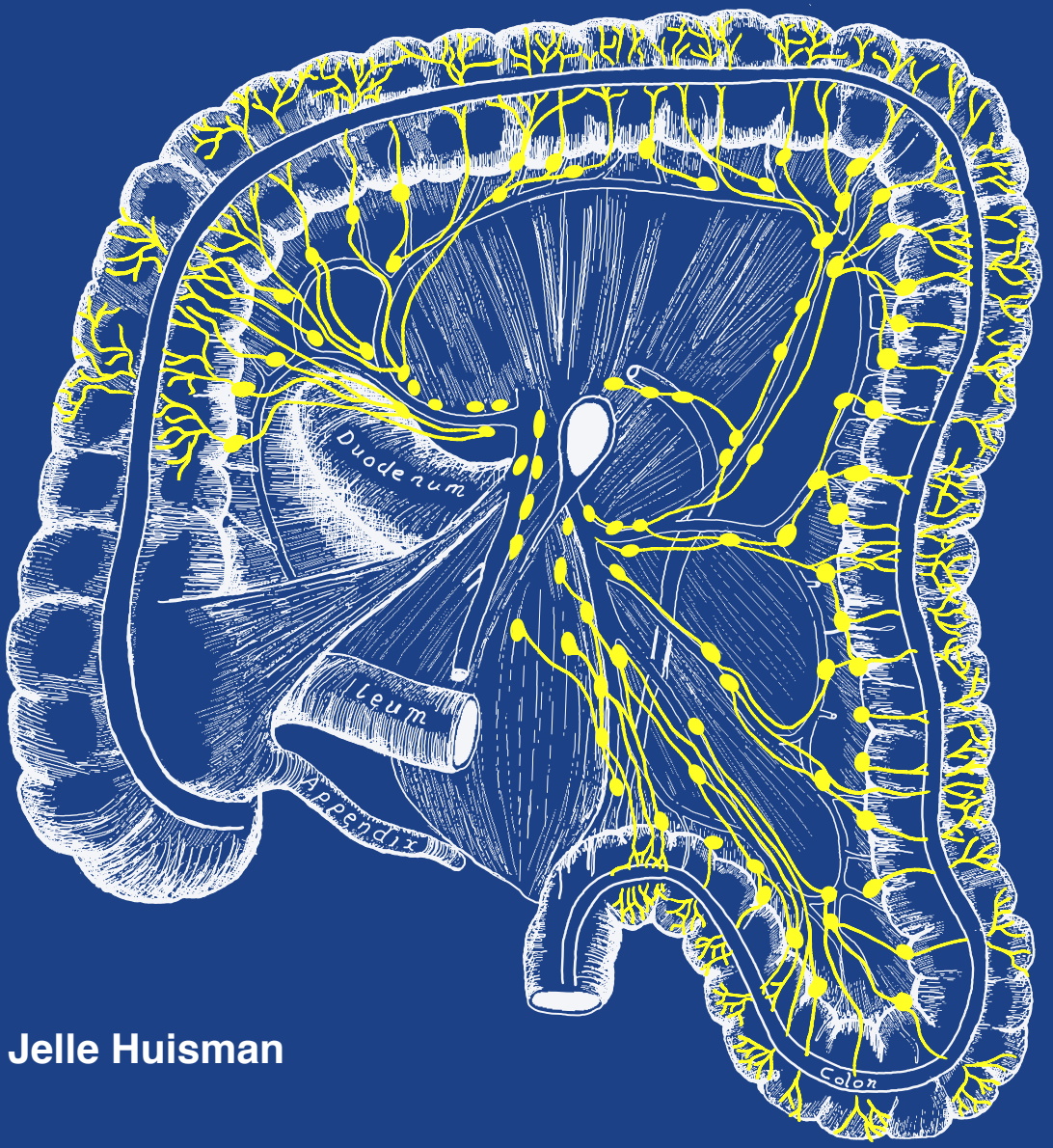
MINIMAL INVASIVE STRATEGIES AND QUALITY IMPROVEMENT IN COLORECTAL CANCER CARE



Jelle Huisman

Minimal invasive strategies and quality improvement in colorectal cancer care

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Minimal invasive strategies and quality improvement in colorectal cancer care
Thesis, University of Utrecht. The Netherlands

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Minimal invasive strategies and quality improvement in colorectal cancer care

Minimaal invasieve behandelstrategieën en kwaliteitsverbeteringen voor dikke darmkanker
(met een samenvatting in het Nederlands)

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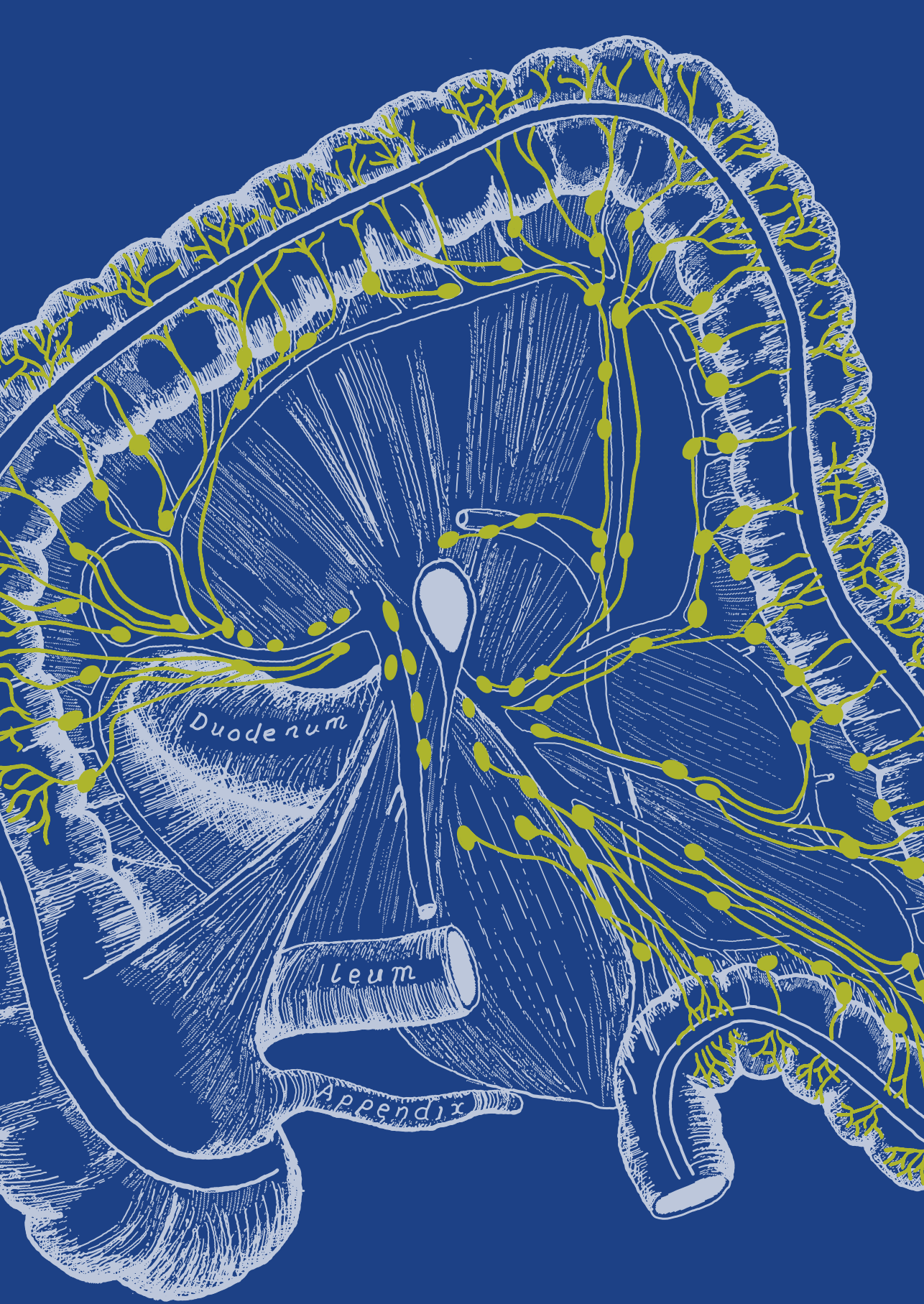
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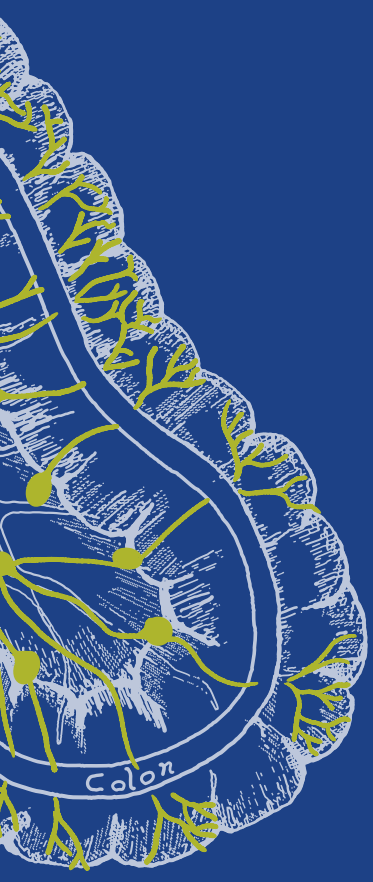
CHAPTER 1

General introduction and outline of this thesis



INTRODUCTION

Colorectal cancer (CRC) is the third most common diagnosed cancer worldwide with more than 1.9 million new cases and 900.000 death per year.[1] Approximately 40% of the cancers are located in the rectum and 60% in the colon. In general, CRC grows slowly and develops from premalignant polyps into localized early CRC and eventually advanced CRC with distant metastases caused by lymphatic or hematological spread of tumor cells. The 5-years overall survival is dependent on tumor stage and is very good for patient with localized early CRC (>95%) and poor for patients with metastatic disease (12%).[2] Patients with localized CRC can be treated with curative intent with surgical resection in most of the cases.

Aim and outline of this thesis:

Colorectal cancer care starts with education of the population regarding risk factors for CRC, symptoms of CRC and bowel screening programs and ends with surveillance for curatively treated patients or palliative therapy for patients with incurable disease. During this pathway, several diagnostic procedures, therapeutic treatments, multidisciplinary team discussions and surveillance procedures occur. A multidisciplinary approach with a multidisciplinary team discussion is essential to improve quality of colorectal cancer care and allows patient tailored treatment.[3,4] The aim of this thesis is to further improve quality of colorectal cancer care. To achieve this, we studied CRC screening, radiological staging and surveillance and the outcome of several treatment modalities (Figure 1).

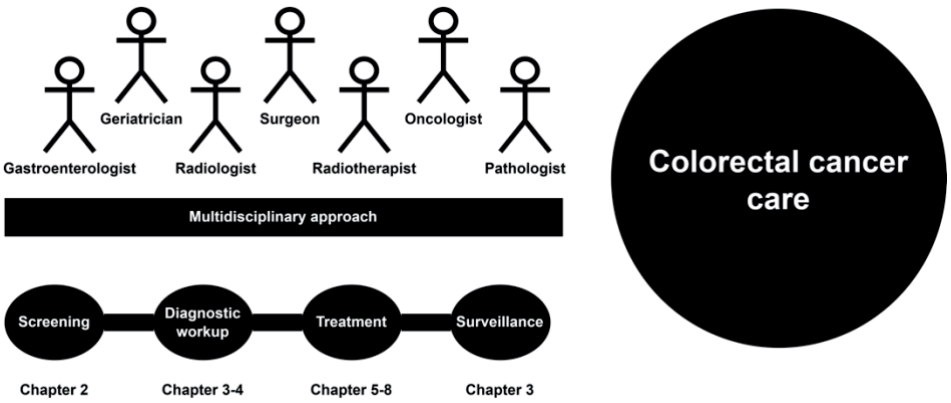


Figure 1. Thesis outline and multidisciplinary approach for colorectal cancer

PART I – Screening

Early detection and removal of premalignant polyps or early stage CRC by colonoscopy decreases the incidence and mortality of CRC.[5] Most of these early neoplasms are asymptomatic and are therefore not detected during regular healthcare visits. In 2014, the national bowel cancer screening program was introduced in the Netherlands for individuals aged 55-75 years to detect asymptomatic (pre)malignant lesions. This population screening program is performed by testing stool samples using home kits with faecal immunochemical test (FIT). Individuals with a positive FIT are referred for colonoscopy. The implementation of this screening program has led to a shift from advanced CRC to early stage CRC or premalignant advanced adenomas (AA) (Figure 2).[6]

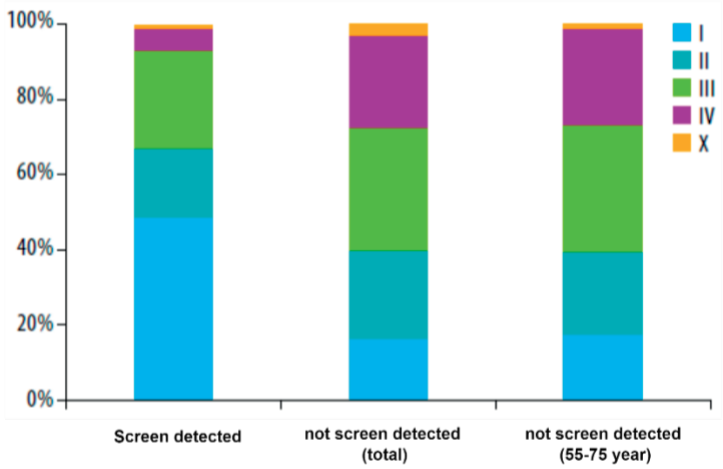


Figure 2. CRC stage among screen detected and not screen detected CRC patients

Computed Tomography Colonography (CTC) is an alternative screening modality for CRC in FIT positive individuals. CTC is less invasive than colonoscopy and has also high diagnostic performance for the detection of CRC.[7-11] A disadvantage of CTC is that it has no therapeutic options and therefore additional colonoscopy is required in case of suspicious findings. Furthermore, CTC is less appropriate for detection of small colorectal lesions and is associated with the detection of extra-colonic incidental findings as side effect of the imaging.[12-14] In clinical practice, CTC is mainly used for patients with severe co-morbidity to exclude CRC. Especially in these patients, extra-colonic findings might be undesirable and may lead to additional

diagnostic and/or therapeutic work-up. In **chapter 2**, we evaluated the intra- and extra colonic yield of CTC in FIT positive individuals of the Dutch national CRC screening program.

PART II – Imaging

Standard workup for CRC patients includes colonoscopy with biopsy for histological confirmation and radiological imaging to detect potential synchronous distant metastases and thereby prevent unnecessary surgery for patients with incurable disseminated disease. About 6% of screen detected CRC and 26% of not screening detected CRC have synchronous distant metastases.[15] Although all CRC cases have the potency to have synchronous lymph node- or distant metastases, the chance of having these metastases increases with the tumor stage. T1 CRCs have a very small risk of synchronous lymph node metastases (2-16%) and synchronous distant metastases (2%).[16-19] Therefore, the added value of radiological staging for patients with T1 CRC, as recommended in most international guidelines, seems questionable.[20-27] Potential negative effects of radiological imaging are the detection of incidental findings that may lead to medicalization and increased healthcare costs. Current radiological imaging modalities are not able to accurately assess the lymph node status of CRC.[28-35] The yield of performing radiological staging for low risk CRC patients; i.e. T1 CRCs, was evaluated in **chapter 3** in a large cohort of patients with pT1 CRC selected from the Dutch Cancer Registry.

Approximately 15-20% of CRC patients present with stenosing CRC. In these patients, the proximal colon cannot be visualized during colonoscopy and consequently potential neoplasms in this part of the colon might be missed as synchronous CRC occurs in 1-7% of patients.[36-38] Most guidelines recommend to perform preoperative CTC or postoperative colonoscopy to evaluate the proximal colon.[39-42] The Dutch guideline recommends to perform colonoscopy 3 months after surgical resection. However, the Dutch Colorectal Audit (DCRA) registers quality of colorectal cancer care in the Netherlands and had preoperative complete visualization of the colon as a quality indicator until 2015. In the study presented in **chapter 4**, we assessed the diagnostic yield of preoperatively performed CTCs in case of stenosing CRC in 3 Dutch hospitals.

PART III – Therapy

Surgical resection with dissection of the draining lymph nodes is the gold standard treatment for localized CRC. This therapy is associated with significant morbidity, permanent (colo)stomies and mortality. Surgical resection could also be considered for polyps at difficult locations which cannot be removed with endoscopic techniques. Even for these small colorectal lesions there are still morbidity and mortality risks of 24% and 2%, respectively.[43]

New minimally invasive treatment modalities have been developed over the years to avoid major surgical resection and to improve quality of life. Advanced endoscopic tissue resection techniques such as endoscopic mucosal resection (EMR), endoscopic full thickness resection (eFTR), transanal endoscopic microsurgery (TEM), transanal minimally invasive surgery (TAMIS) and endoscopic submucosal dissection (ESD) have been introduced for the removal of non-invasive colorectal neoplasms to avoid surgical resection. Moreover, a watch-and-wait approach for selected rectal cancer patients with a good tumor response after neoadjuvant chemoradiation (nCRT) offers patients the option for organ preservation instead of surgical resection. A bridge to elective surgery technique for left sided colon obstruction instead of emergency resection has been applied to prevent surgical complications. Furthermore, endosponge therapy for patients with anastomotic leakage has been developed to improve anastomotic healing rates (Figure 3). **Chapter 5-9** focus on the clinical outcome of these techniques.

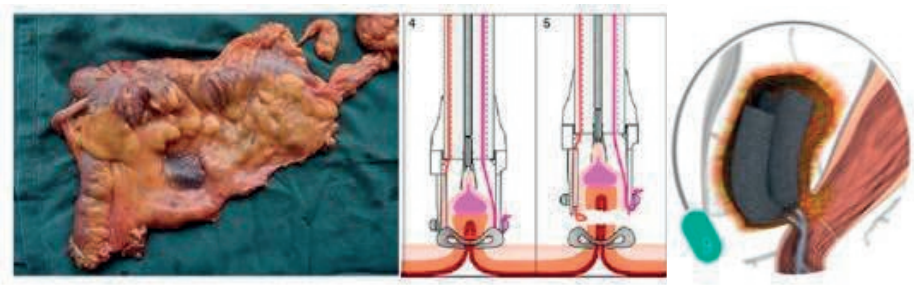


Figure 3. From left to right: surgical resection, endoscopic full thickness resection and endosponge therapy for presacral abscesses.
Image: Ovesco Endoscopy AG, Tübingen, Germany; www.ovesco.com, B. Braun Medical B.V, Melsungen, Germany., www.bbraun.com

EMR is a well-established advanced endoscopic resection technique for large non-pedunculated polyps and is reported to be effective and safe.[44] The prevalence and size of colorectal polyps increases with age. Studies reporting the outcome of endoscopic resection of very large polyps (>40mm) in elderly patients (>75 years) are limited. For optimal decision making whether to recommend removing these polyps in the elderly more information about the safety in this group is warranted. In **chapter 5,** we evaluated the safety of EMR for large non-pedunculated polyps in elderly who are even more at risk for postoperative morbidity.

Despite the availability of advanced endoscopic techniques, the number of referrals for surgical resection of benign polyps has doubled in our hospital since the implementation of the bowel cancer screening program.[45] This has led to the development of a new minimally invasive technique in our hospital to achieve en-bloc resection of colonic polyps and avoid major surgical resection: **colonoscopic assisted laparoscopic wedge resection (CAL-WR)**. One of the potential benefits of this technique is that no anastomosis is needed (Figrue 4). The technique we applied was described in a small cohort of 8 patients and demonstrated promising results in terms of low morbidity and no mortality.[46] However, the technique has not yet been clinically evaluated. In **chapter 6,** we prospectively investigated the safety and effectiveness of CAL-WR for macroscopic benign colonic polyps unsuitable for excision with standard endoscopic techniques.

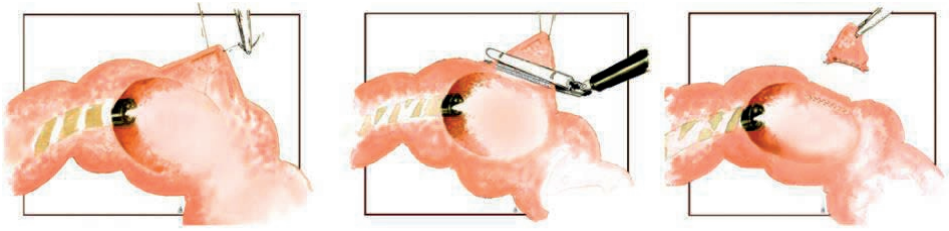


Figure 4. Systematic approach of CAL-WR

Standard therapy for locally advanced rectal cancer is nCRT to downgrade the tumor followed by total mesorectal excision (TME). However, histopathology of resected TME specimen shows disappearance of malignant tumor and lymph nodes – a pathological complete response (pCR) – in 15-20% of patients following nCRT.[47] One could argue that these patients underwent unnecessary major surgical resection. A

watch-and-wait strategy for locally advanced rectal cancer was first proposed by Habr-Gama[48] in 2004 and since then, several studies have reported clinical outcome and oncological safety.[49,50] Selected patients with apparent clinical complete response after chemo-radiation are offered the opportunity for organ preservation with a watch-and-wait policy instead of TME. Organ preservation starts with structural multidisciplinary response evaluation with digital examination, endoscopy, rectal MRI and thoracic and abdominal CT after chemo-radiation to identify the patients with (near-) complete response. In the Isala Hospital, Zwolle, we started structural response evaluation in 2015 in collaboration with the Antoni van Leeuwenhoek Hospital, Amsterdam. In **Chapter 7,** we aimed to evaluate the effectiveness of this multidisciplinary response evaluation by comparing the number of pCRs (unnecessary surgery) after nCRT before- and after implementation of multidisciplinary response evaluation.

When organ preservation with advanced endoscopic techniques or watch-and-wait policy is not possible, the only curative option is oncological resection after proper CRC staging and patient optimization. However, for patients presenting at the emergency department with acute left sided obstruction there is no time for prehabilitation. For decades, the treatment of choice was emergency resection. However, during this emergency setting the morbidity, mortality and permanent colostomy rate is high.[51,52]
Another strategy which is gaining popularity is decompression of the colon followed by delayed resection. Revised guidelines recommend performing this bridge to surgery technique instead of emergency resection.[53] Since 2015 decompressing colostomy (DC) became the standard of treatment for acute left-sided obstruction in our hospital. In **Chapter 8**, we describe a consecutive series of 100 patients with acute left sided (benign or malignant) colorectal obstruction. The aim of the study was to evaluate the outcome of decompressing colostomy in terms of morbidity, mortality and stoma reversal.

One of the most feared complications of surgical resection is anastomotic leakage. Anastomotic leakage occurs in approximately 20% of patients after TME surgery and is associated with presacral abscess formation, emergency surgery, morbidity and permanent colostomy.[54] Conventional treatment consists of creating a deviating ileostomy (if not yet performed primarily), in combination with antibiotics and drainage of the cavity via transanal or percutaneous route. Using this strategy,

almost half of the leaks do not heal and may require major salvage surgery.[54,55] A relative novel minimally invasive therapy is endoluminal vacuum therapy (endosponge) that aims to clean the presacral cavity that subsequently collapses and thereby prevents a chronic sinus and improves anastomotic healing rate. In **chapter 9,** we evaluated the effectiveness of endosponge therapy in terms of restored continuity and functional bowel outcome.

PART IV – Radiological surveillance

Most international guidelines recommend radiological surveillance for stage I–III CRC during 5 years following surgery to detect distant recurrences on early basis.[21,22,25,27] However, the percentage of distant recurrence in patients with T1 CRC is expected to be very low. Potential negative effects of this routine radiological surveillance are the detection of (unwanted) incidental findings, higher healthcare costs for society and anxiety for patients waiting for the results of the scan, while the benefits in terms of detection of distant recurrence is deemed low. In **chapter 3,** we evaluated the yield of radiological surveillance for locally and surgically treated T1 CRC patients. The patients were divided into a low risk group for lymph node metastases (low-risk T1 CRC) and high risk group for lymph node metastases (high-risk T1 CRC), based on histological risk features for lymph node metastases.

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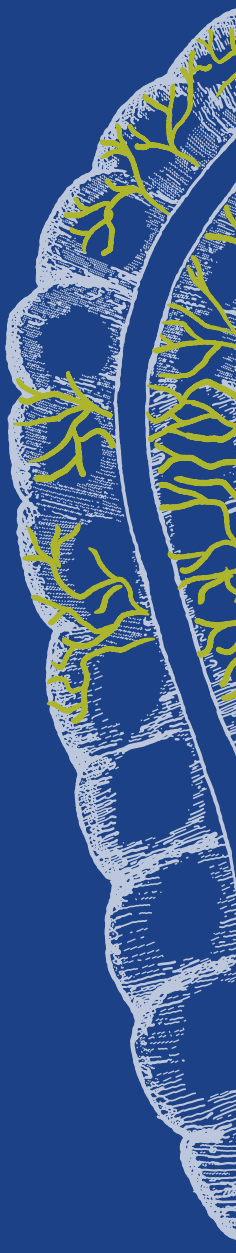
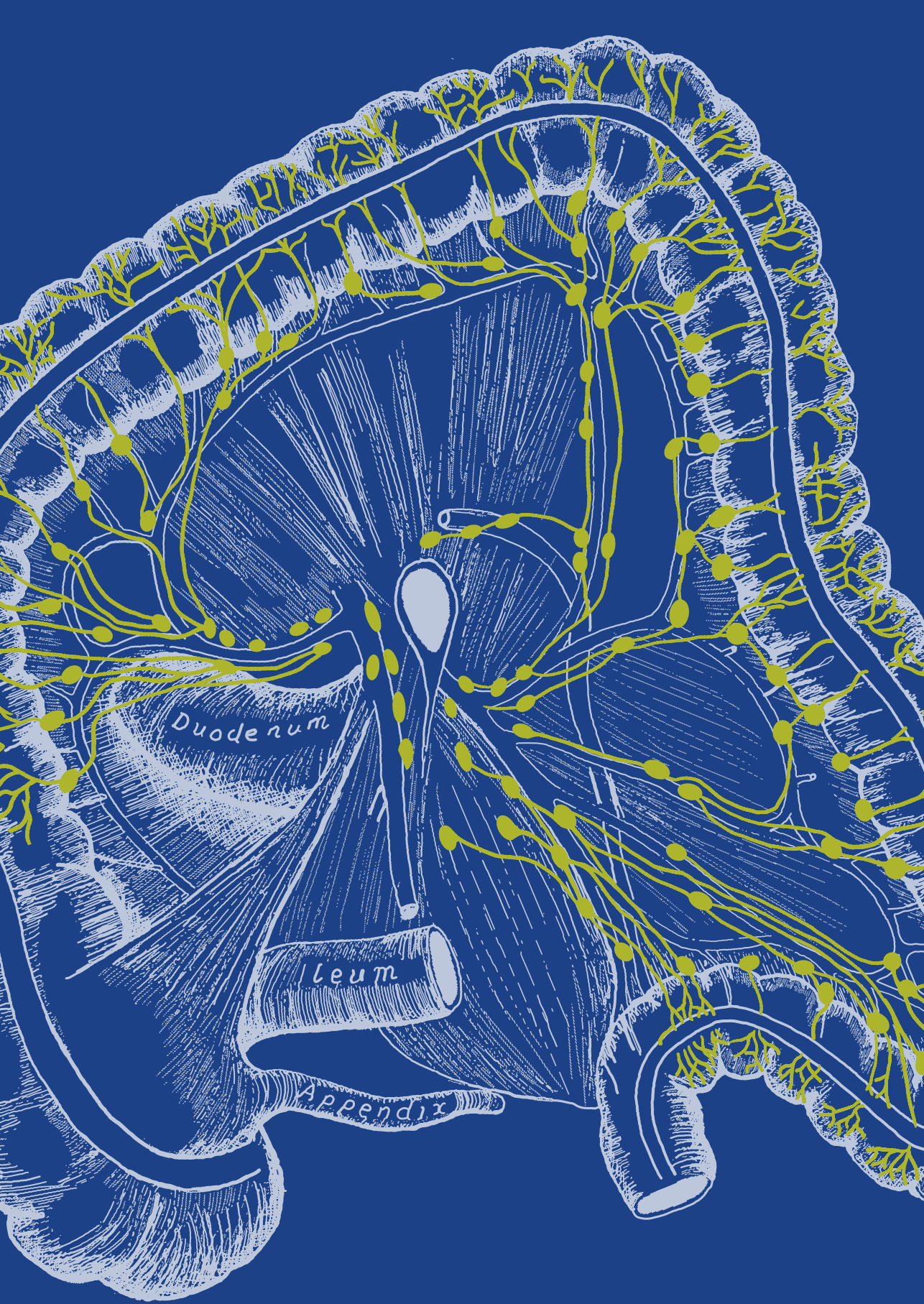
PART I

Screening

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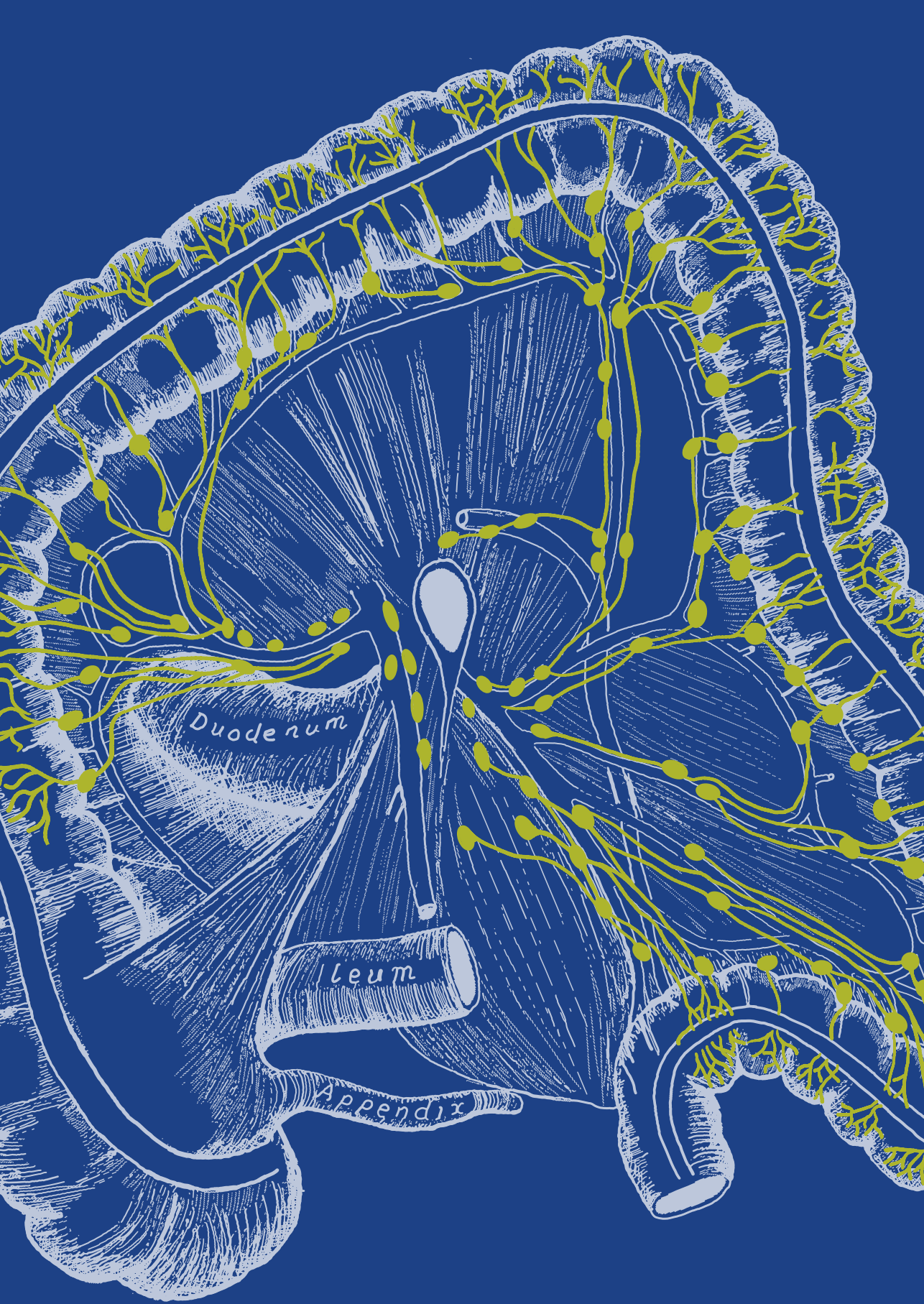
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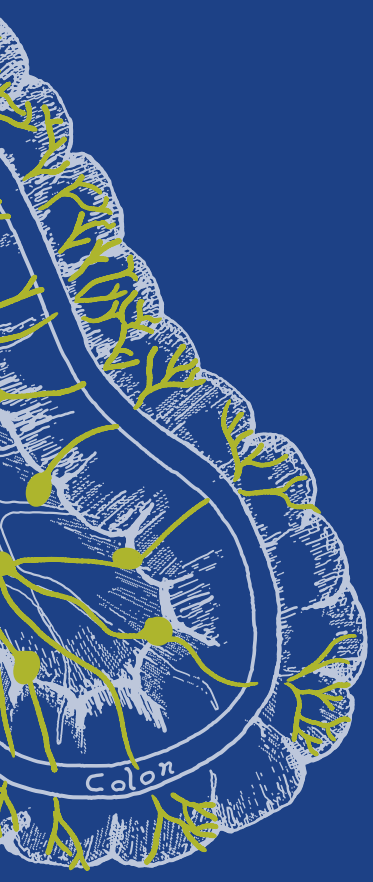
CHAPTER 2

Implications of colonic and extra-colonic findings on CT colonography in FIT positive patients in the Dutch bowel cancer screening program



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ABSTRACT

Objectives

In the Dutch National colorectal cancer (CRC) screening program, patients with a positive faecal immunochemical test (FIT) are referred for a colonoscopy. In a small proportion, because of contraindications, a computed tomographic colonography (CTC) is performed to rule out advanced neoplasia. The aim of our study is to evaluate the intra- and extra-colonic yield of CTC and its clinical implications.

Materials and methods

In this retrospective cohort study, all FIT positive patients who underwent primary (instead of colonoscopy) or secondary CTC (after incomplete colonoscopy) between January 2014 and January 2018 were included. Relevant intra-colonic lesions on CTC were defined as lesions suspected for CRC or >10 mm. Relevant extra-colonic findings were defined as E3 and E4 using the E-RADS classification.

Results

Of the 268 included patients, 66 (24.6%) were suspected to have CRC or 10 mm + lesion on CTC and 56 of them (84.8%) underwent an additional endoscopy. Another 20 patients with <10 mm lesions on CTC underwent additional endoscopy. Overall, 76/268 patients (28.4%) underwent confirmatory endoscopy of which 50 (18.7%) had histologic confirmed advanced neoplasia; 4.9% had CRC and 13.8% advanced adenoma. New relevant extra-colonic findings were detected in 13.8%.

Conclusions

In the Dutch National CRC screening program, a CTC was followed by an endoscopic procedure in more than a quarter of patients, resulting in a significant number of advanced neoplasia. Overall, one out of seven CTCs showed new relevant extra-colonic findings which may lead to further diagnostic/therapeutic work-up. Our results can be important for the informed consent procedure.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and one of the most common types of cancer in the Netherlands.[1–3] In January 2014, the Dutch National CRC screening program was introduced for all individuals aged 55–75 regardless of symptomatic status. This population screening is performed by testing stool samples using home kits with a faecal immunochemical test (FIT). In case of a positive FIT, patients are referred to a colonoscopy screening center for further diagnostics, primarily a colonoscopy. In the period 2014–2017, 6% of the Dutch screenings had a positive FIT. In 81%, an additional colonoscopy was performed resulting in 8% CRC and 42% advanced adenomas (AA).[4] In a small proportion of all FIT-positive screenings (1.7%), a computed tomography colonography (CTC) was performed instead of colonoscopy.[5] Most of them refrained from a colonoscopy because of substantial comorbidity. In case of severe comorbidity, the ultimate goal is than to rule out advanced neoplasia (CRC or advanced adenomas), rather than to find small non-advanced adenomas. For these patients, CTC is a minimal invasive alternative with a high diagnostic performance and less patient discomfort, morbidity and mortality.[6–9] The disadvantage of CTC is the lack of therapeutic options requiring an additional colonoscopy. A side effect of CTC is the detection of extracolonic incidental findings. The clinical relevance of extra-colonic findings is often unknown and requires further investigation depending on the site, size and type of the finding.[10] In a screening population such as a national CRC screening program, incidental findings are undesirable, especially in patients with comorbidities as these findings may lead to additional diagnostic and/or therapeutic work-up.

The use of CTC as an alternative to an intended colonoscopy has been evaluated in the English bowel cancer screening program.[11] All individuals had a positive guaiac-based faecal occult blood test (gFOBT). In this study, advanced neoplasia (CRC or AA) was suspected on CTC in 37.6% and histologically confirmed in 18.5%. Extra-colonic findings were not reported in this study. Data about extra-colonic incidental findings in (asymptomatic) bowel screening populations after a positive FIT test are lacking. Studies that evaluated the extra-colonic findings of CTC in asymptomatic patients without a prior stool test, report clinically important extra-colonic findings (E3 and E4) in 10–16.8%.[6,12] The intra- and extracolonic findings on CTC often have implications for further workup. This should be discussed with individuals during

the informed consent procedure. The aim of our study is to evaluate both intra- and extra-colonic findings on CTC and its clinical implications in FIT positive patients of the Dutch National CRC screening program.

METHODS

This retrospective cohort study was performed in two large teaching hospitals in the Netherlands; Isala Zwolle and the Rijnstate Arnhem. Both hospitals are certified to perform colonoscopy for the Dutch National CRC screening program. Participants with a positive FIT who were referred for an intake interview and underwent a CTC instead of colonoscopy between January 2014 and January 2018 were included (primary CTC group). Patients that underwent a CTC in addition to an incomplete primary colonoscopy in the same study period were also included (secondary CTC group). Patients with a histologically proven CRC who underwent a secondary CTC to rule out synchronous proximal polyps or carcinomas were excluded. The patient details, abnormalities found during CTC, results of subsequent endoscopy and histology reports were recorded and analyzed. An additional subgroup analysis was performed for potential differences between both hospitals in patient selection, indication for CTC and yield of CTC and additional endoscopy. The study was approved by the local medical ethics committee of both hospitals.

Endpoints

The primary endpoint is the presence of clinically relevant intra- and extra-colonic findings on CTC. Relevant intracolonic findings on CTC were defined as lesions suspected for CRC or 10mm+ lesions. After detection of colorectal lesions on CTC, the decision whether or not to perform an additional colonoscopy (or sigmoidoscopy) was made on an individual base. There is no general protocol in the national bowel cancer screening program for the management of suspected colonic lesions. In daily practice, the treating physician and patient (and family members) together will make the decision weighing co-morbidity issues and the risk of a colonoscopy against the risk of developing CRC.

