Improving the management of colorectal neoplasms in clinical practice

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voor papa

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INTRODUCTION

CHAPTER 1

INTRODUCTION

Colorectal cancer (CRC) is one of the most frequent cancers in the Western world, with an incidence of 12,000 and annual mortality rate of 5,000 in the Netherlands.[1] Forty-five percent of symptomatic patients have metastatic disease.[2]

The overall prevalence of adenoma in an asymptomatic population is 25-30% at the age of 50 years and approximately two-thirds of all colonic polyps are adenomatous.[3] Around 95% of CRCs evolve from an adenomatous polyp or sessile serrated lesion (SSL). However, despite its dysplastic character, only 5% of all adenomatous polyps progress to CRC.[3-8]

To reduce both the incidence and mortality rate of CRC, the Dutch Minister of Health, Welfare and Sport (VWS) decided to implement a national bowel screening program in January 2014.[1,9] Individuals aged between 55 and 75 years are now offered biennial colorectal testing using an immuno-faecal occult blood test (I-FOBT) and participants with a positive I-FOBT are referred for colonoscopy.[9-11]

In 10 to 15% of cases, CRC is caused by a combination of hereditary and environmental factors. In 3 to 5%, CRC is due to a hereditary CRC syndrome such as Lynch syndrome (LS) or one of the polyposis syndromes. Around 100,000 people in the Netherlands are thought to have familial CRC but unfortunately most of these patients remain unrecognized.[12,13]

A mismatch repair deficiency (dMMR) is present in more than 95% of Lynch syndrome (LS)-associated colorectal carcinomas and in 15% of sporadic colorectal cancer (CRC).[14-16] LS patients have a lifetime CRC risk of approximately 50%, depending on the underlying gene defect, even with active preventative measures such as surveillance colonoscopy and polypectomy.[17] In LS, a pathogenic germline mutation in one of the DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6* or *PMS2*) causes genomic instability in the tumour. This is referred to as microsatellite instability (MSI) and is the hallmark of LS.[18,19] Tumours with either MSI or loss of MMR protein expression are designated MMR-deficient. Besides identification of LS patients and their families, MMR deficiency testing has additional implications. The outcome of MMR deficiency testing can be important in surgical decision making, as extended colectomy is recommended in young LS patients with CRC.[20] Tumours with MMR deficiency are associated with better overall survival.[21] Moreover, dMMR status has consequences for the choice of adjuvant chemotherapy as MMR-deficient CRC is resistant to 5-fluorouracil (5-FU) monotherapy.[22-26]

Patients with Lynch syndrome (LS) also show increased risk for other LS-associated tumours, including gastric cancer.[27-29] The Prospective Lynch Syndrome Database (PLSD) shows a cumulative incidence of 5.3% to 7.7% for gastric cancer at the age of 75, depending on the underlying gene defect. When diagnosed under the age of 65 years, the 5-year survival rate for gastric cancer is only 61%.[30] In 2013, a group of European experts (the Mallorca group) published revised guidelines for the clinical management of Lynch syndrome.[31] Due to the low risk of gastric cancer and the lack of established benefits, endoscopic surveillance of the upper gastrointestinal (GI) tract was not recommended. However, screening MMR mutation carriers for the presence of *H. pylori* infection was recommended, as *H. pylori* is an important risk factor for gastric cancer in the general population and eradication reduces risk.[32] A recommendation that Dutch physicians screen for *H. pylori* has been in place since 2010.[33]

Since the implementation of a nationwide colorectal screening program in the Netherlands in 2014, the detection of advanced neoplasms (advanced adenomas and early-stage colorectal cancer (CRC)) as well as the number of patients referred for endoscopic or surgical treatment for these lesions has increased.[34-36]

The majority of advanced polyps can be safely removed with standard polypectomy, a well-established procedure for non-invasive colonic neoplasms.[37] For more challenging neoplasms, advanced endoscopic techniques such as endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (eFTR) have improved complete en-bloc local resectability compared with standard polypectomy.[38-43] However, large sessile neoplasms situated at difficult locations in the colon can still be technically challenging to remove endoscopically and may require surgical removal.[44] In a large population study, endoscopic resection of large colonic polyps (→ 20 mm) was successful in 92% of cases, while the remaining 8% required surgery.[8] Segmental colectomy is associated with significant morbidity (24%) and mortality (2%), independent of tumour stage.[45] In the case of benign lesions, surgical treatment results in an overall complication rate of 25.5%, re-intervention rate of 8.1% and a mortality rate of 0.9%.[46] Fortunately, several methods can bridge the gap between endoscopic resection and major surgery.

Recently, Lin et al. reported a CELS-full thickness excision (CELS-FT) procedure for the removal of challenging colonic polyps which combines endoscopic and laparoscopic treatment. A circumferential incision is made in the seromuscular layer over the polyp using laparoscopy, which is subsequently marked with indigo carmine solution. The dissected area is then invaginated into the bowel lumen and a snare is

endoscopically introduced and looped around the polyp. Three patients underwent CELS-FT for problematic benign polyps with minimal blood loss and no perioperative complications. The average surgical time was 179 minutes.[47]

With the development of laparoscopic surgery, laparoscopic-assisted or laparoscopic -monitored colonoscopic polypectomy for the treatment of complex colon polyps has also been described. [48-50] In 2011, Yan et al. reported that colonoscopic-assisted laparoscopic wall excision to remove polyps is also an important combined approach. In this procedure colonoscopy is used to locate the polyp and to monitor the surgical margin. A laparoscopic Endo-GIA stapler is then placed to excise a full-thickness resection of the colonic wall. Colonoscopy is also helpful when assessing the bowel lumen for adequacy and patency.[51] To date, wedge resection has mainly been used in the caecum or ascending colon, a favourable location for use of a linear stapler.[47,52] In 2015, we began performing colonoscopy-assisted wedge resection in the entire colon, using a linear stapler without forming an anastomosis. We modified the technique described by Yan et al. by placing a suture close to the polyp base to provide traction on the colon, enabling better positioning of the stapler. A year later we published our first case series of 8 patients.[52]

In more than half of diagnosed CRCs, the tumour is located in the left part of the colon.[2] Around 1 to 7% of patients with CRC have a synchronous tumour, two thirds of which are located in the same surgical segment.[53-56] Furthermore, 15 to 20% of all patients with CRC present with bowel obstruction. In these patients, colonoscopy might fail to diagnose synchronous tumours proximal to an obstructive cancer that requires secondary surgery.[57-61]

Computed tomographic colonography (CTC) was developed as a non-invasive alternative to colonoscopy for the detection of CRC and polyps. In patients with obstructive CRC, Park et al. reported a 100% sensitivity of CTC in the detection of proximal synchronous CRC and moderate sensitivity (88.6%) in detecting proximal synchronous adenomas, including advanced adenomas.[60] In patients with stenosing CRC, most authorities recommend CTC before surgery to exclude synchronous CRC.[62-65] Two studies reported a change in primary surgical plan due to additional information from CTC (14 and 16%, respectively) in patients with stenosing CRC due to location errors, synchronous adenomas or synchronous carcinomas.[66,67] However, in most cases of stenosing CRC the synchronous tumour is at an advanced stage (T-stage 3 or 4) and therefore visible with regular staging CT, which is now performed in all CRC patients prior to surgery.

Chemotherapy is used to treat colorectal carcinoma at multiple disease stages. It is considered a primarily neoadjuvant therapy in patients with locally advanced colon cancer (cT4bN0-2M0|), an adjuvant treatment in stage III disease and as a component of chemoradiotherapy in patients with advanced rectal carcinoma. The goals are downstaging to enable an R_0 resection in patients with locally advanced cancer, or an increase in disease-free survival in cases with high-risk stadium II-III or low-risk stadium III colon carcinoma. Chemotherapy also has a place in the treatment of metastatic disease.[68]

Fluoropyrimidine monotherapy is the recommended chemotherapeutic treatment for patients with metastatic colorectal cancer (mCRC) who may not tolerate more aggressive therapy.[69-71] Oral capecitabine provides a convenient alternative to standard intravenous fluoropyrimidine and in clinical trials oral capecitabine monotherapy was shown to be as effective as intravenous 5-fluorouracil as a first-line treatment for mCRC. Oral capecitabine is generally associated with an improved safety profile, with lower rates of stomatitis, alopecia, diarrhoea, nausea and grade 3/4 neutropenia.[72-75] However, rates of hand-foot syndrome (HFS) are higher[72,74-76] and data regarding adverse events following oral capecitabine monotherapy for mCRC are limited.

OUTLINE OF THE THESIS

Part I – Management of hereditary colorectal cancer

In up to 15% of CRCs, hereditary and environmental factors play an important role. Lynch syndrome (LS) is responsible for 3 to 5% of cases and familial colorectal cancer (FCC) and other polyposis syndromes for the remaining cases. Identification of individuals at risk for LS or FCC is important because preventative strategies may improve the prognosis or even avert cancer development.

In **CHAPTER 2** we describe a retrospective multicentre study. The aims of the study were to evaluate the proportion of individuals in the Dutch bowel screening program with a positive I-FOBT that fulfil criteria for LS and familial colorectal cancer (FCC) and to evaluate the proportion of participants that require genetic counselling or colonoscopic surveillance.

In **CHAPTER 3** we present the results of a retrospective study of the consequences in clinical practice of testing for mismatch repair deficiency in colorectal cancer. The aims of the study were to evaluate whether MMR deficiency testing leads to (1) identification of Lynch syndrome, (2) a change in surgical treatment and (3) adjustment of systemic therapy in patients with dMMR CRC.

In **CHAPTER 4** we present the results of a retrospective multicentre observational cohort study. We aimed to assess the proportion of LS patients that was tested for *H. pylori* infection and address the question of whether *H. pylori* infection is more prevalent in LS families with known cases of gastric cancer.

Part II – Management of early colorectal neoplasms

The implementation of the national bowel screening program in 2014 led to an increased detection rate of polyps, which are generally removed endoscopically. However, if size and location of the polyp makes endoscopic removal technically difficult or if there is a suspicion for early (T1) cancer, surgical removal is preferred. An increasing number of patients are now treated with minimally invasive surgical procedures rather than segmental resection. To preserve as much of the colon as possible, we recently introduced a modified laparoscopic endoscopic-assisted wedge resection (LEAWR) for advanced polyps that are endoscopically challenging to remove.

In **CHAPTER 5** we discuss a retrospective study to assess the number of referrals for surgery, the type of polyp surgery since the introduction of the national bowel screening program and the morbidity and mortality of conducted surgeries.

In **CHAPTER 6** we present the results of the first cohort treated with limited endoscopy-assisted wedge resection (LEAWR). The aim of this cohort study was to report our experience with this new technique.

In **CHAPTER 7** we describe the results of a prospective multicentre LEAWR study in The Netherlands. The aim of this study was to evaluate the safety and efficacy of our modified endoscopy-assisted laparoscopic wedge resection procedure.

Part III – Management of advanced colorectal neoplasms

As a synchronous tumour is reported in 1 to 7 % of CRC patients, CT colonography is recommended in patients with a stenosing colorectal tumour in order to exclude the presence of a CRC proximal to the primary tumour. In patients with metastatic CRC, palliative chemotherapy can be considered. Capecitabine monotherapy is a treatment option for selected patients with metastatic colorectal cancer (mCRC) and is administered in up to 17% of patients.

In **CHAPTER 8** we present a retrospective single-centre study focussed on the yield and additional clinical implications of CT colonography in patients with stenosing CRC.

In **CHAPTER 9** we describe a single-centre, retrospective study of patients treated at a large community hospital for mCRC. The aim was to provide data on adverse event rates and dose adjustments/discontinuations associated with capecitabine monotherapy in patients with mCRC.

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part 1
MANAGEMENT OF HEREDITARY COLORECTAL CANCER

CHAPTER 2

Identification of familial colorectal cancer and hereditary colorectal cancer syndromes through the Dutch population-screening program: results of a pilot study

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ABSTRACT

OBJECTIVES

In 2014, a population-screening program using immuno-faecal occult blood testing (I-FOBT) has started in the Netherlands. The aims of the present study were to evaluate the proportion of individuals in the Dutch screening program with a positive I-FOBT that fulfill the criteria for familial colorectal cancer (FCC) and to evaluate the proportion of participants that needs genetic counseling or colonoscopic surveillance.

MATERIAL AND METHODS

This retrospective observational study was performed in two large hospitals. Individuals aged between 55-75 years with a positive I-FOBT that underwent colonoscopy were included. A detailed family history was obtained in all individuals.

RESULTS

A total of 657 individuals with a positive I-FOBT test underwent colonoscopy. One hundred twenty (18.3%) participants were found to have a positive family history for CRC, 20 (3.0%) fulfilled the FCC Criteria, 4 (0.6%) the Bethesda guidelines and 1 (0.2%) participant the Amsterdam Criteria. Multiple adenomas (> 10) were found in 21 (3.2%) participants. No cases of serrated polyposis were identified. Based on these criteria and guidelines, a total of 35 (5.3%) required referral to the clinical geneticist and the relatives of 20 (3.0%) participants should be referred for surveillance colonoscopy.

CONCLUSION

Obtaining a detailed family history at the time of intake of participants with a positive I-FOBT in the Dutch surveillance program increased the identification of participants with familial CRC.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in the Western world. More than 13,000 patients are annually diagnosed with CRC in the Netherlands and over 5,000 patients die due to this condition.[1] When CRC is detected because of symptoms, about 45% of the patients have a metastatic disease. Worldwide screening programs have been implemented in order to prevent the development of CRC and to diagnose CRC at an early stage that allows curative treatment.[2-4]

In February 2014, a national screening program has started in the Netherlands.[5] Individuals aged between 55 and 75 years are offered colorectal testing using a biennial immuno-faecal occult blood test (I-FOBT) and participants with a positive I-FOBT are referred for colonoscopy.[5-7] Previous studies have suggested that this program will lead to a reduction of CRC by 20-25%.[2,8]

In approximately 10 to 15% of all CRC cases, CRC is caused by a combination of hereditary and environmental factors. In 3 to 5% of all cases CRC is due to a hereditary CRC syndrome including Lynch syndrome or one of the polyposis syndromes.[9,10] The term "familial CRC" (FCC) is used for individuals with a clinically relevant increased risk (relative risk > 3) of CRC which justifies surveillance by colonoscopy.[11-13] These individuals have one first degree relative (FDR) with early onset (< 50 years) CRC or two first degree relatives with CRC diagnosed at any age. The lifetime risk of developing CRC for these individuals varies from 10 to 25%, depending on the number of relatives with CRC and the age at diagnosis.[14]

In the Netherlands, it has been estimated that about 100,000 subjects have familial CRC, but unfortunately, most of these people are still unrecognized.[9] An important way to improve the identification of familial and hereditary CRC during the population screening for CRC is by informing them about the risk factors including hereditary factors for CRC at invitation (by a brochure which is attached to the invitation letter including a referral to the website http://www.bevolkingsonderzoekdarmkanker.nl) and by obtaining an appropriate family history in individuals with a positive test result that are referred for colonoscopy.[15,15]

The aims of the present study were to evaluate the proportion of individuals with a positive I-FOBT that comply with the criteria of familial/hereditary CRC in the Dutch population screening program, and to evaluate the proportion of patients that need further genetic analysis based on their personal and family history and/or endoscopic findings.

METHODS

Study population and study design

This retrospective observational study was performed at the department of Gastro-

enterology and Hepatology of the Leiden University Medical Center (LUMC) in Leiden and the Isala Clinics in Zwolle, the Netherlands. All participants aged between 55-75 years with a positive I-FOBT and who underwent a colonoscopy between February and October 2014 in Leiden and between March 2014 and November 2015 in Zwolle were included. In both centers a detailed family history was obtained before colonoscopy. Participants included in the LUMC were requested to complete a questionnaire about their family history (Figure 1). Based on this questionnaire, the participants had a significant positive family history if the family history fulfills the criteria of familial CRC, Amsterdam Criteria or the Bethesda guidelines (Table 1).[13,17-21] These criteria and guidelines were used to identify individuals that should be referred to the clinical geneticist or should be advised colonoscopic surveillance.[22]

Colonoscopies were performed by experienced endoscopists certified by the population screening program and polyps detected at colonoscopy were removed if possible. The removed polyps were evaluated by pathologists also certified by the population screening program. The study was approved by the institutional medical ethical committee of the LUMC.

Data collection

All information concerning the family history obtained during intake and colonoscopy results from the participants were collected in a database. The following information was extracted from the database and questionnaires: demographical data, personal history (CRC, Lynch syndrome-associated tumors (LS-AT; tumors of the colon, endometrium, stomach, small intestine, urethra, bile ducts, pyelum, pancreas, ovary or brains) or other tumors) and family history for CRC (number of first-degree relatives (FDRs) and/or second-degree relatives (SDRs) with CRC and age at diagnosis).

Statistical methods

Descriptive statistics were used to characterize the study population, family history and familial CRC risk. Primary outcome measures were positive family history for CRC and fulfillment of the criteria for familial CRC, Bethesda guidelines and Amsterdam Criteria. All statistical analyses were performed using SPSS 22.0.

RESULTS

Colonoscopic findings

A total of 657 participants with a positive I-FOBT underwent colonoscopy and familial cancer risk assessment. The mean age of the study population was in 70.8 years

in Leiden and 67.8 years in Zwolle and participants were predominantly male (57.8% and 62.7%). The findings at colonoscopy of both centers are described in Table 2.

Table 2.
Findings at colonoscopy

Findings colonoscopy	Leiden (n = 332)	Zwolle (n = 325)
Male, n (%)	192 (57.8)	204 (62.7)
Age at inclusion (years), mean (range)	70.8 (62-76)	67.8 (60-76)
Cecal intubation, n (%)	325 (97.9)	320 (98.5)
Serrated polyps, n (%)	66 (19.8)	85 (26.2)
Serrated polyposis*	0 (0.0)	0 (0.0)
Adenomas, n (%)	175 (52.7)	254 (78.2)
AAP, n (%)	152 (45.8)	128 (39.4)
Multiple adenomas, n (%)		
Yes:		
2-9	182 (54.8)	165 (50.8)
10-19	15 (4.5)	6 (1.8)
> 20	0 (0.0)	0 (0.0)
Total	197 (59.3)	171 (52.6)
CRC, n (%)	25 (7.5)	24 (7.4)

*5 serrated lesions proximal of the sigmoid of which 2 > 1 cm, or 20 serrated lesions throughout the colon

A total of 49 participants (7.5%) were diagnosed with CRC and 280 (42.6%) had advanced adenomas (AAP). Multiple adenomas (2 or more) were found in 368 (56.0%) participants and more than 10 adenomas were observed in 21 of the 657 cases (3.2%). In 151 participants serrated polyps were found, none of them complied with the criteria for serrated polyposis.

Table 3.
Patients with evidence for familial or hereditary CRC syndromes

Patient characteristics	Leiden (n=332)	Zwolle (n=325)	Total (657)
Positive family history for CRC in FDR*, n (%)	67 (20.2)	53 (16.3)	120 (18.3)
Fulfill Criteria for familial CRC, n (%)	10 (3.1)	10 (3.4)	20 (3.0)
1 FDR < 50	3 (0.9)	4 (1.2)	7 (1.1)
2 FDR all ages	6 (1.8)	5 (1.5)	11 (1.7)
2 FDR<70, n (%)	2 (0.6)	2 (0.6)	4 (0.6)
1 FDR<70, 1FDR>70, n (%)	0 (0.0)	1 (0.3)	1 (0.2)
2 FDR>70, n (%)	4 (1.2)	2 (0.6)	6 (0.9)
3 FDR/SDR*	1 (0.3)	1(0.3)	2 (0.3)
Fulfill Amsterdam Criteria**	0 (0.0)	1 (0.3)	1 (0.2)
Fulfill Bethesda Guidelines**	1 (0.3)	3 (0.9)	4 (0.6)
Polyposis Syndrome			
Multiple adenomas (> 10)	15 (4.5)	6 (1.8)	21 (3.2)
Serrated polyposis***	0 (0.0)	0 (0)	0 (0.0)
Personal History			
CRC	2 (0.6)	0 (0)	2 (0.3)
LSAT****	3 (0.9)	1 (0.3)	4 (0.6)

* First degree relative (FDR)/ Second degree relative (SDR)

** For the criteria see table 1

*** Serrated polyposis criteria: 5 serrated lesions proximal of the sigmoid of which 2 > 1 cm, or 20 serrated lesions throughout the colon (rectum not included)

**** LSAT: tumors of the colorectum, endometrium, stomach, liver, kidney, small intestine, urethra, bile ducts, pyelum, pancreas, ovary or brains

Personal and family history of colorectal cancer

In total, 120 of the 657 participants (18.3%) had at least one FDR with CRC. Twenty individuals (3.0%) complied the criteria for familial CRC and 4 (0.6%) fulfilled the Bethesda guidelines. One individual (0.2%) met the Amsterdam criteria. The results of family and personal history are shown in Table 3. No significant correlation was found between a positive family history and having multiple adenomas (> 10) or advanced adenomas.

A total of 35 (5.3%) participants should be referred to the clinical geneticist (Table 4) and the relatives of 20 (3.0%) participants should be referred for surveillance colonoscopy (Table 3) according to the clinical guidelines mentioned before.

Table 4.
Proportion of participants that comply with the criteria for referral to the clinical geneticist

	Leiden (n = 332)	Zwolle (n =325)	Total (n = 657)
Bethesda guidelines, n (%)	1 (0.3)	3 (0.9)	4 (0.6)
Amsterdam criteria, n (%)	0 (0.0)	1 (0.3)	1 (0.2)
Multiple adenomas (> 10) , n (%)	15 (4.6)	6 (1.8)	21 (3.2)
Serrated polyposis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
1 FDR <50 with CRC, n (%)	3 (0.9)	4 (1.2)	7 (1.1)
3 FDR/SDR with CRC at any age, n (%)	1 (0.3)	1 (0.3)	2 (0.3)
Total, n (%)	20 (6.0)	15 (4.6)	35 (5.3)

DISCUSSION

This study demonstrated that a detailed family history and/or the use of a family history questionnaire at the time of intake of participants with a positive I-FOBT in the Dutch surveillance program led to the identification of familial CRC families in approximately 3% of the cases. Moreover, a substantial proportion of participants were found to have multiple adenomas (> 10) and need further genetic testing for MUTYH and APC-mutations.

Two previous pilot studies have been performed to identify familial CRC in individuals that participate in a I-FOBT population screening. The first study performed by Dekker et al. in 2011 in the Netherlands showed that 17% of the participants with a positive I-FOBT in the CRC screening program had a positive family history of CRC. Six percent of the participants had an increased familial CRC risk and approximately 4% had an increased familial CRC risk according to the Bethesda guidelines and/or Amsterdam Criteria. No significant differences were found with respect to colonoscopy results between the participants with an average versus an increased familial CRC risk.[23] The second study, conducted in 2006 in Australia, reported a positive family history for CRC in 19.6% of subjects that participated in a I-FOBT screening program. Fourteen percent had an increased familial CRC risk. Of these participants, 4.2% had a high familial risk sufficient to warrant colonoscopic surveillance.[24] Although both studies showed that a substantial proportion of individuals with a positive I-FOBT result had a positive family history for CRC, detailed information on the family history and the level of CRC risk was lacking. Also, the identification of polyposis syndromes was not addressed.

In the present study, 120 (18.3%) participants were found to have a positive family history for CRC in FDR and 4 (0.6%) had a positive family history for a Lynch syndrome associated tumor. It was found that 3.0% of the participants fulfilled the criteria for familial CRC and 0.6% the Bethesda guidelines. One participant fulfilled the Amsterdam Criteria. Multiple adenomas (> 10) were found in 21 participants (3.2%) and no cases of serrated polyposis were detected. Based on the findings according to the current clinical guidelines, a total of 35 (5.3%) participants should be referred to the clinical geneticist and relatives of 20 (3.0%) participants should be referred for surveillance colonoscopy.

Several studies have indicated that the identification of individuals with familial cancer and Lynch syndrome is suboptimal.[25] A previous Dutch study estimated that 100.000 individuals are at risk for familial or hereditary colorectal cancer but currently only a small proportion of these individuals has been recognized.[9] A nationwide population screening program such as the I-FOBT program in the Netherlands

may not only improve the prognosis of patients with CRC and prevent the development of CRC but also may identify high risk individuals. The program provides full information (website and pamphlets) about the fact that a proportion of patients with CRC is caused by genetic factors. In addition, obtaining a detailed family history in all cases with a positive I-FOBT, will identify many cases with an increased risk of CRC which is demonstrated in this study. Systematic use of a family history questionnaire may further improve the identification.

The presence of multiple adenomas may also indicate an underlying genetic disorder, i.e. polyposis. There is no agreement about the number of adenomas that justifies referral to a clinical geneticist for analysis of mutations in the MUTYH-gene and the APC-gene. Originally, the presence of 10 or more adenomas was a criterion for referral. However, a recent study showed that mutations were rarely detected in patients with 10-20 adenomas (mutation detection rate ~3%) and the mutation detection rate increased in patients with > 20 adenomas.[26]

The prevalence of serrated polyposis is still unknown. In the current study, no cases were identified. It is well known that serrated polyps are difficult to detect.[10] However, in the present study experienced gastroenterologists are certainly be able to identify this syndrome.

Regarding the identification of Lynch syndrome, currently, in many countries universal screening is being implemented. This means that all patients with CRC under the age 70 years (or in some countries all CRC patients independent of the age) are tested for expression of the mismatch repair proteins (MMR-proteins) using immuno-histochemical analysis.[22] This new approach will be helpful to identify all Lynch syndrome cases.

The identification of familial CRC will strongly be improved by case finding during population screening programs. The age distribution of CRC in familial CRC (50-75 years) is almost similar as the patients that are invited for the Dutch population screening program (55-75 years). A recent surveillance study among 550 patients with familial CRC showed that the prevalence of advanced adenomas was two-fold higher than reported in "average risk" individuals.[14] A previous study showed that colonoscopic surveillance led to a reduction of CRC by 80%.[16] Usually, colonoscopic surveillance is recommended in familial CRC with five or six year intervals.[27] However, it is still unknown whether a 10 year interval or two yearly I-FOBT screening is as effective as a 5 year-interval-colonoscopic surveillance.

Strengths of the study include the cross-sectional design and the full attention that was paid to the family history and the additional use of questionnaires in Leiden to assess the familial CRC risk. In almost all cases, personal and familial

history was fully verified during intake. Another strength of the study is that the colonoscopies were all performed in two hospitals by well-trained gastroenterologists.

In summary, this pilot study provides a detailed overview of the familial CRC risk assessment in the Dutch I-FOBT screening program that started in 2014. The study demonstrates that a proportion of the patients need further genetic testing and surveillance colonoscopies. The preliminary results of the I-FOBT screening are encouraging. Making optimal use of the patient contact arising from the screening program to identify high risk groups will further improve the prognosis of patients with familial CRC and their families.

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Figure 1. Questionnaire to assess the familial CRC risk given at intake

		Type of cancer	Age at diagnosis
Children			
How many children do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Child 1		
and what type of cancer?	Child 2		
	Child 3		
Parents			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Father		
and what type of cancer?	Mother		
Brothers			
How many brothers do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Brother 1		
and what type of cancer?	Brother 2		
	Brother 3		
Sisters			
How many sisters do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Sister 1		
and what type of cancer?	Sister 2		
	Sister 3		
Family from paternal site			
How many uncles do you have?			
How many aunts do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Uncle 1		
and what type of cancer?	Uncle 2		
	Aunt 1		
	Aunt 2		
Did grandfather or grandmother			
develop cancer?	Yes / No		
If yes, who developed cancer	Grandfather		
and what type of cancer?	Grandmother		
Family maternal site			
How many uncles do you have?			
How many aunts do you have?			
Did they develop cancer?	Yes / No		
If yes, who developed cancer	Uncle 1		
and what type?	Uncle 2		
	Aunt 1		
	Aunt 2		
Did grandfather or grandmother			
developed cancer?	Yes / No		
If yes, who developed cancer	Grandfather		
and what type of cancer?	Grandmother		

Table 1.
Criteria for Familial CRC, the Amsterdam Criteria and Bethesda Guidelines
FCC Criteria

- 1 FDR*<50
- 2 FDR all ages
  - 2 FDR<70
  - 2 FDR>70
- 3 FDR/SDR**

Amsterdam Criteria

- 3 patients with CRC (Amsterdam Criteria I) or Lynch Syndrome Associated Tumor*** (LSAT, Amsterdam Criteria II) of which one is a FDR of the other two and,
- 1 of these 3 patients <50 and,
- 2 consecutive generations in the family are affected and,
- Familial adenomatous polyposis must have been excluded

Evidence for Polyposis Syndrome

- Multiple adenomas (> 10)
- Serrated polyposis****

Revised Bethesda Guidelines

- Patient with CRC<50 or,
- Patient with synchronous or metachronous CRC or LSAT or,
- Patient with CRC and 1 FDR with CRC or LSAT with one of the tumors <50 or,
- Patient with CRC and >2FDR/SDR with CRC or LSAT at any age

*First Degree Relative (FDR)

** Second Degree Relative (SDR)

*** LSAT: tumors of the colorectum, endometrium, stomach, small intestine, urethra, bile ducts, pyelum, pancreas, ovary or brains

**** 5 adenomas proximal of the sigmoid of which 2 adenomas > 1 cm, or 20 serrated lesions proximal of the sigmoid

CHAPTER 3

Consequences of testing for Mismatch Repair deficiency of colorectal cancer in clinical practice

3

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ABSTRACT

INTRODUCTION

Mismatch repair deficiency (dMMR) can be found in Lynch syndrome (LS)-associated colorectal carcinoma and in 15% of sporadic colorectal cancer(CRC). Outcome of MMR-deficiency testing is important for surgical decisions as extended colectomy is recommended in young LS-patients with CRC. Moreover, the finding of a dMMR tumour has consequences for the choices of adjuvant chemotherapy as MMR-deficient CRC is resistant to 5-fluorouracil (5-FU) monotherapy. Aims of our study are to evaluate whether MMR-deficiency testing leads to (1) identification of LS, (2) change in surgical treatment and (3) adjustment of systemic therapy in patients with dMMR CRC.

METHODS

We performed a multicentre, retrospective study, in a community hospital and a University Medical Centre. We included all CRC-patients between 2012 and 2016 who were tested for microsatellite instability. We collected clinical data such as gender, age, referral to clinical geneticist, surgical procedure and choice of chemotherapy.

RESULTS

We analysed 225 CRC's. Twenty-four (10,7%) of 225 CRC were MMR-deficient. Of the 24 patients with dMMR CRC, 18 (75%) were referred to the clinical geneticist and in 9 (37%) patients a MMR mutation was identified. In one (4%) of 24 the patients a subtotal colectomy was performed. In 7 (35%) out of 20 MMR deficient patients the chemotherapy regimen was adjusted.

