,4] In the treatment of colorectal cancer, the introduction of minimally invasive surgical techniques over recent years has led to a wide adaptation of laparoscopic colorectal surgery with over 50% of elective colorectal surgery performed laparoscopically in the Netherlands.[5,6] Benefits of laparoscopic surgery have been described extensively, including decreased morbidity, better pulmonary function, earlier return to functionality, less blood-loss and shorter hospital stay, while maintaining equivalent oncologic outcomes.[7-9] These advantages may be especially beneficial to the elderly, since they suffer most from excess mortality rates throughout the first year after colorectal surgery.[10] On the other hand, the presence of comorbid conditions could limit this benefit and interaction between the particular characteristics of laparoscopic surgery – such as the necessary pneumoperitoneum – and age-related decrease of organ function could potentially increase the complication rate. Furthermore, older patients may set other priorities regarding treatment outcomes, which means that trial results for younger patients cannot automatically be extrapolated to the elderly. Historically, older patients and those with comorbidities have been excluded from clinical trials,[11-13] despite the fact that a myriad of publications have addressed the need for assessing the safety and efficacy of novel treatment options in a study population that is representative of the actual target population. For instance, as early as 1989, the Food and Drug Administration (FDA) issued a recommendation for sufficient elderly to be included in registration trials for chemotherapeutical agents.[14] For surgical trials, such guidance is lacking. Therefore, we set out to investigate characteristics of randomised clinical trials on laparoscopic surgery for colorectal cancer, to determine if elderly patients have been eligible for participation in these trials and if so, if they were sufficiently accrued.

Methods

To identify randomised trials on laparoscopic surgery for colorectal cancer, the United States National Institutes of Health clinical trial registry (www.clinicaltrials.gov) and the International Standard Randomised Controlled Trial Number Register (ISRCTN Register, www.controlled-trials.com) were searched on December 1st 2013, using the search terms "laparoscopy" and "colon OR rectum OR colorectal". Trials without surgical intervention and observational trials were excluded, as were trials on benign disease only and those not comparing laparoscopic surgery to other surgical approaches.

For included trials, the following data were extracted from the registry websites: target disease entities (rectal cancer, colon cancer or colorectal cancer combined), type of surgical intervention and approach, the in- and exclusion criteria with particular focus on age limits, ASA-score, comorbidity and organ function, study objectives and start year of the study. Surgical interventions were classified as laparoscopic versus open surgery, single incision surgery or robotic surgery. Restrictions regarding comorbidity and organ function were classified into the following categories: pulmonary function, cardiac function, restrictions regarding other organ systems or prior medical history and "suitable for surgery" not otherwise specified. For each category, restrictions were labelled as moderate or strict, or none if no exclusion criteria pertaining to that category were mentioned. This classification was modified from the classification previously used by Lewis et al.[15] and full details per category can be found in Appendix 1. Briefly, strict exclusions were those protocol exclusion criteria that required normal or nearly normal laboratory values or organ function whereas moderate exclusions allowed for mildly abnormal values while still imposing some restrictions.

Study objectives (both primary and secondary) were classified into four categories (Appendix 2): oncologic outcome, surgical outcome, patient-related outcome and economic outcome.

Trials were considered as excluding patients based on *age* if they used an upper age limit of 80 years of age or lower; exclusion based on *comorbidity* was recorded for trials that only allowed inclusion of healthy patients or those with mild systemic disease (ASA-score 1 and 2) and exclusion based on *organ function* if they used one or more stringent organ function restrictions.

All included trials were checked for published results in Medline. If results were published, full-text articles were retrieved and cross-referenced for additional in- and exclusion criteria as well as mean or median age and ASA-score of the study

population. Additionally, articles were screened for data regarding specific subgroup analyses of older patients or those with comorbidity. Also, the authors were contacted for additional information regarding the percentage of elderly patients (aged ≥75 years at time of randomisation) in their study population.

Statistical analysis

Only descriptive statistics were used.

Figure 1. Search results and trial selection

		Total (n=)	%
Diagnosis	Colon cancer	20	38%
	Colorectal cancer	17	33%
	Rectal cancer	15	29%
Start year	≤2007	24	46%
	2008-2009	11	21%
	2010-2011	9	17%
	2012-2013	8	15%
Intervention	Laparoscopy vs conventional surgery	36	69%
	Laparoscopy vs robotic surgery	7	13%
	Laparoscopy vs single-incision surgery	9	17%
Recruitment status	Not yet recruiting	2	4%
	Recruiting	20	38%
	Ongoing but no longer recruiting	10	19%
	Completed	20	38%
Published results		21	40%

Table 1. Characteristics of selected trials

Results

Overall, 249 trials were retrieved in the trial registry search (200 from the NIH registry and 49 from the ISRCTN register), of which three were duplicates. After exclusion of 194 trials, a total of 52 were included in the present study (Figure 1). Characteristics of included trials are depicted in Table 1. Trials were more frequently conducted on surgery for colon cancer as compared to rectal cancer. The majority of trials compared laparoscopic surgery to a conventional approach (69%) and 46% of these started before 2007. Seven trials randomised between laparoscopic and robotic or robot-assisted surgery (the first of which started in 2008) and nine trials compared laparoscopy to single-incision surgery (first started in 2009). Overall, 40% of included studies had published (some) study results while 62% was still ongoing at the time of search.

Of the 52 included trials, 7 studies (13%) did not formulate any restrictions regarding upper age limit, ASA-score or organ function, nor any other restrictions regarding physical suitability.

Most trials had a lower age limit for inclusion below 21 years of age (77%, Table 2); only one trial excluded patients younger than 70 years of age, thus focussing specifically on older patients. Nearly two-thirds of trials did not name an upper age limit; four trials (8%) had an upper age limit between 70 and 79 years, 10 (19%) between 80 and 85 years and six trials (12%) excluded patients over 85 years of age. One-third of trials excluded patients with ASA 4 score, while 10% of trials included only patients with ASA score 1 or 2.

In 35% of trials inclusion was limited to patients “regarded as suitable for surgery”, without stating what determined suitability, while almost half of trials specified one or more restriction regarding organ function in the in- and exclusion criteria (Table 2). Restrictions pertaining to cardiac (23%) and pulmonary (21%) function were most common. Only two trials had strict cardiac function restrictions, while none of the trials named stringent restrictions regarding pulmonary functioning. In nine trials (17%), one or more stringent restrictions regarding other organ systems or prior medical history were formulated, of which seven trials did not allow inclusion of patients with any prior malignancies and one trial excluded patients with any history of psychiatric disease.

Overall, 23 trials (44%) excluded elderly patients (Figure 2): 27% based on an upper age limit, 17% based on strict organ function restrictions and 13% based on restrictions regarding ASA-score. Of the 14 trials that excluded elderly based on an upper age limit, 50% did not specify any restrictions regarding organ function and

		Total n= 52		Laparoscopic vs. conventional surgery	Laparoscopic vs. robotic surgery	Laparoscopic vs. single-incision surgery
		n=	%	n=	n=	n=
Lower age limits	None	7	13%	4		
	<21 years	40	77%	27		
	22-59 years	4	8%	4		
	60-64 years	0	-	0		
	65-69 years	0	-	0		
	70+ years	1	2%	1		
Upper age limits	None	32	62%	25	2	5
	<50 years	0	-	0	0	0
	51-64 years	0	-	0	0	0
	65-69 years	0	-	0	0	0
	70-74 years	0	-	0	0	0
	75-79 years	4	8%	3	1	0
	80-84 years	10	19%	6	4	0
	85-90 years	6	12%	2	0	4
ASA-score	ASA 3+ excluded	5	10%	3	0	2
	ASA 4+ excluded	17	33%	12	3	2
	No criteria regarding ASA-score mentioned	30	58%	21	4	5
Organ system restrictions						
Pulmonary function‡	No restrictions	41	79%	28	4	9
	Moderate restrictions	11	21%	8	3	0
	Stringent restrictions	0	-	0	0	0
Cardiac function‡	No restrictions	40	77%	27	4	9
	Moderate restrictions	10	19%	8	2	0
	Stringent restrictions	2	4%	1	1	0
Other organ system restrictions‡	No restrictions	31	60%	18	5	8
	Moderate restrictions	12	24%	10	1	1
	Stringent restrictions	9	17%	8	1	0
"Suitable for surgery" without specifying criteria for determining suitability		18	35%	13	3	2

Table 2. In- and exclusion criteria of selected trials

ASA: American Society of Anaesthesiologists;
‡ Classification of organ function modified from Lewis et al.[15] Details can be found in Appendix 1.

two formulated only vague criteria regarding suitability for surgery. Furthermore, 57% of these studies did allow inclusion of younger patients with poor ASA-score. With regards to end-points of included trials, 90% of all trials included surgical outcome measures, 73% addressed oncologic outcome parameters and 48% economic outcomes, while 42% named patient-related outcome measures as a study objective. Of these, quality of life was most frequently evaluated (35% of trials), followed by functional outcome (15%), aesthetic outcome (10%) and time to resume daily activities (8% of trials).
For 21 of the 52 included trials (40%), a publication of (preliminary) study results was retrieved from Medline. Seventeen of these trials compared laparoscopy to conventional approach; two studies were on robot-assisted surgery and two on single-incision surgery (Table 3). Sixteen studies mentioned the ASA-scores of the included study-population in the final publication and the median number of patients with ASA-scores of 3 or more was 19% (range 3-39%). The median age of studied patients in all published study reports was 67 years (range 58-71, Table 3) only three trials (14%) had a mean or median age of 70 or older. Ten studies (48%) excluded elderly based on restrictions on age, ASA-score, organ function or a combination of restrictions. The number of participants aged ≥75 years, as answered by eleven corresponding authors, ranged from 3% to 37% (Table 3). Although the percentage of patients aged ≥75 years was higher in some studies, the number of patients with ASA-score 3 or 4 in these studies was relatively low, raising questions on the representativity of the elderly that were in fact included. Other than ASA-score, 86% of published trial reports did not mention concurrent disease-rate or comorbidity index of the studied patient population. Only one study specifically reported outcome for elderly patients, although two other studies did include age as a factor in the multivariate analysis.

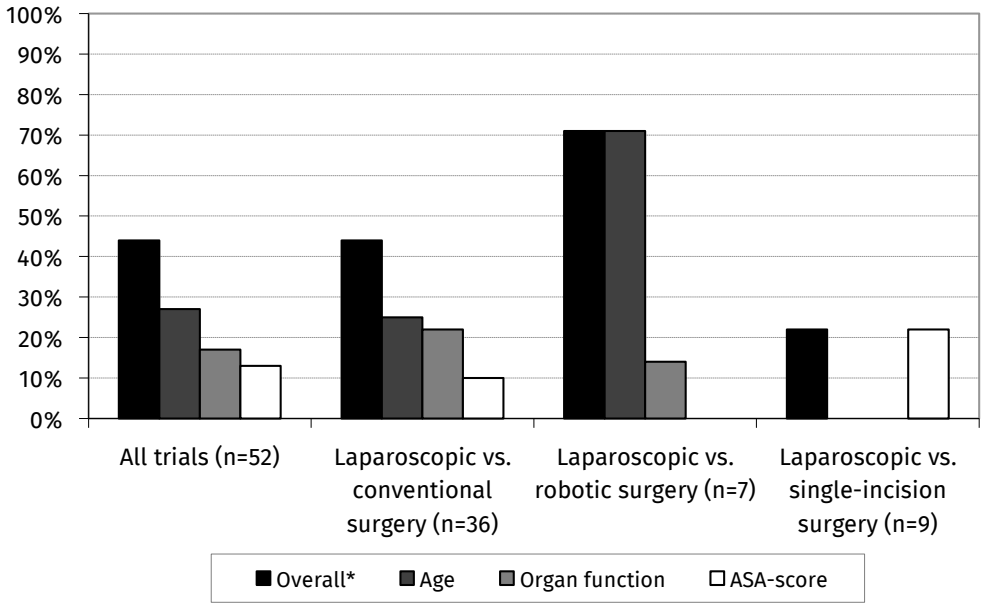


Figure 2. Exclusion of elderly per trial type

* Trials were considered as excluding elderly patients based on age if they used an upper age limit of 80 years of age or lower, if they only allowed inclusion of patients with an ASA-score of 1or 2 and if they used one or more stringent organ function restrictions. Multiple restrictions per trial were possible.
ASA: American Society of Anaesthesiologists

Discussion

In this overview of protocols for randomised trials on laparoscopic colorectal surgery, we demonstrate that although nearly two-thirds of trials did not use an upper age limit for inclusion, 44% of studied trial protocols excluded elderly patients. When an upper age limit was used, half of these studies had no restrictions regarding organ function whatsoever, indicating that chronologic age rather than physical condition was the reason for in- or exclusion. The vast majority of trials did not formulate any restrictions regarding cardiac or pulmonary functioning (77% and 79% respectively), and more than half had no restrictions regarding ASA-score.
The clinical applicability of trial results depends largely on whether the study participants are representative of the population of interest.[16] With increasing age, the incidence of (multiple) concomitant health issues rises equally and, as a result,

data on younger patients cannot automatically be extrapolated to the elderly. As older patients currently represent the majority of newly diagnosed colorectal cancer patients, their participation in clinical trials is important. Our analysis demonstrates however, that although exclusion criteria for clinical trials on laparoscopic colorectal surgery do not always exclude patients based on age, participation of older patients has lagged behind.

There are several potential explanations. First of all, protocol exclusion criteria that are based on limitations in comorbidity or functional status disproportionally disqualify elderly from participation.[15] Some of these limitations will be pertinent and attribute to homogeneous trial populations. Furthermore, in oncology trials with 5-year disease-free survival as primary outcome, recruitment of patients with limited life expectancy may be undesirable. However, it is not unlikely that some exclusion criteria are more or less routinely formulated based on assumptions or prior protocols. As reported by Lewis et al., if exclusion criteria on functional status and organ systems are eased, the enrolment of elderly could almost double in number.[15] In our study, we found that seven study-protocols restricted inclusion of patients with any prior malignancy and one trial excluded patients with any history of psychiatric disease. It is questionable whether such stringent criteria are truly relevant for the study.

On the other hand, while laparoscopy with subsequent pneumoperitoneum affects the cardiopulmonary system especially in those with comorbidity or poor ASA-score, the majority of studies did not formulate any restrictions on pulmonary or cardiac functioning and nearly 60% had no restrictions on ASA-score. Rather, ambiguous in- or exclusion criteria such as “suitable for surgery” were used. This requires the physician’s own interpretation of what suitability entails. Earlier studies on cancer trials have demonstrated that it is important to mention explicitly which specific restrictions are applied.[15,17] They showed that older patients accounted for 63% of participants in trial protocols that specifically stated that patients with a poor performance status were eligible, but only 16% in protocols that did not specify exclusion criteria regarding performance status.[17] Thus, if trial protocols explicitly mandate enrolment of older patients with impairments, this could contribute to a physicians’ willingness to consider elderly for participation.

Finally, earlier reports on the difficulty of patient-accrual for surgical oncology trials have demonstrated that even when older patients are specifically targeted for inclusion, their recruitment remains challenging.[13,18-20] This could be due to the nature of surgical treatment and strong patient or surgeon preferences. Furthermore, there appears to be a lack of knowledge in the elderly population on clinical trials in general and in particular, on the process of randomisation.[21] However, a study

Study	Comparing laparoscopy to type of surgery	No. of patients	Excluding elderly*	Reason for exclusion of elderly	Study population		
					Age**	≥ 75y	ASA 3-4
Kang[27]	Conventional	340	+	Age & organ function	58	4%	3%
Yamamoto[28]	Conventional	1057	+	Age	64	3%	
Braga[29]	Conventional	134			64		18%
Jiménez Rodríguez[30]	Robotic	56	+	Age	65	23%	39%
Park[31]	Robotic	70	+	Age	65		9%
Pas[32]	Conventional	1044	+	Organ function	66	24%	19%
Vlug[33]	Conventional	400	+	Age	66,5	21%	20%
Cheung[34]	Conventional	22			66,5		
Neudecker[35]	Conventional	472			67	23%	27%
Luján[36]	Conventional	204	+	Organ function	67		34%
Poon[37]	Single-incision	50			67		14%
Leung[38]	Single-incision	70			67		
Li[39]	Conventional	145			68		21%
Pappas-Gogos[40]	Conventional	60	+	ASA-score	68,5		
Tsimogiannis[41]	Conventional	40	+	ASA-score	68,5		
Guillou[42]	Conventional	794			69	35%	13%
Kaltoft[43]	Conventional	18			69	28%	11%
Nelson[44]	Conventional	863			69,5		14%
Pascual[45]	Conventional	122			70	37%	38%
Hewett[46]	Conventional	587			70	37%	28%
Veldkamp[47]	Conventional	1248	+	Organ function	71	37%	17%

Table 3. Published trial reports

* Trials were considered as excluding elderly patients based on age if they used an upper age limit of 80 years of age or lower, if they only allowed inclusion of patients with an ASA-score of 1or 2 and if they used one or more stringent organ function restrictions. Multiple restrictions per trial were possible.

** Extracted from mean or median age in years as reported in published articles.
ASA: American Society of Anaesthesiologists

on the attitude of older patients towards enrolment in clinical trials demonstrated that, despite initial hesitation, over 75% of patients were willing to participate after additional explanation of the trial process.[21] The amount of time spent with the patient (by the treating physician or a clinical research assistant) has been shown to enhance the participation of older patients in clinical trials.[22] Moreover, it is important to involve patients' social network such as relatives in discussing trial participation.[20] Table 3 demonstrates that it is indeed possible to include sufficient elderly in a clinical trial. However, questions regarding the representativity of included elderly remain.

Although reasons for deciding to participate in clinical trials do not differ between elderly and younger patients,[16] treatment objectives for younger patients may not always be identical to those important for elderly. When choosing between various treatment options, quality of life and functional outcome after treatment is at least as important for elderly as the oncologic or surgical outcome.[23,24] However, data on these outcome measures are currently lacking. Therefore, it is promising to see that in our analysis 42% of trials addressed patient-centred outcome measures, even those trials studying new innovations as robot-assisted and single-incision surgery.

This study has some limitations. Since we focussed on trial registration, we may not have a full representation of all clinical trials worldwide. However, in compliance with the FDS Amendments Act of 2007,[25] all journals committing to the policy of the International Committee of Medical Journals Editors (ICMJE) require trial registration. Consequently, all peer-reviewed literature on laparoscopic colorectal cancer surgery is likely to come from registered trials. In fact, even trials that commenced before 2007 were registered, as 46% of trials included in this overview started in or before 2007. A second limitation is that there is no consensus on which cut-off values in cardiopulmonary or other organ function represent strict or moderate exclusion criteria and each cut-off can be open to debate. No clear contra-indications for laparoscopic surgery have been formulated in treatment guidelines.[26] In the absence of such criteria, we chose to use a modified classification method formulated by Lewis et al.[15] that was previously used and published in a peer-reviewed journal.

Conclusion

Trial protocol criteria give rise to barriers for the accrual of older patients in trials on laparoscopic colorectal surgery and participation of elderly has lagged behind. This makes decisions on surgical treatment for older colorectal cancer patients based on evidence from randomised trials troublesome, as questions regarding the optimal treatment for the elderly still remain. Future trials should enhance the representativeness of their trial population, and thus the applicability of the outcome to real life populations, by careful consideration of in- and exclusion criteria. This will require using only those criteria truly pertinent for the trial, avoiding ambiguous criteria and also making it explicit whenever no specific limitations are applied to organs system functioning, medical history or other patient-related factors such as age or ASA-score. In addition, to enhance standardisation of in- and exclusion criteria, perhaps there could be a role for established collaborative groups to develop guidelines or recommendations for trial protocols. Furthermore, initiatives should be undertaken to enrol older patients once the trial has commenced.

References

1. Veenhof AA, Vlug MS, van der Pas MH, Sietses C, van der Peet DL, de Lange-de Klerk ES, Bonjer HJ, Bemelman WA, Cuesta MA. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. Ann Surg 2012;255:216-21.
2. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, Mor V, Monfardini S, Repetto L, Sorbye L, Topinkova E. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005;55:241-52.
3. Shahir MA, Lemmens VE, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. Eur J Cancer 2006;42:3015-21.
4. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, Tollenaar RA, Liefers GJ. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. Ann Surg Oncol 2012;19:2428-34.
5. Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. Am J Surg Pathol 2002;26:350-7.
6. Kolfschoten NE, van Leersum NJ, Gooiker GA, Marang van de Mheen PJ, Eddes EH, Kievit J, Brand R, Tanis PJ, Bemelman WA, Tollenaar RA, Meijerink J, Wouters MW. Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals. Ann Surg 2012;257:916-21.
7. Schwenk W, Haase O, Neudecker J, Muller JM. Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev 2005:CD003145.
8. Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy A, Bonjer HJ. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol 2009;10:44-52.
9. Kuhry E, Schwenk WF, Gaupset R, Romild U, Bonjer HJ. Long-term results of laparoscopic colorectal cancer resection. Cochrane Database Syst Rev 2008:CD003432.
10. 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. Ann Surg Oncol 2011;18:1533-9.
11. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061-7.
12. Javid SH, Unger JM, Gralow JR, Moinpour CM, Wozniak AJ, Goodwin JW, Lara PN, Jr., Williams PA, Hutchins LF, Gotay CC, Albain KS. A prospective analysis of the influence of older age on physician and patient decision-making when considering enrollment in breast cancer clinical trials