To classify extra-colonic findings, we used the E-RADS classification, ranging from no extra-colonic abnormalities (E1) to a potentially relevant finding (E4), see Table 1 for details. The complete radiology reports (systematic description of colonic and extra-colonic findings) were reviewed and the findings were categorized according

Table 1 Extra-colonic classification following the CT Colonography reporting and Data System (E-RADS)

Score	Description
E0, limited examination	Compromised by artifact; evaluation of extracolonic tissues severely limited; not used in practice by our program
E1, normal examination or anatomic variant	No extracolonic abnormalities visible; no workup indicated
E2, clinically unimportant finding	Examples: simple liver or kidney cyst, cholelithiasis without cholecystitis; no workup indicated
E3, likely unimportant, incompletely characterized	Example: minimally complex or homogeneously hyperattenuating kidney cyst; workup may be indicated; dependent on specific clinical scenario
E4, potentially important finding	Examples: solid kidney mass, aortic aneurysm; workup generally indicated, but dependent on specific clinical scenario; communicate to referring physician as per accepted practice guidelines

to the E-RADS classification. Clinically relevant extra-colonic findings were defined as an E3 and E4 score.[13] The clinically relevant extra-colonic findings were classified as new if they were not described in formerly available radiology reports. The need for further diagnostic and/or therapeutic workup of extra-colonic findings was discussed with the patient by weighing the pros and cons against each other depending on the type of finding. The costs for additional diagnostic and/or therapeutic workup are provided by the Dutch health insurance company.

Secondary endpoints were the number of patients that underwent an additional endoscopy (colonoscopy or sigmoidoscopy) and the number of advanced neoplasia found. Colonoscopy is the preferred test after positive CTC, but in daily practice also sigmoidoscopy was performed for only distal colonic lesions. Advanced neoplasia was defined as histologically confirmed CRC and/or AA. AA was defined as adenoma ≥10mm, tubulovillous adenoma (>25% villous component) or high-grade dysplasia. Routinely, the endoscopic examination, especially colonoscopy, is performed with conscious sedation (intravenous midazolam and fentanyl).

CTC technique

All CTCs were reviewed by specialized CT radiologists whose experience ranges between 3 and 25 years of working with virtual colonoscopy images. All worked with Philips IntelliSpace Portal with CT-colonography software and computer-aided detection (CAD) and used 3D viewing, or 'filetview', utilizing 2D views in case of relative doubt. Patients were scanned in prone and supine positions. Automatic exposure control was used in all patients. Tube voltage during scanning was 130 kV. Milliamperage values were adjusted according to contrast agent administration and patient size (around 50–95 mAs). Bowel preparation was accomplished by means of

a low-residue diet and cathartic cleansing with oral administration of sodium ioxitalamate (Telebrix Gastro) starting 24 h prior to CTC examination. Spasmolytics (Buscopan) were administered to reduce insufflation-related discomfort and facilitate bowel evaluation. The reporting of extra-colonic findings was performed routinely.

Statistics

All analyses were performed using Statistical Package of Social Sciences version 25 (SPSS), a p-value <.05 was considered significant. Descriptive statistics were reported as median with range or count with proportion. Non-parametric continuous data were compared using Mann–Whitney U test. Categorical data were analyzed using Chi-square test.

Table 2 Baseline characteristics and indications for CTC

Total CTCs	268	
Male - n (%)	156	(58.2)
Age - Median [range]	69	[57-76]
ASA - Median [range]	3	[1-4]
ASA I	*12*	*(4.5)*
ASA II	*85*	*(31.7)*
ASA III	*152*	*(56.7)*
ASA IV	*19*	*(7.1)*
Indications for primary CTC – n (%)	215	(80.2)
Co-morbidity	*185*	*(86.0)*
Patient preference	*26*	*(12.1)*
History of incomplete colonoscopy	*2*	*(0.9)*
Inability for proper bowel preparation	*2*	*(0.9)*
Indications for secondary CTC – n (%)	53	(19.8)
Dolichocolon/ looping	*13*	*(24.5)*
Diverticulosis	*11*	*(20.8)*
Fixed sigmoid	*9*	*(17.0)*
Patient discomfort	*8*	*(15.1)*
Poor bowel cleaning	*3*	*(5.7)*
Poor clinical condition	*2*	*(3.8)*
Incisional hernia	*1*	*(1.9)*
Other	*6*	*(11.3)*

CTC indicates Computed Tomography Colonography; ASA, American Society of Anesthesiologists.

RESULTS

Of the 7008 FIT positive patients who were referred for an intake interview (3042 at Isala and 3966 at Rijnstate), 268 patients (3.8%) were eligible for inclusion (215 patients (3.1%) with primary CTC and 53 patients (0.8%) with secondary CTC. The baseline characteristics and indications for CTC are presented in Table 2.

Intra-colonic findings

Details of relevant intra-colonic findings on CTC and histological findings after confirmatory endoscopy are presented in Figure 1 and Table 3. In the primary CTC group (n = 215), 59 patients (27.4%) were suspected to have clinically relevant lesions on CTC (CRC or 10mm+ lesions). Out of these 59 patients, an additional endoscopy was performed in 49 patients (83.1%); colonoscopy in 25 patients and sigmoidoscopy in 24 patients. In the other 10 patients, endoscopy was not performed due to severe comorbidity (n = 9), or no show (n = 1). In the primary CTC group, 34 patients (15.8%) were diagnosed with advanced neoplasia after confirmatory endoscopy; 10 patients (4.7%) had a histologically proven CRC and 24 patients (11.2%) had one or more AA(s). Another 19 patients with lesions <10mm on CTC underwent additional colonoscopy. Notably, 10 patients had AAs and no patients had CRC in this group. Ultimately, 31.6% (68/215) of patients with a primary CTC underwent an additional endoscopic procedure, resulting in the detection of advanced neoplasia in 44 of 215 patients (20.5%). A complication after endoscopy occurred in one patient. This patient developed a post-polypectomy bleeding, requiring a new endoscopic intervention.

In the secondary CTC group (n = 53), seven patients were suspected to have relevant lesions on CTC; five of them underwent a second colonoscopy with cecal intubation, one underwent sigmoidoscopy and in one patient the intent colonoscopy could not be performed due to stenotic diverticulosis. Three patients (5.7%) had histologically proven CRC and three patients (5.7%) turned out to have an AA. One patient with a lesion <10mm on CTC underwent additional endoscopy; no AA or CRC was found.

All 13 patients with diagnosed CRC were treated with curative intent by surgical- or endoscopic resection or with chemoradiation followed by a Watch and Wait Policy.

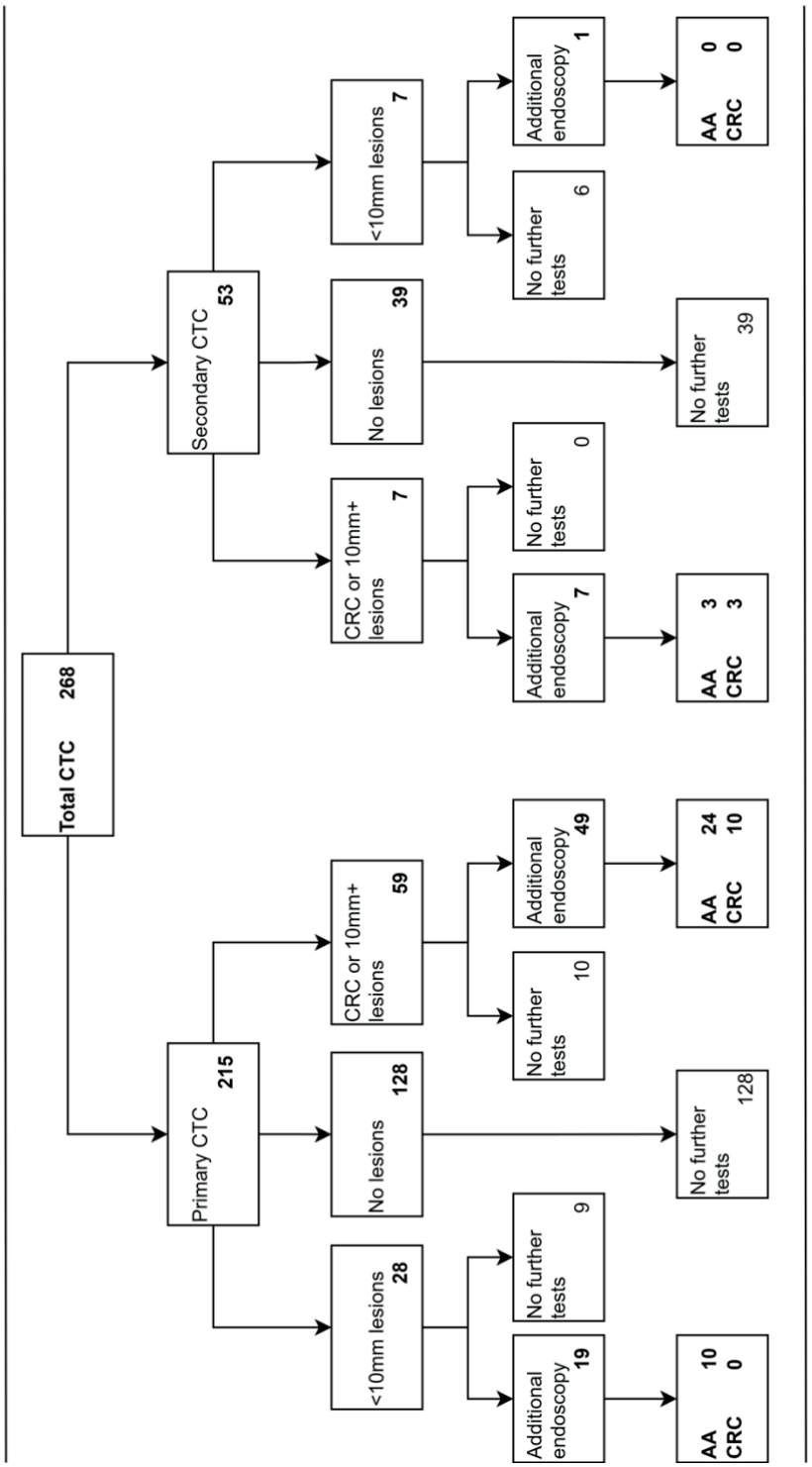

Figure 1. Flowchart of the included patients and results of CTC and histology

Table 3 Intra-colonic findings on CTC and histological findings after endoscopy

	Primary CTC n = 215		Secondary CTC n = 53		Total CTC n = 268	
	CRC or 10 mm+	**<10 mm**	**CRC or 10 mm+**	**<10 mm**	**CRC or 10 mm+**	**<10 mm**
Patients with colonic lesions on CTC (% of total CTCs)	59 (27.4)	31 (14.4)	7 (13.2)	6 (11.3)	66 (24.6)	37 (13.8)
Patients with advanced neoplasia# (% of total CTCs)	34 (15.8)	10 (4.7)	6 (11.3)	-	40 (14.9)	10 (4.7)
CRC (% of total CTCs)	10 (4.7)	-	3 (5.7)	-	13 (4.9)	-
AA (% of total CTCs)	24 (11.2)	10 (4.7)	3 (5.7)	-	27 (10.1)	10 (4.7)

CRC and/or advanced adenoma (=adenoma ≥10 mm, tubulovillous adenoma (>25% villous component), high-grade dysplasia)
CTC indicates Computed Tomography Colonography; CRC, colorectal cancer; AA, advanced adenoma

Extra-colonic findings

Among both primary and secondary CTCs (n = 268), in total 65 (24.3%) showed extra-colonic findings classified as E3 and/or E4. Of these 65 extra-colonic findings, 28 were already detected by previously performed radiological examinations. The remaining 37 findings were classified as new, because they were not detected in formerly available radiological reports. Ultimately, 13.8% (37/268) new extra colonic findings were found; 64.9% (24/37) of these findings resulted in additional follow-up, referral to another specialty or treatment. A detailed overview of the relevant incidental extra-colonic findings is presented in Table 4. The pancreatic lesion turned out to be an ampulla carcinoma and the suspected ossal lesions a chondrosarcoma. The pulmonary lesion was defined as benign after two years of follow-up, and the patient with lymphadenopathy continued follow-up without additional therapy.

Table 4 Overview of new extra-colonic findings on CTC according to ERADS classification

Total CTCs (primary and secondary)	268	
Total new extra-colonic findings (E3 + E4) - n (%)	37	(13.8)
E3 - n (%)	28	(10.4)
Vascular (Abdominal Aortic Aneurysm <5cm or vascular stenosis)	*7*	*(2.6)*
Adrenal incidentalomas	*5*	*(1.9)*
Gastro-esophageal-duodenal wall thickness	*4*	*(1.5)*
Hepatic lesion(s)	*3*	*(1.1)*
Pulmonary lesion(s)	*3*	*(1.1)*
Inguinal hernia	*2*	*(0.7)*
Adnexal lesion	*1*	*(0.4)*
Calcifications pancreas	*1*	*(0.4)*
Hydronephrosis	*1*	*(0.4)*
Renal lesion	*1*	*(0.4)*
E4 - n (%)	9	(3.4)
Abdominal Aortic Aneurysm >5cm	*5*	*(1.9)*
Pulmonary nodule	*1*	*(0.4)*
Pancreatic lesion	*1*	*(0.4)*
Ossal lesion	*1*	*(0.4)*
Lymphadenopathy	*1*	*(0.4)*

Subgroup analysis between both hospitals

Of all 268 CTCs, 153 CTCs (57%) were performed at Isala and 115 (43%) at Rijnstate. We found significant differences between the two hospitals for age, ASA score and indications for primary and secondary CTC (Table 5). Overall, we did not find significant differences between the hospitals for the detection of suspicious intra-colonic (p = 0.216) or extracolonic (p = 0.688) findings on CTC. Histologically confirmed advanced neoplasia was found in 27 patients (17.6%) at Isala hospital and in 23 patients (20.0%) at Rijnstate hospital (p = 0.768).

Table 5 Subgroup analysis between both hospitals

	Isala n = 153	Rijnstate n = 115	p- value
Age – Median [range]	69 [57-76]	67 [57-76]	0.018
ASA – Median [range]	3 [1-4]	3 [1-4]	<0.001
ASA I	*4 (2.6)*	*8 (7.0)*	
ASA II	*45 (29.4)*	*40 (34.8)*	
ASA III	*102 (66.7)*	*50 (43.5)*	
ASA IV	*2 (1.3)*	*17 (14.8)*	
Primary CTC - n (%)	136 (88.9)	79 (68.7)	<0.001
Co-morbidity	*123 (80.4)*	*62 (78.5)*	
Personal preference	*13 (9.6)*	*13 (16.5)*	
History of incomplete colonoscopy	-	*2 (2.5)*	
Inability for proper bowel preparation	-	*2 (2.5)*	
Secondary CTC - n (%)	17 (11.1)	36 (31.3)	<0.001
Dolichocolon/ looping	*4 (23.5)*	*9 (25.0)*	
Diverticulosis	*1 (5.9)*	*10 (27.8)*	
Fixed sigmoid	*2 (11.8)*	*7 (19.4)*	
Patient discomfort	*6 (35.3)*	*2 (5.6)*	
Poor bowel preparation	*1 (5.9)*	*2 (5.6)*	
Poor clinical condition	*1 (5.9)*	*1 (2.8)*	
Incisional hernia	*1 (5.9)*	-	
Additional examination	*1 (5.9)*	-	
Unknown	-	*5 (13.9)*	

ASA indicates American Society of Anesthesiologists; CTC, Computed Tomography Colonoscopy.
^ Mann Whitney U, * Chi square

DISCUSSION

This retrospective study reports the intra- and extra-colonic yield of CTC in FIT positive patients of the Dutch National CRC screening program, and indicates that 24.6% of the patients were suspected to have relevant intra-colonic findings on CTC. After confirmatory endoscopy, 4.9% were diagnosed with CRC and 13.8% with AA. Clinically new or progressing relevant extra-colonic findings were found in 13.8% of the patients.

Although the preferred test for FIT positive patients is colonoscopy, 3.8% of the patients in our study underwent CTC instead of colonoscopy, mostly due to comorbidity. In these patients, CTC is often proposed as an alternative examination to rule out advanced neoplasia, especially CRC. Prior studies suggest CTC has similar sensitivity to colonoscopy to detect CRC and around 85% sensitivity to detect 10mm+ lesions.[14,15] Other studies reported equal detection rates of CRC and AAs at CTC and colonoscopy.[7,16–19] The use of CTC for patients with a positive gFOBT in a national bowel screening program was evaluated by *Plumb et al*.[11] The authors

reported suspected lesions on CTC (CRC or 10mm+ lesions) in 37.6% of the patients with subsequent confirmatory endoscopy in 92%. Ultimately, additional endoscopy after CTC was performed in 33% of all CTC screenings and advanced neoplasia was detected in 18.5% (4.5% CRC). This proportion of advanced neoplasia was low compared to 32.7% detected advanced neoplasia in the group of patients that underwent primary colonoscopy screening in their study.

Our study is the first study that reports the intra- and extra-colonic findings in a FIT positive national bowel cancer screening population. Our CRC or AA detection rate, 4.9% and 13.8% respectively, is comparable to *Plumb et al.* and substantially lower compared to the yield of colonoscopy in our national bowel screening program (8% CRC and 42% AA).[4,11] There are several explanations for this. Differences between the size of the lesion on CTC and colonoscopy might alter the intra-colonic detection rate. Small lesions on CTC can be missed, as CTC is less sensitive in detecting small lesions; 16.9% of the patients in our study with suspected relevant lesions on CTC did not undergo additional endoscopy; furthermore, AA is defined by a tubulovillous histology which can be found in adenomas <10 mm. The question is whether the lower detection rate observed in bowel screening programs has an impact on the life expectancy of patients with serious morbidity. The proportion of patients that did not undergo further investigation in our study is high (16.9%); however, the intra-colonic findings of CTC in these patients with severe co-morbidity most likely do not alter their life expectancy. Also, missed small lesions on CTC will probably not alter life expectancy in this study population. We demonstrated that 70% of the patients had no suspicious intra-colonic findings and could be reassured. In patients that underwent CTC instead of colonoscopy, an additional endoscopy was performed in 28.4% for histological diagnosis or treatment of colonic lesions detected on CTC.

We found new relevant (E3 and E4) extra-colonic findings on CTC in 13.8% of the patients. Several prior studies reported the extra-colonic findings on CTC in asymptomatic, but non-bowel screening populations without prior stool test. *Lin et al.* reported in a systematic review relevant (E3 and E4) extra-colonic findings in 5–37% .[20] A randomized controlled trial in a general Dutch population reported extra-colonic findings in 10%.[6] Furthermore, *Cash et al.* reported in a large cohort of 1410 patients, who underwent screening- or surveillance CTC in patients and aged ≥65 years without prior stool test, E3 and E4 rates of 18.2%.[12] For patients with severe

co-morbidity, detection of extra-colonic findings on CTC might be undesirable and lead to undesired medicalization. Debatable in our results is the question of whether adrenal incidentalomas are clinically relevant as radiologists do not describe adrenal incidentalomas consistently in their reports. However, in our centers, it often led to referral to the endocrinologist, and therefore we scored them as E3 findings.

Colonoscopy remains the gold standard in the CRC bowel screening program and CTC should only be performed in cases of significant comorbidity and in individual cases because of personal reasons. For these cases, the results of our study are important for clinical implication in daily practice and the informed consent procedure. The chance that patients can be reassured after negative intra-colonic findings on CTC is 70%. However, patients should be informed about the possibility of extra-colonic findings on CTC, the risk of missed small intra-colonic lesions and should be aware that they still have a 30% chance that additional endoscopy is recommended following the results of CTC. Physicians should be critical if CTC is recommended in patients unfit for colonoscopy, because one out of six patients did not undergo the indicated additional endoscopy after relevant findings on CTC.

The strength of this study is the multicenter design with a consecutive series of patient who underwent CTC in the setting of the Dutch National bowel screening program. Although, some baseline characteristics were different between the hospitals, the outcome of endoscopy and the extra-colonic findings were similar.

Our study is limited by the retrospective design and the relatively small sample size. Although all radiological reports were reviewed for patients with E3 or E4 findings on CTC, possible radiologic examinations performed in other hospitals are missing. Also, intravenous contrast was not consequently used in the performed CTCs and inter-observer variability might be introduced as the CTCs were not revised. Furthermore, in clinical practice, not every clinically relevant extra-colonic finding will be followed by a diagnostic/therapeutic work-up.

Conclusion

In the Dutch National CRC screening program, a primary CTC was performed in a small proportion of referred FIT positive patients mostly due to severe comorbidity. A primary CTC was followed by an additional endoscopy procedure in more than a quarter of patients. Overall, one out of seven CTCs showed new extra-colonic findings leading to further diagnostic and/or therapeutic work-up. The substantial chance of further investigations following a CTC should be discussed with patients during the informed consent procedure.

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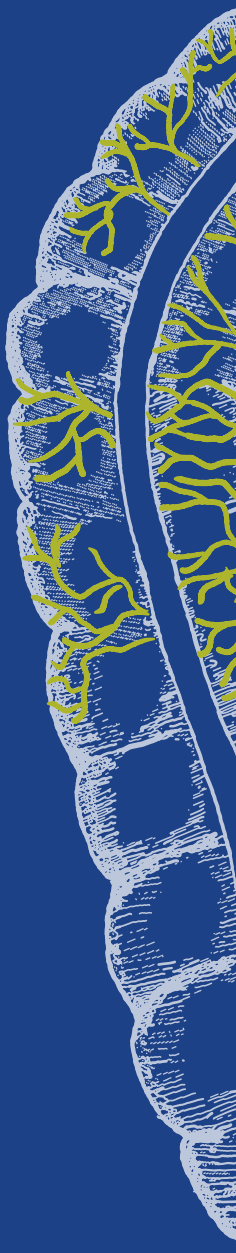
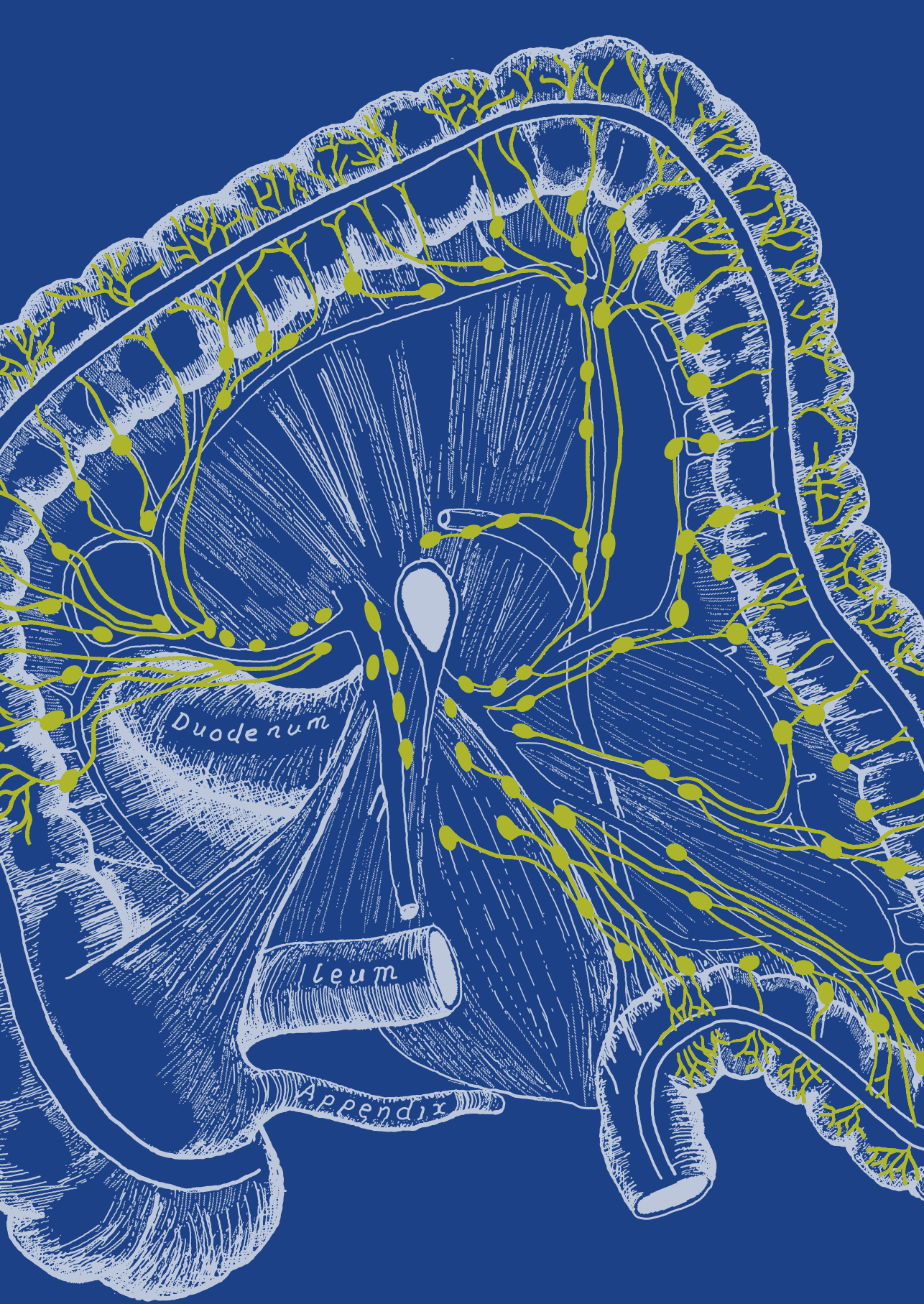
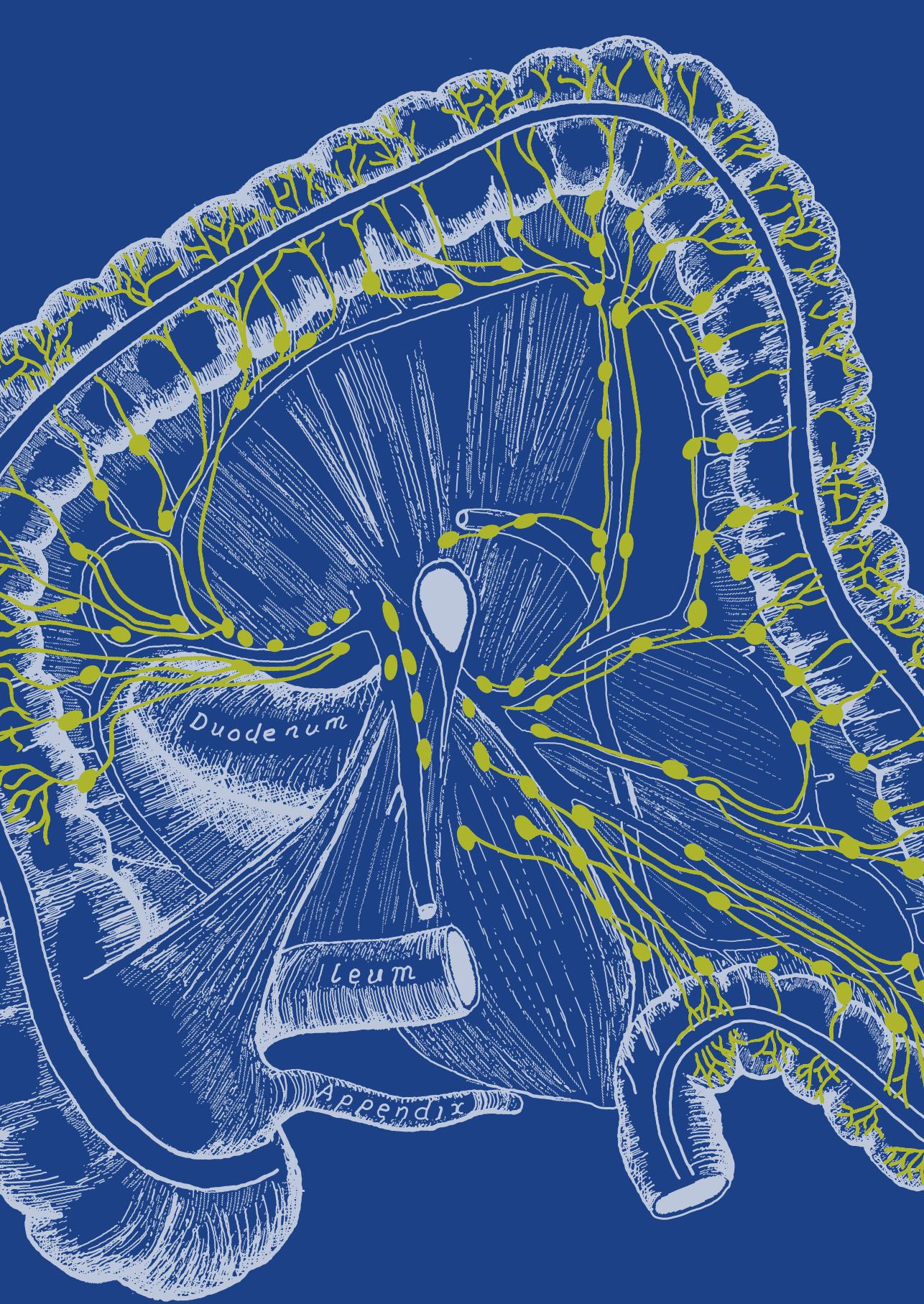
PART II

Imaging




Duodenum
Ileum
Appendix


Duodenum
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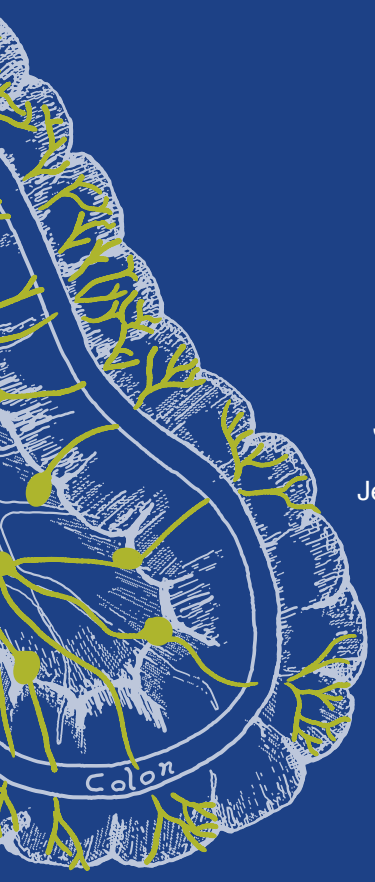
CHAPTER 3

Diagnostic value of radiological staging and surveillance for T1 colorectal carcinomas: a multicenter cohort study



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ABSTRACT

Background

The role of radiological staging and surveillance imaging is under debate for T1 colorectal cancer, as the risk of distant metastases is low and imaging may lead to detection of incidental findings. The aim of this study is to evaluate the yield of radiological staging and surveillance imaging for T1 colorectal cancer.

Methods

In this retrospective multicenter cohort study, all patients of 10 Dutch hospitals with histologically proven T1 colorectal cancer who underwent radiological staging in the period 2000-2014 were included. Clinical characteristics, pathological, endoscopic, surgical and imaging reports at baseline and during follow-up were recorded and analyzed. Patients were classified as high-risk T1 colorectal cancer if at least 1 of the histological risk factors (lymphovascular invasion, poor tumor differentiation, deep submucosal invasion or positive resection margins) was present and as low-risk when all risk factors were absent.

Results

Of the 628 included patients, 3 (0.5%) had synchronous distant metastases, 13 (2.1%) malignant incidental findings and 129 (20.5%) benign incidental findings at baseline staging. Radiological surveillance was performed among 336 (53.5%) patients. The 5-year cumulative incidence of distant recurrence, malignant and benign incidental findings were 2.4% (95% confidence interval: 1.1-5.4%), 2.5% (95% confidence interval: 0.6-10.4%) and 18.3% (95% confidence interval: 13.4-24.7%), respectively. No distant metastatic events occurred among low-risk T1 colorectal cancer patients.

Conclusion

The risk of synchronous distant metastases and distant recurrence in T1 colorectal cancer is low, while there is a substantial risk of detecting incidental findings. Radiological staging seems unnecessary prior to local excision of suspected T1 colorectal cancer and after local excision of low-risk T1 colorectal cancer. Radiological surveillance should not be performed in patients with low-risk T1 colorectal cancer.

INTRODUCTION

The incidence of early colorectal cancer (CRC), i.e. T1 CRC, has been rising since the implementation of bowel screening programs worldwide.[1] Patients with CRC often die due to distant metastases caused by lymphatic or hematological spread of tumor cells. Therefore, the standard diagnostic work-up for CRC includes radiological imaging of the chest and abdomen to exclude synchronous distant metastases and prevent unnecessary major surgery for patients with incurable disseminated disease. However, the risk of lymph node metastases (LNM) and synchronous distant metastases in T1 CRC is low, especially in the absence of histological high-risk features for LNM.[2-5]

In the Netherlands, there is large practice variation among physicians and hospitals whether radiological staging or follow-up should be performed for T1 CRC.[6] In international guidelines there is no consensus whether or not radiological staging and follow-up should be performed.[7-17] Radiological imaging can lead to the discovery of unexpected extra-colonic incidental findings. Although most of these unexpected anomalies are unlikely to be clinically relevant, many require further investigation or follow-up and can result in unnecessary treatments, anxiety for patients and physicians and increased healthcare costs.[18,19] An earlier study reported an incidental finding rate of 16% on radiological staging in patients with stage I-IV CRC.[20] The risk of detecting these findings should be discussed during an informed consent procedure prior to imaging.[21]

To date, there are no studies that have investigated the yield of radiological staging and follow-up imaging in patients with T1 CRC. The aim of this study was to evaluate the diagnostic value in terms of distant metastases or distant recurrence, as well as the incidental finding rate of radiological staging and surveillance imaging in patients with T1 CRC.

METHODS

Study design and patient selection

The study design was a multicenter retrospective cohort study. Patients from 10 Dutch hospitals diagnosed with histological proven T1 CRC between January 2000 and December 2014 were selected from the Dutch Cancer Registry. Patients were

included in the study when they had undergone radiological staging of the abdomen and chest with Computed Tomography (CT), ultrasound (US), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) or chest X-ray, within 2 months after macroscopic or histological diagnosis of the T1 CRC. Patients referred for colonoscopy for a suspected asymptomatic colorectal lesion which was detected on prior imaging were excluded, because most of these patients were already under examination or treatment for a secondary malignancy or had symptomatic incidental findings on the performed imaging, which would distort the incidental finding rate. Other exclusion criteria were hereditary predisposition to CRC, inflammatory bowel disease, metachronous CRC (defined as CRC in the previous 5 years before detection of T1 CRC, synchronous CRC at the time of detection of T1 CRC), non-CRC-related death within 1 year after treatment, non-adenocarcinoma or neo-adjuvant radiotherapy. The study was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (UMCU) (reference number: 15-487).

Endpoints

Primary outcomes were the presence of synchronous distant metastases at radiological baseline imaging and the presence of distant recurrence during follow-up. Distant metastases (synchronous metastases during baseline imaging as well as distant recurrence) were defined as metastases to extra-colonic organs, bones, peritoneum or distant lymph nodes outside the surgical plane, confirmed with histological examination, intra-operative findings (palpation or intra-operative ultrasound) or growth of lesions suspect for metastases during radiological follow-up.

Secondary outcomes were the presence of relevant extra-colonic incidental findings on radiological baseline imaging and during follow-up imaging. Relevant incidental findings were defined as malignant lesions (i.e. histologically proven or lesions suspect for malignancy which showed progression during radiological follow-up) which were not CRC-related, or benign lesions requiring additional treatment, diagnostic examinations, additional follow-up or referral to other medical specialties. Lesions that were already known before T1 CRC diagnosis were not counted as incidental findings.

Data collection

In each participating center, the patient and tumor characteristics, diagnostic and surveillance endoscopic reports, staging and follow-up radiological reports and the histology reports were collected from the electronic patient records. Patient characteristics included age and gender. Tumor characteristics included morphology, size and location of the tumor. Local excision was specified as (en-bloc or piecemeal) snare polypectomy, (en-bloc or piecemeal) endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) or transanal endoscopic microsurgery (TEM). Surgical resection was specified as surgical resection respecting oncological principles including draining lymph nodes. The radiology reports during baseline and follow-up imaging were analyzed to determine the presence of distant metastases and incidental findings. For radiological follow-up, we only analyzed patients that underwent radiological follow-up performed in the context of T1 CRC surveillance and performed at least 2 months after T1 CRC diagnosis. For locally treated T1 CRCs with incomplete histological information in the histology reports, the original specimens were re-evaluated by the local pathologist of each participating hospital in order to provide complete histological information on the cases. For all pedunculated T1 CRCs, double reading by 2 blinded expert gastrointestinal pathologists (M.L. and J.O.) was performed in the context of another study. The data from these evaluations were also used for the current study.[22]

Histological evaluation

The tumors were assessed according to the World Health Organization of tumors.[23-25] T1 CRCs were classified as high-risk T1 CRC if 1 or more of the following risk factors was present: (1) lymphovascular invasion (LVI), (2) poor tumor differentiation, (3) deep submucosal invasion (≥1000µm/SM2-3 in non-pedunculated and Haggitt 4 in pedunculated T1 CRCs), or (4) positive (R1) or undetermined resection margins (Rx). R0 resection was defined as a microscopically cancer-free resection margin, irrespective of the distance in millimeters, as the risk of local intramural residual cancer is comparable between 0.1-1.0mm and >1.0mm margins (in the absence of other histological high-risk features).[26] T1 CRCs were classified as low-risk when all these histological risk factors were absent and as undetermined-risk T1 CRC if at least 1 of the histological parameters was missing or could not be determined, while the other known risk factors were absent.

Statistics

All analyses were performed using Statistical Package of Social Sciences version 26.0 (SPSS). A two-sided p-value of <0.05 was considered statistically significant. Normality was tested using Kolmogorov-Smirnov test. Continuous variables were reported as means with standard deviations if the data were parametric or as medians with ranges if the data were non-parametric. Categorical data were analyzed using Chi-squared test or Fisher's exact test, as appropriate.

The incidence of distant recurrence and incidental findings during follow-up was calculated among patients that underwent abdominal or thoracic imaging which was performed in the context of T1 CRC surveillance using survival analysis. Patients with distant metastases or a second primary malignancy during baseline imaging were excluded for follow-up analysis. The start of follow-up was the date of CRC diagnosis. Patients were censored during follow-up when endoluminal recurrence, distant metastases or a second primary malignancy was found. We used Kaplan Meier and Cox proportional hazard regression analysis to estimate the risk of distant recurrences and incidental findings during follow-up. Since there was a shift from ultrasound or X-ray towards CT over the years, we performed a subgroup analysis to detect differences in radiological outcomes during the different time periods. We divided the patients in 3 time periods: 2000-2004, 2005-2009 and 2010-2014.

RESULTS

Baseline characteristics

A total of 1130 patients with T1 CRC were identified, of which 628 (55.6%) patients met the eligibility criteria and were included in the analysis (Figure 1). An overview of the baseline characteristics is presented in Table 1.

Radiological findings in staging of T1 CRC patients

Of the included T1 CRC patients, synchronous distant metastases on radiological staging were confirmed in 3 of 628 patients (0.5%). These synchronous distant metastases were found in 0 of 78 (0%) low-risk cases, in 1 of 312 (0.3%) high-risk cases and in 2 of 238 (0.8%) undetermined-risk CRC cases. The histological characteristics of these metastatic cases are provided in Table 2. Two of these

patients underwent palliative therapy and one patient underwent curative resection of the lung metastases.