CONCLUSION

The finding of a dMMR CRC had consequences for decisions on chemotherapy in a relative high proportion of patients. We recommend testing in all patients with CRC independent of age at diagnosis, as proper treatment decisions and genetic counselling are very important.

INTRODUCTION

The most common hereditary variant of colorectal cancer worldwide is Lynch syndrome (LS) which accounts for 2-5% of all new CRC cases.[1] In LS patients, the lifetime risk of developing CRC varies between 25 and 75% depending on the underlying gene defect.[2] Other LS-associated tumours are cancer of the endometrium, stomach, hepatobiliary tract, ovaries, urinary tract, and small bowel.[3] LS is characterized by an early age of onset of CRC and a higher risk of developing synchronous and metachronous CRC or LS-associated tumours.[1-3]

In LS, a pathogenic germline mutation in one of the DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6* or *PMS2*) causes genomic instability in the tumour, called microsatellite instability (MSI), the hallmark of LS.[4,5] MSI analysis is performed by polymerase chain reaction (PCR) with specific microsatellite markers. Through immunohistochemistry (IHC) the absence of the MMR proteins can be detected with specific antibodies.[6,7] Tumours with MSI or MMR protein expression loss are called MMR-deficient. MSI is also present in 15% of sporadic CRC due to hypermethylation of the *MLH1* promoter.[8,9] In order to differentiate between LS and sporadic tumours a methylation-specific PCR (MSP) is performed. Patients with MMR deficiency without hypermethylation should be referred to the clinical geneticist for mutation analysis of the MMR-genes.

Through identification of LS families, family members that turn out to be mutation carriers are invited to participate in surveillance programs. Long-term surveillance leads to risk reduction of developing CRC by removing adenomas, the detection of CRC at an earlier stage and reduction of mortality associated with CRC.[10] Until recently, the revised Bethesda guidelines were used to identify individuals with CRC that should be tested for MSI.[11,12] Nowadays however, in many countries MSI analysis or IHC is performed in all CRC patients under the age of 70 years. Subsequently, the chance of missing LS in patients with CRC is low and this also turned out to be cost-effective.[13]

The risk of developing CRC during surveillance with intervals of 1-2 years is 6% in 10 years.[14] The majority of these tumours (>85%) are at stage I or II.[15] In LS patients who developed CRC the risk of developing metachronous CRC is reported to be approximately 16% at 10 years follow-up following segmental resection or hemicolectomy, despite close surveillance.[16] The overall life expectancy gain of subtotal colectomy compared to hemicolectomy at ages 27, 47 and 67 was respectively 2.3, 1, and 0.3 years.[17] Therefore, the option of subtotal colectomy should be discussed in young patients (<60 years) who develop CRC while under surveillance. However, in many cases the diagnosis of LS is not known at time of surgery, unless MSI analyses

and immunohistochemical analysis of the MMR-proteins (IHC) are performed on biopsies taken at endoscopic diagnosis.[18,19]

Tumours with MMR deficiency are associated with a better overall survival.[20] Also many studies showed that patients with MSI-high stage II and III CRC do not benefit from adjuvant chemotherapy with 5-fluorouracil (5-FU).[21-25]
The aim of our study is to evaluate all the above described consequences of MSI-analysis or IHC in daily clinical practice. Are patients with MMR-deficient tumours referred to the clinical geneticist and how many LS families are identified? Does MSI status influence surgical treatment and does it influence the decision on the type of adjuvant chemotherapy?

METHODS

Study design

We performed a multicentre retrospective observational study in the Netherlands. Participating hospitals included a large community hospital, Isala Zwolle, and the Leiden University Medical Centre (LUMC). We included patients from April 2012 to January 2016. Our study was approved by the local research ethics committee. Our primary outcomes are referral to the clinical geneticist, changes in type of surgery and changes in the choice of adjuvant chemotherapy.

Patients

We included all patients with a primary CRC who were analysed for MSI or MMR protein expression loss and were discussed both preoperatively and postoperatively in a multidisciplinary team of specialists. MSI analysis or MMR-protein analysis was performed in all consecutive CRC patients who fulfilled the Bethesda criteria.[12] Additionally, a small proportion of patients were tested according to the new Dutch guideline "Hereditary Colorectal Cancer" published in January 2016, recommending MSI analysis or immunohistochemical testing in all patients with CRC <70 years. This guideline was already implemented a few months before publication in the LUMC what explains a small proportion of patients <70 years included.

Patients who were already diagnosed with LS were excluded. Medical reports were retrieved, including the documentation of the multidisciplinary meeting, surgical report, histology report, correspondence of the clinical geneticist and the treatment of the oncologist. Patients variables (sex, age) and tumour variables (tumour localization, results of MSI analysis, IHC staining and hypermethylation) were documented. The consequences of MSI analysis and IHC were checked from the reports of the surgeon, clinical geneticist and oncologist. We analysed the consequences of MMR deficiency on the treatment and referral policy.

Molecular analysis of CRC

Tumour specimen for MSI or IHC analysis could be obtained preoperatively through colonoscopy biopsies and from the surgical resection specimen after surgery.

Microsatellite instability (MSI) analysis Genomic DNA from the tumour and normal tissue was extracted on either fresh, frozen or paraffin-embedded tumour tissue and was sectioned at 4 µm. The tumour percentage of the tissue has to be above 20% for a sensitive test. MSI analysis is a fluorescent assay based on PCR to detect MSI in the tumour cells. Fluorescently labelled primers were used for co-amplification of 7 markers including 5 mononucleotides repeat markers for MSI determination and 2 pentanucleotide repeat markers to detect potential sample mix-ups or contamination.[26] Tumour samples with more than 2 changed markers out of 5 were classified as MSI-high (MSI-H), 1 out of 5 as MSI-Low (MSI-L) and tumours without a changed marker as microsatellite stable (MSS).

Immunohistochemistry (IHC) was performed by staining the MMR-proteins with anti-MLH1, anti-PMS2, anti-MSH2, and anti-MSH6 antibodies. This is performed on formalin-fixed, paraffin-embedded tissues. The expression of MLH1, PMS2, MSH2, and MSH6 was scored as positive (+), negative with a positive internal control (0/+), and doubtfully negative [when both tumour and internal control stain negative (0/0)], and when the internal control was stronger than the positive tumour cell, it was scored as +/++.[12] Immunohistochemistry was only performed in LUMC.

Hypermethylation (MLH1 promoter) In case of MMR deficient tumours either due to expression loss of the MLH1 protein by IHC or MSI, differentiation between LS and sporadic CRC due to methylation of the *MLH1* promoter was performed by using MSP.[27]

Data management

All data was entered and managed in the data management tool of Research Manager. This program provides a protected environment to ensure the safety of the patients' data. The completed data was converted into an Excel document to analyse the outcomes.

RESULTS

Over a period of almost 4 years we performed MSI and/or IHC analyses in 225 colorectal tumours, 108 MSI analyses in Isala and 117 IHC stainings in LUMC. Of all 225 CRC patients, the mean age was 64.5 (± 9.9) years, 140 (62%) patients were male. Of the 117 IHC that were performed, 41 showed expression loss in one or more of the MMR proteins. Most patients showed dual loss of expression of the MLH1 and PMS2

proteins (N=29, 70,7%), followed by MLH1 alone (N=5, 12,19%), MSH6 (N=4, 9,75%) and the combinations of MSH1+MSH6 (N=2, 4,8%) and MLH1+PMS2+MSH6 (N=1, 4,1%). (Table 1) Twenty-eight patients got additional MSP to exclude hypermethylation of the *MLH1* promoter. In 23 of these 28 patients, the expression loss of the

Table 1.
Results of IHC and MSI analysis

	LUMC	Isala	Total
MMR analysis	**117**	**108**	**225**
MMR analysis on biopsies	58	26	86
Immunohistochemistry staining (IHC)	117	-	117
Loss of MMR protein expression	41	-	41
MLH1	5		
MLH1 + PMS2	29		
MLH1 + PMS2 + MSH6	1		
MSH2 + MSH6	2		
MSH6	4		
MLH1 hypermethylation	29	-	29
MSP performed	28		
MLH1 hypermethylation	23		
MSP not performed	13		
MLH1 hypermethylation assumed due to age	6		
MSI analysis	-	108	108
MSI-High	-	12	12
IN TOTAL:			
Suspect for MMR mutation (LS)	12	12	24

MLH1 protein was caused by *MLH1* promoter hypermethylation. In 6 patients with a mean age of 80 years MSP was not performed because of the assumption that hypermethylation caused the MLH1 protein loss. Following additional MSP analysis, a total of 12 patients were suspected for Lynch syndrome. MSI analysis was performed in 108 patients. Twelve patients (11%) had MSI-high tumours. In total 24 patients were suspected for LS and further analysis was indicated.

Referral to clinical geneticist

A total of 18 patients were referred to the clinical geneticist for DNA analysis. Of these 18 patients, 2 patients cancelled their intake appointment. In 6 referred patients with MSI high tumours hypermethylation of the *MLH1* promoter was found. In 10 patients, genomic DNA analysis was performed and 9 MMR mutations were found (*MLH1* (N=2); *MSH2* (N=1); *MSH6* (N=6)) confirming LS in these patients. In the remaining patient mosaicism caused the MMR expression loss. (Table 2)

Table 2.
Consequences for patients suspect for a MMR mutation (LS): genetic counselling (GC) and surgical treatment.

	Total (n=24)	
Genetic counselling (GC)		
Not referred for GC	**6**	
Referred for GC	**18**	
Actual visited clinical geneticist	16	
Appointment cancelled	2	
MMR analysis	**16**	
MSP	6	
MLH1 hypermethylation	6	
DNA analysis	10	
MMR mutation	9	
Mosaicism	1	
MMR mutation	**9**	
MLH1	2	
MSH2	1	
MSH6	6	
Surgical treatment		
Patients <60 years	**4**	
MMR analysis results available before surgery		**8**
< 60 years	2	
Change in type of surgery	**1**	
Subtotal colectomy	1	

Influence on surgical treatment

Overall, 86 (38%) of the total of 225 analysis that were performed were available pre-operatively. Of 24 patients that were suspected for LS, molecular analysis was performed before surgery in 8 (33%). (Table 2) Four patients out of 24 were aged under 60 years of which 2 were analysed preoperatively. In one of them surgical treatment changed because of MMR deficiency. This 42-year-old female patient underwent a subtotal colectomy instead of a hemicolectomy due to MMR deficiency and positive family history. Further analysis showed that she was a carrier of a MSH2-mutation. The other 3 patients <60 years also turned out to be MMR gene carriers.

Influence on chemotherapy

Of the 54 patients with MMR deficient tumors, 20 patients had an indication for adjuvant chemotherapy according to the advice of the multidisciplinary meeting based on national guideline, including 15 patients with a stage III tumours and 5 with a stage IV tumours. In 7 (35%) patients the regimen choice of chemotherapy type was changed by the test results. Oxaliplatin was added to 5-FU monotherapy in two patients (10%). In 5 (25%) patients with a stage III tumour, 5-FU (Capecitabine) monotherapy was refrained because of MMR deficiency (Table 3).

Table 3.
Consequences for chemotherapy for all MMR-deficient tumors

Chemotherapy	N
MMR-deficient tumours	54
Stage	
I	2
II	8
III	31
IV	10
Unknown	3
Indication chemotherapy*	20
Stage	
III	15
IV	5
Change in chemotherapy	7
Refrained from 5-FU monotherapy (all stage III tumours)	5
Added Oxaliplatin to 5-FU monotherapy	2

*Advised by the multidisciplinary team

DISCUSSION

Molecular testing of CRC for MMR-deficiency is important not only for the identification of Lynch syndrome families but also for the decision-making on surgical treatment in patients suspected of LS and decisions on adjuvant chemotherapy in LS-patients and patients with sporadic MMR-deficient CRC. In the present study, we evaluated the outcome of MSI and IHC analyses in 225 patients. We found that 24 patients should have been referred for further analysis. Strictly, these patients were not all suspected for LS. Patients from Isala with MSI high tumours that were not yet tested to rule out hypermethylation were included in this number. This is explained by the fact that during the study period immunohistochemistry to rule out hypermethylation for Isala patients was performed by the clinical geneticist after referral. Therefore, in Isala, they were suspected for LS because the tumours were MSI high and they should have been referred. Currently, immunohistochemistry analysis is performed in Isala as well. Only 4% of all patients selected for MSI analyses or MMR testing were found to have LS which is lower compared with results of a previous study which reported LS in 9.2% of pre-selected patients, using the Bethesda criteria.[28] The lack of an adequate referral procedure may be the explanation that one third of the patients did not receive proper genetic counseling. A systematic discussion of the result of MSI analyses or IHC should be incorporated in the multidisciplinary meeting and it should be decided who will be responsible for referral to a clinical genetic centre. Irons et al suggested a method where genetic counselors are responsible for initiating conversations about counseling which may improve the compliance rates to the referral. In their study, they had a compliance with referral of only 35,7%, with the surgeon being responsible to refer the patient. Other studies showed the compliance with the referral to the clinical geneticist is higher when they themselves are responsible for initiating conversations about further germline testing. Also, further research was suggested to identify possible barriers to visit the clinical geneticist to finally improve compliance with the referral.[29]

According to the current guidelines extended colorectal surgery (subtotal colectomy) is recommended in patients with evidence for LS and age <60 years. In our study only one patient (4%) underwent a subtotal colectomy instead of hemicolectomy based on a suspicion of LS due to MMR deficiency and a young age (42 years) at diagnosis of CRC. After surgery, an MSH2 mutation was identified. This low number is due to the fact that only 4 of 24 patients were under age 60 years. Another explanation is that the majority of MSI analysis and IHC were performed on the resected

specimen (139 of total 225 (61.7%)) instead of the biopsies. In 2011, Parry et al. investigated the risk of developing metachronous CRC in MMR gene mutation carriers. Of 382 study subjects, 332 had a partial resection. A total of 74 of the 332 subjects were diagnosed with metachronous CRC. Cumulative risk of metachronous CRC was 16% (95% CI 10–25%) at 10 years, 41% (95% CI 30–52%) at 20 years and 62% (95% CI 50–77%) at 30 years after segmental colectomy. These risk estimates could help in the decision-making regarding the extent of primary surgical resection.[30] If biopsies with enough tumour tissue are available preoperatively, MMR testing on the biopsies is preferred as the result might influence the surgical treatment and we recommend to discuss these results during the preoperative multidisciplinary meeting. For instance, in young (<60 years of age) patients with MMR protein expression loss and MSI-H tumours (without *MLH1* hypermethylation) with a strongly suspected family history, a subtotal colectomy should be discussed. Nowadays in some hospitals in the Netherlands there is even a possibility to perform fast track DNA analysis to confirm or rule out LS before surgery within only a few weeks. Another advantage of testing on biopsies is that effects of (chemo-) radiation treatment are avoided in case of rectal cancer.

In the literature, there is an increasing amount of evidence that adjuvant chemotherapy with 5-FU in patients with a stage II or III CRC with MMR-defective tumours does not improve the prognosis. A study of 754 CRC patients showed an improvement of survival in patients who received adjuvant chemotherapy with 5-FU only in patients with a MMR-competent tumor. Overall survival of patients with MMR-deficient tumors did not improve with adjuvant 5-FU monotherapy.[31] Another meta-analysis of several randomized clinical trials confirmed this finding.[32] Therefore, MSI/IHC analysis becomes increasingly relevant for the decision making on adjuvant chemotherapy, especially in patients with stage II or III colorectal cancer. In our study, in 7 (35%) of the 20 patients who had an indication for adjuvant chemotherapy, the initial planned treatment with 5-FU monotherapy was changed due to MMR deficiency. The current guideline in most countries is to restrict MSI/IHC-testing to patients with CRC <70 years. Because decisions on chemotherapy are equally important in patient with CRC >70 years, we recommend to test all CRC patients independent of the age of diagnosis. Moreover, also in the metastatic CRC setting MSI/IHC-testing becomes increasingly relevant since treatment with anti-Programmed Death-1 inhibitor immunotherapy provides durable responses and disease control in pre-treated patients with dMMR/MSI-H metastatic CRC.[33]

The strength of the study is that we evaluated the outcome of MSI and IHC-analysis in clinical practice over a relative long period of time in two large hospitals. One of the limitations is the relatively small sample size and the small number of patients with abnormal MSI/IHC. Another limitation is the different techniques of MMR testing between the two hospitals.

In conclusion, MSI and IHC analysis resulted in the identification of a relatively low number of LS patients possible due to the fact that a considerable number of patients were not referred for genetic counselling. In only one patient the analyses had consequences with respect to the type of surgery. In a substantial number of patients, the results of MSI and IHC had consequences for the choice of chemotherapy. For all these reasons, we recommend to perform MSI and/or IHC in all patients with CRC independent of age, if possible the analyses should be performed on biopsies.

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CHAPTER 4

Equivalent Helicobacter pylori infection rates in Lynch syndrome mutation carriers with and without a first-degree relative with gastric cancer

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ABSTRACT

BACKGROUND

Patients with Lynch syndrome (LS) are at an increased risk of developing gastric cancer. In 2010, a guideline that recommended to screen all patients for *Helicobacter pylori* was implemented in the Netherlands. *H. pylori* is an important risk factor in the development of gastric cancer in the general population, and eradication of the bacterium reduces this risk. We aimed to assess the proportion of LS patients being tested and the yield and also addressed the question whether *H. pylori* infection is more prevalent in LS families with known cases of gastric cancer.

METHODS

Proven mutation carriers from five different Dutch hospitals were included. The implementation of *H. pylori* screening and its outcome was examined. The observation period was 2008–2013. The presence of first-degree family members with gastric cancer was noted, and it was observed if *H. pylori* infection was more prevalent in Lynch families with known cases of gastric cancer. Obtainable endoscopy reports were reviewed.

RESULTS

Four hundred forty-three (male, 184) proven mutation carriers were included. The proportion of patients screened increased after 2010, from 37 to 68 %. Twenty percent of the patients were infected. The 25 patients who had a first-degree family member with gastric cancer did not have a higher infection rate. In 30 % of cases, an endoscopy was performed; in four patients, intestinal metaplasia and in eight patients, gastric cancer was found.

CONCLUSION

The recommendation to screen for *H. pylori* is increasingly followed. The prevalence of infection in this patient group does not differ from the general population. Patients who had a first-degree family member with gastric cancer did not have a higher infection rate.

INTRODUCTION

Lynch syndrome (LS) is an autosomal dominantly inherited syndrome, caused by germ-line mutations in one of the four mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) or epigenetic inactivation of MSH2 through an EpCAM mutation.[1] Patients with LS are at an increased risk of developing cancer, particularly colorectal cancer and endometrial cancer. Cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, and skin are observed more frequently as well.[2–4]

The lifetime risk of gastric cancer is estimated between 2 and 13 % for LS patients. The 5-year survival rate for gastric cancer is only 15 %.[5] There is no evidence for clustering of gastric cancer within specific families.[2,6,7] The risk appears to be highest for MLH1 and MSH2 mutation carriers. The mean age of diagnosis of gastric cancer is 56 years. Higher risks are reported in countries that have other risk factors for gastric cancer such as high incidence of *Helicobacter pylori* infection. This indicates that environmental factors also play a role in the development of gastric cancer in gene carriers.[8]

Intestinal-type adenocarcinoma is reported in 73–79 % of gastric cancer cases in patients with LS.[6,9] This type of cancer is strongly associated with environmental factors, especially *H. pylori* infection. Patients with *H. pylori*-associated chronic gastritis may develop atrophy of the gastric mucosa, followed by intestinal metaplasia. Eventually, adenocarcinoma of the 'intestinal' type can arise.[10] *H. pylori* is classified by the WHO as a group one carcinogen.[11] In contrast, diffuse-type adenocarcinoma is not known to be associated with environmental factors. This type of cancer is notoriously difficult to detect in its early stages.

In 2013, a group of European experts (the Mallorca group) published its revised guidelines for the clinical management of Lynch syndrome.[12] In light of the relatively low risk of gastric cancer and the lack of established benefits, they did not recommend endoscopic surveillance of the upper gastrointestinal (GI) tract. However, they recommended to screen MMR mutation carriers for the presence of *H. pylori* infection and to perform subsequent eradication. For Dutch physicians, the recommendation to screen for *H. pylori* had already been operative since 2010.[13]

To date, there are no data on the results of this recommendation. The aims of the present study were to assess (1) the proportion of LS patients being tested for *H. pylori* infection, (2) the yield of *H. pylori* screening, and (3) the results of upper GI endoscopy if performed. We also address the question whether *H. pylori* infection is more prevalent in Lynch families with known cases of gastric cancer.

MATERIALS AND METHODS

In this retrospective observational cohort study, we examined the medical records of Lynch patients from five Dutch hospitals. Patients were eligible for inclusion if they were proven mutation carriers. The observation time was from December 2008 until December 2013. The study was approved by the ethics committees of the respective centers. The implementation of *H. pylori* screening, the type of test (serology, rapid urease test), urea breath test (UBT), stool antigen test or histology and its outcome were examined within the observation period. No data was available on the specific type of *H. pylori* strain. Unfortunately, due to the retrospective nature of the study, it was impossible to discern if the test was undertaken for screening purposes or due to the presence of symptoms. However, we assume that in the vast majority of the patients, the test was done for screening purposes. The presence of first-degree family members with gastric cancer was evaluated; the reports of upper GI endoscopy were collected and reviewed. Patients were excluded in case of incomplete medical records, i.e., if two major parameters were unknown.

RESULTS

Baseline characteristics

In total, the medical records of 443 (male, 184) proven mutation carriers were reviewed. The mean age was fifty-three (range, 22–90 years). Twenty-three patients had died. There were almost equally as many MLH1, MSH2, and MSH6 mutation carriers (Table 1).

Table 1.
Baseline characteristics of all mutation carriers

Characteristic	Total, *n*	%	Gastric cancer, *n*
All	443		8
Gender			
Male	184	42	5
Female	258	58	4
Alive			
Yes	421	95	5
No	22	5	4
Mutation status			
MLH1	125	28	1
MSH2	140	32	1
MSH6	128	29	1
PMS2	34	8	-
EpCAM	16	4	-

H. pylori screening

Screening for *H. pylori* was performed in 206 mutation carriers (46%). A total of forty-two (20%) patients were found to be infected. Serological testing was performed most often. For three mutation carriers, the type of test that was performed could not be determined (Table 2). Of the patients ascertained to be mutation carriers before 2010, 37% was screened for *H. pylori*. After 2010, the percentage increased to 68%. The percentage of mutation carriers screened varied across the five different hospitals, from 68 to 37%.

Table 2.
Mutation carriers screende for *H. pylori*

Characteristic	Total, *n*	%
All	206	
HP status		
Positive	42	20
Negative	161	78
Unknown	3	2
Type of test*		
Serology	94	42
RET	21	9
UBT	4	2
Stool antigen	42	19
Histology	55	24
Unknown	6	3

*) In sixteen cases two tests were performde.
RET = rapid urease test
UBT = urea breath test

Gastric cancer

Only eight (1.8%) of 443 mutation carriers were diagnosed with gastric cancer. The mean age at diagnosis was sixty-four (range, 51–84 years). Four of eight patients had died, all within one year of diagnosis. Four patients were still alive after a follow-up of one to eleven years after treatment. Five patients with gastric cancer were MSH2 mutation carriers, one of whom developed diffuse-type gastric cancer. Seven patients were screened for *H. pylori*: three by serology and four by histology. One patient was found to be infected. Only one patient had a positive family history for gastric cancer.

Family history (first-degree)

For 356 mutation carriers, the family history was available. Twenty-five of them had at least one first-degree family member with gastric cancer, and seven had more than one first- degree relative with gastric cancer. The infection rate of *H. pylori* in patients with a first-degree relative was 20%, similar to the total group. The age at diagnosis was known for thirty-one family members; the mean age was fifty-three (range, 16–78 years). Of the twenty-five mutation carriers with a positive family history, twelve had an MSH2 mutation. MSH2 mutation carriers were 1.6 times (95% CI 0.7–4.4) more likely to have a positive family history, when compared to the other mutation carriers. However, this difference did not reach statistical significance. See Table 3.

Table 3.
Characteristics of patients with a positive family history for gastric cancer

Characteristic	Total, *n*	%
All	25	
Type of mutatio		
MLH1	6	24
MSH2	12	48
MSH6	5	20
PMS2	1	4
EpCAM	1	4
Number of family members		
One	18	72
Two	7	28
H. pylori status		
Positive	5	20
Negative	14	56
Unknown	6	24
Age of family member at diagnosis (average)	53	

Upper endoscopy

In 132 patients (30%), upper GI endoscopy was performed. In fifty-six cases (42%), no abnormalities were found, and no biopsy was taken. In seventy-six patients (58%), one or more biopsies were taken; the results are shown in Table 4.

In 54% of the cases, the biopsy revealed no abnormalities. Active inflammation was the most commonly found abnormality (30%) and was seen significantly more often in *H. pylori*-positive patients (OR 11.0; 95% CI 3.1–36.0). Intestinal metaplasia was present only in four (5%) of the seventy-six patients. Three of these patients were tested negative for *H. pylori*, using serological testing.

Table 4.
Patient characteristics and results of histological examination of biopsies in 76 Lynch syndrome patients who underwent an Upper-GI endoscopy

Characteristic	Inflammation	Intestinal metaplasia	Intestinal-type adenocarcinoma	Diffuse-type adenocarcinoma	No abnormality
All	23	4	7	1	41
Gender					
Male	7	3	4	1	15
Female	16	1	3	0	26
Type of mutation					
MLH1	6	2	1	-	11
MSH2	8	0	5	1	16
MSH6	7	2	1	-	13
PMS2	2	0	-	-	1
Family history					
Positive	4	2	1	-	6
Negative	17	2	5	1	31
Unknown	2	-	1	-	4
Hp status					
Positive	15	1	1	-	6
Negative	8	3	5	1	34
Unknown	-	-	1	-	1

DISCUSSION

This is the first study to report the outcome of *H. pylori* screening in a large series of LS mutation carriers. The study demonstrates that a substantial proportion of mutation carriers are being tested for *H. pylori.* The recommendation to screen for *H. pylori* has been operative since 2010, and the proportion of patients being tested increased from 37% before 2010 to 68% after 2010. However, we cannot rule out that a small percentage of the tests was performed for complaints instead of for screening purposes. Serology and histology were the tests most commonly used. In 20% of the mutation carriers, *H. pylori* infection was diagnosed, a proportion that is similar to the general population.[14,15] Assuming *H. pylori* is an important risk factor in the development of gastric cancer in Lynch patients, we expected to find a higher infection rate in mutation carriers with a positive family history, as *H. pylori* clusters within families.[16,17] However, a similar percentage of 20% in the group mutation carriers with and without a positive family history tested positive for *H. pylori*.

H. pylori is a proven carcinogen in the general population. The role of *H. pylori* in the pathogenesis of gastric cancer in Lynch syndrome is however still unknown. The fact that gastric cancer in mutation carriers occurs more frequently in countries with a higher prevalence of *H. pylori* infection coupled with fact that the incidence of gastric cancer in Western countries has decreased parallel to the decline of *H. pylori* infection, strongly suggest an important role for this bacterium in the carcinogenesis. There exists ample research that underlines the cost-effectiveness of *H. pylori* screening in the general population. A recent meta-analysis showed that even in low-prevalence countries (America, Canada, UK, and Finland), screening the general population for *H. pylori* was cost-effective in the prevention of gastric cancer.[18] Taking into consideration the benefit of screening the general population for *H. pylori* in the prevention of gastric cancer, obviously, screening Lynch syndrome patients would also be beneficial.

In our study population, the incidence of gastric cancer and intestinal metaplasia was much lower than expected, only eight of the mutation carriers had a malignancy; four patients had intestinal metaplasia. The majority of these patients were negative for *H. pylori.* Only one of eight patients with a malignancy was found positive. However, it should be noted that using histology to search for *H. pylori* in the presence of intestinal metaplasia or gastric cancer may produce a false-negative outcome.

A Finnish study examined the value of upper GI endoscopy surveillance in seventy-three MLH1 mutation carriers and thirty-two mutation-negative family members.[9] It showed a substantial proportion of precursor lesions: *H. pylori* infection was

observed in 26%, atrophy in 14%, and intestinal metaplasia also in 14%. However, in the control group, similar proportions were found. They concluded upper GI endoscopy surveillance was likely not beneficial in MLH1 mutation carriers.

The prevalence of stomach cancer in Lynch patients is lower in the Netherlands than in its surrounding countries. Engel et al. reported Dutch patients to be 76% less likely to develop gastric cancer than German patients.[19] The cause of this difference is unknown. We included only eight patients with stomach cancer. This low incidence (2%) is at least partially attributable to the fact that the registries we used were compiled recently, thereby not including those patients which had already died from stomach cancer.

It is well known that the different mutations have a different phenotype. Various studies have observed that MSH2 mutation carriers have a higher risk for gastric cancer than carriers of the other MMR mutations.[6,12] In our study, almost half of the mutation carriers with a positive family history are MSH2-positive, and of eight patients with gastric cancer, five had an MSH2 mutation. While our sample size is too small to make conclusions, it supports the assumption that MSH2 mutation carriers are at greatest risk for gastric cancer.

In conclusion: a substantial and increasing proportion of mutation carriers is tested for *H. pylori*, and a similar percentage of 20% in the group mutation carriers with and without a positive family history was tested positive. The yield of upper GI endoscopy for finding precursor lesions for gastric cancer is low, in accordance with previous studies. In light of the low risk of gastric cancer and the low yield of precursor lesions, we do not recommend regular upper GI endoscopy for any of the MMR mutations in countries with a low prevalence of gastric cancer. Our data do not seem to support the recommendation for routine *H. pylori* screening in Lynch syndrome patients. It should however be noted that the low incidence of gastric cancer makes a type 2 statistical error likely. Therefore, we think it is presumptuous to make any claims regarding the effectiveness of screening. To answer this question, a large prospective randomized study would be necessary and such a trial would be unethical in a population at an increased risk of gastric cancer. Therefore, we recommend continuing *H. pylori* screening in Lynch syndrome patients.

Compliance with ethical standards: The study was approved by the ethics committees of the respective centers.

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part II MANAGEMENT OF EARLY COLORECTAL NEOPLASMS

CHAPTER 5

Referrals for surgical removal of polyps since the introduction of a colorectal cancer screening programme

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ABSTRACT

AIM

Implementation of the national bowel screening program in 2014 led to an increased detection rate of polyps. In general, polyps should be removed endoscopically. However, if the size and location of the polyp makes endoscopic removal technically difficult or if there is a suspicion for early (T1) cancer, surgery is the preferred method for removal. An increasing number of these patients are treated with minimal invasive surgical procedures instead of a segmental resection. The aim of our study was to assess the number of referrals for surgery and the type of surgery for polyps since the introduction of the national bowel screening program.