(SWOG S0316). Oncologist 2012;17:1180-90.
13. Stewart JH, Bertoni AG, Staten JL, Levine EA, Gross CP. Participation in surgical oncology clinical trials: gender-, race/ethnicity-, and age-based disparities. Ann Surg Oncol 2007;14:3328-34.
14. http://dsca.clinicalaudit.nl/.
15. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, Housman MG, Escarce JJ. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21:1383-9.
16. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Oncol 2005;23:3112-24.
17. Gross CP, Herrin J, Wong N, Krumholz HM. Enrolling older persons in cancer trials: the effect of sociodemographic, protocol, and recruitment center characteristics. J Clin Oncol 2005;23:4755-63.
18. Abraham NS, Hewett P, Young JM, Solomon MJ. Non-entry of eligible patients into the Australasian Laparoscopic Colon Cancer Study. ANZ J Surg 2006;76:825-9.
19. Abraham NS, Young JM, Solomon MJ. A systematic review of reasons for nonentry of eligible patients into surgical randomized controlled trials. Surgery 2006;139:469-83.
20. Hempenius L, Slaets JP, Boelens MA, van Asselt DZ, de Bock GH, Wiggers T, van Leeuwen BL. Inclusion of frail elderly patients in clinical trials: solutions to the problems. J Geriatr Oncol 2013;4:26-31.
21. Townsley CA, Chan KK, Pond GR, Marquez C, Siu LL, Straus SE. Understanding the attitudes of the elderly towards enrolment into cancer clinical trials. BMC Cancer 2006;6:34.
22. Wright JR, Whelan TJ, Schiff S, Dubois S, Crooks D, Haines PT, DeRosa D, Roberts RS, Gafni A, Pritchard K, Levine MN. Why cancer patients enter randomized clinical trials: exploring the factors that influence their decision. J Clin Oncol 2004;22:4312-8.
23. Yellen SB, Cella DF, Leslie WT. Age and clinical decision making in oncology patients. J Natl Cancer Inst 1994;86:1766-70.
24. Harrison JD, Solomon MJ, Young JM, Meagher A, Butow P, Salkeld G, Hruby G, Clarke S. Patient and physician preferences for surgical and adjuvant treatment options for rectal cancer. Arch Surg 2008;143:389-94.
25. Anderson C, Uman G, Pigazzi A. Oncologic outcomes of laparoscopic surgery for rectal cancer: a systematic review and meta-analysis of the literature. Eur J Surg Oncol 2008;34:1135-42.
26. Neudecker J, Sauerland S, Neugebauer E, Bergamaschi R, Bonjer HJ, Cuschieri A, Fuchs KH, Jacobi C, Jansen FW, Koivusalo AM, Lacy A, McMahon MJ, Millat B, Schwenk W. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. Surg Endosc 2002;16:1121-43.
27. Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, Lim SB, Lee TG, Kim DY, Kim JS, Chang HJ, Lee HS, Kim SY, Jung KH, Hong YS, Kim JH, Sohn DK, Kim DH, Oh JH. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. Lancet Oncol 2010;11:637-45.
28. Yamamoto S, Inomata M, Katayama H, Mizusawa J, Etoh T, Konishi F, Sugihara K, Watanabe M, Moriya Y, Kitano S. Short-term Surgical Outcomes From a Randomized Controlled Trial to Evaluate Laparoscopic and Open D3 Dissection for Stage II/III Colon Cancer: Japan Clinical Oncology Group Study JCOG 0404. Ann Surg 2014.
29. Braga M, Frasson M, Zuliani W, Vignali A, Pecorelli N, Di Carlo V. Randomized clinical

trial of laparoscopic versus open left colonic resection. Br J Surg 2010;97:1180-6.
30. Jimenez Rodriguez RM, Diaz Pavon JM, de La Portilla de Juan F, Prendes Sillero E, Hisnard Cadet Dussort JM, Padillo J. [Prospective randomised study: robotic-assisted versus conventional laparoscopic surgery in colorectal cancer resection]. Cir Esp 2011;89:432-8.
31. Park JS, Choi GS, Park SY, Kim HJ, Ryuk JP. Randomized clinical trial of robot-assisted versus standard laparoscopic right colectomy. Br J Surg 2012;99:1219-26.
32. van der Pas MH, Haglind E, Cuesta MA, Furst A, Lacy AM, Hop WC, Bonjer HJ. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-8.
33. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, Gerhards MF, van Wagensveld BA, van der Zaag ES, van Geloven AA, Sprangers MA, Cuesta MA, Bemelman WA. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg 2011;254:868-75.
34. Cheung HY, Chung CC, Tsang WW, Wong JC, Yau KK, Li MK. Endolaparoscopic approach vs conventional open surgery in the treatment of obstructing left-sided colon cancer: a randomized controlled trial. Arch Surg 2009;144:1127-32.
35. Neudecker J, Klein F, Bittner R, Carus T, Stroux A, Schwenk W. Short-term outcomes from a prospective randomized trial comparing laparoscopic and open surgery for colorectal cancer. Br J Surg 2009;96:1458-67.
36. Lujan J, Valero G, Hernandez Q, Sanchez A, Frutos MD, Parrilla P. Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer. Br J Surg 2009;96:982-9.
37. Poon JT, Cheung CW, Fan JK, Lo OS, Law WL. Single-incision versus conventional laparoscopic colectomy for colonic neoplasm: a randomized, controlled trial. Surg Endosc 2012;26:2729-34.
38. Leung AL, Cheung HY, Fok BK, Chung CC, Li MK, Tang CN. Prospective randomized trial of hybrid NOTES colectomy versus conventional laparoscopic colectomy for left-sided colonic tumors. World J Surg 2013;37:2678-82.
39. Li JC, Leung KL, Ng SS, Liu SY, Lee JF, Hon SS. Laparoscopic-assisted versus open resection of right-sided colonic cancer--a prospective randomized controlled trial. Int J Colorectal Dis 2012;27:95-102.
40. Pappas-Gogos G, Tellis C, Lasithiotakis K, Tselepis AD, Tsimogiannis K, Tsimoyiannis E, Chalkiadakis G, Chrysos E. Oxidative stress markers in laparoscopic versus open colectomy for cancer: a double-blind randomized study. Surg Endosc 2013;27:2357-65.
41. Tsimogiannis KE, Tellis CC, Tselepis AD, Pappas-Gogos GK, Tsimoyiannis EC, Basdanis G. Toll-like receptors in the inflammatory response during open and laparoscopic colectomy for colorectal cancer. Surg Endosc 2012;26:330-6.
42. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005;365:1718-26.
43. Kaltoft B, Gogenur I, Rosenberg J. Reduced length of stay and convalescence in laparoscopic vs open sigmoid resection with traditional care: a double blinded randomized clinical trial. Colorectal Dis 2011;13:e123-30.

44. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050-9.
45. Pascual M, Alonso S, Pares D, Courtier R, Gil MJ, Grande L, Pera M. Randomized clinical trial comparing inflammatory and angiogenic response after open versus laparoscopic curative resection for colonic cancer. Br J Surg 2011;98:50-9.
46. Hewett PJ, Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Rieger NA, Smith JS, Solomon MJ, Stephens JH, Stevenson AR. Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. Ann Surg 2008;248:728-38.
47. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy AM. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-84.

Organ system	Moderate restrictions	Strict restrictions
Cardiac	• Adequate cardiac function • No clinically evident congestive heart failure • No difficult to control congestive heart failure • Cut-off for left ventricular ejection fraction ≥40% or lower • Cut-off for shortening fraction ≥25% or lower • No clinically significant cardiac disease • No New York Heart Association (NYHA) grade III or IV disease • No myocardial infarction in past 12 months or shorter • No angina pectoris requiring medication • No unstable heart rhythm • No difficult to control heart rhythm • No symptomatic arrhythmia in past 6 months • Cut-off for QTc > 450ms or higher	• Normal cardiac function • No history of congestive heart failure • Cut-off for left ventricular ejection fraction ≥45% or higher • Cut-off for shortening fraction ≥27% or higher • No New York Heart Association (NYHA) grade II or more • No history of myocardial infraction or ischemic heart disease • No myocardial infarction in past 5 years or longer • No abnormal conduction disease • No arrhythmia requiring treatment
Pulmonary	• Adequate pulmonary function • Cut-off for diffusing capacity for carbon monoxide (DLCO) ≥ 50% or lower • Cut-off for forced expiratory volume in 1 second (FEV1) ≥50% or lower • Cut-off for oxygen saturation (SaO2) at room air ≥93% or lower • Cut-off for total lung capacity ≥50% of normal or lower • No need for oxygen suppletion	• Adequate pulmonary function • Cut-off for diffusing capacity for carbon monoxide (DLCO) ≥ 50% or lower • Cut-off for forced expiratory volume in 1 second (FEV1) ≥50% or lower • Cut-off for oxygen saturation (SaO2) at room air ≥93% or lower • Cut-off for total lung capacity ≥50% of normal or lower • No need for oxygen suppletion

Other organ function restrictions		
Hepatic	• Adequate hepatic function • Cut-off for bilirubin 1.8 times upper limit of normal or higher • Cut-off for bilirubin 1.8 mg/dL or more • Cut-off for aspartate aminotransferase /alanine aminotransferase 1.8 times upper limit of normal or less • Prothrombin time within 25% of normal value	• Normal hepatic function • Normal bilirubin • Cut-off for bilirubin 1.7 times upper limit of normal or less • Cut-off for bilirubin 1.7 mg/dL or less • Normal aspartate aminotransferase / alanine aminotransferase • Cut-off for aspartate aminotransferase /alanine aminotransferase 1.7 times upper limit of normal or less
Renal	• Adequate renal function • Cut-off for creatinine clearance ≥ 60 ml/min or lower • Cut-off for creatinine 1.8 times upper limit of normal or higher • Cut-off for creatinine 1.8 mg/dL or more	• Normal renal function • Normal creatinine • Cut-off for creatinine clearance ≥ 61 ml/min or higher • Cut-off for creatinine 1.7 times upper limit of normal or lower • Cut-off for creatinine 1.7 mg/dL or less
Other cardiovascular	• No poorly controlled hypertension • No systolic blood pressure > 200 mmHg • No diastolic blood pressure > 120 mmHg • No thrombo-embolic disease in past 6 months • No cerebrovascular events with persistent neurological deficits	• No history of hypertension • No hypertension requiring more than 2 antihypertensive drugs • No systolic blood pressure > 160 mmHg • No diastolic blood pressure > 100 mmHg No history of stroke • No history of transient ischemic attack • No prior thrombo-embolic disease (deep venous thrombosis and/or pulmonary embolism)
Psychiatric	• No active psychiatric disease • No mental illness making informed consent impossible • No psychiatric disease in past 5 years • No active substance abuse or addictions	• No history of psychiatric disease • No history of substance abuse
Prior malignancies	• No prior malignancy in past 5 years or shorter • No active/concurrent malignancy • No malignant disease likely to progress in next 5 years	• No prior malignancy • No prior malignancy in past 10 years or longer

Left and right-hand page Appendix 1. Classification of in- and exclusion criteria for organ function

* If multiple criteria per category are listed, then trials will be classified according to the most stringent restriction

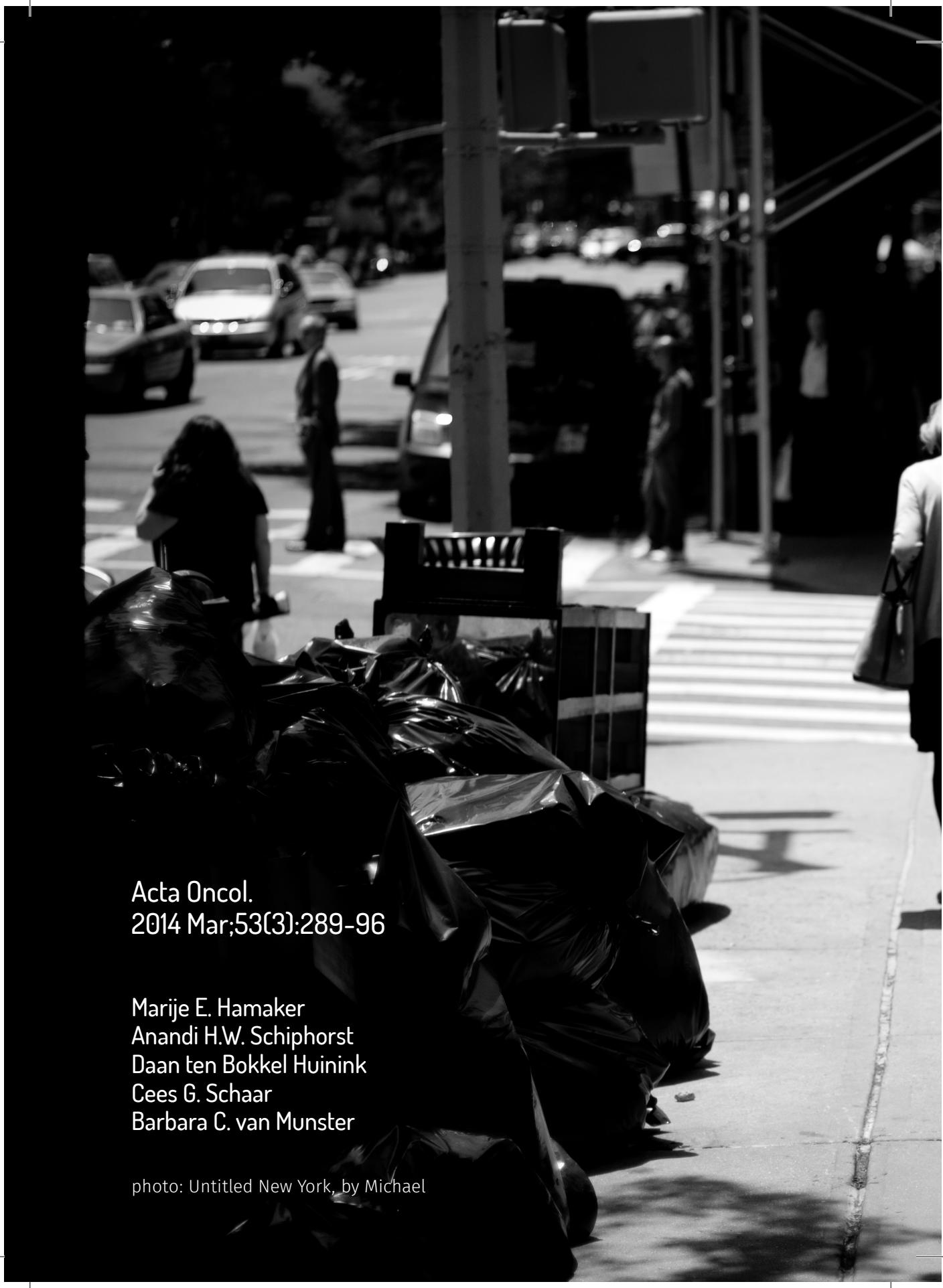
Oncologic outcome	• Overall and disease-free survival • Pathology results (eg margins and number of lymph nodes)
Surgical outcome	• Perioperative morbidity and mortality • Safety • Feasibility • Conversion • Operative time • Blood loss • Pain • Recovery of gastrointestinal function • Immunologic response
Economic outcome	• Cost effectiveness • Health care utilisation • Length of hospital stay
Patient related outcome	• Quality of life • Functional outcome • Time to resume work/daily activities • Care dependence and institutionalisation • Aesthetic outcome

Appendix 2. Classification of outcome measures

* If multiple criteria per category are listed, then trials will be classified according to the most stringent restriction

Part III

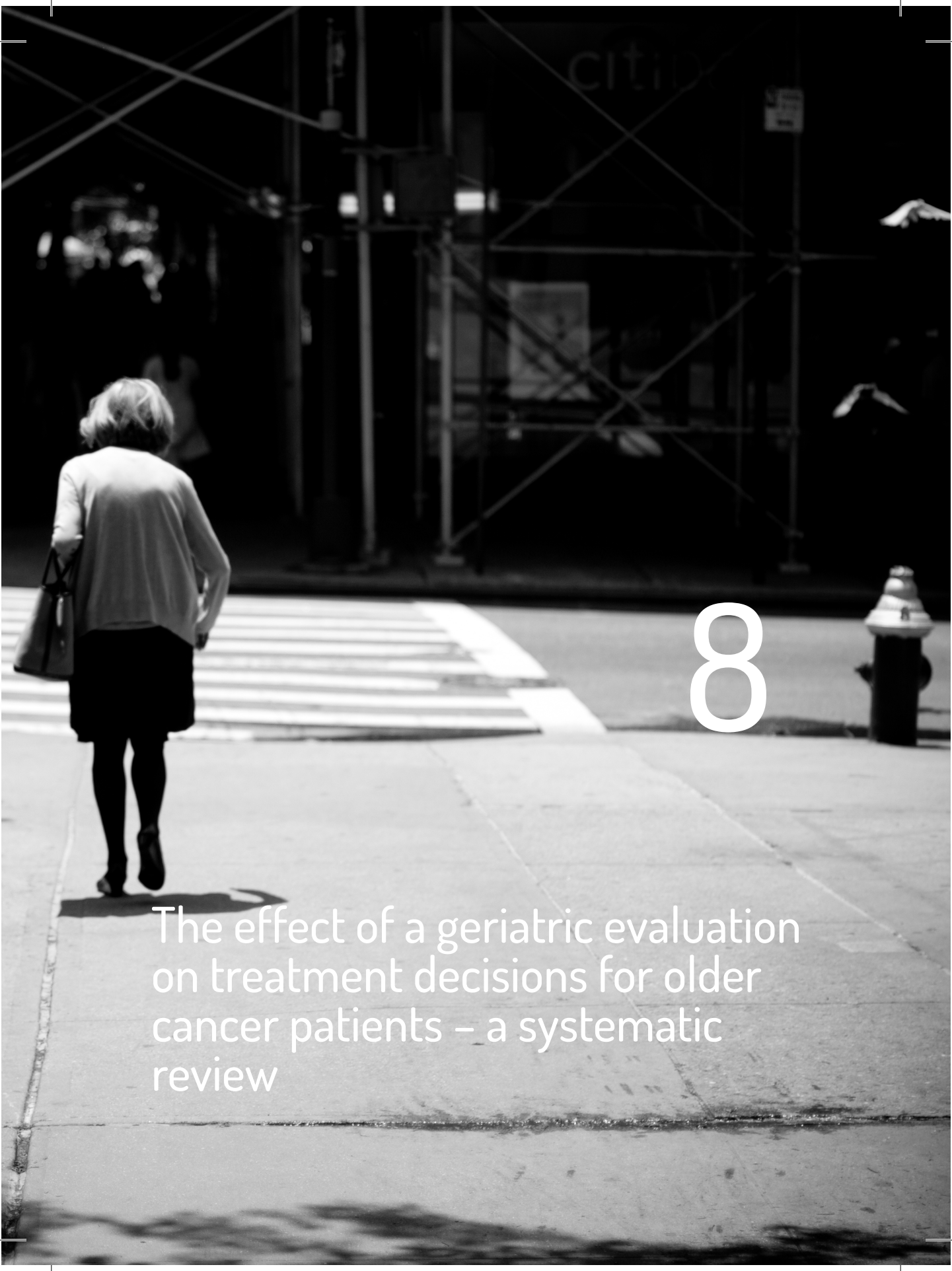
Multidisciplinary care for older cancer patients



Acta Oncol.
2014 Mar;53(3):289-96

Marije E. Hamaker
Anandi H.W. Schiphorst
Daan ten Bokkel Huinink
Cees G. Schaar
Barbara C. van Munster

photo: Untitled New York, by Michael



8

The effect of a geriatric evaluation on treatment decisions for older cancer patients – a systematic review

Abstract

Introduction

Some form of geriatric evaluation is increasingly being incorporated in oncologic care, but its role in treatment decisions remains to be clarified. The aim of this systematic review is to summarize all available data on the effect of a geriatric evaluation on the multidisciplinary treatment of older cancer patients, focussing on oncologic treatment decisions and the implementation of non-oncologic interventions.

Methods

A systematic search in MEDLINE and EMBASE for studies on the effect of a geriatric evaluation on oncologic and non-oncologic treatment for older cancer patients.

Results

Literature search identified 1654 reports (624 from Medline and 1030 from Embase), of which ten studies were included in the review. Three studies used a geriatric consultation while seven used a geriatric assessment performed by a cancer specialist, health care worker or (research) nurse. Six studies addressed a change in oncologic treatment, the initial treatment plan was modified in a median of 39% of patients after geriatric evaluation, of which two-thirds resulted in less intensive treatment. Seven studies focused on the implementation of non-oncologic interventions based on the results of the geriatric evaluation; all but one reported that interventions were suggested for over 70% of patients, even in studies that did not focus specifically on frail older patients. In the other study, implementation of non-oncologic interventions was left to the cancer specialist's discretion.

Conclusion

A geriatric evaluation has significant impact on oncologic and non-oncologic treatment decisions in older cancer patients and deserves consideration in the oncologic work-up for these patients.

Background

As the management of cancer became more complex, it was considered important that all key professionals were involved in clinical decision making for individual patients.[1] For this reason, multidisciplinary teams were introduced to the treatment of the oncologic patient and have been implemented all over the world.[2] Despite differences in their working mechanisms and organisation, its role in cancer care is undisputed.

The imminent ageing of Western societies will introduce a new level of complexity to oncologic decision making. Existing trials do not provide sufficient evidence for this specific population, as older patients and those with comorbid conditions have often been excluded.[3-5] The heterogeneity of the elderly population, with its variation in physiological reserves, comorbidity and geriatric conditions mean that the results of studies in younger or fit patients cannot automatically be extrapolated to older patients. As a result, tailoring of care is needed, based on a thorough evaluation of the patient's overall health status in addition to tumour characteristics and patient preferences. Consequently, some form of geriatric evaluation is increasingly being incorporated in oncologic care,[6] but its role in treatment decisions remains to be clarified.

The aim of study was to systematic review all observational cohort studies on the effect of a geriatric evaluation on the multidisciplinary treatment of older cancer patients, focussing on oncologic treatment decisions and the implementation of non-oncologic interventions.

Methods

Search strategy and article selection

For this study, a geriatric evaluation could consist of a geriatric consultation or a geriatric assessment only. We defined a geriatric consultation as a consultation with a specialist in geriatric or elderly medicine, in which a multidimensional assessment of the patient's health status is performed. An assessment was defined as an evaluation performed by a cancer specialist, health care worker or (research) nurse, focussing on three or more of the following domains, preferably investigated with a validated assessment tool: cognitive function, mood/depression, nutritional status, activities of daily living, instrumental activities of daily living, comorbidity, polypharmacy, mobility/falls, or frailty. The primary outcome measures were defined as an alteration in oncologic treatment plan after geriatric evaluation and the number and type of non-oncologic interventions directly related to the results of the geriatric evaluation. Studies were excluded if the geriatric assessment included less than three geriatric domains, if they only used non-validated assessment tools or if the allocation of treatment was protocolled. In addition, studies were excluded if they only reported statistical associations between outcome of the geriatric evaluation and treatment, but did not describe whether this evaluation genuinely affected treatment decisions as they were being made.

The following search was performed on January 10th 2013, in both Medline and Embase: (geriatrics[MeSH] OR "Geriatric Assessment"[MeSH] OR geriatric*[tiab] OR elderly care[tiab] OR elderly medicine[tiab]) AND (neoplasm[MeSH] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] OR tumors[tiab] OR tumours[tiab] OR neoplasm[tiab] OR malignan*[tiab] OR oncol*) AND (multidisciplin*[tiab] OR interdisciplin*[tiab] OR team*[tiab] OR tumour board* OR tumor board* OR conference*[tiab] OR meeting*[tiab] OR decision*[tiab] OR decision making[tiab] OR decision-making[tiab] OR treatment choice*[tiab] OR intervention*[tiab]). MeSH refers to medical subheading, tiab refers to title and abstract. No limits in age, language or publication date were applied.

The titles and abstracts of all studies retrieved by the search were assessed by one reviewer (MH) to determine which warranted further examination. All potentially relevant articles were subsequently screened as full text by two authors (MH and AS). If only an abstract was available, an effort was made to find the final report of the study by searching Embase and Medline using the names of the first, second and/or final author as well as key words from the title. Also, in case of insufficient data in the original manuscript, the authors were contacted for additional information.

Finally, references of included publications were cross-referenced to retrieve any additional relevant citations.

Data extraction

Data regarding study design and results were independently extracted by two investigators (MH and AS) for each eligible study. Items that were extracted were the type of study, study setting, study population (age, sex, cancer type), method of patient selection, content of the geriatric assessment/consultation, prevalence of geriatric conditions, the change in treatment after the geriatric consultation and the number and type of non-oncologic interventions.

Quality assessment

The methodological quality of each of the studies was independently assessed by two reviewers (MH, AS), using the Newcastle-Ottowa Scale adapted to this subject (Appendix 1a).[7] Disagreement among the reviewers was discussed during a consensus meeting and in case of persisting disagreement, the assistance of a third reviewer (BvM) was enlisted.

Data synthesis and analysis

We summarized the study results to describe our main outcomes of interest. Due to heterogeneity in the study populations, a formal meta-analysis was not considered feasible.