A total of 162 incidental findings were detected at radiological staging in 142 of 628 patients (22.6%). Thirteen (2.1%) patients had a secondary primary extra-colonic malignancy and 129 patients (20.5%) a benign incidental finding. Twenty patients had two incidental findings on baseline staging. An overview of all incidental findings can be found in Table 3.

Figure 1: flowchart of the included patients

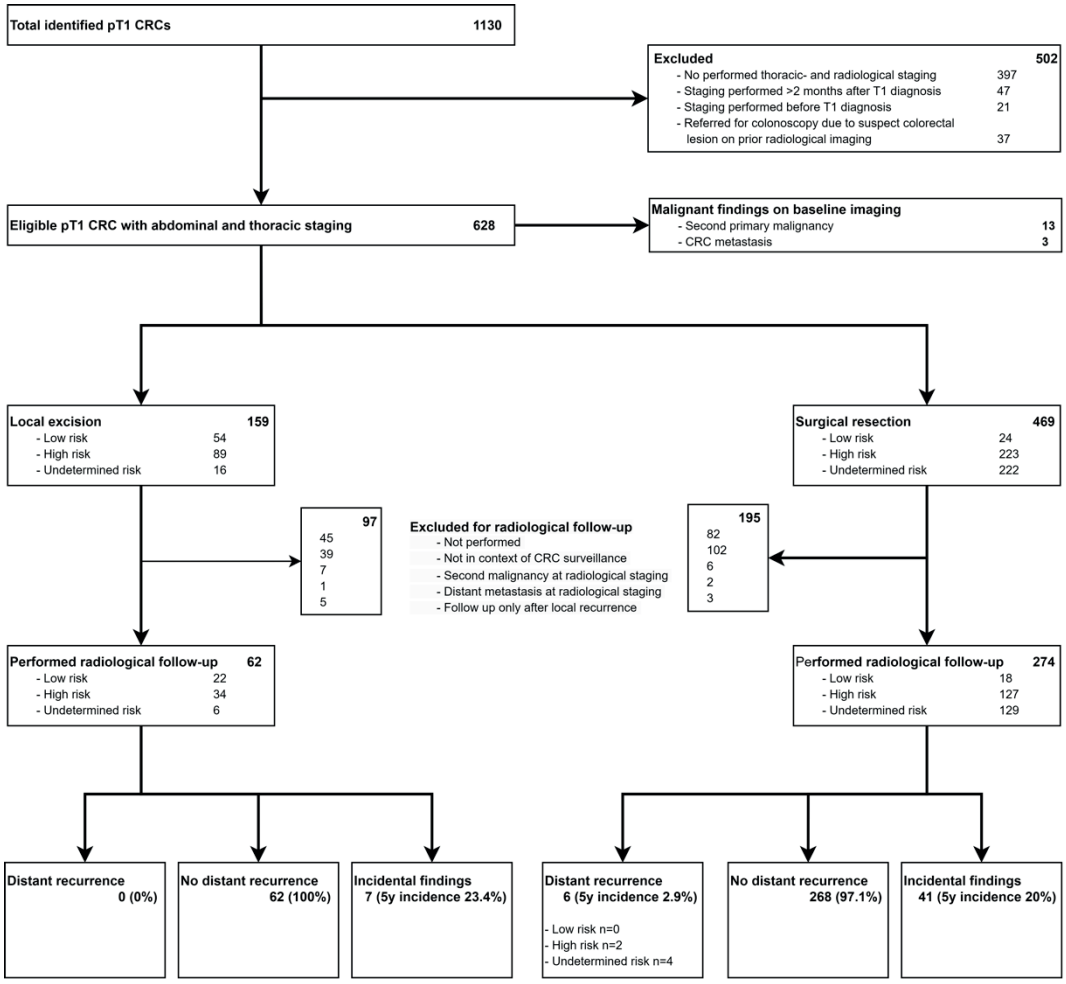


Table 1: Baseline characteristics

Patient characteristics	Patients with radiological staging n (%)	Patients with local excision n (%)	Patients with surgical resection n (%)
Total patients	628	159	469
Male	357 (56.8)	102 (64.2)	255 (54.4)
Age	70 [38-91]	73 [41-88]	69 [38-91]
Histological risk status			
Low-risk	78 (12.2)	54 (34.0)	24 (5.1)
High-risk	312 (49.7)	89 (56.0)	223 (47.5)
Undetermined-risk (unknown)	238 (37.9)	16 (10.1)	222 (47.3)
Tumor size in millimeters – [range]	20 [4-160]	20 [5-60]	23 [4-160]
Tumor location			
Rectum	183 (29.1)	84 (52.8)	99 (21.1)
Left sided	310 (49.4)	65 (40.9)	245 (52.2)
Right sided	133 (21.2)	8 (5.0)	125 (26.7)
Unknown	2 (0.3)	2 (1.3)	-
Tumor morphology			
Pedunculated	197 (31.4)	80 (50.3)	117 (24.9)
Non-pedunculated	358 (57.0)	71 (44.7)	287 (61.2)
Unknown	73 (11.6)	8 (5.0)	65 (13.9)
Lymphovascular invasion			
Present	66 (10.5)	13 (8.2)	53 (11.3)
Absent	344 (54.8)	112 (70.4)	232 (49.5)
Unknown	218 (34.7)	34 (21.4)	184 (39.2)
Differentiation grade			
Grade 1 or 2	500 (79.6)	130 (81.8)	370 (78.9)
Grade 3	29 (4.6)	5 (3.1)	24 (5.1)
Unknown	99 (15.8)	24 (15.1)	75 (16)
Invasion depth			
Superficial	171 (27.2)	74 (46.5)	97 (20.7)
Deep	111 (17.7)	24 (15.1)	87 (18.6)
Unknown	346 (55.1)	61 (38.4)	285 (60.8)
Resection margin based on initial treatment			
R0	444 (70.7)	91 (57.2)	353 (75.3)*
R1 or Rx	184 (29.3)	68 (42.8)	116 (24.7)*
Definitive cancer treatment			
Local excision	159 (25.3)	159 (100.0)	-
Piecemeal snare polypectomy		15 (9.4)	
En-bloc snare polypectomy		64 (40.3)	
Piecemeal EMR		20 (12.6)	
En-bloc EMR		33 (20.8)	
ESD		1 (0.6)	
TEM		23 (14.5)	
Unknown		3 (1.9)	
Primary surgical resection	295 (47.0)	-	295 (62.9)
Completion surgical resection	174 (27.7)	-	174 (37.1)
Lymph node metastases	49 (10.4)		49 (10.4)

CT indicates Computed Tomography; CRC, Colorectal cancer; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; TEM, transanal endoscopic microsurgery.

* the R0 resection was calculated on initial treatment and contained patients with irradical endoscopic resection with subsequently completion surgical resection

Table 2: Original histological specimen of patients with synchronous or recurrent distant metastases.

Event	Histological risk status	Tumor location	Lympho-vascular invasion	Submucosal invasion	Resection	Tumor differentiation	Performed cancer treatment	Total lymph nodes harvested	Lymph node metastases	Location of distant metastases
#1 - Baseline metastases	High-risk	Sigmoid	+	SM3	R0	Grade 2	Primary surgery	1	1	Liver
#2 - Baseline metastases	Undetermined	Rectum	-	N/I	R0	Grade 2	Primary endoscopy	N/A	N/A	Lung
#3 - Baseline metastases	Undetermined	Sigmoid	N/I	N/I	R0	Grade 2	Primary surgery	1	1	Liver
#4 - Distant recurrence	High-risk	Ascending colon	+	SM2	R0	Grade 2	Completion surgery	7	4	Diffuse
#5 - Distant recurrence	High-risk	Cecum	+	N/I	R0	Grade 3	Primary surgery	14	2	Lung
#6 - Distant recurrence	Undetermined	Rectum	N/I	N/I	R0	Grade 2	Primary surgery	2	1	Liver
#7 - Distant recurrence	Undetermined	Rectum	N/I	N/I	R0	N/I	Primary surgery	3	0	Local extraluminal
#8 - Distant recurrence	Undetermined	Rectum	-	N/I	R0	N/I	Completion surgery	0	0	Local extraluminal
#9 - Distant recurrence	Undetermined	Ascending colon	N/I	N/I	R0	N/I	Completion surgery	0	0	Diffuse

N/I indicates not investigated; N/A, not applicable; LNM, lymph node metastases; SM, submucosal invasion.

+ indicates lymphvascular invasion present; - lymphvascular invasion not present

Table 3: Incidental findings at baseline and during follow-up

	Incidental findings during staging (n = 628) n (%)	Incidental findings during follow-up (n = 336) n (%)
Patients with incidental findings	142 (22.6)	48 (14.3)
Total number of incidental findings	162	53
5y cumulative incidence incidental findings, *% (95%CI)*	-	20.4 (15.0-27.5)
Malignant incidental findings	13	4
Renal cell carcinoma	*6*	-
Lung cancer	*3*	*2*
Breast cancer	*1*	-
Urothelial carcinoma of the bladder	*1*	-
Gastrointestinal stroma cell tumor	*1*	-
Non-Hodgkin lymphoma	*1*	-
Prostate cancer	-	*1*
Pancreas cancer	-	*1*
Benign incidental findings	149	49
Hepatic cysts or hemangiomas	*66*	*17*
Benign thoracic lesion	*30*	*14*
Adrenal incidentaloma	*14*	-
Aortic abdominal aneurysm	*11*	*2*
Lymphadenopathy	*5*	*5*
Pancreatic cyst	*4*	-
Gynaecological lesions (uterus/adnex/ovarium)	*4*	-
Symptomatic cholelithiasis	*2*	*2*
Thickened stomach wall	*1*	-
Thickened urinary bladder wall	*1*	-
Mucocele appendix	*1*	-
Renal cyst	*1*	*1*
Spinal degeneration	*1*	-
Hydronefrosis	*1*	*1*
Inguinal hernia	*1*	-
Myxoma	*1*	-
Thyroid nodule	*1*	-
Peri-urethal abnormality	*1*	-
Benign prostate hyperplasia	*1*	*1*
Lipoma	*1*	-
Hepatic cirrhosis	*1*	-
Hepatic steatosis	-	*2*
Colonic wall thickness	-	*2*
Surgical site infection	-	*1*
Abdominal soft tissue mass	-	*1*

y indicates years; CI, confidence interval

Radiological and endoscopic surveillance of T1 CRC after local excision

Of the patients treated with local excision (n=159), 54 had low-risk and 89 high-risk T1 CRC. For the remaining 16 cases with undetermined-risk T1 CRC, the presence or absence of histological risk factors for LNM remained unclear after histological revision (n=7) or the revision could not be performed (n=9).

Radiological surveillance after local excision was performed in 62 of 159 (39.0%) patients (Figure 1). During a median radiological follow-up period of 2.3 years [range: 0.3-5.6 years], no distant recurrence occurred. Malignant incidental findings were detected in 0 patients and benign incidental findings in 7 of 62 patients. The 5-year cumulative incidence of benign incidental findings after local excision was 23.4% (95% confidence interval (CI)) 9.1-54.1%). Details on radiological surveillance and a list of incidental findings can be found in Table 4 and Table 3, respectively.

Endoscopic surveillance was performed in 45 of 54 low-risk patients (83.3%) and in 81 of 89 high-risk patients (91%). Local recurrence occurred in 0 of 45 low-risk patients and in 9 of 81 high-risk patients (Table 4). The 5-year cumulative incidence of local recurrence among the high-risk T1 CRCs was 23.8% (95%CI 11.5-45.5%). All local recurrences were detected with endoscopy. Radiological imaging performed for tumor staging after detection of local recurrence showed synchronous distant metastases in 2 of 9 patients. Notably, one patient with endoscopically treated, completely resected low-risk T1 sigmoid carcinoma showed a new detected malignant sigmoid tumor 2 years later. Local recurrence in this specific case could not be excluded.

Radiological and endoscopic surveillance of T1 CRC after surgical resection

Of the 469 patients treated with surgical resection, 274 (58.4%) underwent radiological surveillance (Figure 1). During a median radiological follow-up period of 3.4 years [range: 0.3-15.4 years], distant recurrence occurred in 3 of 57 rectal cancer patients (5.3%) and 3 of 217 colon cancer patients (1.4%). Malignant incidental findings occurred in 4 of 274 patients and benign incidental findings in 37 of 274 patients. The 5-year cumulative incidence of distant recurrence after surgical resection was 2.9% (95%CI 1.3-6.4%). The 5-year cumulative incidence of malignant and benign incidental findings were 2.8% (95%CI 0.7-11.2%) and 17.7% (95%CI 12.7-24.4%), respectively. Details on histological status of distant recurrences, radiological surveillance and a list of incidental findings can be found in Table 2, Table 4 and Table 3, respectively. All distant recurrences were detected by radiological imaging and no local recurrence was found in these patients. Of the 6 distant recurrence cases, 4 underwent palliative therapy, and 1 patient underwent surgical resection with curative intent of the liver metastases. The last patient received therapy with curative intent for his peritoneal metastases, but developed

Table 4: Local and distant recurrence during follow-up stratified by definitive cancer treatment

	Local excision			Surgical resection	
	Low-risk pT1 CRC	High-risk pT1 CRC	Undetermined risk pT1 CRC	pT1N0	pT1N1
Outcome radiological staging (n = 628)					
	Radiological staging among local treated T1 CRCs (n = 159)			Radiological staging among surgical treated T1 CRCs (n = 469)	
No. of patients, *n (% of all enrolled patients)*	54 (8.4)	89 (14.2)	16 (2.5)	420 (66.9)	49 (7.8)
Synchronous distant metastases, *n (%)*	-	-	1 (6.3)	-	2 (4.1)
Patients with incidental findings, *n (%)*	17 (31.5)	23 (25.8)	5 (31.3)	90 (21.4)	7 (14.3)
Benign incidental findings	14 (25.9)	19 (21.3)	5 (31.3)	85 (20.2)	6 (12.2)
Malignant incidental findings	3 (5.6)	4 (4.5)	-	5 (1.2)	1 (2)
Lung cancer	*1*	-	-	*2*	-
Renal cell carcinoma	-	*3*	-	*3*	-
Gastrointestinal stroma cell tumor	*1*	-	-	-	-
Breast cancer	-	-	-	-	*1*
Urothelial carcinoma of the bladder	*1*	-	-	-	-
Lymphoma	-	*1*	-	-	-
Outcome endoscopic surveillance (n = 628)					
	Endoscopic surveillance after local treated T1 CRCs (n = 141 of 159)			Endoscopic surveillance after surgical treated T1 CRCs (n = 341 of 469)	
No. of patients n, *(% of all enrolled patients)*	54 (8.4)	89 (14.2)	16 (2.5)	420 (66.9)	49 (7.8)
At least 1 surveillance endoscopy, *n (%)*	45 (83.3)	81 (91)	15 (93.8)	309 (73.6)	32 (65.3)
Median follow-up surveillance endoscopy, *months [range]*	13 [3-76]	14 [1-63]	13 [2-139]	29 [3-138]	27 [4-90]
Local endoluminal recurrence cases	-	9	-	5	-
without distant recurrence	-	*7*	-	*4*	-
with distant recurrence	-	*2**	-	*1**	-
Median to local recurrence, *months [range]*	-	26 [4-62]	-	25 [10-52]	-
5y cumulative incidence local recurrence, *%, (95%CI)*	-	23.8(11.5-45.5)	-	2.0 (0.8-5.0)	-
Outcome radiological surveillance (n = 336)					
	Performed radiological surveillance after local treated T1 CRCs (n = 62 of 159)			Radiological surveillance after surgical treated T1 CRCs (n = 274 of 469)	
No. of patients with at least 1 radiological surveillance, *n (%)*	22/54 (40.7)	34/89 (38.2)	6/16 (37.5)	238/420 (56.7)	36/49 (73.5)
Median radiological follow-up, *months [range]*	23 [3-58]	29 [4-67]	41 [9-56]	38 [3-184]	55 [8-70]
Median number of radiological surveillance imaging procedures, *n [range]*	3 [1-8]	4 [1-17]	4 [1-8]	5 [1-20]	8 [1-21]
Distant recurrence cases	-	-	-	3	3
5y cumulative incidence distant recurrence *%,(95%CI)*	-	-	-	1.5 (0.5-4.6)	10.1 (3.3-28.3)
Median to distant recurrence, *months [range]*	-	-	-	12 [8-22]	28 [12-37]
Patients with incidental findings	2	5	-	35	6
Benign incidental findings	2	5	-	31	6
Malignant incidental findings	-	-	-	4	-
Pancreas cancer	-	-	-	*1*	-
Prostate cancer	-	-	-	*1*	-
Incurable lung cancer	-	-	-	*2*	-

CRC indicates colorectal cancer; y, year; CI, confidence interval

* Patients with endoluminal recurrence were censored for distant recurrence analysis during follow-up on the date of local recurrence detection

lung metastases 1 year later. The histological characteristics, tumor location and treatment strategies of the original T1 CRC specimen are provided in Table 2. Of the 4 patients with a malignant incidental finding during follow-up, 1 had pancreatic cancer and underwent radical resection, 1 had prostate cancer, and the last 2 patients died due to incurable lung cancer.

Endoscopic surveillance was performed in 341 of 469 patients (72.7%), with a median follow-up period of 27 [3-138] months (Table 4). Local recurrence occurred in 5 of 341, after a median of 25 [10-52] months. The 5-year cumulative incidence of local recurrence after surgical resection was 2.0% (95%CI 0.8-5.0%). One of these 5 patients had newly detected distant metastases on radiological imaging which was performed for tumor staging after endoscopic detection of local recurrence.

Differences over time

Subgroup analysis of the radiological staging and follow-up for the different time periods can be found in Table 5. We found significant differences in the presence of synchronous distant metastases (p=0.013) and incidental findings (p<0.001) during baseline radiological staging between the different time periods. We found no significant difference in the detection of distant recurrence or incidental findings during the follow-up period between the different time periods. The hazard ratios (HR) for distant recurrence for the period 2005-2010 and 2010-2015 compared to 2000-2005 were HR=0.7 (95%CI 0.1-7.7) and HR=0.6 (95%CI 0.1-5.3) and for incidental findings HR=1.8 (95%CI 0.5-6.0) and HR=1.7 (95%CI 0.5-5.7) respectively.

Table 5: Radiological staging and surveillance of T1 CRC patients divided in three time frames

	Overall cohort 2000-2014 n (%)	2000-2004 n (%)	2005-2009 n (%)	2010-2014 n (%)	p-value
No. of patients with pT1 CRC	1130	239	357	534	
No. of patients with radiological staging	628 (55.6)	80 (33.5)	184 (51.5)	364 (68.2)	
Performed abdominal staging					
CT	464 (73.9)	17 (21.3)	93 (50.5)	354 (97.3)	
Ultrasound	161 (25.6)	63 (78.8)	89 (48.4)	9 (2.5)	
MRI	2 (0.3)	-	1 (0.5)	1 (0.3)	
PET	1 (0.2)	-	1 (0.5)	-	
Performed thoracic staging					
CT	233 (37.1)	3 (3.8)	45 (24.5)	185 (50.8)	
X-ray	394 (62.7)	77 (96.3)	138 (75)	179 (49.2)	
PET	2 (0.2)	-	1 (0.5)	-	
Synchronous distant metastases	3 (0.5)	2 (2.5)	1 (0.5)	0 (0)	0.013*
Patients with incidental findings	142 (22.6)	12 (15)	26 (14.1)	104 (28.6)	<0.001*
Malignant	*13*	*1*	*3*	*9*	
Benign	*129*	*11*	*23*	*95*	
			Radiological surveillance		
Performed follow-up imaging	336 (53.5)	33 (41.3)	95 (51.6)	208 (57.1)	
Distant recurrence cases	6	1	2	3	
5y cumulative incidence of distant recurrence, *% (95%CI)*	2.4% (1.1-5.4)				
Hazard rate distant recurrence, *(95%CI)*		1	0.7 (0.1-7.7)	0.6 (0.1-5.3)	
5y cumulative incidence incidental findings, *% (95%CI)*	20.4% (15.0-27.5)				
Hazard rate incidental findings, *(95%CI)*		1	1.8 (0.5-6.0)	1.7 (0.5-5.7)	
Incidental finding cases during follow-up	48	5	16	27	
Second primary malignancy	*4*	*1*	*3*	*0*	
Benign	*44*	*4*	*13*	*27*	

CT indicates Computed Tomography; MRI, magnetic resonance imaging; PET, Positron Emission Tomography; y, years;
*Chi-squared test
All percentages are number of events divided by number of performed staging or follow-up imaging for each time period.

DISCUSSION

In this large multicenter study, we reported the radiological outcome of staging and follow-up imaging for endoscopically and surgically treated T1 CRCs. We found a very low risk of synchronous distant metastases (0.5%) and distant recurrence during follow-up (2.4%). Furthermore, this study revealed a substantial number of incidental findings detected on radiological staging and follow-up. Therefore, we think that radiological staging and surveillance should not be routinely performed in all T1 CRC patients.

A recent survey showed that approximately 50% of clinicians perform baseline oncological staging after local excision of T1 CRCs, regardless of histological risk status.[6] For patients scheduled for major (primary or completion) surgical resection, it seems obvious to perform preoperative radiological staging to exclude distant

metastases and prevent unnecessary surgery for patients with incurable disseminated disease. However, it is highly questionable whether or not radiological staging is also efficient for low-risk T1 CRCs. This is because these tumors have a negligible risk of metastatic disease, as also confirmed by our current study. In addition, we show for the first time that in almost a quarter of T1 CRC patients, incidental findings were found on radiological staging. This percentage is in line with previous literature on incidental findings on radiological examinations performed for other medical conditions.[27] The percentage of incidental findings on radiological staging even appeared to rise over the years, probably due to the shift of imaging modalities from ultrasound or chest X-ray towards CT. Although incidental findings might occasionally be beneficial and lifesaving, they often are clinically irrelevant, potentially harmful and can cause burden and anxiety for patients and increased healthcare costs.[21,27] Based on the above, it would be reasonable to discourage radiological staging prior to local excision of suspected T1 CRC and after local excision of low-risk T1 CRC.

Endoscopic surveillance after local excision and surgical resection of T1 CRC should be performed according to national guidelines. A recent guideline recommend surveillance colonoscopy 1 year after resection (or up to 6 months, if colonoscopy has not yet been performed preoperatively).[28]

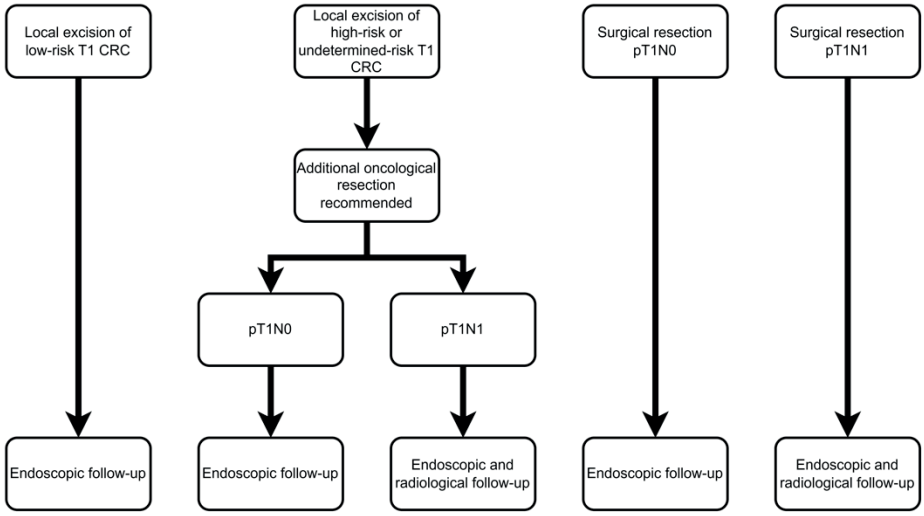
However, radiological follow-up to detect distant CRC recurrences is currently under debate as patients might not derive survival benefit from early detection of asymptomatic distant recurrence.[29-31] Our study suggests a limited yield of radiological follow-up for T1 CRC patients.
Of the patients treated with local excision in our study, no distant recurrence was primarily detected by radiological imaging, while incidental findings occurred in almost 1 of 4 patients (Figure 1). However, 2 censored high-risk T1 patients who underwent local excision, had distant metastases on radiological imaging which was performed for tumor staging after endoscopic detection of local recurrence with routine endoscopic surveillance. Our findings are supported by a recent meta-analysis, which also reported a low risk of distant recurrence after local excision (1.6% after local excision for any T1 CRC and 0.3% after local excision of low-risk T1 CRC).[32] Based on the results of this study and the previous literature, we strongly discourage radiological surveillance for low-risk pT1 CRC patients after local excision, as the risk of distant metastases does not outweigh the risk of incidental

findings. For patients with high-risk or undetermined-risk T1 CRC in which completion surgical resection is not performed, radiological follow-up could be considered according to national guidelines because of the relatively increased risk of metastatic disease. However, evidence that radiological surveillance improves survival outcomes of these CRC patients, is currently lacking.

Of the patients treated with surgical resection, the distant recurrence rate was 2.9%. Distant recurrence occurred more frequently among rectal cancer patients and among lymph node positive (T1N1) patients (10.1%). Histological reports demonstrated pT1N1 in 3 patients, pT1N0 in 1 patient and pT1Nx in the remaining 2 patients. Prior studies reported that intensified follow-up after oncological resection leads to earlier detection of distant recurrences with subsequent more curable treatment options. However, the therapeutic options for distant recurrence are still limited and there is no literature that supports survival benefit.[30,31] In this study, only 1 of the 6 metastatic patients underwent curative therapy. Incidental findings during follow-up were detected in 1 of 5 patients and might lead to anxiety, medicalization and healthcare costs. The risk of distant recurrence among pT1N0 CRC is very low, as is also confirmed by our current study. It is highly questionable whether radiological surveillance should be performed for these patients, as recommended in international guidelines.[8,9,12,14,16] In contrast, the risk of metastatic disease is much higher for patients with histological proven LNM after surgical resection (pT1N1). We think that radiological surveillance imaging should only be considered for patients with histological proven LNM after surgical resection (pT1N1) due to the relatively increased risk of metastatic disease (Figure 2). However, the patients should be informed about the risk and benefits of surveillance imaging.

This study has several limitations. First, we retrospectively analyzed a selected population of histological proven T1 CRC patients. Patients with metastatic T1 CRC who did not undergo excision of the primary tumor were not included in the database. Furthermore, we excluded patients with radiological imaging performed >2 months before or after T1 CRC diagnosis and included only patients with radiological follow-up imaging that was performed in the context of CRC surveillance. This was mainly performed among high-risk patients, which might have resulted in testing bias and might have influenced the rate of synchronous distant metastases or distant recurrence. Of the excluded T1 CRC cases in this study,

Figure 2: Follow-up recommendations after T1 CRC therapy



1 patient had synchronous distant metastases during baseline imaging and 9 patients had distant recurrence. However, none of them had low-risk T1 CRC, making our recommendation to omit radiological staging and surveillance for low-risk T1 CRC even stronger. Second, although our series is the largest T1 CRC cohort to date, the absolute number of distant metastases was low. Third, we found imaging heterogeneity due increasing quality of CT and shift from US towards CT over the years, especially for incidental findings. Also, there may be inter and intra-observer variability between different radiologists in different hospitals. Lastly, as we included patients diagnosed between 2000-2014, the histological features used to estimate the LNM risk were deep submucosal invasion, LVI and tumor differentiation. However, recent insights suggest that deep submucosal invasion may be omitted from risk stratification, whereas tumor budding emerged as new risk factor for LNM.[14,22,33]

Conclusion

the risk of synchronous distant metastases and distant recurrence in T1 CRC is low, especially in low-risk T1 CRC. However, there is a substantial risk of detecting incidental findings leading to medicalization, burden for patients and increased health care costs. Radiological staging seems unnecessary prior to local excision of suspected T1 CRC and after local excision of low-risk T1 CRC. Radiological surveillance should not be performed in patients with low-risk T1 CRC.

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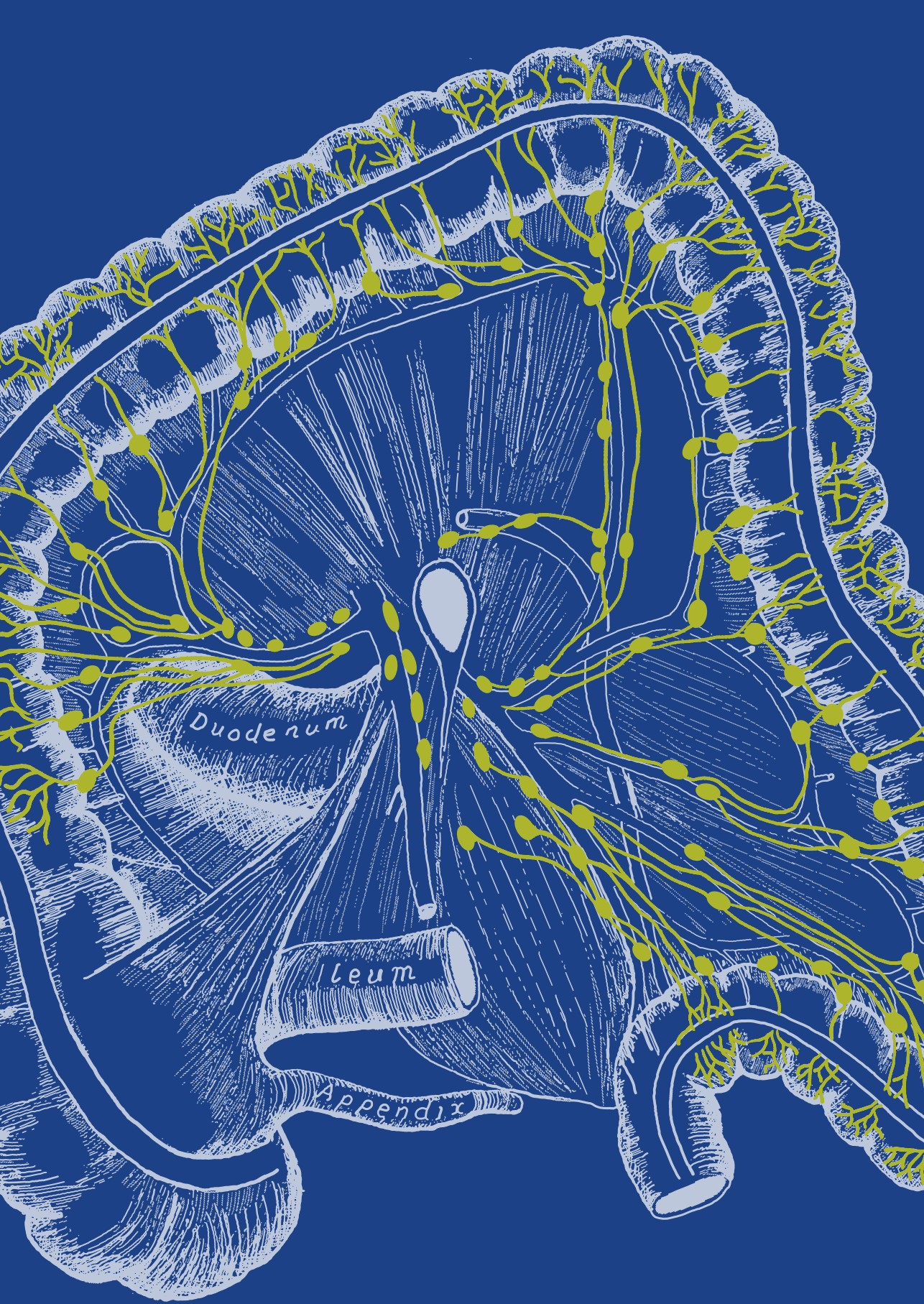
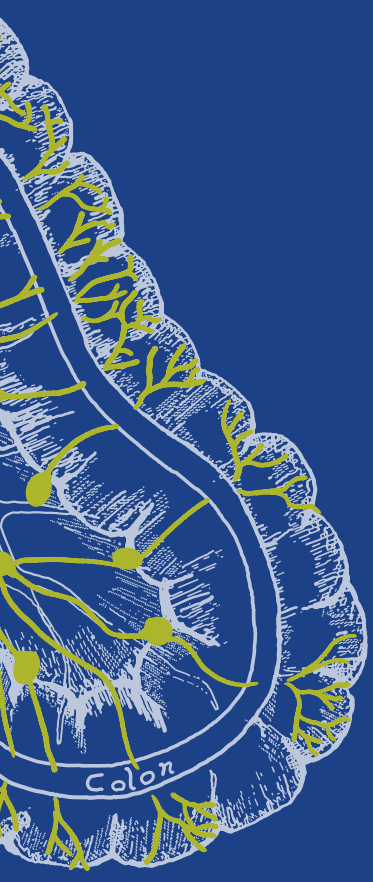

Duodenum
Ileum
Appendix

CHAPTER 4

Consequences of CT- colonography in stenosing colorectal cancer



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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.

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 CT were 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 radiologists who had more than 400 CTC case experiences.

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 indicates Computed Tomography; LUMC, Leiden University Medical Center.

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 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.

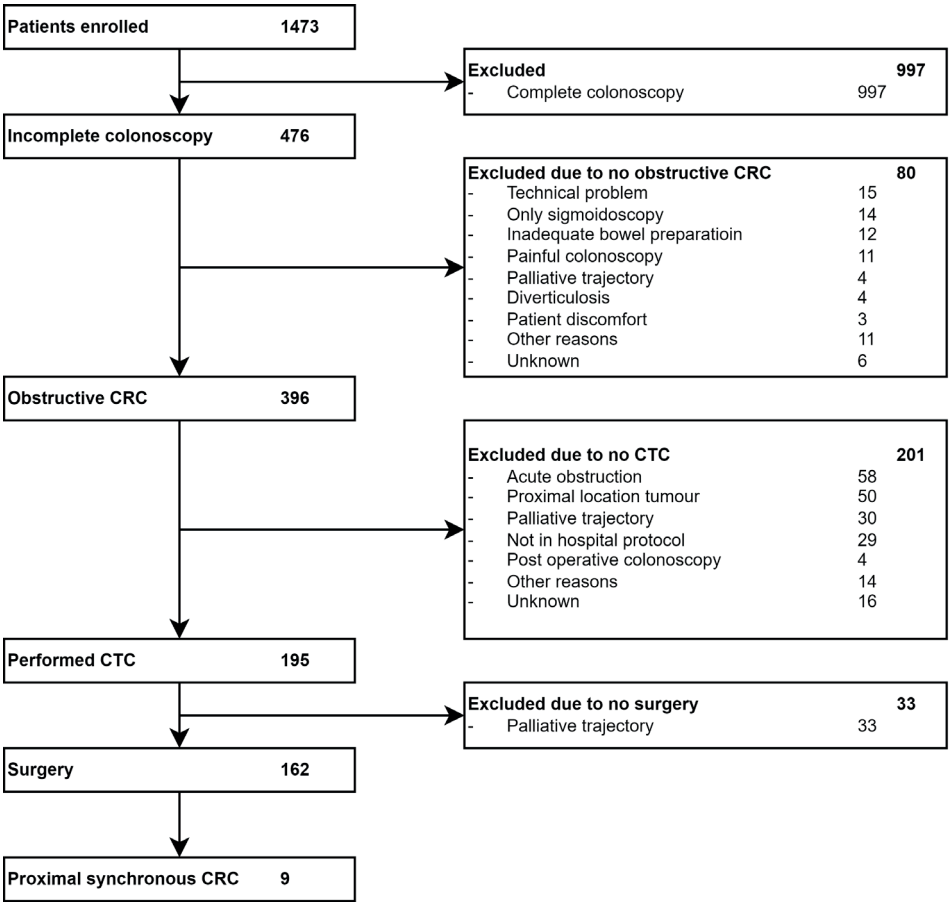

Figure 1: A flowchart of included and excluded patients

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) (Figure 1). A total of 162 patients (male n = 85, 52.4%) with a mean 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.

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 abdominal CT	Modification primary surgical plan	Type of surgery performed	CTC outcome	Days between CTC and CT abdomen
#1	86	M	sigmoid and descending	pT3N0	not performed	yes, extended resection	left-sided hemicolectomy	false positive	-
#2	58	F	sigmoid and ascending	pT3N0	not performed	yes, extended resection	right-sided hemicolectomy	false positive	-
#3	89	M	descending and ascending	pT3N2 + pT3N2	yes	yes, extended resection	extended right-sided hemicolectomy	true positive	5
#4	69	F	sigmoid and caecum	pT3N1 + pT3N0	not performed	yes, extended resection	extended resection	true positive	-
#5	71	M	sigmoid and caecum	pT3N0 + pT2N0	not performed	yes, extended resection	subtotal colectomy	true positive	
#6	90	F	transverse and transverse	pT3N0 + pT2N0	yes	no	extended right-sided hemicolectomy	true positive	14
#7	80	M	hepatic flexure and ascending	pT3N2 + advanced adenoma of 35 mm	not performed	no	right-sided hemicolectomy	true positive	-
#8	67	M	transverse and ascending	pT3N0 + pTisN0	yes	no	extended right-sided hemicolectomy	true positive	6
#9	62	M	sigmoid and 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 indicates years; *CTC,* Computed Tomographic Colonography; *CT,* Computed tomography; M, male; F, female; *p,* pathologically

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 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 (Figure. 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 (Figure. 2c). Postoperative surveillance colonoscopy in this case showed no abnormalities.

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 surveillance 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 added 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] CTC 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. CTC 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 (Figure 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.

