Surgical outcome of colorectal cancer screening

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ISBN: 978-90-816154-3-3
Lay-out: Textcetera, Den Haag
Cover: Jordy van den Nieuwendijk, www.jordy.studio

The printing of this thesis was financially supported by:
ChipSoft, Eclect Interiors, Erbe Nederland, LUMC.

The sponsors, who are gratefully acknowledged, had no involvement in any stage of the study design, data collection, data-analysis, interpretation of the study results or the decision to publish study results.

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PROEFSCHRIFT

Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties.
te verdedigen op donderdag 14 januari 2021
klokke 15.00 u

door

Nina Ciska Angel Vermeer

geboren te Tilburg in 1985

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CONTENTS

CHAPTER 1

Introduction

Population-based screening for colorectal cancer (CRC) was recommended by the Council of the European Union in 2003 and since then screening programmes have been initiated in various countries in Europe.[1] However, CRC screening has not been implemented homogenously across the EU. The existing screening programmes also differ in terms of target ages, screening intervals and primary tests. Finland and the UK were among the first countries to start screening nationwide. In the Netherlands, after years of debate, a population-based programme was introduced in 2014.
Consequently, the first patients with screen-detected (pre)malignant colorectal lesions in the Netherlands were referred to the departments of surgery in 2014. The death of a 75-year-old man following bowel resection for a screen-detected lesion that appeared to be benign raised a lot of questions and was a major motivation to start the research outlined in this thesis. Mass screening implies examination of asymptomatic individuals for the presence of a disease or its precursor lesion in order to treat and cure patients before symptoms occur. But when a diagnosed lesion never becomes symptomatic, there is a large risk of overtreatment. Furthermore, both the subsequent screening test (colonoscopy) and surgical treatment also expose patients to substantial risks. The fatal outcome of the above-mentioned patient shows that the colorectal screening programme can result in potential health loss. The aim of this thesis is to provide insights in possible consequences of a colorectal screening programme from a surgical perspective.

Cancer screening

According to the World Health Organization, screening is defined as the presumptive identification of unrecognised disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population. Screening programmes should be undertaken only when their effectiveness has been demonstrated, when resources are sufficient to cover nearly all of the target group, when facilities exist for follow-up of those with abnormal results to confirm diagnoses and ensure treatment, and when prevalence of the disease is high enough to justify the effort and costs of screening.[2] Ideally, the introduction of an optimal screening test should be followed by an increase in the rate of early disease followed by a decrease in regional disease while the overall detection rate remains constant. For breast and prostate cancer screening, this is not the case; overall cancers are higher, many patients are being treated, and the absolute incidence of aggressive or later-stage disease has not been significantly decreased.[3] But unlike screening for breast or prostate cancer, screening for colorectal cancer (CRC) promises not only to find cancer early, but also to prevent it from occurring.[4]

Colorectal cancer

Worldwide, CRC ranks third in incidence and fourth in mortality with an estimated 1.8 million new cases and 0.9 million deaths in 2018.[5] In the Netherlands, there were more than 5,000 deaths due to CRC in 2017.[6] It is the second leading cause of cancer-related death in developed countries, with a 4.3% estimated lifetime

risk of developing CRC and 1.8% lifetime chance of CRC-related death.[7,8] CRC is usually asymptomatic until late in its course when patients may develop lower gastrointestinal bleeding, obstruction and pain.[9] At the time of diagnosis of CRC, up to one quarter of patients with symptomatic disease have metastases (stage IV).[10] Five-year survival rates are approximately 90% for stage I, while this is around 10% when CRC is detected in stage IV.[11]

Natural history of CRC

Most cases of CRC develop from outgrowths of the colorectal mucosa (adenomas) through a series of genetic alterations, the so-called adenoma-carcinoma sequence. Adenomas can be pedunculated, sessile, or flat. A subgroup of adenomas, i.e. advanced adenomas, is thought to have increased malignant potential. Advanced adenomas (AA) are any adenoma with histology showing 25% or greater villous component, or high-grade dysplasia, or adenoma with size of 10mm or larger.[12] Because adenomas are removed upon detection, research on the natural course of adenomas is scarce. In developed countries, approximately 40-50% of the population develops one or more adenomas in a lifetime. As only 2-5% of the population actually develops CRC in their lifetime, most adenomas will never develop into CRC.[13] Limited evidence suggests that only 5% of adenomas transition into malignancy.[14] Recent study with data from four randomised control trials (RCTs) of sigmoidoscopy screening proposed a new metric for quantifying the relationship between adenoma removal and CRCs prevented: adenoma dwell time avoided. This meta-analysis showed that of 1,000 adenomas followed for 10 years (10,000 dwell years), about 20 CRCs would be predicted to develop, or about one CRC case for every 50 adenomas followed for 10 years.[15]

Another type of precursor lesion are serrated lesions. Serrated lesions can be divided into two subtypes: sessile serrated adenomas and traditional serrated adenomas. Estimates of the proportion of CRCs that originate from serrated lesions range from 5 to 30%, based on genetic alterations.[16] It is hypothesised that detection of serrated lesions by FIT is hampered because these lesions are less likely to bleed compared with adenomas, have a flat appearance, and are more often located in the proximal colon.[16]

CRC Screening

The aim of mass CRC screening is to increase cancer-specific survival by diagnosing disease in an earlier stage. On the one hand, this involves interference with cancer development by treating precursor lesions and, on the other, increasing curative options by treating early-stage cancers. There are various screening modalities available that aim to reduce CRC mortality, including screening colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool-based tests, and multitarget FIT-DNA.[9] Only two methods have been shown to reduce cancer-specific mortality in RCTs: faecal occult blood testing and flexible sigmoidoscopy. RCTs between 1993-1996 showed that screening for bowel cancer using guaiac-based faecal occult blood tests (gFOBTs) can reduce cancer specific mortality by

16% (RR 0.84, CI: 0.78-0.90), over 8 to 13 years.[17-22] RCTs published between 2010-2014 showed that flexible sigmoidoscopy reduces CRC mortality (22-31%) and incidence (18-23%) by detection of early-stage cancer and detection and removal of cancer precursor lesions.[23-26] The gFOBT, as used in all RCTs, detects haem in stool through peroxidase activity and produces a qualitative test result. The faecal immunochemical testing (FIT) is a newer faecal occult blood test and uses antibodies that form a complex in the presence of human globin.[27] Although FIT-based RCTs with long-term follow-up are lacking, a recent observational study demonstrated a 22% reduction in CRC mortality in areas where FIT screening programmes were implemented compared with areas without screening.[28]

A national CRC programme was implemented in the Netherlands in 2014 for all men and women aged 55–75 years, using biennial FIT. Individuals are invited to perform a faecal immunochemical test at home and return their sample by post. Individuals with a positive test outcome are referred for diagnostic colonoscopy during which detected colorectal cancer precursor lesions are removed.[16] Based on the findings at colonoscopy, individuals return to the screening programme after 10 years or are offered a surveillance colonoscopy after three or five years.[29] It is expected that FIT screening will lead to larger incidence and mortality reductions than gFOBT due to the higher sensitivity for CRC and advanced adenomas. A review including nine fair- or good-quality studies on FIT performance published in 2008 found that sensitivity varied between FITs, ranging between 61-91% for CRC and 27-67% for large adenomas.[30] The accuracy of FIT varies with the predefined cutoff level for referral to colonoscopy. The implementation of the national screening programme in the Netherlands has resulted in a higher burden of colonoscopy due to higher-than-expected false-positive rate and higher participation rate. Therefore, the cutoff level for referral to colonoscopy was increased to 47 µg Hb/g faeces in July 2014. A higher cutoff means fewer negative colonoscopies (false-positive FIT results), but more missed advanced neoplasia (false-negative FIT results).[31]

Surgical treatment

In the current multidisciplinary treatment approach, surgery has been the mainstay of colorectal cancer treatment throughout the years. Formal oncological bowel resection with a primary anastomosis is considered the main therapeutic approach for CRCs as well as for large benign lesions that cannot be removed endoscopically. With increasing attention for organ preservation, surgical and endoscopic alternatives have become more widely available. However, because a formal oncological resection is the only way to excise the draining lymph nodes, local excision is only a valuable treatment alternative in the absence of lymph node metastases (LNM).[32] As the risk of LNM varies from about 10% in submucosal invasive CRCs (pT1) to 50% in locally advanced tumours (pT4),[33] a formal bowel resection remains the preferred choice of treatment in most cases. However, the benefits of surgery should always be weighed carefully against its risks. One of the most feared complications in colorectal surgery is an anastomotic leak. In the Netherlands in 2017, anastomotic leakage rates were 4.5% and 7.6% following elective surgery for colon and rectal cancer respectively.

Overall 30-day mortality rates were 2.1% for colon cancer and 1.1% for rectal cancer.[34] However, multiple studies have shown that the 30-day mortality rate highly underestimates the risk of dying in the first year after surgery, indicating that there is a prolonged impact of surgery. Excess one-year mortality rates vary from 15 to 30%.[35] Also, a cross-sectional study of low anterior resection for rectal cancer in the Netherlands in 2011 showed that one third of anastomotic leakages was diagnosed beyond 30 days.[36] Furthermore, one should also consider the effect of surgery on functional outcomes. For example, sexual function, voiding, bladder function, and faecal continence are all at risk after rectal cancer treatment.[37,38] In conclusion, CRC surgery can be considered high-risk surgery.

OUTLINE

The central theme of this thesis is the surgical perspective on CRC screening participation. Despite promising results on the effectiveness of the screening programme as shown in previous RTCs, there are many important issues that remain unexposed and multiple-level consequences that need to be addressed. The studies in this thesis aim to increase the understanding of potential consequences of screening participation. This knowledge is essential in order to make an informed decision about CRC screening participation.

Part I: Screen-related morbidity

Since population screening targets a prevailingly asymptomatic population, it should only be conducted after a careful consideration of both harms and benefits. To evaluate potential harms, a systematic review of all literature on morbidity and mortality attributed to CRC screening using faecal occult blood test or colonoscopy was performed, as shown in **Chapter 2**. A positive faecal immunochemical test (FIT) result may lead to patient distress and concerns at the realisation that an abnormality has been developing without the individual's knowledge. To evaluate potential psychological distress and quality of life as a result of a positive FIT result and subsequent colonoscopy, a large prospective cohort study was conducted with six months follow-up (**Chapter 3**). Treatment and prognosis highly depend on the stage of the tumour at diagnosis. Therefore, at initial staging of patients with CRC, assessment of the chest and liver with computed tomography (CT) is indispensable and the detection of unexpected findings other than metastases unavoidable. A more complete understanding of the frequency and nature of the additional findings on staging CT in the screened population are critical in order to evaluate the benefits and costs of screening as a whole. **Chapter 4** discusses the prevalence, importance and outcomes of unsuspected potentially clinically relevant findings in a population with screen-detected colorectal lesions.

Part II: Surgery for early-stage lesions

The number of patients with early-stage disease will rise as a result of the implementation of CRC screening. Since accurate optical diagnosis of large colorectal lesions remains challenging, and LNM risk is not entirely predictable, the risk of overtreatment of non-malignant lesions is inevitable. A multicentre cohort study was performed to analyse the incentives for surgical referral of patients with benign colorectal lesions and to evaluate the endoscopic and pathological characteristics of these lesions as well as the short-term surgical outcomes (**Chapter 5**). In patients with CRC limited to the submucosa (pT1), the oncological benefits of excision of potentially positive lymph node metastasis and possible residual cancer tissue must be outweighed against the risks of additional surgery. In **Chapter 6**, the surgical outcomes for patients with pT1 CRC and patients with more advanced CRC are compared. The risk stratification provided in this study can be used in the shared decision-making process with the patient on whether or not additional surgery for pT1 CRC should be performed.

Part III: Evaluating treatment of patients with screen-detected colorectal cancer

Screen-detected CRCs have a more favourable stage distribution than those that are symptom-detected, but it remains unclear whether early diagnosis following screening results in better surgical outcomes. Characteristics and surgical outcomes of patients with screen-detected and non-screen-detected colorectal lesions are compared in an overview **Chapter 7** and **Chapter 8**. This overview of daily practice provides insights into the difficulties that the clinician may face when choosing the optimal treatment for CRC, especially in patients with early-stage lesions.

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PART I
SCREEN-RELATED MORBIDITY

CHAPTER 2

Colorectal cancer screening: systematic review of screen-related morbidity and mortality

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Cancer Treatment Reviews 2017 Mar;54:87-98

ABSTRACT

Background: Implementation of mass colorectal cancer screening, using faecal occult blood test or colonoscopy, is recommended by the European Union in order to increase cancer-specific survival by diagnosing disease in an earlier stage. Post-colonoscopy complications have been addressed by previous systematic reviews, but morbidity of colorectal cancer screening on multiple levels has never been evaluated before.

Aim: To evaluate potential harm as a result of mass colorectal cancer screening in terms of complications after colonoscopy, morbidity and mortality following surgery, psychological distress and inappropriate use of the screening test.

Methods: A systematic review of all literature on morbidity and mortality attributed to colorectal cancer screening, using faecal occult blood test or colonoscopy, from each databases' inception to August 2016 was performed. A meta-analysis was conducted to examine the pooled incidence of major complications of colonoscopy (major bleedings and perforations).

Results: Sixty studies were included. Five out of seven included prospective studies on psychological morbidity reported an association between participation in a colorectal screening program and psychological distress. Serious morbidity from colonoscopy in asymptomatic patients included major bleedings (0.8/1000 procedures, 95% CI 0.18 – 1.63) and perforations (0.07/1000 procedures, 95% CI 0.006 – 0.17).

Conclusions: Participation in a colorectal cancer screening program is associated with psychological distress and can cause serious adverse events. Nevertheless, the short duration of psychological impact as well as the low colonoscopy complication rate seems reassuring. Because of limited literature on harms other than perforation and bleeding, future research on this topic is greatly needed to contribute to future screening recommendations.

BACKGROUND

Colorectal cancer (CRC) is one of the leading causes of morbidity and mortality in the Western world. European average 5-year relative survival for patients diagnosed with colon and rectum cancer is 57% and 56% respectively.[1] This 5-year survival rate for patients with colon or rectal cancer varies from respectively 92% and 87% for stage I to respectively 11% and 12% for patients with metastatic, or stage IV cancers.[2] The higher survival rate in earlier stages of colorectal cancer has led to the assumption that treatment of earlier detected colorectal cancer entails improved patient overall prognosis.

In 2003, implementation of organised screening programmes was recommended by the European Union.[3] The aim of mass CRC screening is to increase cancer-specific survival by diagnosing disease in an earlier stage (pre-cancer stage or earlier cancer stage). By the end of 2007, population-based programmes were rolled out nationwide in five countries (Finland, France, Italy, Poland and the United Kingdom). Several EU Member States were in the process of implementing a national population screening programme.[4] A national colorectal screening program was implemented in the Netherlands in 2014 for all men and women aged 55 to 75 years, using the biennial faecal immunochemical testing (FIT). For logistic reasons, there will not be complete coverage of the target population until 2019.

Population screening targets a prevailingly asymptomatic, previously healthy population and should therefore only be conducted after a careful consideration of both harms and benefits. Harmful effects of CRC screening include complications of colonoscopy, possible over-diagnosis, psychosocial distress and complications due to treatment. Information on potential consequences of screening is essential to make a decision about participating in a screening program.[5]

The purpose of this review is to evaluate potential harm as a result of mass screening for colorectal cancer in terms of complications after colonoscopy, morbidity and mortality after surgery, psychological distress and inappropriate use of the screening test.

METHODS

Literature search

Relevant studies published from each databases' inception to August 2016 were identified by searching Pubmed, Medline, Embase, Web of Science and PychINFO (EBSCO). The following search terms were used: colorectal neoplasm, mass screening, mortality, morbidity and Faecal Occult Blood test (FOBT) or FIT. Both free text search and MeSH search for keywords were employed. The search strategy was designed and conducted by a medical librarian in collaboration with the study investigators. The database searches were supplemented with additional references of all retrieved relevant studies. The search was restricted to publications in English language.

Study selection

All types of studies, both retrospective and prospective, describing mass screening for colorectal cancer in adults were considered for inclusion. Studies regarding colorectal cancer screening using either a faecal occult blood test or a colonoscopy were included. All selected studies reporting complications from colonoscopy were included, where the colonoscopy was performed either as a screening modality or as work-up of FOBT positives. Studies were excluded when (i) no full text was available, (ii) a prediction model was used to simulate a cohort, (iii) adverse events after not screen-related colonoscopy were described, (iv) another screening modality than FOBT or colonoscopy was used, (v) or when studies reported outcome of patient with increased risks (i.e. positive family history of colorectal cancer or polyps, surveillance of prior colorectal cancer or polyps and symptomatic patients). Trials using sigmoidoscopy as primary screening method were excluded because the majority of CRC screening examinations performed in the European Union use the FOBT.[4] When multiple studies reported the same cohort, we included data from the most recent report. Title and abstracts of studies identified in the search were independently assessed by two investigators (NV and EB), based on pre-specified inclusion and exclusion criteria. Discrepancies were resolved by consensus.

Data extraction

Our primary outcome measure was morbidity and mortality attributed to the screening test (FOBT or colonoscopy). Morbidity was defined as all early complications after colonoscopy. Major bleeding was defined as bleeding after colonoscopy requiring hospitalization, emergency room visit, need for repeat colonoscopy, transfusion of packed red blood cells or surgery. Bleeding that could be controlled by various endoscopic treatment modalities was not included. Mortality was defined as death within 30 days after intervention. Secondary outcome measures were (i) morbidity and mortality following the subsequent surgery, (ii) screen-related psychological distress and (iii) inappropriate use of the screening test. A proportion of patients will never undergo surgery with its concomitant side effects if they do not participate in a screening programme, since not every screen-detected lesion might become symptomatic or life threatening. Morbidity and mortality following the subsequent surgery are therefore considered related to the screening and as such included in this review. Psychological distress was defined as a state that reflects a person's sadness, frustration and anxiety, manifesting in both mild and severe forms.[6] A screening test is used inappropriately when screening patients with limited life expectancy or providing the test to patients who do not meet the recommended age limits. Furthermore, screening patients with colorectal cancer symptoms is inappropriate, since a false negative result can reassure these patients and may delay or decrease the likelihood of undergoing a colonoscopy. This may lead to under-treatment. Finally, inappropriate use can also be defined by a screening test repeated too soon, so the number of tests within the recommended time frame is too high. In other words; the participant is "not yet due" for screening. Other extracted data included study design, country of origin, number of participants, percentage of participants

with a positive test result, percentage of participants that underwent colonoscopy, age, type of screening test and study period.

Statistical analysis

Summary, descriptive tables of the included studies were constructed. Studies that reported a proportion of patients that experienced a major bleeding or perforation were pooled in two separate meta-analyses. The number of events and total number of included patients were extracted from the full text articles; the number of events per 1000 and corresponding 95% Confidence Interval (95%CI) were calculated and pooled with the METAPROP command in STATA/SE version 12.0 (Stata Corp, College Station, TX). Pooled risk per 1000 and 95%CI was calculated using a random effect model. I^2 was calculated as measure of heterogeneity, which denotes the percentage of total variation across studies that is due to heterogeneity rather than chance.

RESULTS

Description of studies

A total of 3.816 titles and abstracts were screened of which 136 full-text articles were assessed for eligibility (**Figure 1**). Of these, combined with additional articles identified via references, 60 studies were included in this review (**Table 1**). The most common reason for exclusion was relevance (n=34). Other reasons for exclusion were the non-availability of full text, not describing screen-related outcomes and the main focus on interval carcinoma. All reasons for exclusion are shown in **Figure 1**.

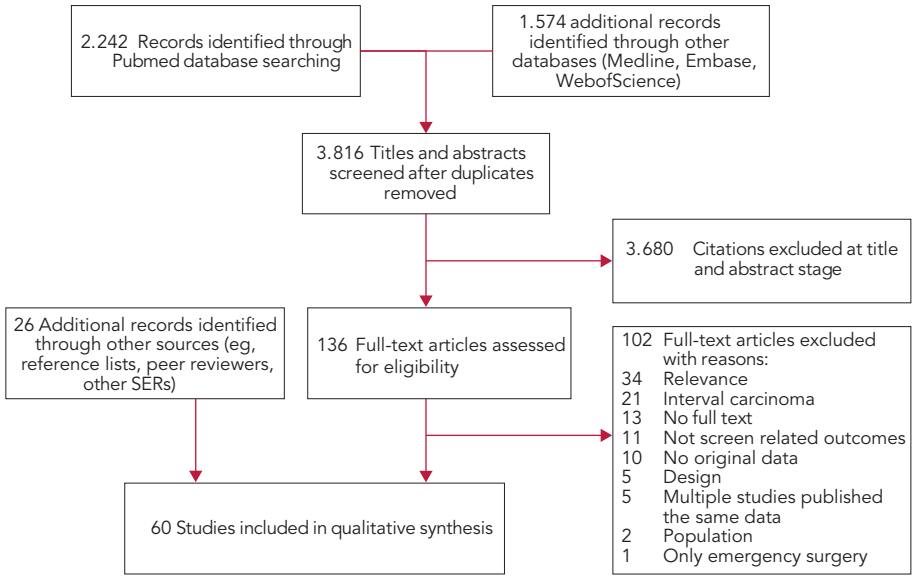

Figure 1. Flow diagram

Table 1. Summary Table of included studies

Author	Year	Study design	Country	No. of participants FOBT (no. of participants with positive FOBT result)
Mant et al.	1990	Observational, PC	UK	931 (67)
Bech et al.	1991	RCT	Denmark	18.779 (374)
Kronborg et al.	1992	RCT	Denmark	57.028 (516)
Mandel et al.	1993	RCT	USA	46.551 (NS)
Kewenter et al.	1996	RCT	Sweden	NS
Lindholm et al.	1997	Observational, PC	Sweden	3548*
Robinson et al.	1999	RCT	UK	75.253 (960)
Imperiale et al.	2000	Observational, RC cross-sectional	USA	NA
Lieberman et al.	2000	Intervention, PC	USA	NA
Nelson et al.	2002	Intervention, PC	USA	NA
Parker et al.	2002	Observational, PC	UK	1541*
Gondal et al.	2003	Intervention, PC	Norway	6266 (302)
Sung et al.	2003	Intervention, PC	China	505 (101)
UK CCSPG	2004	Intervention, PC – pilot	Scotland	271.646 (5.050)
Cotterill et al.	2005	Intervention, PC	Canada	NA
Fisher et al.	2005	Observational, RC	USA	500 (71)
Soon et al.	2005	Observational, RC	USA	NA
Lee et al.	2006	Intervention, PC	Taiwan	NA
MACS Group	2006	RCT	Australia	125 (4)
Strul et al.	2006	Observational, part RC and part PC	Israel	NA
Kim et al.	2007	Observational, RC	USA	NA
Marbet et al.	2008	Observational, PC	Switzerland	NA
Orbell et al.	2008	Observational, PC	UK	697*
Bokemeyer et al.	2009	Observational, PC	Germany	NA
Crispin et al.	2009	Observational, PC	Germany	NA
Fu et al.	2009	Intervention, PC	Singapore	540 (57)
Steele et al.	2009	Intervention, PC	Scotland	339.930 (8.631)
Brasso et al.	2010	Observational, PC	Denmark	507 (253)
Ellul et al.	2010	Observational, case-control	UK	55.931 (1.191)
Xirasagar et al.	2010	Observational, RC	USA	NA
Carlson et al.	2011	Observational, PC	USA	2410 (212)
Kistler et al.	2011	Observational, PC	USA	NS (212)
Garcia et al.	2012	Observational, RC	Spain	63.332 (1.074)
Gupta et al.	2012	Intervention, PC	UK	42.523 (1.488)
Kapidzic et al.	2012	Observational, RC	Netherlands	1821 (NS)
Pox et al.	2012	Observational, PC cross-sectional	Germany	NA
Quintero et al.	2012	RCT	Spain	10.611 (767)
Rutter et al.	2012	Observational, RC	USA	NA
Stoop et al.	2012	RCT	Netherlands	NA
Suissa et al.	2012	Observational, PC	Israel	NA
Zalis et al.	2012	Intervention, PC	USA	NA
Adler et al.	2013	Observational, PC	Germany	NA
Binefa et al.	2013	Observational, RC	Spain	193.093 (1.876)
Chiu et al.	2013	Observational, RC	Taiwan	NS
Denis et al.	2013	Observational, RC, population-based	France	NS
Denters et al.	2013	Observational, PC	Netherlands	NS
Denters et al.	2013	Observational, PC	Netherlands	3828 (NS)
McDonald et al.	2013	Observational, RC	UK	189.319 (NS)
Ng et al.	2013	Intervention, PC	Japan	NS
Stock et al.	2013	Observational, RC	Germany	NA
Bobridge et al.	2014	Observational, PC	Australia	301 (165)
Laing et al.	2014	Observational, PC	USA	NS (45)
Saini et al.	2014	Observational, RC	USA	NA
Zafar et al.	2014	Observational, RC	USA	NA
Castells et al.	2015	RCT	Spain	NS (767)
Miles et al.	2015	Observational, RC	Scotland	296*
Powell et al.	2015	Observational, cross-sectional	USA	901.292 (NS)
Kirkøen et al.	2016	RCT	Norway	3212 (NS)
Le Roy et al.	2016	Observational, RC, population-based	France	NS
Tepes et al.	2016	Intervention, PC	Slovenia	303.343 (15.310)

PC = prospective cohort, RC = retrospective cohort, * completed questionnaire

	No. of participants colonoscopy: primary screening or follow-up after +FOBT	Primary Screening test	Age Range (years)	Years of inclusion
	NS	FOBT	40-74	NS
	NS	FOBT	45-74	1985 – 1989
	NS	FOBT	45-74	1985 – 1990
	12.246	FOBT	50-80	1977-1982, 13yrs follow up
	190	FOBT	60-64	NS, first cohort follow up 7yrs, second 3yrs
	NS	FOBT	60-64	NS
	1.474	FOBT	45-74	1981 – 1991, follow up till 1995
	1.994	Colonoscopy	≥50	1995 – 1998
	3.121	Colonoscopy	50-75, mean 62.9	Feb 1994 – Jan 1997
	3.196	Colonoscopy	50-75	1994 – 1997
	NS	FOBT	50-75	1981 – 1991
	2.821	FOBT, FS	50-64	NS
	476	Colonoscopy	≥50	NS
	4.116	FOBT	50-69	2000 – 2003
	152	Colonoscopy	50-75	NS
	NS	FOBT	≥50	march 2004
	4.859	Colonoscopy	≥ 40	2002 – 2004
	1.000	Colonoscopy	19-84, mean 51	2004
	81	FOBT, FS, colonoscopy	50-54 or 65-69	2004 – 2004
	1.177	Colonoscopy	40-80	1996 – 2003
	3.163	Colonoscopy	Mean 58.1	17 months period
	1.912	Colonoscopy	50-80	2000 – 2001, follow up till 2006
	NS	FOBT	50-70	NS
	269.114	Colonoscopy	≥55	2003 – 2006
	55.993	Colonoscopy	≥55, median 64	2006
	52	FOBT	40-85	augustus-08
	7.314	FOBT	50-69	2000 – 2007
	NA	FOBT	50-75	NS
	1.039	FOBT	60-69	2004 – 2006
	10.959	Colonoscopy	Mean 58.3	2002 – 2007
	90	FOBT	>70	2001, follow up 5yrs
	118	FOBT	≥70	2001 – 2008
	989	FOBT	50-69	2000 – 2010
	1.057	FOBT	60-69	2007 – 2010
	NS	FOBT	50-74	2006 – 2010
	2.821.392	Colonoscopy	≥55	2003 – 2008
	5.722	FOBT, colonoscopy	50-69	NS
	43.456	FOBT, FS, colonoscopy	40-85	1994 – 2009
	1.360	Colonoscopy, CT colonography	50-75	2009 – 2010
	839	Colonoscopy	NS	2003 – 2006
	606	CT colonography	50-85	2005 – 2010
	12.856	FOBT	NS	2006 – 2008
	1.691	FOBT	50-69	2006 – 2013
	18.296	Colonoscopy	>50	2005 – 2010
	10.277	FOBT	50-74	2003 – 2010
	373	FOBT	50-75	NS
	373	FOBT	50-74	2008
	NS	FOBT	50-69	2003
	3.967	FOBT	50-75	2008 – 2012
	8.658	Colonoscopy	≥55	2000 – 2008
	NS	FOBT	50-76	NS
	NS	FOBT	50-74	2011
	399.067	FOBT, FS, colonoscopy	50-75	2010 – 2012
	54.039	Colonoscopy	≥66	2007 – 2008
	5.722	FOBT, colonoscopy	50-69	2009 – 2011
	NS	FOBT	50-69	2000 – 2007, questionnaire 2012
	134.335	Colonoscopy	>50	2009 – 2011
	NS	FOBT	50-74	2013 – 2014
	4.251	FOBT	50-74	2003 – 2012
	13.919	FOBT	50-69	2009 – 2011

Table 2. Summary Table of serious complications from screening colonoscopy

Author	Year	Primary Screening test	Colonoscopies N	Total bleedings N (%)	
Bech et al.	1991	FOBT	374	NS	
Mandel et al.	1993	FOBT	12.246	11 (0.09%)	
Kewenter et al.	1996	FOBT	190	NS	
Robinson et al.	1999	FOBT	1.474	NS	
Imperiale et al.	2000	Colonoscopy	1.994	3 (0.15%)	
Lieberman et al.	2000	Colonoscopy	3.121	6 (0.6%)	
Nelson et al.	2002	Colonoscopy	3.196	13 (0.41%)	
Gondal et al.	2003	FOBT	2.821	4 (0.14%)	
Sung et al.	2003	FOBT	476	1 (0.2%)	
UK CCSPG	2004	FOBT	3.700	NS	
Cotterill et al.	2005	Colonoscopy	152	NS	
Soon et al.	2005	Colonoscopy	4.859	1 (0.02%)	
MACS Group	2006	FOBT, colonoscopy	81	NS	
Lee et al.	2006	Colonoscopy	1.000	NS	
Strul et al.	2006	Colonoscopy	1.177	NS	
Kim et al.	2007	Colonoscopy	3.163	NS	
Marbet et al.	2008	Colonoscopy	1.912	3 (0.15%)	
Bokemeyer et al.	2009	Colonoscopy	269.144	442 (0.16%)	
Crispin et al.	2009	Colonoscopy	55.993	134 (0.24%)	
Ellul et al.	2010	FOBT	1.039	3 (0.29%)	
Xirasagar et al.	2010	Colonoscopy	10.959	NS	
Kistler et al.	2011	FOBT	118	3 (2.54%)	
Garcia et al.	2012	FOBT	989	NS	
Gupta et al.	2012	FOBT	1.057	8 (0.76%)	
Pox et al.	2012	Colonoscopy	1.981.011	2996 (0.15%)	
Quintero et al.	2012	FOBT, colonoscopy	5.722	20 (0.35%)	
Rutter et al.	2012	Colonoscopy	43.456	122 (0.28%)	
Stoop et al.	2012	Colonoscopy	1.360	5 (0.37%)	
Suissa et al.	2012	Colonoscopy	839	NS	
Zalis et al.	2012	Colonoscopy	606	NS	
Binefa et al.	2013	FOBT	1.806	NS	
Chiu et al.	2013	FOBT	18.296	NS	
Denis et al.	2013	FOBT	10.277	97 (0.94%)	
Denters et al.	2013	FOBT	273	1 (0.4%)	
Ng et al.	2013	Colonoscopy	3.967	NS	
Stock et al.	2013	Colonoscopy	8.658	4 (0.05%)	
Zafar et al.	2014	Colonoscopy	54.039	NS	
Castells et al.	2015	FOBT	5.722	1 (0.02%)	
Tepes et al.	2016	FOBT	13.919	NS	

	Major bleedings N (%)	Consequences Major bleedings (n)	Perforations N (%)	Consequences Perforations (n)
	0	NA	0	NA
	3 (0.02%)	Surgery (3)	4 (0.03%)	Surgery (4)
	1 (0.5%)	Readmission and laparotomy (resection)	5	Local suture with laparotomy (2)
	1 (0.07%)	NS	5 (0.34%)	Surgery (5)
	NS	Emergency room (3)	1 (0.05%)	Managed medically
	NS	NS	0	NA
	7 (0.22%)	Transfusion, hospitalization or surgery (7)	0	NA
	NS	Admitted to hospital, repeat colonoscopy (1)	6 (0.21%)	Hemicolectomy (1), local suture (5)
	1 (0.2%)	Blood transfusion (1)	0	NA
	NS	NA	2 (0.05%)	NS
	0	NA	0	NA
	NS	NS	1 (0.02%)	NS
	0	NA	0	NA
	0	NA	0	NA
	0	NA	0	NA
	NS	NS	7 (0.02%)	Ssurgery (4)
	NS	Hospitalization	1 (0.05%)	No surgery
	19 (0.007%)	Surgery (19)	55 (0.02%)	NS
	NS	NS	22 (0.04%)	NS
	NS	NS	0	NS
	1 (0.01%)	NS	2 (0.02%)	NS
	NS	NS	NS	NS
	6 (0.61%)	NS	3 (0.3%)	NS
	1 (0.09%)	Myocardial infarction, blood transfusion (1)	1 (0.09%)	Treated with clip (1)
	573 (0.03%)	NS	439 (0.02%)	NS
	NS	NS	1 (0.02%)	NS
	NS	NS	21 (0.05%)	NS
	NS	NS	0	NA
	0	NA	0	NA
	0	NA	0	NA
	15 (0.8%)	NS	3 (0.18%)	NS
	NS	NS	0	NA
	64 (0.62%)	Blood transfusion (13), endoscopy (29), ICU (4), surgery (2)	10 (0.10%)	Surgery (10)
	1 (0.4%)	Readmission (1)	0	NA
	0	NA	0	NA
	NS	NS	7 (0.08%)	NS
	371 (0.69%)	NS	46 (0.09%)	NS
	20 (0.35%)	NS	NS	NS
	4 (0.03%)	Endoclips (3), surgery (1)	7 (0.05%)	Surgery (7)

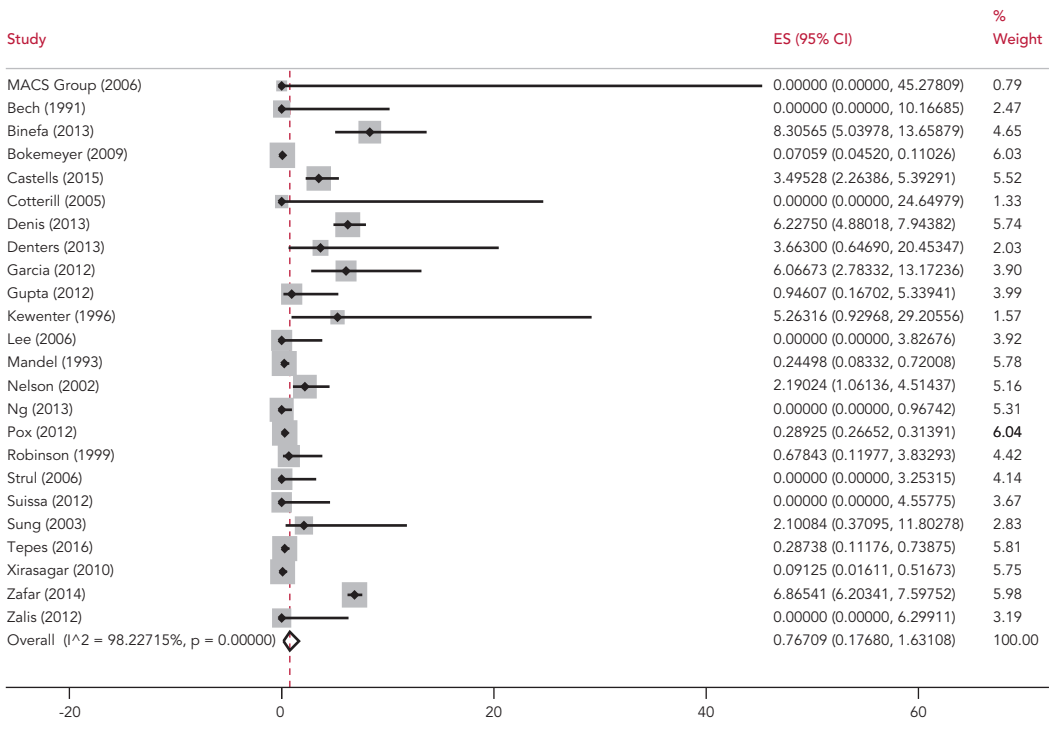

Figure 2. (a) Forest plot major bleedings

Table 1 describes the characteristics of the included studies. The review consists of studies that were conducted in 19 different countries, including Australia (2), Canada (1), China (1), Denmark (3), France (2), Germany (5), Israel (2), Japan (1), Netherlands (4), Norway (2), Scotland (3), Singapore (1), Slovenia (1), Spain (4), Sweden (2), Switzerland (1), Taiwan (2), UK (7) and the USA (16). Sample size of studies varied from 52 to 2.821.392 patients. The majority of the included studies in this review were cohort studies. FOBT was used in 55% of the studies, the remainder used colonoscopies as a primary screening test. Age range of the study populations varied from 40 to 85 years.