Publication			Patients				
Author	Publication year	Abstract (A) or full text (F)	Setting and department	Study population	No. of patients	% male	Median age in years (range)
Aliamus[8]	2011	F	Multidisciplinary thoracic oncology meeting	Lung cancer	47	80%	79 (70-91)
Aparicio[9]	2011	F	Department of gastro-enterology	Various gastro-intestinal tract cancers	21	52%	81 (75-87)
Caillet[10]	2011	F	Oncogeriatric cancer care unit	Various solid cancer types	375	47%	80 (70-99)
Chaibi[11]	2011	F	Multidisciplinary cancer conference	Various cancer types	161	35%	82 (73-97)
Extermann[12]	2004	F	Senior adult oncology programme	Early stage breast cancer	15	0%	79 (72-87)
Frennet[13]	2011	A	Unclear	Various cancer types	53	42%	Mean age 79 (SD 5.9)
Girre[14]	2008	F	Geriatric oncology programme	Various cancer types	105	17%	79 (70-97)
Horgan[15]	2011	F	Tertiary medical oncology clinic	Lung or gastro-intestinal cancer	30	57%	78 (70-88)
Kenis[16]	2013	F	Multicentre study	Various cancer types	1967	36%	76 (70-96)
Welter-mann[17]	2011	A	Department of oncol-ogy/hematology	Various cancer types	50	59%	77 (70-91)

Study method			Outcome	
Method of patient selection	Treatment modabilty under consideration*	Type of geriatric evaluation**	Change in cancer treatment plan	Non-oncologic interventions
Age ≥ 70 years	Unclear	A	X	
Unclear	-	A		X
All consecutive referrals aged ≥ 70 years	Various	C	X	X
Age ≥ 75 years and chemotherapy decision deemed complicated	Chemotherapy	C	X	X
All patients aged ≥ 70 years and eligible for adjuvant treatment	-	A		X
Age ≥ 70 years with VES-13 score ≥ 3	-	A		X
All new referrals aged ≥ 70 years	Various	A	X	
Age ≥ 70 years and assessment deemed necessary by oncologist	Various	C	X	X
Age ≥ 70 years and G8 score ≤ 14	Unclear	A	X	X
All newly diagnosed patients aged ≥ 70 years	-	A		X

Left and right-hand page Table 1. Studies on the alteration of treatment after geriatric assessment or consultation

* Only applicable in studies reporting on outcomes
**An assessment (A) refers to an assessment performed by the cancer specialist/health care worker/nurse; geriatric consultation (C) refers to the assessment as used in standard geriatric care, performed by a geriatrician.
VES-13: vulnerable elders survey-13 (a screening tool for frailty in the general elderly population);
G8: Geriatric 8 (a screening tool for frailty in oncology patients); SD: standard deviation

Results

Study characteristics

The literature search identified 1654 citations (624 from Medline and 1030 from Embase), of which 435 were duplicates. Details on the search and reasons for exclusion can be found in Appendix 2. After exclusion of 1209 publications, ten studies were included in this review.[8-17] Cross-referencing yielded no additional results.

The characteristics of these ten observational cohort studies are summarized in Table 1.[8-17] The first publication is from 2004, but eight of the ten studies were published since 2011.[8,9,11,13,15,17] Median sample size was 50 patients (range 15-1967 patients).[8-17] Study populations were heterogeneous, with only two focusing on a specific type of cancer.[8,12] Three studies used a geriatric consultation,[10,11,15] while the other seven used an assessment performed by a cancer specialist, health care worker or (research) nurse.[8,9,12-14,16,17] Six studies addressed the change in oncologic treatment.[8,10,11,14-16] One of these focussed only on change in chemotherapy regimen,[11] three addressed multiple treatment modalities (i.e. surgery, radiotherapy, chemotherapy etc.)[10,14,15] and for two studies, the treatment under consideration was unclear.[8,16] Eight studies reported on the number and type of recommended non-oncologic interventions.[9-13,15-17]

All studies incorporated an assessment of ADL-impairment and nutritional status as part of the geriatric evaluation (Table 2). IADL-impairment, comorbidity and mood were included in nine out of ten studies; mobility assessment and/or falls risk were included in eight studies, medication use in seven and the social environment in six studies.

Quality assessment

The results of the quality assessment can be found in Appendix 1b. The overall quality of the studies was good. In one study, the inclusion criteria were unclear, while in two studies, there was a potential risk of selection bias due to the inclusion of only a small proportion of the potentially eligible patients.[11,15] For one study, only 61% of included patients were evaluable for changes in oncologic and non-oncologic treatment.[16] There were no other quality concerns.

Prevalence of geriatric conditions

Table 3 lists the prevalence of geriatric conditions, as identified by the geriatric evaluation. The issue most frequently detected was polypharmacy or inappropriate

medication use, present in a median of 67% of patients (range 48-74%), followed by malnourishment with a median prevalence of 63% (range 37-80%). Functional impairments were also common: median prevalence for IADL-impairment 46% (range 38-65%), for ADL-impairment 33% (8-57%) and impaired mobility/falls 33% (20-55%). Approximately one-third of patients suffered from depressive symptoms (median prevalence 34%, range 13-61%), concerns regarding somatic comorbidity (36%, range 11-64%) and cognitive impairments (median prevalence 26%, range 3-38%). Social issues such as insufficient care, social isolation or high caregiver burden were present in a median of 21% of patients (range 13-35%).

Effect on oncologic treatment

Table 4 reports the results of the six studies addressing the effect of a geriatric evaluation on the oncologic treatment choice. In approximately one-third of patients, the geriatric evaluation resulted in a change in cancer treatment; this was 21% for patients undergoing a geriatric consultation (range 20-49%) and approximately 39% in patients receiving an assessment only (range 25-45%). Of the treatment changes, approximately two-thirds consisted of less intensive treatment (Table 4); this was not affected by the performer of the geriatric evaluation.

Effect on non-oncologic treatment

All but one study reported interventions rates of over 70% (Table 5); in the study that formed the exception to this finding, with only 26% of patients receiving non-oncologic interventions, interpretation of geriatric assessment and implementation of interventions was left to the cancer specialist.[16] Overall, social interventions and modification of medication were the most frequent recommendations, suggested in a median of 38% and 37% of patients respectively (range 6-55% and 24-71%, respectively). Nutritional interventions were recommended for a median of 26% of patients (range 7-91%). Psychological interventions, exploration and treatment of cognitive impairment, interventions aimed at mobility and falls risk, and investigations or treatment of previously unidentified or not optimised comorbid conditions were all recommended for approximately 20% of patients (median 16-23%).

	Comorbidity	Medication use	Cognition	Mood	ADL	IADL	Mobility/ Falls	Nutritional status	Social environment
Aliamus[8]	Charlson	-	MMSE	miniGDS	Katz	Lawton	TUG	MNA	-
Aparicio[9]	CIRS-G	+	MMSE	GDS	Katz	Lawton	+	MNA	+
Caillet[10]	CIRS-G	+	MMSE	miniGDS	Katz	-	+	MNA	+
Chaibi[11]	CIRS-G	+	MMSE Clock	GDS	Katz	Lawton	TUG	MNA	-
Extermann[12]	CIRS-G Charlson	+	MMSE	GDSscreen	Katz	Lawton	-	MNA	+
Frennet[13]	-	-	MMSE	-	+	+	TUG	MNA	-
Girre[14]	+	+	-	miniGDS	Katz	Lawton	+	weight loss	+
Horgan[15]	Charlson	+	MMSE Clock	GDS	Katz	Lawton	+	weight loss	+
Kenis[16]	Charlson	+	MMSE	GDS	Katz	Lawton	+	MNA	+
Weltermann[17]	Charlson	+	miniCOG	GDS	Katz	Lawton	TUG	MNA	-

Table 2. Content of geriatric evaluation

+ domain assessed without using a validated assessment tool or tool not mentioned
- domain not assessed

CIRS-G Cumulative illness rating scale-geriatric; MMSE mini mental state examination, GDS geriatric depression scale, TUG timed up and go, MNA mini nutritional assessment

	Number of patients	Comorbidity	Medication use	Cognition	Mood	ADL	IADL	Mobility/ Falls	Nutritional status	Social environment
Aliamus[8]	47	35%	-	*	38%	43%†		nr	63%	-
Aparicio[9]	21	52%	48%	38%	43%	29%	38%	29%	71%	24%
Caillet[10]	375	36%	67%	27%	28%	32%	-	55%	58%	18%
Chaibi[11]	161	47%	nr	26%	34%	32%	60%	20%	65%	-
Extermann[12]	15	64%	67%	26%	13%	33%	40%	-	53%	33%
Frennet[13]	53	‡	‡	‡	-	‡	‡	48%	‡	-
Girre[14]	105	33%	74%	-	53%	42%	54%	20%	46%	17%
Horgan[15]	30	17%	67%	3%	33%	23%	43%	20%	37%	13%
Kenis[16]	1967	39%	#	13%	61%	57%	65%	38%	80%	35%
Weltermann[17]	50	11%	55%	38%	26%	8%	46%	55%	65%	-

Table 3. Prevalence of impairments or issues per geriatric domain

- not included in study
* reported as mean score only: mean mini-mental state score 25.2/30
† combined score of ADL and/or IADL impairments
‡ reported as mean scores only: global score on cumulative illness rating score-geriatric version 10.7±4.6/56, number of medications 6.9±3.7, mini-mental status score 24.8±4.9/30, ADL 5.0±1.2/6, IADL 4.6±1.7/7, mini-nutritional assessment short form 9.0±2.6/14
# median 4 (0-22)
nr not reported

ADL: activities of daily living, IADL: instrumental activities of daily living

	Treatment altered		More intensive treatment		Treatment delay		Less intensive treatment	
	%	n=	%	n=	%	n=	%	n=
Horgan[15]	20%	6/30	3%	1/30	0%		17%	5/30
Caillet[10]	21%	78/375	2%	8/375	2%	7/375	17%	63/375
Kenis[16]	25%	282/1115*	-		-		-	
Girre[14]	39%	36/93	2%	2/93	0%		37%	34/93
Aliamus[8]	45%	22/49	-		-		-	
Chaibi[11]	49%	79/161	28%	45/161	3%	5/161	18%	29/161

Table 4. Alterations in oncologic treatment after geriatric assessment/consultation

- not reported
* not all patients were available for inclusion in this analysis

	Number of patients	**Any intervention**	Nutritional interventions	Psychological interventions	Cognitive exploration and/or treatment	Polypharmacy optimisation	Social Interventions	Interventions aimed at mobility and falls	Investigations for previously unidentified or not optimised comorbidity
Kenis[16]	1115*	**26%**	15%	10%	5%	-	5%	6%	9%
Aparicio[9]	21	**72%**	19%	-	5%	71%	38%	-	19%
Chaibi[11]	161	**76%**	47%	19%	18%	37%	20%	-	-
Frennet[13]	53	**77%**	34%	23%	-	25%	49%	21%	19%
Caillet[10]	375	**83%**	70%	36%	21%	31%	46%	42%	55%
Horgan[15]	30	**93%**	7%	23%	-	63%	-	13%	33%
Weltermann[17]	50	**95%**	18%	10%	14%	24%	6%	19%	3%
Extermann[12]	15	**100%**	91%	45%	18%	64%	55%	-	64%

Table 5. Proportion of patients with non-oncologic interventions after geriatric evaluation

- not reported
* not all patients were available for inclusion in this analysis

Discussion

In this systematic review on the effect of a geriatric evaluation on treatment decisions for older cancer patients, the initial oncologic treatment plan was modified in a median of 32% of patients, and non-oncologic interventions were recommended in a median of 83%. Thus, the inclusion of a geriatric evaluation has significant impact on the treatment decisions for the older cancer patient.

Previous studies on team workings in multidisciplinary cancer care have emphasized the need for greater patient-centeredness.[18,19] They demonstrated that knowledge of comorbid conditions and the patient's psychosocial context greatly increases the likelihood of reaching a treatment decision at a multidisciplinary cancer team conference. Currently, this information is often lacking or receives little attention at the multidisciplinary conference compared to other facets such as the results of imaging studies or histopathological data.[18,19] As a result, treatment decisions have to be based on clinical impressions, which are increasingly inaccurate with increasing age.[12,20] Furthermore, modifications are often implemented only after complications of treatment demonstrate the patient's inability to tolerate standard treatment.[21] Prior studies have demonstrated the predictive value of the presence of geriatric conditions for prognosis, complications of oncologic surgery and chemotherapy tolerance,[22-24] thus allowing for upfront tailoring of treatment to the patient's vulnerability. This explains why the initial oncologic treatment plan was altered in 20-49% of patients when the results of a geriatric evaluation were available. However, this type of evaluation is yet to become a routine part of the work-up of older cancer patients,[25] and currently geriatricians are often not included in multidisciplinary cancer teams.[2] For example, in the elaborate descriptions of the composition and work processes of multidisciplinary teams for various cancer types, the National Institute for Health and Clinical Excellence (NICE) cancer service guidances suggest the involvement of a median of 19 (range 9-30) possible (para) medical professionals, but fails to mention a specialist with specific geriatric knowledge.[26]

We believe that this systematic review provides a valuable overview of all currently available evidence on the effect of a geriatric evaluation on treatment choices in older cancer patients. However, it also has several limitations. Study populations were heterogeneous, investigating a wide range of cancer types and treatment modalities and regimens. This hampers extrapolation of these results to individual oncology practice. In addition, studies reported only on the alteration in treatment, but few reported a follow-up of how patients subsequently fared; we were therefore

unable to ascertain whether the changes made to the treatment plan resulted in overall better outcomes. For some of the included studies, no full text reports have been published, and we had to rely on conference abstracts as the only source of information on the execution and results of the study. Moreover, the content of the geriatric evaluation differed between studies, and the criteria used to define the presence of the geriatric conditions were often not fully reported. Furthermore, most studies did not report on the association between the prevalence of geriatric conditions and treatment alterations.

Another limitation is that due to differences in patient populations and study methods, we could not make a comparison between the effect of a geriatric consultation and an assessment of geriatric domains performed by a cancer specialist, health care worker or (research) nurse. Although study outcomes differed slightly, for instance in the proportion of patients for whom oncologic treatment was modified after the evaluation (median 21% for geriatric consultation; 40% for assessment), it is not possible to know if this was due the type of evaluation or due to other factors, such as patient selection. Most studies using an assessment incorporated standardised interventions based on the results of this assessment in the various geriatric domains. In the one study that left the implementation of non-oncologic interventions to the cancer specialist's discretion, only 26% of patients received such interventions, compared to over 70% of patients with a standardised intervention protocol or a geriatric consultation, despite similar prevalence of geriatric conditions.[16] This demonstrates that any assessment should incorporate a strategy for dealing with the issues that are identified. It is important to realise that the outcome of a screening tool for the possible presence of a particular condition, for instance assessing a patient's mood with the geriatric depression scale, is not the same as making a diagnosis of depression.[27] Screening is a first step, and one that is also used by geriatricians (Table 2). However, a geriatric consultation is superior to an assessment only as it allows for a more precise diagnosis of the various conditions that the assessment screens for. In addition, it will also allow for a more direct implementation of interventions aimed at these conditions. The only study thus far that has addressed the impact of a geriatric consultation on quality of life demonstrated that adding geriatric care to standard in-patient cancer care for hospitalised elderly cancer patients resulted in a significant decrease in the amount of emotional limitations, social dysfunction and bodily pain that these patients experienced at three months; the effect on pain was still significant one year after hospital discharge.[28]

Irrespective of the type of geriatric evaluation that is used, the studies included in this review demonstrate that it will provide information on a patient's somatic,

psychosocial and functional health status that is invaluable to treatment decisions. However, the time-consuming nature of a geriatric evaluation has presented an important limiting factor to its routine implementation in oncology. Studies addressing the possibility of replacing a full evaluation by a frailty screening tool in an attempt to bypass the geriatric evaluation have yielded disappointing results,[22] while tools developed for one aspect, for instance for predicting the toxicity of chemotherapy,[29,30] lack the wealth of information provided by a full evaluation. In an age where the amount of time spent on staging and exploring disease characteristics is rapidly increasing, and more and more money is spent on increasingly sophisticated anti-cancer treatments, taking the time to sit down with a patient and explore what they want and whether or not they will be able to benefit from and tolerate cancer treatment should not be a matter of discussion.

Conclusion

This review demonstrates that a geriatric evaluation, performed by a geriatrician or even a basic assessment of geriatric domains by a (research) nurse, provides invaluable information for the decision-making process and identifies multiple issues that could be modified to improve treatment tolerance and quality of life. Although further research is needed to refine the role of a geriatric evaluation in oncologic decision making, the currently available evidence demonstrates that it can be a worthwhile addition in the oncologic work-up for older patients and geriatric specialists should become a standard part of the multidisciplinary cancer team. It is now up to cancer physicians, researchers, medical directors, government bodies and insurance companies to work together to make better cancer care for older patients a reality.

References

1. Taylor C, Munro AJ, Glynne-Jones R, Griffith C, Trevatt P, Richards M, et al. Multidisciplinary team working in cancer: what is the evidence? BMJ 2010;340:c951.
2. Saini KS, Taylor C, Ramirez AJ, Palmieri C, Gunnarsson U, Schmoll HJ, et al. Role of the multidisciplinary team in breast cancer management: results from a large international survey involving 39 countries. Ann Oncol 2012 Apr;23(4):853-9.
3. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999 Dec 30;341(27):2061-7.
4. Bellera C, Praud D, Petit-Moneger A, McKelvie-Sebilau P, Soubeyran P, Mathoulin-Pelissier S. Barriers to inclusion of older adults in randomised controlled clinical trials on Non-Hodgkin's lymphoma: a systematic review. Cancer Treat Rev. 2013 Nov;39(7):812-7.
5. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003 Apr 1;21(7):1383-9.
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). Crit Rev Oncol Hematol 2005 Sep;55(3):241-52.
7. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottowa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2012.
8. Aliamus V, Adam C, Druet-Cabanac M, Dantoine T, Vergnenegre A. Geriatric assessment contribution to treatment decision-making in thoracic oncology. Revue des Maladies Respiratoires 2011;29(9):1124-30.
9. Aparicio T, Girard L, Bouarioua N, Patry C, Legrain S, Soule JC. A mini geriatric assessment helps treatment decision in elderly patients with digestive cancer. A pilot study. Crit Rev Oncol Hematol. 2011 Jan;77(1):63-9.
10. Caillet P, Canoui-Poitrine F, Vouriot J, Berle M, Reinald N, Krypciak S, et al. Comprehensive Geriatric Assessment in the Decision-Making Process in Elderly Patients With Cancer: ELCAPA Study. J Clin Oncol 2011 Sep 20;29(27):3636-42.
11. Chaibi P, Magne N, Breton S, Chebib A, Watson S, Duron J-J, et al. Influence of geriatric consultation with comprehensive geriatric assessment on final therapeutic decision in elderly cancer patients. Crit Rev Oncol Hematol. 2011 Sep;79(3):302-7.
12. Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J, et al. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol 2004 Jan;49(1):69-75.
13. Frennet M, Kerger J, Cornette P, Humblet Y, Lesage V, de Saint-Hubert M. Impact of comprehensive geriatric assessment (CGA) during oncologic treatment in frail elderly patients. European Geriatric Medicine 2011;2:S35.
14. Girre V, Falcou M-C, Gisselbrecht M, Gridel G, Mosseri V, Bouleuc C, et al. Does a geriatric oncology consultation modify the cancer treatment plan for elderly

patients? J Gerontol A Biol Sci Med Sci. 2008 Jul;63(7):724-30
15. Horgan AM, Leighl NB, Coate L, Liu G, Palepu P, Knox JJ, et al. Impact and Feasibility of a Comprehensive Geriatric Assessment in the Oncology Setting: A Pilot Study. Am J Clin Oncol 2011 Mar 17.
16. Kenis C, Bron D, Libert Y, Decoster L, Van PK, Scalliet P, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. Ann Oncol. 2013 May;24(5):1306-12.
17. Weltermann A, Koller H. Diagnostic yield of a geriatric assessment and a standardized intervention plan in elderly patients with newly diagnosed cancer: a cohort study. Onkologie 2011;Conference publication:pp228.
18. Lamb BW, Taylor C, Lamb JN, Strickland SL, Vincent C, Green JS, et al. Facilitators and Barriers to Teamworking and Patient Centeredness in Multidisciplinary Cancer Teams: Findings of a National Study. Ann Surg Oncol. 2013 May;20(5):1408-16.
19. Lamb BW, Sevdalis N, Benn J, Vincent C, Green JS. Multidisciplinary Cancer Team Meeting Structure and Treatment Decisions: A Prospective Correlational Study. Ann Surg Oncol. 2013 Mar;20(3):715-22.
20. Wedding U, Kodding D, Pientka L, Steinmetz HT, Schmitz S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. Crit Rev Oncol Hematol 2007 Oct;64(1):1-9.
21. Hoeben KW, van Steenbergen LN, van de Wouw AJ, Rutten HJ, Van Spronsen DJ, Janssen-Heijnen ML. Treatment and complications in elderly stage III colon cancer patients in the Netherlands. Ann Oncol. 2013 Apr;24(4):974-9.
22. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening tools for predicting outcome of a comprehensive geriatric assessment in older cancer patients. Lancet Oncol. 2012 Oct;13(10):e437-44.
23. Hamaker ME, Vos AG, Smorenburg CH, de Rooij SE, van Munster BC. The value of geriatric assessments in predicting treatment tolerance and all-cause mortality in older cancer patients. Oncologist. 2012;17(11):1439-49
24. Hamaker ME, Seynaeve C, Wymenga ANM, van Tinteren H, Nortier JWR, Maartense E, et al. Baseline comprehensive geriatric assessment to predict for toxicity of single-agent chemotherapy in elderly metastatic breast cancer patients: Results from the OMEGA study of the Dutch Breast Cancer Trialists' Group. J.Clin.Oncol. 2012;30:15_ suppl abstr 1080. 2012.
25. Audisio RA, Osman N, Audisio MM, Montalto F. How do we manage breast cancer in the elderly patients? A survey among members of the British Association of Surgical Oncologists (BASO). Crit Rev Oncol Hematol 2004 Nov;52(2):135-41.
26. www.nice.org.uk.
27. Mitchell AJ, Bird V, Rizzo M, Meader N. Diagnostic validity and added value of the Geriatric Depression Scale for depression in primary care: a meta-analysis of GDS30 and GDS15. J Affect Disord 2010 Sep;125(1-3):10-7.
28. Rao AV, Hsieh F, Feussner JR, Cohen HJ. Geriatric evaluation and management units in the care of the frail elderly cancer patient. J Gerontol A Biol Sci Med Sci 2005 Jun;60(6):798-803.
29. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, Defelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer 2011 Nov 9.

30. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011 Sep 1;29(25):3457-65.