METHODS

A retrospective cohort study was performed. Patients who underwent surgery for colorectal polyps between January 2012 and December 2017 were included. Exclusion criteria were histologically proven carcinoma prior to surgery. Primary outcomes were number and type of surgical procedures for polyps.

RESULTS

In total, 164 patients were included. An annual increase of procedures for colorectal polyps was observed, from 18 patients in 2012 to 36 patients in 2017. All the procedures before implementation of the screening program were segmental resections and 58.8% of the patients underwent organ preserving surgery after implementation of the screening. Overall complication rate of organ preserving surgery was 16.3%, compared to 44.3% of segmental resections ($p = 0.001$). Overall invasive colorectal cancer was encountered in 23.8% of cases.

CONCLUSION

The number of referrals for surgical resection of colorectal polyps has doubled since the introduction of the CRC screening program with a substantial shift towards organ preserving techniques

INTRODUCTION

Colorectal cancer (CRC) is the second most common malignancy in the Netherlands, with an incidence of 14,258 in 2017. [1] Approximately 95% of CRCs will evolve from an adenomatous polyp or sessile serrated lesion (SSL's). [2] Adenomatous polyps are the most common polyps and account for approximately two-thirds of all colonic polyps. [3] Despite the dysplastic character of the polyp, only 5% of all adenomatous polyps progresses to CRC. Endoscopic screening studies in an asymptomatic population show an overall adenoma prevalence of 25 to 30 percent at the age of 50 years. [2-7]

In order to reduce the incidence as well as the mortality rate of CRC, the Dutch National Institute for Health and Environment (RIVM) introduced the national bowel screening program in January 2014. All men and women aged between 55 and 75 years receive a fecal immunochemical test (FIT) biennially, followed by a colonoscopy in case of a positive FIT result. [8] In a recent systematic review summarizing the results of 6.442 patients, endoscopic resection of large colonic polyps (→ 20 mm) was successful in 92% of the cases. Despite advanced techniques of endoscopic resection, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), colorectal surgery was required in the remaining group. [9] In certain cases surgery is preferred, for instance if size and location of the polyp makes endoscopic removal technically difficult or if macroscopic inspection implies a suspicion for early (T1). In these cases, an en-bloc resection is the best treatment option.

Colorectal surgery is associated with significant morbidity and mortality. For malignant colorectal resections, all patient and procedure related data are collected in the Dutch Colorectal Audit, however, the data for premalignant lesions are not registered. Literature reporting the number of surgical procedures performed for adenomas or SSL's is lacking. Also, it is unclear whether surgical procedures performed for polyps have the same morbidity and mortality rates as surgical procedures performed for colorectal cancer.

The aim of our study was to investigate the number of referrals for surgical resection of colorectal polyps. Furthermore, the type of surgery and its clinical outcome were studied.

MATERIALS AND METHODS

Study design and population

After approval of the institutional review board, a retrospective cohort study was performed. Written consent from patients was not required.

Patients that underwent surgical removal of colorectal polyps between January

2012 to December 2017 were included. The national bowel screening program started in 2014.

Patients were included if they were referred for surgical removal of colorectal polyps that could not be endoscopically removed due to technical reasons (size, position of the endoscope, location) or if upon macroscopic inspection cancer was suspected. If lesions in the left-colon or rectum were suitable for removal by ESD they were referred to another hospital with experience with this. Exclusion criteria were defined as histological proven carcinomas prior to surgery, as well as patients with a genetic predisposition to colorectal cancer (i.e. patients with Lynch syndrome, APC related (attenuated-) adenomatous polyposis coli and serrated polyposis syndrome (SPS). Polyps were defined as lesions histological proven or macroscopically suspicious or (advanced) adenomas, SSL's or early (T1) cancer. Patients who were referred from other hospitals for surgical treatment were excluded.

Primary outcomes were the number and type of surgical procedures. Secondary outcomes were clinical and histological outcome. Clinical outcome was defined as 30-day or in-hospital morbidity and mortality was graded according to the Clavien-Dindo classification (CDG). [10]

Procedures and definitions

All endoscopic examinations were carried out by or under the supervision of a certified gastroenterologist. For the national screening program, all endoscopists and proceedings met the national quality requirements. If applicable, the 'lifting' sign was tested by injecting NaCl 0.9% with Indigo Carmine submucosally. Non-optimal lifting of the polyp was stated as a positive non-lifting sign. An attempt, but unsuccessful endoscopic resection of the polyp was defined as partial removal of the polyp. Colonoscopies performed after a positive fecal occult blood test within the national bowel screening program were defined as screening colonoscopies. Colonoscopies for all other reasons (surveillance following removal of adenomas or SSL's in the past or symptomatic patients) were defined as regular colonoscopies.

All patients were discussed at our weekly colorectal multidisciplinary team meeting. All surgical colorectal procedures were performed by or under the supervision of a specialized colorectal surgeon. The different types of surgery included a segmental colon resection, low anterior resection (LAR), transanal endoscopic microsurgery (TEM) and limited endoscopic-assisted wedge resection (LEAWR). LEAWR is a type of combined endoscopic-laparoscopic surgery (CELS) where no anastomosis is created. [11] During laparoscopy, the involved part of the colon is mobilized to ensure LEAWR. A suture was placed laparoscopically with intraluminal

endoscopic visualization through the base of the polyp. Traction was given on the suture to enable positioning of the linear stapler. Before stapling off the polyp, the patency of the lumen and total inclusion of the polyp tissue was checked endoscopically. Both TEM and LEAWR were introduced in our hospital in 2015. LEAWR was not suitable if the polyp encompassed more than half of the circumference of the colon, in case of diverticulosis or if polyps were located near or at Bauhin's valve. TEM was not suitable for polyps located more than 15 cm from the anal verge. Complications were graded according to the Clavien-Dindo classification (CDG) of complications. [10] Major complications were defined as grade 3b or higher.

Histological material was obtained preoperatively through endoscopically conducted biopsies and/or postoperatively from the surgically resected specimen. Polyps were categorized as hyperplastic, tubular adenoma (TA), tubulo-villous adenoma (TVA), villous adenoma (VA) or sessile serrated lesions (SSL). Adenomas were further subdivided as low-grade dysplasia (LGD; mild to moderate dysplasia) or high-grade dysplasia (HGD; severe dysplasia). For staging invasive cancer, the TNM 5 classification system was used, according to the latest national guideline. High risk features for lymph node metastasis in case of a T1 colorectal carcinoma were defined as poorly differentiated tumour, (lymph)angio-invasive growth and a resection margin of less than 1mm. A low risk T1 colorectal carcinoma was defined as moderate/good differentiated tumour, no (lymph)angio-invasive growth and a free resection margin of 1mm or more. [12]

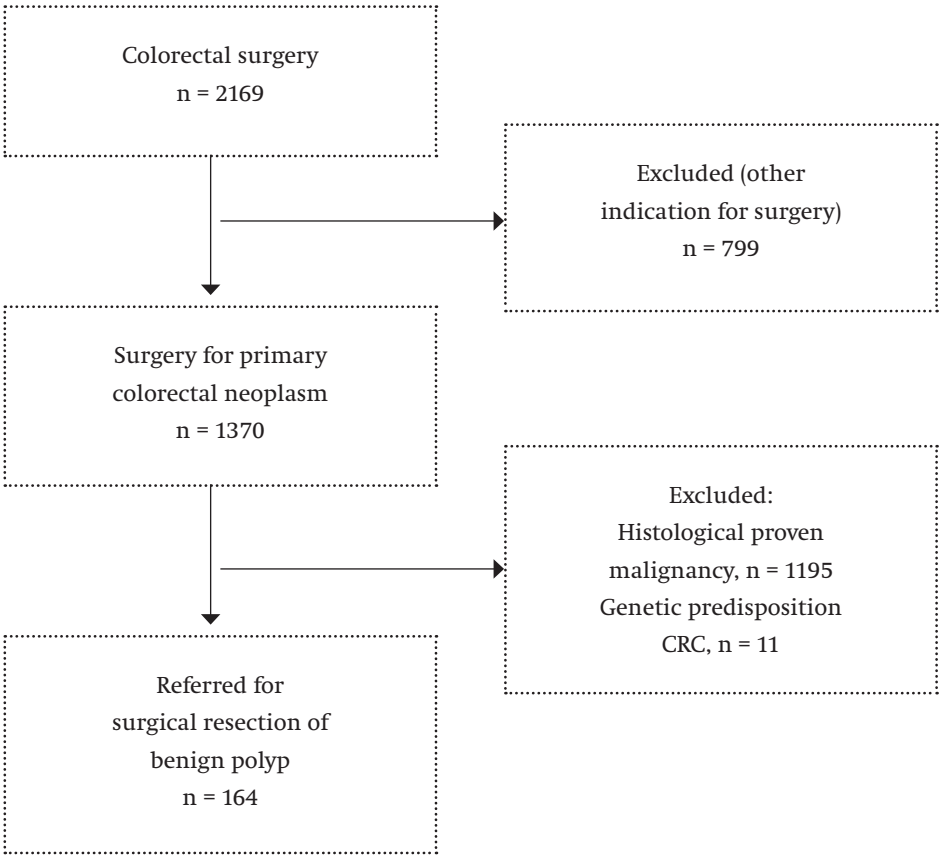
Data management and analysis

For data collection and analysis, both ResearchManager® (Cloud9 Software, Deventer, the Netherlands) and IBM SPSS Statistics, Version 25.0 (IBM Corp. Armonk, NY, USA) were used. Continuous variables were presented, according to the distribution, as median values with the interquartile range (IQR). Continuous data were compared between groups using the Mann-Whitney-U test and categorical data were compared using the Fisher's exact or Fisher-Freeman-Halter Test. P-values of < 0.05 were considered statistically significant.

RESULTS

A total of 2,169 patients were identified who underwent a colorectal surgical procedures between January 2012 and December 2017. Out of this group, 2.005 cases were excluded and 164 patients who were operated for benign polyps were included. (Figure 1)

Figure 1.
Flowchart of the patient selection process



The total number of conducted colonoscopies after implementation of the screening program ranged between 5.141 to 5.517 colonoscopies per year, in comparison to 5.555 colonoscopies in 2012 before implementation of the screening program.

The majority of patients were male (57.3%) with a median (IQR) age of 69 (range 63-74) years. (Table 1) The majority (76.2%) of patients were referred for surgery because of polyps that were technically endoscopically unresectable due to size,

Table 1.
Baseline characteristics

	Total N = 164 (%)
Age (years)	
Median	69
IQR	63-74
Gender	
Female	70 (42.7)
Male	94 (57.3)
BMI (kg/m2)	
Median	26.6
IQR	24.3-29.5
CCI (score)	
Median	3
IR	2-4.8
Morphology	
Sessile	51 (31.1)
Flat	43 (26.2)
Pedunculated	18 (11)
Unknown	52 (31.7)
Size (cm)	
Median	3.5
IQR	2.5-4.5
Location	
Right colon	90 (54.9)
Transverse colon	9 (5.5)
Left colon	37 (22.6)
Rectum and rectosigmoid	28 (17.1)
Preoperative histology	
No dysplasia	4 (2.4)
LGD	90 (54.9)
HGD	50 (30.5)
Unknown	20 (12.2)
Non-lifting sign	
Positive	31 (18.9)
Negative	22 (13.4)
Not performed	111 (67.7)
Endoscopic resection attempts	
One or more attempts	33 (20.1)
No attempts	131 (79.9)
Gastroenterologist's assessment	
Suspect malignant	55 (33.5)
Not suspect	109 (66.4)

IQR = interquartile range; BMI = body mass index; CCI = Charlson comorbidity index

location, and/or non-lifting sign. (Table 2) In total, 45.5% of encountered polyps were sessile, with a median size of 3.5 cm. The majority of polyps (54.9%) were located in the right colon and showed low grade dysplasia preoperatively (62.5%). In 33 cases (20.1%) one or more attempts were made for endoscopic removal. (Table 1) In 29 of these 33 patients no malignancy was suspected. Out of 55 polyps suspecious for an

Table 2.
Surgery characteristics

	Total N = 164 (%)
Indication for surgery	
Endoscopically unresectable	125 (76.2)
Non-radical polypectomy	20 (12.2)
Recurrence in scar tissue	11 (6.7)
Multiple polyps	5 (3.0)
Other	3 (1.8)
Duration of surgery (minutes)	
Median	95
IQR	70-129
Type of surgery	
Ileocecal resection	9 (5.5)
Right hemicolectomy	63 (38.4)
Left hemicolectomy	9 (5.5)
Transverse colon resection	4 (2.4)
Sigmoid resection	18 (11.0)
LAR	12 (7.3)
TEM	22 (13.4)
LEAWR	27 (16.5)
Approach	
Open	23 (14.0)
Laparoscopic/transanal	135 (80.5)
Conversion*	6 (4.3)

IQR = interquartile range; LAR = low anterior resection; TEM = transanal endoscopic micro-surgery; LEAWR = limited endoscopic-assisted wedge resection.
* Percentage of total amount of intended laparoscopic surgeries

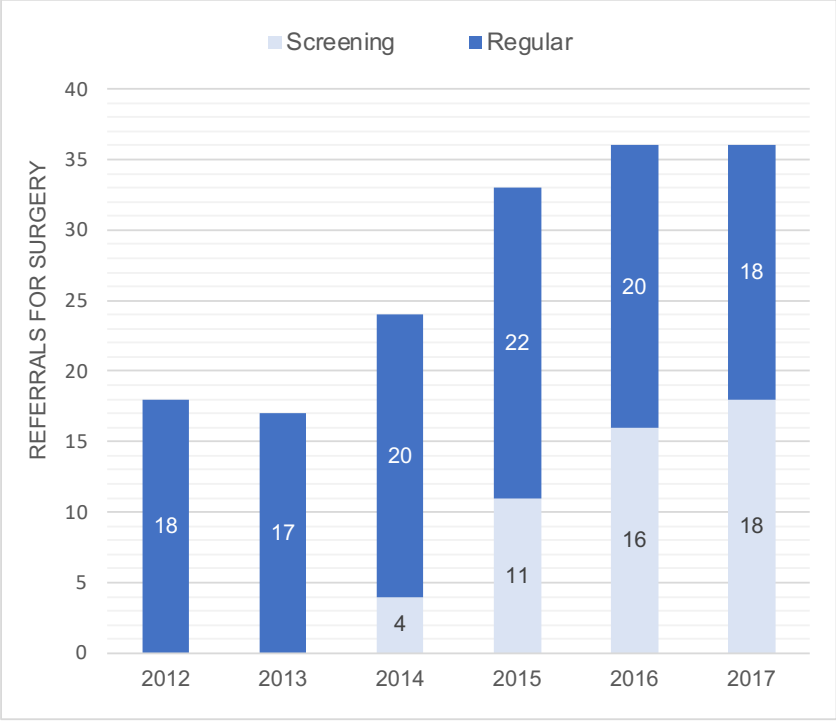
invasive tumor, 20 polyps were malignant (positive predictive value 36.3%). Of the 109 suspected benign polyps, 19 polyps were carcinomas (negative predictive value 82.6%). Of the 49 patients who underwent organ preserving surgery, 15 patients (30.6%) were suspected to have a malignancy. Of the 115 patients who underwent

major surgery, 18 (15.7%) patients had a polyp who was suspicious for an invasive tumor. In 51 out of 55 suspect malignant cases (92.7%) no endoscopic resection attempts were performed.

The main surgical procedure was a segmental colectomy (70.1%), the remaining group of 49 patients (29.9%) underwent a TEM (n = 22) or LEAWR (n = 27). Procedures were performed laparoscopically or transanally in 80.5% (n = 132) with a conversion rate of 4.3% (n = 6). (Table 2)

Before implementation of the national screening program in 2014, the annual number of patients who underwent surgical removal of polyps was 18 (2012) and 17 (2013). (Figure 2) Since the implementation, the absolute number of surgical procedures increased annually to 36 procedures in 2017. The percentage of patients who

Figure 2.
Annual volume of surgical procedures



'Regular' = number of patients who were referred
for surgery after colonoscopy due to other reasons than a screening colonoscopy
'Screening' = number of patients who were referred
or surgery after colonoscopy in case of national screening program

were referred for surgery after a positive FIT result increased from 16.7% in 2014 to 50% in 2017.

From 2012 to 2014, all surgical procedures were major surgical procedures. In the following years the number of organ preserving surgery increased to 21 out of 36 (58.3%) procedures in 2017, resulting in an average of 41.2% organ preserving surgeries after implementation of the screening program.

Clinical and pathological outcome

The overall complication rate was 36.0%, which were mostly minor complications. Only 8 out of 164 patients (4.9%) presented with one or more major complications, of which 7 patients were post-segmental resection. One patient presented with a major complication after an organ preserving procedure, a post-TEM hemorrhage treated surgically. There were no serious complications after LEAWR. In 4 out of 115 segmental resections (3.5%) an anastomotic leakage occurred. Postoperative mortality was zero. A significant lower overall complication rate (16.3%) was seen after organ preserving surgery compared to a segmental resection (44.3%) (p = 0.001). (Table 3)

Table 3. Clinical outcomes

	Total N = 164 (%)	Organ preserving N = 49 (%)	Segmental resections N = 115 (%)	p value
Overall complication rate	59 (36.0)	8 (16.3)	51 (44.3)	.001**
CDG				1.000**
≤ 3a	51 (31.1)	7 (14.3)	44 (38.3)	
≥ 3b	8 (4.9)	1 (2.0)	7 (6.1)	
Anastomotic leakage	4 (3.5*)	-	4 (3.5)	a
Mortality	-	-	-	a
(Re)laparotomy	7 (4.3)	-	7 (6.1)	.200**
Stoma creation at re-intervention				a
Temporary	2 (1.2)	-	2 (1.7)	
Permanent	1 (0.6)	-	1 (0.9)	
Days of admission				< .001***
Median	5	2	5	
IQR	3-6	2-3	4-8	
Readmission	11 (6.7)	2 (4.1)	9 (7.8)	.508**
Days of readmission				.808***
Median	6	6	6	
IQR	5-21	5-7	5-22.5	

CDG = Clavien-Dindo classification; IQR = interquartile range. A Statistical analysis could not be performed.
* Percentage of total primary anastomoses (n = 115).
** Fisher's Exact Test
*** Mann-Whitney U Test

Overall invasive colorectal cancer was encountered in 23.8% of the referred polyps. Fifty percent of the resected polyps appeared to contain high-grade dysplasia, 45% of the resected polyps contained low-grade dysplasia. (Table 4)

In 8 patients that underwent organ preserving treatment for a polyp a colorectal carcinoma was found. An additional oncological resection was indicated in 4 out of the 8 patients due to high risk features for lymph node metastases; this number represents only 8.2% of all patients who received organ preservation. The remaining four patients had a low risk pT1 CRC carcinoma. No major complications occurred within 30 days after additional oncological surgery.

Table 4.
Postoperative pathology

	Total N = 164 (%)	**Organ preserving N = 49 (%)**	**Major surgery N = 115 (%)**
Benign	125 (76.2)	41 (83.7)	84 (73.0)
High grade dysplasia	61	16	45
Low grade dysplasia	55	20	2
No dysplasia	5	3	2
Unknown	4	2	2
Malignant	39 (23.8)	8 (16.3)	31 (27.0)
Low risk pT1	4	4	-
High risk pT1	4	4	-
TNM > pT1	31	-	31

DISCUSSION

Since the introduction of the Dutch CRC screening program in 2014 the number of referrals for the surgical resection of polyps have doubled in our hospital. Thirty percent of these patients were treated using an organ preserving technique. Colorectal cancer was found in 24% of these patients.

Data about surgical referrals for complex polyps are scarce. In one cohort study the number of patients referred for laparoscopic colorectal resection for non-malignant polyps almost tripled after the introduction of the national screening program. [13] The conducted screening colonoscopies after a positive FIT resulted in a higher number of surgical resections compared to the conducted colonoscopies in symptomatic patients. This is related to a higher number of endoscopically detected polyps during screening colonoscopies, which is consistent with results of earlier research in which adenoma prevalence in the screening population was higher than in symptomatic patients. [14]

In our hospital, the increase in surgical referrals for removal of colorectal polyps led to the development of a less invasive surgical technique. This technique (LEAWR), in which laparoscopy and endoscopy are combined, was developed in 2015. One of the great benefits of this minimally invasive technique is that no anastomosis is created. In a pilot study, no complications were observed. [11]

Our study shows a substantial morbidity related to segmental colon resections of polyps. These results are comparable with large cohort studies reporting an reoperation rate of 7.8% and readmission rate of 3.6% after surgery for nonmalignant colorectal polyps. [15,16] Over time, there is a reduction of surgery related morbidity. [16] Morbidity rates for benign lesions are comparable to surgery for colorectal cancer.[17]

In the organ preserving group, 7 patients (14.3%) had a minor complication. Only 1 out of 49 patients (2.0%) who underwent minor surgery presented with a major complication, this concerned a post-TEM haemorrhage, which required surgery. LEAWR did not lead to major complications. A recent study reporting on short- and long-term results of TEM observed similar rates of minor complications in 12 patients (8.8%) and major complications in 2 out of 135 patients (1.5%). [18] Three retrospective studies investigating postoperative complications after different types of CELS observed no complications. [11, 19, 20] These studies were limited by their small sample sizes, ranging from 3 to 23 patients which makes comparison difficult. A prospective study by Wilhelm et al. analyzed 146 patients who underwent CELS, of which 82% underwent local excision and 18% received endoscopy-assisted seg-

mental colon resection. The overall complication rate was 25% and major complication rate was 3%. [21] These results are very comparable to our overall complication rate of 36.0% and occurrence of major complications in 4.9% of patients, especially when considered that in our study 70% of surgeries were segmental resections. Considering a significant lower overall complication rate was encountered in the organ preserving group, this therapy should be first choice if surgical treatment of colon polyps is necessary.

The overall postoperative malignancy rate of 23.8% is in line with malignancy rates between 6.9 and 44.3 percent of surgically resected colorectal polyps reported in the literature. [22-27] A plausible explanation for the differences in percentages,, is selection bias, as polyps that were endoscopically deemed suspicious for early cancer were included in several studies.

In our study we observed a high percentage of right-sided polyps. According to multiple retrospective studies colorectal polyps predominantly exhibit a proximal colonic distribution. [30, 31] Another explanation for the high proportion of right-sided polyps referred for surgery is due to higher risk for complications such as perforation and bleeding associated with the removal of right-sided polyps. [30]

In the majority of the included patients, no attempt was made for an endoscopic removal. This was mainly due to unfortunate polyp characteristics, such as large size; difficult location; non-lifting sign and/or the suspicion of early (T1) carcinoma. In 51 out of the 55 patients where no endoscopic attempt to remove the polyp was made, there was a suspicion of a malignancy with deep invasion. In these cases, an en-bloc resection is advised, which is not always possible by endoscopy. [31-34]

In recent years, endoscopic treatment options are expanding, where the introduction of ESD and endoscopic full thickness resections have enabled local excision of pT1 tumors. The use of these techniques may reduce the referrals for surgery. Our hospital participates in a network with in which all these endoscopic techniques are available. A French study showed a reduction of referrals after the implementation of a regional referral network, however, all included patients were screen detected. [35] Therefore, the influence of a national bowel screening program on referral numbers was not investigated. Prior to referral for surgical excision, it is recommended to consult experts for endoscopic treatment. Repeated colonoscopy before surgery in an expert center can also reduce the rate of surgical referrals by 71%.[36] For rectal lesions, the choice for ESD or TEM has still to be established by a multicenter study (TRIASSIC-study) which is currently still including patients.[37]

There were a few limitations in our study, mainly due to its retrospective design.

At first, a clear definition of an unresectable polyp was difficult to establish and this definition changed over time with the development of endoscopic expertise in our clinic. The therapeutic strategies were based on the endoscopic assessment by different gastroenterologists, which can lead to interobserver variability. In the final years of the study period, complex polyps were extensively discussed with experienced endoscopists. Furthermore, total numbers and success rates of endoscopic treatments (polypectomies) and referrals for ESD to other hospitals during the studied time interval were not available. The increase in surgical referrals due to the implementation of the screening program led to the development of a less invasive technique (LEAWR) which may have reduced the threshold for surgical referrals. In addition, if all referred patients, despite complexity were discussed with more experienced endoscopists, the number of patients who underwent surgery could possibly have been lower. Despite increasing endoscopic possibilities and techniques over time, an increase in referrals for surgery was still observed. However, this study might reflect the consequences of a bowel screening program for daily clinical practice in a large teaching hospital.

In conclusion, the number of referrals for surgery for colorectal polyps has doubled since the introduction of the CRC screening program with a substantial shift towards organ preserving techniques.

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CHAPTER 6

Limited Endoscopic Assisted Wedge Resection for Excision of Colon Polyps

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Diseases of the Colon & Rectum, 2016.

ABSTRACT

BACKGROUND

Combined endoscopic laparoscopic surgical (CELS) removal is used for polyps in the colon that are not suitable for endoscopic removal due to size, location or scarring. However, the placement of a linear stapler can be challenging. Up to now, a wedge resection is mostly documented in the cecum or ascending colon.

OBJECTIVE

We would like to report on our experience with limited endoscopy assisted wedge resections (LEAWR) in the entire colon.

METHODS

A retrospective single-center study was performed. Eight patients were included between March 2015 and April 2016. The laparoscopic surgical technique consisted of placing a suture under endoscopic view through the base of the polyp into the lumen. Subsequently, traction was given on the suture to enable stapling of a wedge of the colon.

MAIN OUTCOME MEASURES

Medical data were collected (i.e., indication for referral for surgery, location and size of the polyp, duration of surgical procedure, length of hospital stay and peri- and postoperative complications). Operative time was defined as total time of general anesthesia.

RESULTS

Eight patients, with a mean age of 74.5 years (range 68-82), were treated. Main indications for laparoscopic resection were the size and difficult location of the polyp. There were no complications. Mean operative time was 132 minutes. Five patients were discharged the day after surgery, the other 3 patients were admitted a total of 2 days.

CONCLUSION

Our study found that LEAWR is a feasible and easy technique for the removal of colon polyps and residual adenomatous tissue in scars not accessible for endoscopic removal. Due to traction given on the suture through the base of the polyp, the linear stapler is easily used for wedge resections of polyps even for those that are not in favorable positions.

INTRODUCTION

The new combined endoscopic laparoscopic surgical (CELS) approach for the removal of difficult colon polyps, the so called CELS-full thickness excision (CELS-FT), was recently described by Lin et al.[1] They describe how to create a defect in the seromuscular layer circumferentially over the location by laparoscopy where indigo carmine solution was injected previously. Then, the dissected area is invaginated into the bowel lumen with a laparoscopic instrument. A snare is introduced and looped around the polyp. Before cutting through the polyp, the peritoneal surface is examined and there is laparoscopic closure to repair the colonic defect.[1] Three patients are described that underwent CELS-FT for difficult benign polyps. The average surgery time was 179 minutes. There was minimal blood loss and there were no perioperative complications. The authors describe a (limited) wedge resections by using a linear stapler without anastomosis is only feasible if the polyps are in a favorable position, such as in the cecum.[1,2] We would like to report on our experience with limited endoscopy assisted wedge resections (LEAWR) in 8 patients in Isala, Zwolle, The Netherlands.

MATERIAL AND METHODS

Study design

A retrospective single-center study was performed in Isala Hospital in Zwolle, The Netherlands between March 2015 and April 2016. We included patients with polyps that were eligible for a combined endoscopic laparoscopic surgical removal. Patients were mainly referred from our own department of Gastroenterology. There were various reasons for referral for surgical resection; endoscopic unresectability, size, localization or incomplete/failed resection. One surgeon, specialized in minimal invasive colorectal surgery, performed all procedures. We collected data on age, gender, localization of the polyp, pre- and postoperative pathology findings, indication for surgical resection, duration of surgical procedure, length of hospital stay and peri- and postoperative complications. We defined complications as excessive blood loss during surgical procedure, postoperative blood loss, perforation and perioperative infections. Operative time was defined as total time of general anesthesia.

Surgical technique

All patients underwent split-dose bowel preparation. Patients were placed under general anesthesia in French position. The surgeon started with a diagnostic laparoscopy with three trocars. At first, the spot in the colon was identified and the concerning part of the colon was mobilized to ensure the LEAWR. Secondly, the

colonoscopy was performed by the gastroenterologist. A suture was placed laparoscopically with intraluminal endoscopic visualization through the base of the polyp. (Figure 1) Traction was given on the suture to enable positioning of the linear stapler (Endo-GIA tristaple, Covidien).(Figure 2) Before stapling off the polyp the patency of the lumen (i.e., the lumen of the colon or in case of a cecal lesion the lumen of the ileum) as well a total inclusion of the polyp tissue was checked endoscopically by the gastroenterologist. (Figure 3) The resected specimen was as removed in an endobag through the 12mm trocart. The surgeon as well as the endoscopist checked the colon for signs of bleeding or perforation before ending the procedure.