Complications after colonoscopy

Thirty-nine studies[7-45] provided information on major morbidity after colonoscopy (Table 2). In these, 2.531.186 colonoscopies were performed for average risk screening, the pooled overall risk of *major bleeding* after colonoscopy was 0.8/1000 (95% CI 0.18 – 1.63) Figure 2a. Of 24 included studies on major bleeding after colonoscopy, 8 studies reported a major bleeding rate of 0%. Half of the included studies provided information on the clinical consequences of the haemorrhage (i.e. surgery, blood transfusion, and readmission). The overall risk of *perforation* after colonoscopy was 0.07/1000 (95% CI 0.006 – 0.17) Figure 2b. Of 37 included studies on perforation after colonoscopy, 15 studies reported a perforation rate of

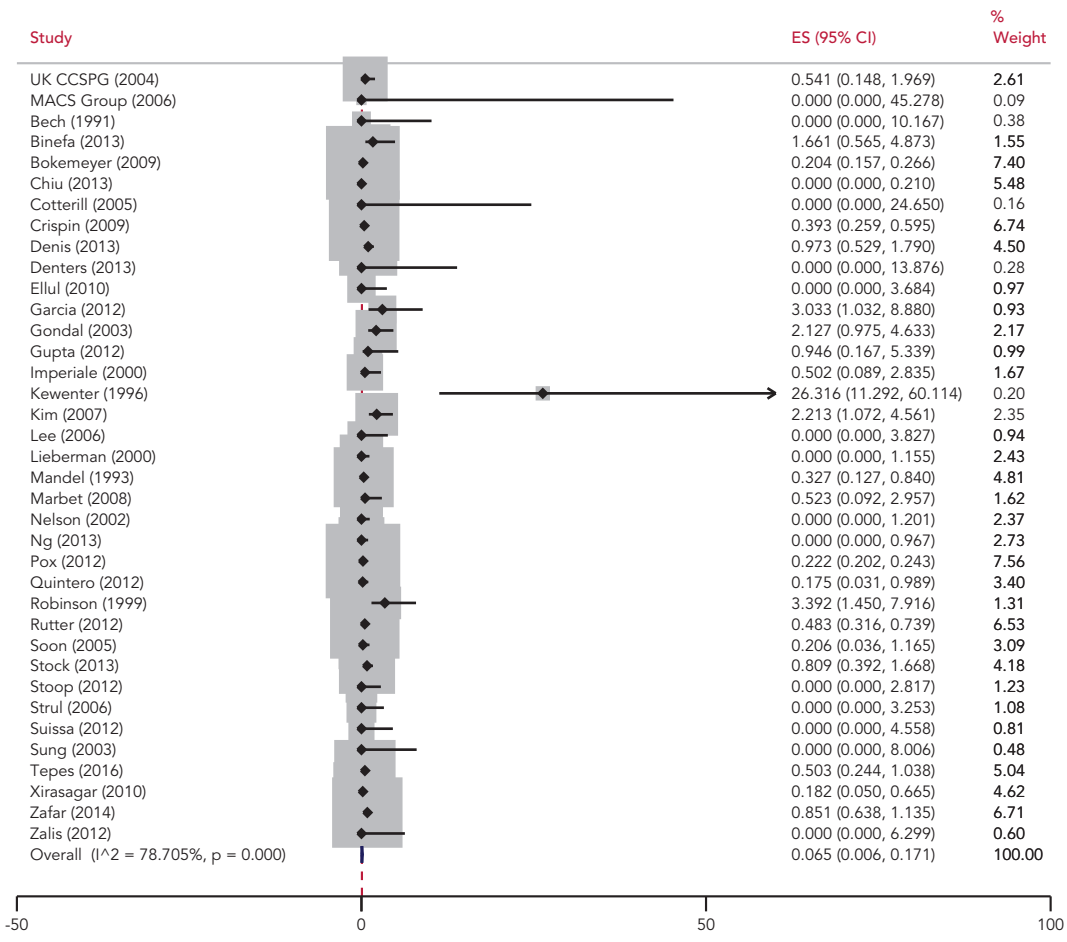

Figure 2. (b) Forest plot perforations

0%. Ten studies reported whether surgical treatment was required, twelve studies reported whether perforation was related to polypectomy. Other complications from colonoscopy were reported in eighteen studies[7,12,16,20,25-27,30,32-34,37-39,43,44,46,47], including cardiovascular events, postpolypectomy syndrome, vasovagal reactions or abdominal pain or discomfort. None of the included studies reported any mortality after colonoscopy.

Morbidity and mortality following surgery

Eight studies reported information on morbidity and mortality after surgical treatment of a mass screen-detected colorectal tumour (Table 3). Because of the clinical heterogeneity of studies, these data were not quantitatively pooled. Overall morbidity rates varied from 14-24%, major complications varied from 0-14%. Reported mortality rates were low, ranging from 0 to 3.3%. The largest study

(n=68.306)[23] reported a re-intervention rate after the primary surgical intervention of 5% (5/101) and no 30 day mortality.

Table 3. Characteristics of studies on morbidity and mortality after surgery following colorectal cancer screening

Author	Year	Surgical procedures N	Total complications N (%)	Major complications N (%)	Death N (%)	Type of complication (N)	Follow up time
Bech et al.*	1991	17	4 (24%)	0	2 (11.7%)	NS	NS
Kronborg et al.	1992	243	NS	NS	8 (3.3%)	NA	5 years
Kewenter et al.	1996	101	14 (14%)	NS	0	additional laparotomy (5) cardiopulmonary complication (1) wound infection (2) complication from colonic pouch (1) anastomotic leakage (4) myocardial infarction (1)	30 days
Robinson et al.	1999	NS	NS	5	0	myocardial infarction anastomotic leakage pulmonary embolism carcinomatosis	30 days
Gondal et al.	2003	48	NS	2 (4%)	0	pulmonary embolism (1) anastomotic leakage (1)	30 days
Fu et al.	2009	5	0	0	0	NA	NS
Gupta et al.	2012	NS	NS	0	1	NA	NS
Le Roy et al.*	2016	175	42 (24%)	24 (14%)	1 (0.6%)	urinary infection (2) thromboembolic event (2) wound healing disorder (6) abdominal abcess (3) colonic stenosis (1) bleeding (1) anastomotic fistula (2) pneumoperitoneum (1) duodenal ulcer (1) occlusive syndrome (1) peritonitis (2) septic shock (2)	

* only adenomas

Screen-related psychological distress

Eleven studies[48-58] evaluated psychological distress or morbidity after receiving an invitation for the mass colorectal cancer screening programme (**Table 4**). Seven of these studies were prospective, and four were retrospective. Different types of questionnaires were administered in different moments of time during follow-up (**Table 4**). The Spielberger State Trait Anxiety Inventory (STAI) and Quality of Life – Short Form Health Survey (SF) were used most frequently.[58] Because of diversity of

study design and type of questionnaire these data were not quantitatively pooled and analyses are largely descriptive.

Response rates varied from 37% to 85%. Five out of seven prospective studies[48,49,52,53,58] reported an adverse effect on psychological well-being in participants who received a positive test result. Largest effects were observed before the screenings test, in anticipation of and shortly after being informed about a positive test result. This effect declined post-colonoscopy[49], disappeared after 1 month[57], 4 months[52] or one year.[48] One study reported no clinically relevant psychological effect of participation in the mass CRC screening, even a decreased anxiety and improvement in some dimensions of health related quality of life (HRQOL) as a consequence of receiving a negative result.[51] The largest prospective study (n = 3.828)[49] reported that patients experienced some psychological distress up to six weeks after the colonoscopy. In two studies the same pattern of declining scores during follow up were observed when comparing participants tested positive with positive findings at work-up (true positives) and participants tested positive with negative findings at work-up (false positives).[48,49] Denters and colleagues used the Psychological Consequences Questionnaire (PCQ) to measure the psychological effects of screening. Surprisingly, no significant differences were observed between true positives and false positives in mean scores, six weeks after colonoscopy.[49]

Inappropriate use of the screening test

Seven studies provided information on the inappropriate use of screening for colorectal cancer (**Table 5**). Because of the clinical heterogeneity of studies, these data were not quantitatively pooled. The majority of studies considered mass screening as potentially inappropriate for patients with limited life expectancy.[25,34,59-62] Other categories reported were: higher than average risk for colorectal cancer[60,61,63], screening of patients outside the pilot group[60,63] or patients not due for screening.[60,61] Inappropriate use of screening is reported up to 35%.[60] The largest cohort[61] (n=901.292) reported a 26.1% rate of patients categorized as potentially inappropriate. Participants being not (yet) due for screening was the category found most frequently. The definition of "not due" used in this study was 9 months for FOBT, 9 years for colonoscopy and 4 years for sigmoidoscopy/barium enema. Time since prior colonoscopy was the predominant reason cases were not due.

Table 4. Characteristics of studies on psychological distress following colorectal cancer screening

Author	Participants *N*	Test	Moment of testing: Invitation letter
Prospective			
Lindholm et al.	2.932	1. Questionnaire: amount of worry 2. Interview: emotional reactions before and after test result	T1 T1
Parker et al.	1.541	1. Psychiatric morbidity: General health questionnaire (GHQ) 2. Spielberger anxiety inventory (SAI)	T1
Brasso et al.	507	Short symptom check list (SCL92): anxiety, depression, somatization	
Denters et al.	3.828	Psychological Consequences Questionnaire (PCQ)	T1
Bobridge et al.	301	1. Demographic Information Survey 2. Quality of life – Short-form 36 (SF-36) 3. Anxiety and Depression – Spielberger State-Trait Inventory 4. Multi-dimensional Health Locus of Control 5. Decision Evaluation Scale applied to CRC screening 6. Colorectal Cancer Risk	
Laing et al.	165	1. Colon cancer worry frequency 2. Situational anxiety – State-Trait Anxiety Inventory (STAI) 3. Mood disturbance	T1
Kirkøen et al.	3.213	1. Demographic Information Survey 2. Quality of Life – Short Form Health Survey (SF-12) 3. Hospital Anxiety and Depression scale (HADS)	T1
Retrospective			
Mant et al.		146	
Orbell et al.		697	
Kapidzic et al.		1.821	
Miles et al.		296	

	Screening result	Pre colono-scopy	Post colono-scopy	1-6 months (n months)	6-12 months (n months)	≥ 1 yr	Duration of effect
	T2 T2		T3	 T3 (1)	 T4 (12)		 Until colonoscopy
	 T1	 T2	 T3	T2 (3) T4 (1)			 1 month
	T1			T2 (3)		T3 (1yr)	≤1 yr
	T1	T2	T3				≥6 wks
	T1		T2			T3 (1yr)	≥1yr
	T2			T3 (4)			4 months
	T2						No effect
						Moment of testing	
	Interview at home by research nurse: degree of distress					after colonoscopy result	
	1. Cognitive and emotional dimensions of illness perception: IPQR 2. Coping 3. State anxiety inventory (STAI)					8 months	
	1. Short Form Health Survey (SF-12) 2. EuroQol classification (EQ-5D) 3. State Trait Anxiety Inventory (STAI-6) 4. Psychological Consequences Questionnaire (PCQ) 5. Cancer Worry Scale (CWS)					15 months (FIT-), 26 months (FIT+)	
	1. Quality of life specific to crc: FACT-C 2. Depression: CES-D 3. Perceived diagnostic delay 4. Trust in FOBT					7.7 yr	

Table 5. Characteristics of studies on inappropriate use of FOB screening test

Author	Year	Partici-pants N	Age (year)	Any reason	Limited life expectancy	Higher than average risk crc	Outside pilot group	Not due
Robinson et al.	1999	1.774	45-74	NS	Died <30d without surgery (n2)			
					Died >30d <2yrs of surgery for adenoma/stage A (n6)			
Fisher et al.	2005	500	all	35%	Life-limiting comorbidities (18%)	Personal history crc/IBD (7%)	<50yr (3%)	5%
Carlson et al.	2011	2.410	≥70	NS	Charlson comorbidity index ≥4 (9%)			
					Dead within 1 year of FOBT result (4%)			
					No follow up after FOBT 122 / 212 (58%)			
Kistler et al.	2011	212	≥70	NS	Limited life expectancy (14.2%)			
					Dead within 5 years of FOBT result (31%)			
					No follow up after FOBT (44.3%)			
McDonald et al.	2013	1.363	all	100%*			<50yr (27.9%)	
Saini et al.	2014	53.346	70-75	NS	Charlson comorbidity index >4 (17%)			
Powell et al.	2015	901.292	>50	26.1%	Limited life expectancy (7.8%)	Colonoscopy indicated (11%)		13.9%

* All requested outside the UK NBCSP

DISCUSSION

This comprehensive review on potential negative side effects of colorectal cancer mass screening has found multiple level consequences that are worth to dwell on. Our findings indicate that colonoscopy as a colorectal cancer screening modality is associated with a low risk of serious adverse events such as bleeding and perforation. Furthermore, being invited for participation in a screening program can cause a short but significant psychological distress. We also found a high risk of inappropriate use of colorectal cancer screening which can lead to over- as well as under treatment.

Comparison to literature

Risk of major bleeding

Our results are only partly comparable to other literature in the screening/surveillance setting. A recent published systematic review of 26 studies (n=3.347.101) estimated that the risk of perforations from colonoscopy in asymptomatic patients was 0.4/1000 colonoscopies. From 22 of those studies (n=3.414.108), the risk of major bleeding from colonoscopy was 0.8/1000 colonoscopies.[64] Our analysis showed similar results for major bleeding.

Risk of perforation

The risk of perforation in our analysis however is lower (0.07/1000). In another recent published systematic review, perforation occurred in 0.3/1000 screening/surveillance colonoscopies.[65] Mortality rates were not applicable. This systematic review by Reumkens et al. showed that the perforation rate for colonoscopy in screening or surveillance setting is approximately fourfold lower than for diagnostic examinations in symptomatic patients (0.3/1000 vs 1.3/1000 examinations, $p<0.001$).[65] This difference in perforation rate is probably associated with higher perforation risk through intervention due to a higher carcinoma rate in symptomatic patients. The remarkable lower perforation risk in our systematic review may be explained by our strict inclusion criteria. Unlike other systematic reviews, all studies that reported outcome of patients with increased risks on colorectal cancer were excluded. The data were excluded when the cohort included participants with above-average risk (i.e. family history of colorectal cancer or polyps, surveillance of prior colorectal cancer or symptomatic patients), unless an average-risk subgroup was reported. This is in contrast with the selection criteria of afore mentioned systematic reviews which also included studies including patients with increased familiar risk or personal history of colorectal cancer.

Screen-related psychological distress

To our knowledge, there are no previous published reviews that discuss colorectal cancer screen-related psychological distress. In breast cancer mass screening, a large effect on psychological distress has been found; the experience of having a false-positive screening mammogram can cause breast cancer-specific psychological distress that may endure for up to 3 years, and reduce the likelihood that a woman will return for their next round of mammography screening.[66,67] This is a remarkable difference with our findings, as there was no evidence of sustained anxiety, worry or QOL in people who receive a false-positive FOBT result.[48-50,53,54,57] A possible reason for the difference is the variety in questionnaires used to measure psychological distress. Future prospective studies are needed to explore this difference and evaluate factors that affect the extent of the outcomes such as gender, personality characteristics or media attention. Also, validated questionnaires are needed so psychological distress can be measured at different time points, including a baseline measure and measurement in a control group.

Strengths and limitations

The major strength of our study is that, to our knowledge, this is the first systematic review that evaluates the negative side effects of colorectal cancer mass screening on multiple levels; we reported on potential complication rates, psychological distress and inappropriate use. Previous (systematic) reviews on screen-related morbidity assessed only morbidity from colonoscopy and included also participants with above-average risk.[43] Possible benefits of screening are not considered in this systematic review.

Some limitations however are worth mentioning. First, heterogeneity was high among studies with outcomes of psychological morbidity. Second, literature on harms

other than perforation and bleeding was scarce, concerning subsequent surgical treatment and incorrect use of the FOBT, precluding generalization of risks and formulation of firm conclusions. Third, complications may be underreported. Real-life post-complication rate could be higher since complication registration is often self-reported. Also, those associated with the anaesthetics, such as cardiopulmonary complications and serious electrolyte disturbances, are not systematically recorded. Last, other important outcomes were not explored in this review such as potential advantages of surgery performed for early colorectal cancers, incidence of extra-colonic findings, prevalence of interval colorectal carcinomas and the extent to which a FOBT could falsely reassure patients and lead to delayed response in recognizing symptoms. Furthermore, it could be of great interest to include trials using sigmoidoscopy as a screening method for future research on adverse effects on CRC screening.

Clinical implications

National challenges

Results of this study could provide a focus for future studies and propose some important implications on both national and clinical level. Although post-colonoscopy complication rate may be low, the consequences should not be underestimated. Colonic perforation is associated with a high rate of morbidity and mortality as it could result in operation, stoma formation, sepsis, prolonged hospital stay and even death.[68] Since the lifetime risk of developing colorectal cancer for the population in the USA and the Netherlands is 2-5%[69,70], the majority of people undergoing screening is neither identified as having cancer nor its precursor lesions. Every potential harm is therefore more worrisome. On a national scale, its consequences can lead to logistical challenges, as these patients often need hospital care and follow-up. The increase in an absolute number of complications is expected due to the rising number of screening and surveillance colonoscopies. Also, the expected increase of the number of advanced adenomas and early carcinomas results in an increase in endoluminal resections. The treatment of endoluminal resections is however time consuming and may cause an additional risk for complications.

One might assume that surgical complications would be more clinically relevant in patients with symptoms since the tumour would be more advanced at that time.[23] When comparing mass screen-detected colorectal cancer patients with an age-matched symptomatic group, the proportion of T1/T2 cancers is significantly higher in the screening group.[71] Although no evidence has been found that tumour stage is an independent risk factor for postoperative morbidity and mortality, evidence suggests that a lower rate of emergency surgeries and preoperative complications can lead to lower postoperative morbidity and mortality.[72] Whether early diagnosis due to mass screening may indeed result in better surgical outcome should be focus of future investigation.

The question may rise whether these complications are a category of side effects due to screening. We believe that a proportion of patients will never undergo surgery

with its concomitant side effects if they do not participate in a screening program. In this way, surgical morbidity and mortality is to a certain extent directly related to screening and therefore worth mentioning. Moreover, we think that in a country with organized screening, mortality and morbidity after screening related surgery should be registered nationally for quality auditing.

Under- and over-treatment

Inappropriate screening of individuals who would not benefit from screening can cause both under- and over-treatment. Screening of symptomatic patients or with a (family) history of CRC can lead to under-treatment as it may delay or decrease the likelihood of undergoing a colonoscopy.[61] Also, screening when patients are not yet due compress the time interval between screening tests and therefore can increase the lifetime risk of a false positive test, and subsequently exposes patients to additional risks. Ideally, these inappropriate candidates to screening could be identified in electronic patient files when organized nationally and can be linked to the organized screening institutions. In order to achieve and maintain appropriate quality and limit the amount of inappropriate screening, organized screening as opposed to spontaneous case-finding is essential.

The risk of over-treatment is largest when the diagnosed cancer would never have presented symptomatically in patients remaining lifetime.[34] Evidence suggests that of all patients aged 70-75 with a Charlson comorbidity index $\geq$4, forty percent underwent screening. On the other hand, one fifth of patients aged $\geq$75 would likely benefit from screening as they have a Charlson comorbidity index of 0.[62] Using chronologic age rather than comorbidity-adjusted life expectancy should encourage clinicians to better tailor screening to older patients. A patient centred approach should be used, one that incorporates health status and individuals preferences. Future studies should therefore focus on identifying high risk individuals in order to optimise screening outcomes. Since this cannot be conducted through randomised controlled trials, we could monitor all screening effects nationally in a prospective manner. This observational data could result in a best practice for the health care community.

CONCLUSION

It is beyond any doubt that colonoscopy is an accurate diagnostic modality for CRC mass screening. Nevertheless, it conveys the possibility of complications as well as overtreatment of non-malignant endoscopic findings. Methods to closely monitor possible side effects of screen-related procedures should be developed. Although the low psychological impact of colorectal cancer screening seems reassuring, expected growing media-hype might enhance possible psychological distress, especially after false-positive FOBTs. Effort should be made to estimate the patient's competing risks of mortality, to decrease over-diagnosis in patients with a poor health status and tailor diagnosis and treatment incorporating health status and individuals preferences.

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CHAPTER 3

Psychological distress and quality of life following positive fecal occult blood testing in colorectal cancer screening

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Psycho-Oncology 2020 Jun;29(6):1084-1091

ABSTRACT

Objective: This study aimed to assess psychological functioning, quality of life, and regret about screening after a positive Fecal Immunochemical Test (FIT) and subsequent colonoscopy, and to evaluate changes over time.

Methods: This is a prospective cohort study. Individuals aged 55-75 with a positive FIT that were referred for colonoscopy between July 2017 and November 2018, were invited to complete questionnaires related to psychological distress and health-related quality of life at three pre-defined time points: before colonoscopy, after histopathology result notification, and after 6 months. Four questionnaires were used: the Psychological Consequences Questionnaire (PCQ), the six-item Cancer Worry Scale (CWS), the Decision Regret Scale (DRS), and the 36-item Short-Form (SF-36).

Results: A total of 1066 participants out of 2151 eligible individuals were included. Patients with cancer showed a significant increase in psychological dysfunction (P=0.01) and cancer worry (P=0.008) after colonoscopy result notification, and a decline to pre-colonoscopy measurements after 6 months. In the no-cancer groups, psychological dysfunction and cancer worry significantly decreased over time (P<0.05) but there was no ongoing decline. After 6 months, 17% of participants with no cancer experienced high level of cancer worry (CWS $\geq$ 10). Yet, only 5% reported high level of regret about screening participation (DRS > 25). A good global quality of life was reported in participants with no cancer.

Conclusion: Some psychological distress remains up to 6 months after colonoscopy in participants who tested false-positive in the Dutch bowel cancer screening program.

BACKGROUND

Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity. Population-based screening for CRC is recommended by the European Union to lower the burden of cancer by discovering early stage disease.[1, 2] In the Netherlands, a national CRC screening program was implemented in 2014, offering all individuals aged 55-75 a Fecal Immunochemical Test (FIT) every 2 years. Individuals are invited to sample a FIT at home and to return the test. The FIT uses antibodies that form a complex in the presence of human globin.[3] With a cut-off level of 47 µg Hb/g feces, as currently applied in the Netherlands for referral for colonoscopy, the sensitivity of FIT is 82.9%.[4] Yet, of all FIT positives who underwent colonoscopy in the Netherlands between 2014 and 2017, many individuals had false-positive result as 90 292 individuals (50.1%) had no abnormalities or non-advanced adenomas.[5] Because screening targets a previously healthy population, harms should be considered carefully in the evaluation of a CRC screening program. In contrast to the prospective registration of some harmful effects of screening, including complications due to colonoscopy or surgical treatment,[6] there is no obliged national audit for potential consequences on psychological functioning. Psychological distress covers a wide spectrum ranging from normal feelings of vulnerability to problems that can become disabling, such as depression, anxiety, or extensive worries.[7] Results from previous studies in cancer patients showed that fear of cancer recurrence (FCR), defined as fear, worry, or concern about cancer returning or progressing, has been identified as one of the most common psychological challenges.[8,9] Studies on cancer worry in screening populations are limited and primarily conducted in screening populations with increased cancer risk.[10,11] Previous meta-analyses in breast cancer screening have shown that false positive screening examinations affect psychosocial functioning that can persist for up to 3 years after the screening.[12,13] Available studies on screen-related psychological distress in CRC screening show that an adverse effect on psychological well-being exists.[14,15] However, data on long-term psychological well-being show conflicting results, and studies with a prospective design are limited.

Aim

The primary aim of this prospective cohort study was to assess psychological functioning, quality of life and regret about screening after a positive screening result, and to evaluate changes over time. Further, we aimed to explore associations between higher levels of psychological dysfunction and cancer worry related to sociodemographic characteristics and colonoscopy results.

METHODS

Study design

This prospective cohort study included patients with a positive FIT who were referred for colonoscopy in the Keizer Clinic between July 2017 and November 2018.

These patients were invited to complete questionnaires related to psychological functioning, cancer worry, regret about screening, and health-related quality of life (HR-QoL) at three pre-defined time points. The Keizer Clinic is a treatment center that collaborates with regional hospitals and the Leiden University Medical Center, and has three locations in different regions of the Netherlands, i.e. in The Hague, Voorschoten and in Assen. Only hospitals fulfilling the criteria as described by the National Health Institute for Public Health and environment (RIVM) are allowed to perform screening colonoscopies. The Keizer Clinic is one of them, and meets all predefined quality criteria.

This study was approved by the Medical Ethics Review Committee of the LUMC (reference number *P16.327*).

Population

The Keizer Clinic treats patients with no medical history or patients with only mild systemic disease, i.e. ASA I or II, according to the American Society of Anesthesiologists Physical Status Classification System. Men and women in the age range of 55-75 were eligible. Participants had to be able to read the Dutch language, have Digital identity (DigiD) and valid email address. Patients who were willing to participate but had no access to the questionnaires due to lack of computer and/or digital identity were excluded. All participants underwent subsequently colonoscopy and were diagnosed with either cancer or no cancer. Participants with no cancer were additionally classified into three groups according to histopathology: no abnormality, non-advanced adenoma (NAAD), and advanced adenoma (AAD). Advanced adenomas were defined as follows: ≥10mm in diameter, with a villous component of more than 25%, or high-grade dysplasia.[16,17]

Procedure

Four questionnaires were used: the 12-item Psychological Consequences Questionnaire (PCQ) to measure screen-specific psychological dysfunction, the 6-item Cancer Worry Scale (CWS) to measure worry of developing cancer, the 5-item Decision Regret Scale (DRS) to measure regret about screening participation, and the 36-item Short-Form (SF-36) to measure health related quality of life.

The PCQ was originally developed to measure the psychological consequences of screening mammography[18] and has previously been used in CRC screening research.[19] Invitees were asked to indicate how often they had experienced each of a list of 12 symptoms over the past week. It evaluates answers on a four-point Likert scale from 0 (not at all) to 3 (quite a lot of the time). The sum of scores resulted in a total score between 0 and 36. Higher scores indicate more psychological dysfunction.

The CWS quantifies the worry of developing (recurrent) cancer and the frequency and impact of worry on mood and daily functioning.[20] It was originally developed to assess fear of developing cancer in women at risk of hereditary cancer.[21]

The 8-item CWS was adapted in 2010 to assess worry about cancer recurrence in curatively treated colorectal cancer patients. Despite the 8-item CWS version already being well utilized in research, previous studies have highlighted concerns about

validity of the final two items.[22] The six-item scale has been tested and validated for the Dutch context.[22] Therefore, the six-item CWS was used in this study. Items are rated from 1 ("never") to 4 ("almost always"). The sum of scores resulted in a total score between 6 and 24, with higher scores indicating more worry. Based on a previous Dutch validation study, we divided patients into 3 categories: no cancer worry (score 6), low level of cancer worry (score 7-9) and high level of cancer worry (score ≥10).[22]

The DRS involves items that assess a patient's regret about health-care decisions.[23] It consists of five items with Likert-scale responses that were transformed into a total score of 0-100, with greater scores associated with higher regret.[24] Based on a validation study in prostate cancer patients, we considered a DRS score of >25 as high level of regret.[24-26]

The SF-36 consists of 36 questions, categorized into eight health dimensions, to measure health-related quality of life. These items are coded, summed, and transformed to a scale from 0 to 100, with higher scores indicating better functioning. There are no standards for determining clinically important differences (CIDs) in SF-36 scale scores for individual CRC patients. Based on a Delphi study the minimal amount of change for CID is at least 5 points, up to 12.5 points on the Social Functioning scale.[27] A Dutch cohort from the general population in 2012 (N=1,294) was used as reference population for this study.[28]

All questionnaires were conducted before colonoscopy (T1), after histopathology result notification after colonoscopy (T2), and 6 months after colonoscopy (T3). Surveys were available online via a digital patient portal, and secured with DigiD. Patients were asked to participate the moment they were called for colonoscopy. Completion of the first questionnaire was required for further participation, and indicated informed consent.

Statistical Analyses

To assess non-response bias, continuous variables of participants and non-participants were compared using an independent samples *t* test. Chi-square tests were used to compare categorical variables. A two-tailed *P*-value was used for all analyses, and *P*-values ≤ 0.05 were considered statistically significant. No adjustment for multiple testing was applied because only a few planned comparisons were made and therefore the probability of making a type I error was limited. Only complete questionnaires were analyzed. Sensitivity analysis was performed by repeating the analyses in both the cohort of patients that completed the PCQ on all time points, and the complete cohort of participants. This analysis showed similar results, allowing to do further analyses on the complete cohort.

Outcomes of the first questionnaires, i.e. before the colonoscopy result notification (T1), were seen as baseline measurement, because participants were unaware of their final diagnosis at this time point. Because the outcome of the questionnaires was not normally distributed, differences in medians were compared. To compare results with other literature mean scores were reported as well. Differences in absolute psychological dysfunction and cancer worry scores at different time points

were assessed using a Wilcoxon signed-rank test, for each subgroup according to histopathology result. The results before colonoscopy (baseline) were compared to those after colonoscopy (T1 vs T2), and the results before colonoscopy to those after six months (T1 vs T3). We hypothesized that a false positive FIT result would lead to decrease in psychological dysfunction (PCQ) and cancer worry (CWS) over time. Also, decision regret towards screening participation and quality of life were assessed. Second, to explore associations between demographic and clinical characteristics with higher levels of psychological dysfunction and cancer worry, logistic regression analyses were performed. Independent variables with *P*-value ≤0.05 in univariable analyses were entered into the multivariable logistic regression model. Median outcome after colonoscopy was chosen as the cut-off value for PCQ. Based on previous literature, the cut-off value of 10 was applied for CWS, indicating high cancer worry. SPSS 23.0 (SPSS Inc., Chicago, IL, USA) was used to manage and analyze the data.

RESULTS

A total of 4842 men and women with positive FIT were referred to the Keizer Clinic for a colonoscopy. Of these 2691 did not meet the inclusion criteria. The inability to validate a personal e-mail address was the main reason for exclusion. In total, 1066 (49.6%) of the remaining 2151 individuals responded and were included for analyses. Table 1 shows the characteristics of participants and non-participants.

Psychological Consequences

In participants with false positive FIT results (i.e. no cancer), the level of psychological dysfunction decreased after colonoscopy result notification (*P*<0.01) (Figure 1, Supplementary Table 1). After 6 months, no additional decline was observed. This was different for the participants with cancer, as their psychological dysfunction increased significantly from pre-colonoscopy to post-colonoscopy (Z= −2.59, *P*=0.01). Six months after the cancer diagnosis, it decreased to the baseline level (Z= −0.18, *P*=0.86) (Supplementary Table 1). Factors associated with higher levels of psychological dysfunction (PCQ ≥3) after colonoscopy are shown in Table 2. The odds of reporting higher levels of psychological dysfunction significantly increased by female gender (adjusted OR 2.50, 1.85-3.37) and histopathology outcome, i.e. NAAD (adjusted OR 2.47, 1.68-3.64), AAD (adjusted OR 3.13, 2.13-4.62), and cancer (adjusted OR 12.28, 5.58-27.03). Age, education, marital status and employment status were non-significant variables.

Cancer Worry

Compared to baseline, all participants with no cancer showed a significant decline of cancer worry over time (*P*<0.05). In participants with cancer, worry significantly increased from pre-colonoscopy to post-colonoscopy (Z= −2.63, *P*=0.008). Six months after the cancer diagnosis, the scores returned to the baseline levels

Table 1. Background characteristics of FIT-positive participants and FIT-positive nonparticipants (nonresponders and persons that did not fulfil inclusion criteria)

	Participants	**Nonparticipants**	***P*-value**
	N=1066	**N=3776**	
Age (years)			
Mean (SD)	64 (5.79)	65 (6.37)	< 0.001*
Male gender (%)	659 (61.82)	2226 (58.95)	0.097**
Pathology (%)†			
No abnormalities	218 (20.45)	855 (22.64)	0.127**
Non-advanced Adenoma‡	384 (36.02)	1342 (35.54)	
Advanced Adenoma	387 (36.30)	1239 (32.81)	
Cancer	69 (6.47)	205 (5.43)	
Missing	8 (0.75)	135 (3.58)	
Education (%)			
Low	215 (20.17)	NA	
Medium	630 (59.09)	NA	
High	135 (12.66)	NA	
Other	86 (8.07)	NA	
Marital status (%)			
Married/cohabiting	900 (84.43)	NA	
Living alone	166 (15.57)	NA	
Employment status (%)			
Employed	536 (50.28)	NA	
Unemployed/retired	529 (49.62)	NA	
Unknown	1 (0.09)	NA	

Note: Significant level set at $P \leq 0.05$.
Abbreviations: FIT, fecal immunochemical test; NA, not available.
* Independent samples t test for continuous variables.
** Chi-square test for categorical variables.
† *P*-value without missing values.
‡ Including serrated polyps.

(Z= −0.24, *P*=0.81) (Supplementary Table 1). A total of 17% (n=26) of individuals with no abnormality and 17% (n=44) of individuals with NAAD scored above cut-off level for high level of cancer worry (CWS ≥ 10), six months after receiving positive FIT result (Figure 2).

As shown in Table 2, factors associated with higher levels of worry about developing cancer (CWS ≥10) after colonoscopy are female gender (adjusted OR 1.48, 1.09-2.01) and histopathology outcome, i.e. NAAD (adjusted OR 2.00, 1.28-3.12), AAD (adjusted OR 2.34, 1.53-3.68), and cancer (adjusted OR 8.35, 4.37-15.97). The odds decreased with higher age (adjusted OR 0.97 per year, 0.95-1.00). Education, marital status and employment status were not significantly related to higher levels of cancer worry.

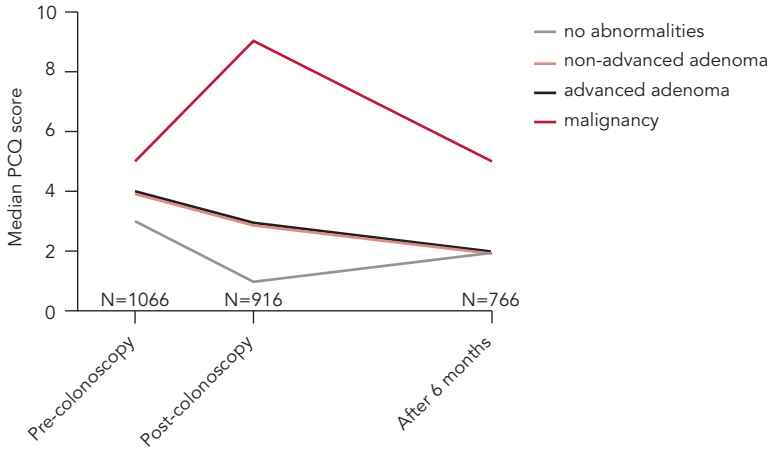

Figure 1. **Changes in median PCQ score in function over time, according to colonoscopy result.**

PCQ, Psychological Consequence Questionnaire, range 0 to 36 with higher scores indicating more psychological dysfunction. Error bars represent the standard error of the mean

Decision Regret

Regret about screening participation, as assessed by the DRS, was generally low. The distribution of regret scores was extremely left-skewed, as the median was zero both direct after colonoscopy (range 0-100) as well as after six months (range 0-60). Of all participants with no cancer, 5% reported a high level of regret (DRS > 25), both after colonoscopy as well as after six months. Of all individuals with cancer, 10% reported high level of regret.

Health-related quality of life

The mean scores for the eight subscales of the SF-36 over time in the cancer and no-cancer groups are presented in Table S2. No relevant changes over time were seen in the no-cancer group. In the cancer group, the mean scores of five of eight subscales decreased (indicating worse functioning) with >5 points directly after the colonoscopy (role limitations due to physical functioning, social functioning, mental health, role limitations due to emotional functioning, and general health). The largest decrease from baseline to six months was observed in the cancer group on the subscales role limitations due to physical functioning (90 to 64) and role limitations due to emotional functioning (91 to 76).

Table 2. Unadjusted and adjusted association between demographic and clinical characteristics of FIT-positive participants with higher levels of screen-related psychological dysfunction (PCQ ≥ 3) and fear of cancer (CWS ≥ 10) after colonoscopy result notification (T2)

	PCQ ≥ 3			**CWS ≥ 10**		
	Unadjusted	**Adjusted**		**Unadjusted**	**Adjusted**	
	Odds ratio†	Odds ratio†	*P*- value‡	Odds ratio†	Odds ratio†	*P*-value‡
Age (years)	0.97 (0.95-0.99)	0.97 (0.94-1.00)	0.075	0.97 (0.95-0.99)	0.97 (0.95-1.00)	**0.037**
Gender						
Male	1 (ref.)	1 (ref.)		1 (ref.)	1 (ref.)	
Female	2.17 (1.64-2.86)	2.50 (1.85-3.37)	**<0.001**	1.41 (1.05-1.88)	1.48 (1.09-2.01)	**0.012**
Pathology						
No abnormalities	1 (ref.)			1 (ref.)		
Non-advanced Adenoma	1.89 (1.31-2.71)	2.47 (1.68-3.64)	**<0.001**	1.77 (1.14-2.75)	2.00 (1.28-3.12)	**0.003**
Advanced Adenoma	2.44 (1.70-3.52)	3.13 (2.13-4.62)	**<0.001**	2.14 (1.39-3.30)	2.34 (1.53-3.68)	**<0.001**
Cancer	9.63 (4.48-20.71)	12.28 (5.58-27.03)	**<0.001**	7.70 (4.06-14.61)	8.35 (4.37-15.97)	**<0.001**
Education						
Low	1 (ref.)			1 (ref.)		
Medium	1.02 (0.73-1.43)	NA	NA	1.08 (0.74-1.57)	NA	NA
High	0.98 (0.61-1.55)	NA	NA	1.07 (0.64-1.77)	NA	NA
Marital status						
Living alone	1 (ref.)	1 (ref.)		1 (ref.)		
Married/ cohabiting	0.70 (0.48-1.00)	0.69 (0.46-1.02)	0.059	1.10 (0.74-1.65)	NA	NA
Employment status						
Unemployed/retired	1 (ref.)	1 (ref.)		1 (ref.)		
Employed	1.30 (1.00-1.69)	1.13 (0.79-1.62)	0.503	1.15 (0.87-1.53)	NA	NA

Note: Significant level set at P≤0.05 and printed in bold.
Abbreviations: CWS, Cancer Worry Scale, range 6 to 24 with higher scores indicating more cancer worry; NA, not applicable; PCQ, Psychological Consequence Questionnaire, range 0 to 36 with higher scores indicating more psychological dysfunction.
† Values in parentheses are 95 per cent confidence intervals.
‡ *P*-value for multi variable logistic regression analyses.