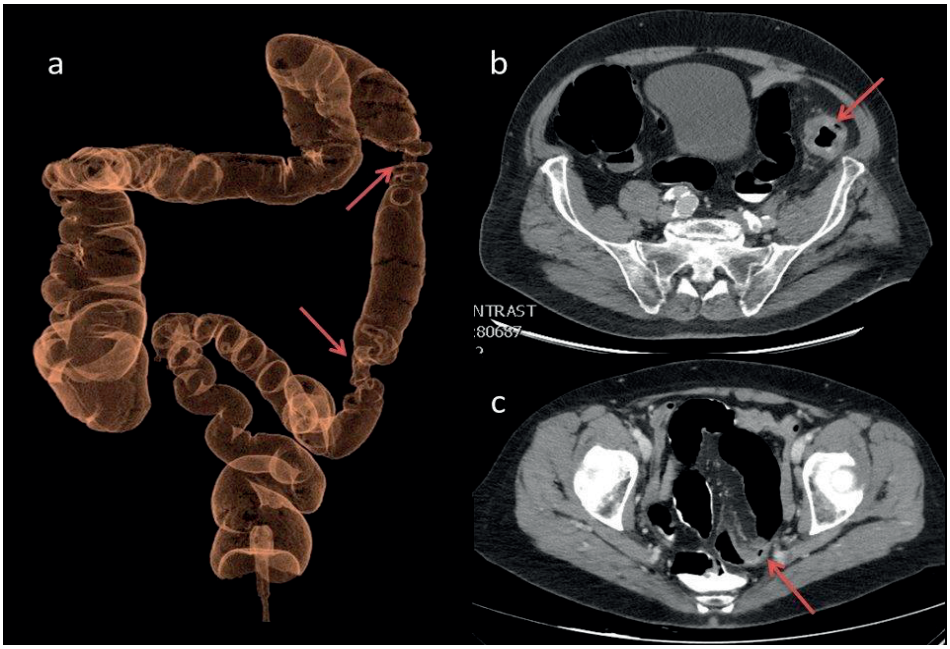

Figure 2. CTC images of both false positive CTCs. Red arrows indicate the suspected tumors on CTC. a 3D image of patient number 1, tumor in sigmoid and false tumor in descending colon. b 2D image of patient number 1, false tumor in descending colon. c 2D image of patient number 2, false tumor in sigmoid

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]

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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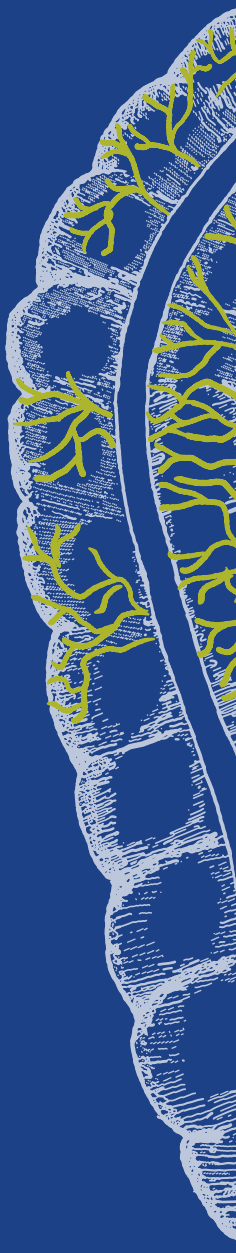
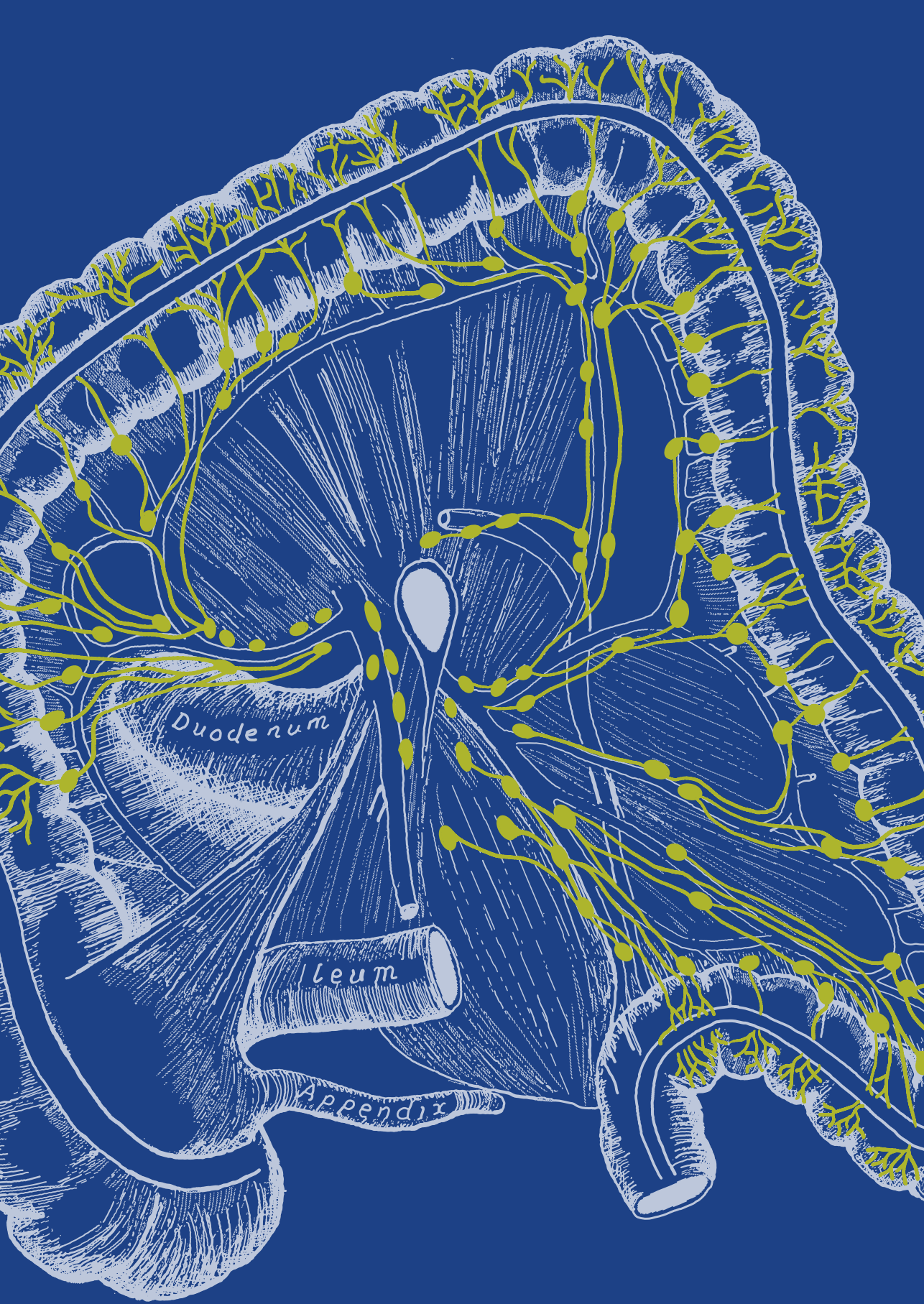
PART III

Therapy

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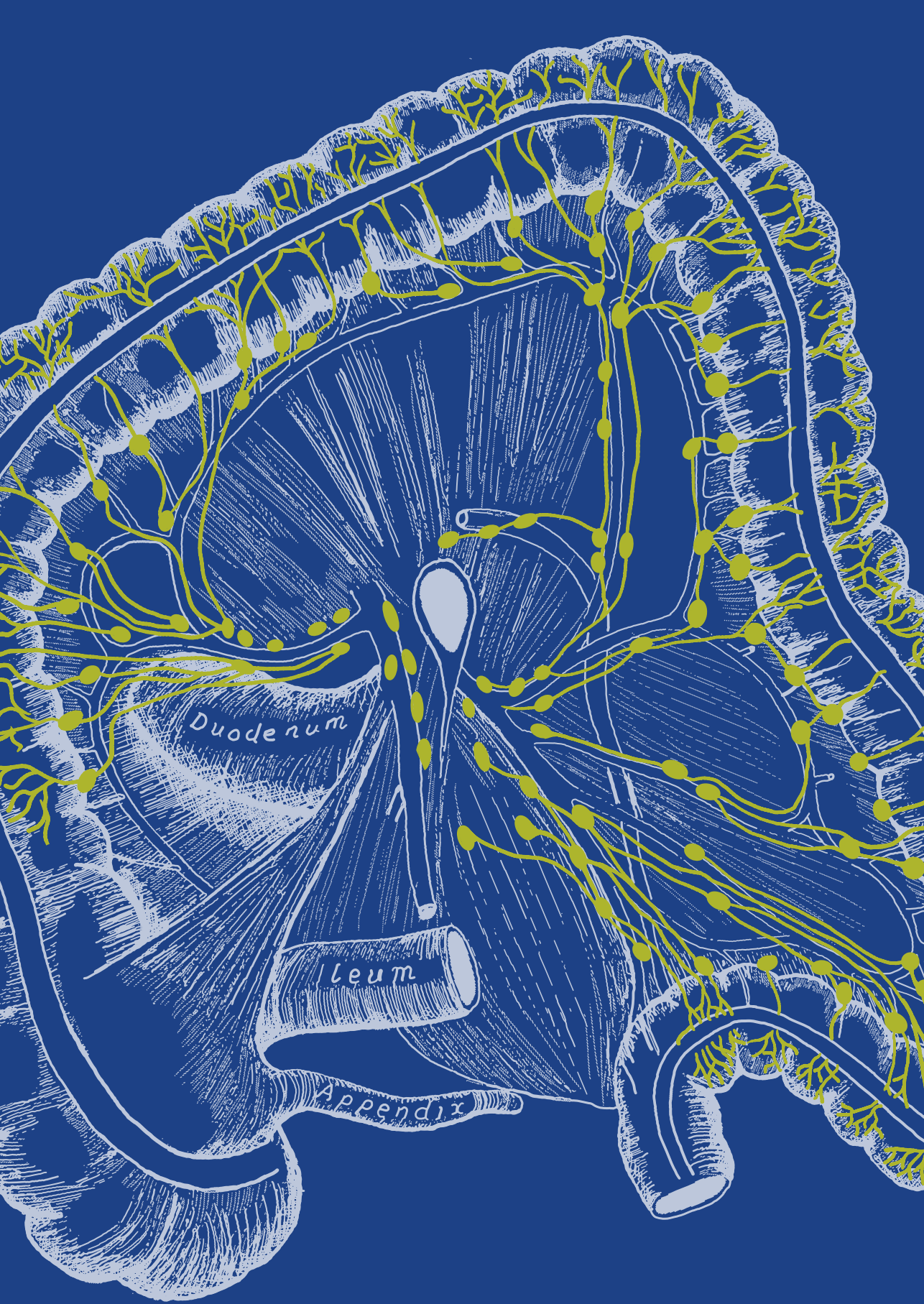
Appendix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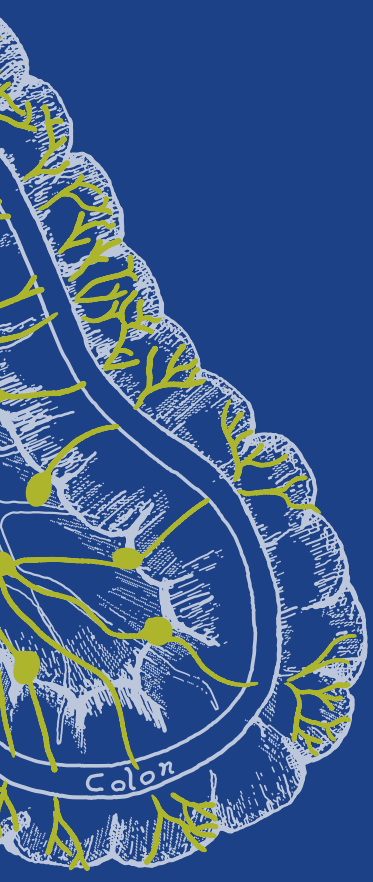
Appendix

CHAPTER 5

Safety of endoscopic mucosal resection (EMR) of large non-pedunculated colorectal adenomas in the elderly



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ABSTRACT

Background

Endoscopic mucosal resection (EMR) has been proven to be safe and effective for the treatment of colorectal adenomas. However, data are limited on the safety of this technique for large polyps and in elderly patients. Aims of our study were to examine the bleeding and perforation rates in patients with large non-pedunculated adenomas (≥20mm) and to evaluate the influence of size (≥40mm) and age (≥75 years) on the complication rates.

Methods

In this multicenter retrospective study, patients who underwent EMR of non-pedunculated adenomas ≥20mm between January 2012 and March 2016 were included. The demographics of the patients, the use of antithrombotic drugs, size of the polyps, type of resection, pathology report, occurrence of post-polypectomy bleeding, and perforation- and recurrence rate were collected.

Results

In 343 patients, 412 adenomas were removed. Eighty patients (23.3%) were ≥75 years of age, 138 polyps (33.5%) were ≥40mm. Bleeding complications were observed in 28 cases (6.8%) and were found significantly more frequent in adenomas ≥40mm, independent of the use of antithrombotic therapy. Five perforations (1.2%) were described, not related to the size of the polyp. There was no significant difference in complication rates between patients <75 years and patients ≥75 years. Bleeding complications rates were significantly higher in patients receiving double antithrombotic therapy.

Conclusion

EMR is safe in elderly patients. EMR of adenomas of ≥40mm was associated with more bleeding complications. Future studies should address how the bleeding rates can be reduced in these patients, especially in those who use double antithrombotic treatment.

INTRODUCTION

Colorectal cancer is the most commonly diagnosed cancer of the gastro-intestinal tract. It is the leading cause of overall cancer death in Western countries after lung cancer.[1–7] In 2012 in Europe, the incidence of colorectal cancer was 60 per 100.000 people, resulting in nearly half a million new cases per year. The mortality rate of 29 per 100.000 accounted for 12.2% of all cancer deaths. The incidence of colorectal cancer is increasing and it is expected to rise from 1.4 to 2.4 million cases annually worldwide by 2035.[1,2]

In many countries, population screening programs for the detection of colorectal cancer have been implemented, usually starting at the age of 50 or 55 and continuing until the age of 75.[5–8] Screening tests including fecal occult blood test (FOBT), sigmoidoscopy or colonoscopy are used to detect early stage colorectal cancer and are proven effective in reducing mortality and morbidity rates.[1,5–7] Such programs lead to the detection of an increasing number of patients with large adenomas.[9] Critics of the colorectal cancer screening programs point towards the lack of evidence for a decrease in overall mortality, possibly due to the advanced age and extensive comorbidity in those found with colorectal cancer. Detection and removal of large polyps in this frail patient group has the potential to lead to morbidity and mortality that could negate any positive effects of the screening.[10] To be able to balance the health benefits with the risks, more information as to the nature and extent of these risks in this subgroup is required.

For the removal of large non-pedunculated polyps, endoscopic mucosal resection (EMR) is the usual treatment, and is reported to be effective and safe.[11–31] However, in polyps of ≥20 mm, piecemeal resection is often required which is associated with higher recurrence rates.[11,15–17,20,32,33]

The prevalence and size of colorectal polyps increases with age, so an increasing number of patients over the age of 75 are likely to undergo EMR. Various studies have reported on the complication rate of endoscopic resection in non-pedunculated polyps ≥20 mm.[11,14,19,27,28,34] However, information about the complication rate of endoscopic resection of giant polyps (≥40 mm) and in elderly patients (≥75 years) is limited.[26,27,34,35] Therefore, aims of our study were to examine the bleeding and perforation rates of endoscopic polyp resection in patients with

large (≥20 mm), non-pedunculated polyps and, in particular, to evaluate the influence of size (≥40 mm) and age (≥75 years) on the complication rates.

METHODS

This multicentre retrospective cohort study was performed between January 2012 and March 2016. For this type of study, formal consent was not required. Patients who had undergone EMR for colorectal non-pedunculated polyps ≥20 mm in Leiden University Medical Centre (LUMC) and Isala in Zwolle were included. Pedunculated polyps and malignant appearing polyps which were biopsied and eventually not removed by EMR were excluded in this study. All procedures were performed by endoscopists who were accredited for the Dutch National Bowel Screening Program. In addition, each had performed at least 100 previous EMRs ≥20 mm.

Procedure and equipment

According to the national guideline, anticoagulant therapy (e.g. marcoumar, acenocoumarol) was stopped 3-5 days before the procedure and restarted on the same day after the procedure.[36,37] The decision to interrupt the use of antiplatelet therapy (e.g. aspirin, clopidogrel, dypiridamol) was evaluated per patient and per type of therapy. Patients using double therapy were instructed to stop one of the antiplatelet drugs before the procedure, in accordance with the guidelines.[36–38] Aspirin could be continued. Double therapy was resumed the day after the procedure. Participants received bowel preparation consisting of picoprep or kleanprep. The mode of sedation was assessed per patient. Most frequently, endoscopic polyp resection was performed under conscious sedation with midazolam and fentanyl. In longer procedures, patients were sedated with propofol and remifentanyl under supervision of an anaesthetic nurse specialist.

Procedures were performed under carbon dioxide insufflation using Olympus CF-HQ190L colonoscopes. The size of the lesion was estimated by the endoscopist during colonoscopy before resection by placing an open biopsy forceps (8 mm) next to the lesion. The standard inject-and-cut EMR technique was applied by injecting a solution of Voluven (Hydroxyethyl starch) plasma expander, indigo carmine and in some cases a low concentration of epinephrine (1:100.000) for mucosal lifting. Argon plasma coagulation (pulsed 2, 25W), adrenaline (1:10.000) or clips were used in the case of bleeding. If necessary, e.g. in the case of visible vessels, wounds were

approximated by clips. APC was also used to treat residual tissue in case of incomplete resection. All patients were observed for at least one hour. After an uncomplicated procedure they were discharged on the same day, or occasionally after an overnight stay.

Histology

Adenomas containing >75% villous architecture were defined as villous adenomas and those comprising 25-75% villous architecture as tubulovillous. Focally present high-grade dysplasia (<10%) was considered as low-grade dysplasia.

Complications

Information on complications was obtained from patients' electronic patient records including nursing and endoscopy reports. Bleeding was defined as early (<48h after completion of procedure) and delayed (>48h after completion of procedure). Bleeding was registered as a complication when resulting in hospital (re)admission, (re-)intervention and/or therapy (e.g. repeat endoscopy, coiling, blood transfusion or surgery). Clip placement, argon coagulation or adrenaline injection to control bleeding during the initial colonoscopy was not considered as a complication. Perforation was diagnosed either periprocedurally by the endoscopist or by an abdominal CT-scan. Minor damage to the muscle wall, which was managed with clips was not defined as a complication, neither was a (suspicion of) perforation that was directly treated during colonoscopy that did not result in hospital admission. If a complication occurred during the removal of multiple polyps in one session, further investigation was performed to assess which polyp caused the complication (bleeding/perforation).

Follow-up

In all patients a control visit or telephone appointment was planned about a month after colonoscopy to discuss histopathologic outcomes and follow up. According to the Dutch guidelines for colonoscopy surveillance, the follow-up endoscopy interval depends on the histopathology report (architecture, extent of dysplasia/carcinoma and margin of specimen), the mode of removal (en bloc or piecemeal), the size and number of the adenomas and the location in the colon.[39] If there is uncertainty histologically about the completeness of polyp removal, a surveillance colonoscopy was scheduled 3-6 months later. During follow-up endoscopy, the scar was macroscopically examined and biopsies were taken only in case of a suspected

lesion. Residual tissue was treated with cold snare, APC or EMR. In two cases the endoscopy reports and patient records were inconclusive as to whether residual tissue had been detected and were therefore reported as missing and not included in follow-up analysis. In all other cases this was clearly documented.

Statistical analysis

Data collection and statistical analysis were performed by means of descriptive statistics with IBM SPSS Statistics 23 and Microsoft Office Excel 2010. Fisher's exact test was used to compare categorical outcome variables. Differences were considered significant if the two-sided P-value was <0.05.

RESULTS

Study group

EMR of lesions ≥20 mm was successfully performed in 343 patients (mean age of 67.4 (SD 8.3); male: n = 201 (58.6%)). One hundred and three patients (30.1%) used antithrombotic drugs; 15.2% antiplatelet drugs, 11.1% anticoagulants and 3.8% double antiplatelet therapy. In sixty-nine patients, multiple lesions ≥20 mm were removed, either in one or more sessions. Table 1 shows an overview of patient and lesion characteristics.

Lesion characteristics

A total of 412 lesions were reported, of which 138 (33.5%) ≥40 mm. The mean size of the resected polyps was 32,3 mm (SD 13 mm). Two hundred and five (50.2%) were sessile and 203 (49.8%) were flat (missing n = 4). Most polyps (81.3%) were resected piecemeal.

Histology

Of all 412 polyps, 145 lesions (37.2%) were tubular adenomas, 158 (43.1%) were tubulovillous adenomas, 10 (2.6%) were villous adenomas and 50 (12.8%) were sessile serrated polyps. In 22 cases, growth patterns were not described in the histology reports. Low grade dysplasia was the most common pathology comprising 301 cases (73.1%). 11 cases (2.7%) showed an intramucosal carcinoma and 18 cases (4.4%) an invasive adenocarcinoma. R0 resection was achieved in 20.8% of all en bloc resections.

Table 1 Patient and lesion characteristics

	n	(%)
Patient characteristics		
Number of patients	**343**	
Mean age, years (±SD)	67.4	(8.3)
≥75 years	*80*	*(23.3)*
Male	201	(58.6)
ASA		
I	*89*	*(26)*
II	*228*	*(66.7)*
III	*25*	*(7.3)*
Missing	*1*	
Antitrombotic therapy	103	(30.1)
Antiplatelet therapy	*52*	*(15.2)*
Anticoagulant therapy	*38*	*(11.1)*
Double therapy	*13*	*(3.8)*
Missing	*1*	
Lesion characteristics		
Number of lesions	**412**	
Size		
Mean mm, (±SD)	*32.3*	*(13)*
Median mm,(IQR [25;75])	*30*	*[20-40]*
20-40mm	274	(66.5)
≥40mm	138	(33.5)
Location		
Ileocecal valve	*11*	*(2.7)*
Cecum	*54*	*(13.1)*
Ascending colon	*84*	*(20.4)*
Hepatic flexure	*37*	*(9)*
Transverse colon	*51*	*(12.4)*
Splenic flexure	*26*	*(6.3)*
Descending colon	*13*	*(3.2)*
Sigmoid	*55*	*(13.3)*
Rectosigmoid	*15*	*(3.6)*
Rectum	*66*	*(16)*
Paris classification		
Sessile (0-1s)	*205*	*(50.2)*
Flat (0-IIa, 0-IIb, 0-IIc)	*203*	*(49.8)*
Histology		
Tubulair adenoma	*145*	*(37.2)*
Tubulovillous adenoma	*168*	*(43.1)*
Villous adenoma	*10*	*(2.6)*
Sessile serrated	*50*	*(12.8)*
Other	*17*	*(4.4)*
No dysplasia	*52*	*(12.4)*
Low-grade dysplasia	*301*	*(73.1)*
High-grade dysplasia	*30*	*(7.3)*
Intramucosal carcinoma	*11*	*(2.7)*
Invasive carcinoma	*18*	*(4.4)*

SD indicates standard deviation; ASA, American Society of Anesthesiologists physical status

Complications

Table 2 provides an overview of the complications per lesion in this study. Detailed results on complications are presented in Tables 3, 4, 5 and 6.

Total bleeding complication rate was 6.8% (n = 28) and occurred significantly more in polyps ≥40 mm compared to polyps 20-40 mm (10.9% vs. 4.7%, p = 0.04). No significant difference was observed in antithrombotic drug use between polyps 20-40 mm and ≥40 mm (p = 0.252). Twice as many bleeding complications occurred when using antithrombotic therapy (10.8% vs. 5.1%, p = 0.051), especially double therapy (31%, p = 0.002) (Tables 5 and 6). No significant difference was observed in patients <75years vs. patients ≥75 years (6.2% vs. 9.3%, p = 0.33). There was one patient who had both an early and delayed bleeding.

Early bleeding (<48h): In 19/412 cases (4.6%) early bleeding was reported. Thirteen of these nineteen cases underwent repeat colonoscopy; four cases needed additional blood transfusion. In the remaining six cases, no colonoscopy was performed. Two of these six patients received a blood transfusion and were sent for angiographic embolisation, the other four were managed conservatively. The mean hospital stay was 2.1 days (range 0-5 days). There was no significant elevated risk in early bleeding for polyps ≥40 mm compared to polyps 20-40 mm (6.5% vs. 3.6%; p = 0.216) and for patients ≥75 years compared to patients <75years (5.8% vs. 4.3%; p = 0.565). The use of antithrombotics resulted in more early bleeding. However, the difference was not significant (7.5% vs. 3.4%; p = 0.117) (Table 5), and mainly due to double antithrombotic use (p = 0.004) (Table 6).

Table 2 Complications and follow-up

	n (%)
Number of lesions	412
Technique	
En bloc	77 (18.7)
R0 resection	*15 (20.8)*
Piecemeal	335 (81.3)
Complications	
Total bleeding complications	28 (6.8)
Early bleeding (<48h)	*19 (4.6)*
Delayed bleeding (>48h)	*9 (2.2)*
Perforations	5 (1.2)
Surgery	16 (3.9)
Follow-up	292 (70.9)
Residual tissue	55 (18.8)
En bloc	*4 (7.3)*
piecemeal	*51 (92.7)*

Table 3 Complications versus polyp size and patients' age

	20-40mm (n = 274)	≥40mm (n = 138)	p value	<75y (n = 326)*	≥75y (n = 86)*	p value
Total bleeding complications (n=28)	13 (4.7%)	15 (10.9%)	0.036	20 (6.2%)	8 (9.3%)	0.331
Early bleeding (n=19)	*10 (3.6%)*	*9 (6.5%)*	*0.216*	*14 (4.3%)*	*5 (5.8%)*	*0.565*
Delayed bleeding (n=9)	*3 (1.1%)*	*6 (4.3%)*	*0.066*	*6 (1.8%)*	*3 (3.5%)*	*0.400*
Perforation (n=5)	3 (1.1%)	2 (1.4%)	1.000	5 (1.5%)	0	0.588

* evaluated per lesion

Table 4 Antithrombotic therapy in relation to polyp size

	20-40mm (n = 274)	≥40mm (n = 138)	p value
Antithrombotic therapy* (n = 120)	85 (31%)	35 (25.4%)	0.252
No antithrombotic therapy* (n = 292)	189 (69%)	103 (74.6%)	

* evaluated per lesion

Table 5 Bleeding complications in antithrombotic therapy

	Antithrombotic therapy* (n=120)	No antithrombotic therapy*(n=292)	p value
Total bleeding complications (n=28)	13 (10.8%)	15 (5.8%)	0.051
Early bleeding (n=19)	*9 (7.5%)*	*10 (3.4%)*	*0.117*
Delayed bleeding (n=9)	*4 (3.3%)*	*5 (1.7%)*	*0.293*

* evaluated per lesion

Delayed bleeding (>48h): In 9 of 412 lesions (2.2%) patients were admitted to the hospital for delayed bleeding and all patients underwent repeat colonoscopy. Three cases required blood transfusion. No CT intervention was needed. The mean hospital stay was 1.9 days (range 0-4 days). Delayed bleeding occurred more in polyps ≥40 mm compared to polyps 20-40 mm (4.3% vs. 1.1%; p = 0.066), however this was not significant. No significant difference was found in delayed bleeding complications in patients ≥75 years compared to patients <75 years. (3.5% vs. 1.8%; p = 0.400). Almost twice as many delayed bleeding complications occurred in patients using antithrombotic drugs compared to patients not using antithrombotic drugs (3.3% vs. 1.7%; p = 0.293), but this difference was not significant (Table 5).

Perforation: Five (1.2%) perforations occurred. One case was managed conservatively, and three cases were successfully closed with clips during the initial endoscopy. Surgical intervention was needed in one case. No significant difference in perforation rate was observed between resection of 20-40 mm and the resection of polyps larger than 40 mm (1.1% vs. 1.4%, p = 1.000). No perforations occurred in elderly patents above the age of 75 (1.5% vs. 0%, p = 0.588).

Other complications: In total, three complications were observed. One patient was admitted for observation after possible aspiration at the end of a colonoscopy under propofol sedation. She was discharged the next day with oral antibiotics without further complications. Another patient was observed after having a post

procedural epileptic insult after discharge. Midazolam/fentanyl was used during endoscopy. Lastly, one patient experienced a painless pneumoscrotum directly after the procedure using propofol without further complications. To the best of our knowledge, no cardiovascular events occurred and no deaths related to colonoscopy were observed.

Surgery

Surgical resection after polypectomy was performed in 16 cases (3.9%). In one patient, surgical intervention was performed because of a perforation during endoscopy. In 15 of these 16 cases, additional surgical resection was performed because of malignant histology of the resected polyp. In five of these fifteen cases, residual carcinoma was found in the surgical specimen. In nine of the fifteen cases, no malignancy was found. One case was lost to follow up as the patient underwent surgery in another hospital.

Follow-up data

In 292 out of 412 cases (70.9%), a follow-up colonoscopy was performed with a mean follow-up time of 6.94 months (SD 5.94 months, 95% CI 6.26-7.63 months). The remaining cases included patients either awaiting a first follow-up procedure (n = 61), patients without indication for surveillance (e.g. comorbidity, advanced age, or colon resection (n = 41)), patients lost to follow-up (n = 9) or patients refusing follow-up (n = 9).

Assessment of polyp removal sites mostly occurred by macroscopic examination of the scar. Residual tissue/ recurrence was found in 55/292 (18.8%) lesions, and was treated with snare or APC. Most residual tissue was found after piecemeal removal, in 51/55 cases (92.7%, $p < 0.05$).

Table 6 Bleeding complications in antithrombotic therapy, subdivided into different therapies

	Antiplatelets (n = 57)		Coumarins (n = 47)		Double therapy* (n = 16)	
	n	*p value*	*n*	*p value*	*n*	*p value*
Total bleeding complications (n = 13)	4	0.511	4	0.293	5	0.002
Early bleeding (n = 9)	*3*	*0.454*	*2*	*0.677*	*4*	*0.004*
Delayed bleeding (n = 4)	*1*	*1.000*	*2*	*0.252*	*1*	*0.304*

* antiplatelet drugs

DISCUSSION

The present study supports the premise that EMR of large non-pedunculated polyps is safe in elderly (≥75 years) patients. EMR of giant adenomas (≥40 mm) is associated with more bleeding complications but did not lead to more perforations.

Various studies have reported on complication rates after EMR. However, information about the complication rate of EMR of giant polyps and EMR in elderly patients is limited.[26,27,34,35] Our retrospective study evaluated the outcomes and safety of EMR in a large cohort of patients who underwent EMR of polyps ≥20 mm. A quarter of the study group were 75 years or older and one third had lesions of more than 40 mm.

The overall complication rates observed in our patients were within the range reported in the literature; early bleeding 0-7.9% and delayed bleeding 0-2.3%.[11,14,19,27,28,34,40] We did not observe any deaths due to the interventions. Some studies have reported increased complication rates (bleeding and perforations) of endoscopic removal of larger lesions ≥30 mm.[12,23,26,35] The perforation rate of our study in patients with polyps ≥40 mm was similar to the perforation rate in patients with polyps of 20-40 mm. These findings are in agreement with the study by *Luigiano et al.*[27] On the other hand, we found a significantly higher total bleeding complication rate in polyps larger than 40 mm compared to 20-40 mm polyps. This finding could not be explained by differences in antithrombotic drug use between both groups. *Sahwney et al.* have also reported lesion size as an independent predictive factor of post polypectomy bleeding.[41]

In elderly patients (≥75 years) we did not find significantly more bleeding complications. Also, no perforations were observed in these patients. *Gómez et al.* evaluated the outcomes and safety of colorectal EMR in patients older than 80 years.[34] They reported a total bleeding rate of 2.3%, and a perforation rate of 3%. The authors concluded that EMR for the removal of polyps ≥20 mm in elderly patients is safe.

Overall bleeding complications were more frequently observed when antithrombotic drugs were used (borderline significant, $p = 0.051$), in particular, in patients who used double antiplatelet therapy ($p < 0.05$). Guidelines on endoscopy

in patients with antithrombotic therapy advise to stop one of antiplatelet drugs when using double therapy 5-7 days before the procedure.[36–38] The other drug can be continued, which is mainly aspirin. Less is known regarding timing of reinitiation of the antiplatelet drug.[38] The drug is restarted the day after the procedure, according to the guidelines.[37,38] Based on our results we would recommend to consider postponement of restarting the antiplatelet drug after the procedure as we observed significantly more early bleeding complications in patients using double therapy. Numbers are however small and future prospective studies should reveal after how many days the risk of bleeding has reduced after large EMR.

Residual tissue or recurrence was observed in 18.8%, which is within the range reported in literature (4.2-40%).[11,14,19,27,28,34] However, our percentage might be an underestimate because scars were not routinely biopsied. Most residual tissue was found, as expected, after piecemeal removal.

This study adds significantly to the existing literature due to its large size, the high proportion of elderly people and the large number of giant adenomas. A further positive aspect is that we were fully informed about the occurrence of complications after polypectomy. The limitations of our study are its retrospective design and lack of routine biopsies of the polypectomy site at the follow-up colonoscopies.

Conclusion

The implementation of screening programs worldwide has led to the detection of increasing numbers of large non-pedunculated adenomas, often in elderly patients. This number is likely to increase further due to population ageing and higher life expectancy. Since surgical removal of giant adenomas at an advanced age is associated with a substantial mortality (5%), endoscopical removal is increasingly performed.[42] Our study showed that EMR is a safe procedure for both elderly patients above age of 75 and for non-pedunculated colorectal polyps larger than 40 mm, although it is associated with significant morbidity, largely due to bleeding. Improved methods are needed to reduce post polypectomy bleeding in patients that use antithrombotic treatments and with giant (≥40 mm) polyps.

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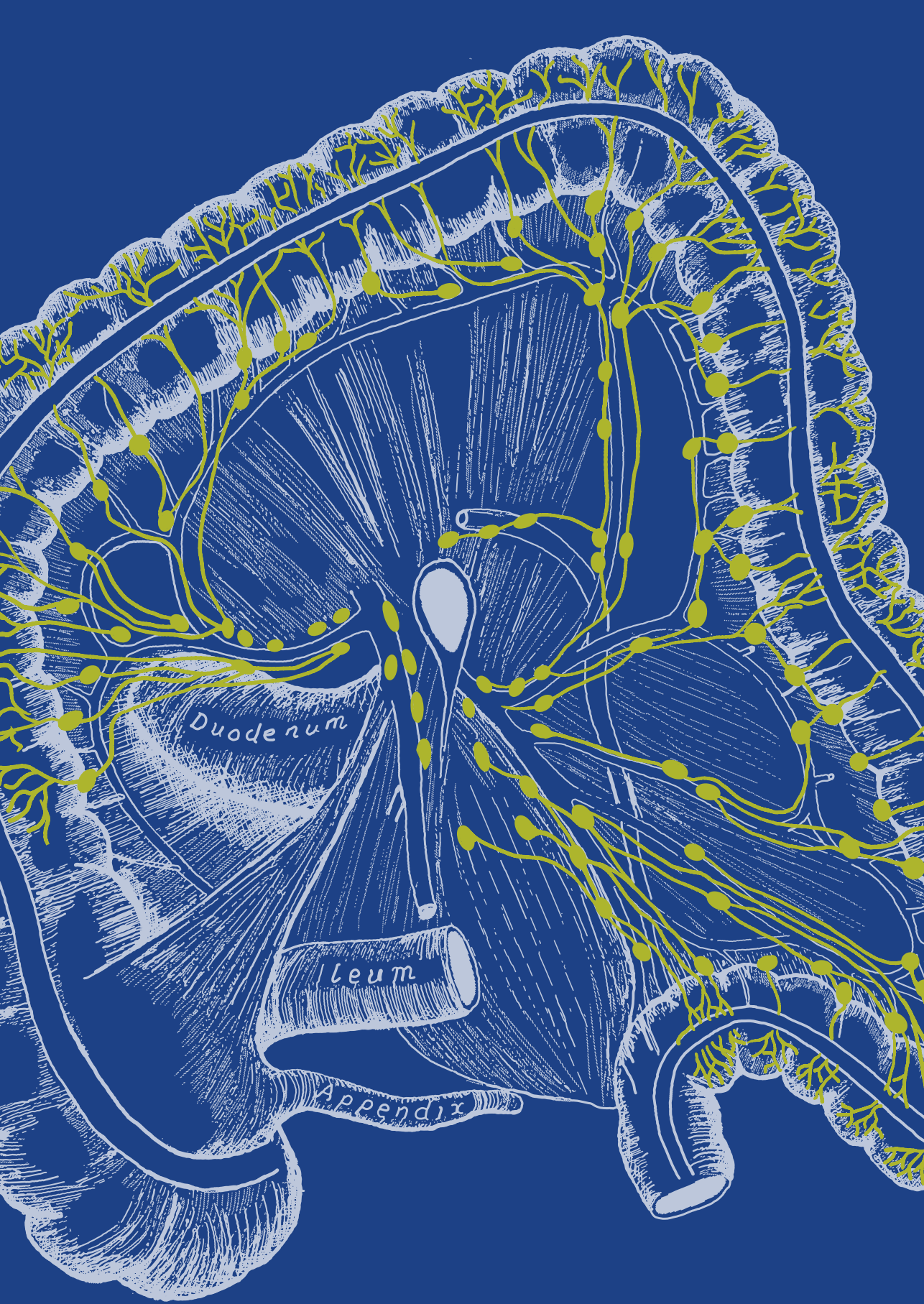
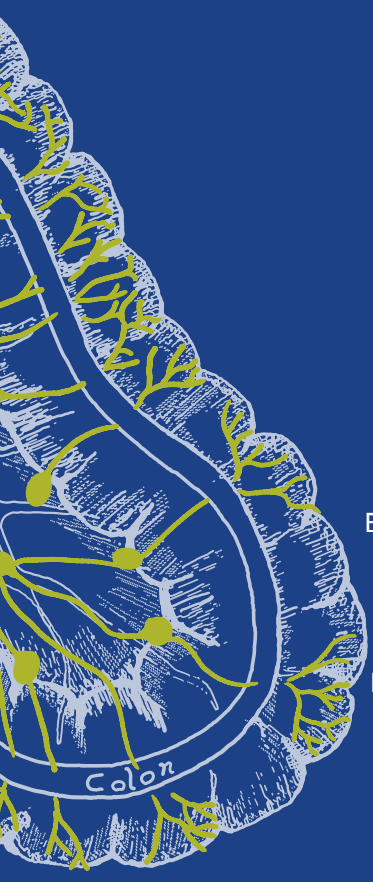

Duodenum
Ileum
Appendix

CHAPTER 6

Colonoscopic-assisted laparoscopic wedge resection for colonic lesions – a prospective multicentre cohort study (LIMERIC-study)



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ABSTRACT

Objective

The aim of this study was to evaluate the safety and efficacy of a modified colonoscopic-assisted laparoscopic wedge resection.

Summary background data

The use of segmental colectomy in patients with endoscopically unresectable colonic lesions results in significant morbidity and mortality. CAL-WR is an alternative procedure that may reduce morbidity.

Methods

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 R0 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.

Conclusion

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

INTRODUCTION

Because the implementation of a nationwide colorectal screening program in the Netherlands in 2014, the incidence of advanced adenomas and early-stage colorectal cancer (CRC) and the number of patients referred for colorectal resection for high grade polyps has increased.[1–3] Endoscopic polypectomy is a well-established treatment for noninvasive 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, 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 2cm 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 tumor stage,[13] and a study of surgery referral for benign colonic lesions showed an overall complication rate of 25.5%, subsequent reintervention 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 1990 s as an alternative to bowel resection for difficult benign lesions.[15] However, most reported series using this technique are single-center 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 8 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 multicenter 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.

METHODS

Study Design and Population

This prospective multicenter longitudinal cohort study was performed between January 2017 and December 2019 in 13 Dutch hospitals specialized in CRC 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 after 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 pathological T1 (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 5 gastroenterologists experienced in EMR/ endoscopic submucosal dissection/ eFTR working in different participating hospitals assessed resectability and the indication for an en-bloc resection based upon 4 endoscopic images of the lesion. Two overview images of the lesion, white light and narrow band imaging (NBI) were used in the assessment, and 2 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 2 specialized pathologists from 1 center to exclude high-risk features defined as angio-lymphatic invasion, poor differentiation, tumor 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 during the same procedure. All included patients underwent split-dose bowel preparation. Patients were placed in French position under general anesthesia. The surgeon started with a diagnostic laparoscopy using 3 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 (ie, the colonic lumen or in case of a caecal lesion, the lumen of the ileum) and a completeness of inclusion of the lesion was assessed endoscopically. The resected specimen was removed in an endobag through the 12mm trocar. The surgeon and 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 colors, 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 tumors 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 tumors. A R_0 resection was defined as a complete resection with no residual tumor in the resection plane, with a margin of at least 1 mm. Incomplete (R_1) resection was defined as tumor invasion of margins. When radicality could not be determined due to coagulation artefacts/ tangential cut, it was defined as a Rx resection.[26] The same classification (R_0, R_1, R_x) was used for benign polyps. Tumor grade and presence/absence of lymph- or blood vessel invasion was addressed specifically, along with tumor 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 6 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 1mm normal colonic mucosa, (3) recurrence of adenomatous tissue or carcinoma detected by follow-up endoscopy, and (4) long-term morbidity after 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. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). A p value < 0.05 (2 sided) was considered significant. Normality was verified using the Kolmogorov- Smirnov test. Descriptive statistics were reported as medians with range for nonparametric data and as means with standard deviation for parametric data. Normally-distributed continuous data were tested using Student 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 after assessment by the expert panel and review of the histological specimen, if indicated (Figure 1). 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 (eg, 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 tumor (group 3). The mean age was 66 years (standard deviation ± 8 years), the majority of the patients were male (56%) and most patients (82%) had an American Society of Anesthesiologists physical status 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 20mm (range 5–50mm). An overview of the baseline characteristics is presented in Table 1.