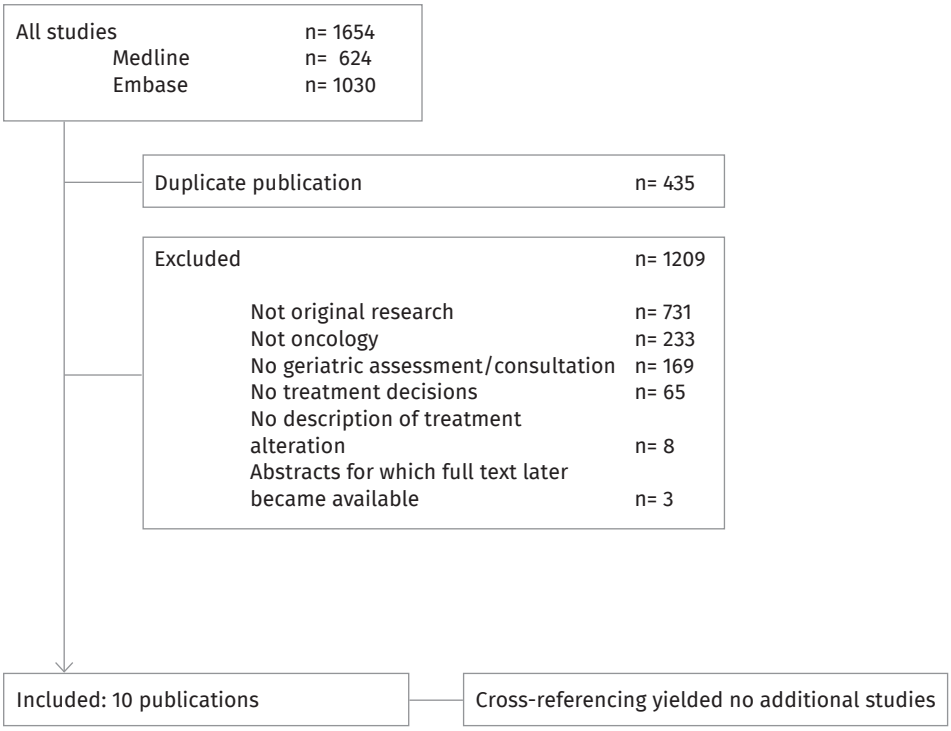
Selection	1. Representativeness of the exposed cohort	+ truly representative of the average *older cancer patient* + somewhat representative of the average *older cancer patient* - selected group of users ? no description of the derivation of the cohort
	2. Ascertainment of exposure *(geriatric assessment/ consultation)*	+ *clearly described and using validated assessment tools* - *using non-validated assessment tools for > 40% of investigated geriatric conditions* ? no description
	3. Demonstration that outcome of interest *(treatment alteration)* was not present at start of study	+ yes - no
Outcome	1. Assessment of outcome *(treatment alterations)*	+ *clear description of method of assessment* ? *unclear description of method of assessment* ? no description
	2. Was follow-up long enough for outcome to occur?	+ yes - no
	3. Adequacy of follow-up of cohorts	+ complete follow-up: all subjects accounted for + subjects to follow-up unlikely to introduce bias: loss to follow-up less than *10%* - follow-up rate less than *90%* ? no statement

Appendix 1a. Quality assessment, based on the Newcastle-Ottowa Scale.[7]

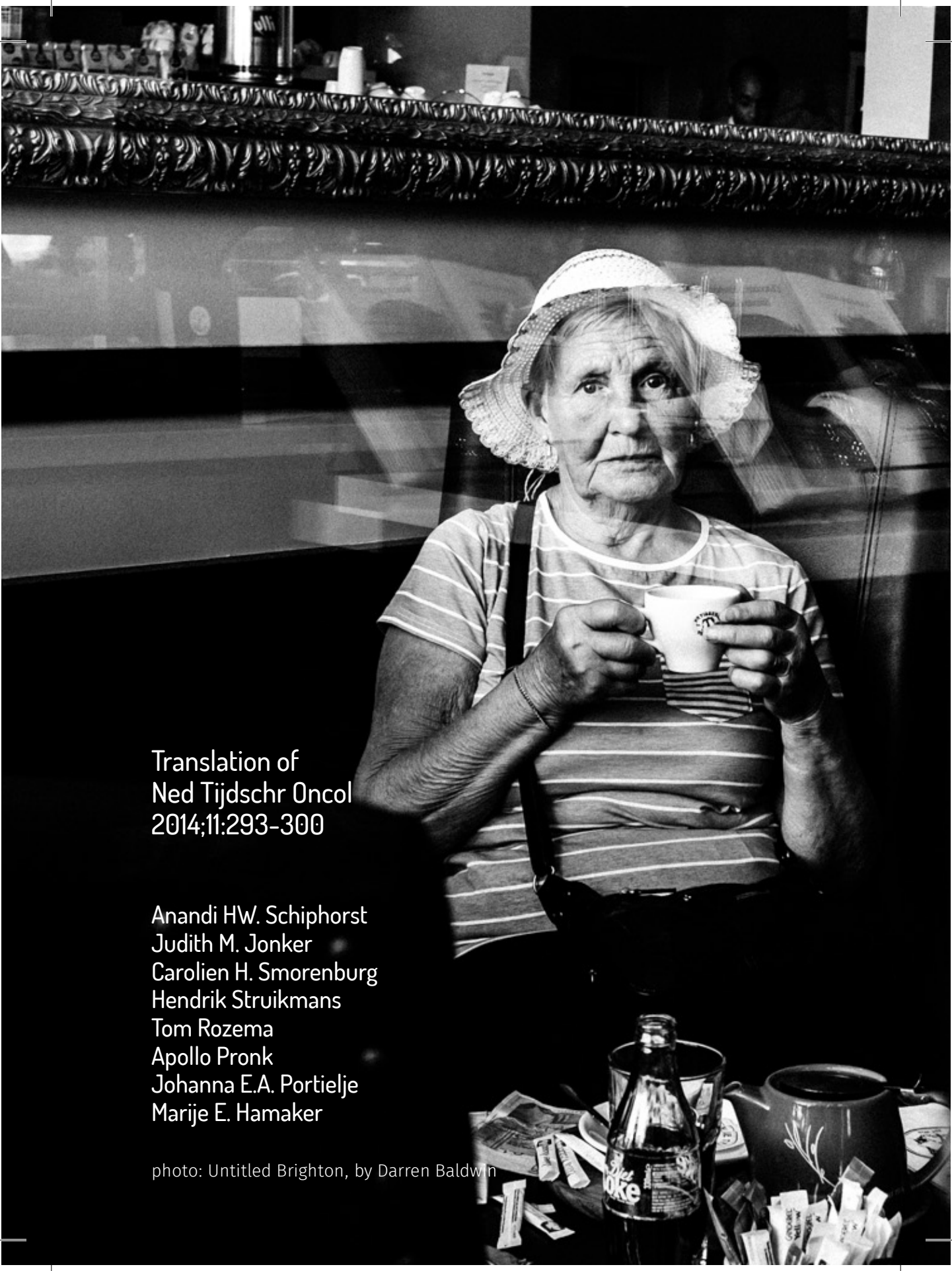
The Newcastle-Ottowa scale functions as an outline for the assessment, but requires the reviewer to fill in several aspects left blank to optimally suit the research question. Textual adjustments used for this review are printed in italics.

Publication	Selection			Outcome		
	Representativeness of exposed cohort	Ascertainment of exposure (geriatric assessment or consultation)	Outcome not present at start of study	Assessment of outcome (treatment alterations)	Sufficient duration of follow-up	Adequacy of follow-up
Aliamus[8]	+	+	+	+	+	+
Aparicio[9]	?	+	+	+	+	?
Caillet[10]	+	+	+	+	+	+
Chaibi[11]	–	+	+	+	+	+
Extermann[12]	+	+	+	+	+	+
Frennet[13]	+	+	+	+	+	+
Girre[14]	+	+	+	+	+	+
Horgan[15]	–	+	+	+	+	+
Kenis[16]	+	+	+	+	+	–
Weltermann[17]	+	+	+	+	+	+

Appendix 1b. Quality assessment of included studies



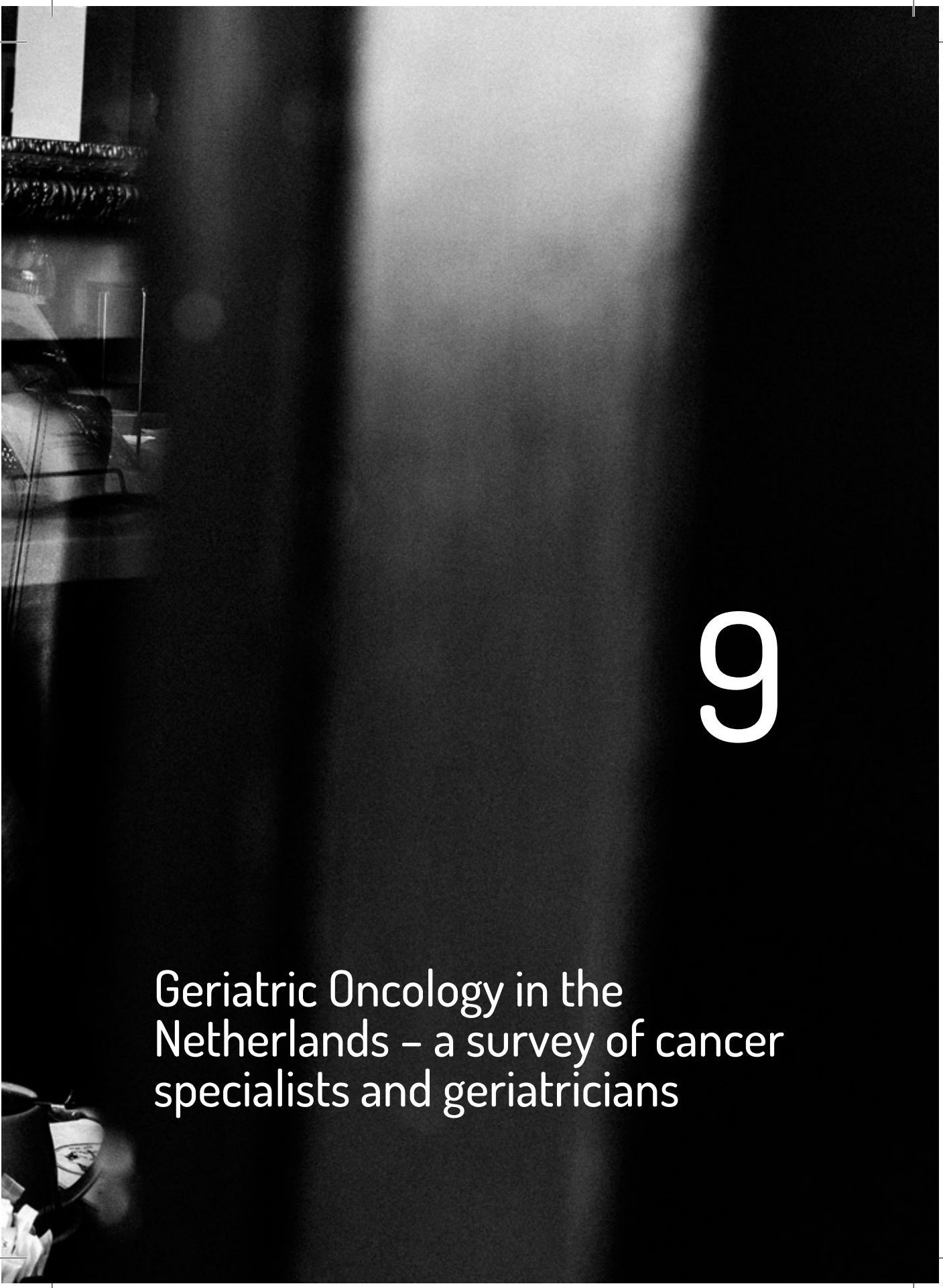
Appendix 2. Search results and study selection



Translation of
Ned Tijdschr Oncol
2014;11:293-300

Anandi HW. Schiphorst
Judith M. Jonker
Carolien H. Smorenburg
Hendrik Struikmans
Tom Rozema
Apollo Pronk
Johanna E.A. Portielje
Marije E. Hamaker

photo: Untitled Brighton, by Darren Baldwin



9

Geriatric Oncology in the Netherlands – a survey of cancer specialists and geriatricians

Abstract

Objectives

The objective of this study was to investigate the current use of geriatric care for elderly cancer patients in the Netherlands and explore potential areas of improvement and obstacles in the implementation of a geriatric evaluation prior to oncologic treatment.

Methods

A web-based survey was sent to 1726 medical oncologists, geriatricians, surgical oncologists and radiation oncologists in the Netherlands.

Results

Overall response rate was 35%. Half of all respondents reported that some form of geriatric evaluation is currently implemented at their hospital; approximately one-third stated that elderly are routinely assessed for the presence of geriatric impairments, while 35% reported that evaluations are performed on an ad hoc basis only. Many respondents felt that current care could be improved by a closer collaboration between cancer specialists and geriatricians, routine geriatric evaluations for all elderly cancer patients, and greater incorporation of its results in oncologic decision-making. Of respondents not using a geriatric evaluation, 83% stated to be interested in its implementation, although 40% said this was currently not their priority and over one-third reported to be unsure of the best format. For over 25%, time constraints were also a significant obstacle.

Conclusion

Our survey demonstrates that one-third of all cancer specialists and geriatricians in the Netherlands use a geriatric evaluation in their care for older cancer patients, or are interested in introducing a geriatric oncology programme. A routine evaluation and closer collaboration between cancer specialists and geriatricians is imperative to successfully optimise care for the growing number of elderly cancer patients.

Introduction

Dutch cancer statistics show that in 2011 over 30,000 new cancer patients were over 75 years of age, an increase of 44% in the last decade.[1] Due to increasing life-expectancy, the incidence of cancer in elderly will subsequently rise in coming years. Clinicians are faced with several dilemmas in the care for older cancer patients. One of these is the lack of reliable evidence on the optimal treatment in these patients; existing guidelines are based on studies in which elderly and those with comorbid conditions were generally excluded.[2]

Ageing is an individual process with an increasing variety in comorbidity, physical reserves, disability and geriatric conditions.[3] Therefore, tailoring of care is needed, based on a thorough evaluation of the patient's overall health status in addition to tumour characteristics and patient preferences. In addition, elderly patients themselves feel that their individual situation, including comorbidities and psychosocial status, deserves more attention in the oncologic treatment decision-making process.[4] However, medical trainees report a lack of specific training on the particular needs of older people, rendering them uncomfortable with making treatment decisions for elderly cancer patients.[5]

For these reasons, it is increasingly advocated that an evaluation of geriatric domains should be incorporated into the standard oncologic work-up of the elderly.[6] Studies have demonstrated that such a multidimensional exploration of the patient's health status can identify previously unrecognised issues in older cancer patients. These can serve to guide treatment decisions[7] and could potentially be modified to improve quality of life and outcomes. However, the implementation of a geriatric evaluation has not yet become standard practice. Identifying potential obstacles could give more insight in measures necessary to improve cancer care for older patients.

Therefore, the objective of this study was a) to analyse the use of geriatric care for older cancer patients in the Netherlands, b) to explore cancer specialists' and geriatricians' opinions about possible areas of improvement and c) to determine which obstacles hinder the implementation of geriatric evaluations for older cancer patients.

Methods

We developed a web-based survey using software developed by SurveyMethods (www.surveymethods.com), the content of which is shown in Figure 1. Briefly, the first half explores the current methods of evaluating older patients prior to oncologic treatment while the second half analyses the degree of satisfaction with current practices, possibilities for improvement and potential barriers for incorporating some form of geriatric evaluation. This survey was sent consecutively to four groups of medical specialists in the Netherlands: medical oncologists registered with the Dutch Association of Medical Oncology (NVMO), geriatricians registered with the Dutch Association of Clinical Geriatricians (NVKG), surgical oncologists registered with the Dutch Association of Surgical Oncology (NVCO) and the Dutch Association of Gastro-Intestinal Surgery (NVGIC) and finally, radiation oncologists registered with the Dutch Association of Radiotherapy and Oncology (NVRO).
No statistical analyses were performed, only descriptive data are presented.
The study protocol was approved by the regional ethical approval commission.

Results

Characteristics of respondents

The overall response rate was 35%. The survey was returned by 267 of the 858 surgical oncologists (31%), 127 of the 394 medical oncologists (32%), 113 of the 251 radiation oncologists (45%) and 95 of the 223 geriatricians (43%). Characteristics of respondents can be found in Table 1. Responses came from all over the country and specialists were mostly working at a large peripheral hospital with one or more geriatricians.

Geriatric evaluation of elderly cancer patients

The use of geriatric evaluations in the care for elderly cancer patients was confirmed by half of all respondents, varying from 65% of medical oncologists to 27% of radiation oncologists (Figure 2). Over one-third of these stated that all elderly cancer patients are routinely assessed for the presence of geriatric syndromes; in another third the geriatric evaluation was performed on an ad hoc basis only while the remaining respondents did not elaborate on the execution of the geriatric evaluation. Surgical oncologists and radiation oncologists stated to refer their elderly cancer patients to a geriatrician for an evaluation, while 75% of the medical

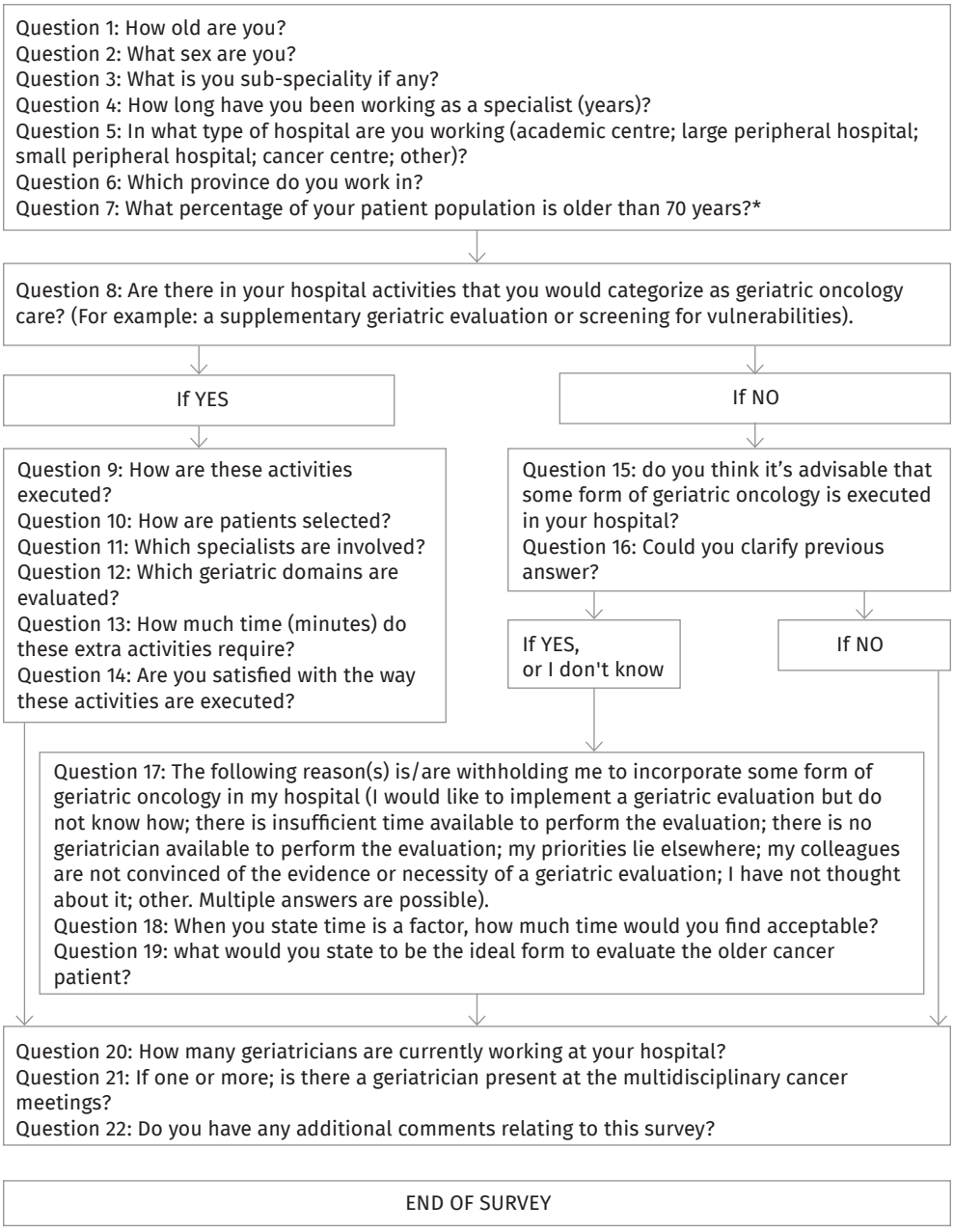


Figure 1. Content of survey

* This question was not included in the geriatricians' version of the survey

oncologists reported that they perform the evaluation themselves and only refer patients if indicated.
When geriatric evaluations are being performed (routinely or ad hoc) the majority of respondents reported that at least four geriatric domains were examined (94% of responses); 52% assessed eight or more domains (geriatricians 85%). Overall, the median duration of the evaluation was reported to be 30 minutes, but with a wide range varying from one minute to more than 5 hours.

Areas of improvement

Of respondents reporting to have implemented a form of geriatric evaluation for their elderly cancer patients, 35% stated to be dissatisfied with the current practice (geriatricians 48%, radiation oncologists 47%, medical oncologists 44% and surgical oncologists 24%). Possible areas of improvement were: a routine (structural) evaluation of all older cancer patients, instead of an ad hoc assessment (40%); a better realization of the evaluation (20%) and an improved incorporation of the evaluations' results in oncologic treatment decisions (13%); 4% of respondents felt that more evidence is needed to support the use of geriatric evaluations in oncologic care for elderly. Additionally, 46% of respondents expressed the desire for a closer collaboration between cancer specialists and geriatricians, including the presence of a geriatrician at the multidisciplinary cancer team conferences. However, 80% stated that currently, a geriatrician rarely attends these meetings even in hospitals employing multiple geriatricians.

Obstacles for implementing a geriatric evaluation in elderly cancer patients

Half of all respondents stated that they do not offer geriatric evaluations to their elderly cancer patients (Figure 2). Only 6% felt these evaluations are not useful and their main argument was that care for elderly patients is an integral part of oncologic care and does not differ from care for younger cancer patients; therefore, geriatric oncology would have no added value.
The larger part of our respondents without a geriatric oncology programme at their institute, stated to be interested in implementing some form of geriatric care for older cancer patients (surgical oncologists 86%, medical oncologists 82%, radiation oncologists 82% and geriatricians 78%). Reasons mentioned were to improve tailoring of care to the patient's capacity to tolerate the treatment burden (56%); to enable a more adequate selection of those patients fit enough for (standard) oncologic treatment (36%); to improve supportive care for the elderly (18%); and because of the increasing incidence of cancer amongst the elderly (8%).

	Total (n=602)	Medical oncologists (n=127)	Geriatri-cians (n=95)	Surgical oncologists (n=267)	Radiation oncologists (n=113)
Response rate	35%	32%	43%	31%	45%
Median age of respondents	45 yrs	46 yrs (29-64 yrs)	44 yrs (31-63 yrs)	45 yrs (30-75 yrs)	45 yrs (27-76 yrs)
% Female	43%	48%	72%	27%	50%
Type of hospital					
Small peripheral	21%	25%	36%	22%	0%
Large peripheral	45%	32%	53%	55%	27%
Academic	25%	35%	6%	17%	50%
Tertiary/categorical	4%	5%	3%	4%	11%
Other	3%	2%	0%	<1%	12%
Median % of patients aged ≥70jr	40%	40% (5-75%)	*	40% (5-80%)	40% (15-80%)
Number of geriatricians at the hospital					
0	12%	12%	1%	11%	27%
1-2	23%	23%	18%	30%	12%
3-4	24%	29%	36%	20%	17%
5 or more	22%	16%	42%	19%	20%
Not mentioned	19%	20%	3%	22%	24%

Table 1. Characteristics of respondents

* This question was not included in the geriatricians' version of the survey

Reasons for not implementing of some form of geriatric oncology are listed in Table 2. The obstacle mostly mentioned was a lack of priority (40%). Many respondents reported uncertainty about the optimal way to implement geriatric oncologic care in daily practice (36%); over one-fourth felt there is insufficient time or staff to perform the evaluation; 12% reported that they felt their colleagues or other cancer specialists were not interested or hesitant.