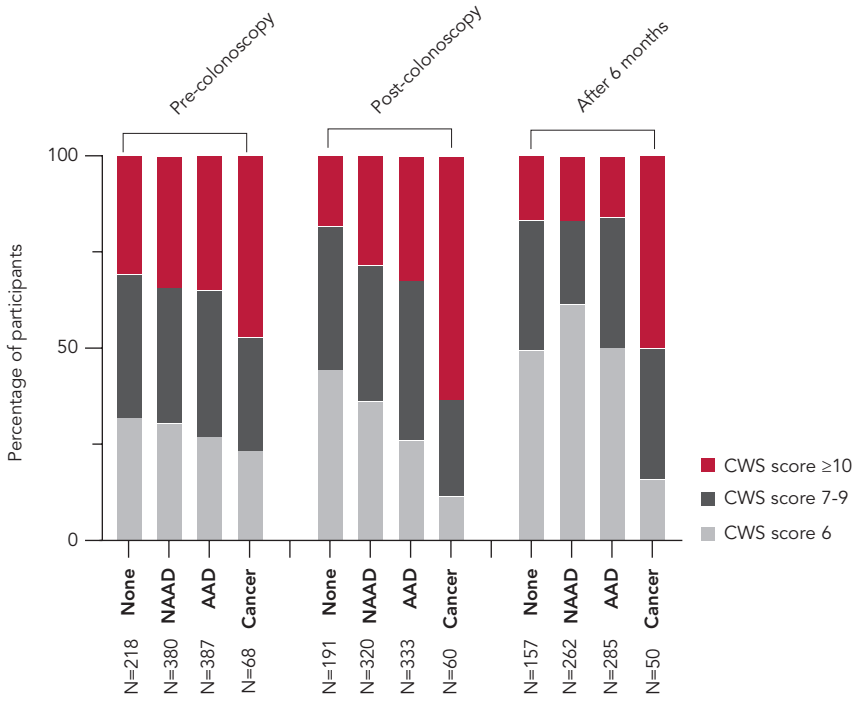

Figure 2. Frequency of scores on the CWS, before colonoscopy, after colonoscopy result notification and 6 months after colonoscopy, according to colonoscopy result.

CWS, Cancer Worry Scale (range 6-24), with a cutoff score of 10 indicating high level of cancer worry. Colonoscopy result: AAD, advanced adenoma, NAAD, non-advanced adenoma; None, no abnormality

DISCUSSION

Most important findings

Results of this large study on psychological impact of CRC screening suggest that individuals with positive FIT have elevated levels of psychological dysfunction and worry about developing cancer.

It is not surprising that psychological dysfunction in patients with no cancer was lower compared to patients with cancer. One would expect an ongoing decrease in psychological dysfunction after the reassuring outcome of colonoscopy. Yet, this was not seen in our study population. Hypothetically, after a false-positive FIT, patients are more aware of the possibility to develop cancer than they were prior to screening.

Interestingly, about one fourth of the participants with no cancer experienced a cancer worry score ≥10 after colonoscopy, indicating high levels of cancer-specific worries. After 6 months, still 1 in six participants experienced high levels of cancer-specific worries. Identifying these individuals seems worthwhile because they may benefit from psychosocial support in order to reduce levels of distress.

We found that FIT-positives in general do not regret their decision to screen for CRC. This is interesting since over half of FIT positive participants who undergo an invasive colonoscopy have no (advanced) neoplasia detected.

Last, as expected, the FIT participants in this study reported a good global quality of life. In participants with no cancer, HR-QoL fortunately was not affected by the colonoscopy. In the participants with cancer, as expected, the effect of colonoscopy result notification on HR-QoL was large. Directly after receiving the cancer diagnosis, patients rated their physical health as significantly worse compared to 2 weeks earlier, even ahead of treatment.

Clinical implications

Ideally, we would have had information from FIT-negatives and individuals that did not participate in screening in order to measure a true and clinically relevant effect on psychological dysfunction level. Two studies provided information on FIT negatives and found a mean PCQ of resp. 2.1 and 2.2.[19,29] However, this low level was not reached in our cohort with FIT positive patients. Even in FIT positive patients with a negative colonoscopy, a mean PCQ score of 3.9 was observed after 6 months. The higher 6-months dysfunction level in patients in our study might be associated with an increased perception of the risk of developing CRC after a false-positive FIT result. This increased perception of risk is also seen in breast cancer patients where Rijnsburger et al. showed that a mean PCQ score of 6 corresponded to a "quite to very high" perceived risk of developing breast cancer.[30]

In the current literature on CRC screening, results are often analyzed by comparing true-positives with false-positives. Denters et al. observed no significant differences between true-positives and false-positives in post-colonoscopy PCQ scores, which is an unexpected outcome. In our study, levels of psychological dysfunction of patients with AAD (defined as true-positives) were more comparable to those of individuals

with no abnormalities, than those of patients with cancer. The observation of Denters et al. might have been different if they had analyzed cancer patients and patients with AAD separately but since their group of participants was relatively small, it may have been underpowered.[19] So in terms of psychological distress, patients with AAD should be reported separately from the patients with cancer.

A systematic review on FCR showed this to vary widely,[31] possibly because there is no consensus about what are clinically relevant levels of FCR. Previous studies in CRC[20] and prostate cancer survivors[32] both showed that one in four had high levels of worry of cancer recurrence (CWS $\geq$ 14 in eight-item CWS), with a median of 5.1 and 7.5 years after surgery, respectively.[20] Although the CWS has been validated for cancer survivors, it has also been used to measure worry about the risk of developing cancer among participants in a cancer surveillance program.[33] The cut-off point $\geq$10, based on a Dutch validation study in cancer patients and survivors, has led to our conclusion that there was a high level (17%) of cancer specific worry up to 6 months in patients with no malignant lesions. However, since there is no data from the general population available, there is a possibility that some of these findings reflect general patterns of psychological distress.

In line with previous research, women were more likely to report cancer worry.[34,35] Logistic regression analyses showed that this difference had not confounded the association between histology and cancer-specific distress. As shown in previous studies, women generally yield higher scores than men on anxiety measures.[35]

The absence of regret in screening participation as observed in our cohort might be explained by the concept of misleading feedback as stated by Hofmann et al.: subjects who have a false positive test might experience a sense of relief. This is ironic because these participants have experienced harm of testing without a benefit. Still, they view themselves to be in the benefiting group and are enthusiastic about testing.[36]

Strengths and limitations

This cohort study is one of the largest prospective studies on quality of life and psychological distress after screening with FIT and one of the first to assess the perception and satisfaction longitudinally of screening participants. Notable strengths are the large group of participants, permitting subgroup analyses and the prospective design of the study. The use of electronic online questionnaires allowed us to minimize the risks of data entry errors, hence no manual data entry was required. This might also contribute to the response rate.

Several limitations have to be mentioned. Most important are selection and participation bias. There was no information on individuals that decline FIT screening, FIT negatives or subjects unexposed to screening. Therefore outcome of this study should be interpreted with a degree of caution. Screening attendees are known to have higher socioeconomic status and better mental health, compared with nonattendees.[37,38] In addition, previous research has shown that volunteers in medical trials are in general more psychologically robust and resourceful than those who choose not to participate.[39] Bearing this in mind, our results can be

underestimated as people who declined participation in the present study might have experienced more negative psychological consequences. This is endorsed by the study of Wangmar et al., in which individuals participating in a CRC screening trial with inadequate health literacy were more likely to experience higher anxiety levels.[35] In addition, individuals with high ASA-score as well as individuals with no computer and/or digital identity were excluded. This might limit the generalizability in the way that a relatively healthy, privileged population was included. There were no ethical considerations regarding this exclusion after our METC application. Another limitation is that we had no information on previous colonoscopy, family or personal history, nor on complications of colonoscopy or surgical treatment. One could assume that an adverse outcome could influence psychological distress and health-related quality of life. Also, we were unable to control for any confounders, such as psychological comorbidities or other life events. Future studies could consider including information on baseline mental health and previous severe illnesses as they likely influence psychosocial experiences during and after the screening process. Finally, the main question remains whether this adverse impact of screening on psychological dysfunction is clinically relevant since no clear cut-off values are available. In addition, as the data were skewed to such an extent, one might question if some of these questionnaires, for example the DRS, were sufficiently sensitive to detect effects of the decision to participate in screening. Despite these limitations, the results of this study are valuable and increase the knowledge on psychological wellbeing of CRC screening participants.

CONCLUSION

In conclusion, there is a certain level of psychological distress up to 6 months among participants who tested false positive in the Dutch bowel cancer screening program. Although differences were small and clinically relevant cut-off values are debatable, an initial positive test result has a negative impact on participants' emotional well-being. Therefore, participants should be informed not only on the assumed benefits of CRC screening such as decreased bowel cancer mortality, but also on the possibility of psychological distress related to screening participation. Yet, despite psychological distress, participants reported no regret about participating to the CRC screening program. Future research should focus on identifying subjects that are likely to develop substantial psychological distress. These patients may benefit from additional counseling or even be advised to decline screening participation.

Acknowledgements

The authors thank H. Putter, professor of Medical Statistics, E. Bastiaannet, assistant professor in Clinical Epidemiology, and M. van Egmond, manager IT and software analyst at the Keizer Clinic, for their contribution to this manuscript.

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APPENDICES

Supplementary Table 1. Median scores of the Psychological Consequence Questionnaire (PCQ) and Cancer Worry Scale (CWS) in function over time, by result of colonoscopy

	Pre-colonoscopy (T1)	**Post-colonoscopy (T2)**	**T1 vs T2 P-value†**	**After six months (T3)**	**T1 vs T3 P-value†**
PCQ (0-36)	Median	Median		Median	
No abnormalities	3.0 N=192	1.0	<0.001	2.0 N=159	<0.001
Non-advanced adenoma	4.0 N=326	3.0	<0.001	2.0 N=268	<0.001
Advanced adenoma	4.0 N=333	3.0	0.003	2.0 N=287	<0.001
Cancer	5.0 N=61	9.0	0.01	5.0 N=51	0.86
CWS (6-24)					
No abnormalities	9.0 N=191	7.0	<0.001	7.0 N=157	<0.001
Non-advanced adenoma	9.0 N=319	7.0	<0.001	6.0 N=262	<0.001
Advanced adenoma	9.0 N=333	8.0	0.02	7.0 N=263	<0.001
Cancer	9.5 N=60	10.5	0.008	9.5 N=50	0.81

Note: Significant level set at P<0.05.

Abbreviations: CWS, Cancer Worry Scale, range 6 to 24 with higher scores indicating more cancer worry; NA, not applicable; PCQ, Psychological Consequence Questionnaire, range 0 to 36 with higher scores indicating more psychological dysfunction.

† The P-value indicates the significance level of differences in observed scores pre-colonoscopy vs post-colonoscopy and pre-colonoscopy vs after six months using a Wilcoxon signed-rank test.

Supplementary Table 2. Mean scores on the Short Form Health Survey (SF-36) before colonoscopy, after colonoscopy result notification and 6 months after colonoscopy, according to colonoscopy result (no cancer vs cancer)

	No cancer†			**Cancer**			
	Pre-colonoscopy	**Post-colonoscopy**	**After six months**	**Pre-colonoscopy**	**Post-colonoscopy**	**After six months**	**Reference group**
SF-36	N=983	N=840	N=703	N=68	N=60	N=49	*N=1294*
Physical functioning	90	89	89	91	90	83	*93*
Role - Physical	91	89	89	90	83	64	*87*
Bodily Pain	87	87	86	90	91	86	*86*
Social functioning	91	89	91	92	84	85	*90*
Mental health	83	81	84	81	75	82	*80*
Role - Emotional	91	88	90	91	78	76	*90*
Vitality	78	77	77	79	78	70	*69*
General health	73	74	74	76	69	69	*76*

Abbreviations: SF-36 = Short Form Health Survey, score ranges 0-100 with higher score indicating better health-related quality of life.

† No cancer includes no abnormalities, non-advanced adenoma, and advanced adenoma.

CHAPTER 4

Impact of additional findings from computed tomography in FIT screen-detected patients with colorectal lesions: a longitudinal cohort study

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Submitted BMJ Open

ABSTRACT

Objectives: Main objective of this study was to examine the prevalence and consequences of additional findings on staging thoracic-abdominal computed tomography (CT) scan in a population with screen-detected colorectal lesions. Additional findings were defined as non-metastatic lesions other than the colorectal lesion, in which further investigation, follow-up, and/or treatment was indicated.
Design: Longitudinal cohort study
Setting: Academic teaching hospital and tertiary care centre in the Netherlands
Participants: Patients with a screen-detected colorectal lesion referred to the Department of Colorectal Surgery that underwent staging thoracic-abdominal CT scan (N=231).
Results: Staging CT revealed distant metastases in 10 patients (4.3%) and 120 additional findings in 103 patients (44.6% of the total cohort). Seventeen of the 103 patients (16.5%) had findings that were confirmed to be clinically important. For the entire cohort, the rate of additional imaging work-up for additional findings that ultimately proved to be benign was 31.2% (72/231). Median time frame between the first staging CT and final diagnosis of these irrelevant additional findings was 15 days (range 0-1176 days).
Conclusions: Despite a more favorable stage distribution, a high prevalence of additional findings which required further investigations was found in this cohort of patients with screen-detected colorectal lesions. Ultimately, 5 out of 6 patients received a diagnosis of a non-important condition. A more complete understanding of the frequency and nature of these additional findings is critical in order to place it into the context of the benefits of screening as a whole.

INTRODUCTION

In the Netherlands, a colorectal cancer (CRC) screening program using faecal immunochemical testing (FIT) was implemented in January 2014. It aims to reduce CRC incidence and increase cancer-specific survival.[1,2] As the vast majority of colorectal neoplasms arise from adenomas, it is assumed that removing these lesions will prevent progression to malignancy and therefore contribute to the decrease of cancer diagnoses. In addition, screening can also identify asymptomatic patients with early-stage malignant disease, potentially leading to higher survival rates.[3] Previous studies have shown that screen-detected CRCs in a FIT-based screening programme are detected more often at an early disease stage than those that are symptom-detected.[4]

Implementing a screening programme has revealed a novel asymptomatic subset of patients that has not been encountered so far. Based upon many national guidelines, all CRC patients, including patients with screen-detected lesions, undergo the same diagnostic track to assess the extent of the disease. As the detection of metastases will impact treatment, radiological assessment of chest and abdomen is indispensable. Approximately 15-25% of the patients with symptomatic CRC has distant metastases at the time of diagnosis.[5-7] With a more favourable stage distribution in screen-detected CRCs, one can assume that less metastases will be detected in this group of patients. However, with the emergence of cross-sectional imaging with improved resolution, the frequency of detection of findings other than metastases increases.[8] This can complicate the diagnostic phase for several reasons. First, atypical findings may enforce clinicians to rule out any pathology by performing additional diagnostic endeavors, being better safe than sorry. Additional investigations can be time-consuming, costly, increase patient anxiety and cause further morbidity. Second, treating non-metastatic findings may imply overtreatment if these findings remain asymptomatic during life time when left untreated. The problem of overdiagnosis is well-established in renal, breast, lung, prostate and thyroid cancer, as well as other conditions.[8] Many reports have addressed the issue of incidental findings in patients undergoing CT colonography (CTC) for CRC screening. However, evidence regarding the magnitude of these risks of overtreatment in a FIT based screening population with staging thoracic-abdominal CT scan is lacking.

Main objective of the current study was to examine the prevalence and sequelae of additional findings on staging thoracic-abdominal CT scan, in a population with screen-detected colorectal lesions.

METHODS

All patients with a screen-detected primary colorectal lesion referred to the Department of Colorectal Surgery of the Leiden University Medical Centre (LUMC) between 1 January 2014 and 31 December 2016 were included in a prospectively

collected database. The LUMC is a large academic teaching hospital and tertiary care centre in the Netherlands. Patients with all colorectal lesions were included, including non-invasive lesions. Emergency presentation with acute surgery, assessment of chest and abdomen with imaging modalities other than CT, as well as patients with recurrent CRC were excluded from this analysis. Electronic patient files were reviewed individually concerning patient characteristics, pathology reports of endoscopic and surgical specimen, comorbidity, and findings on chest and abdominal CT scans. Patients with rectal cancer were additionally staged with a pelvic MRI for estimation of the local invasion, according to the Dutch guideline. This cohort study was approved by the Medical Ethics Review Committee of the LUMC (reference number G16.089).

Patient and Public Involvement

No patients involved.

Statistics

To determine whether there were differences between patients with and without additional findings, variables were compared using independent samples t-test and chi-square tests. A *p*-value below 0.05 was considered to reflect statistical significance. Number needed to scan is akin to number needed to treat (NNT): it represents the number of patients required to undergo a CT scan in order to detect one patient with metastases. It was calculated by dividing 100 by the percentage of patients with metastases, i.e. 1 / (N_0 with metastases / N_0 total number of patients). Descriptive statistical analysis was performed using SPSS® version 24.0 for Windows® (IBM, Armonk, New York, USA).

Definitions

Additional findings were defined as non-metastatic lesions other than the colorectal lesion, detected by the staging thoracic-abdominal CT scan. Indeterminate lung nodules and liver lesions that were initially considered to be non-metastatic but later in time appeared to be metastases were also classified as additional findings. A distinction was made between findings of low importance, i.e. no work-up indicated, and findings of potential or definite importance in which additional work-up was indicated. Importance was assessed during multidisciplinary colorectal cancer team meetings. For the purposes of this study, additional findings were only included if they were (potentially) important, requiring further investigations, follow-up, and/or treatment. Findings that were visible on prior diagnostic investigations, as well as findings in patients with no invasive carcinoma in resection specimen, were re-categorized as findings that were not relevant. Additional findings were classified according to their origin. Lung nodules and liver lesions were classified according to their morphology, location and growth over time. An indeterminate lung or liver lesion was considered benign when there was no subsequent increase in size for at least 12 months. It was defined to be malignant when either a histopathological diagnosis of malignancy was established or treatment was delivered based on clinical

suspicion of malignancy. All relevant radiological investigations for characterisation of the additional findings were analysed and their outcomes assessed. After follow-up studies and/or invasive procedures, the additional finding was either confirmed to be clinically important or proven to be benign. Clinically important outcomes included malignancies, abdominal aortic aneurysms, and other conditions requiring invasive treatment procedures. All other outcomes were considered non-important. Time until diagnosis was defined as median time between staging CT and the investigation that showed the final diagnosis of the finding.

IMAGING STUDIES

A CT scan of chest and abdomen was performed on a 64-slice or 320-slice scanner (Toshiba, Canon Medical Solution, Netherlands). Two scan protocols were applied; either CT colography protocol combined with a chest CT, or a standard chest and abdominal CT. In both protocols, 1.6 ml/kg intravenous contrast agent, Optiray 350 mg iodine/ml (ioversol) (Guerbet, Ireland) or Ultravist 370 mg iodine/ml (iopromide) (Bayer, Whippany), was administered at an injection rate of 0.05 ml/kg/s, followed by a 0.5 ml/kg saline flush at the same rate. All CT scans were obtained in portovenous phase using bolus-tracking, starting the scan 50 seconds after the density in the aorta was 150 Hounsfield Units. Oral contrast agent (Telebrix Gastro, Guerbet) was ingested prior to the scan. Patients who underwent CT colonography received 0.5 ml glucagon (Novo Nordisk) intravenous to minimize bowel movement artefacts. All CT scans were interpreted by certified and specialized abdominal radiologists. The radiology records were reviewed by one author (NV) and classified according to the original report. For more comprehensive scan viewing, the additional findings on chest CT scans were additionally classified by a radiologist specialized in thoracic imaging (HL).

RESULTS

Patients

Of the 231 patients with a screen-detected CR lesion who underwent staging thoracic-abdominal CT scan, 10 patients (4.3%) had distant metastasis at initial diagnosis. The overall median follow-up for all patients with additional findings in the study was 38 months (range 0-66).

Staging CT revealed additional findings in 103 patients (44.6% of the total cohort) (Figure 1). The remaining 118 patients (51.1%) had no additional findings or findings of low importance and underwent no additional evaluation, including patients with findings that were analyzed in another hospital prior to CT (N=3), or because there was no invasive carcinoma in the resection specimen of the colorectal lesion (N=4) Their demographic and pathological characteristics are shown in Table 1. Comorbidity was more often present in patients with clinically relevant findings

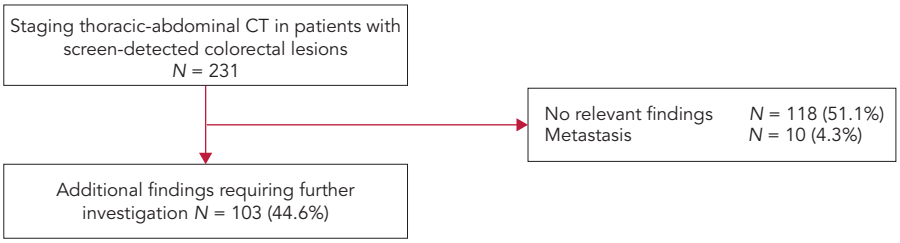

Figure 1. Flow chart

(81.6% vs 69.5%, p=0.039), but there were no significant differences in age, gender, ASA classification, location of primary lesion, and treatment (Table 1). In 89 out of 103 patients (86.4%), further investigations were performed. The majority of the patients with clinically relevant findings underwent additional imaging (44.7%), invasive procedure (22.3%), or follow-up imaging (19.4%). The remaining patients had no work-up because because of loss of follow-up (N=4, 3.9%), no further imaging was conducted despite recommendation (N=4, 3.9%), or because follow-up was not recommended according to national guidelines (N=6, 5.8%).

Additional findings and Outcome

Staging CT revealed 120 thoracic and abdominal additional findings in 103 patients. Twenty-three invasive procedures (colonoscopy, biopsy or additional surgery) and 125 additional follow-up studies were performed in these patients for further evaluation. Overall, time between staging CT and final diagnosis of these findings was median 20 days (range 0-1176 days). Table 2 shows that 17 of the 103 patients (16.5%) had findings that were confirmed to be clinically important, most frequently in the lungs (N=4) and genitourinary tract (N=4). The vast majority of patients (72 out of 86) underwent imaging investigations where no abnormalities of clinical importance were revealed. These lesions were primarily liver lesions (N=40), and adrenal masses (N=13), which were predominantly liver cysts and adrenal adenomas. For the entire cohort, the rate of additional imaging work-up for additional findings that ultimately proved to be benign was 31.2% (72/231). Median time from first staging CT until final diagnosis of these irrelevant additional findings was 15 days (range 0-1176 days) (Figure 2).

DISCUSSION

Despite a more favorable stage distribution, a high prevalence of additional findings which required further investigations was found in this cohort of patients with screen-detected CR lesions. Ultimately, 5 out of 6 patients received a diagnosis of a non-important condition.

Metastatic disease was detected in 4.3% of the patients with screen-detected CR lesions at the time of initial diagnosis, which is low compared to symptomatic patients

Table 1. Comparison of characteristics of patients with FIT screen-detected colorectal lesions, according to the detection of clinically relevant findings on staging thoracic-abdominal CT scan

	No relevant findings N=118	Clinically relevant findings N=103	*P-value*
Age, median (IQR)	67 [64-72]	68 [65-75]	0.105
Gender			0.341
Male	75 (63.6)	59 (57.3)	
Co- morbidity			0.039
No	36 (30.5)	19 (18.4)	
Yes	82 (69.5)	84 (81.6)	
ASA			0.084
I / II	98 (83.1)	79 (76.7)	
III / IV	7 (5.9)	13 (12.6)	
Unknown	13 (11.0)	11 (10.7)	
Location of primary lesion			0.740
Colon	86 (72.9)	73 (70.9)	
Rectum	32 (27.1)	30 (29.1)	
Treatment			0.614
Surgery, carcinoma	89 (75.4)	82 (79.6)	
Surgery, no carcinoma	9 (7.6)	4 (3.9)	
No surgery	14 (11.8)	13 (12.6)	
Other centre for treatment or follow-up	6 (5.1)	4 (3.9)	

Patients with metastatic disease (N=10) are not shown.

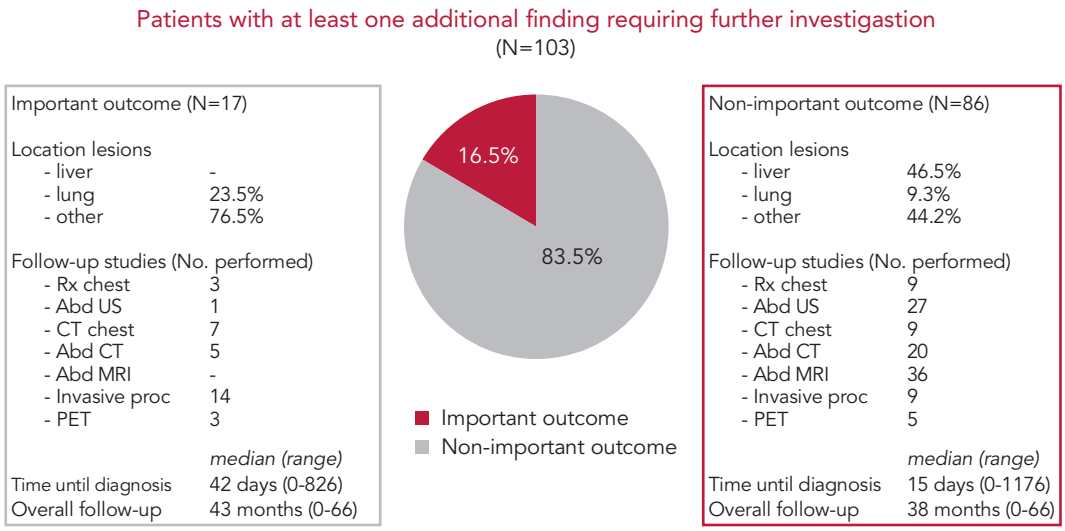

Figure 2. Diagnostic work-up of patients with additional findings on staging thoracic-abdominal CT scan, classified according to their outcome

Rx = radiography, Abd = abdominal, US = ultrasonography, CT = computed tomography, MR = magnetic resonance, Invasive proc = invasive procedure (Including colonoscopy, biopsy, or surgery), PET = positron emission tomography)

Table 2. Final diagnoses and types of treatment of patients with additional findings that were clinically important after further diagnostics / investigations

Patient	Reported Finding	Final diagnosis	Treatment
1-2	Lung nodule	Non-small cell lung cancer (adenocarcinoma)	Lobectomy
3	Lung nodule and liver lesions	Pulmonary large cell neuroendocrine carcinoma with liver metastases	Best supportive care
4	Lung nodule	Non-small cell lung cancer (adenocarcinoma)	Best supportive care
5	Prostate mass and thoracic aneurysm	Prostate cancer and aneurysm of thoracic aorta	Radiotherapy and follow-up imaging
6	Mass urinary tract	Renal cell carcinoma (RCC)	Nephrectomy
7	Mass urinary tract	Renal cell carcinoma (RCC)	Radiofrequency ablation
8	Mass urinary tract	Urothelial cancer of the ureter	Segmental ureteral resection
9-10	Other lesion colon	Synchronous colon cancer	Extended colectomy
11-12	Aneurysm abdominal aorta	Abdominal aortic aneurysms	Surgery
13-14	Aneurysm abdominal aorta	Abdominal aortic aneurysms	Follow-up imaging
15-16	Other	Liver cirrhosis	Hepatic venous pressure gradient measurement, no TIPS
17	Other	Obstructive urolithiasis	Stone removal by ureterorenoscopy

who are diagnosed with synchronous metastases in 15-25% of the cases. In other words, 23 patients had to undergo a thoracic-abdominal CT scan in order to detect one patient with metastatic disease. Although this is a high number "needed to scan", a staging CT will remain a necessity since distant metastases have significant impact on treatment choices. Cross-sectional imaging like CT brings along the detection of non-metastatic findings which makes subsequent investigations often imperative. This study shows a high prevalence of additional findings which require further investigations.

Additional findings have been examined before, but primarily in CT colonography (CTC), which is a commonly used CRC screening test in the USA. The U.S. Preventive Services Task Force (USPSTF) emphasizes that potential harms related to incidental extracolonic findings on screening CTC is an ongoing area of concern with insufficient evidence.[9] The potential harms primarily refers to additional follow-up tests, as well as invasive biopsies or other interventions for what ultimately proves to be benign disease that may have otherwise never presented clinically. In this study, the vast majority of investigations for the patients with additional findings proved to be unnecessary. As shown, over 100 additional follow-up tests were performed and almost 4% of the cohort (nine out of 231 patients) underwent an invasive procedure to prove benign nature of the detected lesion. Fortunately, no complications were observed in these patients. Assuming that the non-invasive investigations are less stressful and the 15 days waiting time until diagnosis is short, potential harm related to further work-up seems to be limited. Nevertheless, since the patient's experience was beyond the scope of this study, this cannot be evaluated. Psychological consequences as a result of the staging CT could either be positive

or negative. Although an unexpected diagnosis could result in feelings of fear and anxiety for both the patient and their relatives, some people might find it reassuring that no abnormalities were found. More research is warranted on the possibility of psychological consequences as a result of cross-sectional imaging like CT.

Previous cost estimates for the diagnostic workup of extracolonic findings in screening CTC studies are around $30 per patient.[10,11] However, these studies did not include the cost of surgical procedures and hospitalization required as part of the workup. Also, the prevalence of additional findings in CTC studies is much lower compared to our cohort[11], limiting its comparability. A longitudinal analysis of the outcomes and potential benefits derived from early detection of a wide variety of relevant diseases is required in order to comment on cost-effectiveness.

One in six patients in this study had findings that were confirmed to be clinically important. While one may be tempted to claim this allegedly collateral screening benefit, the added value of treating these patients with important findings is clearly not established. For example, the synchronous malignant tumours that were found in this cohort were mainly cancers that have a more prolonged natural history, in line with previous literature on extracolonic malignancies in studies with screening CTCs.[11] Unfortunately, most aggressively growing cancers which are generally detected in advanced stage, are rarely found by chance.[12] Therefore this collateral screening benefit is prone to lead-time bias.[13]

Previous CTC studies show an incidence of highly important findings ranging from 4.5% to 13%.[11,14-16] The difference between these studies and the much higher prevalence as observed in our study (44.6%) can be explained by multiple reasons. First, patients in our study underwent CT staging of not only the abdomen but also chest. Second, the key differences between CTC and the staging CT are radiation dose and contrast administration. CTC have low-dose technique and lack of intravenous contrast, and therefore supposedly lower sensitivity. Furthermore, the difference in study populations might attribute to the difference in prevalence of additional findings. As opposed to our study population, in CTC studies only <1% will be diagnosed with CRC.[17] Finally, comparison with other literature is impaired due to the large variety of definitions that are used in different studies. For example, the term "extracolonic findings", as proposed by the working group on virtual colonoscopy, states that all lesions outside the colon should be included.[18] The American College of Radiology Incidental Findings Committee (IFC) defines an "incidental finding" as a lesion detected by an imaging modality performed for an unrelated reason.[8] Based on the latter definition, the lung nodules and liver lesions would have been excluded. However, since the aim of this study was to examine the prevalence and sequela of all (potentially) important non-metastatic lesions, indeterminate lung and liver lesions were included as additional findings.

A particular challenge are the lung nodules. Pulmonary metastases usually occur in patients with either liver metastases, widespread locoregional disease or distal rectal cancer. Metastatic disease restricted to the lungs is observed in only 1-6% of patients with colon cancer and 10-18% in patients with rectal cancer.[19,20] Therefore, the low incidence of pulmonary metastases and the frequent finding of indeterminate

lesions limits the clinical value of routine staging chest CT.[21] For this reason, by the end of this study in January 2017, the pre-operative workup was adjusted in our clinic. Instead of a chest CT, a preoperative X-ray of the chest was conducted in every patient with colon cancer, in order to restrain the number of incidental findings. CT is nowadays only reserved for patients at high risk of lung metastases, including patients with rectal cancer.

This study is the first to describe the prevalence and outcomes of additional findings on staging contrast-enhanced CT in a CRC screening population. The major strengths of this cohort study are the long-term follow-up and the population with predominantly CRCs. Also, as the study population concerns consecutively treated patients in a large teaching hospital, this study reflects daily clinical practice. Limitations are the retrospective design of the study and its single centre origin. Also, only those findings that were documented in the original radiology report were registered. The number of additional findings might have be higher when a radiologist would have interpreted the CT findings within the framework of this study. Due to the retrospective design, no information about psychological consequences could be obtained. This should be the subject of future research. It is important that patients with FIT screen-detected lesions who undergo staging CT should be informed prior to the procedure that additional investigations may be necessary. A more complete understanding of the frequency and nature of these additional findings is critical in order to place it into context of the benefits and costs of screening as a whole.

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PART II
SURGERY FOR EARLY STAGED LESIONS

CHAPTER 5

Multicentre study of surgical referral and outcomes of patients with benign colorectal lesions

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BJS Open 2019 Jul 30;3(5):687-695

ABSTRACT

Background: A multicentre cohort study was performed to analyse the motivations for surgical referral of patients with benign colorectal lesions, and to evaluate the endoscopic and pathological characteristics of these lesions as well as short-term surgical outcomes.

Methods: Patients who underwent surgery for a benign colorectal lesion in 15 Dutch hospitals between January 2014 and December 2017 were selected from the pathology registry. Lesions were defined as complex when at least one of the following features was present: size at least 40 mm, difficult location according to the endoscopist, previous failed attempt at resection, or non-lifting sign.

Results: A total of 358 patients were included (322 colonic and 36 rectal lesions). The main reasons for surgical referral of lesions in the colon and rectum were large size (33.5 and 47 per cent respectively) and suspicion of invasive growth (31.1 and 58 per cent). Benign lesions could be categorized as complex in 80.6 per cent for colonic and 80 per cent for rectal locations. Surgery consisted of local excision in 5.9 and 64 per cent of colonic and rectal lesions respectively, and complicated postoperative course rates were noted in 11.2 and 3 per cent. In the majority of patients, no attempt was made to resect the lesion endoscopically (77.0 per cent of colonic and 83 per cent of rectal lesions).

Conclusion: The vast majority of the benign lesions referred for surgical resection could be classified as complex. Considering the substantial morbidity of surgery for benign colonic lesions, reassessment for endoscopic resection by another advanced endoscopy centre seems to be underused and should be encouraged.

INTRODUCTION

The vast majority of colorectal cancers arise from benign precursor lesions, namely adenomas or serrated polyps.[1,2] Although most polyps never progress to colorectal cancer and identifying polyps at risk remains challenging[3-6], it has been shown that removing adenomas reduces colorectal cancer-related mortality.[7] Together with the long dwell time, this makes colorectal cancer a suitable disease for population-based screening.

In the Netherlands, a colorectal cancer screening programme was implemented in 2014. Every individual aged between 55 and 75 years is invited biennially to participate and perform a faecal immunochemical test (FIT), followed by colonoscopy if the FIT result is positive. Lesions identified by colonoscopy are mostly treated by conventional endoscopic resection, with a minimal risk of complications such as bleeding or perforation.[8-10] Formal oncological bowel resection is still often considered as the main therapeutic approach for large benign lesions, with additional surgical alternatives for rectal lesions, such as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS).[11,12] More recently, 'advanced' endoscopic alternatives have become available, such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (eFTR).

In the European Society of Gastrointestinal Endoscopy (ESGE) guideline published in 2017, Ferlitsch and colleagues[13] proposed a decision tree for the treatment of colorectal neoplasia. In this guideline, *en bloc* EMR, or piecemeal EMR removal if an *en bloc* removal is not feasible, should be considered for all large (20 mm or more) colorectal neoplasias with no endoscopic suspicion of invasive growth. All colorectal neoplasias above 40 mm without any suspicion of invasive growth should be referred to an expert centre. When there is suspicion of invasive growth, referral for *en bloc* endoscopic removal or surgery should also be considered.[13] However, even though advanced endoscopic alternatives are proven safe and effective[14,15], multiple studies[16-18] have shown that surgery for benign neoplasia is still common, and referral patterns vary widely.[19] For obvious reasons, formal segmental bowel resection results in higher morbidity and mortality rates compared with endoscopic resection.[20] Especially for benign lesions, this could raise questions about proportionality of surgery in relation to the anomaly. Up-to-date studies allowing a more in-depth insight of surgically resected benign lesions are sparse, thereby limiting our understanding of the context in which referral for surgery took place. Therefore improvements regarding referral patterns to both surgeons and gastroenterologists remain obscure.

This multicentre cohort study aimed to analyse the motivations for surgical referral of patients with benign lesions of the colon and rectum separately, and to evaluate the endoscopic and pathological characteristics and short-term surgical outcomes.