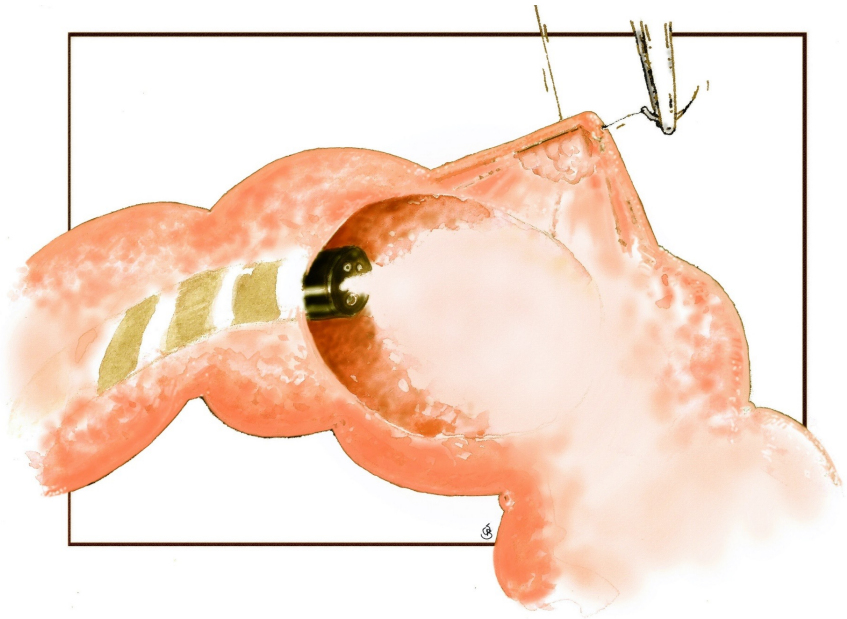

Figure 1.
Placing a suture through the base of the polyp into bowel lumen under endoscopic view

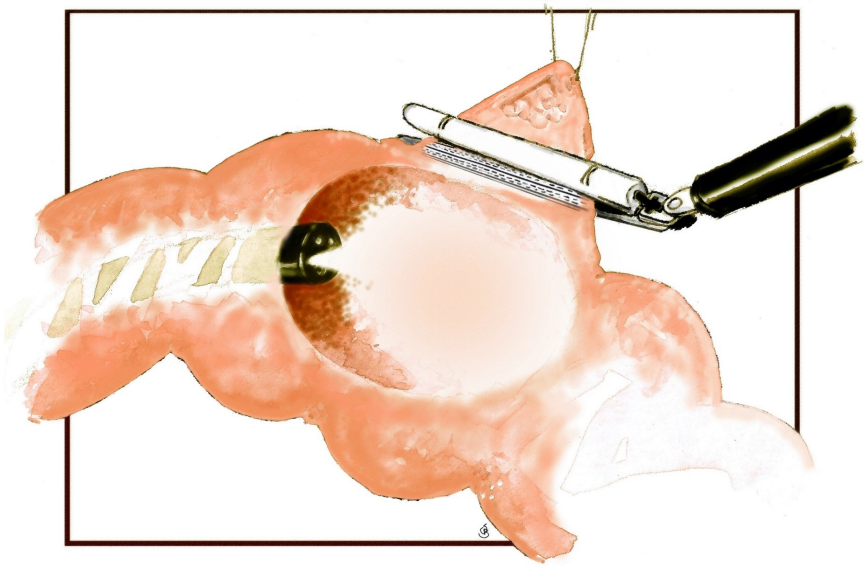

Figure 2.
Traction given on the suture before stapling off and to ensure positioning of the linear stapler

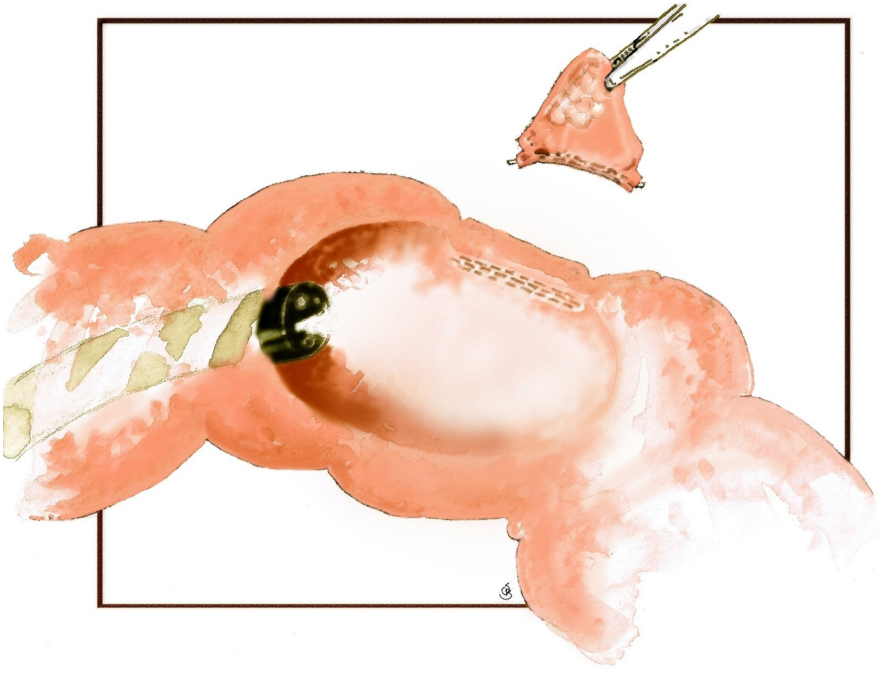

Figure 3.
Before stapling off the polyp the patency of the lumen is checked endoscopically

RESULTS

Eight patients with endoscopically unresectable colon polyps were treated. Seven patients were referred from our own department of Gastroenterology one patient was referred from another hospital.

Seven patients were male and the mean age of all patients was 74.5 years. (Table 1) The main indications for laparoscopic resection were the size and difficult location of the polyp. In three patients the indication was suspected residual adenomatous tissue after poliepectomy. (Table 2, patient 1, 4 and 6) There were no complications in our patients. The mean operative time was 132 minutes. In two patients the operative time was longer. In patient number 2 (Table 2) this is explained by the fact that we started with a transanal endoscopic microsurgery (TEM) procedure, which failed. In the other patient (patient 1, Table 2), two wedge

Table 1.
Demographics and mean operative time

Parameter	n = 8
Age (years), median (range)	74.5 (68-82)
Sex	
Male	7 (87%)
Female	1 (13%)
ASA	
1	-
2	2 (25%)
3	2 (25%)
Operative time (min), median (range)	132 (110-170)

resections were performed. The perioperative blood loss was in negligible. Five patients were discharged the day after surgery, the other 3 patients left the hospital 2 days after surgery.(Table 2) In seven patients the margin of resection was clear of adenomatous tissue. In one patient (patient 1, Table 2) who underwent two wedge resections the margin of resection in one of the specimen was clear of adenomatous tissue. However, radicality of the other specimen was unclear due to the fact that the margin of this lesion (a sessile serrated adenoma with low graded dysplasia) was in the staples of the resection site that were removed before histological examination. Though we are convinced that this polyp is completely removed, we cannot prove radicality and we will plan this patient for surveillance endoscopy. One of eight patients underwent a follow up colonoscopy 6 months postoperatively, there was no stenosis of the colon.

Table 2.
Details of cases undergoing endoscopic assisted laparoscopic full thickness excision

	Age	M/F	ASA	Polyp location	Size mm	Preoperative pathology	Indication	Operative time, min	Final pathology	LOS d	Compli-cations
1	68	M	2	transverse colon/ descending colon (2 polyps)	10/scar*	TA-HGD	difficult location/ SRATAP	165	SSA-LGD /scar tissue	1	none
2	82	M	3	sigmoid	10	AC	early carcinoma	170	pT1NxMx AC	2	none
3	76	M	3	transverse colon	28	TA-LGD	size and difficult location	126	TVA-LGD	2	none
4	78	F	2	cecum, valvula Bauhini	scar**	TA-HGD	non lifting and SRATAP	117	TVA-HGD	1	none
5	79	M	2	splenic flexure	20	TVA-HGD	en-bloc resection^^	119	TVA-HGD	1	none
6	69	M	2	hepatic flexure	scar^	TA-LGD	SRATAP	122	no polyp tissue	2	none
7	70	M	2	cecum	40	SSAP	size and difficult location	110	SSAP	1	none
8	74	M	2	cecum	43	SSAP	size and difficult location	124	TVA-LGD	1	none

Size of the polyp is based on the pathology report.
** a 45mm LST was piecemeal removed, suspected irradicality*
*** a 15mm sessile serrated polyp upon the valvula Bauhini was piecemeal removed, suspected irradicality*
^ a 14mm tubular adenoma with low-grade dysplasia was removed, suspected irradicality
^^ endoscopic suspicion of an early carcinoma

Abbreviations:
AC = adenocarcinoma,
TVA = tubulovillous adenoma,
TA = tubular adenoma,
SSAP = sessile serrated adenoma/polyp,
HGD = high-grade dysplasia, LGD = low-grade dysplasia, SRATAP = suspected residual adenomatous tissue after poliepectomy,
LOS = length of stay

DISCUSSION

We demonstrate limited EAWR is a feasible and safe procedure for polyps in the colon that are not suited for endoscopic removal due to size, place or scarring. Although patient numbers are low, so far we did not encounter any difficulties in placing the stapler. Due to traction given on the suture through the base of the polyp, the linear stapler is also easily used for wedge resections of polyps that are not in a favourable position. In the literature we did not found an earlier publication of using traction on a suture to perform a wedge resection. We performed a limited EAWR for polyps with sessile as well as (semi-) pedunculated morphology. Indication for limited EAWR of (semi-)pedunculated polyps was difficult location due to instability of the scoop.

Obviously, a limited EAWR is not suitable for the resection of malignant polyps, because radical lymph node dissection is not part of this technique.[3] In addition, leaving residual neoplasia could not be ruled out in one patient as described above. Patients with previous biopsies consistent with invasive cancer should be excluded from the limited endoscopic assisted wedge resection. However, we treated one patient (patient 2, table 2) for a polyp that was macroscopically suspect for cancer, because he refrained from treatment with an oncologic bowel resection. Histology in this patient showed a T1 carcinoma with 2.6mm submucosal invasion without angio-invasion or signs of perineural growth.

Even with laparoscopic assistance, endoscopic removal is not always technically possible or may not be effective in cases where a snare cannot be placed over the polyp because of size, location or scarring from previous biopsies. This may lead to piecemeal resection and subsequent inadequate histopathological assessment of the specimen as well as a higher risk of recurrence.[1,4] Endoscopic submucosal dissection (ESD) is a well-established technique that facilitates en bloc excision of large polyps. However, there are several disadvantages to ESD that limit its use in routine clinical practice, including the need for specialized equipment, procedure length and a long learning curve.[5]

Many patients now indicated for ESD can also easily be treated with limited EAWR. Caution is taken when polyps are situated in a sigmoid with multiple diverticula, in these patients endoscopic wedge resection might be challenging.
A possible concern of a limited EAWR could be narrowing of the bowel. We prefer to place the stapler in a transverse direction, this is however not always possible. In our patients we did not have any complaints related to possible narrowing of the colon. In one patient, that underwent a limited wedge resection for an adenoma located in the hepatic flexure, follow up colonoscopy, showed no signs of stenoses.

Two patients had a limited wedge resection on the left side of the colon, they did not report any complaints which could be related to possible narrowing of the colon. In conclusion, limited EAWR is a safe technique with a relative short operative time. The technique seems feasible for colon polyps and residual adenomatous tissue in scars in practically all positions that are not accessible for endoscopic removal. If limited EAWR for any reason is not possible, CELS-FT as described by Lin et al. seems a good alternative.

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CHAPTER 7

Colonoscopic-assisted laparoscopic wedge resection for colonicl esions – a prospective multicentre cohort study (*LIMERIC*-study)

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ABSTRACT

OBJECTIVES

The use of segmental colectomy in patients with endoscopically-unresectable colonic lesions results in significant morbidity and mortality. Modified colonoscopic-assisted laparoscopic wedge resection (CAL-WR) is an alternative procedure that may lower morbidity. The aim of this study was to evaluate the safety and efficacy of our modified CAL-WR.

DESIGN

This prospective multicentre study was performed in 13 Dutch hospitals between January 2017 and December 2019. Inclusion criteria were (1) colonic lesions inaccessible using current endoscopic resection techniques (judged by an expert panel), (2) non-lifting residual/recurrent adenomatous tissue after previous polypectomy or (3) an undetermined resection margin after endoscopic removal of a low risk pT1 colon carcinoma. Thirty-day morbidity, technical success rate and radicality were evaluated.

RESULTS

Of the 118 patients included (56% male, mean age 66 years, SD ± 8 years), 66 (56%) had complex lesions unsuitable for endoscopic removal, 34 (29%) had non-lifting residual/recurrent adenoma after previous polypectomy and 18 (15%) had uncertain resection margins after polypectomy of a pT1 colon carcinoma. CAL-WR was technically successful in 93% and R_0 resection was achieved in 91% of patients. Minor complications (Clavien-Dindo I-II) were noted in 7 patients (6%) and an additional oncologic segmental resection was performed in 12 cases (11%). Residual tissue at the scar was observed in 5% of patients during endoscopic follow-up.

CONCLUSIONS

CAL-WR is an effective, organ-preserving approach that results in minor complications and circumvents the need for surgery. CAL-WR therefore deserves consideration when endoscopic excision of circumscribed lesions is impossible or incomplete.

INTRODUCTION

Since the implementation of a nationwide colorectal screening program in the Netherlands in 2014, the incidence of advanced adenomas and early-stage colorectal cancer (CRC)) as well as the number of patients referred for colorectal resection for high grade polyps has increased.[1-3] Endoscopic polypectomy is a well-established treatment for non-invasive colonic polyps,[4] the majority of which can be removed safely with standard polypectomy. For more challenging polyps advanced endoscopic techniques such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (eFTR) have improved local resectability compared with standard polypectomy.[5-10] Despite the availability of these techniques, large or sessile polyps situated at difficult locations in the colon can still be (technically) difficult to remove endoscopically.[11] A meta-analysis concerning endoscopic removal of 6779 polyps of more than 2 cm reported a success rate of 91%, with a morbidity of 8% and a mortality of 0.3%. However, additional surgical resection was required in 9% of the cases, mostly due to an irradical resection.[12] Segmental colectomy is associated with significant morbidity (24%) and mortality (2%), independent of tumour stage,[13] and a study of surgery referral for benign colonic lesions showed an overall complication rate of 25.5%, subsequent re-intervention in 8.1% and a mortality rate of 0.9%.[14] Fortunately, several methods have been developed to act as intermediate and less invasive steps between endoscopic resection and major surgery. Laparoscopic-assisted polypectomy was first described in the early 1990s as an alternative to bowel resection for difficult benign lesions.[15] However, most reported series using this technique are single-centre studies and are limited by their retrospective design and small sample size (ranging from 4 to 72 patients).[16-20] Nevertheless, a combined endoscopic laparoscopic surgical (CELS) approach has gained popularity due to acceptable recurrence rates, a shorter hospital stay, lower morbidity and improved functional outcomes compared with segmental colectomy.[21-23] The technique we apply here, a modified colonoscopic-assisted laparoscopic wedge resection (CAL-WR), using a linear stapler without making an anastomosis, was previously described in a small cohort of eight patients and yielded promising results in terms of a low morbidity rate and no observed mortality.[16] However, as this technique has not yet been clinically evaluated, the aim of this large multicentre cohort study was to prospectively evaluate the short-term safety and effectiveness of CAL-WR as a means to avoid segmental colectomy in routine clinical practice.

MATERIALS & METHODS

Study design and population

This prospective multicentre longitudinal cohort study was performed between January 2017 and December 2019 in 13 Dutch hospitals specialized in colorectal cancer care. The study was approved by the relevant medical ethics committee (reference no. 16-827/C) and registered in the Netherlands Trial Register as NTR6364 (https://www.trialregister.nl/). The local review board of each participating hospital independently reviewed the study protocol to assess whether the study was locally feasible. Patient demographics, colonoscopy results and histological outcomes were obtained following written informed consent and registered in a web-based database (Castor EDC, Amsterdam, The Netherlands)[24]. Patients with the following colonic lesions were eligible for inclusion: a colonic polyp that could not be removed using current endoscopic resection techniques (group 1), the presence of a non-lifting residual/recurrent polyp in a scar after previous polypectomy (group 2) or an undetermined resection margin after endoscopic removal of a low-risk pT1 colon carcinoma (group 3). The patients in groups 1 and 3 were reviewed by an expert panel before inclusion (see patient selection below). Exclusion criteria were pregnancy, a polyp with more than 50% involvement of the luminal circumference and rectal polyps (less than 15 cm from anal verge endoscopically).

Patient selection and definitions

All eligible patients were registered. In cases with an ostensibly endoscopically-unresectable polyp (group 1), a central expert panel consisting of five gastroenterologists experienced in EMR/ESD/eFTR working in different participating hospitals assessed resectability and the indication for an en-bloc resection based upon four endoscopic images of the lesion. Two overview images of the lesion, white light and narrow band imaging (NBI) were used in the assessment, as well as two near focus images of the lesion (white light and NBI). The panel subsequently excluded cases that were considered suitable for endoscopic removal.

Patients who underwent earlier endoscopic removal of a low-risk pT1 colon carcinoma but with uncertain resection margins, were suitable for inclusion is this study (group 3). Before inclusion, histology of all specimens was re-examined by two specialized pathologists from one centre to exclude high-risk features defined as angiolymphatic invasion, poor differentiation, tumour budding grade 2/3.[25]

Colonoscopic-assisted laparoscopic wedge resection (CAL-WR)

All participating surgeons were experienced colorectal surgeons with dedicated

laparoscopic skills and to ensure uniformity of the procedure were required to complete an e-learning module explaining the CAL-WR technique. Patients were informed about the possibility of CAL-WR failure, in which case the surgeon would convert to a segmental resection or trans-anal minimal invasive surgery (TAMIS) during the same procedure. All included patients underwent split-dose bowel preparation. Patients were placed in French position under general anaesthesia. The surgeon started with a diagnostic laparoscopy using three trocars, the spot in the colon was identified and the concerning section of the colon was mobilized. This approach ensured that the linear stapler could be placed to make CAL-WR possible. Subsequently, colonoscopy using CO_2 for insufflation was performed by the gastroenterologist to indicate the location of the colonic polyp and a suture was laparoscopically placed close to the lesion using intraluminal endoscopic visualization. In the event of a colonic lesion close to the mesentery, CAL-WR might not be possible but sometimes, the colonic wall can be dissected from the mesentery with preservation of the marginal artery of the colon. Traction was then placed on the suture to enable positioning of the linear stapler. Before stapling the lesion, the patency of the lumen (i.e., the colonic lumen or in case of a caecal lesion, the lumen of the ileum) as well as a completeness of inclusion of the lesion was assessed endoscopically. The resected specimen was removed in an endobag through the 12 mm trocar. The surgeon as well as the gastroenterologist checked the colon for signs of bleeding or perforation before completing the procedure.[16]

Histology

The resected specimen was sent fresh, unfixed and in toto, without manipulation of the staple line by the surgeon, to the pathologist. The pathologist removed the staples, the lateral and serosal margins were inked with different colours, the specimen was then stretched on a paraffin block (or mesh), photographed and fixed for 24 hours at room temperature. After fixation, longitudinal sections of length and width of the whole specimen were made and completely included. Histological diagnosis of polyps and tumours was carried out in accordance with current guidelines. The histological grading, classification and the lesion resection margins in mm (horizontal and vertical) were assessed. In the event of invasive carcinoma, the Kikuchi levels were used for pT1 tumours. A R_0 resection was defined as a complete resection with no residual tumour in the resection plane, with a margin of at least 1 mm. Incomplete (R_1) resection was defined as tumour invasion of margins. When radicality could not be determined due to coagulation artefacts/tangential cut, it was defined as a R_x resection.[26] The same classification (R_0, R_1, R_x) was used for benign polyps. Tumour grade and presence/absence of lymph- or blood vessel inva-

sion was addressed specifically, along with tumour budding. When the histological outcome of CAL-WR in group 3 showed no residual neoplastic tissue from the earlier endoscopically incomplete resected low-risk pT1 CRC, the histology of the CAL-WR excision specimen was reviewed by a specialized GI pathologist to ensure that the earlier endoscopically-removed low-risk pT1 scar was resected. When the scar was identified during second reading of the histology and no residual tissue was identified, we considered it a R_0 resection.

Follow-up endoscopy
A follow-up endoscopy was scheduled six months after CAL-WR to evaluate the scar for residual/recurrent adenomatous tissue or cancer. Inspection of the scar was performed with both white light and advanced imaging (NBI or chromo-endoscopy), followed by biopsies even in the absence of visible neoplastic tissue.

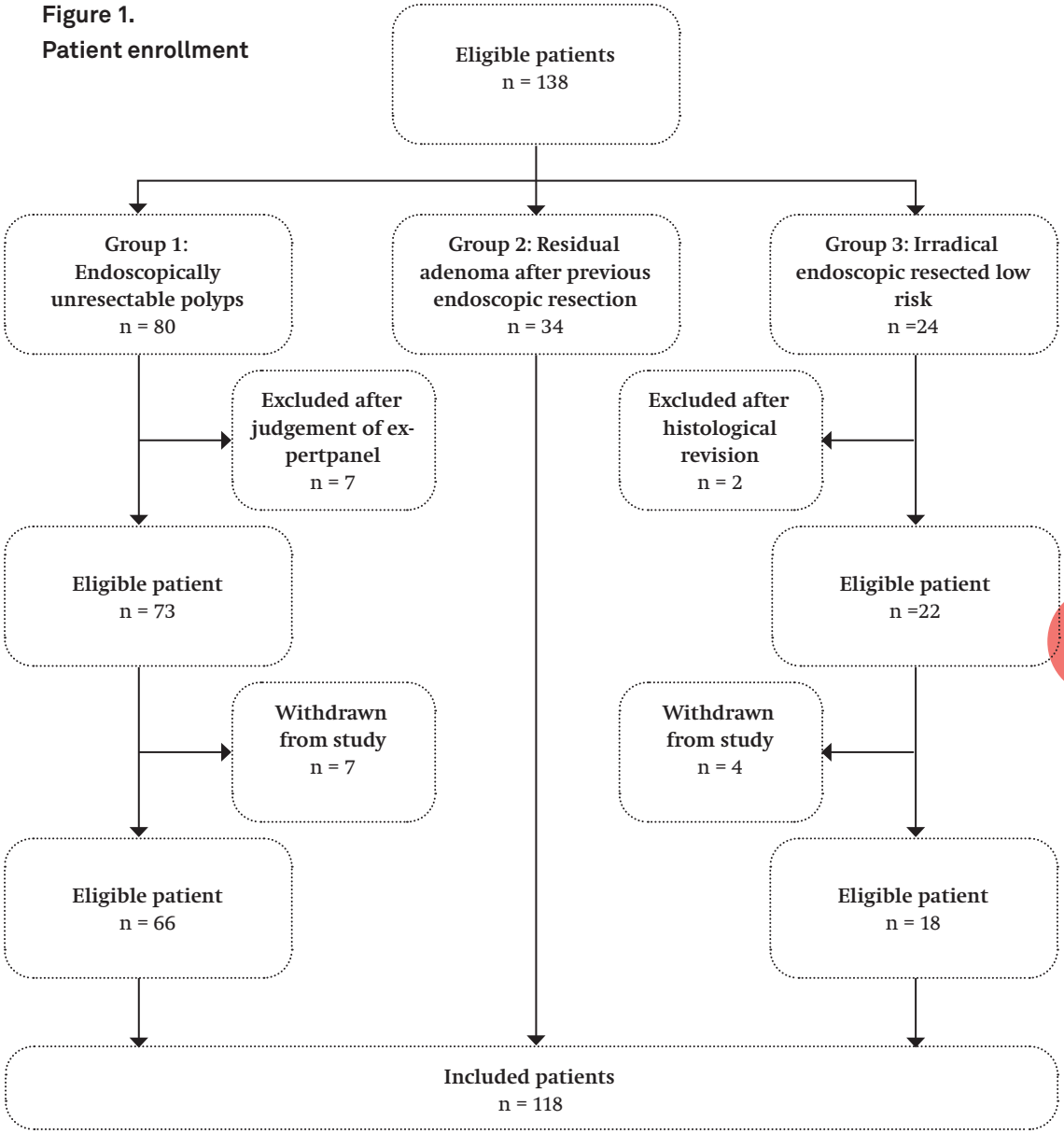
Primary and secondary outcomes
The primary endpoint was the 30-day morbidity rate after CAL-WR according to the Clavien-Dindo classification.[27] Minor morbidity was defined as Clavien-Dindo grade I or II, and major morbidity as Clavien-Dindo grade III or higher. The secondary outcomes were (1) technical success defined as macroscopically-complete wedge resection with a patent lumen, (2) number of radical resections (R_0) defined as free lateral and vertical resection margins of at least 1 mm normal colonic mucosa, (3) recurrence of adenomatous tissue or carcinoma detected by follow-up endoscopy and (4) long-term morbidity following CAL-WR defined as the development of a symptomatic stenosis of the colon.

Statistical analyses
The sample size was determined based on a power calculation assuming a morbidity of 5%, with a desired precision estimate of 4% and a 95% confidence interval. Using these parameters, the sample size was determined to be 115 cases. All analyses were performed using Statistical Package of Social Sciences version 26.0 (SPSS, IBM Corp.). A p-value < 0.05 (two sided) was considered significant. Normality was verified using the Kolmogorov-Smirnov test. Descriptive statistics were reported as medians with range for non-parametric data and as means with standard deviation (SD) for parametric data. Normally-distributed continuous data were tested using Student's T-test. Non-parametrical continuous data were compared using the Mann-Whitney U test. Categorical data are summarized as frequencies with proportions.

RESULTS

Of the 138 eligible patients, 118 were included in the analysis following assessment by the expert panel and review of the histological specimen, if indicated (Figure 1).

Figure 1.
Patient enrollment



In group 1, 66 of the 80 (85.5%) eligible patients were included. Seven patients were excluded based on expert panel assessment and a further 7 patients withdrew from the study for various reasons (e.g., the patient did not undergo CAL-WR or declined to participate in the study). All patients in group 2 were included in the analysis. Of the 24 eligible patients in group 3, 2 patients were excluded after histologic revision and 4 patients withdrew from the study, leaving 18 patients in total.
In 56% of included patients the indication for CAL-WR was an endoscopically-unresectable colonic polyp (group 1), 29% of patients had a residual/recurrent lesion after previous endoscopic removal (group 2) and the remaining patients (15%) had an undetermined resection margin after endoscopic removal of a low-risk pT1 tumour (group 3). The mean age was 66 years (SD ± 8 years), the majority of the patients were male (56%) and most patients (82%) had an American Society of Anaesthesiologists physical status (ASA) of 1 or 2.[28] Almost half of the lesions were located in the caecum. The median size of lesions in groups 1 and 2 was 20 mm [range 5 – 50 mm].

Table 1. Baseline characteristics

	n = 118 (%)
Mean age, years (SD)	**66 (± 8)**
Gender	
Male	66 (56)
ASA*	
1	19 (16)
2	78 (66)
3	21 (18)
Previous abdominal surgery	**20 (17)**
Indications	
Endoscopically-unresectable polyp	66 (56)
Residual adenomatous tissue after prior polypectomy	34 (29)
Irradical resected low-risk pT1	18 (15)
Localization lesion	
Caecum	52 (44)
Ascending colon & hepatic flexure	27 (23)
Transverse colon	11 (9)
Descending colon & splenic flexure	7 (6)
Sigmoid colon	21 (18)
Size of the lesions, per indication [median with range]	
Endoscopically-unresectable polyp, size in mm	20 [range 5 – 50]
Residual adenomatous tissue after prior polypectomy	20 [range 5 – 50]

* American Society of Anesthesiologists physical status

An overview of the baseline characteristics is presented in Table 1.
Successful CAL-WR was performed in 110 of the 118 patients (93%). When a lesion was located in the caecum the technical success rate was 96%, and in twenty-seven of the fifty (54% (n = 27/50)) successfully performed CAL-WR procedures, the polyps showed ingrowth into the appendix. CAL-WR was not considered suitable in 8 patients, 3 of whom had lesions in the rectum, in contrast to an earlier endoscopically estimated location in the sigmoid colon. In two of these cases transanal minimally invasive surgery (TAMIS) was performed, while the other patient underwent endoscopic full-thickness resection (eFTR) during the same procedure. The fourth patient exhibited lesional ingrowth into the ileum, but due to severe comorbidity a CAL-WR was performed in this patient with acceptance of irradicality. Stenosis of the colon was observed in the fifth patient during CAL-WR, due to the earlier endoscopic removal of a colonic polyp. The surgeon therefore converted to a segmental colonic resection. During CAL-WR in the sixth patient endoscopic suspicion of a deep invasive carcinoma arose, for which a right hemicolectomy was performed during the procedure. In the seventh patient a colonic polyp was found close to the mesentery, precluding proper positioning of the linear stapler and the surgeon therefore decided to perform a hemicolectomy. In the remaining patient the surgeon was not able to tension the suture sufficiently to ensure correct positioning of the linear stapler and

Table 2.
Technical success of colonoscopic-assisted laparoscopic wedge resection in patients scheduled for CAL-WR

	Indication CAL-WR			
	Overall	**Endoscopically - unresectable polyp**	**Residual adenomatous tissue**	**Irradical low risk pT1**
	n = 118 (%)	**n = 66 (%)**	**n = 34 (%)**	**n = 18 (%)**
Technical success	110 (93)	63 (95)	31 (91)	6 (89)
Location successful CAL-WR#				
Caecum	50/52 (96)	35/36 (97)	14/15 (93)	1/1 (100)
Ascending colon & hepatic flexure	25/27 (93)	13/14 (93)	8/9 (89)	4/4 (100)
Transverse colon	10/11 (91)	7/7 (100)	3/4 (75)	-
Descending colon & splenic flexure	7/7 (100)	4/4 (100)	2/2 (100)	1/1 (100)
Sigmoid colon	18/21 (86)	4/5 (80)	4/4 (100)	10/12 (83)
CAL-WR not performed				
Reason:	8 (7)	3 (6)	3 (9)	2 (11)
Rectal lesion	3	1	-	2
Ingrowth in ileum[1]	1	-	1	-
Stenosis due to prior endoscopic resection	1	-	1	-
Suspicion of carcinoma	1	1	-	-
Lesion close to mesentery	1	-	1	-
No tension on suture possible	1	1	-	-
Converted into:				
TAMIS	2	1	-	1*
eFTR ^	1	-	-	1
LEAWR with acceptance of irradicality[1]	1	-	1	-
Right-sided hemicolectomy	4	2	2	-

CAL-WR – Colonoscopic-Assisted Laparoscopic Wedge Resection
* TAMIS = Transanal Minimally Invasive Surgery
^ eFTR = endoscopic Full-Thickness Resection
[1] CAL-WR was performed with acceptance of irradicality

the procedure was therefore converted to a right-sided hemicolectomy (Table 2). The patients who successfully underwent a CAL-WR (n = 110) had an overall complication rate of 6%, all of which were minor (Clavien-Dindo grade I-II) and neither reintervention nor mortality was observed. The mean operation time was 58 minutes [range 20 - 138 minutes] and the overall median length of hospital stay after CAL-WR was 2 days [range 1 - 5 days] (Table 3). One patient had an additional segmental resection 5 weeks after CAL-WR due to complaints of a stenosis of the colon. Amongst the 110 patients with a successful CAL-WR, 69% (n = 76) had benign histology, 20% (n = 22) malignant histology, all these CRCs were judged benign by the gastroenterologist as well as the expert panel prior to surgery. Eleven percent (n = 12) showed no residual tumour (following a previous uncertain margin after endoscopic removal of a low risk pT1 carcinoma). Radical resection was performed in 91% of patients who successfully underwent a CAL-WR (n = 110/118). R_1 resection was carried out in 3%. In group 1, radical resection was carried out in 87% and R_1 resection in 5% of patients. In group 2, the radicality rate was 94% and in group 3, 100%. The radicality rate did not differ between lesions up to 30 mm and lesions greater than 30 mm (90% versus 92%, p = 0.78) (Table 4).