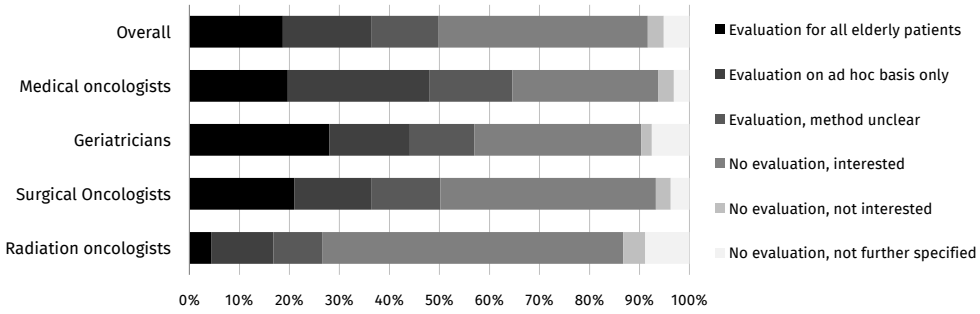


Figure 2. Current use of geriatric evaluations for elderly cancer patients in the Netherlands

	Total	Medical oncologists	Geriatri-cians	Surgical oncologists	Radiation oncologists
My priorities lie elsewhere	40%	48%	48%	39%	37%
I would like to implement a geriatric evaluation but do not know how	36%	17%	35%	38%	44%
There is insufficient time available to perform the evaluation	27%	17%	45%	20%	29%
There is no geriatrician available to perform the evaluation	26%	31%	*	27%	18%
I have not thought about it	25%	31%	3%	31%	27%
My colleagues are not convinced of the evidence or necessity of a geriatric evaluation	12%	7%	29%	5%	13%
I am unconvinced of the evidence or necessity for a geriatric evaluation	3%	7%	3%	2%	3%
Other	3%	7%	-	5%	5%

Table 2. Obstacles for implementation of a geriatric evaluation in elderly cancer patients

Multiple answers were possible
* This answer option was not included in the geriatricians' version of the survey

Discussion

This study provides an insight in the current format of care for older cancer patients in the Netherlands and obstacles that prevent the implementation of geriatric oncologic care. According to half of the responding medical oncologists, geriatricians, surgical oncologists and radiation oncologists, geriatric evaluations are used in the care for elderly cancer patients, sometimes routinely, but mostly on an ad hoc basis. Many respondents want a closer collaboration between cancer specialists and geriatricians in addition to a more routine geriatric evaluation for elderly cancer patients, with better incorporation of its results in oncologic care and the decision-making process. The majority of respondents without geriatric oncology at their hospital stated to be interested in its implementation, but a lack of priority and uncertainty on the optimal set-up for a geriatric oncology programme remain the primary obstacles.

This study has some limitations. First, we frequently used open-ended questions in this survey, allowing for a greater input from our respondents, but requiring a secondary interpretation and categorisation of responses. Although this was done as objective as possible, this categorisation may not fully reflect what respondents would have chosen when pre-formulated answer-options were provided. Second, the response rate was 35%, a well-known issue in survey-based studies. It is not unlikely that those specialists with interest in geriatric oncology responded, making it unclear if these results are representative for all cancer specialists and geriatricians. Nevertheless, one-third of all cancer specialists and geriatricians in the Netherlands state to have implemented geriatric evaluations in elderly cancer patients or is interested in doing so. The imminent ageing of society makes optimal tailoring of care for elderly cancer patients and the consequences of under- and overtreatment an increasingly relevant issue. Knowledge on physiological aging, comorbidity, functionality and psychosocial background of patients is imperative for the assessment of a patient's ability to tolerate treatment, but this information is generally lacking at times of decision making.[8] A recent review on the effect of a geriatric evaluation in elderly cancer patients showed that geriatric impairments are highly prevalent and that their identification results in a change of oncologic treatment in median 32% of older cancer patients.[7] These alterations could consist of both less and more intensive treatment, and occurred even when the oncology team did not express uncertainty regarding the treatment strategy prior to the evaluation.[7] This shows that evaluations on an ad hoc basis only do not suffice and supports the desire expressed by many respondents for a more routine geriatric assessment.

However, we acknowledge that geriatric evaluations also have pitfalls: they are time-consuming and require commitment of staff and other resources. Indeed, many respondents and especially geriatricians report the lack of time as hindering the incorporation of geriatric evaluations into routine practice. Volume-based healthcare financing, such as the system in the Netherlands, places strain on the valuable asset of time within the healthcare process. The initial investment of additional time to explore patients' ability to tolerate and benefit from treatment as well as their own preferences and priorities will finally result in a significant reduction of both over- and undertreatment which allows the routine use of geriatric evaluations to become cost-effective.

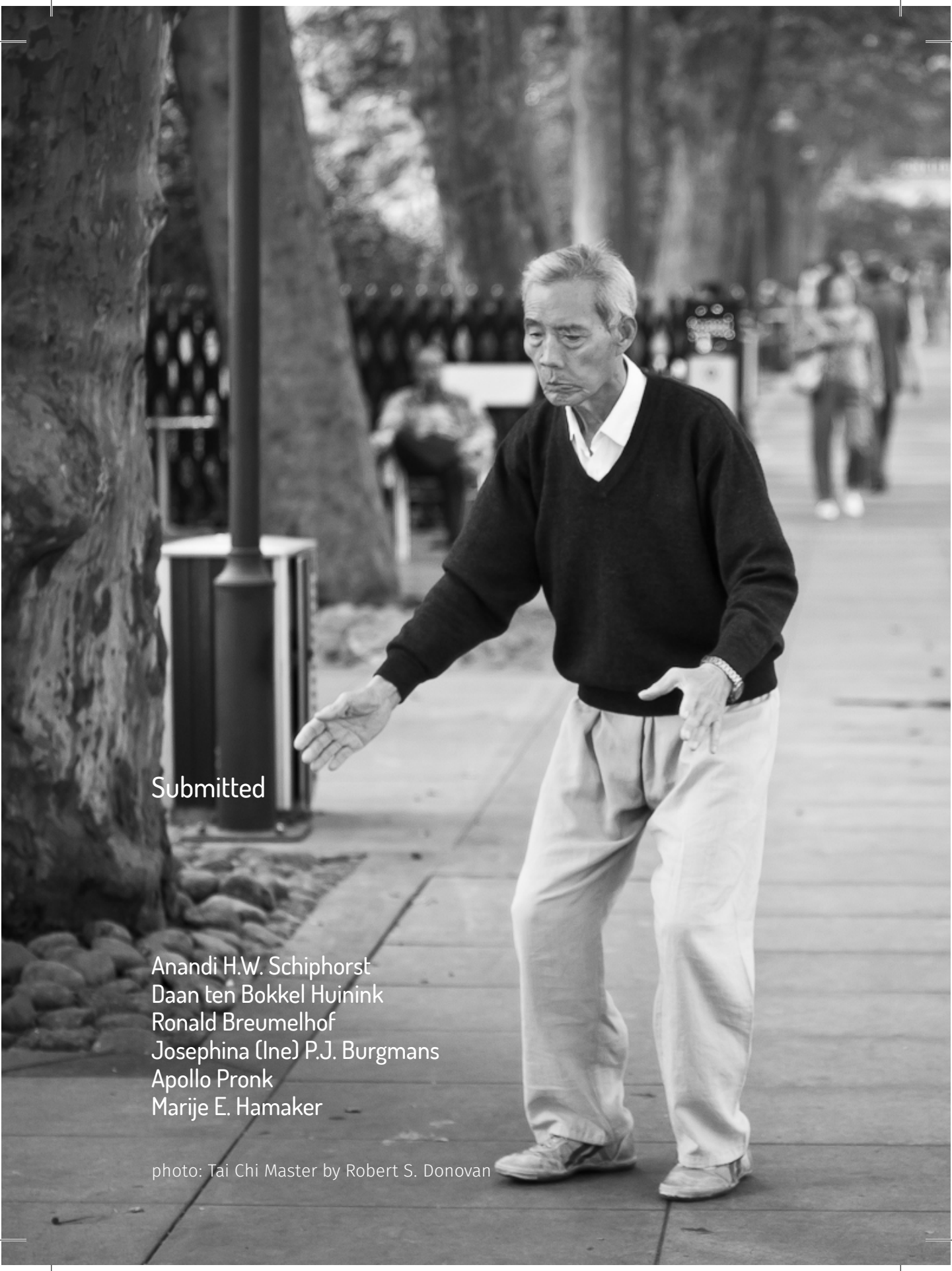
Nevertheless, the introduction of standard geriatric evaluations in oncologic clinical care will pose a significant challenge to healthcare logistics and many respondents state to be unsure of the best set-up of a geriatric oncology programme. The number of elderly cancer patients far exceeds the availability of geriatric consultations; moreover, geriatric medicine is a relatively new and developing field of care, and it is not surprising that over half of responding geriatricians state that their priorities currently lie elsewhere. However, studies have demonstrated that an exploratory geriatric evaluation can be effectively performed by a trained (research) nurse.[9] Incorporation of the results of this evaluation and the involvement of a geriatrician in oncologic decision-making (e.g. during multidisciplinary cancer team conferences) will bring oncologic and geriatric expertise together, allowing for optimal tailoring of care. Moreover, when an exploratory evaluation incorporates a standardised intervention plan, aimed at modifiable geriatric health issues, this is likely to result in an equal number of non-oncologic interventions as a formal geriatric consultation would (both in over 70% of cases).[7] The latter could then be reserved for complex cases or contentious treatment choices.

Conclusion

In addition to the standard oncologic work-up in the Netherlands, there is a desire for a more routine geriatric evaluation of elderly cancer patients and great interest in tailored care for this heterogeneous patient population. A closer collaboration between cancer specialists and geriatricians (preferably in a multidisciplinary team) is imperative to successfully bridge the gap of knowledge between geriatrics and cancer care and to optimise treatment for the growing number of older cancer patients.

References

1. www.cijfersoverkanker.nl.
2. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061-7.
3. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, Mor V, Monfardini S, Repetto L, Sorbye L, Topinkova E. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005;55:241-52.
4. http://www.borstkanker.nl/rapport_ouderen_en_borstkanker
5. Kalsi T, Payne S, Brodie H, Mansi J, Wang Y, Harari D. Are the UK oncology trainees adequately informed about the needs of older people with cancer? Br J Cancer 2013;108:1936-41.
6. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007;25:1824-31.
7. 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 Oncol 2014;53:289-96.
8. Lamb BW, Sevdalis N, Benn J, Vincent C, Green JS. Multidisciplinary cancer team meeting structure and treatment decisions: a prospective correlational study. Ann Surg Oncol 2012;20:715-22.
9. Kenis C, Bron D, Libert Y, Decoster L, Van Puyvelde K, Scalliet P, Cornette P, Pepersack T, Luce S, Langenaeken C, Rasschaert M, Allepaerts S, Van Rijswijk R, Milisen K, Flamaing J, Lobelle JP, Wildiers H. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. Ann Oncol 2013;24:1306-12



Submitted

Anandi H.W. Schiphorst
Daan ten Bokkel Huinink
Ronald Breumelhof
Josephina (Ine) P.J. Burgmans
Apollo Pronk
Marije E. Hamaker

photo: Tai Chi Master by Robert S. Donovan

10

Geriatric assessment can aid in complex treatment decisions for elderly cancer patients

Abstract

Background

Treatment decisions for elderly cancer patients can be complex and challenging. A geriatric assessment may identify unknown medical conditions, give insight on patients' ability to tolerate treatment and guide treatment decisions. Our aim was to study the value of a geriatric consultation in oncologic treatment decision-making.

Methods

Between February 2013 and June 2014, data on cancer patients in our institute, referred for geriatric consultation for clinical optimisation or due to uncertainty regarding their optimal treatment strategy, were entered in a prospective database. Outcome of geriatric evaluations, non-oncologic interventions and suggested adaptations of oncologic treatment proposals were evaluated.

Results

72 patients (median age 82 years) were referred for consultation, over half of which in a curative treatment setting. Prevalence of geriatric syndromes was 93%; mobility was most frequently impaired. Previously undiagnosed conditions (primarily cognitive impairments) were identified in 49% of patients and non-oncologic interventions were initiated in 56%. In addition, time was spent discussing patients' priorities (53% of consultations), expectations on treatment (50%) and advance care planning (14%). For 82% of patients, suggestions were made regarding the optimal treatment decision: a more intensive treatment was recommended in 39% of patients, a less intensive therapy for 42% patients and in 19% of patients only supportive care was suggested. With increasing number of geriatric conditions, the chance of less intensive treatment increased significantly.

Conclusion

A geriatric consultation can aid in tailored treatment decisions and allows for a reduction of over- and undertreatment of elderly cancer patients.

Introduction

The rapid rise in the number of elderly cancer patients[1] will present an unprecedented challenge to cancer specialists, since many questions regarding the optimal management of these patients still remain. Guidelines for oncologic treatment are based on studies in which the elderly and those with comorbidity were generally excluded.[2-4] Although it is known that elderly cancer patients are at an increased risk of treatment-related morbidity,[5] detailed evidence on the optimal oncologic treatment in elderly is lacking. As ageing is an individual process, resulting in an increasingly heterogeneous patient population, tailoring of treatment to the individual patient is needed.

Therefore, some form of geriatric evaluation is increasingly being used in the management of elderly cancer patients.[6] Such a multimodal evaluation may identify unknown medical conditions, give insight on patients' ability to tolerate oncologic therapy and guide treatment decisions.[7-9] Since 2013, multidisciplinary care for elderly cancer patients in our hospital includes geriatric expertise and a geriatric oncology programme has been initiated. Elderly cancer patient with uncertainty regarding the optimal choice for oncologic treatment or questions on the possible optimisation prior to treatment, are increasingly being referred for a geriatric consultation. The aim of this analysis was to assess the yield of these consultations and to determine the effect on treatment decisions.

Patients and methods

Between February 2013 and June 2014, all consecutive cancer patients referred for a geriatric consultation were included in a prospective database for quality control purposes. Patients' selection for geriatric evaluation was done by the referring physician or within a multidisciplinary oncology team (MDT) meeting. These were patients that required clinical optimisation prior to oncologic therapy and those patients with complex oncologic therapy choices, for whom questions regarding the optimal treatment options arose either at diagnosis or in case of disease progression. The geriatric evaluations were performed by a single geriatrician (MH) specialised in geriatric oncology, either during consultation in the out-patient clinic or during hospitalisation. Patients were seen together with their family or caregivers whenever possible. The assessment included evaluation and optimisation of comorbid diseases and medication use, diagnosis and, if applicable, treatment of cognitive

impairments, mood disorders, nutritional status, functional impairments (mobility, activities of daily living and instrumental activities of daily living) and social network or supportive care status. Specific diagnostic tools per geriatric domain were used on indication.

Oncologic treatment options prior to geriatric consultation were formulated by the cancer specialist, based on the information available at that time. Based on the geriatric assessment, an evaluation of patients' capacity to tolerate treatment was made and interventions for optimisation prior to oncologic therapy were proposed by the geriatrician. If necessary, advanced care planning and patients' expectations and priorities in treatment choices were discussed between patients and the geriatrician. If required, the geriatrician suggested an adaptation of oncologic therapy plans, tailored to the patients' capacities, limitations and wishes. When indicated, geriatric follow-up was initiated.

Data collection and analysis

This study was approved by the regional ethics committee and institutional review board. The primary outcome was the effect of the geriatric consultation on (adaptation of) oncologic treatment decisions. Secondary endpoints were the prevalence of geriatric impairments, the incidence of newly diagnosed geriatric syndromes or medical conditions, the number of recommendations regarding non-oncologic interventions and advanced care planning as well as discussions aimed at managing the patient's expectations on treatment options and clarifying the patients' priorities.

The following data were collected: patient demographics (age, sex, comorbidity measured by the Charlson comorbidity index[10], medication use), oncologic data (tumour type and stage, treatment setting and modality, initial oncologic treatment options prior to geriatric consultation, final oncologic treatment following geriatric evaluation) and information on the outcome of geriatric evaluation (prevalence of geriatric syndromes, incidence of newly diagnosed medical conditions, non-oncologic interventions, suggestions regarding oncologic treatment choices, discussions on advanced care planning, clarification of patients' priorities and expectations regarding oncologic treatment).

For the analysis of our primary outcome, treatment decisions following geriatric consultation were classified as intensified oncologic treatment and less intensive treatment or supportive care only.

Statistical analysis was performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was defined as $p<0.05$. The chi-square was used for comparisons between groups.

	Total n= 72
Female: male	42:30
Median age in years (range)	82 (57-94)
Type of malignancy[a]	
Colorectal	41 (57%)
Breast	11 (15%)
Upper GI	9 (13%)
Gynaecological	5 (7%)
Anal	2 (3%)
Lung	2 (3%)
Hematologic	2 (3%)
Urothelial	2 (3%)
Curative setting	44 (61%)
Tumour stage[b]	
I	10 (14%)
II	20 (28%)
III	20 (28%)
IV	20 (28%)

Table 1. Patient demographics

a Two patients presented with multiple synchronous malignancies
b Only for solid tumours

	Prevalence of geriatric syndromes or conditions	Of which newly diagnosed/not previously reported	Suggestions for non-oncologic interventions
Impaired mobility	44 (61%)	14 (19%)	11 (15%)
(Risk of) malnutrition	38 (53%)	1 (1%)	19 (26%)
Care dependence in (I)ADL	34 (47%)	7 (10%)	2 (3%)
Comorbidity	31 (43%)	7 (10%)	5 (8%)
Cognitive impairments	27 (38%)	15 (21%)	15 (21%)
Insufficient social network	17 (24%)	7 (10%)	10 (14%)
Psychological issues	16 (22%)	4 (6%)	10 (14%)
Medication issues	14 (19%)	1 (1%)	12 (17%)

Table 2. Outcome of geriatric assessment: Prevalence of geriatric syndromes and newly diagnosed medical conditions and suggestions for non-oncologic interventions

IADL: Instrumental activities of daily living; ADL: Activities of daily living

Results

Patients

Seventy-two consecutive referrals were included in the present analysis. Patient demographics can be found in Table 1. Median age of patients was 82 years (range 57-94 years) and 58% were female. Median Charlson comorbidity index was 1 (range 0-6) and 45 patients (63%) used five or more medications. The majority of patients (57%) suffered from colorectal cancer (colon cancer n=28, rectal cancer n=13). Other patients presented with breast cancer (15%), upper gastro-intestinal malignancies (13%), gynaecological malignancies (7%), anal cancer (3%), lung cancer (3%), hematologic malignancy (3%) and urothelial cancer (3%). Two patients presented with concurrent malignancies (colorectal cancer in combination with oesophageal cancer in one and with urothelial cancer in another). Most patients were treated in a curative setting (61%); twenty patients (28%) presented with stage IV disease.

Geriatric consultations

In 13 patients (18%), the reason for referral was to optimise patients prior to oncologic therapy. The remaining 59 patients (82%) were referred due to uncertainty regarding the optimal oncologic management, in addition to clinical optimisation. Geriatric consultations were performed during hospitalisation in nine patients (12%); the other patients were seen in the out-patient clinic. In 63 patients (88%), the assessment was done at diagnosis and the remaining patients were assessed at the time of disease progression. Patients were mostly referred by an oncologic or colorectal surgeon (28 patients, 39%); in 25 cases the referring physician was a gastroenterologist (35%), while medical oncologists referred thirteen patients (18%). Other referring physicians were specialists in internal medicine (n=3), pulmonology (n=3) and gynaecology (n=1).

The majority of patients (93%) suffered from one or more geriatric syndromes; these patients presented with a median of three geriatric problems (range 0-8). Mobility was most frequently impaired (61%, Table 2), followed by nutritional status (53%) and (instrumental) activities of daily living (47%). Not previously reported medical or geriatric conditions were identified in 49%; most prevalent were impairments in cognition and mobility (21% and 19% respectively). Non-oncologic interventions were proposed in over half of included patients (56%) on a median of one geriatric domain (0-6, Table 2). Domains that were most frequently amenable to intervention were nutrition (26%), cognition (21%) and mobility (15%). In 50% of consultations, time was spent remedying erroneous assumptions or expectations of the patient

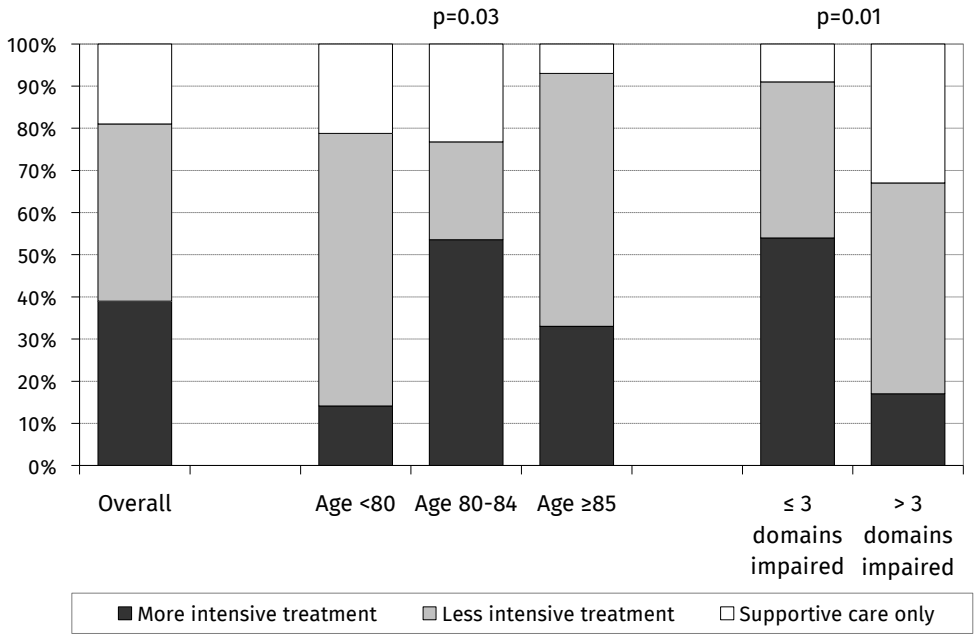


Figure 1. Oncologic treatment suggestions based on geriatric consultation

or family regarding treatment or prognosis while for 53%, the consultation was beneficial in clarifying the patient's priorities and wishes. In addition, advanced care planning was discussed with ten patients (14%).

Treatment decisions

Based on the geriatric consultation, suggestions for the oncologic treatment plan were proposed in 59 patients (82%) and 92% of these suggestions were adopted by the treating cancer specialist (54 patients). In three patients, decisions on oncologic treatment were postponed. The remaining two patients were treated for breast cancer and both chose for the less intensive treatment option while, based on the geriatric evaluation, standard treatment was suggested. Overall, a more intensive treatment was recommended in 23 patients (39%), a less intensive therapy for 25 patients (42%) and in 11 patients (19%) only supportive care was suggested (Figure 1). Intensified treatment was significantly more frequently recommended for patients treated in a curative setting (59% of cases compared to 12% of patients treated in a palliative setting, $p<0.001$). Less intensive treatment options were recommended in 48% of patients treated in a palliative setting and in 38% of those patients treated

with curative intend. Supportive care only was recommended in 40% of patients in a palliative setting, while this was recommended in 3% of patients with curable cancer. Suggestions on (adaptation of) oncologic treatment were irrespective of the type of treatment options (surgery, chemotherapy, radiation therapy or a combination of oncologic treatment modalities).
When comparing patients from different age groups, intensified treatment was least suggested in patients under 80 years of age (14% of patients); for patients aged 80 to 85 years this increased to 53% and in patients aged 85 years and older 33% were recommended to receive a more intensive treatment. With increasing numbers of geriatric problems, the more intensive treatment options were less frequently recommended: when patients had over 3 impaired geriatric domains, more intensive treatment was suggested in only 17% of cases, compared to 54% of patients with three or less geriatric problems (p=0.01, Figure 1). The median number of geriatric problems decreased with increasing age: a median of 4 geriatric impairments in patients aged <80 years, a median of 3 in patients aged 80-84 years and a median of 2 in patients aged 85 years and older.