METHODS

An inquiry was performed into the Pathological Anatomy National Automated Archive (PALGA), the nationwide network and registry of histopathology and cytopathology in the Netherlands with complete national coverage.[21] All patients undergoing a surgical resection for a benign lesion over a 4-year period (January 2014 to December 2017) were eligible. The selection of patients was done retrospectively, by analysing the PALGA histopathology reports of both the polypectomy/endoscopic resection and the pathology report of the bowel resection. Selection of patients was moderated by two investigators.

This study was conducted in four academic hospitals, ten large teaching hospitals and one community hospital in different parts of the Netherlands. Each participating hospital appointed a surgeon responsible for (supervising) the data registration. Data were retrieved from electronic patient records, pathology reports and endoscopy reports. Data were entered in an online, web-based survey, based largely on the Dutch ColoRectal Audit (DCRA), a web-based national audit in which all patients undergoing surgery for primary colorectal carcinoma are recorded prospectively[22]. This research was conducted as part of the DCRA, which is an obligatory audit from the inspectorate of healthcare and requires no informed consent from patients for data collection. Data analyses were performed on an anonymized data set and did not need ethical approval according to Dutch law.

Inclusion and exclusion criteria

Inclusion criteria were benign lesions in the colon or rectum that were treated surgically. Surgical treatment included formal bowel resections, as well as local excisions, such as TEM/TAMIS, and wedge or segmental resections. Endoscopic resections, such as EMR, ESD and eFTR, were excluded. Exclusion criteria were adenocarcinoma (category T1 or above) as well as pathological (suspicion of) invasive carcinoma in the polypectomy specimen together with no residual carcinoma in the surgical specimen, polyposis syndromes, or a non-neoplastic indication for bowel surgery (such as inflammatory bowel disease).

Definitions

Benign colorectal lesions were defined as conventional adenomas (tubular, tubulovillous, villous adenoma, with either low- or high-grade dysplasia) and two types of serrated polyps: sessile serrated adenoma and traditional serrated adenoma. In the present study, lesions were categorized into three groups: lesions referred for suspicion of malignancy; complex lesions, with at least one of the following features: size 40 mm or more, difficult location according to the endoscopist, previous failed attempt at resection, non-lifting sign after submucosal injection; and non-complex lesions (all lesions without one of the above features). The definition of a complex lesion in this study was largely based on features of complexity as defined by the Association of Coloproctologists of Great Britain and Ireland.[12]

A complicated postoperative course was defined as a postoperative complication resulting in a hospital stay of more than 14 days and/or reintervention and/or postoperative mortality. Reintervention was defined as surgical, endoscopic or radiological intervention after primary bowel surgery. This composite outcome measure includes complications and mortality, which are seen as important outcome factors representing quality of care, and has been a quality indicator for several years within the DCRA.[23-25] Descriptive statistical analysis was performed using SPSS® version 24.0 for Windows® (IBM, Armonk, New York, USA).

RESULTS

A total of 358 patients underwent surgical treatment for a benign colorectal lesion in one of the 15 participating hospitals across the Netherlands between 1 January 2014 and 31 December 2017 (*Fig. 1*). The lesions were located in the colon in 89.9 per cent (322 patients) and in the rectum in 10.1 per cent (36). Patient and lesion characteristics are shown in *Table 1*. Some 59.7 per cent of patients with colonic lesions and 53 per cent of patients with rectal lesions were 70 years or younger.

Colonic and rectal lesions were diagnosed through the colorectal cancer screening programme in 45.3 and 50 per cent respectively. Colonic lesions were mainly right-sided, especially in the ileocaecal location (149 of 322, 46.3 per cent). If documented, the size of the lesion was assessed endoscopically as at least 40 mm in 60.1 per cent (143 of 238) of colonic and 77 per cent (20 of 26) of rectal lesions. In the majority of patients, no attempt was made to resect the lesion endoscopically (77.0 and 83 per cent for colonic and rectal lesions respectively), but a biopsy was often taken (85.5 and 87 per cent respectively).

For colonic lesions, histopathology reports of biopsies or endoscopic resection attempts showed a tubulovillous adenoma in 53.4 per cent, followed by tubular adenoma (35.8 per cent), villous adenoma (6.8 per cent), sessile serrated adenoma (2.9 per cent) and traditional serrated adenoma (0.4 per cent). For rectal lesions, there was tubulovillous adenoma in 44 per cent, villous adenoma in 34 per cent and tubular adenoma in 22 per cent. Of the adenomas, the majority contained low-grade dysplasia (colon 76.9 per cent, rectum 63 per cent).

Resection rates differed among the 15 participating hospitals. The proportion of patients who had surgery for benign colorectal lesions in proportion to colorectal surgery for both colorectal cancer and benign lesions varied between 0.5 and 12.8 per cent (*Fig. 2*).

Referral for surgery

The three main reasons for surgical referral of colonic lesions were size considered to be too large (33.5 per cent), suspicion of invasive growth (31.1 per cent) and a non-lifting sign (22.0 per cent) (*Table 2*). For rectal lesions, the main reasons for surgical referral were suspicion of invasive growth (58 per cent), size (47 per cent) and location (28 per cent). If no malignancy was suspected, lesions could be categorized

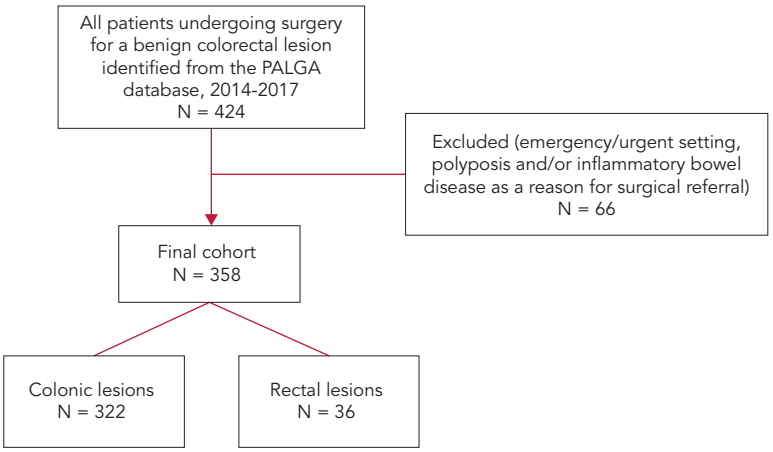

Figure 1. Flow diagram of patient selection

PALGA, Pathological Anatomy National Automated Archive

as complex in 80.6 and 80 per cent of colonic and rectal lesions respectively (*Table 2* and *Fig. 3*). Patients with benign lesions, either complex or non-complex, were referred to another centre for an (additional) endoscopic resection preceding surgical treatment in 1.4 and 13 per cent of cases respectively.

Surgical characteristics and outcomes

Laparoscopic resection was the commonest approach for colonic lesions (274 of 321, 85.4 per cent) and the most commonly performed type of bowel resection was a right-sided colectomy (187 of 322, 58.1 per cent). For rectal lesions, 23 (64 per cent) were resected via a local excision, primarily by TEM or TAMIS procedure (22 of 23). A stoma was constructed in 0.6 per cent of colonic (2 of 321) and 6 per cent of rectal (2 of 36) resections.

Following surgical treatment of colonic and rectal lesions, median hospital stay was 5 and 3 days respectively, the complicated postoperative course rate was 11.2 and 3 per cent, 30-day readmission rate was 4.0 and 0 per cent, and the 30-day or in-hospital mortality rate was 0.9 and 0 per cent. Surgical treatment characteristics and outcomes are summarized in *Table 3*.

Most colorectal lesions were treated by formal oncological resection. For the whole cohort, local or segmental resections were performed in 16 (13.2 per cent) of 121 patients in whom there was suspicion of invasive growth, in 22 (11.5 per cent) of 191 patients with complex lesions, and in ten (22 per cent) of 46 patients with lesions that were not complex. For rectal lesions, these rates were 57 per cent (12 of 21), 75 per cent (9 of 12) and 67 per cent (2 of 3) respectively. Of the 48 patients treated with local or segmental resection, only two (4 per cent) had a postoperative complication.

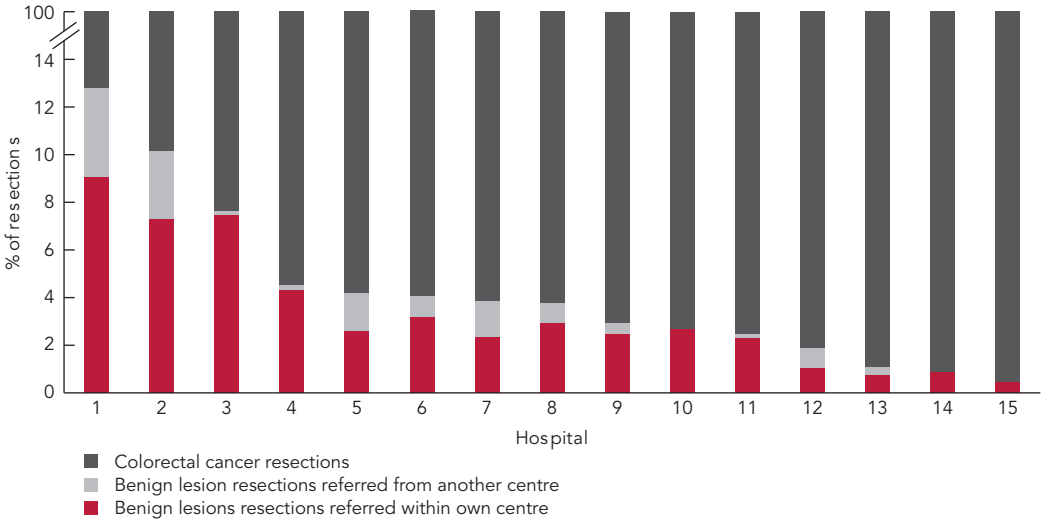

Figure 2. Proportion of operations performed for benign colorectal lesions per centre

Percentage of benign lesion resections of total (benign and colorectal cancer) resections

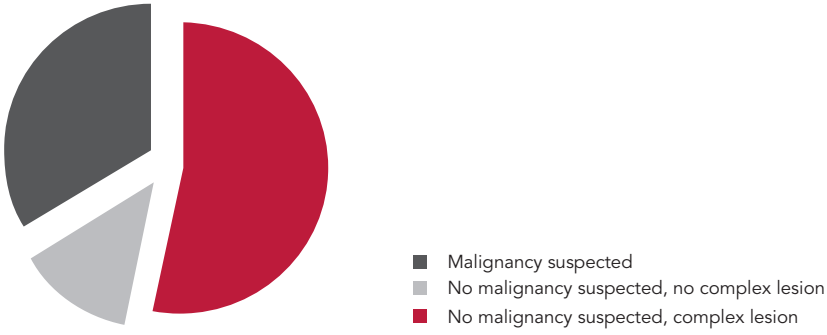

Figure 3. Reason for referral to surgery of 358 patients with benign colorectal lesions, 2014–2017

A complex lesion comprised: size 40 mm or more, difficult location according to endoscopist, previous failed attempt at resection, or non-lifting sign after submucosal injection

Table 1. Patient and lesion characteristics of 358 patients undergoing surgery for benign colorectal lesions, 2014–2017

		Colon (*n* = 322)	Rectum (*n* = 36)
Patient characteristics			
Age (years)	≤ 60	37 of 320 (11.6)	1 (3)
	61–70	154 of 320 (48.1)	18 (50)
	71–80	110 of 320 (34.4)	14 (39)
	≥ 81	19 of 320 (5.9)	3 (8)
Male sex		182 (56.5)	20 (56)
ASA grade ≥ III		71 of 320 (22.2)	7 (19)
BMI (kg/m2)	Unknown	35 (10.9)	2 (6)
	> 30	69 (21.4)	6 (17)
Charlson co-morbidity score	> 2	87 (27.0)	12 (33)
Lesion characteristics			
Diagnosis of lesion	Screening programme	146 (45.3)	18 (50)
	Surveillance	35 (10.9)	6 (17)
	Symptomatic	70 (21.7)	8 (22)
	Incidental finding	25 (7.8)	1 (3)
	Other	46 (14.3)	3 (8)
Location of lesion	Ileocaecal valve	30 (9.3)	
	Caecum	112 (34.8)	
	Appendiceal orifice	7 (2.2)	
	Ascending colon	69 (21.4)	
	Hepatic flexure	24 (7.5)	
	Transverse colon	23 (7.1)	
	Splenic flexure	8 (2.5)	
	Descending colon	21 (6.5)	
	Sigmoid	28 (8.7)	
	Rectum		36 (100)
Endoscopic size of lesion (cm)	0–1.9	13 (4.0)	1 (3)
	2–3.9	82 (25.5)	5 (14)
	4–5.9	74 (23.0)	8 (22)
	≥ 6	69 (21.4)	12 (33)
	Missing	84 (26.1)	10 (28)
Endoscopic removal of lesion			
Assessed as radically removed		5 (1.6)	0 (0)
Attempt to remove failed		62 (19.3)	6 (17)
Reason attempt failed	Non-lifting	43 of 62 (69)	0 (0)
	Complication	0 of 62 (0)	3 of 6 (50)
	Other	16 of 62 (26)	3 of 6 (50)
No attempt to remove		248 (77.0)	30 (83)
If no attempt, was biopsy taken?	Yes	212 of 248 (85.5)	26 (87)
Not known whether attempt was made		7 (2.2)	0 (0)
Histological findings*	Tubular adenoma	100 of 279 (35.8)	7 of 32 (22)
	Tubulovillous adenoma	149 of 279 (53.4)	14 of 32 (44)
	Villous adenoma	19 of 279 (6.8)	11 of 32 (34)
	Sessile serrated adenoma	8 of 279 (2.9)	0 (0)
	Traditional serrated adenoma	1 of 279 (0.4)	0 (0)
	Missing	2 of 279 (0.7)	
Dysplasia adenoma	Low grade	206 of 268 (76.9)	20 of 32 (63)
	High grade	62 of 268 (23.1)	12 of 32 (38)
Dysplasia sessile serrated polyps	No dysplasia	4 of 8 (50)	
	With dysplasia	4 of 8 (50)	

Values in parentheses are percentages. *Histological findings of lesion provided there was a biopsy or attempt at endoscopic removal.

Table 2. Surgical referral characteristics of 358 patients undergoing surgery for benign colorectal lesions, 2014–2017

	Colon (*n* = 322)	**Rectum (*n* = 36)**
Reason for referral for surgical resection*		
Size	108 (33.5)	17 (47)
Endoscopic size of lesion (cm)		
0–1.9	2 of 108 (1.9)	0 (0)
2–3.9	21 of 108 (19.4)	3 of 17 (18)
4–5.9	40 of 108 (37.0)	3 of 17 (18)
≧ 6	20 of 108 (18.5)	8 of 17 (47)
Missing	25 of 108 (23.1)	3 of 17 (18)
Suspicion of invasive growth	100 (31.1)	21 (58)
Location	61 (18.9)	10 (28)
Ileocaecal valve	14 of 61 (23)	
Caecum	32 of 61 (52)	
Appendicular orifice	4 of 61 (7)	
Ascending colon	4 of 61 (7)	
Hepatic flexure	1 of 61 (2)	
Transverse colon	2 of 61 (3)	
Splenic flexure	0 of 61 (0)	
Descending colon	1 of 61 (2)	
Sigmoid	3 of 61 (5)	
Distance from anal verge (cm)		
< 5		3 of 10 (30)
5–10		2 of 10 (20)
> 10		2 of 10 (20)
Unknown		3 of 10 (30)
Non-lifting sign	71 (22.0)	4 (11)
(Suspicion of) incomplete resection after endoscopic removal	31 (9.6)	5 (14)
Incomplete resection based on histological examination	18 (5.6)	0 (0)
Patient preference	5 (1.6)	0 (0)
Symptoms related to lesion	6 (1.9)	0 (0)
Other	13 (4.0)	1 (3)
Categorized reason for referral		
Malignancy suspected		
Yes	100 (31.1)	21 (58)
No	222 (68.9)	15 (42)
Complex lesion	179 of 222 (80.6)	12 of 15 (80)
No complex lesion	43 of 222 (19.4)	3 of 15 (20)
Referral made to another centre†	3 of 222 (1.4)	2 of 15 (13)
Preoperative MDT meeting	186 (57.8)	21 (58)

Values in parentheses are percentages.

* Multiple answers possible;

† for reassessment of possible endoscopic removal.

Table 3. Treatment characteristics and 30-day adverse events after surgery for benign colorectal lesions, 2014–2017

	Colon (*n* = 322)	**Rectum (*n* = 36)**
Surgical procedure		
Ileocaecal resection	44 (13.7)	
(Extended) right colectomy	187 (58.1)	
Transversectomy	6 (1.9)	
(Extended) left colectomy	25 (7.8)	
Sigmoid resection	20 (6.2)	
Subtotal colectomy (caecum to rectum)	2 (0.6)	
Segmental resection of colon	6 (1.9)	
Anterior resection (PME)	4 (1.2)	
Low anterior resection		11 (31)
Abdominoperineal resection		1 (3)
Local excision	19 (5.9)	23 (64)
Other	9 (2.8)	1 (3)
Stoma		
No stoma	319 (99.1)	34 (94)
Defunctioning ileostomy	1 (0.3)	1 (3)
Defunctioning colostomy		1 (3)
End colostomy	1 (0.3)	
Unknown	1 (0.3)	
Complications		
None	240 (74.5)	35 (97)
Surgical	24 (7.5)	1 (3)
Non-surgical	32 (9.9)	0 (0)
Surgical and non-surgical	17 (5.3)	0 (0)
Type unknown	7 (2.2)	0 (0)
Unknown	2 (0.6)	
Reintervention	26 (8.1)	1 (3)
Complicated course	36 (11.2)	1 (3)
Mortality	3 (0.9)	0 (0)
Length of hospital stay (days)*	5 (3–8)	3 (1–5)
Readmission	13 (4.0)	0 (0)

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). PME, partial mesorectal excision.

DISCUSSION

This multicentre cohort study demonstrates that the majority of the benign colorectal lesions referred for bowel resection in the Netherlands were classified as complex. Size was the most common reason for surgical referral, followed by a suspicion of invasive growth, difficult location and non-lifting sign. Referral to another centre with advanced endoscopic expertise to assess the possibilities of an additional endoscopic resection attempt before deciding on surgical treatment was seldom undertaken. The majority of rectal lesions are treated by local excision with only minor morbidity. In contrast, lesions located in the colon were treated mainly by oncological resection, with notable morbidity (complicated course 11.2 per cent) and a mortality rate of 0.9 per cent.

Whereas in most studies on surgical treatment of benign colorectal lesions, no data is provided on location, in the present study a notable difference was seen in motivation for surgery between colonic and rectal lesions. Patients with rectal lesions were more often referred to the surgeon because of suspicion of malignancy (58 per cent for rectal polyps compared with 31.1 per cent for colonic polyps). This might be explained by the possibility of treating large rectal adenomas by local excision, with a relatively low risk of complications due to better accessibility, greater stiffness of the wall, and the whole coverage of the rectal wall by surrounding mesentery, which limits the clinical consequences of anastomotic dehiscence.

Although multiple classification systems have been developed to grade the complexity of a lesion, referral for surgery remains largely subjective. However, referral to an advanced interventional endoscopist seems to be indicated for complex lesions with no evident features associated with the risk of covert malignancy, for example according to the criteria proposed by Burgess and colleagues.[26] In the present study, an attempt at endoscopic resection was made in about one-quarter of lesions with no suspicion of malignancy, and only five patients were referred to another centre for (an additional attempt of) endoscopic resection. Furthermore, if there was no suspicion of malignancy and endoscopic resection was not attempted, a biopsy was taken in the vast majority of cases. The current expert view is that, when a polyp looks benign, biopsy has no advantage over an endoscopic diagnosis, could cause fibrosis and might impede successful endoscopic resection at referral.

A previous Dutch study by Bronzwaer and co-workers[17] has already demonstrated that referral to another centre with advanced interventional endoscopy expertise is seldom considered, comprising an overall rate of 2.4 per cent between 2005 and 2015. It could be argued that all lesions with no suspicion of malignancy and size greater than 2 cm would be appropriate candidates for referral to an advanced interventional endoscopist, according to the ESGE guideline.[13] Following these criteria, more than 90 per cent of lesions in the present study would have been eligible for referral for endoscopic reassessment. Literature on benign colorectal lesions has reported that surgery could have been avoided in up to 70 per cent of patients following reassessment of the lesion by an expert endoscopist, although the sample sizes ere small.[27-30]

Formal oncological resection of benign colorectal lesions would be expected to be associated with higher morbidity and mortality rates compared with local excision alternatives. A large cohort of 12 732 patients studied by Peery *et al.*[31] reported a 14 per cent risk of a major postoperative adverse event and a 30-day mortality rate of 0.7 per cent, in agreement with the present results (10.3 per cent complicated course and 0.8 per cent 30-day mortality rate). For endoscopic resections including conventional polypectomy, EMR and ESD, the primary complications are bleeding and perforation. Delayed bleeding after these endoscopic techniques has been reported in 1.6, 1.2–1.7 and 0.7–2.2 per cent respectively, and perforation in 0.05, 0.3–0.8 and 2–14 per cent.[32,33]

This study has several limitations. First and most importantly, there was no information on lesions treated successfully by endoscopic resection. Thus, it remains unclear to what extent the relative surgery rates change over time. In addition, it is not known to what extent the endoscopic removal of lesions was successful in patients referred to another advanced endoscopy centre for endoscopic resection. Also, some parameters were not registered, in particular the morphology of the lesion according to their appearance (flat, sessile, pedunculated). For that reason, existing scoring systems could not be used to define the difficulty of polypectomy.[34] It remains unclear whether the decision not to attempt an endoscopic resection was based on a single opinion, or whether colleagues in the same hospital were consulted. Furthermore, as in 26.3 per cent of patients there were no data on the size of the lesion, this should be taken into consideration when interpreting the results. Moreover, as no information was available on the number of colonoscopies per centre, variability between the hospitals, as shown in *Fig. 2*, is of limited value. An upcoming surgical alternative for colonic lesions that are not suitable for endoscopic removal is the limited endoscopy-assisted wedge resection[35]. This technique is currently being investigated in a multicentre cohort study, perhaps reflecting the high resection rates in some of the participating hospitals. Other factors that might contribute to the variation in resection rate among different hospitals could be subject for future research. In addition, to put the present results into a wider context, it would have been interesting to have data on how many lesions with an endoscopic suspicion of malignancy were indeed malignant at final histopathological assessment, or how many lesions that were classified as benign turned out to be malignant after surgical resection.

The majority of benign colorectal lesions referred to the surgeon are classified as complex, both for colonic and rectal localizations. Referral to another centre for reassessment of endoscopic resection seems to be underused. When a patient is referred for surgical resection of a colonic lesion, treatment is accompanied with substantial morbidity. A national consensus on when to refer a patient to an advanced interventional endoscopist, and defining what constitutes an advanced interventional endoscopist, would be desirable.

Acknowledgements

The authors thank J. Algie for his contribution to this manuscript, as well as all the surgeons, residents and data managers for the data entry. In addition, they thank the research advisors of PALGA and employees of the pathology departments for their work.

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CHAPTER 6

National cohort study on postoperative risks after surgery for submucosal invasive colorectal cancer

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BJS Open 2018 Dec 24;3(2):210-217

ABSTRACT

Background: The decision to perform surgery for patients with T1 colorectal cancer hinges on the estimated risk of lymph node metastasis, residual tumour and risks of surgery. The aim of this observational study was to compare surgical outcomes for T1 colorectal cancer with those for more advanced colorectal cancer.

Methods: This was a population-based cohort study of patients treated surgically for pT1–3 colorectal cancer between 2009 and 2016, using data from the Dutch ColoRectal Audit. Postoperative complications (overall, surgical, severe complications and mortality) were compared using multivariable logistic regression. A risk stratification table was developed based on factors independently associated with severe complications (reintervention and/or mortality) after elective surgery.

Results: Of 39 813 patients, 5170 had pT1 colorectal cancer. No statistically significant differences were observed between patients with pT1 and pT2–3 disease in the rate of severe complications (8.3 *versus* 9.5 per cent respectively; odds ratio (OR) 0.89, 95 per cent c.i. 0.80 to 1.01, $P = 0.061$), surgical complications (12.6 *versus* 13.5 per cent; OR 0.93, 0.84 to 1.02, $P = 0.119$) or mortality (1.7 *versus* 2.5 per cent; OR 0.94, 0.74 to 1.19, $P = 0.604$). Male sex, higher ASA grade, previous abdominal surgery, open approach and type of procedure were associated with higher severe complication rate in patients with pT1 colorectal cancer.

Conclusion: Elective bowel resection was associated with similar morbidity and mortality rates in patients with pT1 and those with pT2–3 colorectal carcinoma.

INTRODUCTION

The introduction of population-based colorectal carcinoma screening programmes aims to reduce mortality from colorectal cancer. Screening-detected colorectal cancers have a more favourable stage distribution than those that are symptom-detected, but it remains unclear whether early diagnosis following screening results in better surgical outcomes.[1] In January 2014, a nationwide colorectal cancer screening programme was launched in the Netherlands. Individuals aged 55–75 years are offered a biennial faecal immunochemical test (FIT), and diagnostic colonoscopy when the FIT is positive.[2]

A proportion of colorectal cancers limited to the submucosa (pT1) can be treated with minimally invasive endoscopic resection techniques, in contrast to more advanced colorectal cancers.[3] The indication to perform additional surgery depends on the risks of lymph node metastasis and incomplete resection, which is estimated using histological risk factors such as lymphovascular invasion, invasion depth, differentiation grade, tumour budding and resection margins.[4-5,6] Assessment of whether the oncological benefits of excision of potential positive lymph nodes and possible residual cancer tissue outweigh the risks of additional surgery is challenging[7,8]. Evidence regarding the magnitude of these risks is sparse. Studies evaluating surgical morbidity and mortality of colorectal surgery consist mainly of patients with more advanced tumours.[9-11] These risks cannot simply be extrapolated to patients with pT1 colorectal cancer as the clinical characteristics of patients with advanced colorectal carcinoma might be different[12], few treatment alternatives are available, and the risk of cancer-related death is higher.

The aim of this study was to compare short-term postoperative outcomes after elective bowel resection in patients with pT1 and those with pT2–3 colorectal cancer, and to identify the key clinical features associated with severe complications after surgery for pT1 colorectal cancer from which a risk stratification table could be developed to help clinicians guide treatment decisions in patients with pT1 colorectal cancer.

METHODS

This was a population-based cohort study of patients who underwent colorectal surgery for pT1–3 stage colorectal cancer between January 2009 and December 2016 in the Netherlands. The total population in the Netherlands was estimated as 16.6 million people in 2010, according to Statistics Netherlands. Patients were identified from the Dutch ColoRectal Audit (DCRA), formerly known as the Dutch Surgical Colorectal Audit. The DCRA is a web-based national audit, in which information on all patients undergoing surgery for primary is recorded prospectively.[13] The database has complete national coverage as the Dutch Health Inspectorate obliges inclusion of all surgically treated patients with colorectal cancer.

Patients who had an elective oncological resection were included in the study. Those who underwent neoadjuvant treatment, urgent or emergency surgery, or only a local procedure were excluded, as were patients with metastatic disease or synchronous colorectal cancer. Patients treated with a local surgical procedure before bowel resection were not excluded.. As all data in the DCRA are coded, no ethical approval or informed consent was required for this study under Dutch law.[14]

Outcomes

Main outcome measures were overall, surgical and severe complications, and mortality. Definitions are shown in *Table 1*. The reason for selecting the combined outcome of severe complications (reintervention and/or mortality) in this study was because mortality alone was considered an underestimation of the total burden to the patient.[15] If no complication was registered, the authors assumed no complication had occurred. The number of patients with surgically treated colorectal cancer were analysed over time, according to pT category, to determine the effect of the introduction of mass screening.

Risk factors and study parameters

Patient- and tumour-related risk factors associated with morbidity and mortality following elective colorectal surgery in previous literature were used in analyses.[16-19] Factors analysed were: age, sex, cardiac, pulmonary and neurological co-morbidity, ASA grade (I–II *versus* III–V), history of abdominal surgery, BMI, preoperative complications (perforation with peritonitis, abscess, obstruction or ileus, bleeding or anaemia, or other), tumour location (colon or rectum), detection method (non-screen-detected *versus* screen-detected), year of surgery, type of procedure (open, laparoscopic or conversion from laparoscopic to open procedure), type of surgery (right colectomy, left colectomy, sigmoid resection, low anterior resection (LAR), abdominoperineal resection (APR), (sub)total colectomy or other), lymph node yield (less than 12 or 12 or more nodes) and pN category (N0, N1 or N2). Ileocaecal and transverse resections were also categorized as right colectomy. Panproctocolectomy and subtotal colectomy were categorized together as (sub)

Table 1. Definitions

Definition	Description
Overall complications	Complications within 30 days after surgery including cardiac, pulmonary, thromboembolic, neurological, infectious, other general and surgical complications
Surgical complications	Complications within 30 days after primary surgery that were directly related to the surgical intervention, including anastomotic leakage, abscess, bleeding and postoperative ileus
Severe complications	Complications requiring reintervention and/or leading to death within 30 days after primary surgery (mortality)
Mortality	Death within 30 days after surgery
Reintervention	Reoperation (open or laparoscopic surgery) or radiological intervention after primary bowel surgery. Minor interventions such as placement of a central venous catheter, incision of a superficial wound infection or nasogastric intubation were not considered reinterventions

total colectomy. When information on co-morbidity was missing, it was interpreted as absent. For all patients, tumour stage was defined according to the fifth edition of the TNM classification of malignant tumours for colorectal cancer.[20]

Statistical analysis

Baseline characteristics were compared between patients with pT1, pT2 and pT3 colorectal cancer using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Missing data were assumed to be missing at random. For all logistic regression analyses, multiple imputation using a Markov chain Monte Carlo method was performed to adjust for missing values (10-imputation data sets, 25 iterations).[21,22]

The association between pT category (pT1 *versus* pT2–3 colorectal cancer) and short-term postoperative outcomes was evaluated with univariable logistic regression analysis, expressed as odds ratios (ORs) with 95 per cent confidence intervals. Multivariable logistic regression analysis was performed to adjust for possible confounding factors. Age, BMI and year of surgery were analysed continuously in regression analyses; the remaining variables were analysed as categorical.

To identify risk factors associated with severe complications after elective surgery for pT1 colorectal cancer, logistic regression analyses were performed. Independent variables with $P < 0.050$ in univariable analysis were entered into the multivariable logistic regression model. A risk stratification table was developed for severe complications after surgery for pT1 colorectal cancer, stratified for sex (men *versus* women), type of operation (right colectomy *versus* left colectomy *versus* sigmoid resection *versus* LAR *versus* APR) and ASA grade (I–II *versus* III–V). Bootstrapping was performed to calculate 95 per cent confidence intervals.

GraphPad Prism® version 7.02 (GraphPad Software, La Jolla, California, USA) and Microsoft Visio® version 2010 (Microsoft, Redmond, Washington, USA) were used to draw figures. All analyses were performed in IBM SPSS® version 23.0 software (IBM, Armonk, New York, USA). Statistical significance was defined as $P < 0.050$.

RESULTS

Of 51 470 surgically treated patients with colorectal cancer identified, 39 813 fulfilled the inclusion criteria (*Fig. 1*). Some 5170 (13.0 per cent) were diagnosed with pT1, 9701 (24.4 per cent) with pT2 and 24 942 (62.6 per cent) with pT3 colorectal carcinoma. The mean age of the cohort was 71 years and 54.4 per cent were men. Baseline characteristics are shown in *Table 2*. Patients with T1 CRC were significantly younger, more often men, and had a lower ASA grade (all $P < 0.001$). pT1 cancers were more often screen-detected, more frequently diagnosed in 2015–2016 and more often located in the rectum (all $P < 0.001$). Patients with pT2–3 tumours more often had preoperative complications and underwent open surgery more frequently (both $P < 0.001$). Patients treated with a local surgical procedure before bowel resection accounted for 1.3 per cent of the complete cohort. Ileocaecal and

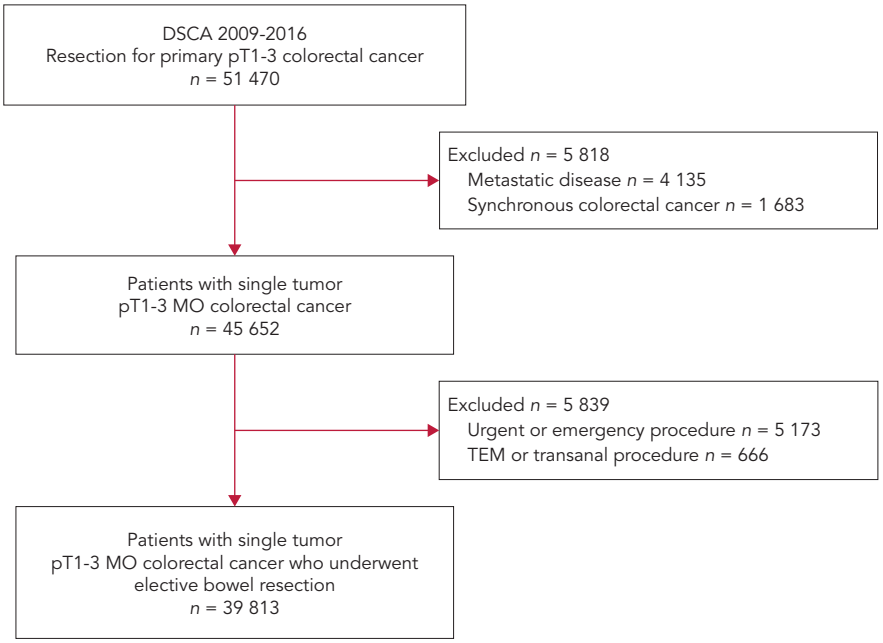

Figure 1. Study flow chart of included patients.
DSCA, Dutch Surgical Colorectal Audit; TEM, transanal endoscopic microsurgery

transverse resections accounted for 0.6 and 2.1 per cent of operations respectively; these were recategorized as right colectomies. Panproctocolectomy and subtotal colectomy accounted for 0.3 and 1.3 per cent respectively, and were recategorized as (sub)total colectomies.

Time trends

An increase in the absolute number of patients treated surgically for colorectal cancer was observed over time, from 3139 in 2009 to 6864 in 2016. The proportion of pT1 cancer increased from 8.1 per cent in 2009 to 17.7 per cent in 2016 ($P < 0.001$) (*Fig. 2*). The steepest increase was between 2014 and 2015 (+4.4 per cent), with 2014 being the year in which the colorectal cancer screening programme was introduced in the Netherlands. The proportion of screen-detected pT1 tumours among all pT1 colorectal cancers increased from 34.6 per cent in 2014 to 61.3 per cent in 2016 ($P < 0.001$) (*Fig. 3*).

Morbidity and mortality in pT1 versus *pT2–3 colorectal cancer*

Complications were observed in a total of 10 828 patients (27.2 per cent). Surgical complications occurred in 13.4 per cent (5334 patients) and severe complications in 9.3 per cent (3711). The 30-day mortality rate was 2.4 per cent. The overall complication rate was significantly lower following surgery for pT1 cancer compared with surgery for pT2–3 disease (23.6 *versus* 27.7 per cent respectively; OR 0.80,

Table 2. Demographic and clinical characteristics of surgically treated patients with colorectal carcinoma, according to pT category (2009–2016)

	pT1 (*n* = 5170)	**pT2–3 (*n* = 34 643)**	**P¥**
Age (years)*	69(9)	71(11)	< 0.001#
Sex			< 0.001
M	2971 (57.5)	18 698 (54.0)	
F	2196 (42.5)	15 936 (46.0)	
Unknown	3 (0.1)	9 (0.0)	
Type of co-morbidity			
Cardiac	1463 (28.3)	9924 (28.6)	0.609
Pulmonary	751 (14.5)	4851 (14.0)	0.314
Neurological	702 (13.6)	5066 (14.6)	0.047
ASA fitness grade			
I–II	4154 (80.3)	26 314 (76.0)	< 0.001
III–V	1005 (19.4)	8092 (23.4)	
Unknown	11 (0.2)	237 (0.7)	
Previous abdominal surgery			0.137
No	3300 (63.8)	22 422 (64.7)	
Yes	1857 (35.9)	12 045 (34.8)	
Unknown	13 (0.3)	176 (0.5)	
BMI (kg/m2)*	27(4)	27(5)	< 0.001#
Preoperative complication			< 0.001
No	4555 (88.1)	25 973 (75.0)	
Yes	584 (11.3)	8402 (24.3)	
Unknown	31 (0.6)	268 (0.8)	
Location of primary tumour			< 0.001
Colon	4397 (85.0)	31 038 (89.6)	
Rectum	773 (15.0)	3605 (10.4)	
Detection method			< 0.001
Non-screen-detected	3412 (66.0)	29 791 (86.0)	
Screen-detected	1695 (32.8)	4531 (13.1)	
Unknown	63 (1.2)	321 (0.9)	
Year of surgery			< 0.001
2009–2014	2733 (52.9)	23 379 (67.5)	
2015–2016	2437 (47.1)	11 264 (32.5)	
Type of procedure			< 0.001
Laparoscopic	3784 (73.2)	20 763 (59.9)	
Laparotomy	1038 (20.1)	11 208 (32.4)	
Conversion†	327 (6.3)	2562 (7.4)	
Unknown	21 (0.4)	110 (0.3)	
Type of surgery			< 0.001
Right colectomy‡	1552 (30.0)	15 786 (45.6)	
Left colectomy	395 (7.6)	3221 (9.3)	
Sigmoid resection	2306 (44.6)	11 413 (32.9)	
LAR	644 (12.5)	2867 (8.3)	
APR	98 (1.9)	664 (1.9)	
(Sub)total colectomy§	126 (2.4)	539 (1.6)	
Other	47 (0.9)	149 (0.4)	
Unknown	2 (0.0)	4 (0.0)	

	pT1 (*n* = 5170)	pT2–3 (*n* = 34 643)	P¥
Lymph node yield			< 0.001
≤ 12	2229 (43.1)	7207 (20.8)	
≥ 12	2911 (56.3)	27 324 (78.9)	
Unknown	30 (0.6)	112 (0.3)	
pN category			< 0.001
pN0	4415 (85.4)	22 652 (65.4)	
pN1	496 (9.6)	8097 (23.4)	
pN2	173 (3.3)	3758 (10.8)	
Unknown	86 (1.7)	136 (0.4)	

Values in parentheses are percentages unless indicated otherwise;
* values are mean(s.d.). LAR, low anterior resection; APR, abdominoperineal resection.
† From laparoscopic to open procedure;
‡ including ileocaecal resection and transverse resection;
§ including panproctocolectomy and subtotal colectomy.
¥ χ^2 test, except #Kruskal–Wallis test.