Figure 1. Patient enrollment

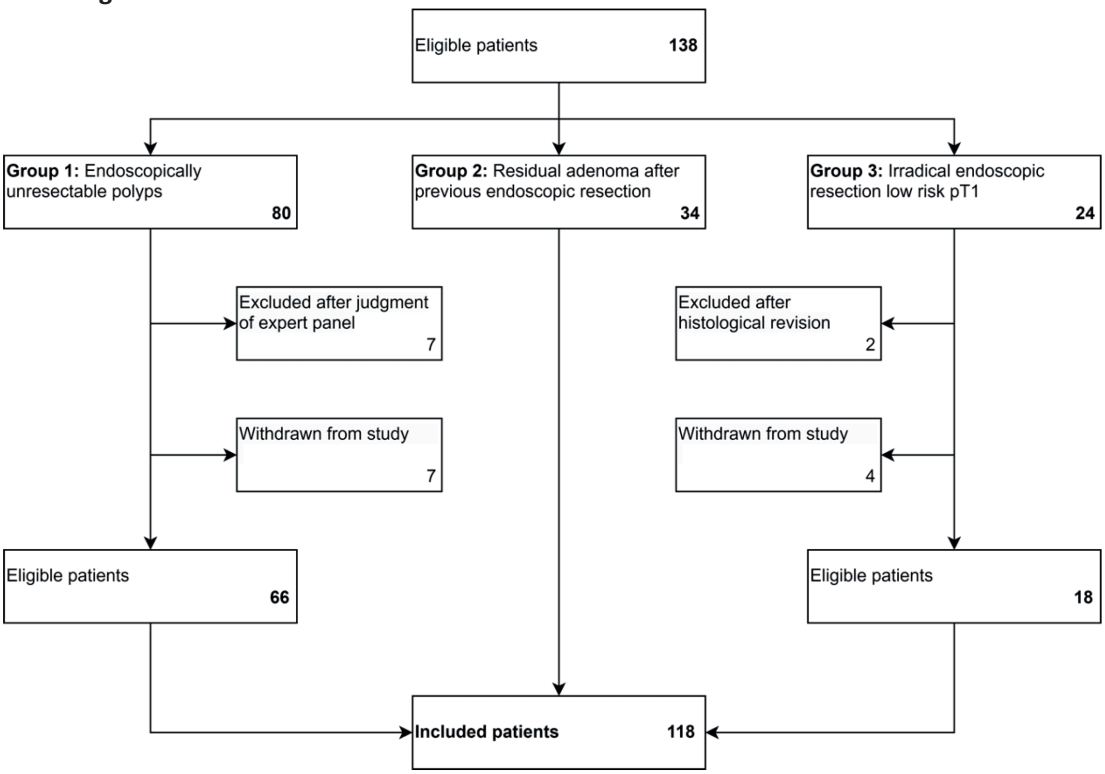

Table 1 Baseline characteristics

	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 [5 – 50]
Residual adenomatous tissue after prior polypectomy	20 [5 – 50]

ASA indicates American Society of Anesthesiologists physical status; SD, standard deviation.

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 2 of these cases transanal minimally invasive surgery was performed, whereas the other patient underwent 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 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 and the expert panel before surgery. Eleven percent (n = 12) showed no residual tumor (after a previous uncertain margin after endoscopic

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

			Indication CAL-WR					
	Overall n = 118 (%)		**Endoscopically-unresectable polyp. n = 66 (%)**		**Residual adenomatous tissue. n = 34 (%)**		**Irradical low-risk pT1 n = 18 (%)**	
Technical success	110	(93)	63	(95)	31	(91)	16	(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	8	*(7)*	*3*	*(6)*	*3*	*(9)*	*2*	*(11)*
Reason:								
Rectal lesion	*3*		*1*		-		*2*	
*Ingrowth in ileum**	*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*		-	
Right-sided hemicolectomy	*4*		*2*		*2*		-	

* CAL-WR was performed with acceptance of irradicality

CAL-WR indicates colonoscopic-assisted laparoscopic wedge resection; eFTR, endoscopic full-thickness resection; TAMIS, transanal minimally invasive surgery.

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 30mm and lesions greater than 30mm (90% vs 92%, p = 0.78) (Supplemental Table 1).

Invasive cancers were diagnosed in 22 patients (20%), 13 of whom had a pT1 tumor, 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 2 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 2 groups: (1) lesions smaller or equal to 25mm (n = 12) and (2) lesions larger than 25mm (n = 7). Although numbers were small, there was no difference in R_0 resection rates (92% vs 86%, p = 1.00) (Supplemental Table 1).

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, days [range]	2 [1-5]
Median operating time, minutes [range]	58 [20-138]

CDG indicates Clavien Dindo Grade of complications

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 1 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, after complaints of a stenosis of the colon (Supplemental Table 1).

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 4) and 3 of these patients underwent R_0 resection of the CAL-WR, 1 of which concerned a lesion with ingrowth into the appendix. In 2 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 4 cases with recurrence were confirmed by histological examination of the resected residue. The residue was treated by cold snare EMR in all 4 cases (Table 5).

Table 4 Follow-up endoscopy

	Overall n = 98 (%)
Follow-up endoscopy	87 (89)
Missing	*11*
*Patient died**	*1*
Patient refused follow-up endoscopy	*4*
No follow-up endoscopy due to COVID-19	*4*
Lost to follow-up	*2*
Median interval between CAL-WR and FU: months [range]	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 Indicates follow-up endoscopy; CAL-WR, colonoscopic-assisted laparoscopic wedge resection

Table 5 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, Rx 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 indicates follow-up endoscopy;. CAL-WR, colonoscopic-assisted laparoscopic wedge resection; LGD, low grade dysplasia; EMR, endoscopic mucosal resection; SSA/P, sessile serrated adenoma/polyp

DISCUSSION

This prospective multicenter 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 CRC screening programs in many countries.[3] CAL-WR seems 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 seems costeffective compared to laparoscopic segmental resection.[29]

To date, few studies have described the use of various 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, 1 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 post-operative 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 was performed. Therefore, the reported 6% morbidity rate in our study seems acceptable, especially in a multicenter design.

Successful CAL-WR in the present study resulted in an overall radical resection rate of 91%, and no significant difference was found in resection rates for lesions <

30mm or > 30mm. 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 1 case the pathologist found loose adenomatous cells in the staple margin, whereas 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 and 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.

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] whereas 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 20mm by the size of the cap.[5,31,33,34] In our study, the median size of lesions was 20mm (range 5–50mm), 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] whereas 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 multicenter prospective design and the relatively large number of included patients, whereas 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.

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.

Supplement Table 1 Histologic outcome of 110 CAL-WR specimens

	Overall n = 110 (%)	Indication CAL-WR		
		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				
R_0 resection	*100 (91)*	*55 (87)*	*29 (94)*	*16 (100)*
R_x resection	*7 (6)*	*5 (8)*	*2 - (6)*	-
R_1 resection	*3 (3)*	*3 (5)*		-
Radicality by size				*Not applicable**
Lesion </= 30mm	*79*	*53*	*26*	
R_0 resection	*71 (90)*	*48 (90)*	*23 (88)*	
R_x resection	*5 (6)*	*3 (6)*	*2 (8)*	
R_1 resection	*3 (4)*	*2 (4)*	*1 (4)*	
Lesion > 30mm	*13*	*8*	*5*	
R_0 resection	*12 (92)*	*7 (88)*	*5 (100)*	
R_x resection	*1 (8)*	*1 (12)*	-	
R_1 resection	-	-	-	
Missing polyps (size)	*2*	*2*	-	
Radicality in case an invasive lesion was found	*22 (20)*	15	4	3
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*	
R_0 resection	*11 (92)*	*10 (100)*	*1 (50)*	
R_x resection	-	-	-	
R_1 resection	*1 (8)*	-	*1 (50)*	
Lesion > 25mm	*7*	*5*	*2*	
R_0 resection	*6 (86)*	*4 (80)*	*2 (100)*	
R_x resection	*1 (14)*	*1 (20)*	-	
R_1 resection	-	-	-	
Invasive lesions found in scar of 'irradical low-risk pT1' (size not applicable)	*3*			

e.g. footnotes, see next page

Supplement Table 1 continued

	Overall n = 110 (%)	Indication CAL-WR		
		Endoscopically-unresectable polyp n = 63 (%)	Residual adenomatous tissue n = 31 (%)	Irradical low-risk pT1 n = 16 (%)
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	-

* Not applicable because original size of polyp is not representative for radicality of removal of scar from a 'irradical low-risk T1'

CAL-WR indicates colonoscopic-assisted laparoscopic wedge resection; SSA/P, sessile serrated adenoma/polyp; LGD, low-grade dysplasia; HGD, high-grade dysplasia; CRC, colorectal cancer.

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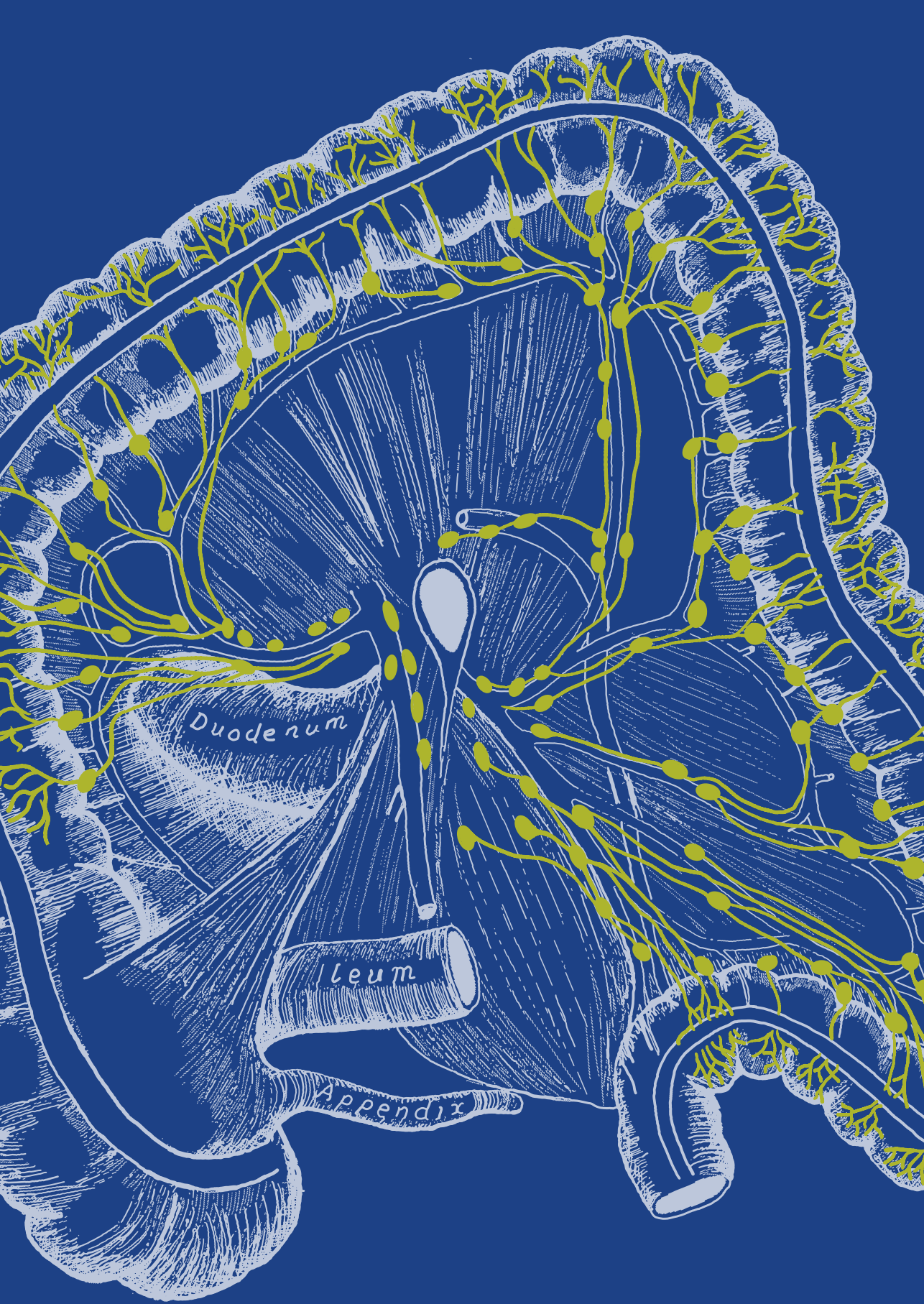
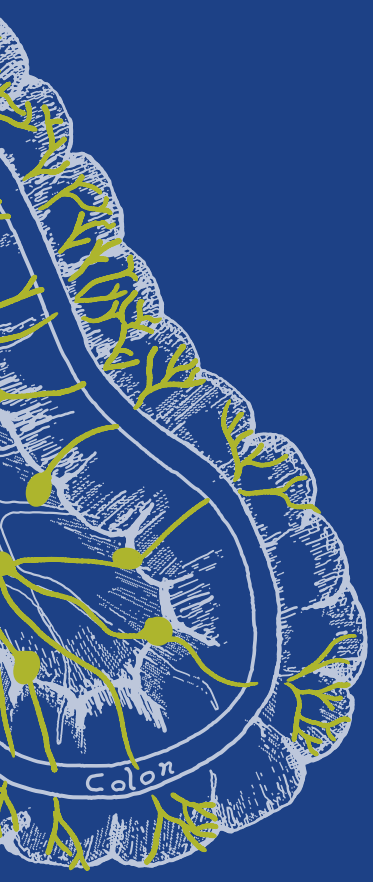

Duodenum
Ileum
Appendix

CHAPTER 7

Avoiding unnecessary major rectal cancer surgery by implementing structural restaging and a watch-and-wait strategy after neoadjuvant radiochemotherapy



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ABSTRACT

Background

Pathologic complete response (pCR) after neoadjuvant chemoradiotherapy (nCRT) is found in 15–20% of patients with locally advanced rectal cancer. A watch-and-wait (W&W) strategy has been introduced as an alternative strategy to avoid surgery for selected patients with a clinical complete response at multidisciplinary response evaluation. The primary aim of this study was to evaluate the efficacy of the multidisciplinary response evaluation by comparing the proportion of patients with pCR since the introduction of the structural response evaluation with the period before response evaluation.

Methods

This retrospective cohort study enrolled patients with locally advanced rectal cancer who underwent nCRT between January 2009 and May 2018, categorizing them into cohort A (period 2009–2015) and cohort B (period 2015–2018). The patients in cohort B underwent structural multidisciplinary response evaluation with the option of the W&W strategy. Proportion of pCR (ypT0N0), time-to-event (pCR) analysis, and stoma-free survival were evaluated in both cohorts.

Results

Of the 259 patients in the study, 21 (18.4%) in cohort A and in 8 (8.7%) in cohort B had pCR ($p = 0.043$). Time-to-event analysis demonstrated a significant pCR decline in cohort B ($p < 0.001$). The stoma-free patient rate was 24% higher in cohort B ($p < 0.001$).

Conclusion

Multidisciplinary clinical response evaluation after nCRT for locally advanced rectal cancer led to a significant decrease in unnecessary surgery for the patients with a complete response.

INTRODUCTION

The standard therapy for locally advanced rectal cancer is neoadjuvant chemoradiotherapy (nCRT) to downstage the tumor followed by surgical resection according to the principles of total mesorectal excision (TME). Despite a favorable oncologic outcome, TME is accompanied with perioperative mortality and morbidity.[1] Histopathology of resected specimens shows disappearance of malignant tumor and lymph nodes —a pathologic complete response (pCR)— in 15–20% of patients.[2] In 2004, Habr-Gama et al.[3] proposed a watch-and-wait (W&W) policy rather than TME surgery for patients with an apparent clinical complete response (cCR). Since then, several other studies have reported on the clinical outcome and oncologic safety of the W&W policy.[4,5] A recent study even advocated an extended observation period for patients with a near cCR.[6] In the last decade, interest in these organ-preservation strategies for selected patients has been increasing, with the aim to improve the quality of life for cancer survivors.

Organ preservation starts with a structural multidisciplinary response evaluation after CRT to identify the patients with a good response. The primary aim of our study was to evaluate the efficacy of this multidisciplinary response evaluation for locally advanced rectal cancer by comparing the number of pCRs (unnecessary surgeries) after nCRT for patients who had no multidisciplinary response evaluation with that for patients who underwent structural multidisciplinary response evaluation in our colorectal unit.

METHODS

Patient inclusion and selection

This retrospective cohort study was performed in a Dutch high-volume colorectal cancer center. All patients identified with locally advanced rectal cancer who underwent a long-course nCRT with curative intent (28 fractions of 1.8-Gy radiotherapy with a twice daily bolus of capecitabine 825 mg/m2) between January 2009 and June 2018 were enrolled in the study and assigned to cohort A or B.

Cohort A consisted of patients without local response evaluation after nCRT (period 2009–2015) who received either a TME resection or further palliative treatment due to the development of widespread distant metastases or a poor condition (Fig. 1).

Cohort B consisted of patients who had response evaluation after nCRT (period 2015–2018) with digital rectal examination, diffusion-weighted (DWI) magnetic resonance imaging (MRI), sigmoidoscopy, and computed tomography (CT).

The patients in cohort B were categorized as having cCR, near cCR, or obvious residual tumor or palliation after nCRT (Fig. 1). The patients with obvious residual tumor underwent a TME resection, and the patients with widespread metastases or a poor condition underwent palliative treatment. The patients with a cCR or near cCR on response evaluation entered the W&W program, as described later. All imaging methods for the patients with cCR or near cCR were referred to the Antoni van Leeuwenhoek hospital (AVL) in Amsterdam, an expert center for W&W, to have a second reading before inclusion in the W&W group.

The patients were categorized as having ‘‘cCR’’ when both endoscopic and radiologic cCRs were achieved or as having ‘‘near cCR’’ if endoscopic or radiologic near cCR was achieved. Endoscopic cCR was defined as a white scar with or without telangiectasia and no palpable abnormalities. Radiologic cCR was defined as the absence of residual tumor on T2W-MRI, with a low signal at the former tumor location on b1000 DWI-MRI and the absence of suspicious lymph nodes on T2W-MRI. Endoscopic near-complete response was defined as a superficial soft irregularity on digital rectal examination, a small residual flat ulcer, or irregular wall-thickening at endoscopy and/or adenomatous tissue with dysplasia at histopathologic examination. Radiologic near cCR was defined as obvious downstaging with or without residual fibrosis but with a heterogeneous or irregular aspect on MRI and/or a small focal area of high signal on b1000 DWI-MRI.[6] The patients with involved mesorectal fascia (MRF) or involved local organs after nCRT were referred to a tertiary center for TME with intraoperative radiotherapy (IORT). The study was approved by the medical ethics committee (reference no. 180805).

Follow-up surveillance procedure for cCR and near cCR after nCRT

The treatment and follow up decisions can be regarded as a three-stage treatment stratification algorithm over time (Fig. 1). In general, the first response evaluation was planned to occur 8 weeks after completion of the nCRT, with the second response evaluation planned to occur 12–16 weeks after the first response evaluation.

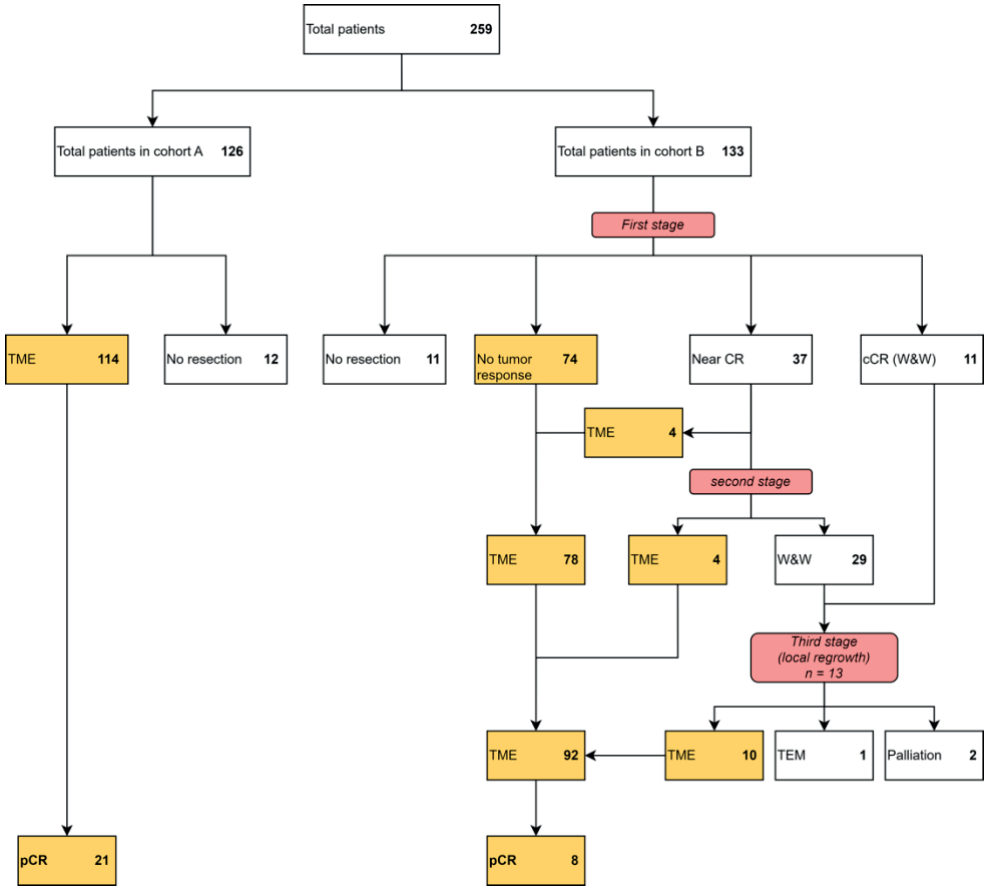

Fig 1. Three stage treatment algorithm for systematic evaluation for TME in cohort A & B. First stage was first multidisciplinary discussion after nCRT. Second stage was second multidisciplinary discussion for patients with near cCR. Third stage was local regrowth W&W group. cCR indicates clinical complete response; W&W, watch-and-wait; TME, Total mesorectal excision; TEM, transanal endoscopic microsurgery.

After the first-stage response evaluation, the patients with cCR after nCRT were offered the W&W policy and underwent intensive follow-up evaluation with endoscopy, rectal MRI, abdominal and thoracic CT, and carcinoembryonic antigen (CEA) screening every 3–6 months (Table 1). The patients with a near cCR at the first-stage response evaluation were offered TME or second-stage response evaluation.

A second-stage response evaluation was performed for the patients with near cCR who did not choose to undergo TME. At this evaluation, the patients were classified as cCR or no cCR. The patients without cCR underwent TME, whereas the patients with cCR were offered the W&W policy with intensive follow up evaluation.

In the third stage (follow-up W&W), the patients submitted for W&W who showed local regrowth at any time during the follow-up period were considered for salvage TME or local excision. The patients with incurable distant metastasis were offered palliative therapy.

Table 1 Follow up watch-and-wait

Year	1				2				3		4		5	
Months	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
CEA	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Endoscopy	x	x	x	x		x		x	x	x	x	x	x	x
Rectal MRI	x	x		x		x		x	x	x	x	x	x	x
Thoracic and abdominal CT		x		x		x		x		x		x		x

X means that the diagnostic test was scheduled
CEA indicates carcinomembryonic antigen; MRI, magnetic resonance imaging; CT, computed tomography

Statistical analysis

The primary outcome of the study was the proportion of pCR defined as the absence of malignant tumor and lymph nodes in the pathologic TME resection specimen (ypT0N0). The secondary outcomes were the stoma-free patient rate and the disease-free survival (DFS) rate in both cohorts. All analyses were performed using Statistical Package of Social Sciences version 24.0 (SPSS, Armonk, NY). A p value lower than 0.05 was considered significant. Descriptive statistics were reported as median with range or as count with proportion.

The baseline characteristics of cohorts A and B were compared using the Mann–Whitney U test for continuous variables and the Chi square test for categorical variables. Univariate analysis was performed to determine the difference between the patient characteristics of cohorts A and B at baseline. Kaplan–Meier survival analysis was used to estimate the probability of pCR after nCRT, local regrowth in the W&W group, and DFS.

For survival analyses of pCR and local regrowth, the start of the follow-up evaluation was the date of the last nCRT, and the end of the follow-up evaluation was the date of interest. For the analysis of pCR, the end of the follow-up evaluation was the date of the TME resection, the date of the last follow-up scan, the date of tumor progression, or the date of death or the date of the decision not to perform TME (palliative group), whichever came first. The patients who underwent TME after the second response evaluation or salvage TME due to local regrowth during W&W were counted in the TME group (Fig. 1). For the analysis of local regrowth, the end of the follow-up evaluation was the date of local regrowth or the date of the last follow-up endoscopy/MRI.

A DFS analysis (non-endoluminal or distant recurrence) was performed for the patients who underwent curative surgery without distant metastasis after nCRT and for the patients submitted to W&W. The start of the follow-up evaluation was the date of curative surgery or the decision for W&W. The end of the follow-up evaluation was the date of recurrence, the date of death, or the date of the last CT, whichever came first. For the stoma-free analysis, we calculated the presence of a stoma at the end of the follow-up period using proportions.

RESULTS

Baseline characteristics

The study enrolled 259 patients: 126 patients in cohort A and 133 patients in cohort B. The baseline characteristics, presented in Table 2, differed significantly between the two cohorts in terms of clinical T stage and N stage.

Cohort A

In cohort A, 114 patients (90%) underwent TME. For the remaining 12 patients, TME was not performed due to the development of incurable distant metastasis after nCRT (n = 6) or comorbidity (n = 3), or because of patient preference (n = 1), and two patients died of sepsis during nCRT.

Cohort B

For cohort B, the third-stage treatment algorithm for stratification over time was evaluated (Fig. 1).

First-Stage Response Evaluation

All the patients in cohort B underwent first-stage multidisciplinary response evaluation. The median observational interval between the end of nCRT and the response evaluation was 8 weeks (range, 5–22 weeks). At this response evaluation, 11 patients (8%) had cCR, 37 patients (28%) had near cCR, 74 patients (56%) had obvious residual tumor, and 11 patients (8%) were assigned to the palliative group (Fig. 1; Table 3).

All 74 patients with obvious residual tumor underwent TME. For 11 patients, palliative treatment was administered because of distant metastasis (n = 5), comorbidity (n = 3), or patient preference (n = 1), and two patients died due to bowel perforation and cardiovascular event.

When 11 patients showed a cCR after the first response evaluation on both endoscopy and MRI, they were entered into the W&W surveillance program. Near cCR was observed in 37 patients (28%), with 15 patients (41%) showing possible residual tumor on both endoscopy and MRI, 15 patients (41%) showing possible residual tumor on endoscopy and cCR on MRI, and 7 patients (19%) showing possible residual tumor on MRI and cCR on endoscopy. Of these 37 patients, 4 underwent primary TME instead of second-response evaluation due to patient preference (n = 3) or symptomatic rectal stenosis (n = 1). The remaining 33 patients underwent second-stage response evaluation.

Second-Stage Response Evaluation

Second-stage response evaluation was performed for the 33 patients (25%) with near cCR after a median of 13 weeks (range, 4–26 weeks) from the first response evaluation. After this response evaluation, 29 patients (88%) were submitted to the W&W. Four patients (12%) had obvious residual tumor and underwent TME. All operations were radical resections with free resection margins (R0), with histopathology showing ypT3N0 (n = 2) and ypT2N0 (n = 2) (Fig. 1).

Third-Stage Response or W&W Evaluation

Altogether, 40 patients were submitted to the definitive W&W surveillance program (11 patients after first-stage and 29 patients after second-stage response evaluation) (Fig. 1). Local regrowth occurred for 13 patients (32.5%) after a median

of 14 months (range, 4–29 months). Of these 13 patients, 11 underwent successful curative and radical salvage surgery (R0) (TME for 10 patients and transanal endoscopic microsurgery (TEM) for 1 patient), and 1 refused TME, with the remaining patient undergoing palliative therapy for incurable osseous metastasis that developed 9 months after nCRT. Local or distant recurrence after salvage TME did not occur in our population.

Table 2 Baseline characteristics

	Cohort A n (%)	Cohort B n (%)	p-value
n	**126**	**133**	
Males	71 (56)	87 (65)	0.135*
Median age, years [range]	66 [32-85]	65 [34-88]	0.354#
Median tumor high from anal verge, cm [range]	6 [2-15]	6 [0-17]	0.883#
cT-stage			0.027*
T2	*2 (2)*	*7 (5)*	
T3	*104 (83)*	*94 (71)*	
T4	*15 (12)*	*25 (19)*	
T3/4	*1 (1)*	*6 (5)*	
missing	*4*	*1*	
cN-stage			
N+	*109 (95)*	*114 (86)*	*<0.001**
N0	*6*	*18*	
Nx	*11*	*1*	

AV indicates anal verge
*Chi-square test. #Mann Whitney U test.

Table 3 Treatment stratification at first response evaluation in cohort B

	Cohort A n (%)	Cohort B n (%)
No. of patients	126	133
Primary TME	114 (90)	74 (56)
No resection	12 (10)	11 (8)
cCR (W&W)	-	11 (8)
Near cCR	-	37 (28)

TME indicates Total Mesorectal Excision; cCR, clinical Complete Response; W&W, Watch and Wait.

The 3-year cumulative incidence of local regrowth after nCRT among the W&W patients was 42% (95% confidence interval (CI), 26–64%; Fig. 2A). Two patients were censored during the W&W follow-up period for incurable distant metastasis (without local regrowth) after 5 and 23 months, respectively.

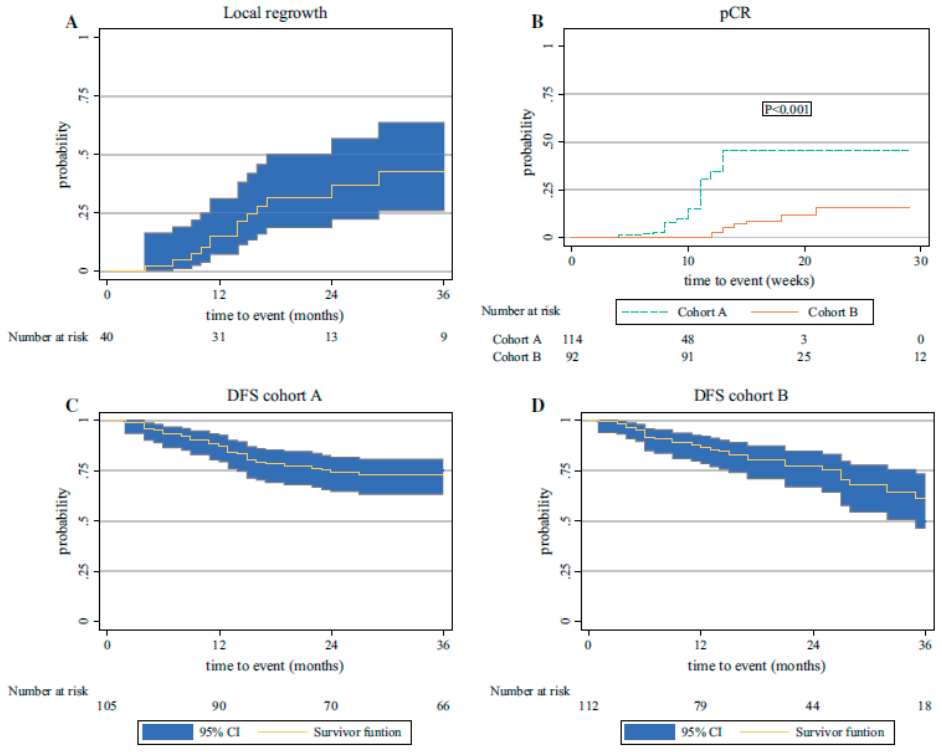

FIG. 2 (A): 3-year cumulative incidence of local regrowth among the W&W cohort (n=40). **(B):** 30-week cumulative incidence of pCR after nCRT (n=206). **(C):** 3-year disease free survival (DFS) among patients with curative therapy after nCRT in cohort A. **(D)** 3-year disease free survival (DFS) among patients with curative therapy after nCRT in cohort B. pCR indicates pathological Complete Response; DFS, disease free survival; CI, confidence interval.

Comparison of TME outcome

Of the 259 patients, 206 (79.5%) underwent TME (114 patients in cohort A and 92 patients in cohort B). Two patients in cohort A and eight patients in cohort B underwent TME with IORT. The overall R0 resection rate was 95% in both cohorts. The findings showed pCR for 21 patients (16.7%) in cohort A and 8 patients (6%) in cohort B (p = 0.006). Among the patients who underwent TME (n = 206), the proportion of pCR was 18.4% in cohort A and 8.7% in cohort B (p = 0.043) (Table 4). The overall interval between nCRT and TME differed significantly. For the overall TME group (n = 206), the interval was 9 weeks (range, 4–29 weeks) in cohort A and 15 weeks (range, 9–129 weeks) in cohort B (p < 0.001), and for the patients with pCR (n = 29), the interval was 10 weeks (range, 4–13 weeks) in cohort A and 14 weeks (range, 12–21 weeks) in cohort B (p < 0.001). This indicates that the variable period between nCRT and TME may have affected the outcome. Therefore, we performed a survival analysis to account for this variable period over time. The 30-week cumulative incidence of pCR was 46% (95% CI,30–65%) for the patients without a multidisciplinary response evaluation (cohort A) and 16% (95% CI, 7–31%) for the patients with a multidisciplinary response evaluation (cohort B) ($P_{log\text{-}rank}$ < 0.001; Fig. 2B).

Table 4 Clinical outcome (pCR)

	Cohort A n (%)	Cohort B n (%)	p-value
Median interval between nCRT and TME, *weeks [range]*	9 [4-29]	15 [9-129]	<0.001#
pCR in total cohort (n = 259)	126	133	
pCR	21 (16.7)	8 (6)	0.006*
No pCR	104 (82.5)	125 (94)	
Missing	*1*	*0*	
pCR for patients with TME (n = 206)	114	92	
pCR	21 (18.4)	8 (8.7)	0.043*
No pCR	93 (80.7)	84 (91.3)	
Missing	*1*	*0*	
30-Week cumulative probability of pCR, *% (95% CI)*	46 (30-65)	16 (7-31)	<0.001$

nCRT indicates neoadjuvant chemoradiotherapy; TME, Total Mesorectal Excision; pCR, pathologic Complete Response; CI, Confidence interval
#Mann Whitney U, *Chi Square, $Logrank test.

Disease-free survival

The DFS analysis included 225 patients (109 in cohort A and 116 in cohort B) who underwent curative surgery or were submitted to W&W. For eight of these patients, follow-up evaluation was not performed or will be performed in future in case of a recent diagnosis. Local- or distant recurrence occurred for 27 patients (24.8%) in cohort A and 27 patients (23.3%) in cohort B (Table 5). The 3-year DFS rate was 73% (95% CI, 63–81%) in cohort A and 61% (95% CI, 46–73%) in cohort B. (Figure 2C and D).

Table 5 Distant and local recurrence

	Cohort A n (%)	Cohort B n (%)	p-value
Total cohort	126	133	
Patients included for disease free survival analysis	109	116	
Total recurrence	27 (24.8)	27 (23.3)	0.793*
Distant recurrence	*23 (21.1)*	*21 (18.1)*	
Local recurrence after TME	*1 (0.9)*	*4 (3.4)*	
Local- and distant recurrence after TME	*3 (2.8)*	*2 (1.7)*	
Median time until recurrence, months [range]	*13 [2-27]*	*12 [1-35]*	*0.768#*
No recurrence	82 (75)	89 (76.7)	0.793*
Median follow-up, months [range]	*58 [0-97]*	*20 [0-49]*	*<0.001#*
3-year disease free survival, *% (95% CI)*	73 (63-81)	61 (46-73)	

TME indicates Total Mesorectal Excision; CI, confidence interval
#Mann whitney U test, *Chi square test, $Logrank test

Stoma-free survival

A stoma was created for 106 patients (84%) in cohort A and 84 patients (63%) in cohort B. Stoma reversal during the follow-up evaluation was performed for 23 patients in cohort A and 29 patients in cohort B. The median time to stoma reversal was 4 months (range, 0–9 months) in cohort A and 3 months (range, 0–33 months) in cohort B. At the end of the follow-up period, 43 patients (34%) in cohort A and 77 patients (58%) in cohort B were stoma free ($p < 0.001$).

DISCUSSION

This study demonstrated a significant decline in TME resections without residual tumor (pCR) since the implementation of the structural multidisciplinary response evaluation after nCRT for locally advanced rectal cancer with the option of a W&W policy for patients with a very good response. With our current approach, the proportion of pCRs after TME decreased from 18 to 9%, and overall, a major TME resection could be avoided for more than 20% of patients, resulting in a 24% increase in stoma-free patients.

In our unit, the goal of structural response evaluation after nCRT is to identify patients with a very good response and offer them the option of organ preservation. To identify as many complete responders as possible, we allow patients with a near cCR at the first-stage response evaluation to have a longer observation period. The idea of this extended period is to maximize the detection of complete responders because current diagnostic techniques are not sufficiently accurate to detect true complete responders, accepting a higher local regrowth rate. A recent study reported that a longer observational period is safe and has no impact on oncologic outcome.[6] With this policy, 40 patients (30%) entered the W&W surveillance program, and 92 patients (69%) underwent TME. Even with our liberal policy of a longer observation period for near complete responders, we had eight patients (6%) who showed a pCR after a TME. Two of these patients had a symptomatic rectal stenosis, and six of the patients had residual abnormalities at endoscopy. A recent paper showed that the majority of missed complete responses were due to residual abnormalities at endoscopy, and to a lesser extent, suspicious findings on MRI such as a high signal on T2W images, diffusion restriction, or dubious lymph nodes.[7] The 3-year cumulative incidence of local regrowth among the W&W group was 42%, which is higher than the 2-year cumulative incidence of 25% in a recent registry study.[5] This recent study also included patients with early rectal cancer (cT1-T2), whereas our study included almost exclusively cT3-4 tumors. Findings have shown an association between a higher original T-stage in a W&W program and a higher regrowth rate.[8] Additionally, we also included patients with a near cCR, and it is suggested that these patients also have a higher regrowth rate.[6] Local regrowth seems to be associated with a higher incidence of distant recurrence.[5,9] In our study, only 1 (2.5%) of the 40 patients experienced local regrowth with distant metastasis during the W&W. The remaining patients were or could have been treated

curatively with salvage surgery, indicating that structural response evaluation with the possibility of the W&W policy might be oncologically safe. Future research should investigate the exact timing and strategy of the restaging and factors associated with cCR or near cCR to maximize the detection of cCR and minimize the local regrowth rate.