Discussion

This study analyses the value of the geriatric oncology program in our institution. We demonstrate that prevalence of geriatric syndromes in elderly cancer patients referred for a geriatric consultation is high and this requires non-oncologic interventions in over half of cases. In nearly 50% of patients, not previously reported medical or geriatric conditions were diagnosed. Treatment decisions were related to the number of geriatric impairments and these were more prevalent in the younger patients. They mostly received the less intensive treatment options.
This analysis has several limitations. First, in this type of observational cohort study, direct comparison of survival and oncologic outcomes is hampered by selection bias and confounding by indication.[11] This would subsequently lead differences in outcome to be incorrectly attributed to treatment decisions, rather than to confounding factors such as poor overall health, which affected both treatment choice and outcome. Therefore, we opted to only describe the outcome of the geriatric consultations. Second, we included patients with various cancer types both in a curative and a palliative setting and at diagnosis or at disease progression. In addition, patients were referred based on the cancer specialists' clinical impression. However, we have no data on the health status or treatment decisions in older patients who were not referred. Despite these limitations, this analysis provides a

good impression of the daily practice and the variety of elderly cancer patients that are being referred for a geriatric consultation.

In recent years, collaboration between cancer specialists and geriatricians has increased to optimise care for elderly cancer patients. Many cancer specialists have become aware of the special needs of their most vulnerable patients and a multidisciplinary, patient-centred approach is considered essential. Geriatric conditions such as malnutrition, functional disability and polypharmacy have been demonstrated to be associated with increased vulnerability and are highly prevalent in older cancer patients.[8, 12, 13] This is in line with the outcome of the geriatric consultations in our patient cohort. The prevalence of (newly indentified) health issues will prompt interventions aimed at optimising patients prior to oncologic therapy.[8,9]

In addition, our study demonstrates that geriatric consultations can aid cancer specialists in making treatment decisions. Deciding on therapy for elderly cancer patients can become complex when patients present with a variety of comorbid conditions and functional impairments. In the absence of guidelines for these patients, the additional insight on a patient's ability to tolerate treatment that a geriatric assessment or consultation can provide may guide these decisions or reinforce the choices made by the referring physician. A careful selection of older patients fit enough for more intensive or standard treatment, and offering less intensive treatment options to frail patients, will aid in reducing the risks of both over- and undertreatment that the elderly are subject to.[7, 14-16]

Previous studies have demonstrated that treatment dilemmas will be greatest in an intermediate group of not-so-fit younger old and the apparently fit oldest old. It has been suggested that this is the group most likely to benefit from a more thorough assessment of health status.[17] Referral patterns in our analysis reflect this: for included patients, the prevalence of geriatric impairments decreased with increasing age. However, a recent review demonstrated that offering a geriatric assessment or consultation to all elderly cancer patients (irrespective of presumed fitness or clinical impression) resulted in an alteration of the oncologic treatment plan in nearly 50% of patients. This was much more frequent than when only cases were referred with questions regarding the optimal oncologic treatment (treatment alteration in 20%).[8] This suggests that routine geriatric assessments have a greater potential for identifying those patients at risk of under- or overtreatment. However, the incorporation of routine geriatric evaluations in standard oncologic care for all elderly cancer patients is currently hampered by the time- and resource-consuming nature of the consultations.[6]

Although our analysis demonstrates a benefit from geriatric consultations, it can be debated whether involving a geriatrician in decision making for all older patients – rather than for selected patients – is desirable or necessary. The abovementioned review demonstrated that a geriatric assessment can be performed within the oncology group using a series of validated screening instruments for relevant geriatric domains.[8] Although this will lack the depth of information that a geriatric consultation would, these assessments have been shown to reap similar benefit in terms of identifying previously unrecognized health issues as well as alterations in treatment.[8] We found that an additional yield of the consultation was clarifying patients' priorities and expectations concerning the proposed treatment options. However, this is mostly due to the time available in the consultation and not necessarily dependent on expertise specific to the geriatrician. Indeed, it can be questioned whether it would not be better that such issues are discussed with someone specialised and experienced in treating cancer, particularly as many geriatricians indicate that oncology is currently not a priority for them.[18] We believe that investing additional time during oncologic consultations to assess vulnerable elderly patients and explore their priorities will reduce both over- and undertreatment and we call on cancer specialists, policymakers and patients to work together to make this possible.

Conclusion

This analysis shows that the implementation of a geriatric oncology program is of great value to the optimisation of elderly cancer patients and reducing their risk of over- and undertreatment. Collaboration between cancer specialists and geriatricians can aid in the care for our most vulnerable cancer patients.

References

1. www.cijfersoverkanker.nl.
2. Schiphorst AH. Representation of the elderly in trials on laparoscopic surgery for colorectal cancer. Colorectal Dis 2014. Accepted for publication.
3. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061-7.
4. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, Housman MG, Escarce JJ. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21:1383-9.
5. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol 2008;9:494-501.
6. Schiphorst AH, Jonker JM, Smorenburg CH, Struikmans H, Rozema T, Pronk A, Portielje JEA, Hamaker ME. [Geriatric Oncology in the Netherlands] Ned Tijdschr Oncol 2014 dec;11(8):293-300
7. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, Mor V, Monfardini S, Repetto L, Sorbye L, Topinkova E. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005;55:241-52.
8. 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 Oncol 2014;53:289-96.
9. Maas HA, Janssen-Heijnen ML, Olde Rikkert MG, Machteld Wymenga AN. Comprehensive geriatric assessment and its clinical impact in oncology. Eur J Cancer 2007;43:2161-9.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
11. Walker AM. Confounding by indication. Epidemiology 1996;7:335-6.
12. Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J, Haley WE, Chen H, Boulware D, Balducci L. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol 2004;49:69-75.
13. Aparicio T, Girard L, Bouarioua N, Patry C, Legrain S, Soule JC. A mini geriatric assessment helps treatment decision in elderly patients with digestive cancer. A pilot study. Crit Rev Oncol Hematol 2010;77:63-9.
14. Wedding U, Kodding D, Pientka L, Steinmetz HT, Schmitz S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. Crit Rev Oncol Hematol 2007;64:1-9.
15. Hoeben KW, van Steenbergen LN, van de Wouw AJ, Rutten HJ, van Spronsen DJ, Janssen-Heijnen ML. Treatment and complications in elderly stage III colon cancer patients in the Netherlands. Ann Oncol;24:974-9.
16. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, Kohne CH, Rostoft S, Lemmens V, Mitry E, Rutten H, Sargent D, Sastre J,

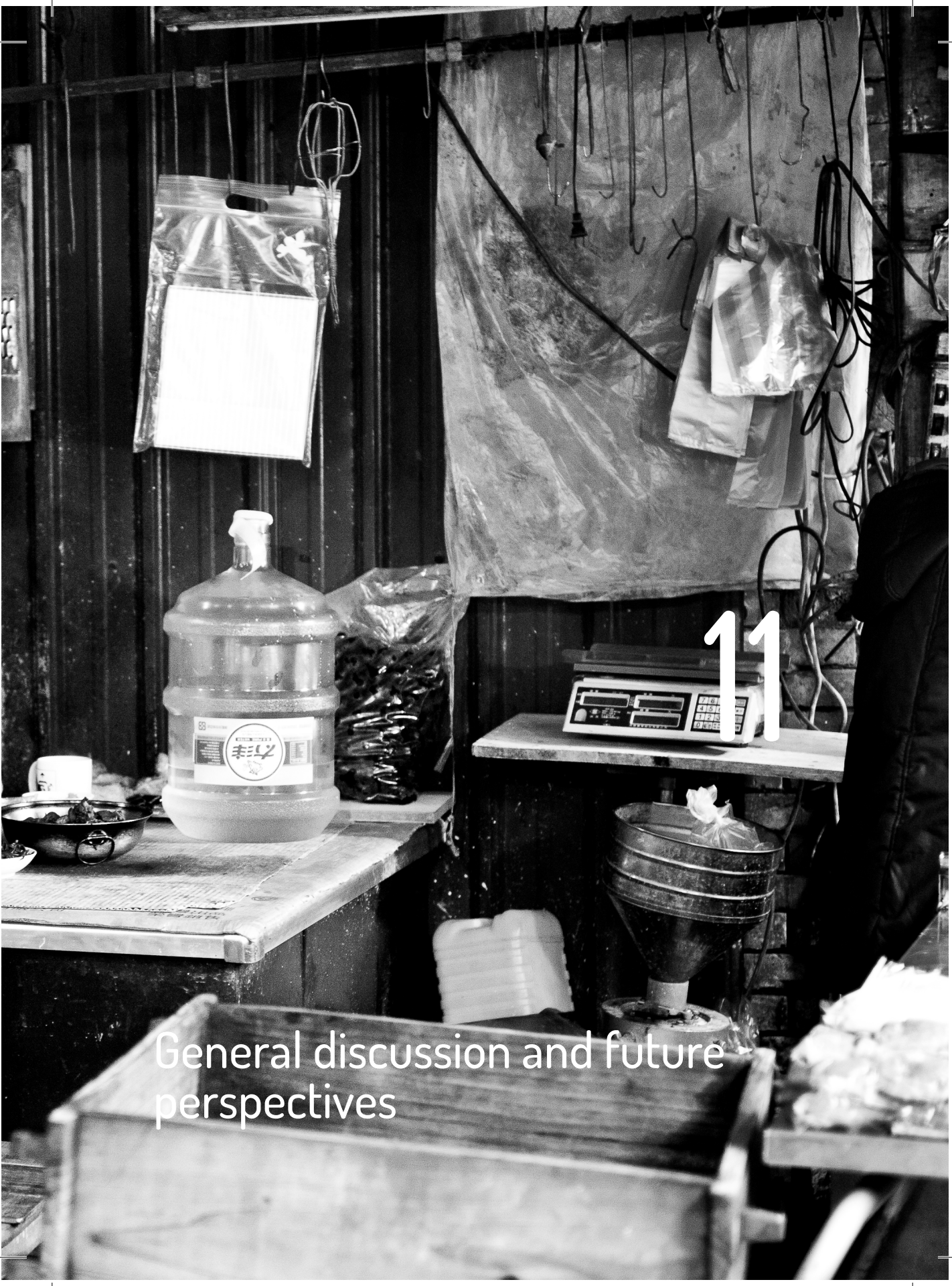
Seymour M, Starling N, Van Cutsem E, Aapro M. Treatment of colorectal cancer in older patients. International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol 2014.

17. Audisio RA, Papamichael D. Treatment of colorectal cancer in older patients. Nat Rev Gastroenterol Hepatol 2012;9:716-25.
18. Jonker JM, Smorenburg CH, Schiphorst AH, van Rixtel B, Portielje JE, Hamaker ME. Geriatric oncology in the Netherlands: a survey of medical oncology specialists and oncology nursing specialists. Eur J Cancer Care (Engl). 2014 Nov;23(6):803-10

Part IV

Discussion and summary

photo: Lunch - Taipei, Taiwan by Jorge Gonzalez



11

General discussion and future perspectives

Introduction

The work presented in this thesis addresses multiple issues concerning the treatment of colorectal cancer in elderly patients. The demographic developments and the rise in incidence of colorectal cancer make management of the rapidly growing number of elderly colorectal cancer patient an increasingly urgent subject. In this chapter, the results of our studies are discussed and future perspectives in the treatment of elderly colorectal cancer patients will be addressed.

Surgery in the aged

Surgery remains the cornerstone of curative therapy for colorectal cancer.[1] With the rise in incidence of colorectal cancer and the ageing of the population, the number of elderly cancer patients presented for colorectal surgery has increased greatly,[2] and this trend is expected to last in the decades to come. Against this background, the management of this heterogeneous patient population will present an immense challenge since colorectal surgery comes with significant morbidity and mortality. Especially in elderly patients, the consequences of morbidity following colorectal surgery are enormous[3,4] and it has been shown that survival is greatly affected by the outcome of surgery mainly in the first postoperative year.[5,6] As presented in **Chapter 5**, when elderly patients suffer from postoperative complications, their survival in the first months after surgery is significantly worse. Other studies have demonstrated that only once the elderly live through the first postoperative year, their survival equals that of the younger patients.[6] On the other hand, when colorectal cancer is left untreated, the consequences may be equally poor, as it can lead to serious cancer-related complications.

Treatment developments in an ageing world

Recent technologic advances in the surgical treatment of colorectal cancer, such as the introduction of minimally invasive surgery, have positively influenced postoperative outcome.[7] However, as demonstrated in **Chapters 2 and 4**, this has not led to a significant decrease in overall morbidity following colorectal surgery, which still affects nearly one-third of patients. Furthermore, although there appear to be great benefits of laparoscopic resections for malignancies in both the colon and the

rectum (such as reduced blood loss, less pain, an attenuated acute phase response), it is unclear if these advantages are the same for elderly and younger patients.
In **Chapter 6**, we performed a population-based study and showed that the elderly are less likely to receive laparoscopic surgery for colorectal cancer as compared to younger patients, while the elderly appear to benefit most. For patients aged ≥75 years, perioperative, three-month and one-year mortality was significantly reduced between 2008 and 2011, concurrent with an increase in the use of laparoscopic surgery. We therefore suggest that older colorectal cancer patients should receive laparoscopic surgery whenever possible.
One of the explanations for the observed improved postoperative survival is the positive effect of laparoscopic surgery on the incidence of postoperative non-surgical complications. With increasing age, there is an exponential rise in cardiopulmonary complications.[3,4] In **Chapter 4**, we investigated whether laparoscopic surgery reduces these adverse events in randomised controlled trials of laparoscopic compared with conventional surgery for colorectal cancer. Although there was insufficient data on the outcome specific for elderly patients in this systematic review, we demonstrated that the incidence of cardiac complications is significantly lower in laparoscopic colectomy compared to conventional resections. In our analysis, this effect was less marked for pulmonary complications, although other (mainly observational) reports demonstrated a reduced incidence of postoperative pneumonia in elderly patients as well.[8]
For rectal resections, we found no benefit of laparoscopic surgery on the incidence of non-surgical complications. As demonstrated in **Chapters 2 and 4**, morbidity from rectal resections is markedly higher as compared to surgery for malignancies in the colon. One explanation is that the greater extent of radical rectal surgery results in an inherent high morbidity rate, in addition to morbidity from neoadjuvant (chemo) radiation therapy. A recent population-based study showed that, although the local recurrence rate is reduced with preoperative radiotherapy, irradiated patients aged ≥75 years suffer more from postoperative complications compared to those only receiving surgery.[9] Therefore, it can be debated whether all elderly patients should receive (full) neoadjuvant therapy and individualised treatment plans should be made for every patient.
Furthermore, although total mesorectal excision (TME) (in some cases combined with neoadjuvant therapy) remains the gold standard of treatment for most rectal cancers, there are less-invasive alternatives for such major treatment in elderly patients. One alternative is local excision of rectal tumours by means of transanal endoscopic microsurgery (TEM). Although radical TME surgery can be avoided using this technique, the benefits should be carefully weighed against higher rates of local

recurrence. Results of TEM as an alternative to TME in elderly patients (median age 80 years) with ≥T2 rectal cancers showed a local recurrence rate of 27% and distant metastasis in 12% after 30 months follow-up.[10] This suggests that nearly two-thirds of patients may profit from this less-invasive alternative. Especially in patients with reduced life expectancy this may be a worthwhile treatment option. Drawbacks of the TEM apparatus are its complex usage and high costs. A new technique for the resection of rectal polyps and cancers is transanal minimally invasive surgery (TAMIS), using disposable flexible ports.[11] This method has lower costs and is more readily available, in addition to good functional results (**Chapter 3**).
The search for alternatives to major rectal cancer surgery is ongoing and reports on treatment of rectal cancer with (chemo)radiation therapy alone or in combination with TEM are emerging.[12-14] However, to date such therapy is still considered experimental and only offered to highly selected patients. Moreover, (chemo) radiation therapy comes with its own morbidity rates[14] and it is unclear how and if the elderly will benefit. Future research should provide answers regarding the optimal choice of therapy for those elderly patients in whom TME surgery is best avoided.

Balancing the risks and benefits

When treatment-related morbidity and mortality is nearly equal to cancer-related morbidity and mortality, deciding whether to subject vulnerable patients to such therapy can become contentious. The paucity of high-quality evidence leaves many questions regarding the optimal management of elderly colorectal cancer patients unanswered. Most available data is observational and subsequently hampered by selection bias and confounding by indication. Moreover, existing treatment guidelines are based on studies in which elderly patients were frequently excluded.[15-17] This was addressed in **Chapter 7**, where we found that 44% of trial protocols from randomised studies on laparoscopic surgery for colorectal cancer excluded older patients from participating, rendering elderly patients underrepresented.
As a consequence, the importance of selecting those patients fit enough for (surgical) therapy is becoming increasingly apparent. In **Chapter 5**, we studied treatment decisions and guideline adherence for patients with low rectal cancer. Decisions on treatment were still largely based on age, not physical condition. Although it is generally acknowledged that active treatment should not be withheld based on a patient's chronologic age, it can be questioned whether all elderly

patients should receive standard treatment. Chronologic age is not the only factor that has to be taken into account when making decisions. Treatment should be tailored to the ability of patients to tolerate treatment and it is important to identify factors that will influence postoperative outcome and can subsequently affect oncologic decision making.

One way to assess these factors is to perform a geriatric evaluation, which entails a multidimensional assessment of a patient's general health condition and functional status.[18] It can provide insights into an individual's probability of survival and allows for directed interventions.[19] In **Chapters 8 and 10**, we addressed the effect of a geriatric consultation on treatment decision making in oncologic therapy. It was demonstrated that a geriatric consultation has the potential to reduce the risks of under- and overtreatment and to guide treatment decision making. Moreover, elderly patients may experience different goals in treatment for colorectal cancer, with post-operative functional independence and quality of life being of relatively greater importance for them as compared to oncologic outcome or extended survival. This holds true especially when a patients' remaining life span is limited. However, little data exists on functional outcome and quality of life for elderly patients after surgery for colorectal cancer. Pooled data from our group suggests there is a permanent loss in physical and role functioning following colorectal resection, especially in elderly patients.[20]

Therefore, exploring a patient's priorities and preferences prior to oncologic treatment will be of great importance in treatment decision making. Although we have demonstrated in **Chapter 10** that a geriatric consultation can be of additional value to assess patients' expectations and priorities in anti-cancer treatment, it can be argued that cancer specialists themselves should also invest more time to define a patient's individualised treatment plan and discuss their patients' goals in oncologic therapy as well as in general well-being. This should also include the possibility and consequence of opting out of (surgical) therapy.

Optimising care for the aged

In addition to risk stratification and guiding treatment decisions, a geriatric assessment may serve to optimise the health status of elderly patients prior to oncologic treatment. The results of the work in **Chapters 8 and 10** show that the number of non-oncologic interventions resulting from a geriatric evaluation or consultation is significant. Although the effect of these interventions is poorly studied to date, it is suggested that they can provide risk-reduction and improve

quality of life.[21, 22]
Cancer specialists are increasingly aware of the needs of their most vulnerable patients and, as outlined in **Chapter 9**, many have implemented some form of geriatric care for their elderly patients or are interested in doing so. Although the value of geriatric care for elderly colorectal cancer patients is increasingly acknowledged, geriatric oncology programmes have jet to be fully established and many cancer specialists and geriatricians express their uncertainty regarding the best format to improve care for the oncogeriatric population.

Future perspectives for an ageing world

Despite the increasing awareness of the vulnerability of the heterogeneous group of elderly colorectal cancer patients, major challenges lie ahead in improving their care. The current evidence for the optimal management of elderly patients presenting with colorectal cancer is mostly observational and of low quality, which hampers the decision-making process. Although randomised trials remain the 'holy grail of research', it remains questionable whether results from randomised studies are applicable for the elderly population. There are several possible methods to improve the current evidence. First, subgroup analysis of elderly patients in large randomised studies may shed some light the outcome for these patients. Second, if these trials would make their data on included elderly available, the representativity of the elderly population in these trials could be adequately assessed. Third, such raw data could be pooled, which will allow for increased insight in the outcome of surgical therapy for the older colorectal cancer patients. Finally, most trials report on short-term results (usually 30 days postoperative) and long-term outcome (mostly after a follow-up of 3-5 years). However, 30-day mortality underestimates 1-year mortality in elderly patients.[23] Therefore, more trial data on the outcome for elderly patients during the first year after resection for colorectal cancer and exploration of risk factors for postoperative morbidity and mortality may clarify the prolonged negative effects of surgery in these patients.
In decision making for elderly colorectal cancer patients, an adequate assessment is essential to stratify patients according to their risk for adverse events. Identifying very fit patients suitable for extensive oncologic therapy or very frail patients in whom (surgical) treatment is best avoided will generally not be a matter of discussion. However, between these two extremes there is a grey area with patients in whom any kind of adverse event can destabilise their health status, leading to loss of independence and life quality. For these patients, decision making is not

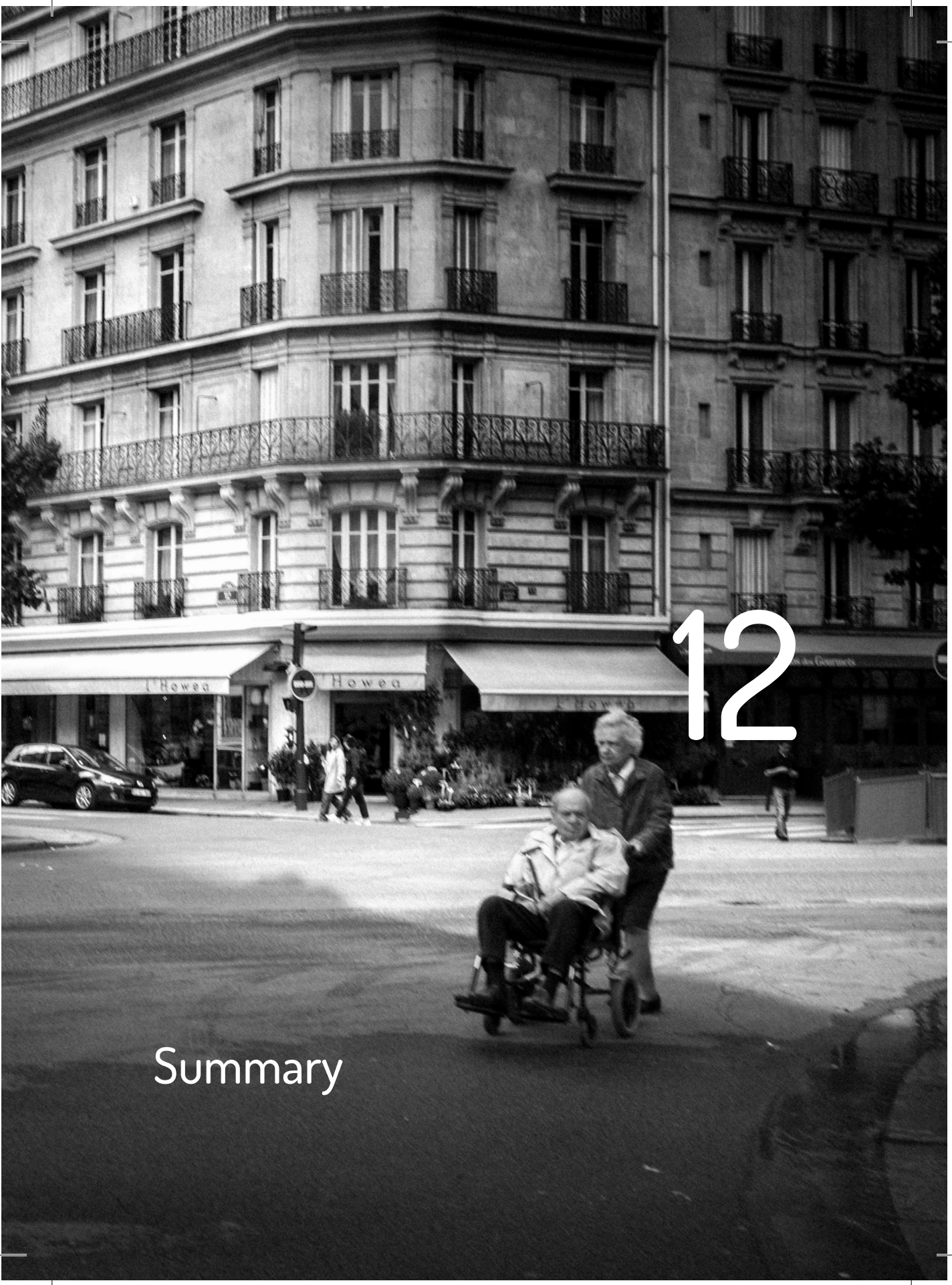
a black-or-white issue. Their management will remain most challenging as our abilities to adequately screen for frailty and assess these patients' risks are still unsatisfactory.[24] Future research should therefore focus on improving the reliability of risk assessment and incorporating this in daily surgical and oncologic practise. In addition, for elderly patients, we should always consider that there is more to life after surgery than merely survival. Data on the effect of oncologic treatment on functionality and quality of life in elderly patients is essential in the decision-making process and this warrants more (prospective) research with endpoints that are relevant for the elderly population. It will be of great importance to actively involve elderly colorectal patients and their relatives in the decision-making process and explore patients' treatment goals and personal preferences. Cancer-related complications, functional status, treatment-induced adverse events and time to benefit from treatment have to be carefully weighed. This will require an investment of time, not only from consulted geriatricians, but also from the cancer specialists themselves. Personalised treatment plans, tailored to a patient's capabilities and restrictions are imperative to improve the care for our most vulnerable elderly colorectal cancer patients.