95 per cent c.i. 0.75 to 0.86, $P < 0.001$). This finding remained statistically significant after adjusting for confounders (OR 0.90, 0.84 to 0.97, $P = 0.008$). Rates of surgical complications (12.6 *versus* 13.5 per cent; adjusted OR 0.93, 0.84 to 1.02, $P = 0.119$), severe complications (8.3 *versus* 9.5 per cent; adjusted OR 0.89, 0.80 to 1.01, $P = 0.061$) and mortality (1.7 *versus* 2.5 per cent; adjusted OR 0.94, 0.74 to 1.19, $P = 0.604$) did not significantly differ between the two groups (*Table 3*). Details regarding types of complication stratified according to pT group are summarized in *Table S1* (supporting information).

Risk stratification in patients with pT1 colorectal cancer

Factors associated with severe complications after surgery for pT1 colorectal cancer are shown in *Table S2* (supporting information). Male sex (adjusted OR 2.21, 95 per cent c.i. 1.76 to 2.79), cardiac co-morbidity (adjusted OR 1.26, 1.00 to 1.59), ASA grade III–IV (*versus* I–II; adjusted OR 1.41, 1.10 to 1.81), previous abdominal surgery (adjusted OR 1.25, 1.01 to 1.56), open approach (adjusted OR 1.60, 1.26 to 2.04), conversion from a laparoscopic to an open procedure (adjusted OR 1.89, 1.33 to 2.67) and subtotal colectomy (*versus* right colectomy; adjusted OR 2.38, 1.40 to 4.05) were independently associated with an increased risk of severe complications. Sigmoid resection was associated with a lower risk of severe complications (*versus* right colectomy; adjusted OR 0.67, 0.52 to 0.87). Using these risk factors, severe complication risk was stratified (*Fig. 4*). Women with ASA grade I–II and pT1 disease who underwent right colectomy or sigmoid resection had the lowest risk of severe complications (5 per cent or less), whereas men with ASA grade III–IV and pT1 disease treated with right or left colectomy had the highest risk of severe complications (more than 19 per cent).

Severe complication risks of surgery for pT2–3 colorectal cancer stratified for the same risk factors showed similar results. Women with ASA grade I–II who underwent sigmoid resection had a 5 per cent risk of severe complications and men with ASA grade III–IV treated with left colectomy had an 18.8 per cent risk (*Fig. 4*).

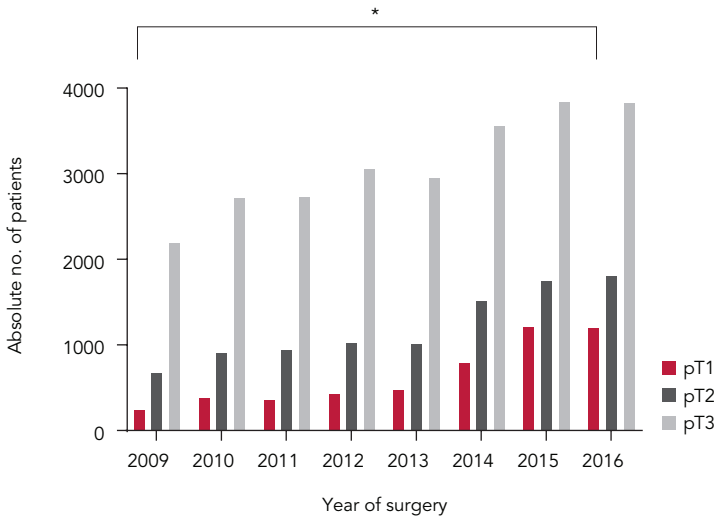

Figure 2. Distribution of surgically treated patients with colorectal cancer over time according to pT category.

*$P < 0.001$ (pT1 2009 versus pT1 2016, χ^2 test)

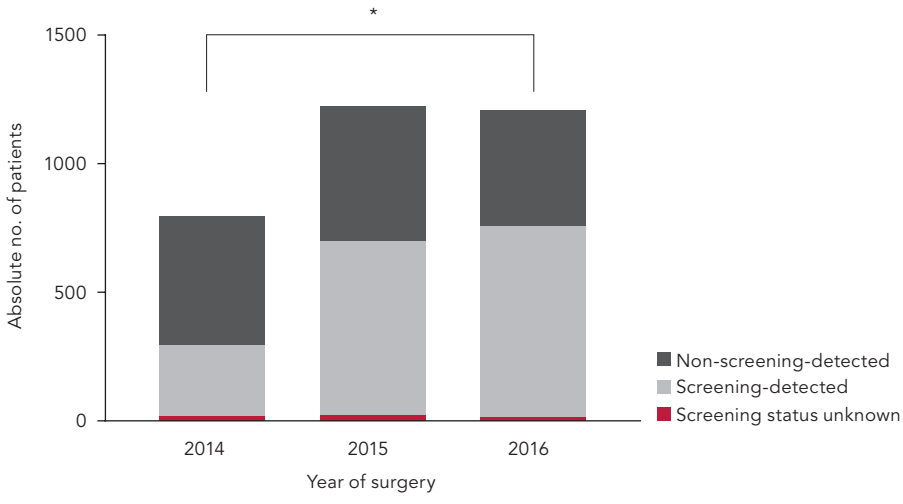

Figure 3. Contribution of screen-detected tumours in patients with pT1 colorectal cancer treated surgically after implementation of mass screening programme in 2014.

*$P < 0.001$ (χ^2 test)

a Complications in women

Type of operation	ASA grade I-II		ASA grade III-IV	
	n	%	n	%
pT1 category				
Right colectomy *	599	5.0 (3.1, 6.8)	150	10.7 (5.8, 16.3)
Left colectomy	134	6.0 (2.2, 10.2)	26	n.a.
Sigmoid resection	762	2.9 (1.8, 4.2)	138	5.1 (1.6, 9.3)
LAR	238	8.0 (4.6, 11.7)	28	n.a.
APR	37	5 (0, 14)	7	n.a.
pT2-3 category				
Right colectomy *	6371	6.1 (5.5, 6.7)	2075	10.0 (8.7, 11.4)
Left colectomy	1062	8.8 (7.2, 10.4)	308	15.9 (11.9, 20.1)
Sigmoid resection	3699	5.0 (4.3, 5.7)	725	11.7 (9.4, 14.1)
LAR	891	6.3 (4.7, 7.8)	201	9.5 (5.6, 13.5)
APR	170	5.3 (2.0, 8.7)	40	13 (3, 24)

b Complications in men

Type of operation	ASA grade I-II		ASA grade III-IV	
	n	%	n	%
pT1 category				
Right colectomy *	579	9.5 (7.3, 12.0)	220	19.1 (14.0, 24.4)
Left colectomy	179	10.1 (5.8, 15.0)	55	24 (12, 35)
Sigmoid resection	1119	6.3 (4.9, 7.9)	279	11.1 (7.6, 15.1)
LAR	312	15.1 (11.0, 19.1)	65	15 (7, 25)
APR	47	15 (6, 27)	7	n.a.
pT2-3 category				
Right colectomy *	5124	8.7 (7.9, 9.4)	2093	16.7 (15.0, 18.3)
Left colectomy	1345	11.5 (9.9, 13.3)	484	18.8 (15.3, 22.3)
Sigmoid resection	5387	8.3 (7.6, 9.0)	1516	13.9 (12.1, 15.6)
LAR	1371	15.0 (13.1, 16.8)	396	22.7 (18.8, 27.1)
APR	340	9.1 (6.3, 12.5)	112	22.3 (14.9, 30.0)

Figure 4. Risk of severe complications (reintervention and/or mortality within 30 days) after colorectal surgery in patients with pT1 and pT2–3 colorectal cancer. Risk of complications in a women and b men with ASA grade I–II and III–IV fitness (pT1: 427 events in 5170 patients; pT2–3: 3284 events in 34 643 patients). Increasing risk is indicated by change in colour from dark green to light green to yellow to orange to red. Values in parentheses are 95 per cent confidence intervals.

** Includes ileocaecal resection and transverse resection. n.a., Not applicable (sample size too small); LAR, low anterior resection; APR, abdominoperineal resection*

Table 3. Unadjusted and adjusted association between pT category of colorectal cancer (pT1 *versus* pT2–3) and postoperative outcomes

	Prevalence of outcome		Unadjusted		Adjusted‡	
	pT1 (*n* = 5170)	pT2–3 (*n* = 34 643)	Odds ratio*	P	Odds ratio*	P
Overall complications	1219 (23.6)	609 (27.7)	0.80 (0.75, 0.86)	< 0.001	0.90 (0.84, 0.97)	0.008
Surgical complications	650 (12.6)	4684 (13.5)	0.92 (0.84, 1.00)	0.062	0.93 (0.84, 1.02)	0.119
Severe complications†	427 (8.3)	3284 (9.5)	0.86 (0.77, 0.96)	0.005	0.89 (0.80, 1.01)	0.061
Mortality	87 (1.7)	880 (2.5)	0.66 (0.53, 0.82)	< 0.001	0.94 (0.74, 1.19)	0.604

Values in parentheses are percentages unless indicated otherwise; * values in parentheses are 95 per cent confidence intervals. † Reintervention and/or death. ‡ Adjusted for age (continuous), sex (men *versus* women), cardiac co-morbidity, pulmonary co-morbidity, neurological co-morbidity, ASA grade (I–II *versus* III–V), history of abdominal surgery (yes *versus* no), BMI (continuous), preoperative complications (yes *versus* no), tumour location (rectum *versus* colon), detection method (non-screen-detected *versus* screen-detected), year of surgery (continuous), type of procedure (open *versus* laparoscopic *versus* laparoscopic + conversion), type of surgery (right colectomy, left colectomy, sigmoid resection, low anterior resection, abdominoperineal resection, (sub)total colectomy or other procedure), lymph node yield (less than 12 *versus* 12 or more), pN category (N0 *versus* N1 versus N2).

DISCUSSION

This population-based cohort study demonstrates that patients undergoing elective bowel resections for pT1 colorectal cancer have similar risks for surgical complications, severe comlications and mortality as those undergoing elective bowel resections for pT2–3 colorectal carcinoma. The absolute difference in overall complication rate following pT1 *versus* pT2–3 was, although statistically significant, considered minor and therefore of little clinical relevance. Implementation of colorectal cancer screening aims to increase cancer-specific survival by diagnosing disease at an earlier stage, but also introduces treatment dilemmas. Early-stage tumours do not necessarily lead to safer surgical procedures.

The risks of postoperative complications after elective surgery for pT1 colorectal cancer have not been well described in previous studies. This is surprising because this type of surgery is frequently performed in clinical practice. Existing literature has focused mainly on advanced staged tumours in patients undergoing emergency surgery, and includes limited analysis of mortality with no morbidity estimates. In the present study an overall postoperative 30-day mortality rate of 2.4 per cent was observed for all patients, comparable with previous population-based studies[11,12,23-25] evaluating mortality risk in patients undergoing elective colorectal cancer resection (1.8–3.5 per cent). Previous reported relaparotomy rates after surgery for colorectal cancer range from 5.8 to 7.2 per cent[26], in accordance with the present study. A recently published study[27] on surgical risks after surgery for non-malignant colorectal polyps showed a low overall 30-day mortality rate of 0.7 per cent and a postoperative adverse event rate of 14 per cent. This, however, might be an underestimation as the American College of Surgeons' National Surgical Quality Improvement Program is not representative of all hospitals in the USA. A recently published multicentre

study[28] from the Netherlands with more than 900 patients undergoing surgery for benign colorectal polyps showed a 30-day mortality rate of 1.4 per cent, which is more in line with the present findings.

Risk factors for severe complications after pT1 colorectal cancer surgery included sex, ASA grade, previous abdominal surgery, type of procedure and type of surgery. This is in line with previous publications, as these factors are frequently used in prognostic scoring for colorectal cancer surgery.[16,18,19,29,30] Most of these existing scoring systems have been based on data of patients with more advanced colorectal carcinoma and include factors such as urgency, perioperative contamination, disseminated cancer, ascites and signs of hypovolaemic shock, which are irrelevant in most early-stage colorectal cancers.[29] The predictive model of the Association of Coloproctology of Great Britain and Ireland was based on a cohort in which 90 per cent of patients had advanced colorectal cancer.[31] The data used to produce the colorectal (CR)-POSSUM model were taken from a wide range of procedures, and more than 30 per cent of the 6790 included procedures were non-elective. In the present study, patient factors such as age, co-morbidity, BMI, tumour location, screening status and pN status were not predictive for severe complications. There has been long-standing controversy about whether age and higher BMI are associated with worse perioperative outcomes. A recent meta-analysis[10] of the effect of BMI failed to show significant influence on overall mortality or reoperation/reintervention rate after laparoscopic colorectal surgery.

A major strength of this study is its nationwide population-based design. Data are compared annually with those in the National Cancer Registry, and show nearly 100 per cent completeness[13,14], thereby reflecting daily clinical practice. It should be emphasized that patients who had neoadjuvant treatment or were operated on in the emergency setting were not included to avoid major confounding of postoperative outcomes. Several limitations should be mentioned. Inherent to a retrospective analysis, unmeasured confounding could be a source of bias. Although adjusting for possible confounders in multivariable analyses including screening status, a healthy user bias cannot be excluded. In previous papers, common factors such as educational level and regular check-up experience were identified as determinants of participation in colorectal cancer screening.[33] Therefore, screened participants could be less vulnerable for postoperative complications, regardless of pT status. The stratified risk model might slightly overestimate the actual risk, because of the decline of short-term mortality after colorectal surgery in the past decade, which was shown in this study as well as in other population-based studies.[24] Finally, the proportion of patients with pT1 colorectal cancer that was clinically staged correctly was not known. Diagnosis by endoscopy or imaging can be misleading and either overestimate or underestimate the actual tumour stage. This may influence surgical risks and oncological benefit in either direction.

Screening programmes target a population regardless of life expectancy. Additional surgery in patients with high-risk pT1 colorectal cancer should be well considered. Clinicians should estimate the patient's competing risks of morbidity and mortality. The risk stratification (*Fig. 4*) helps to estimate individual risks of significant morbidity and can be used before surgery in shared decision-making of whether or not to perform completion surgery for pT1 colorectal cancer.

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APPENDICES

Table S1. Short-term outcomes (within 30 days) of surgically treated patients with colorectal carcinoma (2009–2016)

	T1 *n*=5 170	**T2-3 *n*=34 643**	**P-value**
	n (%)	*n* (%)	
Overall complications			<0.001
No	3 942 (76.2)	24 916 (71.9)	
Yes	1 219 (23.6)	9 606 (27.7)	
Unknown	9 (<1)	118 (0.3)	
Surgical complications			0.064
No	4 520 (87.4)	29 959 (86.5)	
Yes	650 (12.6)	4 684 (13.5)	
Other complications			
Pulmonary	185 (3.6)	1 610 (4.6)	0.001
Cardiac	109 (2.1)	1 057 (3.1)	<0.001
Thromboembolic	23 (<1)	188 (0.5)	0.409
Infection (other than pulmonary/surgical)	124 (2.4)	1 160 (3.3)	<0.001
Neurological	54 (1.0)	435 (1.3)	0.224
Other	289 (5.6)	1 892 (5.5)	0.697
Mortality			0.002
No	5 074 (98.1)	33 618 (97.0)	
Yes	87 (1.7)	880 (2.5)	
Unknown	10 (<1)	145 (0.4)	
Cause of death^			0.521
CRC	0	9 (1)	
Surgery	38 (44)	333 (37.8)	
Other cause	32 (37)	327 (37.2)	
Unknown	17 (20)	211 (24.0)	
Anastomotic leakage*	176 (3.7)	1 247 (3.9)	0.358
Re-intervention	369 (7.1)	2 645 (7.6)	0.216
Re-admission	254 (4.9)	1 706 (4.9)	0.997
Severe complications (re-intervention and/or mortality)	427 (8.3)	3 284 (9.5)	<0.001

^ Percentage of patients deceased<30d, * percentage of patients with anastomosis

Table S2. Univariable and multivariable analyses of variables associated with severe complication rate following colorectal surgery for pT1 colorectal cancer

Parameter	Univariable analyses			Multivariable analyses		
	OR	CI	P-value	OR	CI	P-value
Age, years	**1.02**	**1.01-1.04**	**<0.001**	1.01	1.00-1.02	0.062
Gender						
Female	Reference			Reference		
Male	**2.15**	**1.72-2.69**	**<0.001**	**2.21**	**1.76-2.79**	**<0.001**
Comorbidity						
Cardiac	**1.71**	**1.39-2.10**	**<0.001**	**1.26**	**1.00-1.59**	**0.049**
Pulmonary	**1.57**	**1.23-2.02**	**<0.001**	1.28	0.99-1.67	0.064
Neurological	0.94	0.70-1.26	0.660			
ASA						
I-II	Reference			Reference		
III-V	**1.95**	**1.57-2.43**	**<0.001**	**1.41**	**1.10-1.81**	**0.007**
Previous abdominal surgery						
No	Reference			Reference		
Yes	**1.27**	**1.04-1.56**	**0.019**	**1.25**	**1.01-1.56**	**0.041**
BMI	1.02	1.00-1.05	0.051			
Preoperative complication						
No	Reference					
Yes	1.29	0.96-1.72	0.088			
Tumour location						
Colon	Reference			Reference		
Rectum	**1.61**	**1.26-2.06**	**<0.001**	0.87	0.25-2.99	0.824
Detection method						
Non-screen-detected	Reference					
Screen-detected	0.84	0.67-1.04	0.112			
Year of surgery	1.05	1.00-1.10	0.058			
Type of procedure						
Laparoscopic	Reference			Reference		
Open	**1.91**	**1.52-2.40**	**<0.001**	**1.60**	**1.26-2.04**	**<0.001**
Laparoscopic + conversion^	**2.34**	**1.68-3.27**	**<0.001**	**1.89**	**1.33-2.67**	**<0.001**
Type of surgery						
Right colectomy*	Reference			Reference		
Left colectomy	1.11	0.77-1.61	0.579	1.10	0.76-1.61	0.611
Sigmoid resection	**0.59**	**0.46-0.76**	**<0.001**	**0.67**	**0.52-0.87**	**0.002**
LAR	1.34	1.00-1.80	0.052	1.86	0.52-6.60	0.341
APR	1.25	0.65-2.39	0.508	1.68	0.42-6.63	0.462
(Sub)total colectomy#	**2.08**	**1.28-3.41**	**0.003**	**2.38**	**1.40-4.05**	**0.001**
Other	0.64	0.20-2.09	0.463	0.62	0.18-2.18	0.454
Lymph node yield						
<12	Reference					
≥12	1.12	0.92-1.38	0.255			
Pathological N-stage						
N0	Reference					
N1	0.76	0.52-1.09	0.134			
N2	0.58	0.30-1.15	0.117			

OR = Odds Ratio, 95% CI = 95% Confidence Interval LAR = Low Anterior Resection, APR = Abdomino-perineal resection. ^ From laparoscopic to open procedure, * Including ileocecal resection and transverse resection, # Including panproctocolectomy and subtotal colectomy

PART III
EVALUATING TREATMENT OF PATIENTS WITH SCREEN-DETECTED COLORECTAL CANCER

CHAPTER 7

Introduction of a colorectal cancer screening programme: results from a single-centre study

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Colorectal Disease 2018 Sep;20(9):O239-O247

ABSTRACT

Aim: In 2014, a national colorectal cancer (CRC) screening program was launched in the Netherlands. It is difficult to assess for the individual patients with CRC whether the oncological benefits of surgery will outweigh the morbidity of the procedure, especially in early lesions. This study compares patient and tumour characteristics between screen-detected and non-screen-detected patients. Also, we present an overview of treatment options and clinical dilemmas when treating patients with early-stage colorectal disease.

Method: Between January 2014 and December 2016, all patients with nonmalignant polyps or CRC who were referred to the Department of Surgery of the Leiden University Medical Centre in the Netherlands were included. Baseline characteristics, type of treatment and short-term outcomes of patients with screen-detected and nonscreen-detected colorectal tumours were compared.

Results: A total of 426 patients were included, of whom 240 (56.3%) were identified by screening. Nonscreen-detected patients more often had comorbidity ($P = 0.03$), the primary tumour was more often located in the rectum ($P = 0.001$) and there was a higher rate of metastatic disease ($P < 0.001$). Of 354 surgically treated patients, postoperative adverse events did not significantly differ between the two groups ($P = 0.38$). Of 46 patients with T1 CRC in the endoscopic resection specimen, 23 underwent surgical resection of whom only 30.4% had residual invasive disease at colectomy.

Conclusion: Despite differences in comorbidity and stage, surgical outcome of patients with screen-detected tumours compared to nonscreen-detected tumours were not significantly different. Considering its limited oncological benefits as well as the rate of adverse events, surgery for nonmalignant polyps and T1 CRC should be considered carefully.

INTRODUCTION

Colorectal cancer (CRC) is a common disease in the Netherlands, with approximately 15 800 new cases annually.[1] It is the second leading cause of cancer related death in developed countries, with a 4.3% estimated lifetime risk of developing CRC and 1.8% lifetime chance of CRC related death.[2,3] Screening and treating pre-malignant lesions offer the opportunity for cancer prevention.[4] Zauber and colleagues have demonstrated in the National Polyp Study that polypectomy is the major mechanism by which screening reduces the burden of CRC and associated mortality.[5,6] Various randomized controlled trials showed a 15% relative risk reduction in CRC mortality.[7,8] Based on these results the European Commission has endorsed organized screening for CRC using a faecal occult blood test (FOBT).[9]

In January 2014, a nationwide CRC screening programme was launched in the Netherlands (17 million inhabitants). All individuals aged 55-75 years are offered a biennial faecal immunochemical test (FIT) and diagnostic colonoscopy when the FIT is positive.[10] FIT is a type of FOBT. The Dutch CRC screening programme has a high compliance rate of over 70%. In 2016, 16 114 (45.4%) advanced adenomas and 2944 (8.3%) CRC were detected through screening.[11] Data on the screening process are collected in the national screening register. However, the management of these patients after diagnosis is not part of this register. Consequently, no information is being collected on patients surgically treated for polyps without invasive carcinoma. Furthermore, it remains unclear to what extent patients and surgeons decline additional surgery after endoscopic resection of T1 CRC. According to the Dutch CRC guideline, colorectal resection should be considered in case of high risk for lymph node metastasis (LNM) or risk for R1 resection (cancer cells present microscopically at the resection margin), i.e. positive lymph- or vessel invasion, positive deep tumour margin (≤1mm), poor histological differentiation, piecemeal resection or when deep tumour margin was not assessable.[12] However, evidence supporting this recommendation is sparse.[13] Information on treatment of patients with nonmalignant polyps or T1 carcinoma is of key importance to assess all effects associated with the introduction of mass screening.

The aim of this study was twofold: first, to compare patient and tumour characteristics between screen-detected and nonscreen-detected patients in whom surgery is considered; second, focusing on patients surgically treated for polyps without invasive carcinoma, to investigate to what extent patients and surgeons decline additional surgery after endoscopic resection for T1 CRC.

METHOD

The Leiden University Medical Centre (LUMC) is a large teaching hospital and a tertiary interventional endoscopy centre (TIEC) in the Netherlands. All patients referred to the Department of Surgery of this hospital with a diagnosis of primary

colorectal tumour between 1 January 2014 and 31 December 2016 were included in a prospective colorectal tumour database. Emergency presentation with acute surgery was excluded from this analysis, as well as patients with recurrent CRC. Electronic patient files were reviewed individually concerning patient characteristics, screening status, pathology reports of endoscopic and surgical specimen, comorbidity and perioperative and postoperative complications. For all eligible patients, pathology reports were reviewed to obtain the TNM stage using the fifth edition of the TNM classification of malignant tumours for CRC.[14] T1 CRC was defined as a tumour with invasion through the muscularis mucosa and into, but not beyond, the submucosal layer.[14] This cohort study was approved by the Medical Ethics Review Committee of the LUMC (reference number G16.089).

Statistical analysis

Screening and nonscreening patients were compared. Normally distributed variables were compared using an independent samples *t* test. For nominal variables, we used chi-squared coefficients to assess for statistical significance of outcome differences. A two-tailed *P* value was used for all analyses, and *P* values <0.05 were considered statistically significant. All statistical analysis was performed using the SPSS statistics software V.23.0, IBM Corp, (Armonk, New York, USA).

RESULTS

Screening vs nonscreening patients

Patient and tumour characteristics

Table 1 shows the demographic and clinical characteristics of the 426 included patients of whom 240 (56.3%) were diagnosed through the screening programme. Nonscreen-detected patients more often had a comorbidity ($P = 0.03$), the primary tumour was more often located in the rectum ($P = 0.001$) and there was a higher rate of metastatic disease ($P < 0.001$). A greater proportion of screen-detected tumours compared to the nonscreen-detected tumours were located within the colon (73.8% vs 58.6%). The majority of patients underwent surgery (83.1%). The remaining patients were either referred for treatment to another hospital (4.0%), referred for palliative chemotherapy in case of metastatic disease at presentation (3.8%), declined surgery (3.8%) or surgery was omitted for other reasons (5.4%) (Fig. 1).

Surgically treated patients

Table 2 shows the outcomes of all surgically treated patients ($N = 354$). The majority underwent laparoscopic resection, and (conversion to) open surgery was necessary in 18.4%. Median lymph node yield was 15 (interquartile range 11-19; range 3-39). Nonscreen-detected patients had a significantly higher pathological stage ($P = 0.001$). Of the patients who underwent surgery, 107 (30.2%) had positive nodal disease and 17 (4.8%) had distant metastasis. The median hospital stay was 5 days

Table 1. Demographic and clinical characteristics of patients with screen- and nonscreen-detected colorectal tumours (2014-2016)

	Nonscreen-detected N=186 N (%)	**Screen-detected** N=240 N (%)	**Total** N=426 N (%)	***P* value**
Age, median (interquartile range)	69 [59-77]	67 [65-74]	67 [63-75]	0.48
Gender				0.96
Male	115 (61.8)	149 (62.1)	264 (62.0)	
Female	71 (38.2)	91 (37.9)	162 (38.0)	
Co-morbidity				**0.03**
No	31 (16.7)	61 (25.4)	92 (21.6)	
Yes	152 (81.7)	176 (73.3)	328 (77.0)	
Unknown	3 (1.6)	3 (1.3)	6 (1.4)	
ASA				0.05
I	24 (12.9)	35 (14.6)	59 (13.8)	
II	108 (58.1)	154 (64.2)	262 (61.5)	
III	34 (18.3)	22 (9.2)	56 (13.1)	
IV/V	0	0	0	
Unknown	20 (10.7)	29 (12.0)	49 (11.6)	
Location of primary tumour				**0.001**
Colon	109 (58.6)	177 (73.8)	286 (67.1)	
Rectum	77 (41.4)	63 (26.3)	140 (32.9)	
> 1 tumour	8 (4.3)	8 (3.3)	16 (3.8)	0.60
M1 at diagnosis	29 (15.6)	12 (5.0)	41 (9.6)	**<0.001**
Treatment				0.10
Surgery	159 (85.5)	195 (81.2)	354 (83.1)	
No surgery	19 (10.2)	36 (15.0)	55 (12.9)	
Other centre for treatment	8 (4.3)	9 (3.8)	17 (4.0)	

P < 0.05 was considered to be statistically significant (in bold).

(range 1-68). The risk of one or more postoperative adverse events within 30 days was 38.1%, and 34 patients (9.6%) were readmitted within 30 days. Postoperative adverse events and readmission rates did not significantly differ between the two groups. Also, adverse events and mortality after surgery were not restricted to higher stage tumours. When cases that underwent preoperative treatment were not considered, 37.4% of patients undergoing surgery for Stage 1 disease experienced a postoperative adverse event while this rate was 35.0% for patients with Stage 4 disease. Eight patients died within 30 days after surgery (2.3%), of whom four patients had a nonscreen-detected tumour and four patients had a screen-detected tumour. One patient died after surgery for a screen-detected adenoma due to a cardiac arrest following massive aspiration. Figure 2 shows the distribution of patients according to pathological TNM staging.

Surgery for benign disease

The proportion of patients who underwent surgery without preoperative pathological evidence of malignant disease was 15.0% (53 of the 354 patients that were managed surgically). Invasive cancer was identified in 35 of these 53 patients. The majority (N=16) of the remaining 18 cases with no invasive carcinoma in preoperative

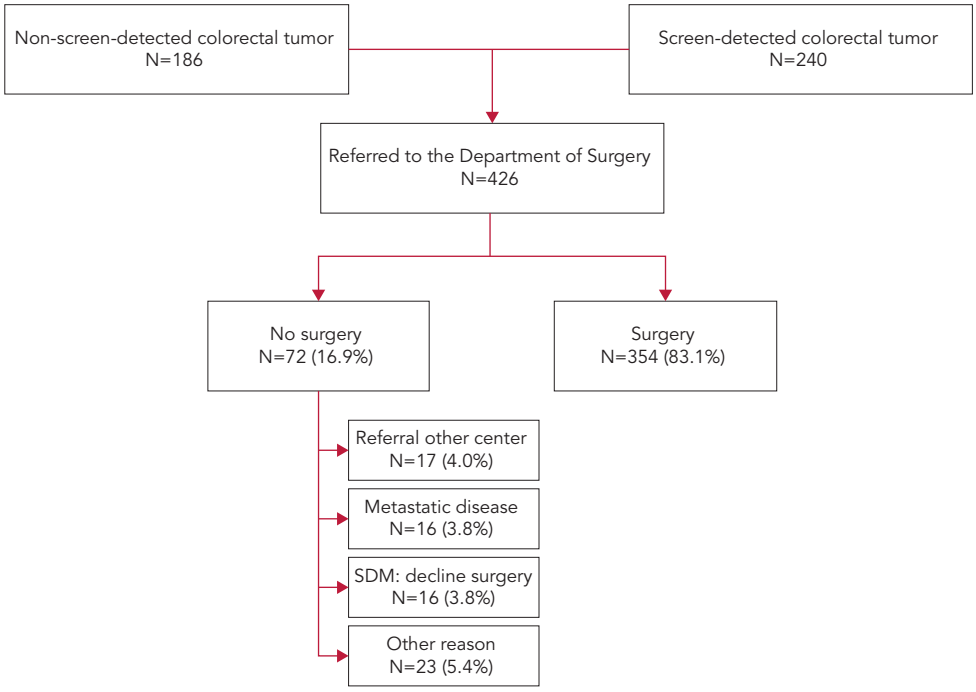

Figure 1. Flow chart treatment strategies after referral to the Surgical Department (2014-2016)

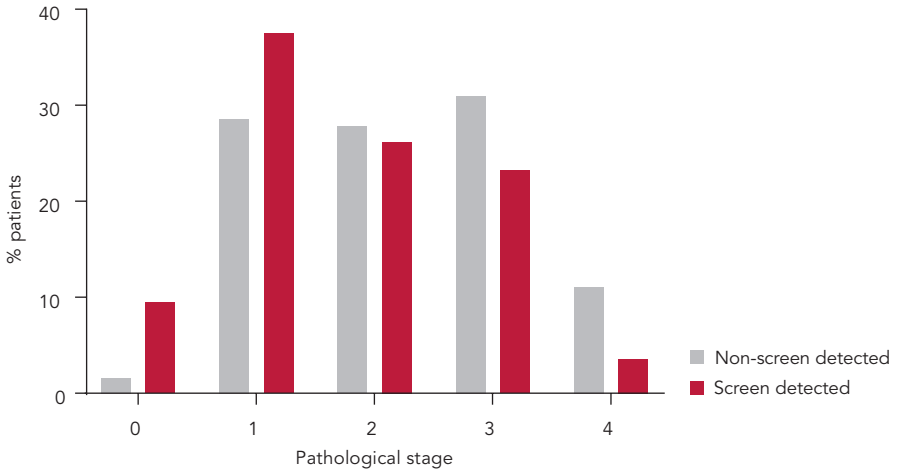

Figure 2. Proportion of surgically treated patients with colorectal carcinoma or polyps without neoadjuvant treatment (2014-2016), according to pathological stage and screening status (*N* = 294)

polypectomy nor in the resection specimen, was screen-detected. Based on size estimated endoscopically, 33.3% of these non-malignant polyps were <3cm, 33.3% were 3-5cm and 33.3% were >5cm. Pathology reports of the surgical specimens of these 18 patients showed that 39% had high-grade dysplasia, 39% had low-grade dysplasia and in the remaining 22% no dysplasia was found.

Treatment decisions after T1 polypectomy

Within the group of patients with T1 carcinoma that did not undergo surgery after polypectomy (*N* = 23), surgery was not performed because of low risk of LNM in 5 cases, 14 patients declined surgery after shared decision making, three patients were referred to another hospital and one patient was unfit for surgery. Of patients undergoing colorectal surgery for a T1 carcinoma that was confirmed pathological prior to surgery (*N* = 23), two patients had LNM (8.7%) (Table 3). There were 16 patients (69.6%) with T1 carcinoma who underwent surgical resection and had no tumour in the resected specimen.

Table 2. Outcomes of surgically treated patients with screen- and nonscreen-detected colorectal tumours (2014-2016)

	Nonscreen-detected N=159 N (%)	**Screen-detected** N=195 N (%)	**Total** N=354 N (%)	*P* **value**
Type of surgery				**0.02**
(Extended) right colectomy	46 (28.9)	62 (31.8)	108 (30.5)	
Transversectomy	2 (1.3)	3 (1.5)	5 (1.4)	
(Extended) left colectomy	6 (3.8)	19 (9.7)	25 (7.1)	
Sigmoïd resection	40 (25.1)	51 (26.2)	91 (25.7)	
Subtotal colectomy	4 (2.5)	4 (2.1)	8 (2.3)	
Total mesorectal excision	38 (23.9)	45 (23.1)	83 (23.4)	
Abdominoperineal resection	13 (8.2)	6 (3.1)	19 (5.4)	
Proctocolectomy	3 (1.9)	-	3 (0.8)	
Partial excision	-	3 (1.5)	3 (0.8)	
Other	7 (4.4)	2 (1.0)	9 (2.6)	
Pathological TNM stage without neoadjuvant treatment				**0.001**
Stage 0	2 (1.3)	16 (8.2)	18 (5.1)	
Stage I	36 (22.6)	63 (32.3)	99 (28.0)	
Stage II	35 (22.0)	44 (22.6)	79 (22.3)	
Stage III	39 (24.5)	39 (20.0)	78 (22.0)	
Stage IV	14 (8.8)	6 (3.1)	20 (5.6)	
Surgery after neoadjuvant treatment	33 (20.8)	27 (13.8)	60 (17.0)	
Postoperative complications according to Clavien Dindo				0.38
No complication	93 (58.5)	126 (64.6)	219 (61.9)	
Grade 1-2	36 (22.6)	46 (23.6)	82 (23.2)	
Grade 3 (intervention)	23 (14.5)	18 (9.2)	41 (11.6)	
Grade 4 (ICU submission)	3 (1.9)	1 (0.5)	4 (1.1)	
Grade 5 (death)	4 (2.5)	4 (2.1)	8 (2.3)	
Readmitted <30 days	18 (11.3)	16 (8.2)	34 (9.6)	0.46

ICU, intensive care unit

P < 0.05 was considered to be statistically significant (in bold).