Invasive cancers were diagnosed in 22 patients (20%), 13 of whom had a pT1 tumour, all of which were R_0 resections. T2 carcinomas were found in 7 patients, 5 of which were R_0 resections (71.4%). The remaining two patients with invasive cancer showed a T3 carcinoma, both of which were resected with radical margins. Three of the twenty-two aforementioned patients underwent resection of a scar after previous removal of a low-risk pT1 (group 3), so size of the resected lesion was not applicable and these 3 cases were therefore excluded from the analysis of lesion size. The other 19 cases of invasive lesions were divided, based on size of the colonic polyp, into two groups: (1) lesions smaller or equal to 25 mm (n = 12) and (2) lesions larger than 25 mm (n = 7). Although numbers were small, there was no difference in R_0 resection rates (92% vs. 86%, p = 1.00) (Table 4). An additional oncological segmental colon resection was performed in 12 patients. In 10 patients the indication for the resection was based on high-risk features after histological examination. In one patient an additional oncological resection was performed due to a carcinoma in another polyp not treated in this study. The remaining patient underwent an additional resection, 5 weeks after CAL-WR, following complaints of a stenosis of the colon (Table 4).

Table 3.
Clinical outcome CAL-WR

	n = 110 (%)
Overall complications	**7 (6)**
Minor complications (CDG I-II)	**7 (6)**
Urinary retention	2
Urinary tract infection	1
Surgical site infection	1
Readmission due to pain	1
Opioid intoxication	1
Paralytic ileus	1
Major complications (CDG* III-IV)	-
Median length of stay [range], days	**2 [1-5]**
Median operating time [range], minutes	**58 [20-138]**

* CDG = Clavien Dindo Grade of complications

Of the 110 patients who underwent a successful CAL-WR, 12 required additional oncological surgical resection and therefore had no indication for follow-up endoscopy after 6 months. Of the remaining 98 patients with an indication for follow-up endoscopy, follow-up was conducted in 87 (89%). The median interval between CAL-WR and follow-up endoscopy was 9 months [range 2 – 32 months] and a CAL-WR scar could be identified in almost 80%. In 4 patients (5%) macroscopic recurrent tissue was found during follow-up endoscopy (Table 5) and 3 of these patients underwent R_0 resection of the CAL-WR, one of which concerned a lesion with ingrowth into the appendix. In two patients the indication for a CAL-WR was a difficult location of the lesion, and in the remaining patient the indication was a non-lifting colonic polyp. All four cases with recurrence were confirmed by histological examination of the resected residue. The residue was treated by cold snare endoscopic mucosal resection (EMR) in all four cases (Table 6).

Table 5.
Follow-up endoscopy

	Overall n = 98* (%)
Follow-up endoscopy	87 (89)
Missing	11
Patient died^	1
Patient refused FU#	4
No FU due to COVID-19	4
Lost to follow up	2
Median interval between CAL-WR and FU# [range], months	9 [2 - 32]
Scar CAL-WR identified?	
Yes	69/87 (79)
Macroscopic residual tissue	4/87 (5)

^ patient died 2.5 months after CAL-WR due to a cerebrovascular accident
# FU = follow-up endoscopy

Table 4.
Histologic outcome of 110 CAL-WR specimens

		Indication CAL-WR		
	Overall n = 110 (%)	**Endoscopically unresectable polyp** n = 63 (%)-	**Residual adenomatous tissue** n = 31 (%)	**Irradical low-risk pT1** n = 16 (%)
Histologic outcome				
SSA/P* no dysplasia	15 (13.5)	12 (19)	3 (10	-
SSA/P LGD^	3 (3)	1 (2)	2 (6)	-
SSA/P HGD°	2 (2)	2 (3)	-	-
Adenoma LGD	41 (37	22 (35)	19 (61)	-
Adenoma HGD	15 (13.5)	11 (17)	3 (10)	1 (6)
T1 carcinoma	13 (12)	10 (16)	1 (3)	2 (13)
Low-risk	12	9	1	2
High-risk	1	1	-	-
T2 carcinoma	7 (6)	4 (6)	3 (10)	-
T3 carcinoma	2 (2)	1 (2)	-	1 (6)
Scar tissue	12 (11)	-	-	12 (75)
Radicality, overall				
R0 resection	100 (91)	55 (87)	29 (94)	16 (100)
Rx resection	7 (6)	5 (8)	2 (6)	-
R1 resection	3 (3)	3 (5)	-	-
Radicality by size				Not applicable[$]
Lesion </= 30mm	79	53	26	
R0 resection	71 (90)	48 (90)	23 (88)	
Rx resection	5 (6)	3 (6)	2 (8)	
R1 resection	3 (4)	2 (4)	1 (4)	
Lesion > 30mm	13	8	5	
R0 resection	12 (92)	7 (88)	5 (100)	
Rx resection	1 (8)	1 (12)	-	
R1 resection	-	-	-	
Size of polyp missing	2	2	-	

Radicality in case an invasive lesion was found	22 (20)			
T1 carcinoma				
R_0 resection	13	10	1	2
T2 carcinoma				
R_0 resection	5	3	2	-
R_x resection	1	1	-	-
R_1 resection	1	-	1	-
T3 carcinoma				
R_0 resection	2	1	-	1
Radicality by size in cases with colon cancer				**Not applicable[$]**
Lesion </= 25mm	12	10	2	
R0 resection	11 (92)	10 (100)	1 (50)	
Rx resection	-	-	-	
R1 resection	1 (8)	-	1 (50)	
Lesion > 25mm	7	5	2	
R0 resection	6 (86)	4 (80)	2 (100)	
Rx resection	1 (14)	1 (20)	-	
R1 resection	-	-	-	
Invasive lesions found in scar of 'irradical low-risk pT1' (size not applicable)	3			
Additional oncologic segmental colon resection	12/110 (11)			
Indication				
T1 carcinoma, high-risk	1	1	-	-
T2 carcinoma	7	4	3	-
T3 carcinoma	2	1	-	1
Another CRC[#]	1	1	-	-
Stenosis	1	-	1	-

[*] SSA/P = sessile serrated adenoma/polyp
[^] LGD = low-grade dysplasia
[°] HGD = high-grade dysplasia
[#] CRC = colorectal cancer
[$] Not applicable because original size of polyp is not representative for radicality of removal of scar from a 'irradical low-risk T1'

Table 6.
Macroscopic residual tissue during follow-up endoscopy

	Indication for CAL-WR	Size of resected polyp[$] (mm)	Location CAL-WR	Histologic outcome CAL-WR	Histologic outcomes FU# endoscopy	Treatment of the recurrence
Case 1	Difficult location of polyp	50	Transverse colon	Adenoma LGD, R^0 resection	Adenoma LGD	Cold snare EMR
Case 2	Non-lifting polyp	10	Transverse colon	Adenoma LGD, R^0 resection	Adenoma LGD	Cold snare EMR
Case 3	Difficult location of polyp	30	Splenic flexure	Adenoma LGD, R^x resection	Adenoma LGD	Cold snare EMR
Case 4	Growth into appendix	15	Caecum /appendix	SSA/P without dysplasia, R^0 resection	SSA/P without dysplasia	Cold snare EMR

[$] endoscopically estimated by gastroenterologist
[#] FU = follow-up endoscopy

DISCUSSION

This prospective multicentre study shows that CAL-WR is a safe and feasible technique for the resection of colonic polyps not amenable to conventional endoscopic resection. CAL-WR has a low morbidity rate, with only 6% minor complications, a high technical success rate (93%) and a radical resection rate of 91%. In the present study, recurrent lesions were found in only 4 patients (5%).

The number of advanced adenomas and early T1 cancers with referrals for surgical treatment of these lesions has increased substantially due to the implementation of national colorectal cancer screening programs in many countries.[3] CAL-WR appears to fill the gap between endoscopic resection and more advanced surgical procedures, which are accompanied by higher morbidity (24%) and mortality (2%) rates.[13]

In the present study only 11% of patients underwent additional oncological segmental resection, indicating that segmental colectomy could be prevented in all other cases. Moreover, CAL-WR appears cost-effective compared to laparoscopic segmental resection.[29]

To date, few studies have described the use of various combined endoscopic laparoscopic surgery (CELS) techniques.[16-20] Reported technical success rates from available literature range from 95% to 100%[16,18-20], comparable to our technical success rate of 93%. Accurate endoscopic judgement regarding lesion location is necessary to select the appropriate patients for CAL-WR, which may in turn result in an even higher technical success rate. In 3 patients in our study, polyps with reported locations in the sigmoid were actually found in the rectum. Furthermore, one polyp showed ingrowth into the ileum and another polyp was judged to be suspicious for a deep invasive carcinoma.

A recent systematic review of CELS involving 101 patients showed no intra- or postoperative complications.[17] Another recent retrospective cohort study (n = 115 patients) showed Clavien-Dindo grade I-II complications in 13% of patients after CELS.[30] In that study, both CAL-WR and another form of CELS such as laparoscopy-assisted endoscopic resection (LAER) was performed. Therefore, the reported 6% morbidity rate in our study appears acceptable, especially in a multicentre design. Successful CAL-WR in the current study resulted in an overall radical resection rate of 91%, and no significant difference was found in resection rates for lesions < 30 mm or > 30 mm. Radical resection rates after CAL-WR in other studies range from 75% to 100%.[16,18,20] None of the previous CAL-WR studies reported recurrence at follow-up endoscopy.[16,18-20] In our study, recurrent adenomatous tissue was detected at follow-up colonoscopy in 5% of cases. In one case the pathologist found loose

adenomatous cells in the staple margin, while the primary resection margin was free of adenomatous tissue. We hypothesize that manipulation of the lesion in this case, either by placing of the suture and/or closure with the stapler, caused adenomatous cells to become embedded in the staple margin. Careful manipulation of the lesion during CAL-WR as well as follow-up endoscopy is therefore strongly recommended. A CAL-WR scar could be identified in 80% of the follow-up colonoscopies and placing a tattoo opposite the CAL-WR site would further improve the scar detection at follow-up endoscopy.

Endoscopic full-thickness resection (eFTR) using an over the scope clip is another relatively new full-thickness technique for the treatment of complex colonic neoplasms. The overall technical success rate of eFTR varies between 84% to 94%[5,31-34], while the complication rate ranges from 9.3% and 14%. The most commonly reported complications are secondary appendicitis, bleeding and traumatic wall lesions. In 2% to 3.5% of cases surgical reintervention is needed to treat complications.[5,31-34] The reported complication rate of eFTR is higher (9.3% – 14%) compared to CAL-WR (6%), as demonstrated by our study. A relatively common complication after eFTR is a secondary appendicitis close to the appendiceal orifice, which requires surgical reintervention. CAL-WR is particularly suitable for these cases, as 27 patients in our study (25%) had a lesion with ingrowth into the appendix, all of which could be treated without complication.

The radical resection rates for eFTR and CAL-WR are similar and vary from 72% to 90% and from 72% to 100%, respectively.[5,16,18,20,31-34] However, the use of eFTR is restricted to lesions of less than 20 mm by the size of the cap.[5,31,33,34] In our study, the median size of lesions was 20 mm [range 5 – 50 mm], indicating that lesion size is less of a limitation compared to eFTR. The recently described Dutch eFTR colorectal registry reported residual/recurrent lesions in 6.4% of patients,[5] while other eFTR studies reported a recurrence/residual rate of between 5.8% and 13.5%.[31-34] Unfortunately, details on whether the primary resection in these cases was complete (R_0 resection) was not provided in these studies.[5,33,34]

Strengths of our study included the multicentre prospective design and the relatively large number of included patients, while the use of expert panels and follow-up with colonoscopy increased external validity. A limitation of our study was that 11% of follow-up colonoscopies have yet not been performed due to COVID-19-related restrictions. Therefore, the actual recurrence rate might be somewhat higher and the long-term outcome of the study is still awaited. Another limitation can be the location of the polyp close to the mesentery, which may preclude placing of the linear stapler and dissection of the colon from the mesentery should

be avoided to prevent necrosis of the colon. Another limitation could be the bowel insufflation during CAL-WR, making the surgery difficult. For this reason, it is important to do the colonic mobilization before insufflation and to use CO_2 because it resolves faster. Future research should focus on the long-term outcomes of CAL-WR, especially concerning malignant neoplasms. Differences in costs between advanced endoscopic removal techniques and CAL-WR should also be taken into account.
In conclusion, CAL-WR is a safe, feasible and organ-preserving technique. CAL-WR should therefore be considered a primary treatment strategy for patients with colonic neoplastic lesions that cannot be removed endoscopically. Furthermore, a specific indication could be polyps with ingrowth into the appendix.

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part III
MANAGEMENT OF ADVANCED COLORECTAL NEOPLASMS

CHAPTER 8

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ABSTRACT

BACKGROUND

In patients with stenosing colorectal cancer (CRC), visualization of the entire colon prior to surgery is recommended to exclude synchronous tumors. Therefore, most centers combine computed tomographic colonography (CTC) with staging CT. The aims of this study were to evaluate the yield and clinical implications of CTC.

METHODS

In this multicenter retrospective study, patients with stenosing CRC that underwent CTC and subsequent surgery between April 2013 and November 2015 were included. Result of the CTC, its influence on the surgical treatment plan, and final histology report were evaluated.

RESULTS

One hundred sixty-two patients with stenosing CRC were included. Nine (5.6 %) synchronous cancers proximal to the stenosing tumor were suspected with CTC. In four of nine patients, the CTC did not change the primary surgical plan because the tumors were located in the same surgical segment. In five of nine patients, CTC changed the surgical treatment plan. Three of these five patients underwent an extended resection and the presence of the tumors was confirmed. Two of these three synchronous CRCs were also visible on abdominal staging CT. In the other two patients, the result of CTC was false positive which led to an unnecessary extended resection in one patient.

CONCLUSION

The yield of CTC was relatively low. In only three patients (1.9 %), CTC correctly changed the primary surgical plan, but in two of them, the tumor was also visible on abdominal staging CT. Moreover, in two patients, CTC was false positive. The clinical value of CTC in stenosing CRC appears to be limited.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer related death in the Western world [1]. In 2012, 471.000 new cases were diagnosed in Europe and 134.000 in the USA [1]. In more than half of the cases, the tumor is located in the left part of the colon [2]. At the time of presentation, 45 % of symptomatic patients have metastatic disease [3].

Of all patients with CRC, 15–20 % present with stenosing CRC. In these patients, colonoscopy might fail to diagnose synchronous tumors proximal to the stenosing cancer which may result in secondary surgery [4–8]. A synchronous tumor is reported in 1–7 % of the patients with CRC [9–11]. In two thirds of the cases, both tumors are located in the same surgical segment [10, 12].

Computed tomographic colonography (CTC) is developed as a non-invasive tool for the detection of CRC and polyps as an alternative to colonoscopy. CTC is highly sensitive (96 %) in the screening for CRC [13–15]. In patients with stenosing CRC, Park et al. demonstrated a sensitivity of 100 % of CTC in the detection of proximal synchronous CRC and moderate sensitivity (88.6 %) in detecting proximal synchronous adenomas, including advanced adenomas. Specificity was 69.8 and 78.8 % for the detection of CRC and adenomas, respectively [16].

In patients with stenosing CRC, CTC is recommended by most authorities to exclude synchronous CRC [17–20]. Two previous studies described a change in primary surgical plan because of CTC in respectively 14 and 16 % of patients with stenosing CRC due to location errors, synchronous adenomas, or synchronous carcinomas [21, 22]. However, in most cases of stenosing CRC, the tumor is in T-stage 3 or 4 and therefore visible on regular staging CT, that is nowadays performed in all patients with CRC prior to surgery. Furthermore, improved endoscopic techniques may prevent patients from unnecessary performed surgery because of (advanced) synchronous adenomas or early carcinomas. The aims of our study were to evaluate the yield and added clinical implications of CTC in patients with stenosing CRC.

MATERIALS AND METHODS

This multicenter retrospective observational cohort study was performed in three Dutch hospitals: Isala in Zwolle, Leiden University Medical Center (LUMC) in Leiden and Slingeland hospital in Doetinchem. Patients were included between 1 April 2013 and 1 November 2015. The study was approved by the institutional ethical committees.

Patients

In this study, stenosing CRC is defined as colorectal cancer diagnosed with colonoscopy and not able to pass by the endoscopist due to stenosing of the lumen by the tumor. Subsequently, the colon proximal to the tumor is not inspected. Obstructive CRC is defined as colorectal cancer presenting with symptoms requiring emergency surgery or stent placement. Preoperative endoscopy with adequate inspection of the colon mucosa in these patients is not possible.

All patients with CRC were discussed in the multidisciplinary CRC team. Patients that underwent incomplete colonoscopy due to stenosing CRC followed by preoperative CTC and subsequent surgical resection were included. Symptomatic patients that presented with obstructive CRC and subsequently underwent emergency surgery without preoperative colonoscopy and CTC and patients that did not undergo surgical resection because of advanced disease were excluded. Figure 1 presents a flowchart of included and excluded patients. Data on sex, age, tumor location, cancer stage, result on abdominal CT, outcome of CTC, and type of surgery as well as data on the postoperative colonoscopy were collected. A change in primary surgical plan was defined as a surgical procedure other then would be performed for stenosing CRC only.

Preoperative imaging

Most patients who complied with the inclusion criteria underwent colonoscopy and a combined CTC with abdominal and thoracic staging CT. In some patients (i.e., patients with abdominal pain), an abdominal CT had already been performed prior to colonoscopy. In these patients, additional CTC and thoracic staging CTwere performed. Tumor location with colonoscopy and CTC (i.e., rectum, sigmoid, descending colon, splenic flexure, transverse colon, hepatic flexure, ascending colon, and caecum) was documented. All CT images were analyzed by experienced

CTC technique

CTC examinations were performed using Philips Ingenuity CT in Isala, Siemens Somatom in Slingeland and Toshiba Aqcuilion One in LUMC (Table 1).

Participants received bowel preparation consisting of 3 × 50 mL of iodinated contrast agent (Telebrix Gastro) on the day prior to CTC combined with a low fiber diet for 1 day. Immediately before CT scanning, 2 mL scopolaminebutyl (20 mg/mL) was injected intravenously and colon distension was achieved with an automatic CO2 insufflator using a rectal catheter. CTC images were obtained with the patient in prone and supine position. Abdominal and thoracic staging was performed during

Table 1.
CTC protocol Isala, LUMC and Slingeland hospital

	Isala	LUMC	Slingeland
Type CT scan	Philips Ingenuity CT 256 slices	Toshiba Aqcuilion One (320 slice)	Siemens Somatom Definition AS 64-slice configuration
Scan parameters			
- Collimation (mm)	128 x 0.625	320 x 0.5	64 x 0.6
- Beam pitch	0.899	-	0.9
- Rotation time (sec)	0.75	0.5	0.5
- Slice thickness (mm)	0.9	1	-
- Tube voltage (Kv)	100	120	120
- mAs with z modulation	85	-	55
Scan delay (sec)	70	50	58
Iodinated contast	Optiray 350	Ultravist 370	Iomeron 300
- Total amount (ml)	125	90-170*	105-150
- rate (mL/sec)	4	2.4-4.4*	2-3.9*

* depends on body weight. CT Computed Tomography, LUMC Leiden University Medical Center.

portal venous phase and during arterial phase after intravenously administering of iodinated contrast. CTC software reconstructed 2-dimensional (2D) and 3-dimensional (3D) images of the bowel. In Isala and Slingeland hospital, 2D and 3D reading strategy were used, in LUMC 2D, strategy only.

CTC computed-aided diagnosis (CAD) system was used as an automatic warning system for bowel wall abnormalities.

Statistics

Descriptive statistics were performed using Statistical Package of Social Sciences version 23 (SPSS). True-positives were defined as tumors detected by CTC and confirmed by surgery and pathological examination. False positives were tumors detected by CTC, but not confirmed by surgery or follow-up.

RESULTS

Patient characteristics

In the multidisciplinary team, 1473 patients with CRC were discussed. One thousand three hundred eleven patients (89 %) were excluded because of various reasons complete preoperative colonoscopy performed (n = 997), incomplete colonoscopy not due to stenosing CRC (n = 80), emergency surgery necessary (n = 58), preoperative CTC not performed (n = 143), no surgical resection performed due to advanced disease (n = 33) (Fig. 1). A total of 162 patients (male n = 85, 52.4 %) with a median age of 71 ± 10 years complied the inclusion criteria.

CTC quality

No complications of CTC were described. In two cases, CTC did not succeed due to poor bowel distension. In the remaining 160 patients, in 131/160 patients (80.9 %) CTC could be assessed reliable as reported by the radiologist. In 29 patients, CTC quality was poor due to inadequate bowel distension (n = 21), large amount of weakly tagged fecal matter (n = 6) or an unknown reason (n = 2).

Synchronous CRC

In nine patients (5.7 %), a proximal synchronous CRC was suspected on CTC. In three patients, abdominal CT was performed before CTC. In these three cases, the synchronous tumor was already visible on abdominal CT. The time interval between abdominal CT and CTC ranged from 5 to 14 days.

Table 2 provides detailed information about age, sex, tumor location, tumor stage, outcome of CT, change in primary surgical plan, type of surgery, CTC outcome, and time between abdominal CT and CTC of the nine synchronous tumors. In four of nine patients with synchronous tumors on CTC, the findings of CTC did not change the primary surgical plan. In one of them, the synchronous tumor was already described on the previously performed staging CT scan. In the other three patients, the tumor was located within the scheduled resection (i.e., a right-sided (extended) hemicolectomy in all of them) (Table 2, patients 6–9). Histological examination confirmed synchronous CRC in three of four patients; in the fourth patient (Table 2, patient no. 7), a 35-mm tubulovillous adenoma was diagnosed in the proximal colon.

In five of nine patients with synchronous tumors on CTC, the CTC changed the surgical treatment plan. In three of these five patients, an extended resection was performed and definitive histology showed three synchronous adenocarcinomas (Table 2, patients 3–5). Two of these were T3 tumors that were also visible on abdominal CT; the third was a T2 tumor and in this patient, a combined CTC with abdominal and

Figure 1.
A flowchart of included and excluded patients

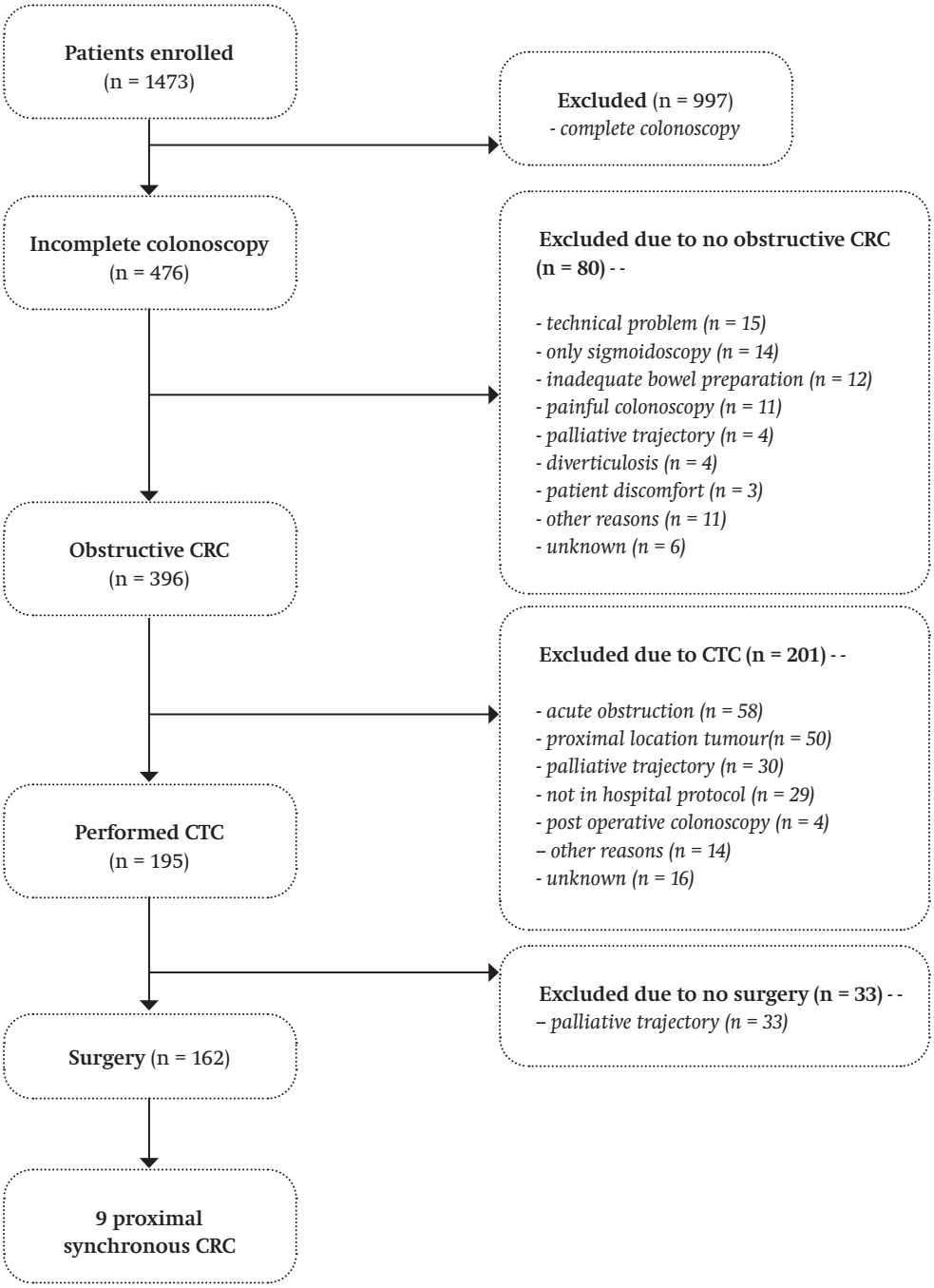


Table 2.
Detailed information on 9 synchronous double tumors suspected by CTC

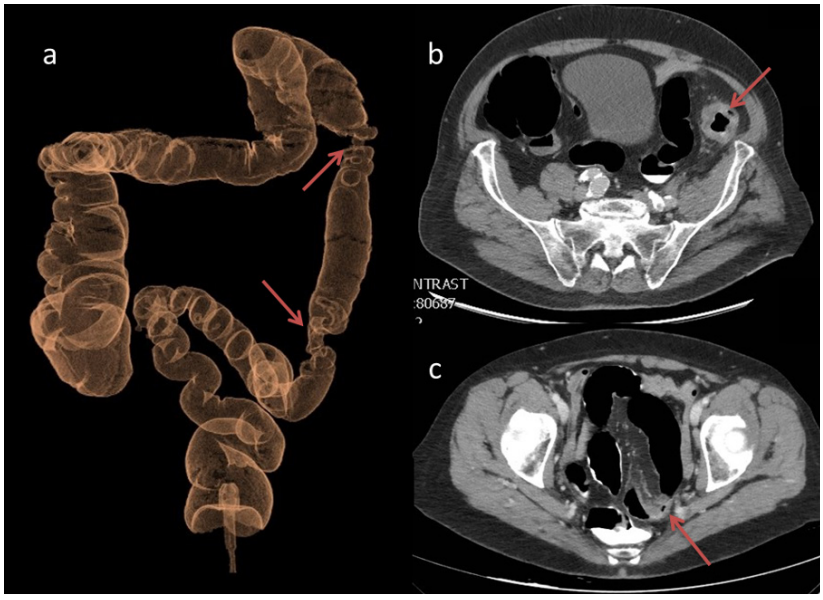
Tumor Number	Age (y)	Sex	Site of tumors detected by CTC†	TNM-stage†	Visible on previous abd CT	Modification primary surgical plan	Type of surgery performed	CTC outcome CTC	Days between and CT abdomen
# 1	86	M	sigmoid + descending	pT3N0	not performed	yes, extended resection	left-sided hemicolectomy	false positive	-
# 2	58	F	sigmoid + ascending	pT3N0	not performed	yes, extended resection	right-sided hemicolectomy	false positive	
# 3	89	M	descending+ ascending	pT3N2 + pT3N2	yes	yes, extended resection	extended right-sided hemicolectomy	true positive	5
#4	69	F	sigmoid + caecum	pT3N1 + pT3N0	not performed	yes, extended resection	extended resection	true positive	-
#5	71	M	sigmoid + caecum	pT3N0 + pT2N0	not performed	yes, extended resection	subtotal colectomy	true positive	
#6	90	F	transverse+ transverse	pT3N0 + pT2N0	yes	no	extended right-sided hemicolectomy	true positive	14
#7	80	M	hepatic flexure + ascending of 35 mm	pT3N2 + advanced adenoma	not performed	no	right-sided hemicolectomy	true positive	-
#8	67	M	transverse + ascending	pT3N0 + pTisN0	yes	no	extended right-sided hemicolectomy	true positive	6
#9	62	M	sigmoid + descending	pT3N1 + pTxNx*	not performed	no	Left-sided hemicolectomy	true positive	-

† First location is the obstructive distal tumor. * no pathology, tumor was left behind by mistake. y years, CTC Computed Tomographic Colonography, abd =abdominal, CT Computed tomography, p pathologically

thoracic staging was performed. In the other two of five patients (Table 2, patients 1 and 2), the result of CTC was false positive and consequently an unnecessary extended resection was performed in one patient (Fig. 2a, b). In the other patient, only one tumor was detected during surgery. In this patient, a stenosing sigmoid tumor was described with colonoscopy. CTC suspected a synchronous CRC in the ascending colon. However, during surgery, no tumor was palpable in the sigmoid and endoscopic ink patterns were not found in the sigmoid, but in the ascending colon, the suspected sigmoid tumor with colonoscopy was actually located in the ascending colon. Subsequently, the surgeon decided to perform a right-sided hemicolectomy only. In this patient, the false positive result of the CTC led to an open procedure instead of a laparoscopic procedure (Fig. 2c). Postoperative surveillance colonoscopy in this case showed no abnormalities.

Figure 2.
CTC images of both false positive CTCs. Red arrows indicate the suspected tumors on CTC.

- **a. 3D image of patient number 1, tumor in sigmoid and false tumor in descending colon.**
- **b. 2D image of patient number 1, false tumor in descending colon.**
- **c. 2D image of patient number 2, false tumor in sigmoid**



Postoperative colonoscopy

To date, 49 of 162 (30.2 %) patients have undergone postoperative surveillance colonoscopy. The interval between surgery and postoperative colonoscopy varied from 25 days to 2 years, and the mean interval was 8.3 months. No metachronous CRC was detected at first surveillanc colonoscopy.