References

1. http://www.oncoline.nl/colorectaalcarcinoom.
2. www.cijfersoverkanker.nl.
3. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol 2008;9:494-501.
4. Colorectal Cancer Collaborative Group. Surgery for colorectal cancer in elderly patients: a systematic review. Lancet 2000;356:968-74.
5. Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, Tollenaar RA, Liefers GJ. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. Ann Surg Oncol 2012;19:2428-34.
6. 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. Ann Surg Oncol 2011;18:1533-9.
7. Schwenk W, Haase O, Neudecker J, Muller JM. Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev 2005:CD003145.
8. Grailey K, Markar SR, Karthikesalingam A, Aboud R, Ziprin P, Faiz O. Laparoscopic versus open colorectal resection in the elderly population. Surg Endosc 2013;27:19-30.
9. Maas HA, Lemmens VE, Nijhuis PH, de Hingh IH, Koning CC, Janssen-Heijnen ML. Benefits and drawbacks of short-course preoperative radiotherapy in rectal cancer patients aged 75 years and older. Eur J Surg Oncol 2013;39:1087-93.
10. Leijtens JW, Rademakers KL, Maas M, Doornebosch PG, Karsten TM, Derksen EJ, Stassen LP, Rosman C, de Graaf EJ, Bremers AJ, Heemskerk J, Beets GL. Resection of rectal tumors: Natural course after transanal endoscopic microsurgery (TEM) without total mesorectal excision (TME) for T2 and T3 rectal carcinoma. Submitted for publication.
11. Albert MR, Atallah SB, deBeche-Adams TC, Izfar S, Larach SW. Transanal minimally invasive surgery (TAMIS) for local excision of benign neoplasms and early-stage rectal cancer: efficacy and outcomes in the first 50 patients. Dis Colon Rectum 2013;56:301-7.
12. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Bailao Aguilar P, Nadalin W, Perez RO. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum 2013;56:1109-17.
13. Perez RO, Habr-Gama A, Lynn PB, Sao Juliao GP, Bianchi R, Proscurshim I, Gama-Rodrigues J. Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. Dis Colon Rectum 2013;56:6-13.
14. Garcia-Aguilar J, Shi Q, Thomas CR, Jr., Chan E, Cataldo P, Marcet J, Medich D, Pigazzi A, Oommen S, Posner MC. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol;19:384-91.
15. Mutasingwa DR, Ge H, Upshur RE. How applicable are clinical practice guidelines to elderly patients with

comorbidities?
Can Fam Physician 2011;57:e253-62.
16. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, Housman MG, Escarce JJ. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21:1383-9.
17. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Oncol 2005;23:3112-24.
18. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007;25:1824-31.
19. Maas HA, Janssen-Heijnen ML, Olde Rikkert MG, Machteld Wymenga AN. Comprehensive geriatric assessment and its clinical impact in oncology. Eur J Cancer 2007;43:2161-9.
20. Hamaker ME, Prins HC, Schiphorst AH, van Tuyl SA, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. J Geriatr Oncol. 2014 Nov 6 (epub ehead of print).
21. Audisio RA, Pope D, Ramesh HS, Gennari R, van Leeuwen BL, West C, Corsini G, Maffezzini M, Hoekstra HJ, Mobarak D, Bozzetti F, Colledan M, Wildiers H, Stotter A, Capewell A, Marshall E. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. Crit Rev Oncol Hematol 2008;65:156-63.
22. Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J, Haley WE, Chen H, Boulware D, Balducci L. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol 2004;49:69-75.
23. Mamidanna R, Almoudaris AM, Faiz O. Is 30-day mortality an appropriate measure of risk in elderly patients undergoing elective colorectal resection? Colorectal Dis 2012;14:1175-82.
24. 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 Oncol 2012;13:e437-44.

photo: La Dépendance by Adrien Leguay



12

Summary

Summary

The number of patients newly diagnosed with colorectal cancer has risen greatly in the past 20 years. This disease is currently the third most common malignancy in the Netherlands where it causes over 5000 deaths each year.
Over half of new cases of colorectal cancer affects patients older than 70 years of age. This number has increased in recent years due to the rapid ageing of the population and increased life expectancy. The management of this growing group of elderly colorectal cancer patients will pose a significant challenge to cancer specialists, since many questions regarding their optimal treatment are unanswered. Treatment guidelines are based on studies that have generally excluded elderly patients and those with concurrent diseases. Moreover, ageing is an individual process that comes with a wide variety of health issues, functional impairments, loss of physical reserves and geriatric conditions. As a result, recommendations for younger, fit patients cannot automatically be extrapolated to the heterogeneous elderly population.
There is a lack of high-quality literature evidence regarding the effect of (surgical) treatment of colorectal cancer on elderly patients. Complications after surgery have great impact on these patients with higher mortality rates during the entire first postoperative year. However, when the cancer is left untreated, this may equally result in serious cancer-related complications. These dilemmas can make treatment decisions for elderly colorectal cancer patients challenging.

The research presented in this thesis focuses on several components of the treatment of colorectal cancer in an ageing world and comprises three parts.
Part I describes technological developments in the treatment of colorectal cancer. A major advancement in recent years has been the introduction of laparoscopic colorectal surgery. The advantages of such minimally invasive techniques for colon surgery have been previously reported and consist of reduced pain, less blood loss and faster recovery. For rectal cancer, the benefits of laparoscopic surgery are less evident and there is still uncertainty whether these benefits weigh up against the technical challenges of laparoscopic rectal surgery. **Chapter 2** provides and compares the results of laparoscopic resections with conventional (open) surgery for cancer in the distal 10cm of the rectum performed between 2006 and 2011 in 166 consecutive patients at the Diakonessenhuis. In this study the duration of surgery was slightly longer for the laparoscopic resections, but there was a faster recovery of bowel function and shorter hospitalisation. Cancer-related results were similar between

both surgical approaches.
Rectal resection carries a high chance of postoperative complications. Therefore, in case of rectal polyps or small tumours, a local (transanal) resection of the lesion can be performed, thus avoiding extensive rectal surgery. The standard procedure for this type of surgery is 'transanal endoscopic microsurgery' (TEM), which uses a complex and costly apparatus with a 4 cm wide metal proctoscope to remove lesions from the rectum with specialised equipment. This technique is not widely available and has a long learning-curve. Moreover, the use of this apparatus may lead to damage to the anal sphincter. A less expensive alternative is the use of a 'flexible port', which is less rigid and can be used in combination with standard laparoscopic instruments. For transanal surgery, the use of this port has scarcely been studied, but it may have an advantage in preserving the postoperative anal sphincter function compared to the rigid TEM apparatus. In **Chapter 3** a series of 37 patients is presented, in whom rectal polyps and cancers were removed using a flexible port. Functional results before and following surgery were measured using a faecal incontinence score. The technique was feasible and in 88% of patients with preoperative impaired continence, the postoperative function was improved. Moreover, there were few complications and good oncologic results.
Although there have been great developments in the surgical treatment of colorectal cancer in the last decades, complication-rates after surgery remain high. Non-surgical complications (such as cardiac and pulmonary complications) affect elderly patients more frequently and are a major cause of death. Reducing these complications after colorectal surgery may improve outcome for elderly patients. **Chapter 4** evaluates the effect of laparoscopic surgery on reducing the number of non-surgical complications. A literature research was performed which compared short-term results of 18 randomised clinical trials with a total of 6135 patients. In these trials, laparoscopic resection of colorectal cancer was compared to conventional resection. This literature review demonstrated that the chance of cardiac complications was over four and a half times increased in conventional surgery for colon cancer compared to laparoscopic colectomy. For rectal cancer however, this effect was not observed. Additionally, for pulmonary complications, the benefit of laparoscopic surgery was less evident and the overall number of patients suffering one or more complications was not different between conventional and laparoscopic surgery.

Part II of this thesis addresses treatment decisions for elderly patients with colorectal cancer. In **Chapter 5**, a study is presented in which treatment decisions are investigated both for elderly and younger patients presenting with cancer in the

distal part of the rectum. Treatment decisions for patients newly diagnosed with low rectal cancer were compared to national guidelines on the treatment for rectal cancer. Elderly received significantly less curative therapy compared with younger patients (83% versus 100%). In metastatic rectal cancer, palliative surgery was initiated significantly less frequent in the older patients and if given, this therapy was generally less extensive in the elderly. Guideline adherence was 87% in younger patients and 62% in older patients; age was the most common reason mentioned for withholding treatment in the latter. Outcome after radical rectal surgery showed that the elderly suffered equally from postoperative adverse events, but mortality rates were almost tripled in the first six months after surgery in elderly patients.
Chapter 6 describes an analysis on the use of laparoscopic surgery for colorectal cancer based on data from the Dutch Cancer Registry between 2008 and 2011. The utilisation of laparoscopy had increased greatly, although elderly patients underwent laparoscopic surgery less frequently (40% of cases compared with nearly half of younger patients). Mortality rates at 30 days, three months and one year decreased over time, concurrent with the rise in use of laparoscopic surgery and risk reduction was greatest for patients aged ≥75 years. Therefore, although the elderly were less likely to receive laparoscopic surgery, they appear to benefit most. For this reason, laparoscopic surgery should be performed whenever possible.
Chapter 7 addresses the representativity of elderly patients in randomised trials on laparoscopic surgery for colorectal cancer. Such studies can provide high quality evidence on the optimal treatment choices for elderly patients, but only if the trial population is representative for the target population. Therefore, it is important to determine whether sufficient elderly patients or those with comorbidities were accrued. We performed an analysis of 52 registered trial protocols on studies that randomised between conventional and laparoscopic surgery for colorectal cancer. It was demonstrated that most studies had no restrictions regarding cardiac or pulmonary comorbidity and over half of studies had no restrictions regarding ASA-score. Elderly patients were excluded in 44% of trial protocols, based on age, comorbidities and/or organ function. When an upper age limit was used, half of these studies had no restrictions on organ function. This shows that chronologic age was reason for exclusion, rather than physical condition. Average age of included patients in published reports was below 70 years in 86% of studies.

Part III of this thesis studies the role of a geriatric medicine in the multidisciplinary care for elderly cancer patients. Collaboration with geriatricians is increasingly being sought in the management of older patients with colorectal cancer. A geriatric consultation or evaluation entails a multidimensional assessment of a patient's

general health condition and functional status. **Chapter 8** describes a review of the literature on the effect of a geriatric evaluation on treatment decisions in elderly cancer patients. Ten observational studies were included in this analysis which showed that initial oncologic treatment proposals were adjusted in one-third of patients following a geriatric evaluation. This adaptation could consist both of intensified treatment or less intensive oncologic treatment. Additionally, non-oncologic interventions were recommended in 83% of patients, for instance nutritional interventions or medicine adaptations. Therefore, a geriatric evaluation has significant impact on oncologic and non-oncologic treatment decisions in older cancer patients and deserves consideration in the work-up for these patients.
In **Chapter 9** the results of a national survey of 1726 cancer specialists (medical oncologists, surgeons and radiation oncologists) and geriatricians are presented. The response rate of this web-based survey was 35%. Half of respondents reported that some form of geriatric evaluation is currently implemented at their hospital; approximately one-third stated that elderly are routinely assessed for the presence of geriatric impairments. Many respondents felt that current care could be improved by a closer collaboration between cancer specialists and geriatricians, routine geriatric evaluations for all elderly cancer patients, and greater incorporation of its results in oncologic decision-making. Of respondents not using a geriatric evaluation, 83% stated to be interested in its implementation, although 40% said this was currently not their priority and over one-third reported to be unsure of the best format. For over 25%, time constraints were also a significant obstacle.
Chapter 10 studies the value of a geriatric consultation in 73 elderly cancer patients. These patients were referred to the geriatrician to optimise their health status prior to oncologic therapy or due to uncertainty regarding the optimal choice of treatment. The prevalence of geriatric problems was high (93%) and in over half of patients non-oncologic interventions were recommended. Previously undiagnosed conditions (primarily cognitive impairments) were identified in 49% of patients and for 82% of patients, suggestions were made regarding the optimal treatment decision. In addition, time was spent discussing patients' priorities (53% of consultations), expectations regarding treatment (50%) and advance care planning (14%). This analysis showed that a geriatric consultation can aid in complex treatment decisions and in optimising elderly patients before commencing oncologic treatment.

In **Chapter 11** the findings of the research done in this thesis are discussed and future perspectives in the care for elderly colorectal cancer patients are addressed.

photo: Dimanche 05.10.08 is like a meeting by Maelis

13

Dutch Summary
Samenvatting in het Nederlands

Introductie

Het aantal nieuwe patiënten met darmkanker (kanker van de dikke darm en de enkeldarm, ook wel colorectaal carcinoom) is in de laatste decennia fors toegenomen. Momenteel is het de derde meest voorkomende maligniteit in Nederland en sterven er jaarlijks ruim 5000 patiënten aan deze ziekte.
Meer dan de helft van alle nieuwe gevallen van darmkanker treft mensen die ouder zijn dan 70 jaar. Door de dubbele vergrijzing in Nederland en de stijgende levensverwachting zal dit aantal de komende jaren verder toenemen. De behandeling van deze groeiende groep ouderen met darmkanker vormt een grote uitdaging voor kankerspecialisten. Richtlijnen voor de behandeling zijn gebaseerd op studies waar oudere en kwetsbare patiënten over het algemeen niet aan mee gedaan hebben. Daarom kunnen deze resultaten niet gegeneraliseerd worden en zijn ze mogelijk niet toepasbaar voor de oudere patiënt. Er is weinig wetenschappelijke bewijs van hoge kwaliteit over de effectiviteit van de behandeling van darmkanker bij ouderen. Veroudering is bovendien een individueel proces, wat gepaard kan gaan met een variatie aan bijkomende ziektes, functionele beperkingen, fysieke belemmeringen en geriatrische syndromen. Tegelijkertijd kent de behandeling van darmkanker een hoge kans op complicaties en juist bij ouderen zijn de gevolgen van deze complicaties veel ernstiger. De optie van niet-behandelen kan ook resulteren in ernstige complicaties, bijvoorbeeld ten gevolge van de doorgroei van darmkanker. Deze dilemma's zorgen ervoor dat er nog vele vraagtekens zijn in de optimale behandelkeuzes voor ouderen met darmkanker.

Het onderzoek in dit proefschrift richt zich op een aantal onderdelen in de behandeling van darmkanker in een verouderende wereld en bestaat uit drie delen.
Deel I beschrijft technische ontwikkelingen in de behandeling van darmkanker. Een belangrijke ontwikkeling in darmchirurgie betreft het uitvoeren van kijkoperaties (ook wel laparoscopische of minimaal-invasieve chirurgie genoemd). De voordelen van dergelijke operaties zijn voor dikke darmkanker reeds aangetoond en bestaan onder andere uit minder bloedverlies, minder pijn en een sneller herstel na de operatie. Voor endeldarmkanker bestaat er nog onduidelijkheid of de voordelen van een kijkoperatie opwegen tegen de technische uitdagingen.
Hoofdstuk 2 geeft een overzicht van de resultaten van kijkoperaties bij kanker in de onderste 10cm van de endeldarm. De uitkomsten van laparoscopische en conventionele endeldarmoperaties, uitgevoerd tussen 2006 en 2011 bij 166 opeenvolgende patiënten, werden vergeleken. In deze studie bleek de operatieduur

voor een kijkoperatie langer, maar het herstel na deze operatie werd bespoedigd in vergelijking met de conventionele operatie. Dit uitte zich onder andere in een kortere opnameduur en sneller herstel van de functie van de darm. Daarnaast waren de oncologische resultaten en de overleving vergelijkbaar tussen beide groepen.
Omdat het verwijderen van de endeldarm gepaard gaat met een hoge kans op complicaties wordt er bij poliepen en kleine tumoren zonder uitbreiding in de lymfeklieren vaak gekozen voor het lokaal verwijderen van de tumor via de anus. De standaard behandeling hiervoor is 'transanale endoscopische microchirurgie' (TEM), een lastige en kostbare techniek waarbij een buis van 4cm breed in de anus ingebracht wordt. Vervolgens wordt er lucht in de endeldarm geblazen en kan met behulp van speciale instrumenten en een speciale camera een gezwel uit de endeldarm verwijderd worden. Deze apparatuur is niet in elk ziekenhuis beschikbaar. Daarnaast leidt het gebruik van de brede, metalen buis mogelijk tot schade aan de anale kringspier. Een alternatieve methode is het gebruik van een 'flexibele poort'. Dit is een zachte, kunststof buis met enkele werkkanalen die al gebruikt wordt bij kijkoperaties via één incisie. De techniek is goedkoper en beter beschikbaar, maar nog weinig beschreven voor het verwijderen van tumoren en poliepen uit de endeldarm. Voor deze toepassing is er mogelijk een voordeel in de postoperatieve functie van de kringspier ten opzichte van de starre brede buis die bij een TEM gebruikt wordt. In **Hoofdstuk 3** wordt een cohort van 37 patiënten gepresenteerd, bij wie poliepen en tumoren uit de endeldarm verwijderd werden middels een flexibele poort. Hierbij werd gekeken naar de functionele uitkomsten van een dergelijke operatie. De pre-operatieve fecale incontinentie-score werd vergeleken met de postoperatieve incontinentiescore. Het bleek dat de techniek goed uit te voeren was en dat bij 88% van de patiënten met preoperatieve stoornissen in de fecale continentie de functie na de operatie verbeterd was. Daarnaast waren er weinig complicaties en goede oncologische resultaten.
Hoewel er grote technische ontwikkelingen op het gebied van chirurgische behandeling van darmkanker zijn geweest de laatste jaren, blijft de kans op complicaties na dergelijke chirurgie hoog. Niet-chirurgische complicaties (zoals problemen aan hart en longen) komen vooral bij oudere patiënten voor en lijden vaak tot overlijden. Het terugdringen van deze complicaties na colorectale chirurgie zou een verbetering van de uitkomsten kunnen geven. In **Hoofdstuk 4** wordt onderzocht of het verwijderen van darmkanker met een kijkoperatie een gunstig effect heeft op het terugdringen van deze niet-chirurgische complicaties. Er werd een literatuuronderzoek uitgevoerd waarbij de korte termijnresultaten van 18 gerandomiseerde trials met in totaal 6153 patiënten werden onderzocht. Bij deze studies werd laparoscopie vergeleken met conventionele darmkankerchirurgie.

Uit dit onderzoek bleek dat de kans op cardiale complicaties ruim 4,5x lager was bij laparoscopische chirurgie ten opzichte van conventionele chirurgie voor dikke darmkanker. Dit effect werd echter niet gezien voor endeldarmkanker. Voor pulmonale complicaties was er geen duidelijk voordeel van laparoscopische chirurgie. Het totaal aantal patiënten dat één of meer complicaties ondervond na colorectale chirurgie was nauwelijks verschillend tussen conventionele en laparoscopische chirurgie.

Deel II van dit proefschrift gaat in op behandelkeuzes voor ouderen met darmkanker. In **Hoofdstuk 5** wordt een studie beschreven naar de keuzes voor behandeling van kanker laag in de endeldarm bij ouderen en jongeren. In een cohort van patiënten, nieuw gediagnosticeerd met endeldarmkanker, werd gekeken of de behandelkeuzes overeenkwamen met de landelijke richtlijn voor de behandeling van endeldarmkanker. De ouderen bleken significant minder vaak curatief te worden behandeld dan de jongere patiënten (83% versus 100%). In het geval van uitgezaaide endeldarmkanker kregen de ouderen minder vaak een (palliatieve) behandeling en deze behandeling was vaak minder belastend. Bij jongeren werd in 87% van de gevallen de richtlijn gevolgd, terwijl dit bij 62% van de ouderen het geval was. De meest genoemde reden voor het niet volgen van de richtlijn was bij ouderen de leeftijd. De uitkomsten van uitgebreide endeldarmchirurgie lieten zien dat ouderen evenveel complicaties ondervonden als jongeren maar als dit bij ouderen gebeurde, dan was de kans op overlijden in de eerste 6 maanden na de operatie bijna 3 maal hoger dan bij jongere patiënten.
Hoofdstuk 6 beschrijft een analyse naar het gebruik van laparoscopische chirurgie voor colorectaal carcinoom op basis van cijfers van de Nederlandse kankerregistratie tussen 2008 en 2011. Het gebruik van laparoscopie bleek sterk gestegen, hoewel ouderen minder vaak laparoscopisch geopereerd werden (in 40% van de gevallen versus bijna de helft van de jongere patiënten). De sterfte na 30 dagen, drie maanden en één jaar nam fors af, gelijk opgaand met de toename van het aantal laparoscopische resecties. De risicoreductie was het grootst voor patiënten ≥75 jaar. Bij ouderen werd dus minder vaak gekozen voor een laparoscopische behandeling terwijl zij het meest konden profiteren. Om de uitkomsten na chirurgie voor colorectale tumoren te verbeteren, zou zo frequent mogelijk gekozen moeten worden voor een laparoscopische resectie.
Hoofdstuk 7 behandelt de vraag of ouderen voldoende vertegenwoordigd zijn in gerandomiseerde studies over laparoscopische chirurgie voor darmkanker. Dergelijke studies kunnen bewijs van hoge kwaliteit geven over de optimale therapiekeuze voor ouderen, maar alleen als de deelnemers een goede afspiegeling vormen van

de gehele patiëntengroep. Daarom is het belangrijk om te weten of er voldoende oudere en/of kwetsbare patiënten deel kunnen nemen aan deze studies. Er werd een onderzoek gedaan naar 52 geregistreerde onderzoeksprotocollen voor dergelijke studies. Hierbij werd gevonden dat veruit de meeste studies geen beperkingen gaven wat betreft hart- of longaandoeningen om mee te kunnen doen aan het onderzoek. Meer dan de helft had geen restricties wat betreft ASA-score (een score die wat zegt over bijkomende ziektes van een patiënt en de ernst daarvan). Oudere patiënten werden in 44% van de protocollen geëxcludeerd op basis van leeftijd, bijkomende ziektes of orgaanfunctie. Als voor leeftijd een bovengrens werd aangehouden om te mogen participeren, bleek in de helft van de gevallen dat er geen beperkingen waren wat betreft orgaanfunctie. Hieruit blijkt dat chronologische leeftijd de reden voor exclusie was, in tegenstelling tot fysieke conditie. De gemiddelde leeftijd van patiënten in gepubliceerde studies was in 86% van de gevallen onder de 70 jaar.