Table 3. Histological assessment of T1 colorectal carcinoma (2014-2016)

	Polypectomy only N=23, N (%)	**Polypectomy + Surgery** N=23, N (%)	**Total** N=46, N (%)
Screen-detected	19 (82.6)	20 (87.0)	39 (84.8)
Colon	13 (56.5)	17 (73.9)	30 (65.2)
Rectum	10 (43.5)	6 (26.1)	16 (34.8)
Risk lymph node metastasis			
Lymphatic or vessel invasion	9 (39.1)	2 (8.7)	11 (23.9)
Not specified in pathology report	4 (17.4)	8 (34.8)	12 (26.1)
No lymphatic or vessel invasion	10 (43.5)	13 (56.5)	23 (50.0)
Differentiation grade			
Good-moderate differentiated	19 (82.6)	14 (60.9)	33 (71.7)
Not specified in pathology report	4 (17.4)	8 (34.8)	12 (26.1)
Poorly differentiated	0	1 (4.3)	1 (2.2)
Tumour margin			
Resection margin >1mm	8 (34.8)	3 (13.0)	11 (23.9)
Resection margin unclear	6 (26.1)	5 (21.7)	11 (23.9)
Not specified in pathology report	2 (8.7)	8 (34.8)	10 (21.7)
Resection margin ≤1mm	7 (30.4)	7 (30.5)	14 (30.5)
Haggitt/Kikuchi level			
Haggitt/Kikuchi level 1	3 (13.0)	2 (8.7)	5 (10.9)
Haggit/Kikuchi level >1	10 (43.5)	7 (30.4)	17 (36.9)
Not specified in pathology report	10 (43.5)	14 (60.9)	24 (52.2)
Budding			
Yes	7 (30.5)	5 (21.7)	12 (26.1)
Not specified in pathology report	15 (65.2)	16 (69.6)	31 (67.4)
No	1 (4.3)	2 (8.7)	3 (6.5)

DISCUSSION

The primary aim of this study was to provide an overview of daily practice since the introduction of our nationwide CRC screening programme in a single institution. It gives an insight into the difficulties that the clinician may face when choosing the optimal treatment of CRC. It is not the purpose of this paper to evaluate mass screening as it will take some years to assess whether CRC and/or overall mortality will decrease as a result of screening. We are not able to draw meaningful conclusions in this regard from this single-centre report. Yet, in the absence of long-term follow-up and lacking large prospective studies regarding the impact of CRC screening, this overview of observational data can serve as a template for future research. In this respect, there are several patient categories worth mentioning.

Screening vs nonscreening patients

Despite having less comorbidity, more early stage tumours and a lower proportion rectal surgery in the screening group, postoperative morbidity, mortality and readmission rates did not differ. A possible explanation for this lack of significance is the relatively small sample size. Other studies, with higher inclusion rates, showed that the 30-day mortality after surgery for screen-detected tumours, was lower compared to a comparable age group that was never invited for screening (resp. 1.1% *vs* 2.8%).[15] While this may be due to patients who participate in the programme being of better

health than their nonparticipating counterparts, Morris *et al.* suggest that it could also relate to the greater proportion of earlier stage tumours detected by the screening programme carrying less risk than the later stage tumours diagnosed outside the program.[15] From a surgical point of view, there is no reason to assume a difference in morbidity rate between surgeries for T1 and T3 lesions. Furthermore, in other screening studies, patients diagnosed through screening are frequently younger.[16]
It is noteworthy that, within the screen-detected group, 43.3% of primary tumours were located in the distal colon (splenic flexure to rectosigmoid junction) and 26.3% were located in the rectum. These different proportions compared to the nonscreen-detected group (28.5% and 41.4% resp.) are in line with previous literature. A higher proportion of tumours found by screening are located in the colon[17], especially in the left side of the bowel.[15] Blood released from tumours in the right side of the colon has to travel along a greater length of the bowel than that from tumours in the left side of the colon. This may lead to a greater chance of the haemoglobin being degraded as it passes through the bowel. Degraded haemoglobin will not react with the FOBT and this may lead to false-negative results[15]. Second, differences in stool consistency with blood being more homogeneously distributed when originating from the right side, would also favour the detection of left-sided neoplasia.[18]

Surgery for benign disease

It is difficult to predict which adenomatous polyps are likely to develop into a malignancy. The majority of polyps will not develop into adenocarcinoma; histology and size determine their clinical importance.[19] It is estimated that about 2.5 adenomatous polyps per 1000 per year progress to cancer.[20] Since the introduction of mass screening, the number of nonmalignant polyps is rising substantially, as well as their referrals for surgical resection. As a recent French study showed, most nonmalignant colorectal polyps are removed with endoscopic resection. Of 4251 patients who underwent a colonoscopy for positive FOBT with a nonmalignant polyp, 4.1% were referred for surgical resection. Among the significant risk factors for referral to surgery related to polyps (e.g. size, location or morphology), a polyp size $\geq$20mm had the strongest weight.[21] Of the 354 patients who underwent surgery in this analysis, 18 patients (5.1%) underwent bowel resection because a nonmalignant polyp could not be safely removed endoscopically. One might assume this rate to be higher in other clinics, as our centre is a TIEC with large experience removing in large adenomas endoscopically. The distribution of nonmalignant polyps referred for surgery in this study revealed a majority of polyps located on the right side, in accordance with the findings in other series of laparoscopic colectomy for polyps[22]. This may reflect the reluctance of the endoscopists to resect large and difficult polyps in the right colon because of the fear of complications like perforation of the relatively thin right colonic wall.[23] An additional argument for surgical resection is the risk of unexpected cancer. Recent published TREND Study for large rectal adenomas, showed an unexpected cancer rate of 13%.[24] Apparently, endoscopic assessment of possible invasive component remains difficult.
As surgery carries risks on morbidity and mortality, shared decision-making should be implemented in the process of deciding on treatment of nonmalignant colorectal

polyps. In this study, the postoperative adverse event rate was 16.7% and one patient died following surgery for a nonmalignant colorectal polyp. Recent published analyses of 12 732 patients from more than 500 hospitals across the USA undergoing surgery for nonmalignant colorectal polyps, showed a major morbidity rate of 14.0% and a 30-day mortality rate of 0.7%. After age 80 years, the mortality rate increased to 3.0%.[25] In the French study mentioned previously, surgical complications occurred in 24.0% and one patient died following surgery (0.5%). This is lower than the mortality rates for surgery for CRC. In the Netherlands in 2015, surgery for colon and rectum cancer was associated with a 30-day morbidity rate of 28% and 37% and mortality rate of 2.3% and 1.2% resp.[26] Understanding these risks becomes especially important given the evidence that many complex nonmalignant colorectal neoplasms can be effectively and safely managed with endoscopic resection[25]. With the implementation of new types of endoscopic resection, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), the need for surgery for precancerous lesions can be reduced further.[27] Obtaining a second opinion from a TIEC can limit surgery and, in case of unexpected cancer, surgery can still be performed.

Treatment decisions after T1 polypectomy

Submucosal invasive CRCs account for up to 12% of polyps in polypectomy series.[28] Because a formal oncological resection is the only way to excise the draining lymph nodes, local excision is only a valuable treatment alternative in the absence of LNM. In this study, 8.7% of patients undergoing surgery for a T1 carcinoma that was confirmed pathological prior to surgery had LNM, in accordance with previous literature as LNMs are reported in 8%-16% of patients.[29,30] In T1 CRC with the deepest level of invasion, LNM risk of over 20% has been reported.[31] According to a systematic review of 17 studies, the strongest independent pathological predictors for LNM in T1 CRC were lymphatic invasion, poor histological differentiation, submucosal invasion ≥1mm, and budding.[29] In the current Dutch guideline, only lymphatic or vessel invasion, poor histological differentiation and resection marge ≤1mm are mentioned.[12] The Japanese Society for Cancer of the Colon and Rectum (JSCCR) guideline also includes submucosal invasion ≥1mm and budding as features in which additional surgery should be considered.[32] At the time the Dutch guideline was implemented, there was no national colorectal screening programme. Treating patients with T1 CRC was less common at that time. Due to the introduction of mass screening, the number of patients with T1 CRC is rising and this requires an update of the national guidelines. Furthermore, several histological findings (i.e. depth of submucosal invasion and budding) gain importance in the decision-making process for additional surgery.

Interestingly, according to a T1 study of 140 surgical resection specimens, a positive margin was not associated with nodal metastasis. Also, none of the malignant polyps with carcinoma present between 0.1 and 1mm from the margin showed residual carcinoma in these 140 surgical specimens.[33] Not surprisingly, pooled-data analysis of 1900 patients with malignant polyps showed that positivity of resection margin was significantly predictive of the presence of residual disease (OR 22; 95% CI: 10.3-46.6, $P < 0.0001$).[34] A positive margin defined by carcinoma cells reaching the diathermied

base may therefore require additional local resection but not necessarily surgery if no other adverse factors are present.

This study contains a considerable number of patients with endoscopic resection for T1 CRC in whom additional surgery was not performed because of patients being unwilling or considered to be unfit for surgery. In 18 of these 23 patients, not performing surgery was not in accordance with the national guideline. Previous retrospective analysis from Germany of 249 patients with T1 CRC with solely follow-up showed that relapse or LNM occurs in 6.8%, even during a long-term follow-up interval of more than 20 years. This German cohort also included a significant proportion of patients with high-risk cancers who refused surgery or were considered too unfit to undergo oncological resection.[13] In a multicentre study involving 792 pT1 CRC patients treated with endoscopic resection without proceeding to surgical resection for various reasons, local recurrence or metastasis was observed in 18 cases (2.3%), with an average interval between endoscopic resection and recurrence of 19.7 ± 9.2 months. Oka *et al.* concluded that endoscopic resection without additional surgical resection was valid for cases of well-differentiated or moderately differentiated adenocarcinoma with a depth of submucosal invasion < 1mm and no lymphatic or venous involvement.[35] On the other hand, there is also risk of recurrence after surgical resection for T1 CRC, reported in 2%-4% of patients.[36,37] The recent retrospective analysis of 1071 patients with surgically resected T1 CRC showed 41 patients (4.0%) diagnosed with recurrent cancer local or in distant organs, with a median interval between endoscopic resection and recurrence of 49.0 months (interquartile range 19.6-81.5).[30] So, even in the presence of high-risk factors, surveillance rather than operative resection might be reasonable, taken into consideration the mortality rate of oncologic colorectal resection[13] and relative low recurrence rate after endoscopic resection.

The major strength of this cohort study includes the various treatment modalities in practice and attention to both endoscopic and surgical details. This is the first overview of treatment choices since the introduction of CRC screening in the Netherlands. The study has some limitations. First, it was limited by its retrospective design with patients in a single centre. Second, because of the relatively small sample size, analyses on recurrence were not feasible.

CONCLUSION

Because screening programmes aim to identify patients with earlier stage disease, a risk of overtreatment is inevitable. This study shows that a considerable number of patients were treated surgically with no evidence of invasive carcinoma. Also, in patients with submucosal invasive CRC, surgery is frequently omitted which is not in line with the national guideline. Large-scale multicentre prospective investigations are needed to evaluate the long-term outcomes after treatment for polyps without invasive carcinoma and submucosal invasive colorectal tumours, guiding the decision when to perform oncologic resection or when follow-up examinations are sufficient. To optimize treatment for the individual patient, therapeutic alternatives should be evaluated in a multidisciplinary team setting.

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CHAPTER 8

Postoperative outcomes of screen-detected vs non-screen-detected colorectal cancer in the Netherlands

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JAMA Surgery 2018 Dec 1;153(12):e183567

ABSTRACT

Importance: The nationwide fecal immunochemical test-based screening program has influenced surgical care for patients with colorectal cancer (CRC) in the Netherlands, although these implications have not been studied in much detail so far.

Objective: To compare surgical outcomes of patients diagnosed as having CRC through the fecal immunochemical test-based screening program (screen-detected) and patients with non-screen-detected CRC.

Design, setting, and participants: This was a population-based comparative cohort study using the Dutch ColoRectal Audit and analyzed all Dutch hospitals performing CRC resections. Patients who underwent elective resection for CRC between January 2011 to December 2016 were included.

Interventions: Colorectal cancer surgery.

Main outcomes and measures: Postoperative nonsurgical complications, postoperative surgical complications, postoperative 30-day or in-hospital mortality, and complicated course (postoperative complication resulting in a hospital stay >14 days and/or a reintervention and/or mortality). A risk-stratified comparison was made for different postoperative outcomes based on screening status (screen-detected vs not screen-detected), cancer stage (I-IV), and for cancer stage I to III also on age (aged <70 years and >70 years) and American Society of Anesthesiologists score (I-II and III-IV). To determine any residual case-mix-corrected differences in outcomes between patients with screen-detected and non-screen-detected cancer, univariable and multivariable logistic regression analyses were performed.

Results: In total, 36 242 patients with colon cancer and 17 416 patients with rectal cancer were included for analysis. Compared with patients with non-screen-detected CRC, screen-detected patients were younger (mean [SD] age, 68 [5] vs 70 [11] years), more often men (3777 [60%] vs 13 506 [57%]), and had lower American Society of Anesthesiologists score (American Society of Anesthesiologists score III+: 838 [13%] vs 5529 [23%]). Patients with stage I to III colon cancer who were screen-detected had a significantly lower mortality and complicated course rate compared with non-screen-detected patients. For patients with rectal cancer, only a significant difference was found in mortality rate in patients with a cancer stage IV disease, which was higher in the screen-detected group. Compared with non-screen-detected colon cancer, an independent association was found for screen-detected colon cancer on nonsurgical complications (adjusted odds ratio, 0.81; 95% CI, 0.73-0.91), surgical complications (adjusted odds ratio, 0.80; 95% CI, 0.72-0.89), and complicated course (adjusted odds ratio, 0.80; 95% CI, 0.71-0.90). Screen-detected rectal cancer had significantly higher odds on mortality.

Conclusions and relevance: Postoperative outcomes were significantly better for patients with colon cancer referred through the fecal immunochemical test-based screening program compared with non-screen-detected patients. These differences were not found in patients with rectal cancer. The outcomes of patients with screen-detected colon cancer were still better after an extensive case-mix correction, implying additional underlying factors favoring patients referred for surgery through the screening program.

INTRODUCTION

With an estimated number of 15 800 new cases and 5100 deaths in 2015, colorectal cancer (CRC) is the second most common cause of cancer-related death in the Netherlands.[1] To increase CRC-specific survival, organized screening programs have been endorsed by the European Commission.[2] A national CRC screening program was introduced in 2014 in the Netherlands. The program is gradually implemented with a complete rollout by 2019. By then, all men and women aged 55 to 75 years will be invited to participate in the program by a biennial fecal immunochemical test (FIT).

Because the FIT has a sensitivity of around 75% for CRC, screening is an iterative process.[3] In the Netherlands, participation rates are high compared with other countries[4] from 71.3% in 2014[5] to 73% in 2016.[6] Colonoscopy participation after a positive screening FIT was 77.8% in 20145 and 82.8% in 2016.[6]

To allow a comprehensive appreciation of the CRC screening program targeting a supposedly asymptomatic population, an integrated view of the harms and benefits is necessary, including those of surgical treatment. However, literature on morbidity and mortality after surgical treatment of CRC detected through a screening program is limited.[7]

The primary aim of this study was to examine whether patients undergoing surgery for CRC following diagnosis through the FIT-based screening program have different surgical outcomes compared with nonscreening patients and to what extent an extensive case-mix correction can adjust for any differences found. In addition, an overview is given of patient, tumor, and treatment characteristics of the surgically treated screen-detected CRCs in the Netherlands, based on the data registered in the Dutch ColoRectal Audit (DCRA).

METHODS

Data from the DCRA, formerly known as the Dutch Surgical Colorectal Audit (ie, DSCA), were extracted for this study.[8] In this nationwide and disease-specific audit, data on various patient, tumor, treatment, and short-term (30-day) outcome characteristics are collected of every patient undergoing a resection for primary CRC in the Netherlands.

Patient Selection

The DCRA is an obligatory audit from the inspectorate of health care, which required no informed consent from patients for data collection. Data analyses were performed on an anonymized dataset and do not need ethical approval according to Dutch law. Eligibility criteria required patients to have undergone surgical treatment for primary CRC between January 1, 2011, and December 31, 2016, and be registered in the DCRA before March 31, 2017 (n = 63 370). Minimal data requirements were information on tumor location, date of surgery, and 30-day or in-hospital mortality (n = 63 136).

For the objective of this study, only patients in whom the surgery took place in an elective setting were selected (n = 55 531). Furthermore, the heterogenous group of patients with multiple synchronous colorectal tumors (n = 1873) were excluded.[9] This resulted in 53 658 patients eligible for analyses. For trend analysis, all patients (2011-2016) were selected (eFigure in the Supplement). For the comparison of the outcomes of screen-detected vs non-screen-detected patients, all patients were selected who underwent surgery since the start of the nationwide CRC screening program in 2014.

Data

The following data were retrospectively extracted from the DCRA database: patient characteristics, disease characteristics, (pre)procedural characteristics, postoperative outcomes within 30 days after resection or in hospital, and whether the patients were referred through the screening program. Invited birth cohorts for the screening program in the 3 years were 1938 to 1941, 1945 to 1955, and 1957. Only patients who were referred through the screenings program after a positive FIT and were diagnosed as having a CRC that was surgically resected were marked as screen-detected CRC. All missing values were 10% or less and no imputation was conducted (eTable 1 and eTable 2 in the Supplement).

Outcome Parameters

Outcome parameters were nonsurgical postoperative complications (pulmonary, cardiac, thromboembolic, infectious, neurologic, other), surgical postoperative complications, complicated course (postoperative complication leading to a hospital stay of >14 days and/or a reintervention and/or mortality), and postoperative mortality (≤30 days or in hospital during the same admission).

Data Analysis

Colon and rectal cancer were analyzed separately. To evaluate trends over time and the impact of the implementation of the nationwide screening program on the DCRA, data on complicated course and mortality were evaluated for all included patients, according to year of registration. Differences in baseline characteristics were compared between non-screen-detected patients during 2011 to 2013 and 2014 to 2016 and between screen-detected and non-screen-detected patients during 2014 to 2016. Patients registered between 2014 to 2016 were stratified into homogenous subgroups based on known risk factors (age, American Society of Anesthesiologists [ASA] classification, cancer stage), and differences in outcomes (complicated course and mortality) of screen-detected vs non-screen-detected patients were assessed.
Absolute risk differences with corresponding 95% CIs were compared between screen-detected and non-screen- detected patients. Differences in categorical variables were analyzed using a χ^2 test and for nonnormally distributed continuous variables (eg, length of stay), a nonparametric Mann-Whitney U test was used. To evaluate differences in outcomes between screen-detected and non-screen-detected patients from 2014 to 2016, univariable and multi-variable logistic

regression analyses were performed, and the results were expressed as odds ratios with corresponding 95% CIs. To adjust for differences in case mix, factors included in the multivariable analysis consisted of age, sex, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), ASA score, Charlson comorbidity score, any tumor-related complication, previous abdominal surgery (not further specified), pathological (p)T-classification, presence of metastasis, additional resection due to tumor invasion, and additional resection due to metastasis. For colon cancer, the location of the tumor within the colon (cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid) was added to the case mix. For case-mix correction in rectal cancer, tumor distance from the anal verge, clinical (c)T-classification, preoperative radiotherapy, and surgical procedure (low anterior resection, abdominoperineal resection, or other procedure) were added to the model. Preoperative radiotherapy was categorized as no radiotherapy, short-course radiotherapy with immediate (≤3 week) surgery, short-course radiotherapy with delayed (>3 week) surgery, or chemoradiotherapy/long-course radiotherapy. A P value less than .05 was considered statistically significant. SPSS 24.0 Statistics for Windows (IBM Corp) was used for all analyses.

RESULTS

Baseline Characteristics

In total, 36 242 patients with colon cancer and 17 416 patients with rectal cancer were included for analysis. Table 1 provides a comprehensive overview of patient and tumor characteristics of 23 508 patients prior to the start of the screening program (2011-2013) and for 23 872 non-screen-detected and 6278 screen-detected patients since the start of the screening program (2014-2016). Of all patients undergoing surgery for CRC since the moment of introduction of the screening program, 4696 patients (22.8%) with colon cancer and 1582 patients (16.6%) with rectal cancer were screen-detected, respectively.

Compared with the patients with colon cancer diagnosed before the start of the screening program (2011-2013), the non-screen-detected patients between 2014 and 2016 had a higher ASA score, BMI, and Charlson score. For patients with rectal cancer, only BMI and Charlson score were significantly different. Comparing non-screen-detected patients with screen-detected patients between 2014 to 2016, almost all patient and tumor characteristics differed significantly. This was also found for the different workup and surgery characteristics and length of stay (Table 2). For patients with rectal cancer, no significant differences were found between non-screen-detected patients compared with screen-detected patients for the proportion of patients being discussed in a multidisciplinary team meeting and the proportion of patients being converted after an initial laparoscopic approach.

Table 1. Patient and tumor characteristics of non-screen and screen-detected colorectal cancer[ab]

Characteristic	Colon					
	Non-screen-detected, No. (%)		P Value: non-screen-detected 2014-2016 vs 2011-2013	Screen-detected, 2014-2016, No. (%)	P Value: screen-detected (2014-2016) vs non-screen-detected (2014-2016)	
	2011-2013	2014-2016				
Total patients, No.	15610	15936	NA	4696	NA	
Age, y						
≤60	2625 (17)	2678 (17)	0.96	160 (3)	<0.001[c]	
61-70	4572 (29)	4621 (29)		3009 (64)		
71-80	5452 (34)	5596 (35)		1527 (33)		
≥81	2957 (19)	3029 (19)		0 (0)		
Men	8227 (53)	8464 (53)	0.44	2706 (58)	<0.001	
American Society of Anesthesiologists score III+[d]	3653 (23)	4120 (26)	<0.001	638 (14)	<0.001	
Charlson Score 3+[d]	1857 (12)	2332 (15)	<0.001	362 (8)	<0.001	
Body mass index, ≥30[d,e]	2547 (16)	2959 (19)	<0.001	1175 (25)	<0.001	
Previous abdominal surgery	5597 (36)	5788 (36)	0.42	1432 (31)	<0.001	
Location of Tumor						
Ascending colon up to and including hepatic flexure	7217 (46)	7370 (46)	0.24	1523 (32)	<0.001	
Transverse colon up to and including splenic flexure	1487 (10)	1592 (10)		494 (11)		
Descending colon	869 (6)	935 (6)		346 (7)		
Sigmoid colon	6037 (39)	6039 (38)		2333 (50)		
Distance from anal verge, cm						
≤5	NA	NA	NA	NA	NA	
6-10	NA	NA		NA		
>10	NA	NA		NA		
Preoperative tumor complications	5128 (33)	5105 (32)	0.06	197 (4)	<0.001	
cT stage						
cT1	NA	NA	NA	NA	NA	
cT2	NA	NA	NA	NA	NA	
cT3	NA	NA	NA	NA	NA	
cT4	NA	NA	NA	NA	NA	
cTX/unknown	NA	NA	NA	NA	NA	
pT stage						
(y)pT0-1	1409 (9)	1646 (10)	<0.001	1211 (26)	<0.001	
(y)pT2	2768 (18)	2807 (18)		1184 (25)		
(y)pT3	9205 (59)	9018 (57)		2009 (43)		
(y)pT4	2144 (14)	2422 (15)		287 (6)		
M-stage tumor						
M0	13970 (89)	14287 (90)	0.65	4489 (96)	<0.001	
M1	1640 (11)	1649 (10)		207 (4)		
Cancer stage[d]						
I	3207 (21)	3518 (22)	<0.001	1847 (39)	<0.001	
II	5707 (37)	5701 (36)		1209 (26)		
III	4766 (31)	5024 (32)		1372 (29)		
IV	1617 (10)	1570 (10)		191 (4)		
0/X	313 (1)	123 (1)		77 (1)		

Abbreviations: cT, clinical tumor; NA, not applicable; pT, pathological tumor.

[a] Missing per category are reported in eTable1 in the Supplement. All variables had 10% or less missing values.

[b] χ^2 Test was used for all categorical variables.

[c] Analysis by χ^2 was done for different subgroups than shown in this Table (because of low number [<5] of cases in ≥1 subcategory) for age (≤70 vs >70 years).

	Rectum				
	Non-screen-detected, No. (%)		P Value: non-screen-detected 2014-2016 vs 2011-2013	Screen-detected, 2014-2016, No. (%)	P Value: screen-detected (2014-2016) vs non-screen-detected (2014-2016)
	2011-2013	2014-2016			
	7898	7936	NA	1582	NA
	2025 (26)	2040 (26)	0.64	48 (3)	<0.001[c]
	2693 (34)	2667 (34)		1068 (68)	
	2335 (30)	2326 (29)		466 (30)	
	843 (11)	895 (11)		0 (0)	
	4928 (62)	5042 (64)	0.12	1071 (68)	0.002
	1309 (17)	1409 (18)	.05	200 (13)	<0.001
	687 (9)	758 (10)	0.001	112 (7)	0.003
	1193 (15)	1351 (17)	0.01	332 (21)	<0.001
	2427 (31)	2426 (31)	0.80	395 (25)	<0.001
	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA
	2849 (38)	2971 (38)	0.02	436 (28)	<0.001
	3008 (40)	3027 (39)		627 (40)	
	1576 (21)	1789 (23)		501 (32)	
	2010 (26)	1636 (21)	<0.001	66 (4)	<0.001
	318 (4)	411 (5)	<0.001	233 (15)	<0.001
	1826 (24)	1835 (23)		541 (34)	
	4471 (58)	4617 (58)		690 (44)	
	674 (9)	818 (10)		42 (3)	
	439 (6)	253 (3)		75 (5)	
	1469 (19)	1619 (21)	0.02	500 (32)	<0.001
	2463 (31)	2374 (30)		555 (35)	
	3606 (46)	3560 (45)		486 (31)	
	323 (4)	343 (4)		24 (2)	
	7255 (92)	7281 (92)	0.80	1544 (98)	<0.001
	643 (8)	655 (8)		38 (2)	
	1410 (18)	1639 (21)	0.001	644 (41)	<0.001
	1469 (19)	1500 (19)		293 (19)	
	3622 (46)	3911 (49)		525 (33)	
	530 (7)	556 (7)		28 (2)	
	867 (11)	330(4)		92(6)	

[d] Pathologic stage was used for colon cancer, and clinical stage was used for rectum. Stage 0 to X includes stage 0 or stage X (unknown or not judgeable).

[e] Calculated as weight in kilograms divided by height in meters squared.

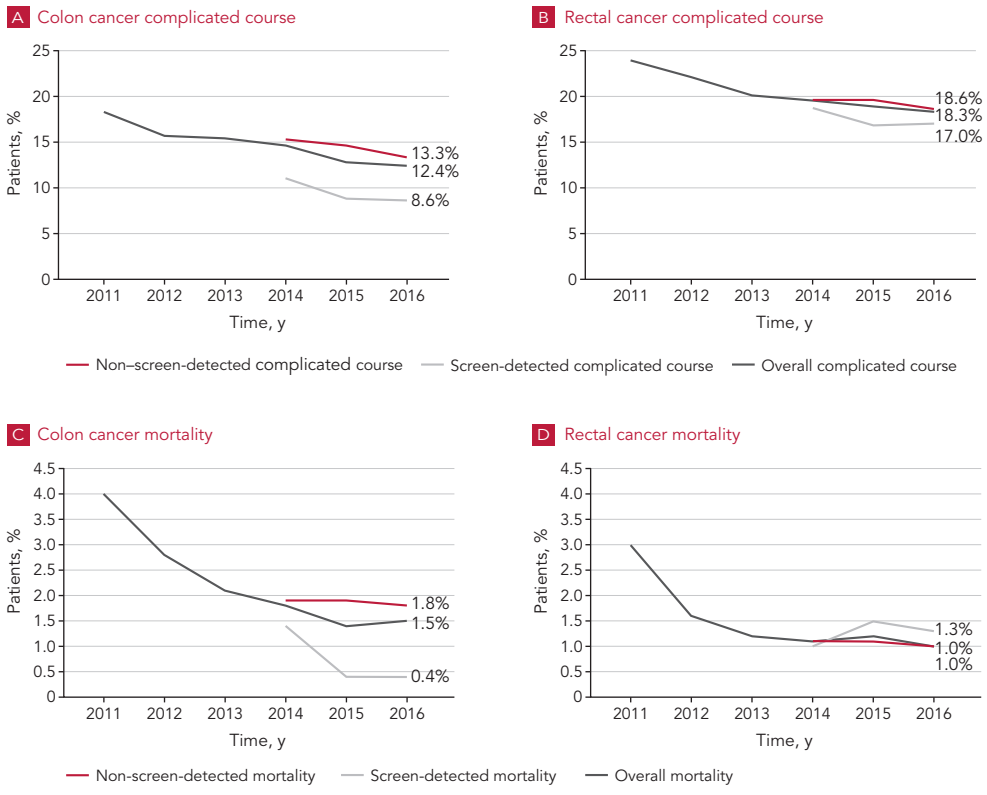


Figure 1. Trends of postoperative adverse outcomes for non-screen-detected, screen-detected and overall colorectal cancer.

Trends of different outcomes (complicated course and mortality), separately shown for colon and rectal cancer. From 2014 and on, the outcomes are shown separately for 3 subgroups: (1) overall (all patients), (2) non-screen-detected and (3) screen-detected patients.

Adverse Outcome Over Time

Figure 1 shows the crude trend of complicated course and mortality of patients with primary CRC between 2011 and 2016 for colon (Figure 1A) and rectal cancer (Figure 1B). Patients with colon cancer diagnosed through the screening program had a complicated course rate ranging from 11% (2014) to 8.6% (2016) and a mortality rate declining from 1.4% (2014) to 0.4% (2015 and 2016). In the same time (2014-2016), complicated course for patients with non-screen-detected CRC ranged from 15.3% (2014) to 13.3% (2016) and mortality from 1.9% (2014) to 1.8% (2016). Both postoperative complicated course (screen-detected: 434 [9.2%] and not-screen-detected: 2293 [14.4%]; $P < .001$) and mortality (screen-detected: 30 [0.6%] and not screen-detected: 295 [1.9%]; $P < .001$) differed significantly between patients with screen-detected and non-screen- detected colon cancer undergoing surgery

between 2014 and 2016. For patients with rectal cancer diagnosed through the screening program, postoperative complication rate ranged from 18.7% (2014) to 16.8% (2015), and mortality rate ranged from 1.5% (2015) to 1.0% (2014). For patients with non-screen- detected rectal cancer, this postoperative complication rate varied from 29.6% (2014 and 2015) to 18.6% (2016) and mortality rate declined from 1.1% in 2014 and 2015 to 1.0% in 2016. For patients with rectal cancer, no significant differences were found for complicated course (screen-detected: 266 [17.2%] and not screen-detected: 1511 [19.2%]; P = .06) and mortality (screen-detected: 19 [1.2%] and not screen-detected: 81 [1.1%]; P = .33) between screen-detected and non-screen-detected patients during 2014 to 2016.

Stratified Comparison of Screen-Detected vs Non-Screen-Detected CRC

In Figure 2, patients with screen-detected and non-screen-detected CRC are compared regarding complicated course and mortality. Patients diagnosed as having colon cancer through the screening program had a significantly lower postoperative complication rate and mortality compared with non-screen-detected patients for stage I to III, with a similar (non- significant) result for stage IV (Figure 2A).

For patients with rectal cancer, higher stage was associated with an increase in complication rate in screen-detected patients, and this was more pronounced compared with non-screen-detected patients (Figure 2B). No significant differences of complication rates between screen-detected and non-screen-detected patients were found for each of the cancer stages. Similar mortality rates were found for stage I to III, with a significantly higher mortality rate after resection of screen-detected compared with non-screen-detected stage IV rectal cancer.

In Figure 2C, complicated course and mortality are shown for stage I to III colon cancer with a stratified comparison based on operative risk using age (≤70 years and >70 years) and ASA score (I-II and III-IV). Lower complication and mortality rates in the screen-detected compared with non-screen-detected populations were observed for any of the operative risk groups except for mortality in young and fit patients (≤70 years with ASA score I-II). These effects reached statistical significance for complicated course in all risk groups, except for patients older than 70 years with ASA score III to IV. For patients with rectal cancer, none of the stratified risk groups revealed a significant difference in complicated course or mortality (Figure 2D). A nonsignificant but noteworthy trend was found toward a higher risk of complicated course and mortality after resection of screen-detected rectal cancer in frail elderly patients (age >70 years with ASA score III-IV).

Case Mix-Adjusted Comparison of Screen-Detected vs Non-Screen-Detected CRC

For colon cancer, surgery of screen-detected patients was independently associated with lower odds on nonsurgical complications (adjusted odds ratio [AOR], 0.81; 95% CI, 0.73-0.91), surgical complications (AOR, 0.80; 95% CI, 0.72-0.89), and complicated course (AOR, 0.80; 95% CI, 0.71-0.90) compared with surgery for patients with colon cancer that were not screen-detected (Table 3). Whether colon cancer was detected through screening was not associated with mortality in multivariable analysis.

Table 2. Workup and surgery characteristics and length of stay of non-screen-detected and screen-detected colorectal cancer[a,b]

Characteristic	Colon					
	Non-screen-detected, No. (%)		P Value: non-screen-detected 2014-2016 vs 2011-2013	Screen-detected, 2014-2016, No. (%)	P Value: screen-detected (2014-2016) vs non-screen detected (2014-2016)	
	2011-2013	2014-2016				
Total patients, No.	15610	15936	NA	4696	NA	
Workup						
Entire visualization of colon	12202 (79)	13221 (83)	<0.001	4354 (93)	<0.001	
Discussed in MDT	13386 (87)	15053 (95)	<0.001	4537 (97)	<0.001	
Neo adjuvant chemotherapy	308 (2)	374 (2)	0.02	27 (0.6)	<0.001	
Neoadjuvant radiotherapy						
No	15481 (99)	15850 (100)	0.02	4684 (100)	0.01	
SCRT-IS	37 (0.2)	17 (0.1)		5 (0.1)		
SCRT-DS	77 (0.5)	65 (0.4)		7 (0.1)		
CRT/long course	15 (0.1)	4 (0)		0 (0)		
Procedure						
Ileocecal resection	169 (1)	101 (0.6)	<0.001	12 (0.3)	<0.001	
Right hemicolectomy	7251 (48)	7713 (49)		1656 (36)		
Transversectomy	404 (3)	359 (2)		83 (2)		
Left hemicolectomy	1588 (10)	1606 (10)		623 (13)		
Sigmoid resection	5815 (38)	5834 (37)		2271 (49)		
(Low) anterior resection	NA	NA		NA		
Abdominoperineal resection	NA	NA		NA		
Other	NA	NA		NA		
Surgical approach						
Open	6849 (44)	3732 (24)	<0.001	527 (11)	<0.001	
Laparoscopic	8735 (56)	12142 (76)		4150 (89)		
Other[d]	11 (0)	9 (0)		6 (0)		
No laparoscopic conversion	7184 (86.2)	10454 (87.8)	0.004	3719 (91.5)	<0.001	
Additional resection due to tumor invasion						
No	14107 (90)	14441 (91)	0.74	4589 (98)	<0.001	
Yes, limited	859 (6)	860 (5)		66 (1)		
Yes, extensive	644 (4)	635 (4)		41 (0.9)		
Additional resection due to metastasis	585 (4)	661 (4)	0.068	83 (2)	<0.001	
Stoma[c]						
No	13947 (90)	14572 (92)	<0.001	4534 (97)	<0.001	
End colostomy	778 (5)	754 (5)		56 (1)		
Other	739 (5)	562 (4)		90 (2)		
Unknown	16 (0.1)	13 (0.1)		3 (0.1)		
Completeness of resection						
Radical resection[c]						
R0	14944 (98)	15620 (98)	<0.001	4658 (100)	<0.001	
R1	258 (2)	215 (1)		21 (0.4)		
R2	121 (0.8)	42 (0.3)		3 (0.1)		
Circumferential margin positive (≤1 mm)	NA	NA	NA	NA	NA	
Median lymph[e] nodes removed, median (IQR)	15 (12-21)	18 (13-24)	<0.001[f]	16 (12-22)	<0.001[f]	
Positive lymph node ratio, %[c]	9.0%	7.8%	p<0.001	5.7%	<0.001	
Length of stay, median (IQR), d	6 (5 - 10)	6 (4 - 9)	p<0.001[f]	5 (4 - 7)	<0.001[f]	

Abbreviations: CRT, chemoradiotherapy; IQR, interquartile range; MDT, multidisciplinary team meeting; NA, not applicable; SCRT-DS, short-course radiotherapy with delayed surgery; SCRT-IS, short-course radiotherapy with immediate surgery.

a Missing per category are reported in eTable 2 in the *Supplement*. All missing were 10% or less.

b χ^2 Test was used for all categorical variables.

c Analysis by χ^2 was done for different subgroups than shown in this Table (because of low number [<5] of cases in 1 or more subcategory) for neoadjuvant radiotherapy (categorized into yes vs no neoadjuvant radiotherapy), stoma (unknown was excluded for analysis), and radical resection (R0 vs R1-2).

	Rectum				
	Non-screen-detected, No. (%)				
	2011-2013	2014-2016	P Value: non-screen-detected 2014-2016 vs 2011-2013	Screen-detected, 2014-2016, No. (%)	P Value: screen-detected (2014-2016) vs non-screen-detected (2014-2016)
	7898	7936	NA	1582	NA
	6707 (86)	6864 (87)	0.11	1494 (95)	<0.001
	7715 (98)	7828 (99)	0.001	1563 (99)	0.65
	NA	NA	NA	NA	NA
	1401 (18)	2926 (37)	<0.001	1005 (64)	<0.001
	2924 (37)	1354 (17)		286 (18)	
	528 (7)	769 (10)		46 (3)	
	3045 (39)	2887 (36)		245 (16)	
	NA	NA	<0.001	NA	<0.001
	NA	NA		NA	
	NA	NA		NA	
	NA	NA		NA	
	NA	NA		NA	
	5197 (66)	5214 (66)		1148 (73)	
	2289 (29)	2165 (27)		214 (14)	
	353 (5)	511 (7)		213 (14)	
	3365 (43)	1450(18)	<0.001	136 (9)	<0.001
	4278 (54)	6034 (76)		1247 (79)	
	249 (3.2)	433 (6)		196 (12)	
	3499 (86.4)	5236 (91)	<0.001	1087 (92.3)	0.23
	7380 (93)	7283 (92)	<0.001	1551 (98)	<0.001
	240 (3)	317 (4)		22 (1)	
	278 (4)	336 (4)		9 (0.6)	
	226 (3)	253 (3)	0.23	11 (0.7)	<0.001
	1316 (17)	2066 (27)	<0.001	609 (43)	<0.001
	3442 (45)	3065 (41)		331 (23)	
	2864 (38)	2422 (32)		473 (34)	
	9 (0.1)	5 (0.1)		0 (0)	
	7273 (96)	7199 (95)	0.03	1380 (98)	<0.001
	266 (4)	335 (4)		31 (2)	
	27 (0.4)	11 (0.1)		0 (0)	
	464 (7)	406 (5)	0.006	37 (2)	<0.001
	12 (9-17)	15 (11-20)	<0.001[f]	15 (11-19)	<0.001[f]
	8.6%	6.8%	<0.001	4.9%	<0.001
	8 (6 - 13)	7 (5 - 11)	<0.001[f]	5 (4 - 9)	<0.001[f]

d Other surgical approach (eg, local excision, transanal endoscopic microsurgery, single-port transanal surgery).

e Excluded for rectum were the local excisions (total patients analyzed: non-screen-detected rectum, 2011 to 2013, n = 7652; 2014 to 2016, n = 7565; and screen-detected rectum, 2014-2016, n = 1415).

f Mann-Whitney *U* test.