DISCUSSION

Most current guidelines recommend preoperative CTC in patients with stenosing CRC [17–20]. Our multicentre retrospective study evaluated the added clinical value of this recommendation. We demonstrated the clinical value of CTC to be very limited. In 3 out of 162 patients, CTC was meaningful in terms of detection of a second primary CRC that changed the primary surgical treatment strategy. However, two of these tumors were also detected on the abdominal CT leaving an Badded value^ in only 1 out of 162 (0.6 %) patients with stenosing CRC. Moreover, in two patients, the CTC was false positive leading to an unnecessary extended resection in one patient.

Previous studies reported stenosing CRC in 15–20 % of the cases and synchronous tumors in 1–7 % [4–11]. CT colonography has similar sensitivity as colonoscopy in detecting CRC and has moderate sensitivity in detecting advanced adenomas [13–15]. Park et al. demonstrated a high sensitivity of CTC for detection of proximal synchronous tumors, but limited capability of CTC in differentiating advanced adenomas from CRC in patients with stenosing CRC [16].

Preoperative CTC has some advantages when compared to colonoscopy performed 3 months after primary surgery: (1) CTC could prevent the need of secondary surgery in case of a synchronous tumor and (2) it could prevent growing of secondary tumors into a more advanced stage when detection and treatment are delayed. But CTC has also some disadvantages: (1) it is another burden for patients, (2) synchronous tumors are often already visible on regular staging CT, (3) sensitivity of CTC is lower in stenosing CRC due to technical difficulties associated with stenosing CRC, and finally, (4) the technique is not able to differentiate between large adenomas and CRC and between T1 and T2 tumors that could result in unnecessarily performed extended resections in some patients that could have been treated endoscopically [16, 23].

In three cases (1.8 %), the scheduled type of surgery had been changed and a more extended surgery was performed. However, in two of these cases, previous performed abdominal CT already showed the second tumor. Two previous studies described a change in surgical plan in 14–16 %, due to location errors, synchronous CRC, or synchronous adenomas [21, 22]. In these studies, the primary surgical plan

was changed in 4 and 11 % due to location errors. However, tattooing colorectal tumors during endoscopy is currently standard of care, which limits the role of CT scan in determination of the location anyway. Moreover, most stenosing tumors are at stage T3 or T4 (for instance in our study in 90 % of the patients) and might therefore likely have been visible on abdominal staging CT, which is performed nowadays in all patients prior to surgery. The presence of a previous performed abdominal CT was not mentioned in these studies. CT colonography can be useful in detecting synchronous CRC and synchronous adenomas. In the abovementioned studies, the detection of synchronous CRC or adenomas changed the surgical plan in 10 (7.3 %) and 5 (4.1 %) patients, respectively. Obviously, most adenomas can be removed endoscopically but also early (T1) carcinomas could be attempted to be removed endoscopically first. The stage of the synchronous tumors was not mentioned in above described studies. In our study, in one of the four patients with suspected synchronous CRC but no change in the primary surgical treatment plan, the postoperative histology showed no synchronous CRC but a proximal 35-mm tubulovillous adenoma.

Another possible disadvantage of CTC is the consequence of a false positive result. In this study, CTC was false positive in two patients (1.2 %) and the second primary tumor detected by CTC was not confirmed during surgery and at histological examination. This resulted in an unnecessary extended resection in one patient. In the other patient, no tumor was manifested during surgery. In both false positive CTCs, only 2D images were evaluated and suspected for a synchronous CRC at initial diagnosis (Fig. 2). In retrospect, reassessment of these CTCs in 2D by the radiologist, the result of CTC was similar as at initial diagnosis; however, endoluminal 3D images were not suspect for a second tumor and also the CAD system had not warned for an abnormality.

Our study has some limitations. First of all, it has a retrospective design. Secondly, the number of synchronous CRC was relatively low, although the numbers are larger than reported in previous studies. Thirdly, not all surveillance reports were available because they were performed in other surrounding hospitals. Therefore, it cannot be ruled out that postoperative surveillance endoscopies did reveal CRC where CTC was (false) negative. Finally, in Isala and Slingeland hospital, both 2D and 3D reading strategy were used. Some radiologists viewed only 2D images, some used both strategies. In LUMC, only 2D reading strategy was used. Although a large study showed no significant difference between 2D and 3D reading strategy, CTCs might be false positive using 2D reading strategy only as shown in our study [24].

In conclusion, CTC is highly sensitive in detecting proximal synchronous tumors in patients with stenosing CRC according to previous studies. However, our data

suggest very limited clinical benefit of CTC in patients with stenosing CRC and also potential harm in terms of unnecessary extended surgery. In view of our results, a colonoscopy performed, for instance at an interval of 3 months after curative surgery, appears to be a good alternative if full attention is paid to detect synchronous cancers on staging CT. Future prospective studies should
be performed to address the question which strategy is the most optimal for patients with stenosing CRC.

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CHAPTER 9

Tolerability of capecitabine monotherapy in metastatic colorectal cancer, a real-world study

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Drugs in R&D, 2017.

ABSTRACT

BACKGROUND

Capecitabine monotherapy is a treatment option for selected patients with metastatic colorectal cancer (mCRC) and is administered to up to 17% of patients. Data are limited regarding adverse events and dosing practices associated with capecitabine monotherapy in real- world situations.

OBJECTIVES

To provide real-world data on adverse event rates and dose adjustments/discontinuations associated with capecitabine monotherapy in patients with mCRC.

METHODS

This retrospective study analyzed data from CRC patients scheduled to receive up to 8 planned cycles of capecitabine monotherapy between 2009 and 2013 at a single large community hospital in the Netherlands. Data on adverse events (hand-foot syndrome (HFS), gastrointestinal events (GIEs), hematological adverse events, and cardiotoxicity) as well as relative dose intensities, dose reductions, and discontinuations were evaluated.

RESULTS

Data from 86 patients (45 female, mean age at start of treatment 69 years) were included. A total of 46.5% of patients experienced HFS and 44.2% experienced a GIE at some time during treatment. Hematological events and cardiotoxicity were rare. Most patients (77%) started at below the recommended dose and patients at the lowest dose also had the lowest median relative dose intensities. Dose reductions and discontinuations occurred in 15% - 25% of patients who experienced HFS or GIE over the course of 8 cycles.

CONCLUSIONS

HFS and GIEs were very common in patients treated with capecitabine monotherapy in a real-world clinical setting. Most patients started treatment at below the recommended dose and 15% - 25% of patients who had HFS or GIE had a dose reduction or discontinuation.

INTRODUCTION

Fluoropyrimidine monotherapy is a recommended chemotherapeutic treatment option for patients with metastatic colorectal cancer (mCRC) who are frail or may not tolerate more aggressive therapy [1–3]. Oral capecitabine provides a convenient alternative to the standard intravenous fluoropyrimidine, 5-fluorouracil. In clinical trials, oral capecitabine monotherapy has been shown to be as effective as intravenous 5-fluorouracil as first-line treatment for mCRC, and is generally associated with an improved safety profile with lower rates of stom- atitis, alopecia, diarrhea, nausea, and grade 3/4 neutropenia [4–7]; however, reported rates of hand-foot syndrome (HFS) are higher with capecitabine. HFS is characterized by erythema, dysesthesia and/or paresthesia of the palms of the hands or soles of the feet. In more advanced stages, desquamation, ulceration, and blistering can occur. HFS occurs in approximately 54% of patients (17% grade 3/4) who receive capecitabine treatment [4, 6–8]. Grade 3/4 hyperbilirubinemia is also higher with capecitabine and occurs in approximately 23% of patients [4, 6, 7]. The approved regimen for capecitabine is 1250 mg/m^2 twice daily for 14 days, followed by 7 days off [9]. In phase III trials, 34% of patients received a reduced dose due to the occurrence of adverse events [4].

In phase III trials including older patients ([70 years of age), who represent a key group in which capecitabine monotherapy may be indicated, grade 3/4 adverse events occurred in 12–22% of patients, including grade 3/4 HFS, diarrhea, venous thromboembolism, neutropenia, throm- bocytopenia, and hemorrhage [8, 10]. Eighteen percent of elderly patients experience dose delays due to adverse events while receiving capecitabine monotherapy and 15% discontinue treatment due to adverse events [8, 10]. Most real-world studies of physician prescribing pat- terns in mCRC have focused on the impact of effective biologic and combination treatments that have extended survival in mCRC in recent years [11–13]. These analyses of retrospective data of treatment patterns have reported that 9–17% of patients receive capecitabine monotherapy as first-line treatment, 5–9% as second-line treatment, and as many as 17% receive this regimen as third-line treatment [11–13]. An observational study of capecitabine-based therapy in routine first-line treatment of mCRC reported that 56% of patients received capecitabine-based treat- ment—54% of these as combination therapy and 46% of these as monotherapy. Of patients who received monotherapy, 65% were older than 75 years of age [14]. Rates of grade 3/4 adverse events associated with capeci- tabine monotherapy were highest for HFS, bilirubin ele- vation, anemia, and neuropathy, which all occurred in 4% of patients [14].

Despite these few studies, real-world data are limited with regard to the adverse events and dosing practice associated with oral capecitabine monotherapy in mCRC in the oncology clinic. While realizing its inherent limitations, this study sought to provide real-world data on the occur- rence of adverse events in patients treated with capecitabine monotherapy for mCRC at a single large community hospital.

METHODS

This was a single-center, retrospective study of patients treated at a large community hospital in Zwolle, The Netherlands, for mCRC. Data were collected for toxicity in relation to dose and exposure time for patients diagnosed with adenocarcinoma. We limited our period of analysis to the planned eight cycles (±6 months) of capecitabine monotherapy, as recommended in the Dutch pharma- cotherapeutic guidelines for capecitabine monotherapy in mCRC. In these guidelines, capecitabine monotherapy is considered a good option when no immediate response is needed (for instance in case of relatively limited tumor load), or in patients who are deemed too frail to start with combination therapy.

Institutional Review Board approval was obtained for this retrospective analysis, and key data that were collected included capecitabine dose by cycle; adverse event data for hematological events (neutropenia, leukopenia, thrombo- cytopenia, anemia), cardiac events (angina pectoris, heart failure, myocardial infarction, arrhythmia/conduction dis- order, myocarditis, ECG changes), hand-foot syndrome, and gastrointestinal (GI) events (diarrhea, nausea, vomit- ing, constipation, mucositis, abdominal pain, stomatitis, loss of appetite); and dose reductions and discontinuations. Patient data were excluded if the patient received anti- cancer therapy other than capecitabine, and only the first eight cycles of therapy were retained for patients who received more than eight cycles of therapy or an additional eight cycles at a later start date.

For the adverse event analyses, patients were counted if they had the adverse event concerned and if they had a dose reduction or discontinuation of treatment during that cycle. The cause of dose reduction or discontinuation was not explicitly stated to be the adverse event in question but was tracked for the patients who had that adverse event in that cycle. Discontinuation in cycle 8 could be due to adverse events, progression, or simply the end of planned treat- ment. This analysis has not looked beyond eight cycles, but some patients were treated for much longer than eight cycles.

Relative dose intensity (RDI) was calculated for each patient to determine the dose received relative to the planned schedule to dose over eight cycles. Receipt of the starting dose for eight cycles represented 100%. Reduced doses were scored

based on their relative proportion of the starting dose. For example, if 1250 mg/m^2 twice daily was the starting dose, then a reduction to 1000 mg/m^2 was scored as 80% of the dose for that cycle, and a reduction from 1000 to 750 mg/m^2 was scored as 75% of the dose for that cycle. RDI was calculated as the number of cycles at the starting dose plus the number of cycles at a reduced dose (e.g. four cycles x 1.0 + four cycles x 0.8) divided by eight total cycles.

RESULTS

Data for 86 patients (45 female, 41 male; mean age at start of treatment, 69 years [range 45–83]; 57% C70 years of age) treated with capecitabine monotherapy for mCRC between 2009 and 2013 were analyzed for side effects occurring during eight planned cycles of treatment. A total of 355 patients started palliative systemic therapy for mCRC at our center during this time period. Twelve patients started cycle 1 with a dose of 750 mg/m^2 twice daily (mean age 64.4 years), 54 patients started at a dose of 1000 mg/m^2 twice daily (mean age 71.5 years), and 20 patients started at a dose of 1250 mg/m^2 twice daily (mean age 67 years). In total, 35 patients were still taking cape- citabine in cycle 8 (Table 1), of whom 49% were on the lowest dose. A total of 41% of patients completed at least four cycles of therapy at the starting dose, and 21% com- pleted eight cycles of therapy at the starting dose. The numbers of patients on the lowest dose stayed relatively constant or increased as patients moved from higher doses in the later cycles of therapy.

Table 1.
Number of patients starting each cycle by dose

Cycle	750 mg/m^2	1000 mg/m^2	1250 mg/m^2	Total
1	12	54	20	86
2	11	47	18	76
3	12	40	12	64
4	15	27	10	52
5	5	22	8	45
6	16	19	7	42
7	16	14	7	37
8	17	11	7	35

Relative Dose Intensity

A box plot of the RDIs for all 86 patients included in the study is shown in Fig. 1. The median RDIs for patients who started at the 750, 1000, and 1250 mg/m^2 twice-daily doses were 37.5, 67.2, and 68.75%, respectively. Twenty-five percent of patients at the 750 mg/m^2 twice-daily dose received 100% of the planned dose compared with 18.5% of patients at the 1000 mg/m^2 twice-daily dose, and 30% of patients at the 1250 mg/m^2 dose.

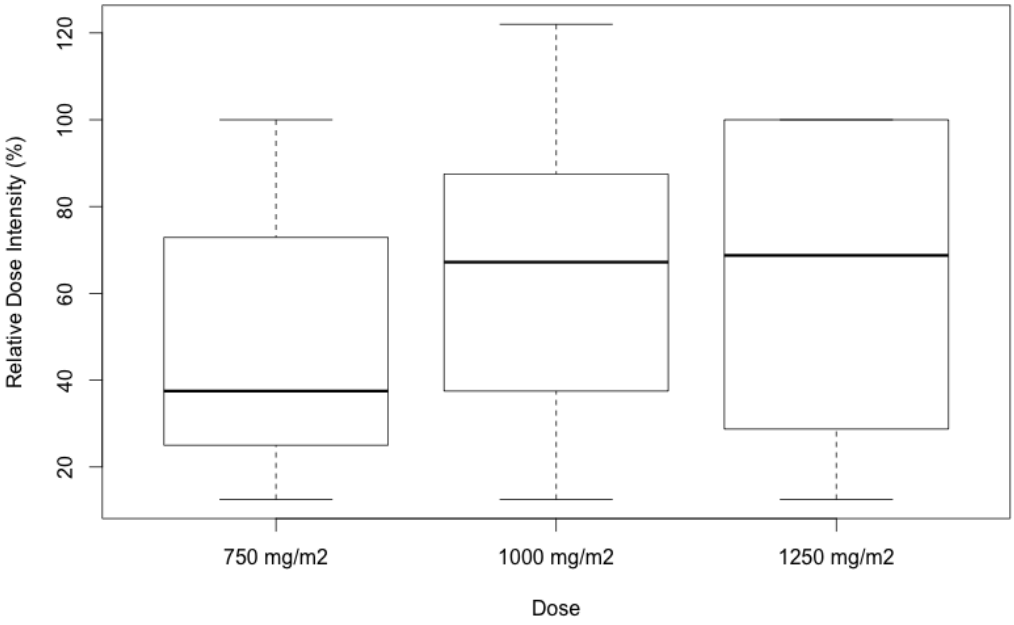

Figure 1. Relative Dose Intensities

Rates of Hand-Foot Syndrome

HFS events were common in all cycles and at all dose levels. A total of 46.5% of patients experienced HFS at some time during treatment (Fig. 2a). Newly developing HFS was observed in all cycles, and persistent or recurrent HFS events were responsible for 54.5% of total HFS events (n = 88 events). HFS events appeared to increase

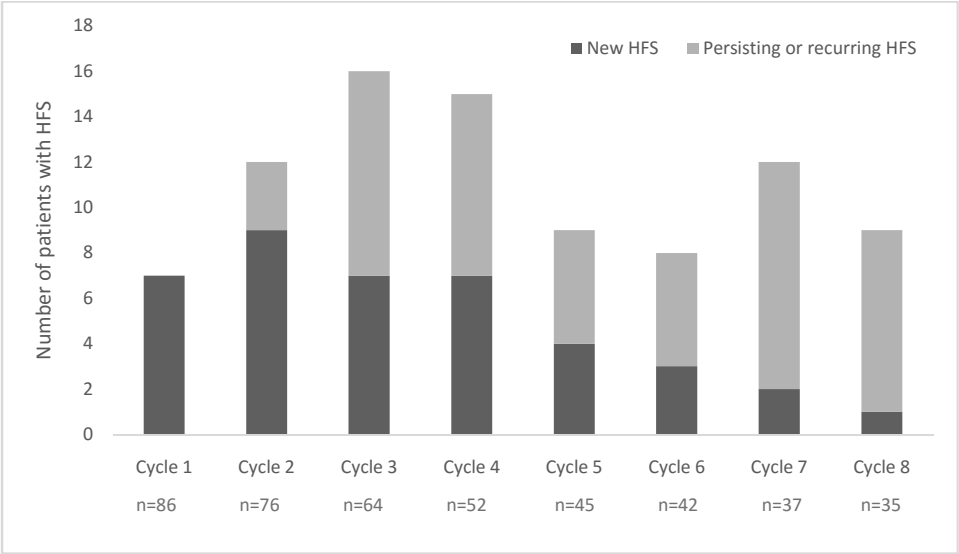

Figure 2a. Rates of hand-foot syndrome (HFS) by cycle, all patients (n=86)

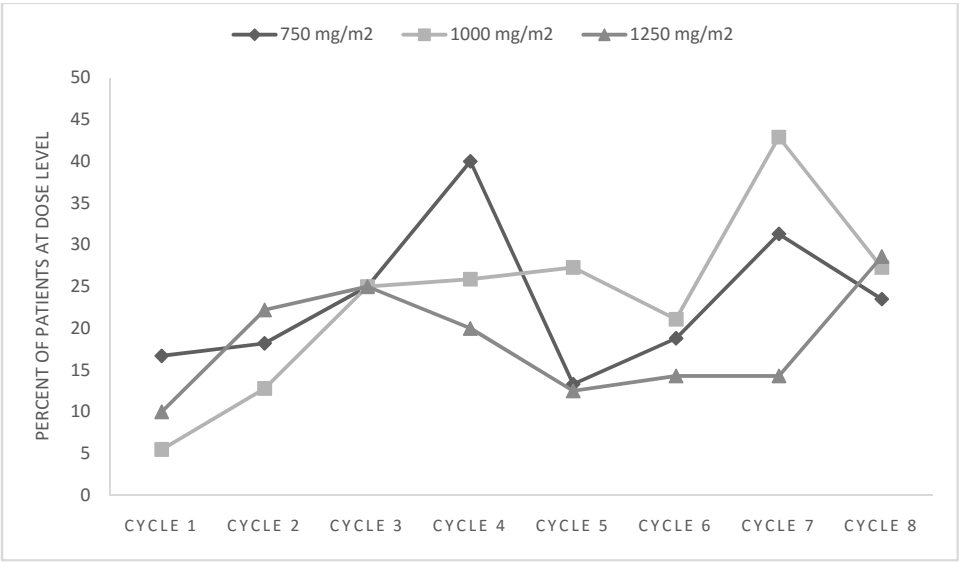

Figure 2b. Rates of HFS by cycle according to dose (twice daily)

over time for patients at all three doses (Fig. 2b), which is most clearly seen at the 1000 mg/m^2 dose. After the first cycle (8.1% HFS reported), 15–32% of patients reported HFS in each cycle. Over the course of eight cycles, 22 patients had dose

reductions and 15 discontinued treatment during a cycle in which they reported HFS, often within four cycles of treatment (Table 2).

Table 2.
Number of dose reductions of discontinuations in patients reporting HFS by cycle

Cycle	Patients with HFS Events[a]	Reduction	Discontination
1	7	1	2
2	12	2	1
3	16	6	2
4	15	3	4
5	9	2	1
6	8	1	1
7	12	4	1
8	9	2	3
Total	88	21	15

[a]new, persisting or recurring HFS events

Rates of Gastrointestinal Adverse Events

GI events were common in all cycles (Fig. 3a), and most first-time events were in the first three cycles. A total of 44.2% of patients experienced a GI adverse event at some time during treatment. In any given cycle, between 14 and 25% of patients reported GI events. Persistent or recurring GI events accounted for 54.8% of total GI events (n = 84 events). Evaluation of GI events by dose level showed that more patients at the 750 mg/m^2 dose level experienced GI events in later cycles, while these events were less common for patients at the 1000 mg/m^2 dose level and were not observed for patients at the 1250 mg/m^2 dose in cycles 4–8 (Fig. 3b). Over the course of eight cycles, 13 patients had dose reductions and 21 discontinued treatment during a cycle in which they reported a GI event (Table 3). Most of these treatment modifications were performed in the first four cycles of capecitabine therapy. The most common GI events were diarrhea, nausea, vomiting, and abdominal pain (Table 4).

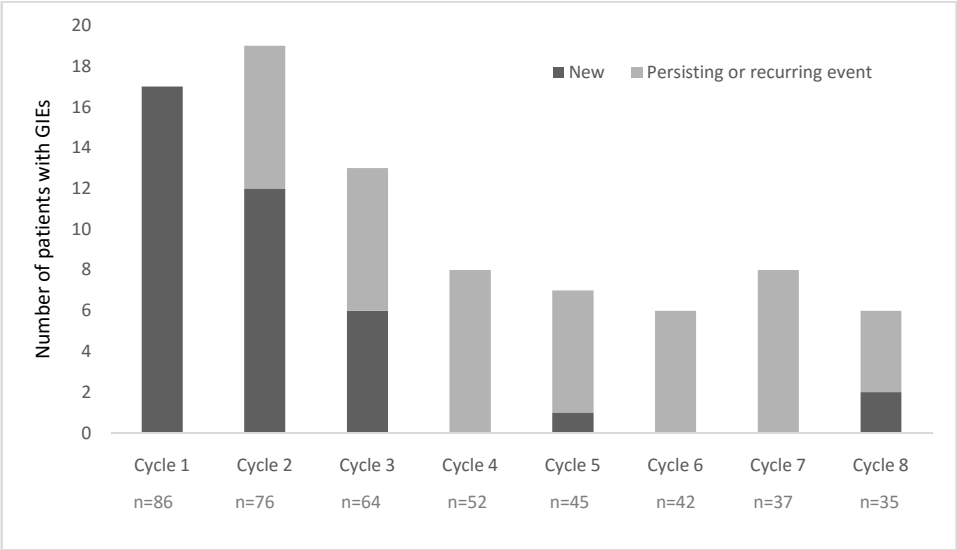

Figure 3a. Rates of gastrointestinal events by cycle, all patients (n=86)

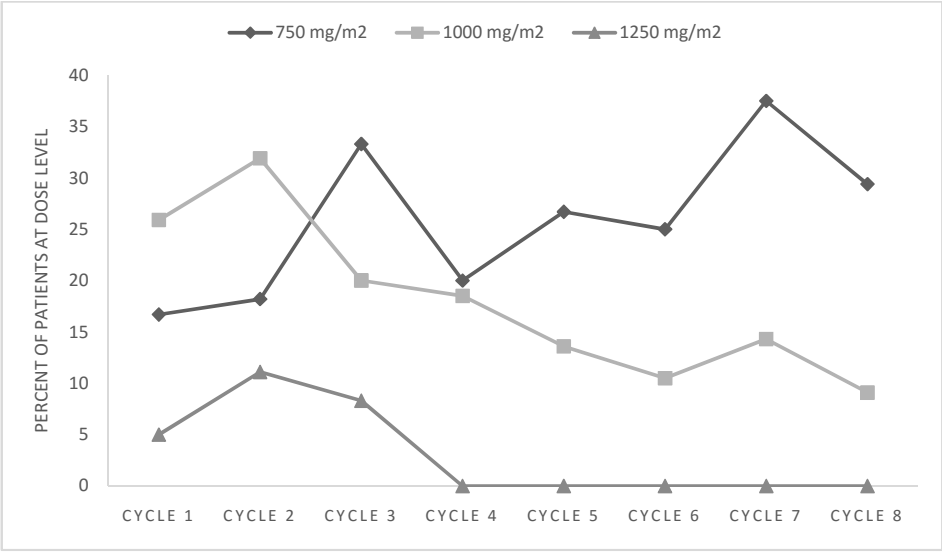

Figure 3b. Rates of gastrointestinal events by cycle according to dose (twice daily)

Table 3.
Number of dose reductions of discontinuations in patients reporting gastrointestinal events by cycle

Cycle	Patients with GI Events[a]	Reduction	Discontination
1	7	3	1
2	19	3	7
3	13	2	4
4	8	1	3
5	7	1	0
6	6	0	1
7	8	3	1
8	6	0	4
Total	84	13	21

[a]new, persisting or recurring GI events

A comparison of the total percentage of patients affected by either HFS or a GI event over eight cycles is shown in Fig. 4.

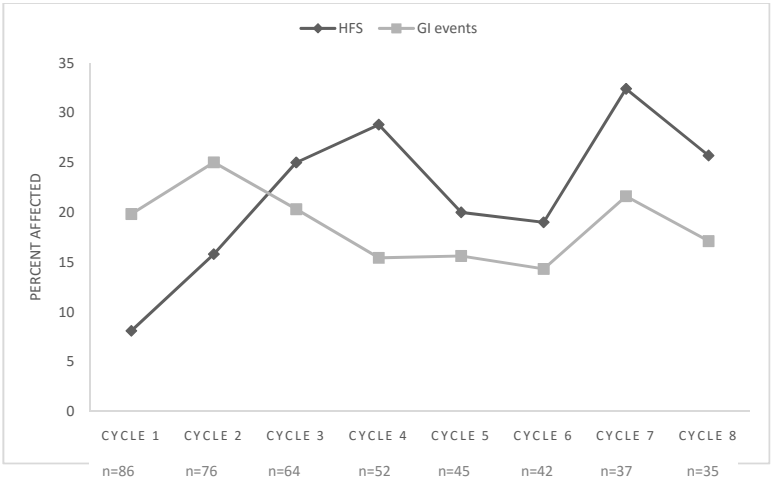

Figure 4. Rates of gastrointestinal (GI) events and hand-foot syndrome (HFS) by cycle, all patients (n=86)

Table 4.
Gastrointestinal Events by Type (n=86)

Event type	n (%)*
Diarrhea	21 (24.4)
Nausea	21(24.4)
Vomiting	17(20.0)
Abdominal Pain	16(18.6)
Constipation	5(5.8)
Stomatitis	3(3.5)
Decreased appetite	1(1.2)

*numbers represent all patients who had that gastrointestinal event in any cycle but not recurrent events

Rates of Hematological and Cardiac Adverse Events

Six hematological adverse events occurred in five patients during the first four cycles of therapy. One patient at the 1250 mg/m^2 dose had neutropenia in cycle 1 that was treated with a dose interruption and dose reduction to 1000 mg/m^2 in cycle 2. The patient experienced neu- tropenia again in cycle 2 but without dose adjustments. One patient each at the 1000 mg/m^2 dose experienced leukopenia and thrombocytopenia in the third cycle. Leukopenia was managed with a dose interruption in that cycle and the thrombocytopenia was managed with a dose reduction to 750 mg/m^2. One patient at the 750 mg/m^2 dose experienced anemia in cycle 2, and one patient at the 1000 mg/m^2 dose experienced anemia in cycle 4. The patient discontinued in this cycle but the recorded data did not explicitly state that anemia was the cause.

Six cardiotoxicity events were reported in five patients (mean age 71 years), i.e. chest pain, unregulated heartbeat, atrial fibrillation with pulmonary embolism, dyspnea on exertion and cough, arrhythmia/conduction disorder. Five of these were at the 1000 mg/m^2 dose, and atrial fibrillation recurred in one patient who had been reduced to the 750 mg/m^2 dose in a different cycle. There was one dose reduction and one discontinuation among patients who reported a cardiac adverse event for that cycle.

DISCUSSION

An important and ongoing point of attention influencing treatment outcomes for cancer patients is the tolerability of chemotherapeutic drugs. This is even more important in the palliative setting. The gold standard in clinical research is to investigate these questions in randomized controlled clinical trials but these are expensive and cumbersome trial designs and are rarely suitable for assessing daily practical questions. A good alternative to get more insight into these types of questions is with so-called real-world studies. In this real-world study, a retrospective analysis was per- formed on data from patients treated for eight planned cycles of therapy with a commonly used chemotherapeutic drug (capecitabine) for mCRC. We chose to analyze only patients receiving capecitabine monotherapy to reduce unwanted interactions and influence by other anticancer drugs in the treatment. We were able to evaluate the rates of adverse events in patients for whom treatment was selected based on each patient's clinical situation and personal preference in real-world oncology treatment decision-making situations rather than based on selective clinical trial inclusion criteria.

In this study, we have evaluated dosing adjustments and adverse events in patients treated with capecitabine monotherapy for mCRC. We evaluated rates of occurrence and persistence of HFS, GI events, hematological adverse events, and cardiotoxicity over the course of eight sched- uled cycles of capecitabine monotherapy and rates of dose reductions and discontinuation. The rates of adverse events reported in this study are similar to those of reported clinical trials of capecitabine monotherapy. The rate of HFS in this study (46.5% overall) is consistent with rates observed in phase III clinical trials of 30–53.5% [4, 8, 10] and with the rate of 42% reported in an observational study that included patients who received capecitabine as monotherapy or in combination treatment [14]. The rate of GI events in this study was 44.2%; previous studies have reported that between 11 and 50% of patients experience one GI event, including diarrhea, vomiting, nausea, or abdominal pain, while receiving capecitabine monotherapy [4, 8, 10]. Our results are consistent with these findings. Neutropenia, observed in only one patient in this study (1.1%) has been reported to occur in 1% of patients in clinical trials [4, 8]. Rates of other hematological adverse events were also low in this study, similar to previous studies [4, 8, 10]. Cardiotoxicity, observed in 5% of patients in this study, was either very rare (approximately 1%) or not reported due to occurring at lower than the 5% threshold for reporting in previous studies [4, 8, 10]. It was not possible to establish if this difference could be explained by the current population being more frail than those described in previous controlled trials.

Most patients in this study (77%) started under the approved dose of 1250 mg/m^2 twice daily, 63% started at 1000 mg/m^2 twice daily, and 14% started at 750 mg/m^2 twice daily. Of note, the reduced starting doses used here are not the recommended reduced starting doses for special populations (75% of starting dose for renal impairment) [9], and phase III trials evaluated a starting dose of 1250 mg/m^2 twice daily or used 1000 mg/m^2 twice daily in elderly patients C70 years of age [4, 8, 10]. Patients in this study who received the 1000 mg/m^2 twice-daily dose had a mean age of 71.5 years, consistent with age as an explanation for the use of this reduced dose. However, patients in the study who received 750 mg/m^2 twice daily had a mean age of 64.4 years, suggesting that this population was considered frail by their physician. Although this suggests that physi- cians are reducing the starting dose of capecitabine in anticipation of adverse events, our real-world data did not provide an explicit explanation for these treatment decisions.