In **Deel III** van dit proefschrift wordt de rol van de geriater (een ziekenhuisspecialist voor oudere mensen) in de multidisciplinaire zorg voor ouderen met kanker onderzocht. In toenemende mate worden geriaters betrokken bij de behandeling van ouderen met darmkanker, zoals ook blijkt uit de eis van de Nederlandse inspectie voor de gezondheidszorg om de geriater te raadplegen voorafgaand aan een darmoperatie bij oudere patiënten. De geriater kan een geriatrische evaluatie uitvoeren waarbij een breed scala aan mogelijke gezondheidsproblemen onderzocht wordt, zoals de voedingstoestand en functionaliteit van patiënten, medicatiegebruik en het sociale netwerk van patiënten.
Hoofdstuk 8 geeft een overzicht van de resultaten van een literatuurstudie over het effect van een geriatrische evaluatie op behandelbesluiten bij ouderen met kanker. Tien observationele studies werden geïncludeerd. Er werd aangetoond dat het initiële oncologische behandelplan bij één-derde van de patiënten werd aangepast nadat er een geriatrische evaluatie had plaatsgevonden. Deze verandering kon bestaan uit zowel minder intensieve behandeling als meer intensieve behandeling. Daarnaast werden bij 83% van de patiënten niet-oncologische interventies aanbevolen ter optimalisatie van de uitgangspositie van de patiënt voorafgaand aan de kankerbehandeling (bijvoorbeeld voedingsadviezen, medicatieaanpassingen, behandeling van psychische aandoeningen). Er is een duidelijk voordeel van de betrokkenheid van een geriater in de multidisciplinaire zorg en besluitvorming rondom de behandeling van oudere kankerpatiënten.
Hoofdstuk 9 presenteert de resultaten van een nationaal enquêteonderzoek, waarvoor 1726 kankerspecialisten (oncologen, chirurgen en radiotherapeuten) en geriaters zijn aangeschreven. Het responspercentage was 35%. De helft van

de respondenten gaf aan dat er momenteel een vorm van geriatrische evaluatie plaatsvindt voor ouderen met kanker; een derde hiervan is routinematig. Veel respondenten vonden dat de zorg verbeterd zou kunnen worden door een betere samenwerking tussen kankerspecialisten en geriaters en door de evaluaties meer routinematig te verrichten. Daarnaast zouden de uitkomsten van de geriatrische evaluaties beter benut moeten worden in de besluitvorming rondom oncologische behandelingen. Van de respondenten die geen evaluaties gebruiken, zegt 83% geïnteresseerd te zijn in de implementatie hiervan. Echter, 40% gaf aan dat dit momenteel geen prioriteit voor hen is en meer dan een derde weet niet goed in welke vorm dit geïmplementeerd zou moeten worden. Andere belangrijke obstakels waren de logistieke bezwaren en de tijdsinvestering die een dergelijke evaluatie met zich meebrengt.
Hoofdstuk 10 beschrijft een onderzoek naar de meerwaarde van een geriatrisch consult voor oudere kankerpatiënten. In deze studie werden 73 oudere kankerpatiënten verwezen naar de geriater om hun uitgangspositie te optimaliseren voorafgaand aan de oncologische behandeling of omdat er twijfel was over de optimale therapiekeuze. Het vóórkomen van geriatrische problematiek bij deze groep patiënten was hoog (93%) en bij ruim de helft van de patiënten waren een of meer niet-oncologische interventies nodig. Bij 49% van de patiënten werden nieuwe medische aandoeningen gediagnosticeerd; dit betrof vooral cognitieve stoornissen. Het grootste deel van de patiënten werd verwezen vanwege twijfel over de behandelkeuze en voor deze patiënten bleek een geriatrisch consult van toegevoegde waarde voor het maken van beslissingen rondom eventuele behandeling.

In **Hoofdstuk 11** worden de bevindingen van de onderzoeken in dit proefschrift bediscussieerd en wordt gekeken naar toekomstperspectieven in de zorg voor ouderen met darmkanker.

Part V

Appendices

List of authors and affiliations

D ten Bokkel Huinink, MD	Department of Clinical Oncology Diakonessenhuis, Utrecht
IHM Borel Rinkes, Professor, MD, PhD	Department of Surgical Oncology University Medical Center Utrecht, Utrecht
R Breumelhof, MD, PhD	Department of Gastroenterology Diakonessenhuis, Utrecht
JPJ Burgmans, MD	Department of Surgery Diakonessenhuis, Utrecht
A Doeksen, MD, PhD	Department of Surgery Diakonessenhuis, Utrecht
ME Hamaker, MD, PhD	Department of Geriatric Medicine Diakonessenhuis, Utrecht and Zeist
JM Jonker, MD	Department of Geriatric Medicine Rijnland Hospital, Leiderdorp
BS Langenhoff, MD, PhD	Department of Surgery Tweesteden and St. Elisabeth Hospital, Tilburg
J Maring, MD, PhD, FEBS	Department of Surgery Tweesteden and St. Elisabeth Hospital, Tilburg
BC van Munster, MD, PhD	Department of Internal Medicine Academic Medical Centre, Amsterdam Department of Geriatric Medicine Gelre Hospitals, Apeldoorn
JEA Portielje, MD, PhD	Department of Medical Oncology Haga Hospital, Den Haag

A Pronk, MD, PhD, FEBS	Department of Surgery Diakonessenhuis, Utrecht
T Rozema, MD	Department of Radiation Oncology Verbeeten Institute, Tilburg
CG Schaar, MD, PhD	Department of Internal Medicine Gelre Hospitals, Apeldoorn, The Netherlands
CM Smorenburg, MD, PhD	Department of Medical Oncology Netherlands Cancer Institute/ Antoni van Leeuwenhoek Hospital, Amsterdam
H Struikmans, Professor, MD, PhD	Department of Radiation Oncology Medical Centre Haaglanden Department of Clinical Oncology Leiden University Medical Centre, Leiden
NM Verweij, MD	Department of Surgery Diakonessenhuis, Utrecht
DDE Zimmerman, MD, PhD, FEBS	Department of Surgery Tweesteden and St. Elisabeth Hospital, Tilburg

Review and opposing committee

Prof. dr. J.T.A. Knape
Prof. dr. P.D. Siersema
Prof. dr. M. van Vulpen
Prof. dr. J.W.R. Nortier
Prof. dr. H.J.T. Rutten
Dr. M.R. Vriens
Dr. H.A.A.M. Maas

List of publications

Schiphorst AH, Jonker JM, Smorenburg CH, Struikmans H, Rozema T, Pronk A, Portielje JEA, Hamaker ME. Geriatrische oncologie in Nederland – een enquête naar de huidige zorg, knelpunten en mogelijkheden tot verbetering.
Ned Tijdschr Oncol 2014 dec;11(8):293-300

Schiphorst AH, Pronk A, Borel Rinkes IH, Hamaker ME. Representation of the elderly in trials on laparoscopic surgery for colorectal cancer.
Colorectal Dis. 2014 dec;16(12):976-985

Hamaker ME, Prins MC, **Schiphorst AH**, van Tuyl SA, Pronk A, van den Bosch F. Long-term changes in physical capacity after colorectal cancer treatment.
J Geriatr Oncol. 2014 Nov 6 (epub ehead of print)

Jonker JM, Smorenburg CH, **Schiphorst AH**, van Rixtel B, Portielje JE, Hamaker ME. Geriatric oncology in the Netherlands: a survey of medical oncology specialists and oncology nursing specialists. *Eur J Cancer Care (Engl)*. 2014 Nov;23(6):803-10

Hamaker ME, **Schiphorst AH**, Verweij NM, Pronk A. Improved survival for older patients undergoing surgery for colorectal cancer between 2008 and 2011.
Int J Colorectal Dis. 2014 Oct;29(10):1231-6.

Hamaker ME, Jonker JM, Maas HA, **Schiphorst AH**, Portielje JEA, Smorenburg CH. The geriatricians' perspectives on geriatric oncology in the Netherlands – results of a national survey. *European Geriatric Medicine*. 2014 Aug;5(4):265-269

Schiphorst AH, Langenhoff BS, Maring J, Pronk A, Zimmerman DD. Transanal minimally invasive surgery: Initial experience and short term functional results.
Dis Colon Rectum. 2014 Aug;57(8):927-32.

Schiphorst AH, Verweij NM, Pronk A, Hamaker ME. Age-related guideline adherence and outcome in low rectal cancer. *Dis Colon Rectum*. 2014 Aug;57(8):967-75.

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 Oncol*. 2014 Mar;53(3):289-96.

Schiphorst AH, Doeksen A, Hamaker ME, Zimmerman DD, Pronk A. Analysis of Short-Term Follow-up after Laparoscopic versus Conventional Total Mesorectal Excision for Low Rectal Cancer in a Large Teaching Hospital. *Int J Colorectal Dis*. 2014;29(1):117-25

Schiphorst AH, Pronk A . Een vrouw met een perianale huidafwijking. *Ned Tijdschr Geneeskd*. 2012;156(39):A4093.

Schiphorst AH, Twigt BA, Elias SG, van Dalen T. Randomized clinical trial of LigaSure versus conventional suture ligation in thyroid surgery. *Head Neck Oncol*. 2012 Jan 18;4:2.

Te Riele AS, **Schiphorst AH**, Pronk A, Verleisdonk EJ. Afgebroken K-draad tijdens schroefosteosynthese van collum femoris bij een jonge patiënt. *Ned Tijdschr Traumatol*. 2010 jun;18(3):78-80.

Schiphorst AH, Besselink MG, Boerma D, Timmer R, Wiezer MJ, van Erpecum KJ, Broeders IA, van Ramshorst B. Timing of cholecystectomy after endoscopic sphincterotomy for common bile duct stones. *Surg Endosc*. 2008 Sep;22(9):2046-50.

Schiphorst AH, Pronk A, Ruitenberg HM, Spliet WG, Sonneveld DJ. Abdominaal caverneus lymfangioom bij een volwassene: een zeldzame cysteuze afwijking. *Ned Tijdschr Heelk*. 2008 aug;17(6): 238-241.

Schiphorst AH, Besselink MG, Venneman NG, Go PM. Symptomatisch galsteenlijden: een operatie-indicatie. *Ned Tijdschr Geneeskd*. 2006 Nov;150(44):2405-9.

Photo attributions

Cover
Still reading by Pedro Ribeiro Simões
Taken on October 21, 2010. Évora, Portugal.
CC BY 2.0 https://www.flickr.com/photos/pedrosimoes7/5114099242

Chapter 1, p. 8, 9
Old Woman, Trinidad Cuba by Chris Goldberg
Taken on February 7, 2009. Trinidad, Cuba.
CC BY-NC 2.0 https://www.flickr.com/photos/chrisgold/3261756946

Chapter 2, p. 16, 17
Afternoon On The Bench by Nate Edwards
Taken on February 22, 2014. London, UK.
CC BY-NC 2.0 https://www.flickr.com/photos/nate2009/12935855864

Chapter 3, p. 36, 37
Exchanging some facts by Pedro Ribeiro Simões
Taken on October 21, 2010. Évora, Portugal.
CC BY 2.0 https://www.flickr.com/photos/pedrosimoes7/9650158117

Chapter 4, p. 52, 53
Delgada by Martin Garrido
Taken on June 21, 2011. Vietnam.
CC BY 2.0 https://www.flickr.com/photos/martingarri/6172174341

Chapter 5, p. 78, 79
Shared Picnic by «davemc»
Taken on September 3, 2014. London, UK.
CC BY-SA 2.0 https://www.flickr.com/photos/wavydavygravy/15181129632

Chapter 6, p. 100, 101
Untitled by Konrad Lembcke
Taken on October 13, 2013. Hanoi, Vietnam.
CC BY-ND 2.0 https://www.flickr.com/photos/konradlembcke/10227521364

Chapter 7, p. 114, 115
Afternoon Read by Leon Fishman
Taken on June 3, 2012. Brooklyn, NY, USA.
CC NY 2.0, https://www.flickr.com/photos/leonfishman/7353167476

Chapter 8, p. 138, 139
Untitled New York by Michael
Taken on June 15, 2011. Lenox Hill, New York City, NY, USA.
CC BY 2.0 https://www.flickr.com/photos/helloturkeytoe/5837032070

Chapter 9, p. 160, 161
Untitled by Darren Baldwin
Taken on July 19, 2013. Hampton Court, Brighton, UK.
CC BY 2.0 https://www.flickr.com/photos/drjbaldwin/9352963762

Chapter 10, p. 172, 173
Tai Chi Master by Robert S. Donovan
Taken on June 8, 2011. Shanghai, China.
CC BY 2.0 https://www.flickr.com/photos/booleansplit/5809910543

Chapter 11, p. 188, 189
Lunch by Jorge Gonzalez
Taken on February 13, 2011. Taipei, Taiwan.
CC BY-SA 2.0 https://www.flickr.com/photos/macabrephotographer/5441050959

Chapter 12, p. 198, 199
La Dépendance by Adrien Leguay
Taken on October 2, 2008. Paris, France.
CC BY-ND 2.0 https://www.flickr.com/photos/adriensteamboy/9804384474

Chapter 13, p. 204,205
Dimanche 05.10.08 is like a meeting by Maëlis
Taken on October 2, 2008. Ménilmontant, Paris, France.
CC BY-NC-SA 2.0 https://www.flickr.com/photos/somethingintheair/2915480847

Acknowledgements (Dankwoord)

Dit proefschrift is tot stand gekomen dankzij de steun en hulp van vele mensen. Een aantal van hen wil ik graag in het bijzonder bedanken.

Mijn promotor Prof. Dr. IHM Borel Rinkes, beste Inne, de allereerste keer dat ik je sprak hadden we het al over promoveren. Een heel aantal jaar en een opleiding verder is het dan toch gelukt! Je enthousiasme voor het onderzoek is aanstekelijk en super motiverend. Heel veel dank voor al je hulp en input bij dit proefschrift. Ik vind het een enorme eer dat jij mijn promotor bent en dat ik de eerste 2 jaar van mijn opleiding tot chirurg mocht volgen in het UMCU onder jouw supervisie.

Mijn co-promotor dr. A Pronk, beste Apollo, jij bent van groot belang geweest gedurende mijn opleiding tot chirurg en tijdens dit project. Je suggestie om 'eens met Marije te gaan praten' bleek een groot succes of om in je eigen woorden te spreken: een echte 'gebraden eend'. Heel erg bedankt voor je steun en vertrouwen en de afgelopen jaren. Ik ben heel blij dat ik nog even onder jouw supervisie mag werken in het Diakonessenhuis en zie er erg naar uit om nog veel van je te leren de komende tijd.

Mijn co-promotor dr. ME Hamaker, beste Marije, zonder jou was dit proefschrift er nooit gekomen. Je toewijding aan het onderzoek is ongekend bewonderenswaardig. Met je haarscherpe analyse, kritische blik en enorme inspiratie is dit proefschrift in 2 jaar tijd in sneltreinvaart tot stand gekomen. Ik heb ontzettend veel van je geleerd en denk met veel plezier terug aan de gezelligheid die het doen van samen onderzoek met zich heeft meegebracht. Ik hoop in de toekomst nog veel samen te kunnen werken en mooie dingen te bereiken.

Geachte leden van de promotiecommissie, Prof. dr. J.T.A. Knape, Prof. dr. P.D. Siersema, Prof. dr. M. van Vulpen, Prof. dr. J.W.R. Nortier, Prof. dr. H.J.T. Rutten, Dr. Maas en Dr. Vriens, graag wil ik u bedanken voor het beoordelen van het manuscript en het plaatsnemen in de commissie.

Maatschap Chirurgie, veel dank voor jullie steun zowel tijdens mijn opleiding als voor dit project. Ik ben jullie erg dankbaar voor de kansen die ik gekregen heb en de geweldige opleiding die ik onder jullie hoede heb mogen doen. Ik vind het een voorrecht dat ik nog wat langer deel mag uitmaken van jullie team.

In het bijzonder wil ik dr. van Dalen noemen. Beste Thijs, ondanks dat onze plannen voor het mammaonderzoek voortijdig strandden heb je me ongelofelijk gesteund met het mogelijk maken van dit onderzoekstraject. Ik ben je heel erg dankbaar voor alles wat je voor mij hebt betekend, zowel in het onderzoek als in mijn opleiding. Fantastisch om te zien dat, mede dankzij jouw inspanningen, het chirurgische onderzoek in het Diak zo'n ontwikkeling heeft gemaakt de laatste jaren en ik ben erg trots dat mijn kaft straks ook op de muur zal prijken.

Maatschap interne geneeskunde/MDL/klinische geriatrie, veel dank voor jullie bijdrage aan dit onderzoek. Wat boffen jullie met Marije in de maatschap! Bedankt voor de prettige samenwerking de afgelopen jaren.

Bestuur van de Aart Huisman Stichting, veel dank voor de steun aan mijn en volgend onderzoek naar de behandeling van kanker bij ouderen. Geweldig dat dit onderwerp zo een warm hart toe wordt gedragen.

Alle mede auteurs die het schrijven van de artikelen in dit proefschrift mede mogelijk gemaakt hebben wil ik graag bedanken voor hun werk en input.
In het bijzonder David Zimmerman. Zonder jou als initiator van het eerste stuk over de laparoscopische rectumchirurgie was dit hele project wellicht nooit ontstaan. Zelfs vanuit Tilburg heb je me enorm geholpen met het TAMIS artikel en ik ben je erg dankbaar voor je vertrouwen en hulp binnen de wetenschap en de coloproctologie. Geweldig hoe jij anderen kunt enthousiasmeren voor het vak waar je zelf zo veel passie voor hebt. Ik hoop dat we in de toekomst nog vaker kunnen samenwerken. Daarnaast Norbert Verweij: veel dank voor je inzet, hopelijk is het werk in dit proefschrift een mooie basis waar jij verder op kunt bouwen. Ik zie er erg naar uit om daaraan mee te werken.

Collega assistenten en PA's chirurgie in het Diakonessenhuis, wat heerlijk om met zoveel gezellige types te mogen samenwerken. In de afgelopen jaren heb ik een hoop collega's zien komen en gaan, maar de sfeer was altijd erg goed. Ondanks dat ik nu geen assistent meer ben, hoop ik nog in de app-groep te mogen blijven (hoewel daar niet altijd de meest diepgaande gesprekken in gevoerd worden..;)) en uitgenodigd te worden voor de vrijdagmiddag borrel.

Collega flex-plek onderzoekers Jan Paul, Kim, Martijn, Charlotte, Danique, Ine, Olivier en Frans-Jasper, veel dank voor de gezellige afwisseling en de klaaguurtjes. Veel inspiratie toegewenst voor jullie eigen projecten!

Dames van het secretariaat heelkunde in het Diakonessenhuis en UMCU, dank voor de logistieke ondersteuning.

Vele lieve vrienden in Utrecht en daarbuiten, veel dank voor jullie sociale ondersteuning. Vooral Carolien en Pieter, wat super jammer dat jullie er vandaag niet bij kunnen zijn maar wat een goed excuus. Hopelijk hebben jullie de reis van jullie leven! Lieve Caro, heel erg bedankt voor al je betrokkenheid en hulp met mijn onderzoek. Wat geweldig dat we onze kids samen kunnen laten opgroeien en grappig om te zien dat die kleintjes net zulke goede vriendjes zijn als wij. Ik hoop dat dat nog lang zo blijft, ook straks vanuit BoZ.

Familie Simonis, ondanks dat jullie van de 'koude kant' zijn, vormen jullie een warm nest. Ik moet nog steeds wat oefenen met het 'Simonissen', maar dat komt vanzelf goed. De Roellies: heel veel dank voor al jullie hulp bij ons thuis en de interesse in mijn proefschrift.

Mijn paranimfen Katrien en Wenche.
Katrien, mijn maatje binnen de vakgroep. Samen structureel te weinig slaap en te weinig tijd, echt de moekes. Wat gezellig dat we zoveel overeenkomsten hebben en super fijn dat jij mijn paranimf bent. Ik hoop dat we nog lang samen kunnen blijven werken en als je de vaten zat bent dan mag je altijd komen overlopen naar de GE...!
Wenche, wat ben ik gelukkig dat je vandaag als 'doorgewinterde' paranimf naast mij staat en dat we al 16 jaar veel lief en leed gedeeld hebben. Heerlijk dat we ook de afgelopen jaren zo een fijne tijd hebben gehad in Utrecht, met elkaar en elkaars gezinnen. Hopelijk gaan we in de toekomst ook als bekkenbodem collega's samenwerken!

Naomi en Matthijs, Berend en Karlijn.
Wat fijn om samen in zo een leuk gezin op te kunnen groeien! Broer en zus (plus aanhang) zoek je niet zelf uit maar wij hebben met elkaar geboft. Mooi om te zien dat we samen met ieders gezin ook zoveel lol hebben en dat er steeds meer neefjes en nichtjes komen. Ik hoop dat zij net zo fijn op kunnen groeien als wij gedaan hebben.
Naomi, ongelofelijk bedankt voor je vele werk aan dit geweldige boek. Wat is het mooi geworden!!

Lieve pap en mam, dit proefschrift is voor jullie. Jullie hebben altijd je best gedaan voor onze ontwikkeling en ons gestimuleerd om te bereiken wat we wilden. Ik kon altijd terugvallen op jullie onvoorwaardelijke steun en liefde en ben daar heel erg dankbaar voor. Lieve Pap, veel dank voor al je input bij mijn werk en onderzoek. Dit boekje is ook een beetje van jou. Lieve mam, bedankt voor je eeuwige geduld, begrip en hulp.

Mijn kleine aapje Flip en mopje Robin, wat een feest maken jullie van het leven! Heerlijk dat jullie er zijn om van elke dag te genieten. Dit boekje heeft niet veel mooie tekeningen maar die maar die gaan jullie er vast in zetten.

Lieve Rein, de combinatie van opleiding, onderzoek en kleine kinderen is niet altijd de beste maar het is bijna klaar...! Wat fijn dat je er altijd voor me bent, rust brengt tijdens stress momenten en goede adviezen geeft. Samen zijn we het beste team, ik hoop dat we heel gelukkig samen oud worden. Ik hou van je!

Curriculum Vitae Auctoris

Anandi Schiphorst was born on the 23rd of May 1980 in Heerlen, the Netherlands, and moved to 's-Hertogenbosch when she was four years old. After graduating from the Sint-Janslyceum (gymnasium) in 1998, she started her medical study at the University of Groningen. At the end of her studies, she spent six months in Boston at the Center for Engineering in Medicine (Shriners Burns Hospital and Massachusetts General Hospital) to perform research for her master thesis (supervised by dr. H Tolboom and prof. MJH Slooff). After obtaining her medical degree in 2005, she moved to Utrecht and started working as a resident not in training, first at the department of surgery at the Groene Hart Hospital in Gouda (dr. RT Ottow) and later at the surgical department of the Diakonessenhuis in Utrecht (dr. GJ Clevers). In 2007 she was accepted for the surgical residency program
at the University Medical Center Utrecht where she spent the first two years of her surgical training under supervision of prof. IHM Borel Rinkes. She returned to the Diakonessenhuis in 2009 to continue her residency (dr. GJ Clevers and later dr. Th van Dalen) and chose to sub-specialise in GI surgery from 2011, supervised by dr. A Pronk. During this time she started the research as described in this thesis, which accelerated in October 2012 when dr. Pronk introduced her to dr. Hamaker. At the end of 2013, she was given the opportunity to work full time during nine months on her PhD-thesis under the auspices of prof. IHM Borel Rinkes, dr. A Pronk and dr. ME Hamaker. Her surgical residency was completed in December 2014 and in February 2015 she will start with a fellowship for minimally invasive colorectal and pelvic floor surgery at the Diakonessenhuis in Utrecht. Anandi married Rein Simonis in 2010 and together they have a son Flip and a daughter Robin.