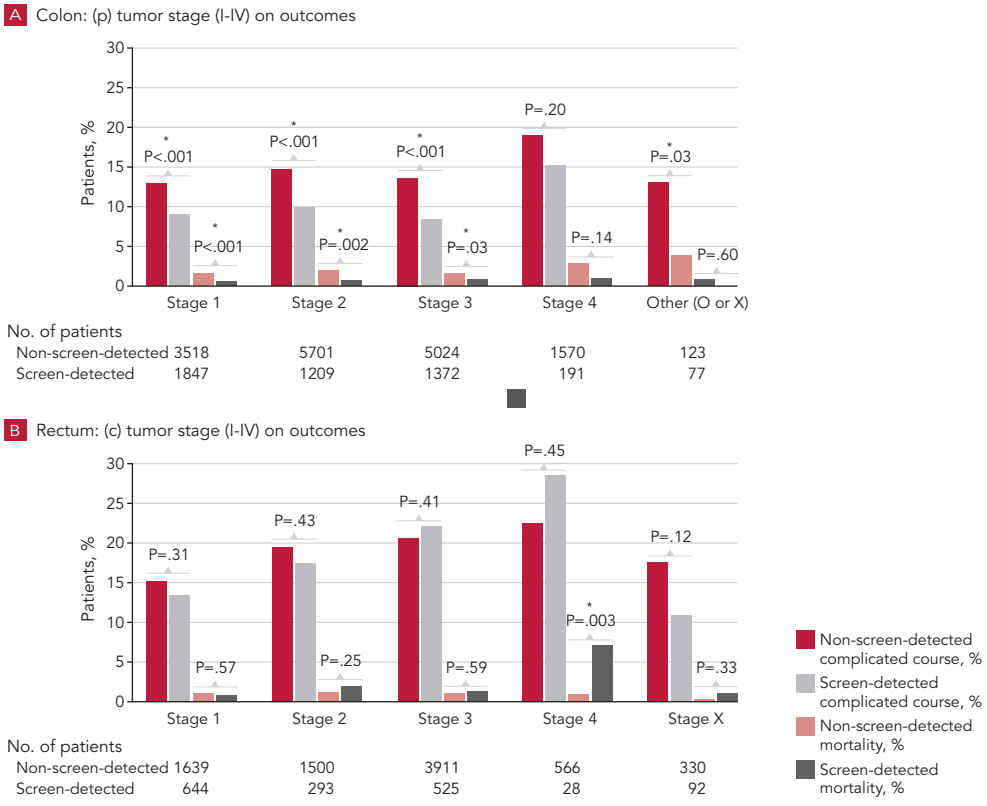
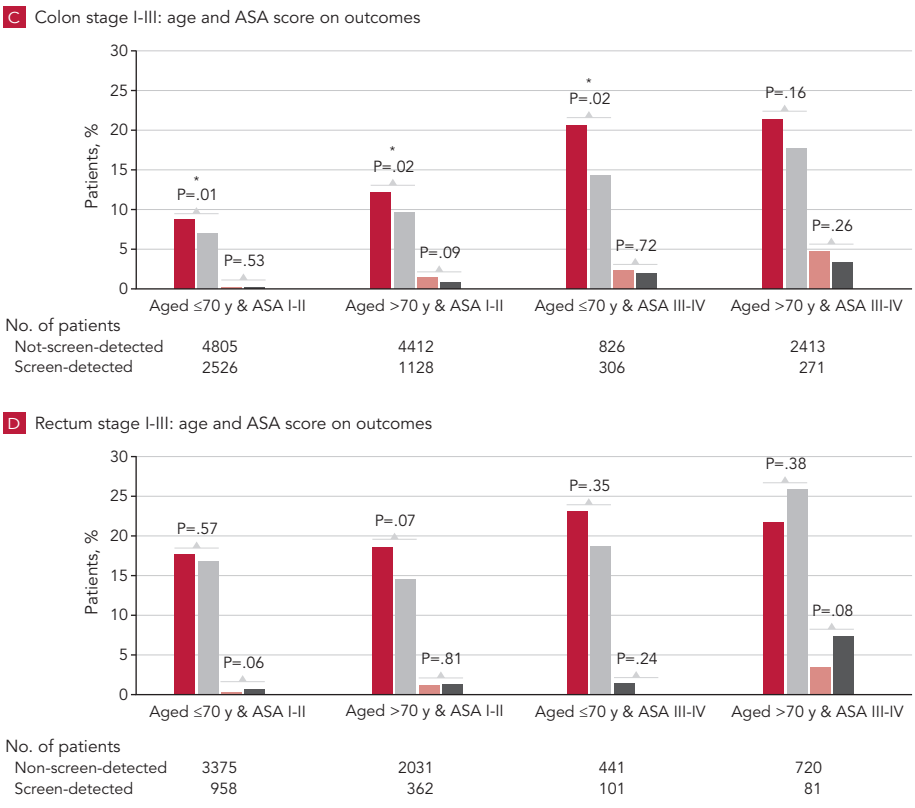


Figure 2. Risk-stratified comparison of postoperative adverse outcomes for non-screen-detected and screen-detected colorectal cancer

Risk stratified comparison on outcomes (complicated course and mortality) between screen-detected and non-screen-detected patients for colon and rectal cancer separately. A, Colon cancer, differences in outcomes for pathologic (p) tumor stage I to IV (and other) between screening and nonscreening patients. B, Rectal cancer, differences in outcomes for clinical (c) tumor stage I to IV (and other) between screening and nonscreening patients.

Referral through the screening program was not independently associated with any postoperative complication after rectal cancer surgery. However, surgery in patients with screen-detected rectal cancer was associated with a significantly higher risk of mortality compared with patients with non-screen-detected rectal cancer (AOR, 2.27; 95% CI, 1.31-3.96).



C, Colon cancer, differences in outcomes of patients with tumor stage I to III (pT1-3N0-2M0) stratified on age (≤70 y vs >70 y) and American Society of Anaesthesiologists (ASA) score (I-II vs III-IV). D, Rectal cancer, differences in outcomes of patients with tumor stage I to III (cT1-3N0-2M0) stratified on age (≤70 y vs >70 y) and ASA score (I-II vs III-IV). Missing values in Figure 2C not screen detected, n=14, screen-detected, n=1. Missing values in Figure 2D not screen detected, n=9; screen detected, n=0.

a *Significant difference* (χ^2) between *screen-detected and non-screen-detected patients.*

DISCUSSION

Surgery for screen-detected colon cancer was associated with better postoperative outcomes compared with non-screen-detected patients, even when an extensive case-mix adjustment was applied. This was not observed for rectal cancer. Most patient, tumor, and surgical treatment characteristics of the group of screen-detected CRC were significantly different compared with the group of non-screen-detected CRC in the same period. Besides a shift toward lower stages, patients with screen-detected cancers had fewer preoperative tumor-related complications such as bleeding or ileus. American Society of Anesthesiologists and Charlson

scores were also more favorable in patients with screen-detected CRC, although more pronounced in colon cancer than in rectal cancer. However, significantly more patients with screen-detected CRC had a BMI more than 30. Also in line with expectations, treatment differed between the screen-detected and non-screen-detected group with less need for preoperative radiotherapy, more laparoscopic procedures, fewer stomas, less extensive resections for local ingrowth, and fewer simultaneous resections of metastases in the patients with screen-detected tumors. The question remains whether extensive case-mix correction can sufficiently adjust for differences between characteristics of screen-detected and non-screen-detected patients, or if the variable screening represents factors that are unmeasured or unadjusted for. However, despite extensive case-mix correction, we still observed significant differences in outcomes of screen-detected compared with non-screen-detected patients for colon cancer. Therefore, one might consider adding screening as a variable in future case- mix models.

For patients with rectal cancer, screening did not reveal any statistical association for postoperative complications in the multivariable model. Although the case-mix-adjusted odds ratio on postoperative mortality was surprisingly higher in patients with screen-detected rectal cancer, an important remark has to be made interpreting this finding. Owing to the low event rate of mortality (n = 100) relative to the df used in the model (df = 29), the model could be less stable, thereby possibly affecting the reliability of the outcome. Also, there might be a chance of a type I statistical error in this analysis since we do not have a plausible explanation for this finding. This aside, analysis of the stratified subgroup did reveal a few additional events among the frail elderly patients and stage IV screen-detected rectal cancer. Stage IV screen-detected cancer may consist of a specific category of patients, with either aggressive tumor biology or relatively small asymptomatic primaries that eventually will develop metastases at an asymptomatic stage or patients who neglect initial symptoms and retrospectively should have been diagnosed earlier.

It is generally agreed that screening will eventually result in earlier stage at diagnosis and that this is associated with a better prognosis.[10-13] However, the impact of fecal occult blood tests screening on a surgical CRC audit is less clear with several potential influences. First, earlier cancer stage will enable more nonsurgical treatment using endoscopic removal (with or without laparoscopic assistance), and these patients are not included in the DCRA. Second, more patients might be candidates for minimally invasive procedures, such as laparoscopic surgery or local excision, with a positive impact on postoperative outcomes.[14,15] Third, screening will diagnose a group of patients at an earlier cancer stage, which is oncologically relevant, but will not have a significant impact on short- term morbidity and mortality in the DCRA. For example, a shift from T1-3N1M0 (stage III) to T1-3N0M0 (stage II) colon cancer will reduce the need for adjuvant chemotherapy and is associated with better long-term survival, but the type of surgery (segmental colonic resection) remains identical and there might not be any benefit visible in the DCRA for the in-hospital/30- day period. Finally, a (possibly small) negative effect on the overall outcomes in the DCRA could even exist if patients with locally advanced or metastatic tumors are diagnosed

Table 3. Differences in postoperative outcomes between non-screen-detected and screen-detected colorectal cancer[a]

	No. (%)		Absolute risk reduction, % (95% CI)	Univariable vs multivariable[b]	Screen-detected vs. Non-Screen-detected Odds Ratio (95% CI)
Operation year 2014-2016	**Screen-detected**	**Non-screen-detected**			
Colon[c,d]					
Total. No.	4696	15936	NA	NA	NA
Nonsurgical postoperative complication	555 (11.8)	2941 (18.5)	6.7 (5.6 - 7.8)	Univariable	0.59 (0.54 - 0.65)[e]
				Multivariable	0.81 (0.73 - 0.91)[e]
Surgical postoperative complication	563 (12.0)	2714 (17.0)	5.0 (3.9 - 6.1)	Univariable	0.66 (0.60 - 0.73)[e]
				Multivariable	0.80 (0.72 - 0.89)[e]
Complicated course	434 (9.2)	2293 (14.4)	5.2 (4.2 - 6.2)	Univariable	0.61 (0.54 - 0.68)[e]
				Multivariable	0.80 (0.71 - 0.90)[e]
Mortality	30 (0.6)	295 (1.9)	1.3 (1.0 - 1.6)	Univariable	0.34 (0.23 - 0.50)[e]
				Multivariable	0.74 (0.49 - 1.12)
Rectum[c,f]					
Total. No.	1582	7936	NA	NA	NA
Nonsurgical postoperative complication	293 (18.5)	1733 (21.8)	3.3 (1.1 - 5.4)	Univariable	0.81 (0.71 - 0.93)[e]
				Multivariable	0.99 (0.85 - 1.15)
Surgical postoperative complication	323 (20.4)	1837 (23.1)	2.7 (0.4 - 4.8)	Univariable	0.85 (0.75 - 0.97)[e]
				Multivariable	0.99 (0.86 - 1.15)
Complicated course	266 (17.2)	1511 (19.2)	2.0 (-0.1 to 4.0)	Univariable	0.93 (0.80 - 1.07)
				Multivariable	1.03 (0.88 - 1.21)
Mortality	19 (1.2)	81 (1.0)	-0.2 (-0.9 to 0.2)	Univariable	1.27 (0.79 - 2.06)
				Multivariable	2.27 (1.31 - 3.96)[e]

Abbreviation: NA, not applicable.

[a] Univariable and multivariable analysis for the odds on different preoperative and postoperative outcomes for 2014 to 2016 for screen-detected vs non-screen-detected patients undergoing surgery for primary colorectal cancer.

[b] Frequency of missing values in multivariable analysis colon: 49 (0.2%) (missing: sex, n = 10; age, n = 12; American Society of Anesthesiologists score, n = 7; previous abdominal surgery, n = 21). Frequency of missing values rectum: 191 (2%) (missing: sex, n = 8; age, n = 8; American Society of Anesthesiologists score, n = 2; tumor distance from anal verge, n = 167).

[c] The following factors were included in the multivariable model to correct for differences in case mix between patients: age, sex, body mass index, American Society of Anesthesiologists score, Charlson comorbidity score, any tumor-related complication, previous abdominal surgery, pathologic tumor classification, presence of metastasis, additional resection due to tumor invasion, and additional resection due to metastasis.

[d] Added for the colon: location of tumor within colon.

[e] Significant values.

[f] Added for the rectum: received radiotherapy (no short-course radiotherapy with immediate surgery, short-course radiotherapy with delayed surgery, or chemoradiation/long-course radiotherapy), procedure (lower anterior resection, abdominal perineal resection, or different), clinical tumor classification, and tumor distance from anal verge.

somewhat earlier by screening, making them eligible for resection, while they would otherwise have been treated by systemic or supportive therapy and therefore would not be registered in the DCRA.

Amri et al compared long-term outcomes in colon cancer surgery of non-screen-detected patients with screen-detected patients but with the important difference that screen-detected patients were referred through screening colonoscopy.[16] They found patients with screen-detected colon cancer to have better outcomes independent of their cancer stage. A possible contributing factor for this observation, also observed by Saraste et al,[17] is that patients in the screening program had a more extensive workup with optimized preoperative multi-disciplinary team meeting discussion and preoperative visualization of the entire colon. Tumor biology may also be different in screen-detected cancers,[18,19] such as the speed of tumor growth, tissue invasiveness, and the ease of the tumor of causing symptoms (eg, bleeding). Additionally, healthy user bias might play a role. For example, it is known that people with a low socioeconomic status are less likely to participate in a CRC screening program[20-23] but have a higher risk of developing CRC and more coexisting morbidities compared with people with a high socioeconomic status.[24] The present data and the study by Amri et al[16] suggest that screen-detected colon cancer represents a different population of patients undergoing surgical resection. In the transition phase toward a fully implemented colorectal screening program, this might have implications for benchmarking surgical outcomes, possibly urging us to add screening to the case-mix model.

For rectal cancer, outcomes between screen-detected and non-screen-detected patients did not differ. One of the potential explanations might be that rectal cancer is becoming symptomatic at a relatively early stage compared with colon cancer, which reduces the differences between screen-detected and non-screen-detected cancers.

Limitations

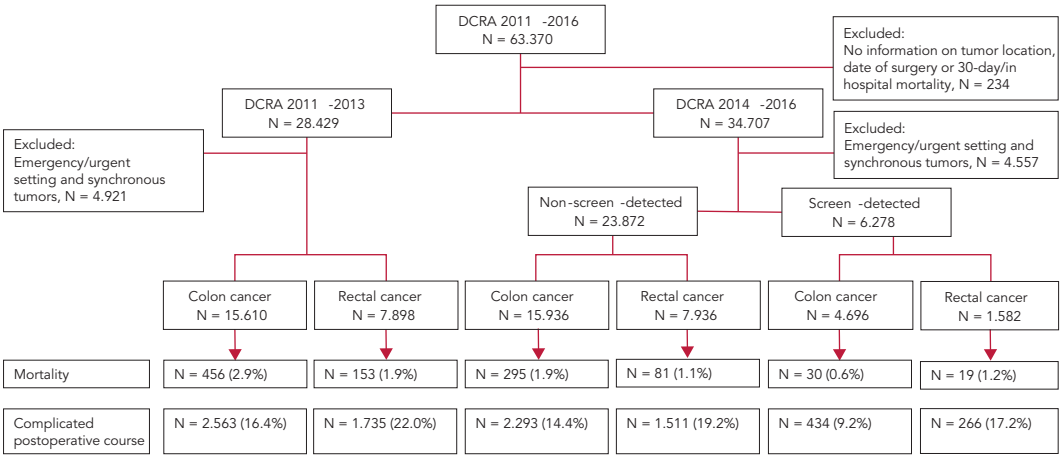
Besides the strength of the present study, such as the usage of population-based data, which reflect daily practice and the large numbers of patients, several limitations have to be taken into account. A certain extent of missing data are unavoidable in population-based studies. As also mentioned before, one might argue that some potential contributing factors to the difference observed were not included in the case-mix correction, such as substance abuse (eg, smoking), nutritional status prior to surgery, or other (unknown) factors. Moreover, stage distributions might also change over time independent of the screening program, making the current findings less consistent over time. Also, this study lacks information on people not participating in the screening program, in whom the FIT was false negative, or people not receiving a colonoscopy after a positive FIT owing to patient preferences. In addition, some patients with screen-detected cancers do not undergo surgical resection. These patients may undergo endoscopic removal of low-risk T1 tumors, be unfit for surgery, or have irresectable disease. Finally, although impossible to prove or quantify, the start of the screening may have already affected characteristics of the non-screen-

detected CRC population through earlier identification and the creation of more awareness about the disease.

CONCLUSIONS

From a surgical perspective, patients diagnosed as having a CRC detected through the national FIT-based CRC screening program represent a different population. Surgery for screen-detected colon cancer was associated with better postoperative outcomes compared with non-screen-detected patients, even when an extensive case-mix adjustment was applied. Future studies on surgical outcomes of CRC treatment should be aware of these differences and consequently take this into account in their comparison models.

APPENDICES



eFigure. Flowchart of the study patient selection

eTable 1. Missing values of Table 1 per category

	Colon			Rectum		
Patient	**Non-Screen-detected**		**Screen-detected**	**Non-Screen-detected**		**Screen-detected**
Year of operation	2011-2013	2014-2016	2014-2016	2011-2013	2014-2016	2014-2016
Total patients	15610(100)	15936 (100)	4696 (100)	7898 (100)	7936 (100)	1582 (100)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age	4/15610 (0)	12/15936 (0)	0/4696 (0)	2/7898 (0)	8/7936 (0)	0/1582 (0)
Gender	0/15610 (0)	8/15936 (0)	2/4696 (0)	0/7898 (0)	8/7936 (0)	0/1582 (0)
ASA score	24/15610 (0)	6/15936 (0)	1/4696 (0)	5/7898 (0)	2/7936 (0)	0/1582 (0)
Charlson Score	0/15610 (0)	0/15936 (0)	0/4696 (0)	0/7898 (0)	0/7936 (0)	0/1582 (0)
BMI (kg/m2)	0/15610 (0)	0/15936 (0)	0/4696 (0)	0/7898 (0)	0/7936 (0)	0/1582 (0)
Previous abdominal surgery	27/15610 (0)	17/15936 (0)	4/4696 (0)	14/7898 (0)	7/7936 (0)	1/1582 (0)
Tumor						
Location of Tumor	0/15610 (0)	0/15936 (0)	0/4696 (0)	-	-	-
Distance from anal verge	-	-	-	465/7898 (6)	149/7936 (2)	18/1582 (1)
Tumor complications	116/15610 (1)	33/15936 (0)	15/4696 (0)	65/7898 (1)	9/7936 (0)	0/1582 (0)
Clinical tumor T-stage	-	-	-	170/7898 (2)	2/7936 (0)	1/1582 (0)
Pathological T stage	84/15610 (1)	43/15936 (0)	5/4696 (0)	37/7898 (0)	40/7936 (1)	17/1582 (1)
M-stage tumor	0/15610 (0)	0/15936 (0)	0/4696 (0)	0/7898 (0)	0/7936 (0)	0/1582 (0)
Tumor stage	0/15610 (0)	0/15936 (0)	0/4696 (0)	0/7898 (0)	0/7936 (0)	0/1582 (0)

eTable 2. Missing values of Table 2 per category

	Colon			Rectum		
Patient	**Non-screen-detected**		**Screen-detected**	**Non-screen-detected**		**Screen-detected**
Year of operation	2011-2013	2014-2016	2014-2016	2011-2013	2014-2016	2014-2016
Total patients	15610(100)	15936(100)	4696(100)	7898(100)	7936(100)	1582(100)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Work-up						
Entire visualization of colon	84/15610 (1)	39/15936 (0)	27/4696 (1)	113/7898 (1)	48/7936 (1)	10/1582 (1)
Discussed in MDT	169/15610 (1)	59/15936 (0)	8/4696 (0)	17/7898 (0)	12/7936 (0)	2/1582 (0)
Neo adjuvant chemotherapy	0/15610 (0)	0/15936 (0)	0/4696 (0)	-	-	-
Neo adjuvant radiotherapy	0/15610 (0)	0/15936 (0)	0/4696 (0)	0/7898 (0)	0/7936 (0)	0/1582 (0)
Surgery						
Procedure	383/15610 (2)	323/15936 (2)	51/4696 (1)	59/7898 (1)	46/7936 (1)	7/1582 (0)
Surgical approach	15/15610 (0)	53/15936 (0)	13/4696 (0)	6/7898 (0)	19/7936 (0)	3/1582 (0)
Laparoscopic conversion	400/8735 (5)	230/12142 (2)	87/4150 (2)	277/4278 (6)	285/6034 (5)	69/1247 (6)
Additional resection due to tumor invasion	0/15610 (0)	0/15936 (0)	0/4696 (0)	0/7898 (0)	0/7936 (0)	0/1582 (0)
Additional resection due to metastasis	0/15610 (0)	0/15936 (0)	0/4696 (0)	0/7898 (0)	0/7936 (0)	0/1582 (0)
Stoma	128/15610 (1)	22/15936 (0)	7/4696 (0)	34/7652 (0)	15/7565 (0)	5/1415 (0)
Completeness of resection						
Radical resection	287/15610 (2)	59/15936 (0)	14/4696 (0)	99/7652 (1)	21/7565 (0)	4/1415 (0)
Circumferential margin	-	-	-	766/7898 (10)	290/7936 (4)	96/1582 (6)
Lymph nodes	26/15610 (0)	11/15936 (0)	4/4696 (0)	14/7652 (0)	1/7565 (0)	0/1415 (0)
Length of Stay						
median LOS in days (IQR)	113/15610 (1)	44/15936 (0)	5/4696 (0)	81/7898 (0)	28/7936 (0)	0/1582 (0)

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CHAPTER 9

Summary, discussion and future perspectives

SUMMARY

As with all cancer screening programmes, the expected reduction in cancer cases and deaths must be weighed against the burden of screening and possible side effects. The aim of this thesis is to provide insights in consequences of CRC screening participation from a surgical perspective. We investigated potential harm in terms of serious morbidity from colonoscopy, additional findings on imaging, and psychological impacts following a positive faecal immunochemical test (FIT) result. Second, studies were performed to gain more in-depth insight into surgical referral patterns for benign colorectal lesions and CRC lesions with only submucosal invasion (pT1), thereby contributing to the understanding of whether early diagnosis following CRC screening results in better surgical outcomes. Third, surgical outcomes of screen-detected patients were compared with symptomatic patients. This final chapter summarises the main findings of this thesis, along with the implications for future research.

Part I: Screen-related morbidity

In the first part of this thesis we investigated the harmful effects of CRC screening. Chapter 2 reports on a systematic review of the literature on potential harm attributed to CRC screening using faecal occult blood test or colonoscopy. In total, 60 studies were included, from each database's inception date to August 2016. Our findings indicate that subsequent colonoscopy as a CRC screening modality is associated with a low risk of serious adverse events. Serious morbidity from colonoscopy in asymptomatic patients included major bleedings (0.8/1000 procedures, 95% CI 0.18–1.63) and perforations (0.07/1000 procedures, 95% CI 0.006–0.17). An increase in the absolute number of complications is expected due to the rising number of screening and surveillance colonoscopies. Therefore, although post-colonoscopy complication rates may be low, the consequences should not be underestimated. Second, we found a high risk of inappropriate use of CRC screening which can lead to both undertreatment and overtreatment. Screening of symptomatic patients could lead to undertreatment as it may delay or decrease the likelihood of undergoing a colonoscopy. Overtreatment occurs when cancer is diagnosed in patients who would never have experienced symptoms had it remained undetected and untreated. Third, there are limited number of studies on psychological morbidity after CRC screening participation. Overall, an association was reported between participation in a CRC screening programme and psychological distress. However, these data could not be pooled quantitatively because of the diversity of study design and types of questionnaires. We therefore initiated a prospective study on psychological distress and quality of life following positive FIT instead. The results of this large study are described in Chapter 3 and suggest that individuals with positive FIT have elevated levels of psychological dysfunction and worry about developing cancer, regardless of colonoscopy outcome. Interestingly, about one fourth of the participants with false-positive FIT experienced high levels of cancer-specific worries after colonoscopy. Identifying these individuals seems worthwhile because they may

benefit from psychosocial support in order to reduce levels of distress. We also found that the vast majority of FIT positives in our study did not regret their decision to screen for CRC and reported a good quality of life.

Chapter 4 outlines a relative unexposed aspect of CRC screening: the impact of additional findings on staging computed tomography (CT). All patients, including patients with screen-detected lesions, undergo the same diagnostic track to assess the extent of the disease. With a more favourable stage distribution in screen-detected CRCs, one can assume that less metastases will be detected in this group of patients. However, the frequency of detection of findings other than metastases is surprisingly high. The aim of chapter 4 was to describe the prevalence and outcomes of non-metastatic additional findings in a FIT-based screening population in order to assess the impact of these findings. Our study showed that although additional findings were observed in half of the cohort, for the vast majority the additional investigations turned out to be unnecessary. A more complete understanding of the frequency and nature of these additional findings is critical in order to examine it in the context of the overall benefits and costs of CRC screening, and to develop guidelines and recommendations for specific additional findings.

Part II: Surgery for early-stage lesions

In the second part of this thesis, we investigated the surgical outcome for early-stage lesions. The impact of CRC screening is likely to take place through two different mechanisms: the reduction of incidence rates by treatment of precursor lesions, and the improvement of the prognosis by treating early-stage cancers. Therefore, it is important to be aware of the surgical outcome of early-stage lesions.

It is known that the vast majority of CRCs arise from benign precursor lesions, namely adenomas or serrated polyps. Limited evidence suggests that only 5% of adenomas may develop into malignancy.[1] Yet all colorectal lesions that are found during colonoscopy are currently removed. Precursor lesions, as well as a proportion of CRC limited to the submucosa (pT1), can be treated with minimally invasive endoscopic resection techniques. Lesions that are too complex for endoscopic removal are often referred for surgery. We performed a multicentre study to investigate the reasons for referral for surgery and the surgical outcomes of patients with benign colorectal lesions. Data from 15 hospitals were included in this study and the results can be found in Chapter 5. Most benign colorectal lesions referred for bowel resection were classified as complex (53%) or suspected for malignancy (34%). Size was the most commonly reported reason for surgical referral of benign lesions, followed by a suspicion of invasive growth. Lesions located in the colon were treated mainly by oncological resection. In the latter patient population, a complicated disease course was found in 11.2% of the cases and a mortality rate of 0.9% was observed. In contrast, 64% of patients with a rectal lesion were treated with local excision instead of a formal oncological resection, with no mortality reported. Given the higher morbidity and mortality rates in formal oncological surgery compared to advanced endoscopic procedures,[2] this could raise questions regarding the proportionality of surgery in relation to the anomaly, especially for benign lesions. Contrary to what

one would expect, referral to a centre with advanced endoscopic expertise to assess the possibilities of an additional endoscopic resection attempt before undertaking surgery was seldom undertaken. The results of our study indicate that a national consensus on when to refer a patient to an advanced interventional endoscopist would be desirable to diminish the substantial morbidity of surgical resection.

The implementation of CRC screening programmes has led to an increase in patients with early-stage tumours, with 40% of all CRCs in screening populations diagnosed as T1 CRC.[3] For decades, formal oncologic surgery has been the cornerstone of treatment, including patients with T1 CRC. Assessment of whether the oncological benefits outweigh the risks of surgery is challenging in these patients, especially since studies evaluating surgical morbidity and mortality consists mainly of patients with more advanced tumours. The population-based cohort study in Chapter 6 provides insight into the short-term postoperative outcomes after elective bowel resection in patients with pT1 and patients with pT2-3 CRC. No statistically significant differences were observed between patients with pT1 and pT2–3 disease in the rate of severe complications (8.3 vs 9.5%; OR 0.89, 95% CI 0.80-1.01), surgical complications (12.6 vs 13.5%; OR 0.93, 0.84-1.02) or mortality (1.7 vs 2.5%; OR 0.94, 0.74-1.19). We identified key clinical features associated with severe complications after surgery for pT1 CRC and developed a risk chart. This risk stratification helps estimate individual risks of significant morbidity and can be used before surgery in shared decision-making about whether to undergo formal oncologic surgery for pT1 CRC.

Part III: Evaluating treatment of patients with screen-detected colorectal cancer

In the third part of this thesis we focus on the treatment of patients with screen-detected CRC. In chapters 7 and 8 we compared patient and tumour characteristics between screen- and non-screen-detected patients in whom surgery is considered to provide an overview of daily practice since the introduction of the screening. In Chapter 7, we demonstrated that screen-detected patients had less comorbidity: the primary tumour was more often located in the colon and there was a lower rate of metastatic disease. In addition, the population-based cohort study as described in Chapter 8 showed that patients with screen-detected colon cancer had more favourable postoperative outcomes compared to patients with non-screen-detected colon cancer, even after an extensive case-mix correction. For rectal cancer, screen-detected was not associated with better outcomes compared to non-screen-detected. One might conclude from these findings that the "screening" factor seems to represent differences in unknown factors, e.g. tumour biology or non-registered patient characteristics such as smoking, nutritional status and socio-economic class. Adding screening as a variable should be considered in future research when comparing surgical outcomes of CRC treatment.

DISCUSSION AND FUTURE PERSPECTIVES

CRC is one of the leading causes of mortality and morbidity, with approximately 15,000 new cases annually and around 5,000 deaths due to CRC in the Netherlands.[4] The impact of CRC screening on mortality rates is likely to take place mainly through two different mechanisms: the reduction of incidence rates and the improvement of the prognosis of screen-detected cases. Using mathematical models that mimic a hypothetical population, estimations are made to predict long-term incidence and mortality. These models predict a CRC mortality decrease up to 47%, after 30 years of screening.[5] A recent observational study demonstrated a 22% reduction in CRC mortality in areas where FIT screening programmes were implemented compared with areas without screening.[6]

Screening evaluation

In the Netherlands, a large number of people are invited for CRC screening. However, only a small proportion of the participants benefit from screening. Dutch screening data from 2014 until 2017 showed that 6% of participants had a positive FIT test result and were referred for diagnostic colonoscopy. In the first round, 8% of people attending for colonoscopy were found to have cancer, and advanced adenomas (AA) were found in 42%. This positive predictive value (PPV) declined to 41% (AA or CRC) in the second round. The sensitivity for CRC turned out to be 85.5%, which was higher than expected.[7] But despite improved sensitivity of FIT screening for CRC, this still implies that one in seven CRCs are missed and that almost half of the FIT-positive participants undergo an invasive colonoscopy without detection of advanced neoplasia. In addition, evidence suggests that most adenomas will never develop into CRC.[1] However, all adenomas and sessile serrated lesions are routinely removed during colonoscopy as it is impossible to predict which ones will become malignant. With a detection rate of 4.4% for CRC, this means 250 people need to be screened to detect one person with cancer.

Comparing the overall benefit of screening is difficult since the results of most clinical trials are presented as relative risk reduction or odds ratios, and these ignore the role of event rate on overall clinical benefit. Instead, the number needed to screen (NNS) could be applied as a measure of screening efficiency, defined as the number of people that need to be screened to prevent one death from the cancer of interest. It can be calculated as NNS equals 1 divided by absolute risk reduction. Using this calculation, at age 60, when risk of death from CRC over the next 10 years is 0.33%, a 22% mortality reduction still requires 1,429 persons to be screened to avoid one death. This is in line with the literature that indicates that to prevent one death from CRC, screening with FOBT may require offering annual testing to an estimated 500-1,500 people for 5-10 years.[8,9] This means a large number of people need to be screened in order to save a few lives. But still, the NNS for CRC screening is lower compared to other screening programmes recommended by the EU, i.e. breast and cervical cancer screening. The NNS for breast cancer screening is 2,000, meaning that for every 2,000 women invited for screening over a period of 10 years, one

death from breast cancer will be prevented.[10] The NNS in cervical cancer screening is unknown, but up to 2,700 women have to be screened with cytology in order to detect one cancer.[11] Different from other screening programmes, the effect of screening on cancer incidence in CRC screening may be of even greater importance than the effect of early detection of cancer in reducing CRC mortality.[12] Other metrics have been proposed in order to estimate screening outcomes, such as the number needed to screen to detect one case with advanced neoplasia,[13] number needed to screen to detect one individual with sessile serrated polyps,[14] number of adenomas needed to remove, and adenoma dwell time avoided.[12]

Biases in screening

A common cause of overstating or distorting the true screening effects are lead-time bias and length-time bias. Lead time is survival time that is added to a patient's survival time because of an earlier diagnosis, irrespective of a possibly postponed time of death.[15] Therefore, it may appear that screening extends survival, but if the person dies at a time in life that previously has been the usual course of the disease, the person's life has not been prolonged. It is difficult to disentangle how much of an observed improvement in survival is real and how much is due to lead-time bias.[15] Length bias is more subtle than lead-time bias, defined as the increment in survival among screen-detected cases because of the over selection of slowly growing cancers.[16] It has been hypothesised that length bias could be a problem in breast cancer screening, whereas screening would preferentially detect slowly-growing cancers (with longer latency), which have more favourable prognoses, while cancers escaping the screening tests, i.e. interval cancers, would have a worse prognosis. If this selection occurs, a less favourable pattern of prognostic factors in interval cancers as compared to cancers occurring in the absence of screening would be expected.[17] However, this was not observed in a recent Italian study using FIT. This multicentre study showed that interval CRCs had no worse pattern in terms of prognostic factors compared to cancers diagnosed in the absence of screening, as well as compared to screen-detected CRCs, adjusted for stage.[17] An extreme form of length-biased sampling is overdiagnosis. It occurs when cancer is confirmed by the pathologist, but the lesion lacks true malignant potential because of competing causes of death. Since cancer is primarily a disease of aging, competing causes of death can account for a large proportion of deaths, even in people with indolent cancer.[18] Literature suggests this might also be a problem in CRC screening. A large study with data from the Veterans Affairs Health Care System showed that of all patients aged 70–75 with a Charlson comorbidity index >4 (indicating poor health and shortened life expectancy), 40% underwent screening.[19] It is very unlikely that these patients would benefit from screening participation because of their competing risks.

Personalised screening – tailored approach

Currently, the strategy for CRC screening is the same for all individuals. Organised CRC screening programmes with faecal occult blood test are recommended by the European Council for individuals aged 50-74 years,[20] in the Netherlands it is

recommended for individuals aged 55-74 years. Age is the only factor that is applied to identify the target population. Since all individuals within the target age range potentially suffer from the burden of screening and are at risk of its harmful effects, uniform screening is probably not the best screening strategy. Ideally, screening would only target those individuals that would benefit most. Personalised screening could contribute to the benefit-harm ratio of CRC screening if it would only detect high-risk individuals.

In order to personalise screening, we might have to reconsider the target age range. Recently, the American Cancer Society (ACS) recommended that CRC screening start at age 45.[21] Their recommendation was based on an increase in CRC incidence among young adults in North America, Australia and China.[22] This increase was also observed in Europe.[23] On the other hand, there are also individuals outside this age limit who might benefit from screening. Observational data from American veterans showed that of 97,786 veterans aged >75, 24.6% had a Charlson comorbidity index of 0, indicating excellent health and good life expectancy.[19] These individuals might have benefited from screening participation had they been invited. This reasoning is reinforced by the ACS, as their recent guideline update shows that for individuals aged 76 to 85 years clinicians should individualise CRC screening decisions.[21] Using comorbidity-adjusted life expectancy rather than chronological age should contribute to improved tailored screening of older patients. Moreover, offering screening to younger patients with additional risk factors could identify higher-risk individuals earlier, which in turn could reduce cancer mortality.