The strength of our study was the comparison of pCR before and after the introduction of structural response evaluation for all patients with locally advanced rectal cancer who underwent nCRT, whereas most studies have focused only on the outcome of W&W. For this analysis, we used complete follow-up information on patients who had cCR, near cCR, or obvious residual tumor after response evaluation, and we also reported a complete follow-up evaluation of the patients before multidisciplinary response evaluation was introduced.

A limitation of this study was that the interval between nCRT and TME surgery differed between the two cohorts. Although the first multidisciplinary response evaluation was performed after 8 weeks in both cohorts, the prolonged interval between CRT and TME among the W&W patients might have influenced the tumor response. Another limitation was that the study was performed in a single center with a relatively small number of patients, making it difficult to extrapolate the results to other settings and to perform accurate survival analysis. The study was underpowered to perform adequate DFS analysis. Furthermore, the difference in the median follow-up period between the two cohorts made it difficult to perform accurate DFS analysis. Selection bias might have been introduced by historical influences over the years, such as the introduction of (re)staging MRI, an nCRT indication for patients with N1, and a prolonged observational interval between nCRT and restaging. Furthermore, the definition of near cCR is relatively subjective.

Conclusion

We reported a significant decrease in unnecessary surgery for patients with a complete response since the implementation of structural response evaluation and a W&W program for patients with locally advanced rectal cancer.

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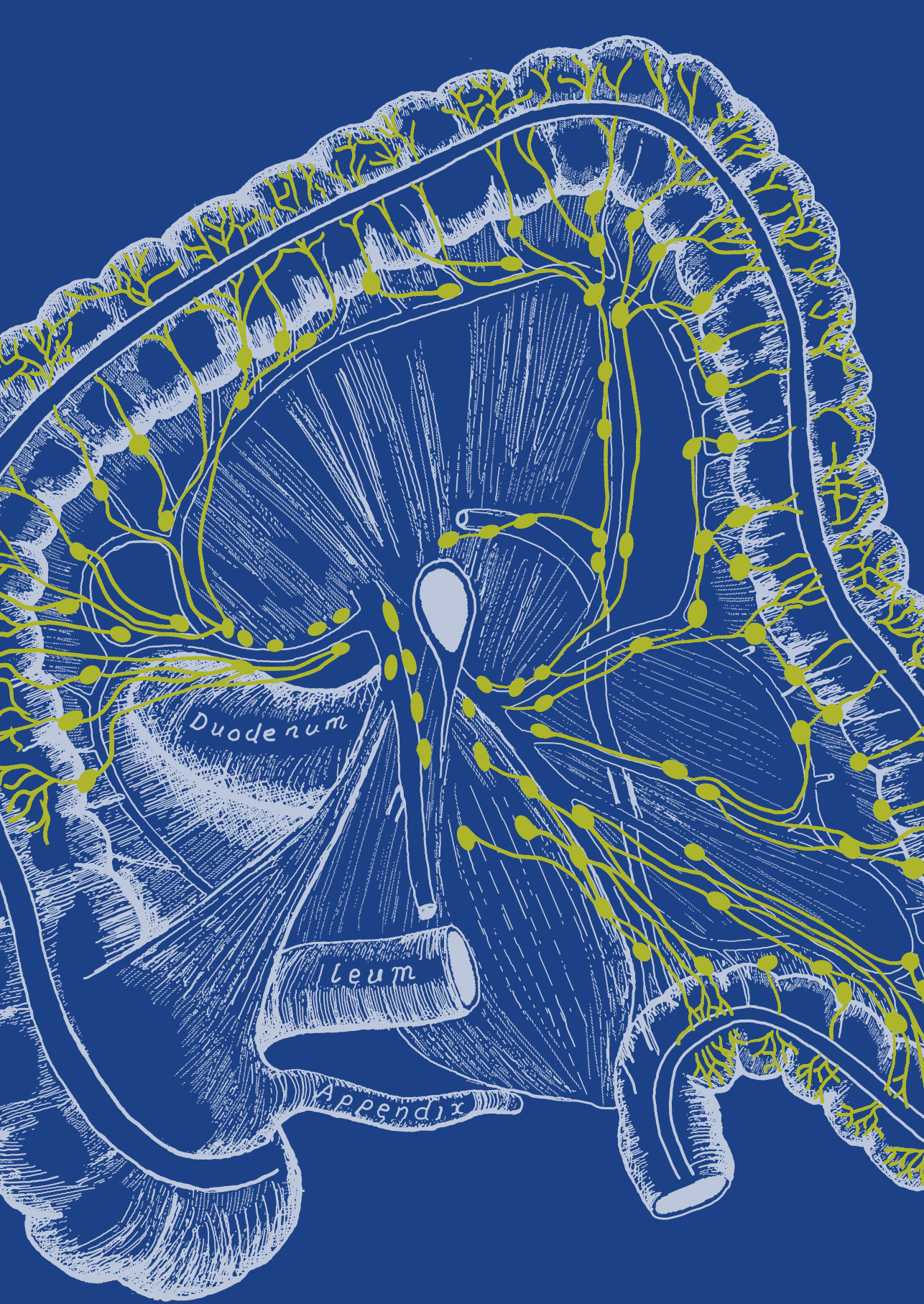
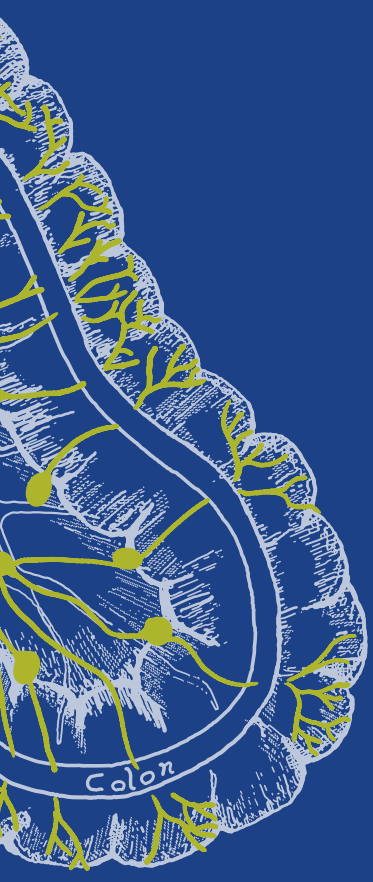

Duodenum
Ileum
Appendix

CHAPTER 8

Clinical outcome of decompressing colostomy for acute left-sided colorectal obstruction: a consecutive series of 100 patients



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ABSTRACT

Purpose

Aim of our study was to evaluate the outcomes of a consecutive series of patients who were treated with a decompressing colostomy (DC) for acute left-sided colorectal obstruction.

Methods

A consecutive series of 100 patients with acute left-sided colorectal obstruction who underwent DC from January 2015 to August 2020 was retrospectively analyzed. Demographic characteristics, etiology of the obstruction, postoperative morbidity- and mortality rates, DC-related complication and stoma reversal rates were evaluated.

Results

Of the 100 included patients, 64 had malignant- and 36 had benign obstruction. The mean age was 69 years, 42% was male, and the ASA score was 2. Morbidity and mortality rates after DC construction were 20 and 2%, respectively. In 39% of the patients, DC ended up as a permanent stoma and in 61% as bridge to surgery. DC related complication rate was 32%, with a re-intervention rate of 9%. Elective colorectal resection was performed in 59 cases (59%) with subsequent postoperative morbidity rate of 20%. Stoma reversal rate was 77% for the patients who underwent DC as Bridge to surgery. Stoma reversal was performed in 66% of the patients with benign obstruction and in 36% for oncological obstruction.

Conclusion

DC as bridge to possible elective resection for acute left-sided colorectal obstruction is an effective strategy with low morbidity and mortality rates and a high stoma reversal rate, especially for benign obstruction. However, DC is less appropriate for patients in whom DC turns out to be a permanent stoma due to a relatively high stoma related complications.

INTRODUCTION

Large bowel obstruction accounts for 2–4% of all surgical admissions and mostly occurs in the frail elderly.[1,2] In 75% of the cases the obstruction is located in the left hemi-colon, which is often a life-threatening situation requiring immediate intervention.[3] The most common cause of left-sided obstruction is colorectal cancer (CRC (60%) followed by diverticulitis (10%).[3,4]

The conventional treatment for acute left-sided colonic obstruction is acute surgical resection. However, this strategy, especially in the elderly, is under debate since it is associated with high morbidity (32–64%), mortality (7–35%) and high permanent colostomy rates (40–48%).[1,2] Furthermore, acute resection does not allow adequate diagnosis of the origin of the obstruction. In case of malignancy, tumor staging is necessary to prevent over-treatment in patients with incurable disease or under-treatment if neoadjuvant chemo- or radiotherapy is mandatory.

Colonic decompression therapy i.e., endoscopic stent placement or decompressing colostomy (DC) followed by delayed resection is an alternative treatment gaining popularity. This strategy avoids the need for a laparotomy in acute setting, facilitates optimization of the clinical condition and allows adequate tumor staging. This strategy is associated with less morbidity and mortality with similar oncologic outcome.[5–7]

Several studies examined the safety and feasibility of self-expandable metal stent (SEMS) placement as a bridge to surgery (BtS) in left-sided colonic obstruction. These studies showed that SEMS is associated with less mortality and morbidity compared to acute colonic resection.[8–10] However, the oncological implications of colonic tumor stenting are still controversial due to tumor perforation and proposed impaired oncological outcome.[11] Colonic stent placement should be avoided in patients with stenotic diverticulitis as it is associated with perforation, however, a stenotic diverticulitis can hardly be distinguished from stenotic CRC in acute setting.[12,13]

In the Netherlands, acute resection for oncological obstruction has decreased since the implementation of the revised guidelines in 2014.[14] In our hospital, a DC became the standard treatment for acute left-sided obstruction for all causes of left-sided

obstruction. Bridging with a colonic stent placement was not performed in our hospital since the implementation of the revised guidelines. Aim of this study was to evaluate the outcome of a consecutive series of 100 patients treated with a DC for acute left-sided colorectal obstruction.

METHODS

Study design

This retrospective consecutive cohort study was performed in Isala, a large teaching hospital in the Netherlands. The study was approved by the medical ethics committee (reference number: 181002). All patients with acute left-sided colorectal obstruction confirmed by abdominal CT, who were treated with DC between January 2015 and August 2020 were included. Demographic characteristics, surgical parameters, etiology of the obstruction, postoperative morbidity and mortality rates and DC-related complication rates were evaluated for all patients. Furthermore, morbidity rates related to delayed resection and stoma reversal rate were analyzed.

Outcome parameters

Preoperative patient comorbidity was classified using the American Society of Anesthesiologists (ASA) scores.[15,16] Morbidity and mortality were defined as 30-day post-surgical events. Morbidity was graded according to the validated Clavien-Dindo (CD) classification of surgical complications; major complications were defined as CD grade IIIa or higher and minor complications were defined as CD Grade II or lower.[17] DC related morbidity was defined as 1-year postoperative stoma-related events and also graded according to the CD classification.

Treatment

Colonic decompression was achieved by creating a blowhole or loop colostomy. Both techniques were used based upon the severity of the distension of the colon or the preference of the surgeon. With the blowhole colostomy, a small incision in the right upper-abdomen and the transverse colon was made. The opened colonic wall was fixed at skin level with absorbable sutures. Using the loop colostomy technique, a transverse colon loop was lifted above the skin and a plastic rod was passed underneath it. The colon was opened and fixed with absorbable sutures. All patients received enteral feeding as soon as possible after surgery. Eligibility for

subsequent elective resection was discussed in the colorectal multidisciplinary team (MDT) meeting. Standard workup consisted of sigmoidoscopy with biopsies, in case of malignancy thoracic and abdominal CT and rectal MRI in case of a rectal malignancy. Patients received neoadjuvant (chemo)-radiotherapy, resection of liver metastasis or hyperthermic intraperitoneal chemotherapy (HIPEC) if indicated according to national guidelines. Elective resection was preferably performed laparoscopically with primary anastomosis construction. Adjuvant chemotherapy was given if indicated depending on tumor stage, patient preference and comorbidity. Colostomy closure was performed in the same procedure if deemed safe by the operating surgeon.

Statistical analysis

All analyses were conducted using Statistical Program for the Social Sciences (SPSS) version 24.0. A 2-sided p-value <0.05 was considered significant. Descriptive statistics and statistical analysis were performed. Normality was tested using Kolgomorov–Smirnov test. If variables were distributed normally they were described as mean with standard deviation. If variables were non-parametrical they were described as median with range. Normally distributed continuous data were tested using students T-test. Non- parametrical continuous data were compared using Mann–Whitney U test. Categorical data were tested using Chi-square test or Fisher exact in case of less than 5 counts.

RESULTS

Baseline characteristics

A series of 100 consecutive patients (Table 1) were included. Left-sided colonic obstruction was caused by CRC in 54 patients (54%), extra-colonic malignancy in 10 patients (10%), stenotic diverticulitis in 32 patients (32%) and other benign causes in 4 patients (4%). Sixty-one patients (61%) underwent DC as BtS and in 39 patients (39%) DC turned out to be a permanent stoma as palliative treatment. The mean age was 69 ± 13 years, 42% were male and the median ASA score was 2 [range 1–4]. The mean age and median ASA score were significantly different (p = 0.002 and p = 0.000, respectively) for patient with DC as BtS (age: 66 ± 11 years, ASA 2 [range 1–3]) compared to DC as palliative treatment (age: 74 ± 15 years, ASA 3 [range 2–4]). For the 39 patients who underwent palliative therapy, elective resection was

not performed due to incurable metastatic disease (n = 20), unfit for resection due to comorbidity (n = 11) and patient preference (n = 8).

Table 1 Baseline characteristics and decompressing colostomy details

	n (%)
Total patients	100
Male	42 (42)
Mean age, *years ± StD*	69 ± 13
ASA score, *median [range]*	2 [1-4]
Malignant obstruction	64 (64)
CRC	*54*
Cervical cancer	*3*
Ovarian cancer	*2*
Peritoneal metastasis	*2*
Endometrial cancer	*1*
Prostate cancer	*1*
Lymphoma	*1*
Benign obstruction	36 (36)
Diverticulitis	*32 (32)*
Crohn's stenosis	*1 (1)*
Anastomotic stricture	*1 (1)*
External endometriosis	*1 (1)*
unknown	*1 (1)*
Location of obstruction	
Rectum	*19 (19)*
Sigmoid	*65 (65)*
Descending colon	*13 (13)*
Transverse colon	*3 (3)*
Type of DC	
Blowhole	*58 (58)*
Loop	*42 (42)*

StD indicates standard deviation; CRC, Colorectal Cancer; ASA, American Society of Anesthesiologists; DC, decompressing colostomy

Decompressing colostomy construction

DC was constructed depending on clinical condition after a median of 1 [range 0–7] day from initial presentation. Fifty-eight patients (58%) received a blowhole colostomy and 42 patients (42%) a loop colostomy. The median hospital stay after DC was 7 [range 3–29] days. Morbidity after DC occurred in 20 patients (20%); minor morbidity in 19 patients and major morbidity (ICU admission due to aspiration pneumonia) in 1 patient. Mortality occurred in 2 patients, in one of them due to ischemic colitis and in the other due to an aspiration pneumonia. DC related complications occurred in 32 patients (32%) during 1 year of follow up and are presented in Table 2. Of the 32 patients with DC-complications, 18 (30%) occurred

in the BtS group and 14 (36%) in the palliative group (p = 0.504). In the BtS group, 3 patients had a major stoma complication; 2 patients had a prolapse requiring surgical intervention, and 1 patient had a stenosis requiring local revision. In the palliative group, 6 patients had a major stoma complication; 4 patients had a prolapse requiring conversion to end colostomy and 2 patients developed a stenosis, requiring local revision. We did not found significant differences in patient characteristics, complication rate after DC construction or DC-related complications between patients who underwent blowhole- and loop colostomy.

Table 2 Decompressing colostomy details

	n (%)
DC purpose	
Bridge to surgery	*61 (61)*
Palliation	*39 (39)*
Morbidity DC construction	20 (20)
Clavien Dindo I-II	*19 (19)*
Clavien Dindo >IIIa	*1 (1)*
Mortality DC construction	2 (2)
Hospital stay after DC, *median [range]*	7 [3-29]
1- year DC related morbidity	32 (32)
Prolapse	*20*
PSH	*5*
Stenosis	*4*
Wound infection	*1*
Stoma dehiscence	*1*
Pyoderma gangrenosum	*1*

DC indicates decompressing colostomy; PSH, parastomal hernia.

Elective resection (bridge to surgery)

Elective segmental colon resection was performed in 59 of 100 patients (59%) (Table 3). Eight of these 59 patients (14%) underwent resection with primary anastomosis and simultaneous DC reversal and another 8 patients underwent resection with simultaneous closure of the DC and creation of an end colostomy (Hartmann procedure). For the remaining 41 patients, elective resection was not performed in 39 patients and 2 patients were lost to follow up (Figure 1). The median hospital stay after elective resection was 5 days [range 2–53] and the median time between DC and colonic resection was 10 weeks [range 2–60]. Forty-three patients (73%) were planned for laparoscopic resection. Laparoscopy was converted to an open procedure in 12 of these patients, because of complex diverticulitis (n = 8), or multivisceral resections for cT4 tumors (n = 4). A primary open procedure was planned in 16 patients. The morbidity rate after resection was

20%; minor morbidity in 11 patients and major morbidity 1 patient (pulmonary embolism requiring admission to intensive care). Mortality occurred in 1 patient (2%).

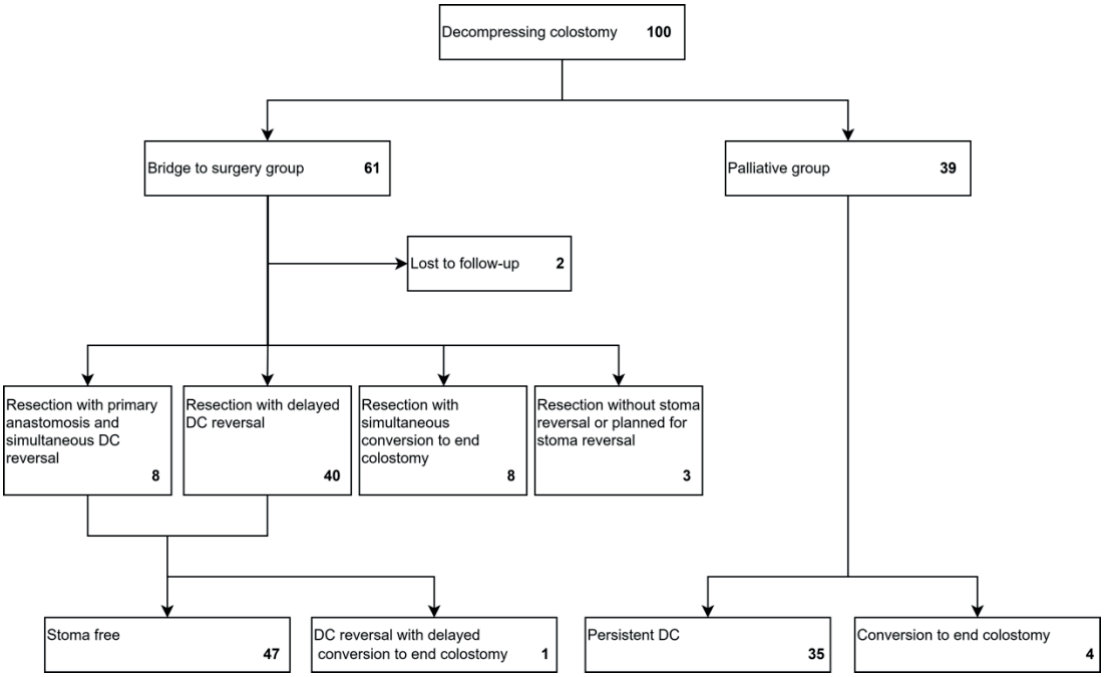

Figure 1 Flowchart of the included patients.

Decompressing colostomy reversal

Of all enrolled patients (n = 100), 47 (47%) were stoma free at the end of the follow up period (Table 4 and Figure 1). The median follow up from DC placement until end of study period (stoma reversal, death or last hospital visit) was 5 months [range 0–40]. The median time from DC to stoma reversal was 6 months [range 0–21]. In the BtS group, the DC was reversed in 56 of 61 patients (92%). However 9 of these reversed patients, underwent DC reversal with conversion to an end colostomy (Figure 1). This resulted into 47 stoma free patients at the end of the follow up (77%). Two patients are still waiting for stoma reversal which is postponed due to the COVID-19 pandemic. For the patients with a DC for palliative reasons, no patients had restored continuity. Morbidity after DC reversal occurred in 4 of 56 patients (7%); minor morbidity in 3 patients and major morbidity in 1 patient.

Table 3 Resection details and stoma reversal

	n (%)
Total patients	100
Total resections performed	59 (59)
Resection type	
Sigmoid resection	*39 (66)*
Low anterior resection	*9 (15)*
Left-sided hemicolectomy	*8 (14)*
Abdominal perineal resection	*1 (2)*
Right-sided hemicolectomy	*1 (2)*
Subtotal colectomy	*1 (2)*
Resection with primary anastomosis and simultaneous DC reversal	8 (14)
Resections with simultaneous conversion to end colostomy	8 (14)
Laparoscopic resection	43 (73)
Conversion to open surgery	12
Morbidity after resection	12 (20)
Clavien Dindo I-II	*11 (19)*
Clavien Dindo >IIIa	*1 (2)*
Mortality after resection	1 (2)
Hospital days after resection, *median [range]*	5 [2-53]

DC indicates decompressing colostomy.

Subgroup analysis; acute oncological obstruction versus acute benign obstruction

Subgroup analysis was performed among patients who had DC for an acute oncological obstruction (n = 64) and for an acute benign obstruction (n = 36). These results can be found in Table 5. Baseline characteristics were significantly different for tumor location (p = 0.000). Morbidity rate after DC construction and 1-year DC related complication rate were similar among both groups. Twenty-three patients (36%) in the oncological group were stoma free at the end of the follow up period compared with 24 patients (66%) in the benign group (p = 0.001).

Table 4 delayed stoma reversal

	n (%)
Total patients	100
Delayed DC reversal	40 (40)
DC reversal with delayed conversion to end colostomy	*1*
Waiting for planned stoma reversal	*2*
Morbidity stoma reversal	4 (10)
Clavien Dindo I-II	*3 (8)*
Clavien Dindo >IIIa	*1 (3)*
Mortality stoma reversal	-
Hospital days after stoma reversal, *median [range]*	3 [1-7]
Stoma free at end follow-up	47 (47)

DC indicates decompressing colostomy.

Table 5 subgroup analysis among patients with oncological obstruction compared with benign obstruction

	Acute oncological obstruction n (%)	Acute benign obstruction n (%)	p-value
Total patients	64	36	
Male	28 (44)	14 (39)	0.636*
Mean age, *years ± StD*	70 ±14	67 ±11	0.323^
ASA score, *median [range]*	2 [1-4]	2 [1-3]	0.694#
Location of obstruction			0.000*
Rectum	*17 (27)*	*2 (6)*	
Sigmoid	*31 (48)*	*34 (94)*	
Descending colon	*13 (20)*	-	
Transverse colon	*3 (5)*	-	
Type of DC			0.427*
Blowhole	*39 (61)*	*19 (53)*	
Loop	*25 (39)*	*17 (47)*	
DC purpose			0.010*
Bridge to Surgery	*33 (52)*	*28 (78)*	
Palliation	*31 (48)*	*8 (22)*	
Median hospital stay after DC, *days, [range]*	7 [3-21]	7 [4-29]	0.799#
Minutes DC construction, *median, [range]*	30 [13-97]	35 [16-70]	0.109#
Mortality DC construction	2 (3%)	-	0.407*
Morbidity DC construction	10 (16)	10 (28)	0.145*
Clavien Dindo I-II	*10*	*9*	
Clavien Dindo ≥IIIa	-	*1*	
Morbidity resection	8 (13)	4 (11)	0.518*
Clavien Dindo I-II	*7*	*4*	
Clavien Dindo ≥IIIa	*1*	-	
Morbidity stoma reversal	2 (3)	2 (5)	1.000*
Clavien Dindo I-II	*2*	*1*	
Clavien Dindo ≥IIIa	-	*1*	
1- year DC related morbidity	18 (28)	14 (39)	0.268*
Stoma free at end follow up	23 (36)	24 (66)	0.001*

StD indicates standard differentiation; ASA, American Society of Anesthesiologists; DC, decompressing colostomy

*Chi-square test or Fisher Exact, #Mann-Whitney U test, ^ Students T-test

DISCUSSION

In this study, we reported permanent DC as definitive treatment in 39% of the patients with acute left sided colorectal obstruction. For the remaining 61%, DC was used as a bridge to surgery, of which eventually 77% were stoma free at the end of the study period. DC resulted in a stoma related morbidity rate of 32% and a re-intervention rate of 9%. Therefore, a DC seems not to be the best strategy for permanent decompression of the colon but should be used as BtS alone.

We found a morbidity rate of 20% after construction of DC, which is similar to prior studies.[7,18,19] Elective resection was performed in 59 patients (59%) with a subsequent morbidity rate of 20%. The permanent stoma rate of 23% among patients with DC as BtS we found is comparable to other studies.[6,7,20–22]

Subgroup analyses for patients with an oncological obstruction compared to a benign obstruction demonstrated a significant difference in location of obstruction, as a result of the high number of patients with stenosing diverticulitis in the sigmoid part of the colon in the benign obstruction group. Furthermore, the stoma reversal rate in the benign group (66%) was significantly higher compared to the oncological group (36%), which might be explained by the fact that patients with benign obstruction are often completely cured with subsequently stoma reversal at the end of the treatment, while patients with an oncological obstruction had their stoma as a palliative treatment rather than a bridge to surgery. Morbidity rate after DC construction and long term DC related complications were similar for both groups. Therefore, DC seems safe for acute oncological and benign obstruction with subsequent high stoma reversal for patients with benign acute left sided obstruction.

In the Isala Hospital, DC as BtS has became the standard therapy for acute left-sided colorectal obstruction based upon the Dutch guidelines. For patients with acute left-sided colonic obstruction, the origin of the obstruction is not always clear. In particular, the distinction between CRC and diverticulitis on preoperative imaging may be difficult. DC postpones the need for emergency resection with subsequent elective resection and allows optimizing the clinical condition and nutritional state, adequate preoperative tumor staging, neo-adjuvant chemo- or radiotherapy if indicated and allows laparoscopic resection by a specialized colorectal surgeon. The

construction of a DC is a relatively fast and controlled procedure with a success rate of nearly 100% and can be performed in almost every patient. More than 70% of the patients in our study underwent laparoscopic resection. In contrast, emergency resection in a patient with left-sided obstruction is mostly performed with open surgery, as laparoscopy is generally difficult due to the distended colon.[23]

Disadvantages of the DC are the need for multiple surgical interventions, stoma related complications such as parastomal hernia and stenosis and a high incisional hernia rate after reversal.[24] However, resection with primary anastomosis and simultaneous stoma reversal was performed in 14%, which reduces the total number of surgical procedures. Another reason to avoid a DC could be an assumed negative influence on quality of life in patients for whom DC turns out to be a permanent stoma. However, all existing quality of life studies focused on patients with definitive colostomy, which raises the question if these results are applicable on temporary colostomies as used in the BtS group.[25,26]

Most previously performed studies on this topic are concerning patients with malignant colorectal obstruction due to colon cancer. For obstructive colon cancer, there is obviously a role for SEMS placement. A nationwide, propensity score–matched study comparing DC and SEMS placement for non-locally advanced obstructive colon cancer revealed advantages and disadvantages of the 2 bridging techniques.[21] In this study, the permanent stoma rate for DC was 30% compared to 20% for the SEMS group, which difference was not statistically significant. Oncologic outcome was slightly in favor of DC, but statistical significance was not reached and the duration of follow-up was relatively short.[21] For left-sided colonic obstruction due to CRC, there is substantial evidence that SEMS is the preferred treatment in the palliative setting.[5,27,28] However, placement of a SEMS is a technically demanding procedure that requires specific skills, needs careful patient selection depending on tumor characteristics (length and location of the stenosis), and has a risk of perforation and unsuccessful decompression. Available guidelines recommend SEMS, provided that the lesion is amenable to stenting and the endoscopist has sufficient experience with SEMS placement. However, these recommendations are based on low quality evidence.[12] An alternative strategy for patients with palliative intent is placement of an end colostomy, which is associated with lower stoma related complications, such as prolapse or parastomal hernia, compared to a DC.[28]

Strength of our study is the consecutive series of patients presenting with heterogeneous etiologies of colorectal obstruction, reflecting common clinical practice. Most studies focussed on DC in the BtS-approach in colorectal cancer patients only. However, clinical reality is different with variable causes of obstruction and different treatment goals in patients with curable or incurable disease. Moreover, we specifically reported DC related morbidity, as it highly impacts quality of life and the outcome of patients who did not underwent additional treatment. Limitations of our study are the single center design and its retrospective design. However, due to the analysis of a consecutive series inclusion bias might be limited. Furthermore, stoma related complications such as parastomal hernia, stenosis or prolapse can develop after 1 year.[29,30] Therefore, the real proportion of complications might be even higher.

Conclusion

DC as bridge to possible elective resection for acute left-sided colorectal obstruction is an effective strategy with low morbidity and mortality rates and a high stoma reversal rate, especially for benign obstructions. However, DC is less appropriate for patients in whom DC turns out to be a definite stoma due to a relatively high stoma related complication rate.

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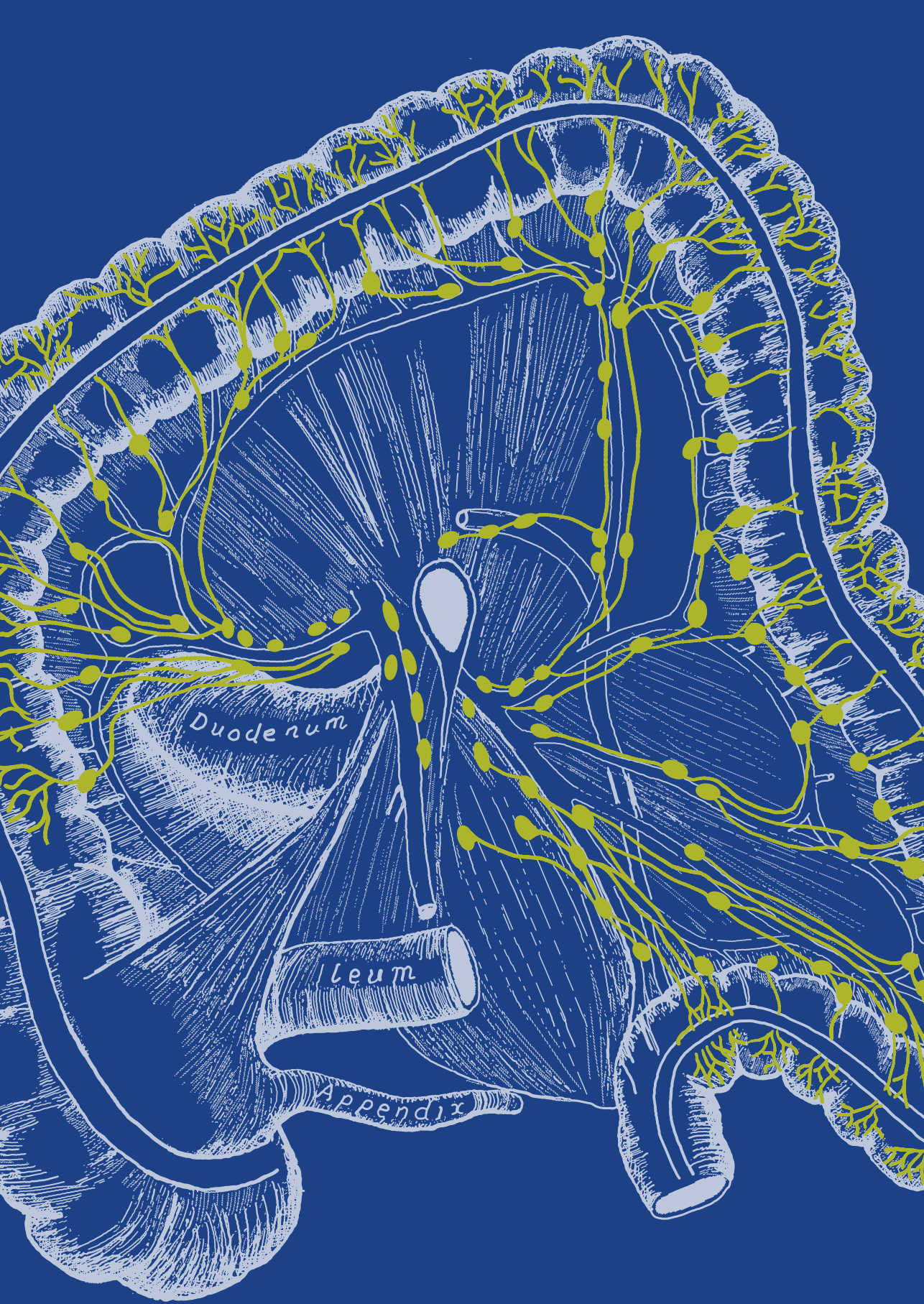
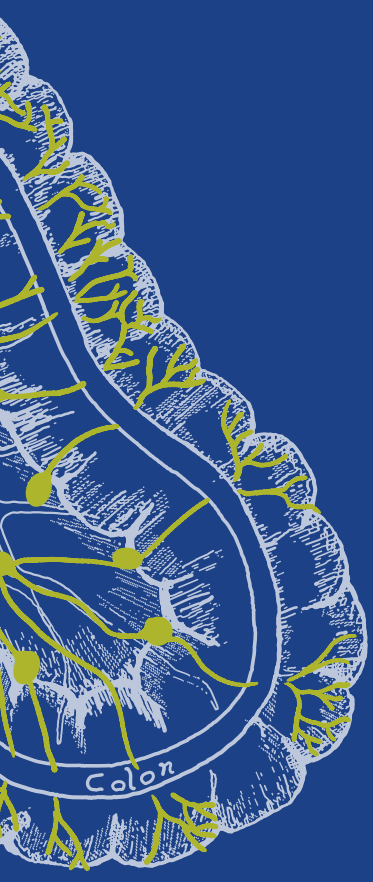

Duodenum
Ileum
Appendix

CHAPTER 9

Effectiveness of endosponge therapy for the management of presacral abscesses following rectal surgery



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Techniques in coloproctology, 2019

ABSTRACT

Background

Anastomotic leak after rectal surgery is reported in 9% (range 3–28%) of patients. The aim of our study was to evaluate the effectiveness of endosponge therapy for anastomotic. Endpoints were the rate of restored continuity and the functional bowel outcome after anastomotic leakage.

Methods

This was a multicenter retrospective observational cohort study. All patients with symptomatic anastomotic leakage after rectal surgery who had endosponge therapy between January 2012 and August 2017 were included. Functional bowel outcome was measured using the low anterior resection syndrome (LARS) score system.

Results

Twenty patients were included. Eighteen patients had low anterior resection (90%) for rectal cancer. A diverting ileostomy was performed at primary surgical intervention in 14 patients (70%). Fourteen patients (70%) were treated with neoadjuvant (chemo-)radiotherapy. The median time between primary surgical intervention and first endosponge placement was 21 (5–537) days. The median number of endosponge changes was 9 (2–28). The success rate of the endosponge treatment was 88% and the restored gastrointestinal continuity rate was 73%. A chronic sinus occurred in three patients (15%). All patients developed LARS, of which 77% reported major LARS.

Conclusions

Endosponge therapy is an effective treatment for the closure of presacral cavities with high success rate and leading to restored gastrointestinal continuity in 73%. However, despite endosponge therapy many patients develop major LARS.

INTRODUCTION

Anastomotic leakage (AL) after rectal surgery is reported in 9% (range 3–28%) of the patients and is associated with forming of presacral abscesses, emergency surgery, morbidity, permanent colostomy, prolonged hospital stay and even mortality.[1] Several risk factors have been associated with AL; level of the anastomosis, neoadjuvant (chemo)-radiotherapy (CRT), male gender, tumor size and other comorbidities.[2–4] A recent study reported 30-day postoperative AL rate of 13.4% in patients with rectal cancer surgery, which increased during follow-up to 20%.[5]

A significant proportion (36%) of patients with AL develop a chronic sinus, 50% of which may heal spontaneously over time.[5,6] Conventional treatment consists of antibiotics, radiological therapy (transanal or transgluteal drainage) or surgical therapy (diverting loop ileostomy, endoluminal drainage or dismantling of the anastomosis).

Endosponge therapy is a relatively novel minimally invasive endoluminal vacuum therapy for presacral abscesses that aims to clean the presacral cavity that subsequently collapses.[7–10] Therefore, it may prevent the development of a chronic sinus and may improve the anastomotic healing rate. A review by *Strangio et al*. reported high success (94%) of endosponge therapy for the treatment of presacral abscesses.[11] *Gardenbroek et al.* reported high effectiveness of vacuum-assisted early transanal closure of AL in patients with inflammatory bowel disease (IBD) who had ileal pouch–anal anastomosis (IPAA).[12] *Borstlap et al.* recently demonstrated restored gastrointestinal continuity in 67% of the patients who had vacuum-assisted early transanal closure after AL, especially when the endosponge therapy was started within 3 weeks of primary surgical intervention.[13] The aim of our study was to evaluate the effectiveness of endosponge therapy. Endpoints were the rate of restored continuity and the functional bowel outcome in patients with anastomotic leakage after rectal surgery.

METHODS

Study design and patient selection

This retrospective cohort study was performed in two Dutch high-volume colorectal cancer centers: Isala hospital and IJsselland hospital. All eligible patients with

symptomatic AL after rectal surgery treated with endosponge therapy between January 2012 and August 2017 were included. Patients with postoperative signs of AL and AL confirmed by computed tomography (CT) scan were considered eligible. Patients with colonic cancer, patients who underwent Hartmann's procedure as primary surgical procedure and patients who underwent transanal endoscopic microsurgery (TEM) were excluded. The study was approved by the medical ethics committee of Isala hospital (reference number: 171215).

All patients were discussed in a preoperative multidisciplinary team meeting and had an open or laparoscopic total mesorectal excision (TME) or IPAA. In case of surgery for rectal cancer, neoadjuvant short-course radiotherapy (5 × 5 Gy.) or long-course chemo-radiotherapy was given depending on the stage of disease. The presacral abscess was evaluated during every endosponge exchange. The abscess was considered closed if the cavity was covered with granulation tissue and the size of the cavity was too small for another endosponge placement. At that moment, the endosponge therapy stopped.

Endosponge procedure

The endosponge therapy was performed with or without conscious sedation depending on the patient's preference. Depending on the size of the cavity 1–3 polyurethane endosponges (Endo-SPONGE®, B. Braun Medical B.V., Melsungen, Germany) were placed in the deepest point of the presacral cavity through a plastic overtube under endoscopic guidance. If necessary, the endosponge was tapered to achieve collapse of the cavity. The endosponge was connected to a vacuum suction device that created a constant negative pressure of 150 mmHg. The endosponges were changed twice a week to prevent the granulation tissue from growing into the endosponge. In most patients, the first endosponge was placed by the surgeon and gastroenterologist together. If needed, the anastomotic defect was dilated with an endoscopic balloon to facilitate drainage and the placement of the endosponge which if necessary was done under radiologic assistance. The next endosponge changes were performed by the gastroenterologist alone. Depending on surgeon preference, transanal closure of the defect was performed after a short period of endosponge therapy (vacuum-assisted early transanal closure) to achieve shorter endosponge therapy duration. A detailed description of this procedure can be found in the paper of *Borstlap et al.* [13]

Outcomes

Primary outcome was the restored gastrointestinal continuity rate at the end of the follow-up.