Dose reductions and treatment discontinuations were common in this study, occurring in 17–24% of patients who experienced HFS and 15–25% of patients who expe- rienced a GI event. Dose reductions or cessation of treat- ment most likely due to adverse events occurred predominantly within the first four cycles of therapy. Timely recognition and management of the clinically rel- evant HFS and GI toxicity is therefore of utmost impor- tance in order to prevent early termination of treatment.

Cassidy et al. reported that 34% of patients starting treatment at 1250 mg/m^2 twice daily required a dose reduction for adverse events, while Cunningham et al. reported that 15% of elderly patients who started capeci- tabine treatment at 1000 mg/m^2 twice daily discontinued due to adverse events [4, 8]. In addition, Feliu et al. reported that dose delays occurred in 18% of elderly patients treated with capecitabine 1250 mg/m^2 twice daily [9]. In our analysis, the occurrence of HFS and GI events was not related to the dose of capecitabine, which may suggest that lower starting doses and dose reductions do not improve adverse event rates, nor do they prevent them from occurring. In an observational study by Stein et al., the incidence of HFS increased with duration of treatment and was higher in younger patients than in older patients (46 vs. 37%; p = 0.0014) despite similar median daily doses of capecitabine [14].

It is unclear whether dose reductions might negatively impact efficacy outcomes. Cassidy et al. reported a similar risk of disease progression in patients who required dose modification while receiving capecitabine monotherapy compared with those

who did not, while patients who required dose modifications while taking 5-fluorouracil/ leucovorin had a 12% higher risk of disease progression [4]. Stein et al. reported that patients who experienced HFS had higher response rates, progression-free survival (PFS), and overall survival (OS) than patients without HFS. The authors postulated that a trend in improved PFS and OS in patients who received a capecitabine dose reduction might be related to the occurrence of HFS in this population [14].

This study provides some insights into the clinical decisions that were considered necessary in the best interests of the patient and what impact these decisions had on the dosing and schedule of capecitabine. However, there were significant limitations of this study, including its small size, its retrospective nature and lack of control group, and the quality of the real-world data we were able to obtain. The patient record data used in this study often did not include clear reasons for treatment discontinuation or dose reductions, therefore these could not be directly correlated to adverse events. In addition, they did not include consistent information on the grade of adverse events, which would have been informative.

CONCLUSION

This study has provided important information on the rates of adverse events and dosing practices in patients sched- uled to be treated with eight cycles of capecitabine monotherapy for mCRC in a real-world setting. The most frequently occurring adverse events were HFS and GI toxicity. These adverse events often led to dose reductions or even termination of treatment, possibly impairing the benefit of fluoropyrimidines in these patients. This infor- mation should be of value to practitioners who treat patients with mCRC, particularly older or frail patients.

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Compliance with Ethical Standards

Conflict of interest Jan Willem B. de Groot and Wilko Coers have received consulting fees and/or honorarium for writing support from Nordic Pharma International. Laura W. Leicher, Metin Tascilar, and Jacques C. de Graaf have not received any financial or other support.

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part IV
SUMMARY AND DISCUSSION

CHAPTER 10

In the first part of this thesis, we focus on the management of hereditary colorectal cancer.

CHAPTER 2 concerns a retrospective observational study in two large hospitals that aimed to evaluate the proportion of individuals with a positive I-FOBT in the Dutch population screening program that fulfil criteria for familial/hereditary CRC. Another goal was to evaluate the proportion of patients that need further genetic analysis based on their personal and family history and/or endoscopic findings.

A total of 657 individuals with a positive I-FOBT test underwent colonoscopy, 120 of whom (18.3%) were found to have a positive family history for CRC, 20 (3.0%) fulfilled criteria for familial colorectal cancer (FCC), 4 (0.6%) the revised Bethesda guidelines and in one case (0.2%) the Amsterdam Criteria. Multiple adenomas (>10) were found in 21 (3.2%) participants. No cases of serrated polyposis were identified. Based on the current guidelines, a total of 35 (5.3%) required referral to a clinical geneticist and the relatives of 20 (3.0%) participants were referred for surveillance colonoscopy.

More (pilot) studies have been performed to identify familial CRC in individuals that participate in a I-FOBT population screening. A study, performed by Dekker et al. in 2011 in the Netherlands, showed that 17% of the participants with a positive I-FOBT in the CRC screening program had a positive family history of CRC.[1] The percentage we found in our study was comparable with the percentage found by Dekker et al. Another pilot study, conducted in 2006 in Australia, reported a positive family history for CRC in 19.6% of subjects that participated in a I-FOBT screening program.[2] This is also similar with the percentage we found of 18,3%. Although both studies showed that a substantial proportion of individuals with a positive I-FOBT result had a positive family history for CRC, detailed information on the family history and the level of CRC risk was lacking. Also, the identification of polyposis syndromes was not addressed.

Making optimal use of the patient contact arising from the screening program is very important to identify high risk groups (patients with familial CRC and their families). Our study demonstrates that a proportion of the patients need further genetic testing and surveillance colonoscopies. Several previous studies have showed that the identification of individuals with familial cancer and Lynch syndrome is suboptimal.[3] A previous Dutch study estimated that in The Netherlands 100.000 individuals are at risk for familial or hereditary colorectal cancer but currently only a small proportion of these individuals has been recognized.[4] The age distribution of CRC in familial CRC (50-75 years) is almost similar as the patients that are invited for the

Dutch population screening program (55-75 years).[5] The prognosis of patient with familial CRC and their families will improve when de identification is more optimal. Earlier detection of advanced adenomas can prevent the evolution into a CRC. Approximately 95% of CRCs will evolve from an adenomatous polyp or sessile serrated lesion. Despite the dysplastic character of the polyp, only 5% of all adenomatous polyps progresses to CRC in "average risk" individuals.[6] But a recent surveillance study among 550 patients with familial CRC showed that the prevalence of advanced adenomas was two-fold higher than reported in "average risk" individuals.[5] Literature showed that colonoscopic surveillance led to a reduction of CRC by 80%.[7]

In this study we demonstrated that a nationwide population screening program, such as the I-FOBT program in the Netherlands, may not only improve the prognosis of patients with CRC and prevent the development of CRC but also may identify high risk individuals by obtaining a detailed family history. Detection of patients with a positive family history improves care for these patients and their family members. It is therefore essential to document family history of CRC during the routine intake before colonoscopy. In the current era of the electronic patient file, making this a standard part of the report should not be a problem.

In **CHAPTER 3** we performed a multicentre, retrospective study to evaluate whether MMR deficiency (dMMR) testing leads to (1) identification of LS, (2) a change in surgical treatment and (3) changes to systemic therapy in patients with dMMR CRC.

Analysing the outcome of dMMR testing in 225 CRCs, we identified 24 (11%) MMR-deficient CRC patients. Of these patients, 18 (75%) were referred to a clinical geneticist and a pathogenic MMR variant was identified in 9 (37%). One (4%) of the 24 patients underwent a subtotal colectomy, while the chemotherapy regimen was adjusted in 7 (35%) of 20 patients with an MMR-deficient tumour.

Only 4% of all patients selected for MSI analyses or MMR testing were found to have LS which is lower compared with results of a previous study which reported LS in 9.2% of pre-selected patients, using the revised Bethesda criteria.[8] The lack of an adequate referral procedure may be the explanation that in our study 25% of the patients did not receive proper genetic counseling. Literature showed a low compliance with referral of 35,7%, when the surgeon is being responsible to refer the patient. Compliance with the referral was higher when the clinical geneticist was responsible for initiating conversations about further genetic counseling.[9] Further research Is needed to identify possible barriers to visit the clinical geneticist ro finally improve compliance with the referral as also suggested by Irons et al.

In 2011, Parry et al. investigated the risk of developing metachronous CRC in

MMR gene mutation carriers. Cumulative risk of metachronous CRC was 16% (95% CI 10–25%) at 10 years, 41% (95% CI 30–52%) at 20 years and 62% (95% CI 50–77%) at 30 years after segmental colectomy. These risk estimates could help in the decision-making regarding the extent of primary surgical resection.[10] A subtotal colectomy is recommended according to the current guidelines in patients with evidence for LS and age <60 years. In our study only one patient (4%) underwent a subtotal colectomy instead of hemicolectomy based on a suspicion of LS due to MMR deficiency and a young age (42 years) at diagnosis of CRC. After surgery, a MSH2 mutation was identified. This low number is due to the fact that only 4 of 24 patients were under age 60 years. In addition, the majority of MSI/IHC were performed on the resected specimen (139 of total 225 (61.7%)) instead of on the biopsies. Due to the possible consequences on the surgical treatment, it is preferable to perform MMR testing preoperatively on the biopsies.

There is an increasing amount of evidence that adjuvant chemotherapy with 5-FU in patients with a stage II or III CRC with MMR-defective tumours does not improve the prognosis. A study of 754 CRC patients showed an improvement of survival in patients who received adjuvant chemotherapy with 5-FU only in patients with a MMR-competent tumor. Overall survival of patients with MMR-deficient tumors did not improve with adjuvant 5-FU monotherapy.[11] In our study, in 7 (35%) of the 20 patients who had an indication for adjuvant chemotherapy, the initial planned treatment with 5-FU monotherapy was changed due to MMR deficiency. The MMR status of a CRC is becoming increasingly important due to implications regarding the choice of chemotherapy and immunotherapy. Chalabi et al. showed major pathological responses (<5% viable tumour cells) and a 57% complete response rate in patients with dMMR CRC treated with neo-adjuvant ipilimumab and nivolumab.[12] Together with excellent immunotherapy results in dMMR metastatic CRC reported by Overman et al., these are a very promising developments.[13] To ensure optimal treatment decisions in CRC patients, MSI or IHC analysis should be performed in all patients with CRC < 70 yrs and in patients with CRC > 70 yrs in case there might be an indication for (neo-)adjuvant chemotherapy.

In conclusion, MSI and IHC analysis resulted in identification of LS patients, a patient that needed extended colorectal surgery and a substantial number of patients that required adjustment of the chemotherapy protocol. The study also demonstrated that a substantial proportion of the patients (25%) were not referred to the clinical geneticist. A systematic discussion of the result of MSI/IHC should be incorporated in a multidisciplinary meeting and also, who is responsible for the referral to the clinical geneticist, to improve the referral of patients with MMR-deficient tumor.

In **CHAPTER 4** we retrospectively investigated the proportion of LS patients currently tested for *Helicobacter pylori* infection and addressed the question of whether *H. pylori* infection is more prevalent in LS families with known cases of gastric cancer.

Of the 443 (male, 184) proven mutation carriers included, 206 (46%) were screened for *H. pylori* and 42 (20%) were found to be positive. Of the patients ascertained as mutation carriers before 2010, 37% was screened for *H. pylori*. After 2010, this percentage increased to 68%. Family history was available for 356 mutation carriers, 25 of whom had at least one first-degree family member with gastric cancer, while seven had more than one first-degree relative with gastric cancer. The *H. pylori* infection rate in patients with a first-degree relative was 20%.

This is the first study to report the outcome of *H. pylori* screening in a large series of LS mutation carriers. We found a *H. pylori* infection in 20% of the mutation carriers, a proportion that is similar to the general population.[14,15] The recommendation to screen for *H. pylori* has been operative since 2010, and the proportion of patients being tested increased from 37% before 2010 to 68% after 2010. Assuming *H. pylori* is an important risk factor in the development of gastric cancer in Lynch patients, we expected to find a higher infection rate in mutation carriers with a positive family history, as *H. pylori* clusters within families.[16,17] However, the proportion of patients affected with *H. pylori* in this group was similar to the *H. pylori* infection rate in the total group.

H. pylori is a proven carcinogen in the general population, but it's role in the pathogenesis of gastric cancer in Lynch syndrome is still unknown. The fact that gastric cancer in mutation carriers occurs more frequently in countries with a higher prevalence of *H. pylori* infection coupled with fact that the incidence of gastric cancer in the general population in Western countries has decreased parallel to the decline of *H. pylori* infection, strongly suggest an important role for this bacterium in the carcinogenesis.

The recommended screening for *H. pylori* is increasingly followed. To prove the effectiveness of this guideline, a large prospective randomized study in LS families would be necessary. However, a meta-analysis showed that even in low-prevalence countries (America, Canada, UK, and Finland), screening the general population for *H. pylori* was cost-effective in the prevention of gastric cancer.[18] Taking into consideration the results of this meta-analysis and the high risk of developing of gastric cancer in LS families, screening of LS patients would also be beneficial.

In the second part of this thesis, we focus on the treatment of early colorectal neoplasms.

CHAPTER 5 concerns the level of referrals for surgical resection of colon polyps and the type of surgery following the introduction of the national bowel screening program in the Netherlands in 2014. The included patients underwent surgery for colorectal polyps between January 2012 and December 2017 in Isala in Zwolle, The Netherlands. The exclusion criterion was histologically proven carcinoma prior to surgery. Primary outcomes were number and type of surgical procedures for polyps.

In total, 164 patients were included. An annual increase in the number of referrals for surgical resection for colorectal polyps was observed, rising from 18 patients in 2012 to 36 patients in 2017. We divided the included patients into two subgroups, (1) patients who underwent an segmental resection and (2) patients who underwent organ preserving surgery. The following surgical procedures felt into the latter group: transanal endoscopic microsurgery (TEM), limited endoscopic-assisted wedge resection (LEAWR). Procedures performed before the implementation of the screening program were exclusively segmental resections, whereas after implementation 58.8% of procedures were organ-preserving surgical procedures. The overall complication rate for organ-preserving surgery was 16%, compared to 44% for segmental resections (p = 0.001). Only in the group with segmental resections there were reinterventions, in 6.1% (n = 7/115). A readmission rate of 6.7% (n = 11/164) was found, in the subgroup with organ-preserving surgery the readmission rate was 4.1% (n = 2/49) and in the group with segmental resection this rate was 7.8% (n = 9/115). Invasive colorectal cancer was encountered in 24% of cases overall.

Data about surgical referrals for complex polyps are scarce. In one cohort study the number of patients referred for laparoscopic colorectal resection for non-malignant polyps almost tripled after the introduction of the national screening program.[19]

Substantial morbidity related to segmental colon resections of polyps was found in our study, comparable with results in large cohort studies reporting a reoperation rate of 7.8% and readmission rate of 3.6% after surgery for nonmalignant colorectal polyps.[20,21] In the organ preserving group, 7 patients (14.3%) had a minor complication. Only 1 out of 49 patients (2.0%) who underwent minor surgery presented with a major complication, this concerned a post-TEM haemorrhage, which required surgery. LEAWR did not lead to major complications. A recent study reporting on short- and long-term results of TEM observed similar rates of minor complications in 12 patients (8.8%) and major complications in 2 out of 135 patients (1.5%).[22] Three retrospective studies investigating postoperative complications after different types of combined endoscopic and laparoscopic surgery (CELS) observed no complications.[23-25] These studies were limited by their small sample sizes, ranging from 3 to 23 patients which makes comparison difficult. A prospective study by

Wilhelm et al. analyzed 146 patients who underwent CELS, of which 82% underwent local excision and 18% received endoscopy-assisted segmental colon resection. The overall complication rate was 25% and major complication rate was 3%.[26] These results are very comparable to our overall complication rate of 36.0% and occurrence of major complications in 4.9% of patients, especially when considered that in our study 70% of surgeries were segmental resections.

In the majority of the included patients in our study, no attempt was made for an endoscopic removal. This was mainly due to unfortunate polyp characteristics, such as large size; difficult location; non-lifting sign and/or the suspicion of early (T1) carcinoma. In these cases, an en-bloc resection is advised, which is not always possible by endoscopy.[27-30] In recent years, endoscopic treatment options are expanding, where the introduction of ESD and endoscopic full thickness resections have enabled local excision of pT1 tumors. The use of these techniques may reduce the referrals for surgery. Prior to referral for surgical excision, it is recommended to consult experts for endoscopic treatment. Repeated colonoscopy before surgery in an expert center can also reduce the rate of surgical referrals by 71%.[31]

A clear definition of an unresectable polyp was difficult to establish, and this definition changed over time with the development of endoscopic expertise in our clinic. The therapeutic strategies were based on the endoscopic assessment by different gastroenterologists, which can lead to interobserver variability. The increasing number of referrals for surgical resection due to the implementation of the screening program led to the development of a less invasive technique (LEAWR). This technique, in which laparoscopy and endoscopy are combined, was developed in 2015. One of the great benefits of this minimally invasive technique is that no anastomosis is created. In a pilot study, no complications were observed.[32] This new technique may have led to a lower threshold to refer the patient for a surgical resection. Despite increasing endoscopic possibilities and techniques over time, an increase in referrals for surgery was still observed.

This study reflects the consequences of a bowel screening program for daily clinical practice in a large teaching hospital. It revealed a doubling of the referral rate for surgical resection of colorectal polyps since the introduction of the CRC screening program, but with a substantial shift towards organ-preserving techniques. The low complication rate of organ-preserving techniques makes these procedures an attractive option in cases where endoscopic techniques fail. This therapy should be first choice if surgical treatment of colon polyps is necessary.

In **CHAPTER 6** we report our experience with limited endoscopy-assisted wedge resections (LEAWR) in the entire colon.

Eight patients were treated (mean age 74.5 years; range 68-82 yrs). The main indications for LEAWR were size and difficult location of the polyp. The mean operative time was 132 minutes and there were no complications. Five patients were discharged the day after surgery and remaining 3 patients were discharged 2 days after surgery, with no complications found.

In this pilot study, we found that LEAWR is feasible and allows easy removal of colonic polyps and residual adenomatous tissue in scars inaccessible to endoscopic removal. Due to traction provided by the suture through the base of the polyp, the linear stapler can be easily used for wedge resections of polyps, even for those in unfavourable positions.

In the literature we did not find an earlier publication of using traction on a suture to perform a wedge resection.

We performed a limited EAWR for polyps with sessile as well as (semi-) pedunculated morphology. Indication for limited EAWR was difficult location of the polyp and thereby an unstable position of the endoscope. Even with laparoscopic assistance, endoscopic removal is not always possible or may not be effective in cases where a snare cannot be placed over the polyp because of size, location or scarring from previous biopsies. This may lead to piecemeal resection and subsequent inadequate histopathological assessment of the specimen as well as a higher risk of recurrence.[33,34] Endoscopic submucosal dissection (ESD) is a well-established technique that facilitates an en-bloc excision of large polyps. However, there are several disadvantages to ESD that limit its use in routine clinical practice, including the need for specialized equipment, procedure length and a long learning curve.[35] Many patients now indicated for ESD can also easily be treated with limited EAWR.

Caution is taken when polyps are situated in a sigmoid with multiple diverticula, in these patients endoscopic wedge resection might be challenging. A possible concern of a limited EAWR could be narrowing of the bowel. We prefer to place the stapler in a transverse direction, this is however not always possible. In our patients there was no evidence for possible narrowing of the colon.

Due to the encouraging results, in collaboration with the Dutch T1 colorectal working group we initiated a multicentre trial to evaluate this technique in broader clinical practice.

CHAPTER 7 focuses on the results of a large prospective multicentre study in 13 Dutch hospitals conducted between January 2017 and December 2019. The aim of this study was to prospectively evaluate the short-term safety and efficacy of our modified colonoscopic assisted laparoscopic wedge resection (CAL-WR), also known as limited endoscopic assisted laparoscopic wedge resection (LEAWR) as described in **CHAPTER 6**. And also, to assess whether this new technique can replace segmental colectomy in routine clinical practice.

Of the 138 eligible patients, 118 were included in the analysis following assessment by the expert panel and review of the histological specimen, if indicated. The main indication for CAL-WR was an endoscopically unresectable colonic neoplasm (56%). Almost half of the neoplasms were in the caecum. Successful CAL-WR was performed in 110 of the 118 patients (93%). In the case of lesions found in the caecum the technical success rate was 96%, and in twenty-seven of the fifty (54%) successfully performed CAL-WR procedures the neoplasms showed ingrowth into the appendix. The patients who underwent a successful CAL-WR (n = 110) had an overall complication rate of 6%, all of which were minor (Clavien-Dindo grade I-II) and neither reintervention nor mortality was observed. Radical resection was performed in 91% of patients who successfully underwent a CAL-WR (n = 100/110), and an additional oncologic segmental resection was performed in 12 cases (11% (n = 12/110)) of the patients who successfully underwent a CAL-WR. Residual tissue at the scar was observed in 5% (n = 4) of patients who successfully underwent a CAL-WR during endoscopic follow-up.

To date, few studies have described the use of various combined endoscopic laparoscopic surgery (CELS) techniques.[23,32,36-38] Reported technical success rates from available literature range from 95% to 100%[23,32,37,38], comparable to our technical success rate of 93%. A recent systematic review of CELS involving 101 patients showed no intra- or postoperative complications.[36] Another recent retrospective cohort study (n = 115 patients) showed Clavien-Dindo grade I-II complications in 13% of patients after CELS.[39] In that study, both CAL-WR and another form of CELS such as laparoscopy-assisted endoscopic resection (LAER) was performed. Therefore, the reported 6% morbidity rate in our study appears acceptable, especially in a multicentre design.

Our overall rate of radical resection (91%) of a CAL-WR is comparable to the mentioned percentage in the available literature, radical resections rates in other studies range from 75% to 100%.[23,32,36-38] Recurrent adenomatous tissue was detected at follow-up colonoscopy in 5% (n = 4) of cases. In one case the pathologist found loose adenomatous cells in the staple margin, while the primary resection margin

was free of adenomatous tissue. We hypothesize that manipulation of the lesion in this case, either by placing of the suture and/or closure with the stapler, caused adenomatous cells to become embedded in the staple margin. Careful manipulation of the lesion during CAL-WR as well as follow-up endoscopy is therefore strongly recommended. None of the previous CAL-WR studies reported recurrence at follow-up endoscopy.[1,23,32,36-38]

Endoscopic full-thickness resection (eFTR) using an over the scope clip is another relatively new technique for the treatment of complex colonic neoplasms. The overall technical success rate of eFTR varies between 84% to 94%[40-44], while the complication rate ranges from 9.3% and 14%. In 2% to 3.5% of cases surgical reintervention is needed to treat complications.[40-44] The reported complication rate of eFTR is higher (9.3% – 14%) compared to CAL-WR (6%), as demonstrated by our study. A relatively common complication after eFTR is a secondary appendicitis close to the appendiceal orifice, which requires surgical reintervention. CAL-WR is particularly suitable for these cases, as 27 patients in our study (25%) had a lesion with ingrowth into the appendix, all of which could be treated without complication.

The radical resection rates for eFTR and CAL-WR are similar and vary from 72% to 90% and from 72% to 100%, respectively.[32,37,38,40-44] The recently described Dutch eFTR colorectal registry reported residual/recurrent lesions in 6.4% of patients,[40] while other eFTR studies reported a recurrence/residual rate of between 5.8% and 13.5%.[40-44] In our study we found a recurrence/residual adenomatous tissue at follow-up colonoscopy in 5% (n = 4) of cases. Which is similar to the reported percentages of the eFTR. Unfortunately, details on whether the primary resection in these cases was complete (R_0 resection) was not provided in these studies.[40,43,44] The use of eFTR is restricted to lesions of less than 20 mm by the size of the cap.[40,41,43,44] In our study, the median size of lesions was 20 mm [range 5 – 50 mm], indicating that lesion size is less of a limitation compared to eFTR.

In conclusion, in our prospective study we found that CAL-WR is an effective, organ-preserving approach that results in minor complications and circumvents the need for more advanced surgical procedures, which are accompanied by higher morbidity (24%) and mortality (2%) rates.[45] In the present study only 11% of patients underwent additional oncological segmental resection, indicating that segmental colectomy could be prevented in all other cases. CAL-WR therefore deserves consideration when endoscopic excision of circumscribed lesions is impossible or incomplete. In addition, indications for this technique may expand to patients with T1 CRC diagnosed during colonoscopy. If this procedure is considered for these patients, they should be informed that an additional oncologic resection might be necessary,

depending on the presence of high-risk histological factors for lymph node metastasis.

Moreover, combining CAL-WR with a sentinel node procedure might be considered in the future. If technically possible, CAL-WR may also be suitable in cases with a T1 CRC with less favourable characteristics. Future research should include a cost-effectiveness analysis of CAL-WR and a prospective trial comparing CAL-WR with eFTR and/or ESD.

In the third part of this thesis, we focus on the management of advanced colorectal neoplasms.

CHAPTER 8 concerns the clinical relevance of CT colonography for patients with stenosing CRC. At the time of our study, most guidelines recommend preoperative CTC in patients with stenosing CRC.[46-49] The aims of the study were to evaluate the yield and added clinical implications of CTC in stenosing CRC.

One hundred sixty-two patients with stenosing CRC were included. Nine (5.6%) synchronous cancers proximal to the stenosing tumour were suspected based on CTC. While in four of the nine patients CTC did not change the primary surgical plan because the tumours were in the same surgical segment, the surgical treatment plan in the remaining five patients was changed by CTC. Three of these five patients underwent an extended resection, and the presence of synchronous tumours was confirmed. However, two of the three synchronous CRCs were also visible on abdominal staging CT. In the other two patients, the CTC result was false positive, which led to an unnecessarily extended resection in one patient.

Previous studies reported stenosing CRC in 15–20 % of the cases and synchronous tumors in 1–7 %.[50-57] CT colonography has similar sensitivity as colonoscopy in detecting CRC and has moderate sensitivity in detecting advanced adenomas.[58-60] Park et al. demonstrated a high sensitivity of CTC for detection of proximal synchronous tumors, but limited capability of CTC in differentiating advanced adenomas from CRC in patients with stenosing CRC.[61]

Preoperative CTC has some advantages when compared to colonoscopy performed 3 months after primary surgery: (1) CTC could prevent the need of secondary surgery in case of a synchronous tumor and (2) it could prevent growing of secondary tumors into a more advanced stage when detection and treatment are delayed.

Two previous studies described a change in surgical plan in 14–16 %, due to location errors, synchronous CRC, or synchronous adenomas revealed by performing CTC.[62,63] In these studies, the primary surgical plan was changed in 4 and 11% due to location errors. However, tattooing colorectal tumors during endoscopy is

currently standard of care, which limits the role of CT scan in determination of the location. Moreover, most stenosing tumors are at stage T3 or T4 (in our study in 90 % of the patients) and might therefore likely have been visible on abdominal staging CT, which is performed nowadays in all patients prior to surgery. The presence of a previous performed abdominal CT was not mentioned in these studies. In the abovementioned studies, the detection of synchronous CRC or adenomas changed the surgical plan in 7.3% and 4.1% of the patients, respectively. The stage of the synchronous tumors was not mentioned in above-described studies. In our study, in one of the four patients with suspected synchronous CRC but no change in the primary surgical treatment plan, the postoperative histology showed no synchronous CRC but a proximal 35-mm tubulovillous adenoma.

We demonstrated the clinical value of CTC seems to be very limited. In 3 out of 162 patients, CTC was meaningful in terms of detection of a second primary CRC that changed the primary surgical treatment strategy. In two patients, the CTC was false positive and even leading to an unnecessary extended resection in one patient. Based on our research, our recommendations at the time of the article was to perform active screening for synchronous carcinomas using abdominal staging CT and not CTC for the detection of synchronous tumours. Several years have passed since our article and in the current Dutch Colorectal Cancer Guideline, a CTC does not have a place in the preoperatively full imaging of the colon at diagnosis, only when a colonoscopy is contraindicated.

In **CHAPTER 9** we describe the outcomes of a retrospective study that analysed data from CRC patients scheduled to receive up to 8 planned cycles of capecitabine monotherapy. Patients were treated between 2009 and 2013 at a single large community hospital in the Netherlands. The aim of this study was to provide real-world data on adverse event rates and dose adjustments/discontinuations associated with capecitabine monotherapy in patients with metastatic CRC (mCRC). Adverse events we defined as: (1) hand-foot syndrome (HFS), (2) gastrointestinal events (GIE), (3) hematological adverse events and (4) cardiotoxicity. We chose to analyze only patients receiving capecitabine monotherapy to reduce unwanted interactions and influence by other anticancer drugs in the treatment.

We included data from 86 patients (45 females, mean age at start of treatment 69 years). HFS was experienced by 46.5% of patients and 44.2% experienced a GIE at some time during treatment. Neutropenia as haematological adverse event was found in one patient (1.1%). Cardiotoxicity was found in 5%. Most patients (77%) started with a dose lower than recommended and patients at the lowest dose also

had the lowest median relative dose intensities. Dose reductions and discontinuations occurred in 15 to 25% of patients who experienced HFS or GIE over the course of 8 cycles.

Comparison with the available literature shows us similar adverse events rates of capecitabine monotherapy. The rate of HFS in our study (46.5% overall) is consistent with rates observed in phase III clinical trials of 30–53.5% and with the rate of 42% reported in an observational study that included patients who received capecitabine as monotherapy or in combination treatment.[64-67] The rate of GIE in our study was 44.2%; previous studies have reported that between 11 and 50% of patients experience one gastrointestinal event, including diarrhea, vomiting, nausea, or abdominal pain, while receiving capecitabine monotherapy.[64-66] Our results are consistent with these findings. The haematological adverse events were rare in our study, 1.1%, comparable to the previous reported 1% in the available literature.[64-66] In our study the cardiotoxicity was observed in 5% of the patients. Previous studies reported 1% cardiotoxicity, or it was not reported at all, due to occurring at lower than the 5% threshold for reporting in previous studies.[64-66] It was not possible to establish if this difference could be explained by the current population being more frail than those described in previous controlled trials.

Most patients in this study (77%) started under the approved dose of 1250 mg/m^2 twice daily. The reduced starting doses used here are not the recommended reduced starting doses for special populations (75% of starting dose for renal impairment),and phase III trials evaluated a starting dose of 1250 mg/m^2 twice daily or used 1000 mg/m^2 twice daily in elderly patients >70 years of age.[64-66,68] Patients in this study who received the 1000 mg/m^2 twice-daily dose had a mean age of 71.5 years, consistent with age as an explanation for the use of this reduced dose. However, patients in the study who received 750 mg/m^2 twice daily had a mean age of 64.4 years, suggesting that this population was considered frail by their physician. Although this suggests that physicians are reducing the starting dose of capecitabine in anticipation of adverse events, our real-world data did not provide an explicit explanation for these treatment decisions.