Several studies have evaluated different risk factors and their potential in a more personalised screening approach. Established risk factors for CRC include age, male gender, excess body fat, tobacco smoking, alcohol intake, inflammatory bowel disease, consumption of processed meat, and a family history of CRC or adenoma.[24,25] Individuals with a family history of CRC have a two-fold risk of developing CRC,[26] but male gender and faecal haemoglobin (Hb) concentration have even higher predictive value for CRC.[24,27,28] In the Netherlands, a cutoff of 47 µg Hb/g faeces (equal to 275 ng Hb/ml faeces) is used for a positive test. However, previous literature has shown that faecal Hb concentration of 8-10 µg Hb/g faeces was associated with a higher risk for the detection of CRC or advanced adenomas (AA) at consecutive screenings (Hazard ratio 8). Therefore, one might assume that individuals with faecal Hb concentrations just below the cutoff (8-47 µg Hb/g faeces) may benefit from a shorter screening interval. This should translate in a reduction of interval cancers but possibly at the cost of increased colonoscopy demand. On the other hand, individuals without any faecal Hb detected could benefit from longer screening intervals. This might reduce the number of negative colonoscopies. In addition, men have higher faecal haemoglobin concentrations compared to women, and multiple studies confirm higher FIT sensitivity for men than for women.[29-31] The reason for this gender difference, however, is not clear. Use of aspirin and non-steroidal anti-inflammatory drugs might be more common in men, and colonic transit time might be faster in men which could be associated with less degradation of faecal hemoglobin.[32] Gender differences in interval cancer rates might raise the question

whether different screening strategies for men and women should be applied. Therefore, a strategy with adjusted intervals based on previous Hb concentration in FIT, in combination with patient preferences, life expectancy and health status could be the key to personalised screening.

Personalised screening – Identifying individuals at high risk of burden

Since CRC is detected in only 0.4% of the screened individuals with FIT, it is essential to be able to select only those individuals who would benefit most, as described in the previous section. Personalised CRC screening could further be of benefit in identifying individuals at risk of experiencing psychological harm as a result of screening participation. As outlined in this thesis, both screening participation and surgical treatment for screen-detected lesions can have a negative impact on participants' well-being. In selected cases these drawbacks could outweigh the presumed benefits of screening.

Some individuals with positive FIT are at risk of experiencing psychological dysfunction and worry about developing cancer. Almost 1 in 5 individuals with false-positive FIT still experience high levels of cancer worry, six months after being told they have no cancer.[33] Based on previous literature, it is assumed that individuals who are more likely to experience higher anxiety levels are people living alone, with inadequate health literacy, and/or non-working individuals.[34] This is assumed to be a vulnerable group as their with cancer concerns could be derived from a lack of social support, a fear or additional life burden or a fear of facing a potential cancer diagnosis alone. Furthermore, individuals with limited literacy skills might have difficulty understanding the information provided. Previous research on CRC worry and CRC screening-related anxiety also showed higher levels of anxiety in women than in men. However, it should be noted that women generally yield higher scores than men on explicit anxiety measures. Furthermore, it is important to identify subjects that are likely to develop substantial psychological distress. These patients could benefit from additional counselling or even be advised to decline screening participation.

Another crucial aspect in the burden of screening is the impact of the additional surgery. For decades, formal oncologic surgery has been the cornerstone of treatment of colorectal lesions and is associated with considerable morbidity and mortality. And as described in this thesis, given that the oncologic resection is the same, early-stage tumours do not necessarily lead to safer surgical procedures. In line with previous publications, risk factors for severe complications within 30 days after elective CRC surgery included sex, ASA grade, previous abdominal surgery, type of procedure and type of surgery. Women with ASA grade I-II who underwent sigmoid resection had a 5% risk of severe complications (reintervention and/or mortality), whereas men with ASA grade III-IV treated with left colectomy had an 19% risk. This risk stratification as described in this thesis might help to estimate individual risks of significant morbidity directly after surgery, but it is also important to acknowledge the long-term results. Especially in older patients, surgery could have a prolonged impact on postoperative mortality and mortality.[35] It is therefore

an important improvement to report the 90-day morbidity and mortality rate in the Dutch ColoRectal Audit (DCRA), instead of the 30-day records, which have been used historically.

Treatment for minimal-risk disease

Currently, one of the major challenges of CRC screening from a surgical perspective is the optimal treatment of early-stage lesions. With the introduction of screening, the detection of early-stage CRC has increased to approximately 40% of all screening detected cancers.[3] It is quite difficult to assess whether the oncological benefits of excision of potential positive lymph nodes and possible residual cancer tissue outweigh the risks of additional surgery, especially in these early-stage tumours. As lymph node metastases are reported in only 8-12% of patients with T1 CRC,[36] one could assume that a lot of patients would benefit from minimally invasive treatment alternatives. There is growing evidence that endoscopic resection is also safe for T1 CRCs at low risk for lymph node metastasis, provided that an en-bloc resection will be performed.[37,38] Moreover, an endoscopic resection attempt does not negatively affect oncologic outcome in high-risk T1 CRC.[39] Another upcoming surgical alternative for colonic lesions that are not suitable for endoscopic removal is the limited endoscopy-assisted wedge resection.[40]

However, prerequisite for successful treatment of early-stage lesions is an optimal optical and histological diagnosis. The optical differentiation between adenomas and T1 CRC, and the prediction of invasion depth are crucial to the subsequent treatment strategy. Described in this thesis, suspicion of invasive growth was one of the most common reasons for surgical referral of benign lesions. Also, referral to a tertiary interventional endoscopy centre (TIEC) for reassessment of endoscopic resection seems to be underused. Since the use of advanced imaging techniques to support optical diagnosis has only recently gained traction in Western countries it is expected that in the coming years expertise in this field will be further developed, resulting in increased referrals to TIECs for a subset of patients.

The lack of good evidence and guidelines regarding the clinical care of patients with T1 CRC motivated a group of hospitals to collaborate on this topic, resulting in the foundation of the Dutch T1 CRC working group in 2014 (www.t1crc.com). The group is a multicentre collaboration between gastroenterologists, surgeons and pathologists. The main aim is to perform high-quality research concerning the detection, diagnosis, treatment and surveillance of T1 CRC in order to increase knowledge and awareness and decrease the number patients that will be referred for surgery without any benefit. Current research projects of the Dutch T1 CRC working group concern biomarkers for lymph node metastasis in T1 CRCs (STONE project), education to improve discrimination between non-invasive neoplasia and early CRC with optical diagnosis (OPTICAL II study), limited endoscopy-assisted laparoscopic wedge resections for the treatment of difficult colon polyps (LIMERIC study), and the validation of various existing risk models for T1 CRC (risk model validation).

Areas in need of future study

The current positive predictive value of FIT makes a substantial proportion of diagnostic colonoscopies unnecessary. Almost half of the FIT-positive participants had no advanced adenoma or CRC detected on screening colonoscopy. The first evaluation report with Dutch data from 2014-2017 showed that there were over 20,000 FIT-positive individuals each year that underwent a colonoscopy without having advanced neoplasia detected.[7] This is in line with previous model-based impact studies that predict that by 2044 between 19,700 and 26,300 individuals in the Netherlands will have undergone diagnostic colonoscopies due to false-positive FITs.[5] Aside from these diagnostic colonoscopies, a considerable proportion of colonoscopies are performed for surveillance purposes. With the complete roll-out of mass screening, it is expected that this proportion will further increase. In addition to the potential harm caused by these unnecessary invasive procedures, overuse of colonoscopies also leads to a waste of health care resources. In order to reduce the burden of false-positive tests, future studies are needed aimed primarily at optimising current screening modality with FIT and colonoscopy. In addition, it is also important to encourage research involving non-invasive screening alternatives.

Optimising colonoscopy

Colonoscopy is the most commonly performed gastro-intestinal endoscopic procedure and considered the 'gold standard' investigation of the colon. Nevertheless, the accurate optical diagnosis of polyps remains difficult. In large non-pedunculated adenomas, the rate of unexpected malignancies varies between 7 and 14%.[41] Also, the OPTICAL trial, in which Dutch endoscopists systematically evaluated large polyps in a stepwise manner, resulted in a sensitivity for optical diagnosis of T1 CRC of 79%.[42] As the successful treatment of early-stage lesions starts with optical differentiation, ways to increase the sensitivity of colonoscopy should be subject to further study. Colonoscopy is currently performed using white light. Advanced imaging with narrow band imaging (NBI) or magnification chromoendoscopy (MCE) could be applied for optical differentiation between non-invasive and invasive polyps, based on local expertise and available resources. Fluorescence molecular endoscopy (FME) could also be a promising tool to improve optical diagnosis. FME visualises lesions based on their biological properties rather than their morphology.[43] There are several biomarkers available that are conjugated to a fluorophore and accumulate in tumours. A dedicated near-infrared fluorescence imaging system enables detection of tumours during the procedure. Clinical studies with fluorescence colonoscopy have been published before, using GE-137 (peptide against c-Met),[44] or bevacizumab-800CW (antibody against vascular endothelial growth factor A).[43,45] Since a fluorescent anti-CEA monoclonal antibody (SGM-101) has been shown to be safe to use during colorectal surgery,[45] this might be a promising target for colorectal imaging as well. In addition, the application of artificial intelligence (AI) technology is also likely to contribute to polyp detection and differentiation practice. It is anticipated that the implementation of AI will transform the field of endoscopy because it will help endoscopists to highlight potential lesions

during colonoscopy, distinguish neoplastic polyps from non-neoplastic polyps, and help predict areas of invasive cancer within a polyp.[46]

Non-invasive screening

The opportunity to improve the impact of current CRC screening programmes has driven innovative research to develop non-invasive screening tests with biomarkers, defined as biological entities that can be measured, for example in blood or tumour tissue, to be used as indicators of pathological processes.

Non-invasive testing for CRC is most advanced in testing for stool, for example faecal occult blood, globin or DNA mutations. A multitarget stool DNA test has been shown to have superior sensitivity compared to FIT with cutoff 100 ng Hb per ml (92.3% vs 73.8% for CRC) and an overall cancer detection similar to colonoscopy. But despite detecting more cancers, multitarget stool DNA testing did generate more false-positive results than FIT specificities as specificity was 89.8% for DNA testing versus 96.4% for FIT.[47] Serum tests, such as serum proteomics, nuclear matrix proteins and serum DNA, are also subject of current research.[48] But the potential to use serum markers in early detection is unclear, and they are not included in screening guidelines.

The use of the gut microbiome as a diagnostic tool for CRC has also been proposed.[49,50] The gut microbiome, defined as the microbial communities that populate our intestinal tract, is emerging as a relevant factor in human disease.[51] Supported by evidence showing an association between bacterial organisms and CRC carcinogenic and progression, it has been hypothesised that the gut microbiome might also play a crucial role in the development of CRC.[52] Recent meta-analysis and a validation study showed that microbiome-based CRC prediction models enable a very high diagnostic potential for CRC.[51] Prospective studies of these biomarkers are needed to establish whether they can identify individuals at elevated risk of CRC and provide the possibility of disease prevention.

A novel approach within the field of biomarker exploration is the faecal volatolome, composed of faecal volatile organic compounds (VOCs). These compounds are gaseous carbon-based chemicals, which are end products of human metabolism. The overall metabolic state of an individual is reflected by emitted VOCs. Composition of the faecal volatolome could be altered by cancer growth. This means that analysis of VOCs originating from breath and faeces can provide a metabolomics biomarker profile that could be used as a diagnostic tool.[53] The potential of the faecal volatolome as a potential non-invasive marker for the detection of neoplastic lesions in the colon has been subject of various studies, using either chemical analytical or pattern-recognition techniques. A recent systematic review demonstrated a high diagnostic value for the detection of both CRC and AA based on faecal VOCs.[54] However, with regard to mass screening, the cost-quality ratio is of utmost importance. To date, VOC tests for the detection of CRC and AA are still far from being ready to be used in a public health setting. Future studies should focus on the validation of faecal VOC biomarkers, preferably linked to the population-based screening, to develop tailor-made sensors to be used in clinical practice.

Key weaknesses of all current available screening modalities are their intermittent application and one-size-fits-all design. In pursuit of precision health, trends matter more than momentary snapshots. Ideally, in order to prevent diseases to occur or improve prognosis by early diagnosis, non-invasive longitudinal monitoring should be available to everyone at risk, with minimal interference of human behaviour. An example of such technology is the 'smart' toilet, which is self-contained and operates autonomously by leveraging pressure and motion sensors. It analyses the user's urine, calculates the flow rate and volume of urine, and classifies stool according to the Bristol stool form scale. Each user of the toilet is identified through their fingerprint and distinctive features of their anoderm.[55] In future research, additional assays could be added in this system, including microbiome analysis and biochemical stool analyses.

Lifestyle

Despite the promising results of the colorectal screening programme, the greatest survival benefit might come from approaches that improve overall health status in unscreened persons. Multiple studies have shown that lifestyle factors such as smoking, physical activity, alcohol intake, body weight and diet quality affect life expectancy and incidence of chronic diseases. A recent large cohort study provided a quantification of this survival benefit associated with modifiable lifestyle factors.[56] A low-risk lifestyle was defined as having a normal weight (body mass index 18.5–24.9), moderate alcohol intake (5–30 g/day), high diet quality (upper 40% of alternate healthy eating index), physical activity (>3.5 h/week moderate to vigorous intensity activity), and/or never smoke. At age 50, adherence to a low-risk lifestyle was associated with a longer life expectancy free of major chronic diseases of approximately 10 years. Therefore, it is advised that policy makers translate these exciting data into programmes that encourage positive lifestyle choices, instead of management of preventable morbidity.

In conclusion, for all mass screening programmes, an individual centred approach should be used – one that incorporates health status and individual preferences. Future studies should therefore focus on identifying high-risk individuals in order to optimise screening outcomes. Improvement of screening tests, minimal invasive treatment and solid shared decision-making strategies are needed to minimise the burden of current CRC screening. Using complete and evidence-based data, individuals should be able to discuss the pros and cons of screening participation.

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Nederlandse samenvatting

Darmkanker is een kwaadaardige tumor in de dikke darm (colon) of de endeldarm (rectum). Het is een van de meest voorkomende vormen van kanker wereldwijd. De kans dat iemand gedurende zijn leven darmkanker krijgt is ongeveer 5%.[1] In Nederland wordt jaarlijks de diagnose bij meer dan 15.000 keer gesteld en overlijden er circa 5.000 mensen aan de gevolgen van darmkanker.[2] Darmkanker ontstaat vrijwel altijd uit poliepen, maar lang niet alle poliepen ontaarden in kanker. Als kanker ontstaat uit een poliep, dan duurt dat ongeveer 15 jaar. Wanneer een tumor groeit zal deze de darmwand ingroeien en zich verspreiden door het lichaam via lymfeklieren en/of de bloedbaan.[3] Indien de diagnose in een vroeg stadium wordt gesteld (stadium I) is de 5-jaars overleving ongeveer 90%. De kans op overleving na 5 jaar daalt tot 10% indien de tumor is uitgezaaid naar andere organen (stadium IV).[4]
In Nederland werd in 2014 het bevolkingsonderzoek naar darmkanker ingevoerd. Mensen van 55 jaar tot en met 75 jaar ontvangen elke twee jaar een ontlastingtest per post. In het laboratorium wordt onderzocht of er bloed in de ontlasting aanwezig is wat onder andere kan worden veroorzaakt door een darmpoliep of darmkanker. Als er een bepaalde hoeveelheid bloed in de ontlasting wordt aangetroffen is een kijkonderzoek van de binnenkant van de darm (coloscopie) aanbevolen. Als er bij het kijkonderzoek poliepen gevonden worden kunnen deze meestal meteen worden verwijderd. Wanneer er tijdens de coloscopie darmkanker wordt gevonden, of als er poliepen gezien worden die niet tijdens de coloscopie verwijderd kunnen worden, volgt meestal een verwijzing naar een chirurg. Er kan dan een operatie volgen waarbij een deel van de darm wordt verwijderd, al dan niet na voorbehandeling met chemotherapie en/of radiotherapie.

Het bevolkingsonderzoek darmkanker is bedoeld om de sterfte door darmkanker te verminderen. Het veronderstelde effect van het bevolkingsonderzoek is tweeledig: enerzijds wordt darmkanker voorkomen door het verwijderen van poliepen, anderzijds wordt darmkanker in een vroeg stadium vastgesteld waardoor de kansen op genezing groter zijn. De behandeling in een vroeg stadium kan bovendien minder belastend zijn. Aanvullende chemotherapie na een operatie is bijvoorbeeld minder vaak nodig. Een rekenmodel voorspelt dat door het bevolkingsonderzoek in de toekomst ruim 1 op 3 sterfgevallen aan darmkanker wordt voorkomen.

Het bevolkingsonderzoek darmkanker valt onder de regie van het RIVM (Rijksinstituut voor Volksgezondheid en Milieu). In opdracht van het RIVM wordt een landelijke monitoring van het bevolkingsonderzoek darmkanker verricht door het Integraal Kankercentrum Nederland. Het Landelijk Evaluatieteam Colorectaal Kanker (LECO) verzorgt de landelijke evaluatie.

De eerste evaluaties van het bevolkingsonderzoek laten zien dat de deelnamegraad hoger is dan verwacht en dat de ziekte vaker in een vroeg stadium wordt gevonden.[3, 5] Het is nog te vroeg om een daling te zien in darmkankersterfte. Echter, zoals met elk bevolkingsonderzoek moet de daling van het aantal nieuwe ziekte- en sterfgevallen worden afgewogen tegen de mogelijke nadelen van het bevolkingsonder-

zoek. Een volledig beeld van zowel de baten als de lasten is noodzakelijk voor de potentiële deelnemer om de juiste afweging te maken om al dan niet mee te doen aan het bevolkingsonderzoek.
Tot recent bleken echter verschillende aspecten van het bevolkingsonderzoek vanuit chirurgisch perspectief onderbelicht. Het overlijden van een 75-jarige patiënt illustreert dit in extreme mate. Deze patiënt had geen klachten die pasten bij darmkanker maar bij het bevolkingsonderzoek werd een grote darmpoliep vastgesteld. Hij werd geopereerd en bij weefselonderzoek bleek de poliep goedaardig. Het postoperatief beloop verliep gecompliceerd en uiteindelijk kwam de patiënt te overlijden. Uit deze casus kwamen diverse onderbelichte aspecten van het bevolkingsonderzoek naar voren. Bij gebrek aan een landelijke registratie bleken de risico's van chirurgie voor goedaardige afwijkingen onduidelijk. Ten tweede bestond er een reële kans op overlijden aan iets anders dan aan de gevolgen van deze poliep, wanneer de patiënt zich niet had laten opereren. Dit maakte hem mogelijk slachtoffer van overdiagnostiek en overbehandeling. De vraag ontstond of de deelnemer aan het bevolkingsonderzoek op de hoogte is van alle risico's van deelname.

Dit proefschrift onderzoekt een aantal aspecten van het bevolkingsonderzoek naar darmkanker vanuit chirurgisch oogpunt. Zo beschrijven we in het eerste deel de mogelijke nadelen van deelname aan het bevolkingsonderzoek naar darmkanker. In het tweede deel evalueren we de uitkomsten van chirurgie in een vroeg stadium van de ziekte. Tot slot worden in het derde deel de patiënten die via het bevolkingsonderzoek ontdekt zijn, vergeleken met patiënten die gediagnosticeerd zijn met darmkanker buiten het bevolkingsonderzoek.

DIT PROEFSCHRIFT

Hoofdstuk 1 is een inleiding over het ontstaan en de behandeling van darmkanker en het bevolkingsonderzoek naar darmkanker in het algemeen.

Deel 1: Screening gerelateerde morbiditeit

In het eerste deel van dit proefschrift beschrijven we de mogelijke nadelen van screening met een ontlastingstest of coloscopie. **Hoofdstuk 2** betreft een samenvatting van de bestaande wetenschappelijke literatuur over risico's van het bevolkingsonderzoek waarbij in totaal 60 studies zijn meegenomen. Hieruit blijkt dat een coloscopie als screeningsmodaliteit gepaard gaat met een zeer laag risico op complicaties. De kans op een grote bloeding of perforatie bleek kleiner dan 0,1%. Echter, omdat het bevolkingsonderzoek stapsgewijs wordt ingevoerd zullen het aantal coloscopieën en daarmee het absolute aantal complicaties in de toekomst toenemen. Daarom is het van belang dat de risico's hiervan niet worden onderschat. Ook kan deelname aan het bevolkingsonderzoek leiden tot zowel onder- als overbehandeling, zo blijkt uit bestaande literatuur. Een fout-negatieve uitslag, dus een niet afwijkende uitslag bij een deelnemer die de ziekte wel heeft, kan bij iemand

met klachten van darmkanker leiden tot uitstel van diagnostiek. Aan de andere kant kan overbehandeling optreden wanneer de afwijking nooit klachten zou hebben gegeven. Tot slot werd er in onderzoek aangetoond dat deelname aan het bevolkingsonderzoek psychologische gevolgen zou kunnen hebben. Omdat deze literatuur beperkt was zijn we zelf een onderzoek gestart; de SCOOP studie (Screening voor Colorectaal carcinOOm: Psychische gevolgen). In **hoofdstuk 3** beschrijven we de resultaten van deze studie waarin ruim 1.000 patiënten met een positieve ontlastingtest en coloscopie zijn onderzocht. Hun psychologisch functioneren, zorgen over kanker, kwaliteit van leven en spijt over deelname aan het bevolkingsonderzoek werd op drie momenten gemeten: voor de coloscopie, na het verstrekken van de coloscopie uitslag en 6 maanden na de coloscopie. Hieruit bleek, zoals verwacht, dat mensen die werden gediagnosticeerd met kanker (de zgn. 'terecht-positieven') meer psychologisch disfunctioneren ervoeren dan mensen die geen kanker bleken te hebben (de zgn. 'vals-positieven'). Opvallend was wel dat bij de deelnemers zonder kanker enig psychologisch disfunctioneren en kanker-specifieke zorgen aanwezig bleven, tot zes maanden na de coloscopie-uitslag. Deelnemers zonder kanker ervoeren geen vermindering in hun kwaliteit van leven, terwijl deelnemers met kanker een duidelijke vermindering van kwaliteit van leven ervoeren na hun testuitslag. Vrijwel niemand bleek spijt te hebben van deelname aan het bevolkingsonderzoek. Hoewel de gemeten verschillen niet groot zijn en de klinische relevantie voor discussie vatbaar is, pleiten wij ervoor dat deelnemers aan het bevolkingsonderzoek worden gewezen op de mogelijke psychologische nadelen van deelname.

Alle patiënten met een grote poliep of darmkanker die worden verwezen naar de chirurg krijgen radiologische onderzoeken van borst en buik om de uitgebreidheid van de ziekte te bepalen en om eventuele uitzaaiingen vast te stellen. Patiënten die via het bevolkingsonderzoek worden gediagnosticeerd ondergaan ditzelfde traject. Het verschil is echter dat de kans op het vinden van uitzaaiingen aanzienlijk kleiner is bij mensen die via het bevolkingsonderzoek komen dan bij mensen die klachten hebben. In het LUMC kregen alle verwezen patiënten een CT-scan met contrastmiddel van zowel de borst- als buikorganen. Bij het maken van een dergelijke CT-scan is er een relatief grote kans op het vinden van andere afwijkingen dan uitzaaiingen. Dit wordt ook wel een nevenbevinding of "bijvangst" genoemd. In **hoofdstuk 4** beschrijven we het vóórkomen en de uitkomsten van dergelijke nevenbevindingen bij een groep patiënten die via het bevolkingsonderzoek werd verwezen naar de polikliniek Chirurgie. Bijna de helft van de 231 onderzochte patiënten had een nevenbevinding waarvoor aanvullend onderzoek of een behandeling werd verricht. Deze aanvullende onderzoeken bleken echter in de meeste gevallen overbodig omdat de nevenbevinding goedaardig bleek. De gevolgen van deze "bijvangst" kunnen zowel positief als negatief worden uitgelegd. Zij maken hoe dan ook onderdeel uit het bevolkingsonderzoek en moeten als zodanig meegewogen worden bij de evaluatie van het bevolkingsonderzoek.

Deel 2: Chirurgie voor afwijkingen in een vroeg stadium

Omdat nog onvoldoende duidelijk is welke poliepen mogelijk uitgroeien tot darmkanker worden de meeste poliepen tijdens de coloscopie direct verwijderd door de maag-darm-lever arts. Indien de poliep niet (veilig) verwijderd kan worden tijdens de coloscopie wordt de patiënt verwezen naar de chirurg om een darmoperatie te bespreken. Dit heeft het voordeel dat hiermee niet alleen de tumor wordt verwijderd maar ook de lymfeklieren die de tumor omgeven. Darmchirurgie gaat echter gepaard met een hoog complicatierisico. Tot 2% van de patiënten komt te overlijden binnen 30 dagen na de operatie.[6] Het verwijderen van een poliep tijdens de coloscopie (de zgn. endoscopische behandeling) kent een veel lager complicatierisico. Omdat er in Nederland alleen een registratie bestaat voor operaties van darmkanker, was het onduidelijk hoe vaak er voor goedaardige darmpoliepen werd geopereerd. Daarom hebben we onderzocht wat de redenen zijn om een patiënt met een goedaardige darmpoliep naar de chirurg te verwijzen. Wij hebben hiervoor een nieuw database-managementsysteem gebouwd waarmee data in verschillende ziekenhuizen kon worden ingevoerd. In **hoofdstuk 5** evalueren we de verwijzingen en uitkomsten van patiënten met goedaardige darmpoliepen. Data uit 15 Nederlandse ziekenhuizen laten zien dat de grootte van de poliep en de verdenking op een kwaadaardigheid de meest voorkomende redenen waren waarom een patiënt werd verwezen naar een chirurg. In totaal hadden 11% en 3% van de patiënten met resp. colon- en rectumpoliepen die werden geopereerd een ernstige complicatie. Een verwijzing naar een ander centrum om de mogelijkheden van een endoscopische behandeling opnieuw te beoordelen gebeurde slechts in 2% van de colonpoliepen en 8% van de rectumpoliepen. De resultaten van deze studie kunnen bijdragen aan het optimaliseren van behandelstrategieën voor deze poliepen. Met name in het licht van de ernstige consequenties van chirurgie zou er meer aandacht moeten komen voor een herbeoordeling in een expertisecentra voor endoscopie. Dan kan wellicht een deel van de patiënten toch endoscopisch behandeld worden en worden zij niet blootgesteld aan de risico's van een darmkankeroperatie.

Het zogenaamde T-stadium toont de mate waarin de tumor door de darmwanden groeit, waarbij een T1 tumor zich beperkt tot de binnenste laag van de wand en een T4 tumor buiten de wandlagen groeit. Door de invoering van het bevolkingsonderzoek wordt darmkanker nu vaker in een vroeg stadium gediagnosticeerd: van 17% T1 bij diagnose voor de start van het BVO, betreft dit nu 40%. Tot recent was een darmoperatie de voorkeur van behandeling voor T1-darmkanker. Inmiddels wordt darmkanker in een vroeg stadium soms ook endoscopisch behandeld. Dan worden echter niet de lymfeklieren rondom de tumor verwijderd. Bij de keuze van de optimale behandeling voor T1-darmkanker is het dus vaak een afweging tussen enerzijds de oncologische veiligheid (wegnemen van mogelijke lymfklieruitzaaiingen) en anderzijds de risico's van de operatie. Om een goed beeld te krijgen van de risico's van de operatie voor T1-darmkanker hebben we een onderzoek gedaan met landelijke data van verschillende jaren. In **hoofdstuk 6** hebben we de korte-termijn-uitkomsten vergeleken tussen darmoperaties voor T1-darmkanker en darmoperaties voor verder gevorderde darmkanker (T2-T3). De kans op een ernstige complicatie,

chirurgische complicatie en sterfte bleek hetzelfde in beide groepen. Dit betekent dat ook chirurgie voor vroeg stadium darmkanker een aanzienlijk complicatierisico kent. Tevens waren enkele klinische factoren geassocieerd met een hoger operatierisico voor T1 darmkanker. Met deze factoren hebben we een tabel ontwikkeld zodat het risico op een ernstige complicatie meer gespecificeerd kan worden op elk individu. Deze risicotabel kan van waarde zijn voor zowel arts als patiënt wanneer er in de spreekkamer een afweging wordt gemaakt om al dan niet te opereren bij een vroeg stadium darmkanker.

Deel 3: Evaluatie van de behandeling van patiënten met darmkanker, gedetecteerd via het bevolkingsonderzoek

In het derde deel van dit proefschrift worden twee groepen darmkankerpatiënten met elkaar vergeleken: de groep waarbij darmkanker is vastgesteld via het bevolkingsonderzoek en de groep waarbij de ziekte werd vastgesteld buiten het bevolkingsonderzoek. In **hoofdstuk 7** beschrijven we de patiënt- en tumorkenmerken van beide groepen die behandeld zijn in het LUMC. Patiënten via het bevolkingsonderzoek hadden minder vaak andere aandoeningen, minder vaak endeldarmkanker en minder vaak uitgezaaide ziekte in vergelijking met de andere groep. In **hoofdstuk 8** vergelijken we de behandeluitkomsten van beide groepen met nationale data. De verschillen tussen beide groepen mogen niet zomaar geweten worden aan "screening". Bij een dergelijke vergelijking van behandeluitkomsten zijn namelijk veel factoren van invloed. Daarom moet er gecorrigeerd worden voor alle factoren die mogelijk invloed hebben op de uitkomst (zgn. casemix-correctie). De mogelijkheid om voor factoren te corrigeren blijft echter wel beperkt tot de data die beschikbaar zijn. In deze studie observeerden we dat patiënten met colonkanker via het bevolkingsonderzoek betere postoperatieve uitkomsten hadden in vergelijking met geopereerde patiënten met colonkanker buiten het bevolkingsonderzoek. Dit verschil was niet zichtbaar voor patiënten met rectumkanker. Men zou hieruit kunnen concluderen dat de factor "verwijzing vanuit het bevolkingsonderzoek" een onbekende gunstige factor representeert voor een patiënt met colonkanker. Dit zou bijvoorbeeld onderliggend de tumorbiologie of bepaalde patiëntkarakteristieken kunnen zijn. De factor "verwijzing vanuit het bevolkingsonderzoek" zou daarom als een belangrijke variabele kunnen fungeren bij toekomstig onderzoek naar uitkomsten van darmkankerchirurgie.

CONCLUSIE

Het is inmiddels zes jaar geleden dat in Nederland het bevolkingsonderzoek naar darmkanker op landelijk niveau werd geïntroduceerd. Of de sterfte aan darmkanker op termijn zal afnemen zal nog moeten blijken, hiervoor is het nog te vroeg om conclusies te trekken. Met dit proefschrift wordt vanuit een chirurgisch perspectief getracht een bijdrage te leveren aan een volledig beeld van zowel de baten als de lasten van deelname aan het bevolkingsonderzoek.

De belangrijkste conclusies van dit proefschrift zijn:

- Een coloscopie als screeningsmodaliteit gaat gepaard met een zeer laag complicatierisico (<0.1%).
- Mensen met een positieve ontlastingstest die geen kanker blijken te hebben ervaren een zekere mate van psychologisch disfunctioneren en kanker-specifieke zorgen, tot zes maanden na deelname.
- Met een CT-scan van borst en buik ter stagering bestaat een relatief grote kans op het vinden van andere afwijkingen dan uitzaaiingen. Omdat de meeste nevenbevinding goedaardig zijn, zijn veel aanvullende onderzoeken overbodig.
- De meest voorkomende redenen om patiënten met goedaardige darmpoliepen naar een chirurg te verwijzen zijn de grootte van de poliep en de verdenking op een kwaadaardigheid. Operaties voor goedaardige darmafwijkingen gaan gepaard met aanzienlijke risico's.
- Een geplande operatie voor darmkanker in een vroeg stadium gaat gepaard met dezelfde kans op een ernstige complicatie en/of sterfte als een geplande darmoperatie in een verder gevorderd stadium (resp. 8,3% versus 9,5% en 1,7% versus 2,5%).
- Patiënten die via het bevolkingsonderzoek worden gediagnosticeerd met colonkanker lijken op korte termijn betere postoperatieve uitkomsten te hebben in vergelijking met geopereerde patiënten met colonkanker buiten het bevolkingsonderzoek.

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CURRICULUM VITAE

Nina Vermeer werd geboren op 23 september 1985 in Tilburg. Na het behalen van het VWO-diploma aan het St. Odulphuslyceum te Tilburg en te zijn uitgeloot voor de studie geneeskunde begon zij in 2003 met de studie Psychologie aan de Universiteit van Tilburg. In 2004 werd de overstap gemaakt naar België nadat zij voor de tweede keer was uitgeloot voor de studie geneeskunde in Nederland. De bachelor geneeskunde werd behaald aan de Universiteit van Hasselt. De studie werd voortgezet aan de Katholieke Universiteit van Leuven waar zij in 2011 cum laude afstudeerde. De coschappen werden doorlopen in onder andere het Stuivenberg ziekenhuis in Antwerpen en het Academisch ziekenhuis Paramaribo, Suriname. Het laatste jaar van de opleiding werkte zij initieel op de afdeling chirurgie van het Universitair Ziekenhuis Leuven om vervolgens af te studeren in de richting huisartsgeneeskunde.

Na haar afstuderen werkte zij tussen 2011 en 2013 als arts-assistent heelkunde in het Elisabeth-TweeSteden ziekenhuis te Tilburg waarna ze werd aangenomen voor de opleiding tot chirurg in regio Leiden. In juli 2013 is zij gestart in het Groene Hart ziekenhuis te Gouda onder supervisie van opleider dr. R.F. Schmitz. De opleiding tot chirurg werd tussen augustus 2016 tot december 2017 onderbroken voor de start van het promotieonderzoek bij de afdeling chirurgie aan het LUMC (promotor prof. dr. C.J.H. van de Velde en co-promotor dr. K.C.M.J. Peeters) waarvan de resultaten in dit proefschrift zijn beschreven. Vanaf 2017 heeft zij haar opleiding tot chirurg voortgezet in het Alrijne ziekenhuis te Leiderdorp (opleider dr. A.M. Zeillemaker) waar zij momenteel met veel plezier werkzaam is. In 2021 hoopt zij haar opleiding tot chirurg met specialisatie gastro-instestinale en oncologische chirurgie af te ronden.

Nina is getrouwd met Fabian Holman en zij wonen met hun twee zoontjes Jan Anne (3 jaar) en Faas (2 jaar) in Den Haag.

DANKWOORD

Allereerst gaat mijn dank naar alle medeauteurs voor hun actieve en kritische inbreng bij diverse manuscripten, alsmede naar alle patiënten die bereid zijn geweest tot deelname in diverse studies. Zonder hen was dit proefschrift er niet geweest.

Prof. dr. van de Velde, beste Cock, ik beschouw het als een eer dat ook ik onder uw leiding onderzoek heb mogen uitvoeren. Uw jarenlange toewijding aan de wetenschap zijn indrukwekkend.

Dr. Peeters, beste Koen, ik had dit met niemand anders willen doen. Je ideeën, je kennis, je onuitputtelijke vriendelijkheid, je humor en eindeloze geduld hebben in grote mate bijgedragen aan dit proefschrift.

Heleen, je bent een bron van inspiratie. Creatief en vol lef. Mijn moeder had je daarom ook zo leuk gevonden denk ik.

Maxime, ik ben zo blij dat ik je heb leren kennen. Een nieuwe vriendschap en tevens elkaars getuige van dit huwelijk met de wetenschap, hoe bijzonder!

Dank aan mijn J-10 vrienden.
Aan Anne Stiggelbout, Esther Bastiaannet, Yvette en Martine, voor hun wijsheid, de gezelligheid en al hun hulp.
Aan Jesse, je weet het, imputeren kun je leren!
Aan Yara Backes en Leon Moons, voor hun inspirerende en oprechte manier van (samen) werken.
Aan Arthur Gerritsen van der Hoop en Matthieu van Egmond voor hun belangrijke bijdrage aan de SCOOP studie.
Aan alle verpleegkundigen van de Keizer Kliniek voor hun inspanningen om patiënten te includeren.
Aan Roderick Schmitz, Anneke Zeillemaker, Gerrit Jan Liefers, Bert Bonsing, Sven Mieog en Alexander Vahrmeijer voor de ruimte die ze mij gaven, hun interesse, maar ook voor de uitdaging die ik nodig had.
Aan de Heelkunde staf van het Alrijne ziekenhuis en met name de GE-Onco groep. Jephta van den Bremer, Willem van Gijn, Willem Hueting, Sacha Koch, Peter Neijenhuis, Carmen van der Pol: dank voor de stimulerende en leuke werkomgeving waarin ik mijn proefschrift heb kunnen afronden.

Aan Jan, Rick, Noor, Gert, Jesse, Oona, Sabrina en Geof. Ze weten waarom.
Aan Lasse, never a dull moment with you!

Aan Liselore, omdat haar deur altijd open staat. Sus!
Aan Vera en Hans, voor hun liefdevolle aandacht.
Aan Hetty. Fantastische Hetty. Praktisch familie, zo waardevol.

Dank aan Jordy van den Nieuwendijk voor het ontwerp van de kaft.
Dank aan Rachel Schraven voor de foto.

Aan Fabian, voor wat begon met enkele inspirerende krabbels op een papiertje in de Italiaanse zon tot uiteindelijk het lezen van al mijn stukken. Wat een trip. Dank voor al je aanmoediging, je zorg, je liefde.

Mijn lieve papa en mama. Vreemd om dit te schrijven, wetende dat jullie het niet lezen. Ik heb alles aan jullie te danken. Papa voor zijn nuance. Mama voor haar lef. Ik glimlach bij het idee hoe jullie dit zouden ervaren.