Secondary outcomes were the success rate of the endosponge therapy, presence of a chronic sinus and the functional bowel outcome after AL. Success of the endosponge treatment was defined as a cavity reduced in size and covered with granulation tissue that was too small to allow placement of a new endosponge at the end of the endosponge therapy. A chronic sinus was defined as a proven presacral abscess that was still present 1 year after primary surgical intervention.

Functional bowel outcome

Functional bowel outcome was assessed postoperatively using the validated quality of life questionnaire (low anterior resection syndrome score (LARS score)).[14,15] The results of the LARS score were categorized into three groups: (1) no LARS (0–20 points), (2) minor LARS (21–30 points) or (3) major LARS (31–42 points).

A control group was created using the institutional colorectal cancer database, consisting of patients with rectal cancer without AL. These patients were matched with the endosponge group for CRT.

Statistical analysis

All analyses were performed using Statistical Package of Social Sciences version 22 (SPSS). A p value < 0.05 was considered significant. Normality was tested using Kolmogorov–Smirnov test. Normally distributed variables were described as mean with standard deviation (StD) and nonparametrical distributed variables were described as median with range. Categorical data were tested using Chi-square test or Fisher's exact test. Normally distributed continuous data were tested using Student's T test. Non-parametrical continuous data were tested using Mann–Whitney U test. Additionally, the non-parametrical continuous data were divided into two groups based on the median and tested with Chi-square or Fisher's exact test. Survival analysis was performed to estimate the probability for stoma reversal and success rate of the endosponge after resection using Kaplan–Meier analysis. Start of follow-up was primary resection and end of follow-up was date of interest; stoma reversal date, last endosponge exchange date, date of death or end of follow-

up. End of follow-up for patients without stoma reversal or not censored was last hospital visit.

For subgroup analysis, patients were divided into early and late endosponge groups based on the median number of days between primary surgical intervention and start of the endosponge therapy. Patients who started endosponge therapy before the median cutoff point were allocated to the early endosponge group and patients who started endosponge therapy on or after the cutoff point were allocated to the late endosponge group. The difference in stoma reversal between early and late endosponge groups was calculated using the log rank test.

A multivariate linear regression analysis was performed to determine whether occurrence of AL influences the LARS scores taking into account other potential confounders or patient characteristics at baseline.

RESULTS

Baseline characteristics

A total of 20 patients were eligible for inclusion in our study. Baseline characteristics are presented in Table 1. Fourteen of 20 (70%) patients were diverted during primary surgery. Three of the six patients who were not initially diverted at primary surgical intervention were diverted at the time AL was detected, two patients received endosponge therapy without diverting ileostomy and the other patient had Hartmann's procedure followed by endosponge therapy of the presacral abscess. Re-intervention before the start of the endosponge therapy was performed in 8 of 20 patients: surgical drain placement (n = 4), diverting ileostomy (n = 3) and dismantling of the anastomosis with Hartmann's procedure (n = 1). In 3 of the 20 enrolled patients, the anastomotic defect was transanally closed after a median of 2 [range: 2-3] endosponge changes.

The median time between primary surgical intervention and anastomotic leak detection, median time between primary surgical intervention and first endosponge placement, median number of endosponge changes and median duration of the endosponge therapy are presented in Table 2. No endosponge-related adverse events were reported.

Table 1 Baseline characteristics

	Total patients n (%)	Early endosponge n (%)	Late endosponge n (%)	p-value
No. of patients	20	10	10	
Males	14 (70)	5 (50)	9 (90)	0.14 [α]
Mean age, *years (StD)*	64 (±10)	64 (±11)	64 (±10)	0.95 [β]
Distance (centimeter) from AV, *median [range]*	8.5 [5-12]	8 [6-12]	9 [5-10]	0.27 [γ]
Etiology				0.47 [α]
Rectal cancer	18 (90)	8 (80)	10 (100)	
Inflammatory Bowel Disease	2 (10)	2 (20)	-	
Type of procedure				0.47 [α]
Total Mesorectal Excision	18 (90)	8 (80)	10 (100)	
Ileal Pouch-Anal Anastomosis	2 (10)	2 (20)	-	
Laparoscopic procedure	16 (80)	9 (90)	7 (70)	0.58 [α]
Neoadjuvant chemo-radiotherapy	14 (70)	5 (50)	9 (90)	0.14 [α]
Short course nCRT	11 (55)	4 (40)	7 (70)	
Long course nCRT	3 (15)	1 (10)	2 (20)	

Std indicates standard differentiation; AV, anal verge; nCRT, neoadjuvant chemo-radiotherapy
[α]Fischer's Exact test, [β]Student's T-test, [γ]Mann Whitney U test

Outcome of endosponge therapy

Endosponge treatment was successful in 17 of 20 patients (85%). In 14 of the 20 patients (70%), continuity was restored. Six patients received a definitive stoma because of a chronic sinus (n = 3), proctectomy (n = 1), local recurrence (n = 1) and one patient died because of tumor progression. A chronic sinus has developed in three patients (15%). The median time from primary resection to stoma reversal was 10 [3–15] months (Table 2). The overall cumulative probability of endosponge therapy success was 88% (95% CI = 57–97%) and the overall cumulative probability of stoma removal was 73% (95% CI = 44–87%). Individual follow-up characteristics after primary resection are presented in Figure 1.

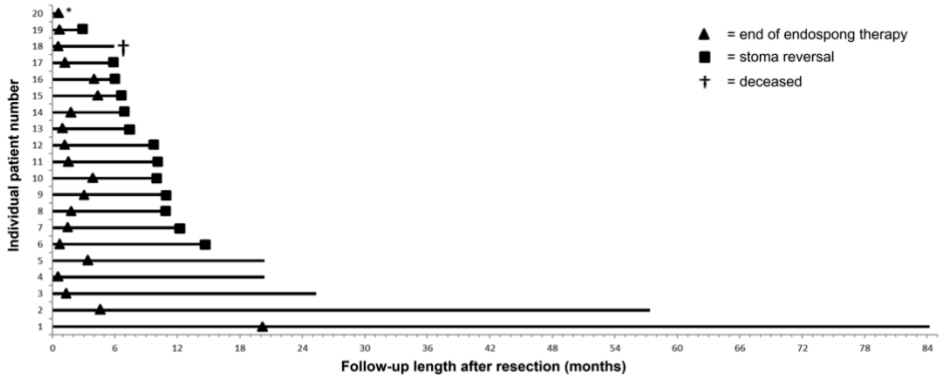

Fig. 1 Individual follow-up characteristics after resection. Fourteen patients (70%) were reversed successfully. *No primary diverting stoma.

Outcome of early versus late endosponge group

Ten patients were classified as being in an early endosponge group and 10 patients in a late endosponge group based on the study median of 21 days from primary surgery until first endosponge placement. Reasons for the delay of endosponge placement in the late endosponge group were: the presacral abscess became clinical relevant only after 3 weeks (n = 5), re-laparotomy with surgical drainage (n = 2), end colostomy (n = 1), diverting ileostomy (n = 1) and antibiotic therapy prior to endosponge therapy (n = 1). An overview of the results of the early and late endosponge therapy is presented in Table 2.

Table 2 Clinical outcome endosponge

	Total group n = 20	**Early endosponge n = 10**	**Late endosponge n = 10**	**p-value**
Days until AL detection, *median [range]*	12 [3-67]	10 [3-19]	21 [4-67]	0.10 [α]
Days until first endosponge, *median [range]*	21 [5-537]	11 [5-20]	30 [21-537]	<0.001[α]
No. of endosponge changes, *median [range]*	9 [2-28]	6 [2-28]	14 [2-26]	0.45 [α]
Duration endosponge therapy, *days [range]*	25 [3-115]	20 [3-115]	25 [5-80]	0.79 [α]
Follow up (months), *median [range]*	10 [3-84]	8 [3-25]	12 [6-84]	0.08 [α]
Success endosponge therapy	17 (85)	8 (80)	9 (90)	-
Restored continuity, *n (%)*	14 (70)	7 (70)	7 (70)	-
Median until stoma reversal, *months [range]*	10 [3-15]	7 [3-11]	10 [6-15]	0.15 [α]
Chronic sinus, *n (%)*	3 (15)	2 (20)	1 (10)	-

AL indicates anastomotic leakage

[α]Mann Whitney U.

In the early group, the endosponge therapy was successful in 8/10 patients and anastomotic healing occurred in 7/10 patients. Two patients had a permanent colostomy because of a chronic sinus, unresolved by endosponge. The other patient without restored gastrointestinal continuity died 6 months after endosponge therapy because of tumor progression. The median time until stoma reversal was 7 months. In the late endosponge group, the endosponge therapy was successful in 9/10 patients and anastomotic healing occurred in 7/10 patients. Three patients did not have intestinal continuity restored because of: chronic sinus (n = 1), local recurrence (n = 1) and proctectomy (n = 1). The patient with a permanent colostomy due to a chronic sinus was treated in the beginning with conventional therapy and has eventually started endosponge therapy 537 days after primary surgical resection without success. The median time until stoma reversal in the late endosponge group was 10 months.

The overall cumulative probability of stoma removal for patients in the early endosponge group was 77% (95% CI = 22–93%) compared with 70% (95% CI = 23–88%) for patients in the late endosponge group. This difference in absolute risks was not statistically significant (p = 0.31). Also, no statistically significant difference in the success rate of endosponge therapy and the presence of a chronic sinus was found between the early and late endosponge groups.

Quality of life

Fourteen patients who had endosponge treatment received the questionnaire. Six patients were not invited to fill in the questionnaire because of a permanent colostomy. Thirteen patients (93%) responded to the questionnaire. Thirty-two patients in the control group (without AL) received the questionnaire. Twenty-one (66%) of them responded to the questionnaire. Baseline characteristics between the endosponge group and the control group are presented in Table 3.

Table 3 Baseline characteristics LARS

	Endosponge after anastomotic leakage	No anastomotic leakage	p-value
LARS score, *points [range]*	37 [23-42]	30 [4-41]	0.009[α]
Major LARS	*10 (77)*	*10 (48)*	
Minor LARS	*3 (23)*	*6 (29)*	
No LARS	-	*5 (24)*	
Age, *years (StD)*	67 ±7	64 ±8	0.43[β]
Response time questionnaire, *years [range]*	3.1 [1.5-4.5]	2.6 [2.3-2.8]	0.26[α]
Time from stoma reversal to questionnaire date *years [range]*	2.6 [0.8-3.5]	2.3 [1.8-2.8]	0.46[α]
Distance tumor to anal verge, *cm [range]*	8.5 [5-12]	10 [5-15]	0.07[α]
Neoadjuvant chemo-radiotherapy, *n (%)*	8 (62)	16 (76)	0.36[γ]
Laparoscopic procedure	10 (77)	19 (91)	0.35[γ]

LARS indicates Low Anterior Resection Syndrome; StD, standard differentiation
[α]Mann-Whitney U test, [β]Students T-test, [γ]Fischer's exact test.

The median LARS score in the endosponge group was 37 [range: 23–42] points and 30 [range: 4–41] points in the control group (p = 0.009). The median time between stoma reversal and date of the quality of life questionnaire was 2.6 [range: 0.8–3.5] years in the endosponge group and 2.3 [range: 1.8–2.8] years in the control group (p = 0.47). No significant difference between these two groups in age, response to questionnaire time, distance to anal verge, CRT and laparoscopy procedure was found. In the endosponge group, three patients (23%) had minor LARS and ten

patients (77%) had major LARS. In the control group, five patients (24%) had no LARS, six patients (29%) had minor LARS and ten patients (48%) had major LARS. In the multivariate analysis, the LARS score was significantly associated with endosponge therapy (β = − 7.595, p = 0.02) (Table 3). No significant difference in LARS scores was found between the early and late endosponge groups (p = 0.72).

DISCUSSION

We reported a large series of 20 patients who were treated with endosponge therapy after AL. This study is, to the best of our knowledge, the first study that describes the long-term functional bowel outcome after endosponge therapy in patients with AL compared with a control group consisting of patients without AL after TME. The majority of our patients (90%) were treated for rectal cancer and 70% of the patients received neoadjuvant (chemo-)radiotherapy. There was a high success rate (88%) of endosponge therapy, restored bowel continuity rate of 73% and major LARS in 77% of the patients after endosponge therapy.

These findings are in line with previous studies that reported on the outcome of endosponge therapy. *Mussetto et al.* reported successful endosponge therapy with restored gastrointestinal continuity in 10 of the 11 patients (91%) after anastomotic leakage.[16] *Strangio et al*. described a completely healed cavity after endosponge therapy in 94% of the cases and anastomotic healing in 56–92% of the cases.[11] The majority (90%) of these patients were treated for rectal cancer and patients with generalized peritonitis were excluded. *Borstlap et al.* demonstrated an anastomotic healing rate of 67% in patients with AL who had vacuum-assisted early transanal closure.[13] However, 93% of the patients had persistent AL 2 weeks after transanal closure, requiring conservative monthly endoscopic follow-up (43%), redo endosponge therapy (32%), redo transanal surgical closure (18%), percutaneous drainage (4%), or end colostomy (4%). Furthermore, they reported that early start of endosponge therapy (before 3 weeks) resulted in higher stoma reversal rate and lower proportion of a chronic sinus. Therefore, early treatment of the presacral abscess might be advocated to improve anastomotic healing rates and reduce the development of a chronic sinus. Our study demonstrated a similar success rate of the endosponge therapy, similar anastomotic healing rates and a lower proportion

of a chronic sinus compared to *Borstlap et al*. [13] We found no significant difference in our study between the early and late endosponge groups for these parameters. A chronic sinus occurred in 15% of the patients in our study. Previous studies reported a persistent sinus rate at 1 year of 48% after AL without endosponge therapy.[5,6] The proportion of chronic sinus found in our study is low compared to these studies, suggesting that endosponge is a good therapy to prevent the development of chronic sinus. However, endosponge was not used in these two earlier studies. Furthermore, a study reported a late abscess in 25% of the patients after successful endosponge. A prolonged interval between primary surgery and AL detection was the only predictive factor in this study.[17] Until now, no late abscesses were seen in our study.

AL and chronic sinus are associated with impaired functional bowel outcome. Improvements of the functional bowel outcome can be expected especially in the first year after surgery. In the following years, the functional outcome will remain stable.[18] We assessed the functional outcome using the LARS score questionnaire after a median of more than 2 years after stoma reversal. Patients with AL who had endosponge therapy had significantly higher LARS scores than patients without AL in the control group. We used patients without AL as a control group, because most patients who presented with AL that did not have endosponge therapy had their anastomosis taken down or resected and received an end colostomy. All patients in our study had LARS (77% had major LARS and 23% minor LARS) after endosponge therapy compared to 76% in the control group. *Borstlap et al.* also reported high LARS scores after combined surgical and endoscopic treatment for AL (81% had major LARS and 13% minor LARS).[13] A systematic review of patients without AL following rectal cancer surgery reported major LARS in 38–62%, minor LARS in 22–28% and no LARS in 10–38%.[19]

Our study and the results from the previous literature mentioned above demonstrate that patients with AL who had endosponge therapy have a higher risk of developing (severe) LARS compared with patients without AL. The main causes of LARS are probably the AL and fibrosis in the abscess cavity during endosponge therapy causing reduced neorectal compliance. Another explanation of our high LARS scores after endosponge therapy could be that the endosponge group has a lower anastomosis than the patients in the control group, although this was not a

statistically significant difference. No significant difference in functional bowel outcome was found between the early and late endosponge groups.

Limitations of this study are the small number of included patients and the long period over which patients were entered into our database, even though we have reported the fifth largest series worldwide. There might have been selection bias because of the retrospective design. Patients diagnosed with AL who were offered other therapies (i.e., dismantling of the anastomosis with creation of an end or loop colostomy) or transanal tube drainage were not included in our analysis. Patients with abdominal sepsis or generalized peritonitis were selected for dismantling of the anastomosis rather than endosponge therapy. Furthermore, no baseline LARS questionnaires were used.

Endosponge therapy resulted in a high rate of restored gastrointestinal continuity. Despite this positive outcome, a substantial number of patients had major LARS after an AL and endosponge therapy. This factor together with the duration of the therapy with several endosponge changes, frequent hospital visits, psychological factors and the occurrence of late abscess recurrence after successful endosponge therapy needs to be considered before the start of the endosponge therapy and could be of importance for the informed consent procedure. Future studies should evaluate which patients benefit from endosponge therapy over conventional treatment.

Conclusion

Our results show that endosponge therapy is an effective treatment for the closure of presacral cavities after rectal surgery with high success rate (88%) leading to restored gastrointestinal continuity in 73% of patients. A significant proportion of patients developed major LARS despite endosponge treatment. This should be taken into consideration when contemplating salvaging an anastomosis with endosponge.

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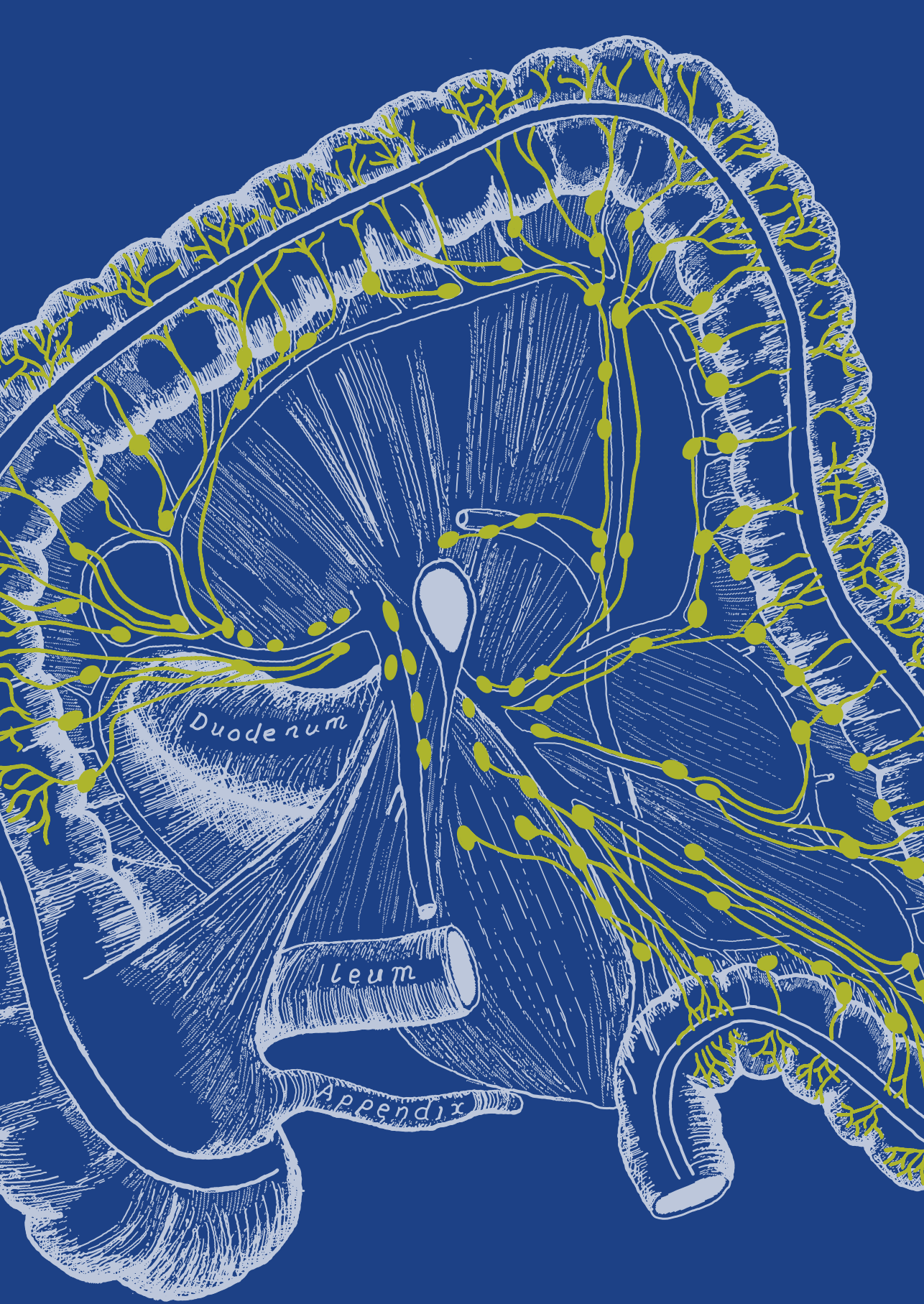
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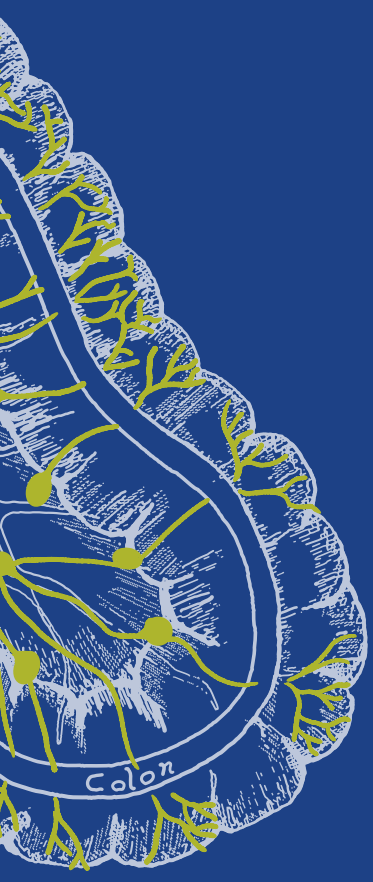
Appendix

CHAPTER 10

General discussion, clinical implications and future perspectives



In the near past, all patients with stage I-III colorectal cancer (CRC) underwent preoperative radiological imaging to exclude distant metastases followed by major surgical resection. The widespread implementation of national bowel screening programs has led to a shift towards detection of early CRC and advanced pre-malignant polyps.[1] Early CRC has a better prognosis compared to advanced CRC and has a low risk of lymph node and distant metastases.[2] This has led to new insights in colorectal cancer care with adjusted diagnostic staging approaches, and the development of new minimally invasive treatment modalities with less morbidity and mortality. Nowadays, a multidisciplinary approach with patient tailored treatments allows organ preservation for selected patients.

In this thesis, we evaluated the quality of care during several aspects of the colorectal cancer care pathway. We focused on CRC screening, radiological staging- and surveillance and less invasive treatment modalities for colorectal neoplasms.

PART I - CRC screening

In **chapter 2**, we evaluated the outcome of Computed Tomography Colonography (CTC) as alternative to colonoscopy in faecal immunochemical test (FIT) positive individuals in 2 Dutch hospitals. CTC was performed instead of colonoscopy because of significant comorbidity in the majority (86%) of cases. Relevant intracolonic findings (CRC or 10 mm+ lesions) were detected by CTC in approximately a quarter of patients. Ultimately, almost 30% of the patients with any suspected lesion on CTC underwent confirmatory endoscopy (which was declined in the first place). After confirmatory endoscopy, 4.9% were diagnosed with CRC and 13.8% with advanced adenoma.

The proportion of advanced neoplasia we found was substantially lower compared to the outcome of colonoscopy screening in our national bowel screening program (8% CRC and 42% advanced adenomas).[3] This suggests that CTC has a lower diagnostic yield to detect advanced neoplasia. It should be noted that a small proportion of patients with suspected relevant lesions on CTC in our study declined indicated confirmatory colonoscopy and furthermore, villous histopathology, as feature of an advanced adenoma, occurs in approximately 5% of adenomas <10 mm.[4]

Extra colonic incidental findings on CTC were detected in 13.8% of patients, of which 64.9% underwent additional follow-up, treatment or referral to another medical specialty. It is highly questionable if detection of (asymptomatic) incidental findings in patients with severe comorbidity is desirable and improves overall survival. This aspect of abdominal imaging should at least be discussed with patients prior to performing CTC.

Clinical implications CRC screening

- CTC seems to have a lower diagnostic performance to detect advanced adenomas compared to colonoscopy and should therefore only be performed for individual cases unable to undergo colonoscopy to exclude CRC.
- Colonoscopy remains the gold standard for FIT positive individuals.
- Patients should be informed about the possibility of extra-colonic incidental findings, the potential risk of missed intra-colonic lesions and the chance of additional endoscopy following the results of CTC.
- Physicians should be critical whether CTC should be performed in patients unfit for colonoscopy.

Future perspectives CRC screening

Although CTC seems to have a high diagnostic performance to detect CRC, the risk of interval carcinomas due to a lower sensitivity of CTC for smaller lesions is unknown. This knowledge cap is currently being investigated in a nationwide cohort study, initiated by Erasmus Medical Center.[5]

Several widely available screening strategies for CRC such as guaiac-based fecal occult blood tests (gFOBT), FIT, colonoscopy, CTC and faecal DNA decrease CRC related mortality. However, all these techniques also have limitations.[6] Emerging methods for CRC screening, including blood or breath tests as well as advanced endoscopic and radiological imaging techniques are developing and might play a role in the future.

Liquid biopsy is a rapidly developing field and has the potential to realize early CRC detection. Various tumor-derived products can be detected in blood, of which ctDNA seems the most promising for CRC detection.[7-12] ctDNA are sequences of DNA detected in the peripheral blood derived from tumor cells undergoing

apoptosis, necrosis and secretion. Tumor-specific (epi)genetic alternations, such as driver mutations, chromosomal copy number alterations and methylation can be detected in ctDNA and used for cancer detection. A recent systematic review reported promising results of ctDNA markers for CRC detection.[13] However, prospective studies should provide further evidence before it can be used in clinical practice.[13] Liquid biopsies have also potential for population based screening. However, studies that compare ctDNA with FIT and colonoscopy, and studies that focus on detection of pre-malignant lesions are currently lacking.

Analysis of volatile organic compound (VOC) in exhaled air through an electronic nose (eNose) is a promising patient friendly diagnostic tool for the detection of CRC.[14,15] However, the breathprints are not yet fully elucidated. Exo- and endogenous factors might influence VOCs in breathprints. Clinical validation studies are needed to provide definitive evidence to bring ctDNA analysis to clinical practice. Furthermore, the diagnostic accuracy of the eNose might be improved by training the eNose to recognize specific breath patterns using machine learning.

Positron emission tomography (PET) using a radiolabeled glucose analog (Fluorodeoxyglucose, FDG) is a diagnostic imaging technique used in several cancer types. However, PET has some pitfalls, including false positive results, variable FDG uptake and physiological uptake of FDG in specific organs.[16] Fluorescence molecular endoscopy, a novel technique using targeted fluorescent optical imaging agents to visualize tissues of interest, has shown to be safe and feasible for the detection of a variety of diseases, such as esophageal carcinoma and colorectal polyps.[17-19] Interestingly, the fluorescent dye can be replaced for a tracer with dual PET and fluorescence functions, and thus will generate target specific accumulation of the respective tracer. This ultimately leads to next generation PET imaging, as has recently be shown for early detection and surveillance of brain, head, neck and breast cancer in mice.[20] The translation from target specific in vivo fluorescence imaging to target specific PET imaging for the detection of colorectal neoplasms can be seen as a logical next step. However, we are waiting for the first clinical results.

Ultimately, all screening roads will lead to colonoscopy. Even though the diagnostic performance of colonoscopy is improved by using enhanced imaging techniques such as chromoendoscopy, narrow band imaging (NBI) and wider viewing angles, still colorectal lesions are missed during colonoscopy.[21] Computer-aided detection (CAD) based on artificial intelligence algorithms is an upcoming technique that might further improve the detection rate.[21]

PART II - Radiological staging

The quality and availability of CT scans has increased over the years, which improved tumor staging. However, radiological imaging might also be harmful in case of unwanted incidental findings or false positive results.

In **chapter 3,** we reported on the outcome of radiological staging of T1 CRCs. In this study we found limited yield of radiological staging for T1 CRC and potential harm due to clinically irrelevant incidental findings of radiological imaging. Only 0.5% of the screened patients had synchronous distant metastases during baseline radiological imaging and none of them was diagnosed with low-risk T1 CRC. The incidental finding rate was 22.4% and increased over the years probably because of a shift from imaging with abdominal ultrasound or chest X-ray towards CT.

This raises the question whether routine radiological staging should be performed for T1 CRC patients. A recent survey showed that approximately 50% of Dutch clinicians would perform baseline oncological staging after local excision of T1 CRC, regardless of histological risk status.[22] For patients with T1 CRC scheduled for major (primary or completion) surgical resection, it seems obvious to perform preoperative radiological staging to exclude distant metastases and prevent unnecessary major surgery in case of incurable disseminated disease. However, it is highly questionable whether or not radiological staging is also efficient for low-risk T1 CRCs. This is because these tumors have a negligible risk of metastatic disease, as also confirmed by our study. In addition, we show for the first time that incidental findings on radiological staging were found in almost a quarter of the T1 CRC patients. Based on above, it would be reasonable to discourage radiological staging prior to local excision of suspected T1 CRC and for patients that turn out to have no histological risk factors for lymph node metastases after local excision (low-risk T1). The very low risk of having distant metastases does not outweigh the risk of irrelevant incidental findings and healthcare costs. Whether or not radiological staging should be performed for patients with high-risk T1 or undetermined-risk T1 after local excision who declined completion surgical resection is still a matter of debate.

Clinical implications radiological staging T1 CRC

- Routine radiological staging for T1 CRC before local excision is not necessary.
- Radiological staging should be reserved for T1 tumors with high risk of lymph node metastases prior to surgical resection.
- Patients should be informed about the possibility of detection of extra-colonic incidental findings.

Future perspectives radiological staging

The histological risk factors for lymph node metastases are currently under debate worldwide. Future studies should identify biomarkers for lymph node metastases. The STONE project from the Dutch T1 CRC working group is currently investigating these biomarkers for lymph node metastases in a large cohort of T1 CRCs (www.t1crc.com). Furthermore, future studies should investigate whether radiological staging should be performed in patients with undetermined-risk or high-risk T1 CRC who declined completion surgical resection.

In **Chapter 4**, we explored the consequences of CTC in patients with stenosing CRC. Preoperative CTC was performed in almost half of the patients with stenosing CRC in our study period, even though the Dutch guideline recommended to perform postoperative colonoscopy instead of preoperative CTC. We found very limited clinical benefit of CTC in our study and potential harm in terms of unnecessary extended surgery due to false positive CTC. Proximal colonic lesions were detected in 9/162 (5.7%) patients but led to a change of the primary surgical treatment strategy in only 1 (0.6%) patient.

The high proportion of performed preoperative CTC could be explained by the obligatory items of the Dutch colorectal audit (DCRA) and subsequent health care insurances. The DCRA had preoperative complete colon visualization as quality indicator until 2015. As shown in our study, there is limited yield and potential harm of CTC. There is no evidence to support the demand of the DCRA. We recommend performing postoperative colonoscopy instead of preoperative CTC. The following arguments support this recommendation: nowadays, all patients with stenosing CRC undergo abdominal staging CT. Large lesions will also be visible on abdominal CT, which further decreases the need for preoperative CTC. The quality of CTC in

stenosing CRC is lower due to technical difficulties with air insufflation (in our study had 19% of cases poor CTC quality). It might be possible that the false positive CTCs in our study were due to bowel contractions or insufficient air insufflation. Finally, CTC is not able to differentiate between advanced adenomas and CRC and between T1 and T2 tumors.[23,24] This could result in unnecessarily performed extended resection for neoplasms that could have been treated endoscopically as new techniques such as endoscopic submucosal dissection (ESD), endoscopic full thickness resection (eFTR) and colonoscopy assisted laparoscopic wedge resection (CAL-WR) have been developed to remove T1 CRCs.

Clinical implications stenosing CRC

- We recommend postoperative colonoscopy instead of preoperative CTC for stenosing CRC.

PART III - Treatment of colorectal neoplasms

In **chapter 5,** we assessed the safety of endoscopic mucosal resection (EMR) of large non-pedunculated colorectal polyps in elderly patients. We included 343 patients, of which a quarter were >75 years and a third had a large polyp (>40 mm). The overall complication rate was 8% (6.8% bleeding complication and 1.2% perforation). Large polyp size (>40 mm) was a risk factor for bleeding, but not for perforation. Among the elderly (>75 years), we did not find more bleeding complications or perforations as compared to younger patients. This study supports the premise that EMR of large non-pedunculated polyps is safe in elderly. It offers elderly patients a non-surgical option for management of colorectal lesions. Only 5% of the patients in our study had malignant histology, requiring completion surgical resection. The result of our study are in line with other studies that reported similar complication rates after EMR of polyps >2cm in elderly.[25-28]

Clinical implications EMR in elderly

- EMR of large colorectal lesions (>2cm) can be performed safely in elderly.
- The choice to perform EMR should be made on individual basis weighing comorbidity and complications with potential survival benefits.

Future studies EMR in elderly

Less is known about the long-term survival benefit after EMR in elderly. It is questionable whether or not EMR in elderly prevents CRC-related death. On the other hand, patients are getting older and might feel the psychological burden from unremoved large polyps, as they may develop into a malignant lesion. One recent retrospective study reported the long-term survival after EMR in elderly (median age 80 years; IQR 78-83).[26] They reported a median overall survival of 6.7 years and a 5-year survival rate of almost 80% of the patients after EMR. Age over 79 years and Charlson comorbidity index (CCI) >2 were independent predictors of shorter survival.

The decision to undertake an EMR in elderly needs to be individualized. Introducing CCI might offer objective assessment of the comorbid state and lead to safer decision making. However, future prospective studies regarding risk factors and long-term survival benefit are needed.

Furthermore, we found more early bleeding complications in our study in patients with double anti platelets therapy. Guidelines on endoscopy recommend stopping one of the antiplatelets drugs prior to EMR. However, less is known regarding timing of reinitiating of antiplatelet drugs. According to guidelines, the drug is restarted the day after the procedure. Future studies should investigate whether postponement of restarting the antiplatelet decreases the risk of early bleeding complications, without leading to excess cardiovascular complications.

In **chapter 6,** we assessed the safety and effectiveness of a modified colonoscopic-assisted laparoscopic wedge resection (CAL-WR), using a linear stapler without making an anastomosis for local excision of benign colonic lesions not amendable to conventional endoscopic resection (LIMERIC-I trial). This prospective multicenter study showed that CAL-WR is an effective and safe technique to achieve en-bloc resection of colonic lesions. The technical success and R0 resection rates were both >90%. Minor complications occurred in 6% of patients and no major (surgical re-intervention) complications were observed.

Since the implementation of national bowel screening programs, the number of referrals for surgical resection of advanced adenomas and early T1 colon cancers increased substantially, even with the availability of new minimally invasive techniques such as ESD and eFTR.[29] ESD is a technically challenging endoscopic

procedure, especially in the right-sided colon, and is associated with a long learning curve (>100 procedures) and only available in a few hospitals. eFTR is a new endoscopic technique for en-bloc resection of colonic lesions, but is limited to lesions with a maximum size of 15-20 mm.

CAL-WR is suitable to fill the gap between endoscopic resection and more invasive surgical procedures which are accompanied with higher morbidity (24%) and mortality (2%) rates. CAL-WR could be considered for colonic neoplastic lesions with less than 50% involvement of the luminal circumference in which conventional endoscopic resection cannot be performed (Figure 1). For polyps with a very small risk of malignancy, (piecemeal) EMR seems preferable because of the less invasive nature of the technique. However, it should be noted that frequent endoscopic surveillance after piecemeal EMR is necessary and piecemeal EMR is associated with high risk of residue and recurrence.[30] For small lesions (<20 mm), eFTR or CAL-WR could be considered both to achieve en-bloc resection. eFTR is a relatively novel therapy with more or less similar outcome compared to CAL-WR. The technical success of eFTR varies between 84-94%, R0 resection rate between 72-90% and the complication rate ranges from 9-14% with surgical re-intervention in 2-3%.[31-35] For suspected rectal lesions, ESD or transanal endoscopic microsurgery (TEM) could be considered to achieve en-bloc resection. CAL-WR is not suitable for these lesions because of location in the pelvic and eFTR is challenging because of decreased elasticity of the rectal wall.

Clinical implications colonoscopic assisted laparoscopic wedge resection (CAL-WR)

- CAL-WR could be considered for benign colonic lesions with <50% involvement of the luminal circumference, not amendable for conventional endoscopic excision.
- CAL-WR could play an important role for the removal of T1 colon cancer in the future. However, the oncological safety should be investigated first.

Future perspectives CAL-WR

In the LIMERIC-I trial we showed effectiveness and safety of CAL-WR to achieve en-bloc resection. CAL-WR has the potential to remove T1 (or even T2) colonic cancer which has a low risk of lymph node metastases. However, due to the invasive

character of these lesions, the long-term oncological outcome should be studied first. Theoretically, it is possible that malignant cells remain in the staple line or that malignant cells are transferred to the abdominal cavity during the procedure. In the LIMERIC-II trial, we will investigate the oncological outcome and cost effectiveness of CAL-WR for invasive T1 CRCs. We hypothesize that 50% of patients have no histological risk features for lymph node metastases and are treated curatively with CAL-WR. The other half should undergo completion surgical resection.

The decision to perform completion surgical resection is based on the estimated risk of lymph node metastases using histological risk features. Using this strategy, still a significant proportion will undergo surgical resection for negative lymph nodes with potential harm and no benefit. A wedge resection combined with sentinel node identification using fluorescence followed by a watch-and-wait procedure for lymph node negative patients seems a promising technique and might further reduce the need for surgical resection. Prior studies using fluorescence injection for sentinel lymph node identification in early colon cancer showed promising results, but need to be investigated in larger cohorts.[36] The SENTRY trial (study proposal submitted to Koningin Wilhelmina fonds (KWF)) is aimed to prospectively determine the oncological safety of a colonic wedge resection combined with sentinel node procedure, used as additional treatment of endoscopic resected high-risk T1 or low-risk T2 colonic cancer, followed by watchful waiting in case of tumor negative sentinel node.