Dose reductions and treatment discontinuations were common in this study, occurring in 17–24% of patients who experienced HFS and 15–25% of patients who experienced a GIE. Cassidy et al. reported that 34% of patients starting treatment at 1250 mg/m^2 twice daily required a dose reduction for adverse events, while Cunningham et al. reported that 15% of elderly patients who started capecitabine treatment at 1000 mg/m^2 twice daily discontinued due to adverse events.[64,65] On this point, a comparison between our found percentage and the percentages mentioned

in the literature is difficult duo to different therapy regims (different adjusted starting dose). In our analysis, the occurrence of HFS and GIE was not related to the dose of capecitabine, which may suggest that lower starting doses and dose reductions do not improve adverse event rates, nor do they prevent them from occurring. In an observational study by Stein et al., the incidence of HFS increased with duration of treatment and was higher in younger patients than in older patients (46 vs. 37%; p = 0.0014) despite similar median daily doses of capecitabine.[66]

The tolerability of chemotherapeutic drugs is an ongoing point of attention influencing treatment outcomes for cancer. This is even more important in the palliative setting. The most frequently occurring adverse events were HFS and GI toxicity. These adverse events often led to dose reductions or even termination of treatment in our study, possibly impairing the benefit of fluoropyrimidines in these patients. These results should be taken in consideration when treating patients with mCRC, particularly older or frail patients. Therefore, it is becoming more important to select appropriate patients who may benefit from this treatment. Growing evidence indicates that adjuvant chemotherapy with 5-FU monotherapy in patients with a stage II or III CRC with MMR-deficient tumours does not improve prognosis and seems to confer no improvement in overall survival.[69] Therefore, to identify such patients, MSI or IHC analysis should be considered in all patients with CRC before starting chemotherapy.

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CHAPTER 11

VERBETEREN VAN DE BEHANDELING VAN DIKKE DARMPOLIEPEN EN DIKKE DARMKANKER IN DE DAGELIJKSE KLINISCHE PRAKTIJK

In het eerste deel van dit proefschrift ligt de focus op het opsporen en de behandeling van erfelijke dikke darmkanker.

In ongeveer 15% van de patiënten met dikke darmkanker spelen erfelijke en omgevingsfactoren een belangrijke rol. Het Lynch syndroom (LS) is verantwoordelijk voor 3 tot 5% hiervan. In de overige gevallen spelen familiaire dikke darmkanker (FCC) en andere poliepsyndromen een rol. Het opsporen van personen met risico op LS, FCC of andere poliepsyndromen is belangrijk omdat preventieve maatregelen of onderzoeken de uitkomst van dikke darmkanker kunnen verbeteren of zelfs het ontstaan van dikke darmkanker kunnen voorkomen.

HOOFDSTUK 2 gaat over een onderzoek in twee grote ziekenhuizen in Nederland uitgevoerd. Doel was het aantal personen te analyseren dat voldeed aan de criteria voor familiaire of erfelijke dikke darmkanker. Ook werd onderzocht hoeveel patiënten, die waren opgespoord via het bevolkingsonderzoek dikke darmkanker, verdere genetische analyse nodig hadden op basis van de uitkomst van het darmonderzoek.

In 18,3% van de personen die een darmonderzoek ondergingen naar aanleiding van een positieve screeningstest in het bevolkingsonderzoek (BVO DDKS), was er sprake van een positieve familiegeschiedenis voor dikke darmkanker. In totaal werd 5,3% van de deelnemers doorverwezen naar een klinisch geneticus voor verder onderzoek. Bij 3% van de deelnemers werden familieleden verwezen voor een screenend dikke darmonderzoek wegens een verhoogd risico op dikke darmkanker.

Het verkrijgen van een uitgebreide familiegeschiedenis van deelnemers met een positieve test in het BVO DDKS verhoogt de opsporing en identificatie van families met verhoogd risico op erfelijke dikke darmkanker.

Door het opsporen van deelnemers met een positieve familiegeschiedenis, wordt het mogelijk om de zorg voor deze patiënten en hun naasten te verbeteren. Het is daarom essentieel om de familiegeschiedenis uit te vragen en te documenteren tijdens de intake voor het darmonderzoek. In het huidige tijdperk van het elektronisch patiëntendossier zou het geen probleem moeten zijn om dit een standaard onderdeel van het dossier te maken.

In **HOOFDSTUK 3** laten we de resultaten zien van een onderzoek in meerdere Nederlandse ziekenhuizen naar de toegevoegde waarde van het testen naar het verlies van bepaalde eiwitten (mismatch repair deficiëntie) in de dikke darmtumor. Mismatch repair is een normaal proces dat fouten die gemaakt worden bij het kopiëren van het DNA in een cel als deze zich deelt, opspoort en herstelt. Een mismatch repair deficientie (dMMR) is aanwezig in meer dan 95% van de met Lynch-syndroom (LS) geassocieerde dikke darmkanker en in 15% van de sporadisch voorkomende dikke darmkanker. Lynch syndroom is een genetische afwijking die een verhoogd risico geeft op het ontwikkelen van onder andere dikke darmkanker. In deze studie is onderzocht of testen op verlies van deze eiwitten in de dikke darmtumor leidt tot (1) het opsporen van patiënten met het Lynch syndroom, (2) een wijziging van de chirurgische behandeling en (3) een wijziging van chemotherapeutisch middel bij patiënten met dikke darmkanker waarbij sprake is van dMMR.

Bij 24 van 225 patiënten (11%) met dikke darmkanker was sprake van een MMR-deficiënte dikke darmkanker. Van deze patiënten werden 18 (75%) verwezen naar een klinisch geneticus voor aanvullend DNA-onderzoek en bij 9 (37%) werd er daadwerkelijk een afwijking in het DNA gevonden. Eén (4%) van de 24 patiënten onderging een vrijwel volledige dikke darmverwijdering (subtotale colectomie). Het chemotherapiebeleid werd aangepast bij 7 (35%) van de 20 patiënten met een dMMR dikke darmkanker die een indicatie hadden voor chemotherapie.

Met de analyse van MMR-status werden weinig patiënten gediagnosticeerd met het Lynch syndroom, 25% van de patiënten werd echter ten onrechte niet verwezen voor genetisch onderzoek. De invloed van analyse naar dMMR lijkt meer invloed te hebben op de keuze van chemotherapie dan op keuze voor het type operatie.

De MMR-status van dikke darmkanker wordt steeds belangrijker voor de behandeling met chemotherapie en immunotherapie, wat steeds vaker gegeven wordt. Uit onderzoek blijkt dat dMMR dikke darmkanker niet goed reageert op een bepaalde vorm van chemotherapie die vaak gegeven wordt voor dikke darmkanker. Daarnaast laat recent onderzoek van Chalabi en collegae juist zien dat dMMR dikke darmkanker een goede respons lijken te hebben op immunotherapie. Er werd een volledige respons gezien in 57% van de patiënten met dMMR dikke darmkanker die werden behandeld met 2 verschillende immunotherapieën.[1] Ander onderzoek liet goede resultaten zien van immunotherapie bij uitgezaaide dMMR dikke darmkanker.[2] Deze onderzoeken zijn veelbelovende ontwikkelingen in het personaliseren van de behandeling van dikke darmkanker.

Om de behandeling van dikke darmkanker te personaliseren en daarmee te optimaliseren, zijn wij van mening dat onderzoek naar dMMR van dikke darmkanker

essentieel is. Wij raden aan om alle patiënten met dikke darmkanker jonger dan 70 jaar, en patiënten ouder dan 70 jaar waarbij een indicatie voor chemo- of immunotherapie kan bestaan, te screenen op dMMR.

In **HOOFDSTUK 4** komen de resultaten van een onderzoek aan bod dat is uitgevoerd bij patiënten met het Lynch syndroom (LS). We hebben de frequentie van onderzoek naar de maagbacterie *Helicobacter pylori* onder LS-patiënten geanalyseerd en gekeken of de infectie met de maagbacterie vaker voorkomt in LS-families met bewezen maagkanker. Het Lynch syndroom geeft naast een verhoogd risico op dikke darmkanker, een verhoogd risico op het ontwikkelen van maagkanker ten opzichte van mensen die geen genetische afwijking hebben. Daarnaast is het bekend dat een infectie met de maagbacterie *Helicobacter pylori* een rol speelt in het ontstaan van maagkanker bij de normale populatie. Daarom lijkt het belangrijk om patiënten met een verhoogd risico te screenen op een infectie met *Helicobacter pylori.*

Van de 443 LS-patiënten werden 206 (46%) getest op *Helicobacter pylori*. Hiervan bleken 42 patiënten (20%) de maagbacterie bij zich te dragen. In 2010 is in de richtlijn vastgesteld dat er getest moet worden op de maagbacterie bij patiënten met het Lynch syndroom. Van de patiënten die vóór 2010 als LS-patiënt werden gediagnosticeerd, werd 37% getest op maagbacterie. Na 2010 is dit percentage gestegen tot 68%. Van 356 LS-patiënten waarvan de familiegeschiedenis bekend was, hadden 25 LS-patiënten ten minste één eerstegraads familielid met maagkanker. Zeven LS-patiënten hadden meer dan één eerstegraads familielid met maagkanker. Het percentage van een infectie met *Helicobacter pylori* bij LS-patiënten met een eerstegraads familielid was 20%.

Dit onderzoek laat zien dat sinds de invoering van de richtlijn in 2010 de aanbeveling om te testen op een infectie met de maagbacterie *Helicobacter pylori* vaker wordt gevolgd. Een infectie met de maagbacterie komt even vaak voor bij LS-patiënten als bij de algemene bevolking. LS-patiënten met een eerstegraads familielid met maagkanker hadden niet vaker een infectie met de maagbacterie.

Wat de precieze waarde is van het testen bij LS-patiënten op een infectie met *Helicobacter pylori* is niet geheel duidelijk. Aangezien de maagbacterie een bekende risicofactor is voor de ontwikkeling van maagkanker in de algemene bevolking en LS-patiënten al een verhoogd risico hebben op maagkanker, raden we desondanks aan om het testen op een infectie met *Helicobacter pylori* in deze risicogroep voort te zetten.

In het tweede deel van dit proefschrift ligt de focus op de behandeling van vroeg stadium dikke darmkanker.

De invoering van het bevolkingsonderzoek dikke darmkanker (BVO DDKS) in 2014 heeft gezorgd voor een toegenomen aantal gevonden dikke darmpoliepen, welke normaal gesproken verwijderd worden tijdens het darmonderzoek (endoscopische verwijdering) door de maag-darm-leverarts (MDL-arts). In sommige gevallen heeft een chirurgische verwijdering (operatie) de voorkeur, bijvoorbeeld als de grootte of plaats van de dikke darmpoliep een endoscopische verwijdering technisch lastig of onmogelijk maakt, of als er sprake is van een verdenking op een vroeg stadium dikke darmkanker (T1 dikke darmkanker). Een toenemend aantal patiënten wordt behandeld met orgaansparende operaties (minimaal invasieve operatie) om zoveel mogelijk van de dikke darm te sparen. Dit geeft minder nadelige effecten voor de patiënt ten opzichte van een uitgebreidere dikkedarmoperatie. Om zoveel mogelijk dikke darm te sparen tijdens de operatie hebben we in 2015 in de Isala in Zwolle een aangepaste chirurgische operatietechniek geïntroduceerd (LEAWR of ook wel CAL-WR) voor endoscopisch niet te verwijderen dikke darmpoliepen.

In **HOOFDSTUK 5** is gekeken in welke mate het aantal verwijzingen voor een chirurgische verwijdering van dikke darmpoliepen is gestegen na de invoering van het bevolkingsonderzoek naar dikke darmkanker (BVO DDKS) in 2014. Daarnaast is het type operatie geanalyseerd. De patiënten die zijn onderzocht ondergingen een operatie voor dikke darmpoliepen tussen januari 2012 en december 2017. Als er sprake was van bewezen dikke darmkanker voorafgaand aan de operatie kon de patiënt niet worden meegenomen in het onderzoek.

In totaal werden 164 patiënten geïncludeerd in het onderzoek. Er werd een duidelijke jaarlijkse toename gezien van het aantal verwijzingen voor een chirurgische behandeling van dikke darmpoliepen, waarbij er in 2012 slechts 18 patiënten werden verwezen. In 2017 ondergingen 36 patiënten een dikkedarmoperatie om een dikke darmpoliep te verwijderen. Vóór de invoering van het BVO DDKS werd bij de chirurgische verwijdering van een dikke darmpoliep, een groter stuk dikke darm verwijderd (segmentresectie). Echter, na invoering in 2014 ging het in bijna 60% van de operaties om minder invasieve orgaansparende ingrepen, waarbij er zo min mogelijk gezond dikke darmweefsel werd verwijderd. Complicaties bij orgaansparende ingrepen traden in 16% van de gevallen op, vergeleken met 44% bij segmentresecties van de dikke darm.

Samenvattend, is er sprake van een verdubbeling van het aantal verwijzingen voor een chirurgische behandeling van dikke darmpoliepen na de invoering van het BVO DDKS. Daarentegen was er een duidelijke verschuiving naar meer orgaanspa-rende chirurgische behandeltechnieken. Vanwege het lagere complicatierisico van orgaansparende technieken, zijn deze ingrepen een aantrekkelijke optie wanneer de poliep tijdens het inwendige darmonderzoek niet kan worden verwijderd door de MDL-arts.

In **HOOFDSTUK 6** worden de eerste resultaten getoond van een aangepaste chirurgische techniek om dikke darmpoliepen te verwijderen. Deze chirurgische techniek is in de Isala in 2015 als aanpassing op een langer bestaande techniek ont-wikkeld. Door het plaatsen van een hechting door de darmwand nabij de poliep, kan de chirurg de poliep van de darm weg trekken en daarmee het stuk darm wat wordt verwijderd beperken. Daarnaast hoeft er geen nieuwe verbinding gemaakt te worden tussen twee stukken dikke darm die overblijven na een uitgebreidere verwijdering. Bij deze gecombineerde ingreep werken chirurg en MDL-arts nauw samen. De chi-rurg begint met het vrijmaken van het stuk dikke darm waar de poliep zich bevindt, waarna de MDL-arts via inwendig darmonderzoek (endoscopie) op zoek gaat naar de precieze locatie van de poliep. Op aanwijzing van de MDL-arts kan de chirurg onder camerazicht een hechting plaatsen bij de poliep. Vervolgens trekt de chirurg met de hechting de poliep van de darm, en kan hij met een nietapparaat de poliep omsluiten en verwijderen. De verwijdering vindt ook onder camerazicht vanuit de dikke darm plaats om de accuratesse en de doorgankelijkheid van de darm te waarborgen. Na het verwijderen van de poliep controleren de chirurg en de MDL-arts de buiten- en binnenzijde van de darm op bloeding en lekkage.

Acht patiënten werden in de eerste serie behandeld met deze aangepaste tech-niek (LEAWR of ook wel CAL-WR). De belangrijkste indicaties waren de grootte en de moeilijke locatie van de poliep. De gemiddelde operatieduur was 132 minuten en er waren geen complicaties. Vijf patiënten werden de dag na de operatie ontslagen en drie patiënten werden gedurende 2 dagen opgenomen, waarbij geen complicaties optraden.

In deze pilotstudie hebben we vastgesteld dat LEAWR/CAL-WR een goede tech-niek is voor relatief eenvoudige chirurgische verwijdering van poliepen en achter-gebleven poliepweefsel in littekens die niet toegankelijk zijn voor endoscopische verwijdering door de MDL-arts.

Door het gebruik van de hechting die naast de poliep geplaatst wordt, kan het nietinstrument dat gebruikt wordt gemakkelijker worden geplaatst, zelfs op minder

toegankelijke plekken van de dikke darm. Vanwege deze bemoedigende resultaten hebben wij, in samenwerking met de Nederlandse T1 colorectale werkgroep, een groot Nederlands onderzoek in meerdere ziekenhuizen gestart om deze techniek in de bredere klinische praktijk te onderzoeken.

In **HOOFDSTUK 7** worden de resultaten beschreven van de nationale studie die is opgezet naar aanleiding van de aangepaste LEAWR/CAL-WR die is beschreven in **HOOFDSTUK 6.** Het onderzoek is uitgevoerd tussen januari 2017 en december 2019 in 13 ziekenhuizen in Nederland. De doelen van het onderzoek waren het beoordelen van (1) de korte termijn veiligheid en effectiviteit (volledige verwijdering van de poliep) van onze aangepaste LEAWR/CAL-WR en (2) beoordelen of deze nieuwe techniek de uitgebreidere darmoperatie kan vervangen in de toekomst. De techniek werd uitgevoerd zoals beschreven in **HOOFDSTUK 6.** Patiënten konden deelnemen als er sprake was van één van de volgende indicaties: 1. dikke darmpoliepen die door de MDL-arts niet verwijderd konden worden; 2. overgebleven polypeus weefsel na endoscopische verwijdering; of 3. een vroeg stadium van dikke darmkanker welke geen ongunstige kenmerken liet zien.

Er werden 138 patiënten aangemeld voor mogelijke deelname aan het onderzoek, waarvan na beoordeling door een expert panel van MDL-artsen en pathologen uiteindelijk 118 patiënten werden meegenomen in de analyse. De belangrijkste indicatie voor de ingreep was een endoscopisch niet te verwijderen dikke darmpoliep (56%). In 110 patiënten (93%) was de ingreep technisch succesvol. Bij poliepen gelokaliseerd in het coecum(begin van de dikke darm) was het succespercentage zelfs 96%. In 54% van de geslaagde CAL-WR was er sprake van ingroei van de poliep in de appendix (blindedarm). Bij 6% van de patiënten die een CAL-WR ondergingen traden complicaties op. Deze waren mild-gering van ernst en van re-interventie of overlijden was geen sprake. De effectiviteit van de CAL-WR, uitgedrukt als een radicale (totale) verwijdering van de afwijking, was 91%. Bij 12 patiënten (11%) was er op basis van de pathologie van de verwijderde dikke darmpoliep een aanvullende oncologische darmoperatie nodig. Bij een controle darmonderzoek 6 maanden na de ingreep werd bij 4 patiënten (5%) toch restweefsel gezien op de plek van het litteken van de CAL-WR.

Concluderend, is de CAL-WR een effectieve, minimaal invasieve en orgaansparende behandeling voor dikke darmpoliepen. De ingreep heeft een laag risico op complicaties en kan een uitgebreide darmoperaties voorkomen. Deze nieuwe techniek verdient het daarom te worden overwogen wanneer endoscopische verwijdering van een dikke darmpoliep door de MDL-arts niet mogelijk of onvolledig is.

Mogelijk kunnen de indicaties voor een CAL-WR in de toekomst uitgebreid worden naar vroeg stadium dikke darmkanker. Patiënten dienen vooraf geïnformeerd te worden dat – wanneer er toch sprake blijkt van verder gevorderde dikke darmkanker – een aanvullende operatie soms noodzakelijk is. Ook zou het interessant zijn om te onderzoeken of CAL-WR valt te combineren met lymfeklierverwijdering bij andere stadia van vroege dikke darmkanker.

In het derde en laatste deel van dit proefschrift ligt de focus op de behandeling van gevorderde dikke darmkanker.

Van de patiënten met dikke darmkanker heeft 1-7% een tweede dikke darmtumor. Deze tumor kan lang onontdekt blijven wanneer het onderste gezwel de darm afsluit en zo inwendige beeldvorming van de darmen onmogelijk maakt. Aanbevolen wordt dan ook om bij een afsluitend gezwel in de dikke darm een dikke darm CT-scan (CTC) te verrichten, om een tweede tumor uit te sluiten.

In **HOOFDSTUK 8** is gekeken naar de klinische betekenis van de dikke darm CT-scan voor patiënten met een afsluitende dikke darmtumor. Het doel van het onderzoek was om de opbrengst van de scan en de toegevoegde klinische waarde van deze speciale CT-scan te beoordelen.

In totaal werden 162 patiënten met een afsluitend dikke darmtumor meegenomen in ons onderzoek. Bij negen patiënten (5,6%) werd op de dikke darm CT-scan (CTC) een tweede tumor hogerop in het darmkanaal gevonden. Bij vier van deze patiënten werd het operatieplan niet gewijzigd, doordat de tumoren zich bevonden in hetzelfde deel van de dikke darm. In drie van de negen patiënten werd er een uitgebreidere dikkedarmoperatie gedaan. Bij twee van deze drie patiënten, was het tweede gezwel ook zichtbaar op de reguliere CT scan die gemaakt wordt ter uitsluiting van uitzaaiingen. Bij de overige twee patiënten gaf de CTC een vals positief resultaat, wat leidde tot een onnodig langdurige operatie bij één patiënt.

Samenvattend, lijkt de opbrengt van CTC relatief laag en vond een terechte aanpassing van het chirurgisch plan plaats in slechts 1.9% van de patiënten. In twee gevallen was de tweede dikke darmtumor ook zichtbaar op de standaard CT-scan die wordt gemaakt bij diagnose. Daarnaast gaf de CTC bij 2 patiënten onterechte verdenking op een bijkomende (2e) tumor. De waarde van de CTC bij een afsluitend dikke darmtumor lijkt dus beperkt.

Op grond van de resultaten van ons onderzoek, adviseren wij om de standaard CT, die gemaakt wordt ter uitsluiting van uitzaaiingen, nauwkeurig te beoordelen

op een mogelijke 2e tumor in het darmkanaal en raden een CTC af voor de detectie van een tweede dikke darmtumor. Het advies is om binnen 3 maanden na de dikke-darmoperatie van het afsluitende dikke darmgezwel een inwendig darmonderzoek te verrichten om de rest van de dikke darm te beoordelen.

Als de dikke darmkanker verder is gevorderd en uitgezaaid blijkt te zijn, kan (palliatieve) behandeling met chemotherapie gegeven worden om progressie van de ziekte te remmen. Van de patiënten met uitgezaaide dikke darmkanker (mCRC) wordt 17% behandeld met Capecitabine.

In **HOOFDSTUK 9** laten we resultaten zien van een onderzoek onder patiënten met uitgezaaide dikke darmkanker die gepland stonden voor 8 kuren met capecitabine. Het doel was om het optreden van bijwerkingen, dosisaanpassingen of staken van de behandeling te analyseren. Patiënten werden tussen 2009 en 2013 behandeld in een groot perifeer ziekenhuis in Nederland.

In totaal werden 86 patiënten geïncludeerd. De voornaamste bijwerking was hand-voetsyndroom (HFS, 46.5%), wat wordt gekenmerkt door roodheid, zwelling, droogheid, blaren, kloofjes, jeuk en pijn van handen en voeten. De verschijnselen ontstaan binnen enkele dagen tot maanden na start van de behandeling en verdwijnen meestal geleidelijk na het staken van de behandeling. Klachten van het maagdarmstelsel (GIE) traden op in 44.2% van de patiënten. De meeste patiënten (77%) begonnen met een dosis onder de aanbevolen dosering. Dosisverlaging en staken van de behandeling kwamen voor bij 15 tot 25% van de patiënten die HFS of GIE doormaakten in de loop van de 8 kuren.

Handvoetsyndroom en bijwerkingen van het maagdarmstelsel kwamen vaak voor bij patiënten die werden behandeld met Capecitabine als monotherapie voor uitgezaaide dikke darmkanker. Bovendien zorgen bijwerkingen in een aanzienlijk aantal patiënten voor aanpassing van de dosis of zelfs stoppen van de behandeling.

Het is essentieel om geschikte patiënten te selecteren die mogelijk baat hebben bij deze behandeling. Er is steeds meer bewijs dat aanvullende chemotherapie met 5-FU (Capecitabine via het infuus) monotherapie bij patiënten met een stadium II of III dMMR dikke darmkanker de prognose niet verbetert en geen verbetering lijkt te brengen in de algehele overleving.[3] Om deze patiënten te identificeren, is het van belang om onderzoek naar de MMR-status van dikke darmkanker te doen alvorens er gestart wordt met chemotherapie. Concluderend is ons advies dat dMMR-analyse van dikke darmkanker moet worden verricht bij alle patiënten jonger dan 70 jaar, en bij patiënten ouder dan 70 jaar wanneer er mogelijk een indicatie is voor chemo- of immunotherapie.

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APPENDICES

List of publications

2016

Equivalent Helicobacter pylori infection rates in Lynch syndrome mutation carriers with and without a first-degree relative with gastric cancer

Eline C. Soer, Laura W. Leicher, Alexandra M. J. Langers, Paul C. van de Meeberg, Egbert-Jan van der Wouden, Jan Jakob Koornstra, Marloes Bigirwamungu-Bargeman, Hans F. A. Vasen, Wouter H. de Vos tot Nederveen Cappel

Int J Colorectal Dis 2016; 31:693–697 DOI 10.1007/s00384-016-2524-7

Identification of familial colorectal cancer and hereditary colorectal cancer syndromes through the Dutch population-screening program: results of a pilot study

Sanne J. H. van Erp*, Laura W. Leicher*, Simone D. Hennink, Zeinab Ghorbanoghli, Simone A. C. Breg, Hans Morreau, Maartje Nielsen, James C. H. Hardwick, Jan A. Roukema, Alexandra M. J. Langers, Wouter H. de Vos tot Nederveen Cappel and Hans F. A. Vasen

Scandinavian Journal of Gastroenterology, 2016;51 (10): 1227–1232

** both authors contributed equally*

2017

Consequences of testing for Mismatch Repair deficiency of colorectal cancer in clinical practice

L.W. Leicher*, M.H.A. Lammertink*, S.R. Offerman, H. Morreau, M.M. de Jong, J.W.B. de Groot, H.L. van Westreenen, H.F.A. Vasen, W.H. de Vos tot Nederveen Cappel

Scandinavian Journal of Gastroenterology 2017;53:632-636qq

** both authors contributed equally*

Tolerability of capecitabine monotherapy in metastatic colorectal cancer, a real world study

Laura W. Leicher, Jacques C. de Graaf, Wilko Coers, Metin Tascilar, Jan Willem B. de Groot

Drugs R D 2017; 17:117–124, DOI 10.1007/s40268-016-0154-

Limited Endoscopic Assisted Wedge Resection for Excision of Colon Polyps
Laura W. Leicher M.D., Wouter H. de Vos tot Nederveen Cappel M.D. PhD, Henderik L. van Westreenen M.D. PhD
Diseases of the Colon & Rectum: March 2017 - Volume 60 - Issue 3 - p 299–302

Consequences of CT- colonography in stenosing colorectal cancer
Huisman JF, BSc, Leicher LW, MD, de Boer E, MD, van Westreenen HL, MD PhD, de Groot JW, MD PhD, Holman FA, MD, van de Meeberg PC, MD PhD, Sallevelt PEJM, MD PhD, Peeters KCMJ, MD PhD, Wasser MNJM, MD PhD, Vasen HFA, MD PhD, de Vos tot Nederveen Cappel WH, MD PhD
Int J Colorectal Dis 2017; 32:367–373, DOI 10.1007/s00384-016-2683-6

2021

Referrals for surgical removal of polyps since the introduction of a colorectal cancer screening programme
D. Bosch*, L.W. Leicher*, N.C.A. Vermeer, K.C.M.J. Peeters, W.H. de Vos tot Nederveen Cappel, H.L. van Westreenen
Colorectal Disease 2021; 23: 672-679
** both authors contributed equally*

2022

Colonoscopic-assisted laparoscopic wedge resection for colonicl esions – a prospective multicentre cohort study (LIMERIC-study)
Laura W. Leicher, Jelle F. Huisman, Wilhelmina M.U. van Grevenstein, Paul Didden, Yara Backes, G. Johan A. Offerhaus, Miangela M. Laclé, Freek C.P. Moll, Joost M.J. Geesing, Niels Smakman, Jochim S. Terhaar Sive Droste, Emiel G.G. Verdaasdonk, Frank ter Borg, A. Koen Talsma, G. Willemien Erkelens, Edwin S. van der Zaag, Ruud W.M. Schrauwen, Bob J. van Wely, Ingrid Schot, Maarten Vermaas, Jeroen D. van Bergeijk, Colin Sietses, Wouter L. Hazen, Dareczka K. Wasowicz, Dewkoemar Ramsoekh, Jurriaan B. Tuynman, Yasser A. Alderlieste, Rutger-Jan Renger, Frank A. Oort, Ernst Jan Spillenaar Bilgen, Frank P. Vleggaar, Hans F.A. Vasen, Wouter H. de Vos tot Nederveen Cappel, Leon M.G. Moons, Henderik L. van Westreenen
Annals of Surgery 2022, May 1;275(5);933-939

Curriculum Vitae

Laura Wenny Leicher werd op 17 december 1985 geboren te Delft. Ze groeide op als oudste in een gezin met 3 kinderen. In 2005 behaalde zij haar VWO-diploma aan het Thomas a Kempis college in Zwolle. Al op hele jonge leeftijd wist Laura dat ze arts wilde worden, de studiekeuze lag dan ook al vast voor haar middelbare schoolcarrière. Ze werd helaas uitgeloot voor de studie Geneeskunde en besloot om een jaar Rechten te gaan studeren in Amsterdam. In 2006 kon ze toch beginnen met haar opleiding Geneeskunde aan de Vrije Universiteit te Amsterdam. In oktober 2013 behaalde ze haar artsendiploma, tijdens haar coschappen had ze haar zinnen gezet op de MDL. In 2014 ging zij aan de slag als ANIOS MDL in de Isala in Zwolle, en in 2015 kon zij beginnen met de opleiding tot maag-darm-leverarts in Isala/UMCG. Tijdens haar vooropleiding Interne geneeskunde is ze in het onderzoek gerold, en dit is uitgemond in een promotietraject met als een groot onderdeel daarvan het opzetten van een landelijk multicenter prospectief cohortonderzoek. Ten tijde van de verdediging is zij net een maand klaar als MDL-arts. Om haar vak verder te verrijken en te verdiepen is zij geïnteresseerd in management van de zorg en het ziekenhuis en zorgoptimalisatie, hiervoor volgde zij meerdere cursussen van de Academie voor Medisch Specialisten en VvAA over dit onderwerp.

Dankwoord

Prof. Dr. H.F.A. Vasen, beste Hans, veel dank voor de enthousiaste begeleiding en het vertrouwen om dit proefschrift tot een prachtig einde te brengen.

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Dr. W.H. de Vos tot Nederveen Cappel, beste Wouter, mijn eerste zaalsupervisor op de afdeling toen ik als ANIOS begon, vrijwel meteen een prettige collegiale klik. Het eindeloze geduld wat je op kan brengen jegens patiënten en collega's, de rust die je kan bewaren in soms toch wat frustrerende situaties bewonder ik.

Voor de LIMERIC-studie heb ik samen mogen werken met de T1 CRC werkgroep uit Utrecht en 13 ziekenhuizen. Met elkaar hebben we een hele mooie landelijke prospectieve studie op kunnen zetten. Ik wil alle betrokken MDL-artsen en chirurgen bedanken voor hun enthousiaste inzet en de hulp om de LIMERIC tot een goed einde te brengen.

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