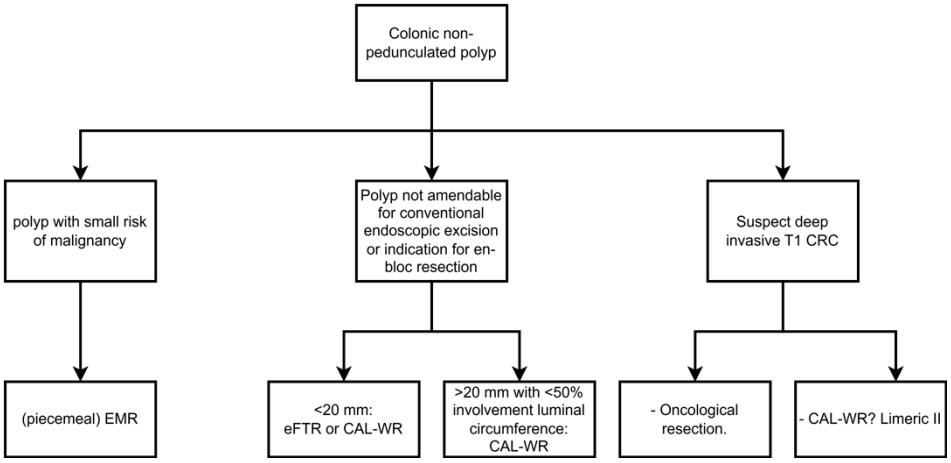


Figure 1: treatment decision for colonic neoplastic lesions

In **chapter 7,** we demonstrated a significant decline in total mesorectal excision (TME) without residual tumor (i.e., pathological complete response (pCR)), since the implementation of structural response evaluation after neoadjuvant chemoradiation (nCRT) for locally advanced rectal cancer with the option of a watch-and-wait policy for patients with a very good response. In this study we included patients with clinical complete response after nCRT and also allowed patients with near complete response at the first response evaluation to have a longer observational period to maximize the detection of complete responders. Prior studies reported that a longer observational period is safe and has no impact on oncological survival.[37]

Although the proportion of pCR has halved since the implementation of the response evaluation, still 9% of the patients had pCR and underwent unnecessary surgery, even with our liberal policy with longer observation for near complete responders. This means that we are still not able to identify all complete responders with current diagnostic techniques. A small proportion of the patients will develop a benign symptomatic stenosis after nCRT and has a clear indication for surgery. For the others, the majority of the missed complete responders were due to residual abnormalities at endoscopy and to a lesser extent suspicious findings on magnetic resonance imaging (MRI).[38]

Clinical implications watch-and-wait for locally advanced rectal cancer

- All patients with locally advanced rectal cancer who underwent nCRT should have response evaluation to identify (near) complete responders.
- For patients with complete tumor response, a watch-and-wait strategy with intensified surveillance could be considered instead of major TME.

Future perspectives watch-and-wait locally advanced rectal cancer

Assessing tumor response after chemo-radiation is challenging. White light endoscopy provides only morphological information, while MRI cannot always distinguish tumor tissue from fibrosis. Future studies should be performed to investigate the exact timing of restaging and factors associated with clinical complete response or near clinical complete response to maximize the detection of complete responders as well as minimize the risk of distant metastases in the waiting time.

Quantitative fluorescence endoscopy (QFE) is a novel endoscopic technique that visualizes and quantitatively measures the presence of targeted fluorescence tracers in tissue. A pilot study using Vascular endothelial growth factor A (VEGFA) targeted QFE shows promising results with improved response assessment after chemoradiation in rectal cancer patients.[39] This technique must be further evaluated in prospective studies.

Immune checkpoint blockade is a promising treatment for mismatch-repair deficient colorectal cancers, with less comorbidity than surgery or chemo-radiation. A recent study of 12 patients with mismatch-repair deficient locally advanced rectal cancer who underwent neoadjuvant PD-1 blockade showed clinical complete response (MRI, endoscopy and digital examination) in all 12 patients after 6 months of follow-up.[40] This treatment might further prevent surgical resection, but longer oncological follow-up is needed.

In **chapter 8**, we evaluated the clinical outcome of decompressing colostomy (DC) for acute left-sided malignant or benign colorectal obstruction. In our consecutive series of 100 patients who underwent DC, it appeared that a large proportion of the patients (39%) had DC as palliative treatment and did subsequently not undergo surgical segment resection. For the other patients, DC as bridge to surgery is an effective and safe therapy with high stoma reversal rate at the end of the follow-up period. DC followed by delayed resection allows adequate tumor staging, neo-adjuvant treatments if mandatory, and facilitates optimization of clinical condition. It could also prevent patients with incurable disseminated disease to undergo unnecessary major surgical segment resection.

Alternative to DC is colonic decompression using a self-expandable metallic stent (SEMS). A previous study compared both techniques as bridge to delayed surgical resection and reported no significant differences in permanent stoma rate or oncological outcome.[41] The decision to perform DC or SEMS as decompressing technique should be individualized based on treatment purpose, patient and tumor characteristics, patient preferences and the local availability and experience of both bridges techniques.[42]

For palliative patients there is substantial evidence that SEMS placement is the preferred treatment.[43-45] However, placement of a SEMS is a technically demanding procedure that requires specific skills, needs careful patient selection and is not available in every hospital. Furthermore, the stent may become obstructed due to tumor growth or fecal impaction. DC however, seems not to be the best option for palliative patients. In our study we reported high DC-related complications such as prolapse and parastomal hernia. A better alternative to DC might be an end colostomy.[46] End colostomy is associated with lower morbidity than surgical resection and is also associated with less stoma related complications such as parastomal hernia or prolapse than DC and should therefore be considered for patients with palliative purpose.

Clinical implications decompressing colostomy as bridge to surgery for acute left-sided colorectal obstruction

- Careful patient selection for decompressing colostomy should be made during presentation on the emergency department.
- Decompressing colostomy seems a good strategy for patients with acute left-sided obstruction as bridge to surgical resection.
- Decompressing SEMS or end colostomy seems the preferred palliative treatment.

Future perspectives decompressing colostomy

Whereas treatment options for left-sided colorectal obstructions have been evaluated, less is known about options for right-sided colonic obstruction. Most patient with right-sided obstruction are treated with emergency resection, which is accompanied with high morbidity and stoma creation. Decompressing loop ileostomy is not recommended for these patients because it can lead to a closed loop obstruction associated with bowel necrosis or blowout. Stent placement in the right-sided colon might be more challenging because the scope is less maneuverable, and the tumors are often bulky. A systematic review that compared acute resection with SEMS as bridge to surgery in acute right-sided colonic obstruction suggest an advantage of SEMS over emergency resection.[47] However, this study concerns only retrospective analysis and the majority of the patients underwent emergency resection and only a small proportion SEMS. Selection bias might be introduced as patients with sepsis or blowout were excluded for SEMS.

A recent retrospective Swedish study reported improved survival after diverting stoma compared to emergency resection for acute right-sided obstruction. However, the baseline characteristics were significantly different for age and comorbidity between both groups.[48] Future prospective studies should investigate the best strategy for acute right-sided obstruction in potentially curable as well as incurable colonic obstruction.

In **chapter 9**, we evaluated the outcome of endosponge therapy for anastomotic leakage after TME or ileoanal pouch-anal anastomosis (IPAA). In this study, we demonstrated that endosponge therapy is an effective treatment for presacral abscesses and resulted in a high rate of restored gastrointestinal continuity. The downside is that it is also associated with frequent low anterior resection syndrome (LARS), probably due to fibrosis and less rectal bowel wall compliance. In our study almost 3 out of 4 patients had restored continuity after endosponge treatment at the end of the follow-up period and 15% had a persistent chronic sinus. A previous snapshot study reported a persistent chronic sinus in almost half of the patients after anastomotic leakage without endosponge therapy.[49]

Clinical implications endosponge therapy for anastomotic leakage

- Endosponge therapy should be considered and started as soon as possible when CT reveals a pelvic fluid collection.

Future perspectives endosponge therapy

Although endosponge has shown to contribute to the treatment of anastomotic leakage and successfully decreases the chronic sinus rate there is still space for improvements.

Early detection of anastomotic leakage and early start of endosponge therapy seems associated with better clinical outcome.[50] In our study we divided patients in an early endosponge group (<21 days) and late endosponge group (>21 days). We found no significant difference in clinical outcome, although the number of included patients was small.

The duration and number of endosponge changes should also be further evaluated. Endosponge therapy is an expensive and time-consuming therapy. In our study the median number of endosponge changes was 9 [2-28], which means that some patient went to the hospital several times a week for almost 4 months. The clean-

trial suggests that a short period of endosponge followed by transanal closure of the cavity is an effective alternative.[50] Further studies should evaluate the duration of endosponge and timing of transanal closure.

Even more important than optimization of the endosponge therapy is preventing anastomotic leakage. The aetiology for anastomotic leakage is a multifactorial mix of both modifiable and non-modifiable factors. Physicians should strive to prevent anastomotic leakage by preoperative optimization of clinical condition and placement of diverting stoma for specific cases. The IMARI trial currently investigates whether the one-year anastomotic integrity rate can be improved by a multi-interventional program including mechanical bowel preparation with oral antibiotics, tailored full splenic flexure mobilization, intraoperative fluorescence using indocyanine, routine postoperative CRP measurement and endosponge with early transanal closure.[51]

PART IV - surveillance

In **chapter 3,** we examined the yield of radiological surveillance in T1 CRC. In this retrospective multicenter study, we demonstrated that the yield of radiological surveillance is low in terms of detection of distant recurrence. The distant recurrence rate among 346 patients that underwent radiological surveillance was 2.4% and the incidental findings rate was 20.4%. Among the patients with distant recurrence, no patients had low-risk T1 CRC.

The goal of radiological surveillance is early detection and thereby improving therapeutic options and overall survival. The first question is who to consider for radiological surveillance to best balance benefits and risks of surveillance. Radiological surveillance will lead to extra health care costs, anxiety for patients whilst awaiting their scan results affecting their quality of life and detection of incidental findings with the possibility of false positive results.
For endoscopically or surgically treated low-risk T1 CRC it would be reasonable to discourage radiological surveillance. For patients with proven lymph node metastases following surgical resection (T1N1), radiological surveillance is recommended in (inter)national guidelines. The most difficult question is whether or not radiological surveillance should be performed for endoscopically treated

high-risk or undetermined-risk p1 CRC, who declined completion surgery. Unfortunately, our study was underpowered to answer this question. In general, it remains questionable if radiological surveillance should be performed in the first place for any CRC, as survival might not be increased by radiological surveillance.[52-56]

The second question is at what time interval surveillance should be performed. Prior studies demonstrated that intensified follow-up resulted into early detection of distant recurrence, but did not show long term survival benefit.[52-56] Recently, the Dutch revised guideline recommended to perform only one routine CT 1 year after treatment combined with frequent Carcino-Embryonic-Antigen (CEA) measurements.[57] A recent meta-analysis reported that the majority of colorectal distant recurrence occur within 3 years from diagnosis but might also occur after >6 years rarely.[58]

Clinical implications of radiological surveillance T1 CRC

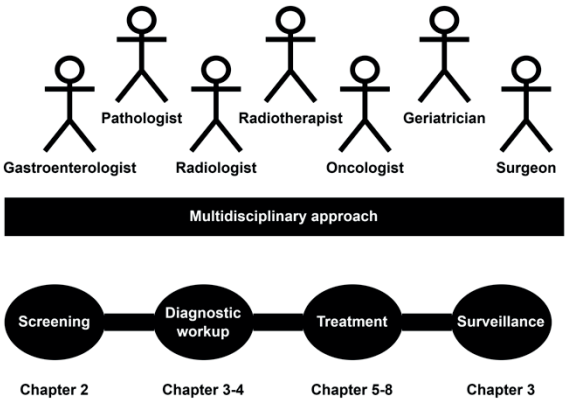
- Radiological surveillance should not be performed for locally treated low-risk T1 CRC.
- Radiological surveillance should be considered after local excision of high-risk and undetermined-risk T1 CRC according to national guidelines.

Future perspectives radiological surveillance

The challenge for the future is to identify which patients are at high risk to develop distant recurrence and should be considered for radiological surveillance. Lymph node metastases is an important pathway for the development of distant recurrence. Approximately half of the T1 CRC patients with distant recurrence have metastases caused by lymphatic spread of tumor cells.[59] The lymph node status can nowadays only be accurately determined after surgical resection including the draining lymph nodes. However, using this strategy approximately 80-90% of the patient with T1 CRC will be overtreated due to negative lymph nodes in the surgical specimen. Other diagnostic tools to estimate lymph node status are currently developing. Biomarkers for lymph node metastases are currently analyzed in the STONE project from the T1 CRC working group (www.t1crc.com). The role of CAL-WR combined with sentinel node procedure seems promising and will be investigated in the SENTRY trial (study proposal submitted to KWF).

Conclusion of the thesis

Multidisciplinary team effort is becoming increasingly important to improve colorectal cancer care and allows patient tailored treatment. The trend towards detection of an increasing number of early colorectal cancers due to national bowel screening programs led to new minimally invasive treatment innovations and allows organ preservation in selected patients with subsequent improvement of their quality of life.



SUMMARY CLINICAL IMPLICATIONS OF THIS THESIS

PART I: CRC screening

- CTC seems to have a lower diagnostic performance to detect advanced adenomas compared to colonoscopy and should therefore only be performed for individual cases unable to undergo colonoscopy to exclude CRC.
- Colonoscopy remains the gold standard for FIT positive individuals.
- Patients should be informed about the possibility of extra-colonic incidental findings, the potential risk of missed intra-colonic lesions and the chance of additional endoscopy following the results of CTC.
- Physicians should be critical whether CTC should be performed in patients unfit for colonoscopy.

PART II: CRC staging

Staging T1 CRC

- Routine radiological staging for T1 CRC before local exision is not necessary.
- Radiological staging should be reserved for T1 CRCs with high risk of lymph node metastases prior to surgical resection.
- Patients should be informed about the possibility of detection of extra-colonic incidental findings.

Stenosing CRC

- We recommend postoperative colonoscopy instead of preoperative CTC for stenosing CRC.

PART III: Treatment of colorectal neoplasms

EMR

- EMR of large colorectal lesions (>20 mm) can be performed safely in elderly.
- The choice to perform EMR should be made on individual basis weighing comorbidity and complications with potential survival benefits.

CAL-WR

- CAL-WR could be considered for benign colonic lesions with <50% involvement of the luminal circumference, not amendable for conventional endoscopic excision.
- CAL-WR could play an important role for the removal of T1 colon cancer in the future. However the oncological safety should be investigated first.

Watch-and-wait for locally advanced rectal cancer

- All patients with locally advanced rectal cancer who underwent nCRT should have response evaluation to identify (near) complete responders.
- For patients with complete tumor response, a watch-and-wait strategy with intensified surveillance could be considered instead of major TME.

Decompressing colostomy as bridge to surgery for acute left-sided colorectal obstruction

- Careful patient selection for decompressing colostomy should be made during presentation on the emergency department.
- Decompressing colostomy seems a good strategy for patients with acute left-sided obstruction as bridge to surgical resection.
- Decompressing SEMS or end-colostomy seems the preferred palliative treatment.

Endosponge therapy for anastomotic leakage

- Endosponge therapy should be considered and started as soon as possible when CT reveals a pelvic fluid collection.

PART IV: Radiological surveillance T1 CRC

- Radiological surveillance should not be performed for locally treated low-risk T1 CRC.
- Radiological surveillance should be considered after local excision of high-risk or undetermined-risk T1 CRC according to national guidelines.

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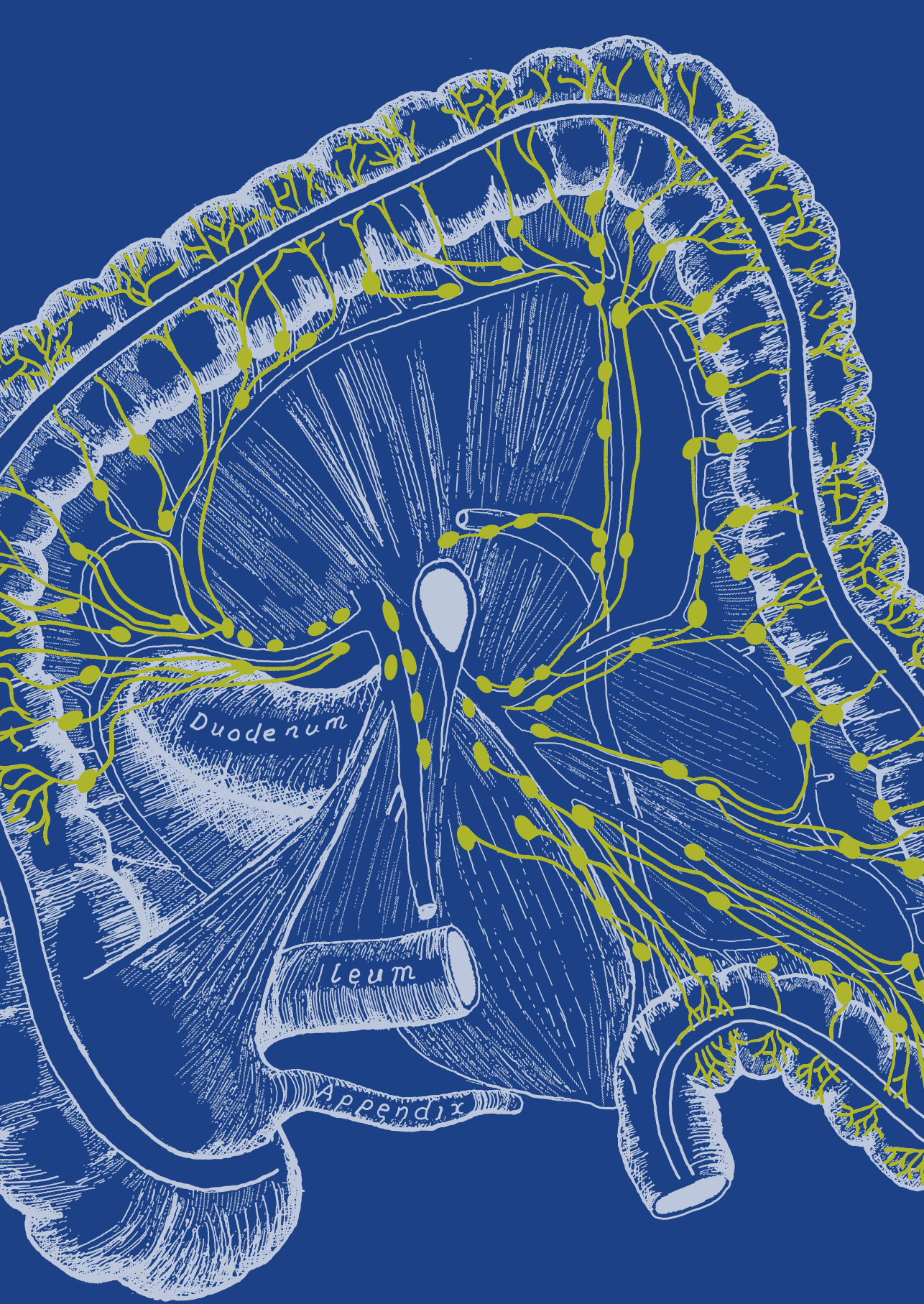
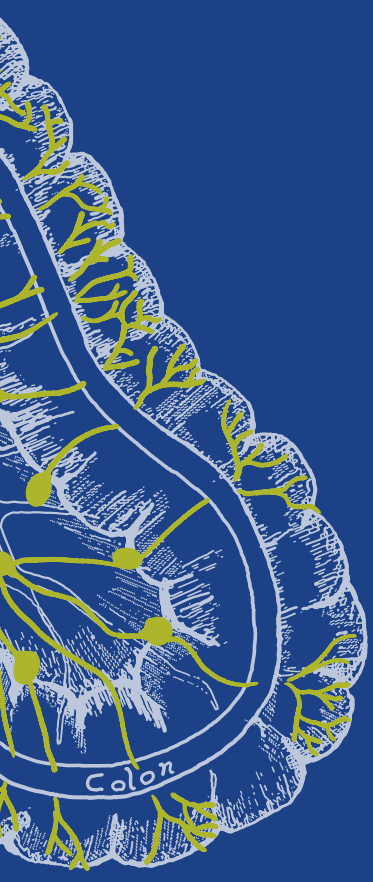

Duodenum
Ileum
Appendix

APPENDICES

Summary in Dutch
Contributing authors
List of publications
About the author
Acknowledgements



SUMMERY IN DUTCH (NEDERLANDSE SAMENVATTING)

Dikke darmkanker is de op twee na meest voorkomende kankersoort in Nederland. Jaarlijks worden in Nederland meer dan 12.000 mensen getroffen door deze ziekte en overlijden er 4500 patiënten. Darmkanker is meestal een langzaam verlopende kwaadaardige ziekte, die met name voorkomt bij oudere mensen. De tumor ontwikkelt zich gedurende een proces van vele jaren uit een goedaardige poliep. Uiteindelijk kan darmkanker zich via lymfeklieren en bloedvaten zich verspreiden naar andere organen. De overleving van darmkanker na behandeling van een tumor in een vroeg stadium is goed. Bij vaststelling van een tumor in een verder gevorderd stadium neemt de kans op overleving af.

De standaardbehandeling voor patiënten met darmkanker zonder uitzaaiingen is een operatie waarbij een gedeelte van de dikke darm wordt verwijderd. Tijdens de operatie wordt behalve het aangedane dikke darm deel ook het omliggende vetweefsel met de daarin liggende lymfeklieren weggehaald. Deze ingreep gaat echter gepaard met een kans van 25% op complicaties en 2% op overlijden als gevolg van de chirurgische ingreep zelf. De standaard work-up voorafgaand aan iedere operatie bestaat uit een CT-scan van de buik en de borstholte om te beoordelen of er sprake is van uitzaaiingen naar andere organen. Indien deze uitzaaiingen naar andere organen er zijn is een darmoperatie niet altijd meer zinvol en moet de behandeling in eerste instantie gericht zijn op de behandeling van de uitzaaiingen.

Sinds de start van het bevolkingsonderzoek voor darmkanker in 2014 wordt dikke darmkanker steeds vaker in een vroeg stadium opgespoord. Bij het bevolkingsonderzoek worden individuen van 55 tot 75 jaar met een afwijkende ontlastingstest (faecal immunochemical test (FIT)) uitgenodigd voor endoscopisch onderzoek van de dikke darm met als doel vroege opsporing van asymptomatische darmtumoren. Vroeg stadium darmkanker heeft een zeer kleine kans op uitzaaiingen naar de lymfeklieren (2-16%) en andere organen (0.3-2%) en daarmee een goede overleving. Hoe groot het risico op uitzaaiingen is kan worden onderzocht als de patholoog de verwijderde tumor bekijkt onder de microscoop.

De verschuiving van het tumorstadium waarin darmkanker wordt vastgesteld heeft de laatste jaren geleid tot nieuwe inzichten in de behandeling van deze ziekte. Bij

het vinden van de tumor in een vroeg stadium en met een laag risico op uitzaaiingen naar lymfeklieren en organen wordt steeds vaker een lokale behandeltechniek toegepast, waarbij alleen de tumor wordt verwijderd, dus zonder het omliggende vetweefsel en lymfeklieren. Het voordeel van een lokale behandeling is dat er aanzienlijk minder risico is op complicaties en vrijwel geen risico op overlijden ten gevolge van de ingreep. Het nadeel is dat omliggende lymfeklieren, waarin zich potentieel kwaadaardige tumorcellen bevinden, niet worden verwijderd. Voor patiënten met een zeer laag risico op uitzaaiingen naar lymfeklieren of organen volstaat een lokale behandeling, aangezien de overlevingswinst door een grote operatie inclusief verwijdering van de lymfeklieren niet opweegt tegen de risico's van deze ingreep.

In dit proefschrift is de kwaliteit van zorg gedurende verschillende aspecten van de darmkanker zorgketen onderzocht. Het eerste deel is gericht naar screening op darmkanker binnen het bevolkingsonderzoek. In het tweede deel is gekeken naar de waarde van radiologische beeldvorming bij patiënten met darmkanker. Het derde deel is gericht op verschillende behandelmogelijkheden van patiënten met darmkanker of een voorstadium daarvan. Tot slot wordt in het vierde deel de radiologische controle na behandeling van vroeg stadium darmkanker bekeken.

Hoofdstuk 1 bestaat uit een korte introductie van het onderwerp, het doel en een uiteenzetting van dit proefschrift.

DEEL I – SCREENING DARMKANKER

In **hoofdstuk 2** wordt de uitkomst van speciaal op de dikke darm gerichte CT scan (CT colografie (CTC)) als alternatief voor colonoscopie onderzocht bij mensen met een afwijkende ontlastingstest (FIT) van het bevolkingsonderzoek. In deze studie werd CTC uitgevoerd in plaats van colonoscopie vanwege ernstige comorbiditeit in de meerderheid van de gevallen (86%). Tijdens CTC werden relevante afwijkingen (darmkanker of poliepen groter dan 10 mm) vastgesteld in ongeveer een kwart van de patiënten. Uiteindelijk werd in totaal bij 30% van de patiënten in tweede instantie alsnog een colonoscopie uitgevoerd (waarvan in eerste instantie af werd gezien) aan de hand van de bevindingen bij CTC. Tijdens colonoscopie werd darmkanker in 4.9% van de patiënten vastgesteld en grote poliepen (advanced

adenomen) in 13.8%, hetgeen een stuk lager is dan de uitkomsten van reguliere colonoscopie bij het bevolkingsonderzoek in Nederland (8% darmkanker en 42% adenomen). Dit suggereert dat CTC een lagere potentie heeft om darmkanker en relevante poliepen te detecteren dan de reguliere colonoscopie volgend op het bevolkingsonderzoek.

(Niet relevante) nevenbevindingen van CTC in andere organen werden gezien in 13.8% van de patiënten, waarvan 64.9% werd verwezen naar een andere medisch specialist, aanvullend onderzoek nodig had of follow up van de gevonden afwijking. Het is sterk de vraag of het vinden van niet relevante bevindingen in andere organen bij patiënten met ernstige comorbiditeit wenselijk is en leidt tot een langere overleving. De mogelijkheid van het vinden van deze bijvangst moet in ieder geval besproken worden met de patiënten voorafgaand aan de radiologische beeldvorming.

DEEL II – RADIOLOGISCH ONDERZOEK VOOR STADIERING DARMKANKER

In **hoofdstuk 3** onderzoeken we de uitkomsten van radiologische beeldvorming ter beoordeling van de aanwezigheid van uitzaaiingen naar andere organen bij patiënten met een vroeg stadium darmkanker (T1 carcinomen). In onze studie vonden we zeer weinig meerwaarde van dit radiologisch onderzoek. Slecht 0.5% van de patiënten had uitzaaiingen naar andere organen en bij meer dan 22% werd (niet relevante) bijvangst vastgesteld.

Bij alle patiënten waarbij uitzaaiingen zijn vastgesteld werden na beoordeling door de patholoog bij microscopisch onderzoek risicokenmerken gezien op lymfekliermetastasen of waren deze risicokenmerken niet te beoordelen. Bij patiënten zonder risicokenmerken op lymfeklieruitzaaiingen (dit noemen we laag risico T1) werden geen uitzaaiingen naar andere organen vastgesteld bij stadiëringsonderzoek of tijdens de follow up. Het is daarom sterk de vraag of standaard bij iedere patiënt met vroeg stadium darmkanker (zoals in de meeste internationale richtlijnen geadviseerd wordt) een radiologisch onderzoek verricht moet worden ter evaluatie van eventuele uitzaaiingen naar andere organen.
Voor patiënten met een laag risico T1 carcinoom volstaat een lokale behandeling. Radiologische beeldvorming lijkt voor deze patiëntenpopulatie overbodig gezien de

zeer lage kans op uitzaaiingen en detectie van relatief veel niet-relevante bijvangst. Voor patiënten die gepland staan voor een (aanvullende) grote darmoperatie is het advies om wel radiologische beeldvorming te verrichten gezien de impact van de operatie. Grote darmoperaties kunnen daarmee voorkomen worden bij niet geneesbare ziekte door uitzaaiingen in organen.

In **hoofdstuk 4** onderzoeken we de consequenties van CTC bij patiënten met een endoscopisch niet te passeren darmtumor. In sommige gevallen wordt tijdens colonoscopie een grote darmtumor gevonden die met een endoscoop niet te passeren is, waardoor een gedeelte van de darm niet endoscopisch beoordeeld kan worden. Een tweede kwaadaardige darmtumor, hetgeen in 1-8% van de gevallen voorkomt, kan hierdoor in eerste instantie gemist worden. In zulke gevallen kan een CTC gemaakt worden om het resterende darmgedeelte radiologisch te bekijken. Indien een tweede tumor wordt vastgesteld moet de chirurg mogelijk een grotere (uitgebreidere) operatie verrichten om beide tumoren gelijktijdig te verwijderen. Lange tijd was het beoordelen van de gehele dikke darm met endoscopie of CTC vooraf aan een operatie een kwaliteitseis van de Dutch Colorectal Audit (DCRA). De Nederlandse richtlijn darmkanker adviseerde ten aanzien hiervan om een endoscopisch onderzoek 3 maanden na operatie te verrichten.
In dit hoofdstuk beschrijven we een beperkte opbrengst van de CTC. Een tweede afwijking in de proximale dikke darm (het deel van de dikke darm dat door endoscopie niet beoordeeld kon worden) werd bij 5.7% van de patiënten vastgesteld, maar heeft in slechts 0.6% geleid tot een aanpassing van het operatieplan. Ook was bij twee patiënten de CTC fout positief (CTC liet een tweede darmtumor zien, hetgeen een drogbeeld bleek), na een achteraf onnodige grotere operatie. Op basis van ons onderzoek adviseren wij daarom om geen preoperatieve CTC te verrichten, maar volgens de Nederlands richtlijn 3 maanden na operatie een colonoscopie. Dit advies wordt ondersteund door de volgende argumenten: grote darmafwijkingen worden op een ‘gewone’ CT scan, die tegenwoordig voorafgaand aan elke operatie gemaakt wordt, bijna altijd gezien. Daarnaast is CTC niet geschikt om onderscheid te maken tussen goedaardige poliepen en T1 carcinomen en tussen T1 carcinomen en T2 carcinomen (tumoren die dieper in de darmwand doorgroeien), waardoor een onnodige grotere operatie verricht wordt voor afwijkingen die potentieel endoscopisch behandeld kunnen worden.

DEEL III – BEHANDELING VAN DARMKANKER

In **hoofdstuk 5** onderzoeken we de veiligheid van piecemeal endoscopisch mucosale resectie (EMR), een geavanceerde endoscopische behandeltechniek voor verwijdering van poliepen, bij oudere patiënten (>75 jaar) met grote poliep(en). In deze studie laten we zien dat een EMR van grote poliepen bij ouderen veilig is en niet geassocieerd is met een hoger risico op complicaties. Bij 95% van de patiënten was deze techniek succesvol en kon een grote darmoperatie voorkomen worden. Toekomstige studies zouden echter nog wel moeten uitwijzen of verwijdering van goedaardige poliepen bij oudere patiënten ook overlevingswinst geeft.

In **hoofdstuk 6** onderzoeken we de veiligheid en effectiviteit van een door Isala aangepaste hybride operatietechniek (colonoscopic-assisted laparoscopic wedge resection, (CAL-WR)) voor de verwijdering van complexe darmpoliepen die niet met een standaard endoscopische techniek verwijderd kunnen worden. Bij deze nieuwe gecombineerde techniek voert de chirurg door middel van een kijkoperatie een wigresectie uit (dit betekent dat alleen het deel van de darm wordt verwijderd waar de poliep zich bevindt), onder direct zicht van endoscopie om te controleren of de poliep in zijn geheel binnen het snijvlak is. Het grote voordeel van deze techniek ten opzichte van een normale darmoperatie is dat er geen nieuwe aansluiting (naad) tussen beide darmlissen gemaakt hoeft te worden. In deze studie laten we zien dat de CAL-WR in >90% succesvol was en de poliep in >90% in zijn geheel (vrije snijranden bij microscopisch onderzoek door de patholoog) verwijderd kon worden. Complicaties, die allen mild waren zonder re-interventies, traden in slechts 6% van de patiënten op. CAL-WR is een veelbelovende en eenvoudige nieuwe orgaansparende techniek die wereldwijd toepasbaar is en uitermate geschikt voor de verwijdering van complexe poliepen die voorheen verwezen werden naar de chirurgie voor een grote darmoperatie. Daarnaast heeft CAL-WR ook de potentie voor de verwijdering van vroeg stadium darmkanker (T1 carcinomen). We zullen echter vanwege het invasieve karakter van darmkanker moeten wachten op de langetermijnuitkomsten alvorens CAL-WR eventueel ook definitief als standaardbehandeling voor vroeg stadium darmkanker gebruikt kan worden.

In **hoofdstuk 7** onderzoeken we het effect van multidisciplinaire structurele response evaluatie na chemotherapie en bestraling van gevorderde endeldarmkanker. De standaardbehandeling voor gevorderde endeldarmkanker is

voorbehandeling met chemotherapie en bestraling, gevolgd door een operatie. Er blijkt echter dat 15-20% van de patiënten een pathologisch complete respons (pCR) heeft na voorbehandeling; dat wil zeggen dat er bij het microscopisch onderzoek van het operatiepreparaat geen enkele tumorcel meer wordt teruggevonden en de patiënten achteraf gezien dus onnodig geopereerd blijken te zijn. In onze studie laten we zien dat het percentage van patiënten dat onnodig geopereerd zijn vanwege een complete tumorrespons (pCR) gehalveerd is sinds de invoering van multidisciplinaire response evaluatie na de voorbehandeling met endoscopie, MRI en CT. Nieuwe studies zullen echter moeten uitwijzen of in de toekomst onnodige operaties ten gevolge van complete tumorrespons na voorbehandeling helemaal voorkomen kunnen worden.

In **hoofdstuk 8** onderzoeken we de uitkomsten van een ontlastend colostoma bij patiënten met een acute linkszijdige verstopping van de dikke darm door obstructie van een tumor of door ontsteking van darmuitstulpingen (diverticulitis). Jarenlang was de voorkeursbehandeling voor deze patiënten een operatie in spoedsetting met verwijdering van het aangedane segment. Deze ingreep in acute setting gaat echter gepaard met veel complicaties en sterfte. Steeds vaker wordt daarom een overbruggingstechniek gebruikt, waarbij in spoedsetting een ontlastend stoma wordt aangelegd of een colon stent geplaatst wordt om op een later moment een darmresectie onder betere omstandigheden uit te voeren. In hoofdstuk 8 beschrijven we dat een ontlastend stoma als 'overbruggingstechniek naar definitieve verwijdering van de tumor/ obstructie' veilig en effectief is met het uiteindelijk opheffen van het stoma bij een groot percentage van de patiënten. Naast een laag complicatie- en sterfterisico, kan met deze tweetrapsstrategie goede preoperatieve tumor stadiëring worden verricht, voorbehandeling met chemotherapie en/of radiotherapie worden gegeven indien noodzakelijk en de conditie van de patiënt geoptimaliseerd worden voorafgaand aan de grote darmoperatie. Ook kan een grote darmoperatie bij patiënten die niet geneesbare ziekte blijken te hebben voorkomen worden.
In onze studie blijkt dat 39% van de patiënten met een acute verstopping een ontlastend colostoma hebben gekregen voor niet geneesbare ziekte. Voor deze palliatieve patiëntengroep lijkt een ontlastend colostoma echter niet de voorkeur te hebben gezien de hoge stomagerelateerde complicaties zoals een parastomale hernia en prolaps. Een eindstandig colostoma of endoscopische stentplaatsing door de tumor lijkt voor deze patiëntencategorie een beter alternatief.

In **hoofdstuk 9** beschrijven we de uitkomsten van endosponge therapie voor de behandeling van naadlekkage, een gevreesde complicatie die in 20% van de patiënten voorkomt na operatie van de endeldarm. Standaard behandelopties voor naadlekkages zijn antibiotica, ontlastend stoma en drainage van de abcesholte. Er blijkt echter dat bij de helft van de patiënten na therapie een chronische lek/holte overblijft, waarvoor een grote hersteloperatie nodig is. Endosponge therapie is een relatief nieuwe behandeling, waarbij twee keer per week endoscopisch een spons (aangesloten op een vacuüm systeem) wordt geplaatst in de holte, die daardoor schoon wordt en uiteindelijk verdwijnt.

We laten zien dat endosponge therapie effectief is, waarbij uiteindelijk slechts 1 op de 7 patiënten een chronische lek/holte overhoudt en 70% van de patiënten stomavrij is na behandeling. Toch lijkt er ruimte voor verbetering. Endosponge therapie is een dure en tijdrovende behandeling. Vroege plaatsing van de endosponge (door middel van snelle herkenning van naadlekkage) lijkt geassocieerd met betere resultaten. Daarnaast zou een korte endosponge behandeling gevolgd door chirurgisch sluiten van het defect een alternatief kunnen zijn. Dit moet echter in nieuwe studies onderzocht worden.

DEEL IV: FOLLOW UP

In **hoofdstuk 3** onderzoeken we de waarde van radiologische follow up na behandeling van vroeg stadium darmkanker (T1 carcinomen). Standaard follow up bij darmkanker bestaat uit radiologische- en endoscopische follow en bloedonderzoek met tumormarkers gedurende de eerste vijf jaar na behandeling. De kans op uitzaaiingen bij vroeg stadium darmkanker is echter heel erg klein. (Inter-) nationale richtlijnen geven geen specifiek advies of radiologische follow up verricht moet worden bij deze vroege darmtumoren. In hoofdstuk 3 beschrijven we dat uitzaaiingen tijdens de follow up bij slechts 2% van de patiënten worden vastgesteld en (niet relevante) bijvangst bij 14.8%. Er waren geen patiënten met uitzaaiingen tijdens de follow up met een laag risico tumor. Voor deze patiënten met een laag risico tumor is radiologische follow up overbodig en dient daarom niet verricht te worden. Het zorgt voor extra zorgkosten, angst bij patiënten in de wachttijd voor de CT scan en het vinden van niet relevante bijvangst met de mogelijkheid van fout positieve uitkomsten, terwijl de kans op uitzaaiingen

uitermate klein is. Voor hoogrisicopatiënten die tijdens de operatie lymfeklieruitzaaiingen blijken te hebben adviseert de Nederlandse richtlijn wel radiologische follow up. Het nut van deze follow up met betrekking tot de overleving is een onderwerp waar veel discussie over is.

Conclusie van dit proefschrift

Een multidisciplinaire aanpak voor darmkanker is van toenemend belang voor patiënt gerichte zorg en voor verbetering van de kwaliteit van zorg. De trend naar detectie van darmkanker in een vroeg stadium door invoering van het bevolkingsonderzoek heeft geleid tot nieuwe minimaal invasieve behandelmogelijkheden en orgaansparende therapie voor daartoe geselecteerde patiënten, resulterend in verbetering van kwaliteit van leven voor de patiënt.

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Submitted

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ABOUT THE AUTHOR

Jelle Huisman was born on May 14th, 1990 in Enschede, the Netherlands. After graduating from high school (gymnasium, Kottenpark college, Enschede) in 2008, he started studying Life Science and Technology at the University of Groningen and obtained his propaedeutic year. In 2010, he attended medical school at the University of Groningen and graduated in 2016. During his final year of Medical school, he performed his research internship at the department of Gastroenterology and Hepatology of Isala Hospital, Zwolle, under supervision of dr. Wouter de Vos tot Nederveen Cappel.

During his first year of working as a resident not in training to Gastroenterology and Hepatology at Isala Hospital, his interest in scientific research arose. He started a PhD trajectory under supervision of dr. Wouter de Vos tot Nederveen Cappel and dr. Erik van Westreenen at Isala Hospital, investigating quality of colorectal cancer care and minimal invasive therapies. During his PhD, Jelle coordinated (multicenter) studies, presented several posters and had oral presentations at (inter)national conferences such as Digestive Disease Week (DDW). He participated in the initiation of a multicenter study to investigate colonoscopic-assisted laparoscopic wedge resection for the treatment of T1 colon cancer (LIMERIC-II) and received a large grand on his work.

In 2019, he started his residency program in Gastroenterology and Hepatology in Isala Hospital and recently moved to the University Medical Center Groningen to finish the last part of his residency. In addition to his residency and research projects, Jelle enjoys playing hockey and bicycle racing. Jelle lives happily together in Zwolle with his partner Vera and their daughter Sophie.

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