Clinical Aspects of MR Colonography as a Diagnostic Tool

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This review has been accepted as a thesis together with three previously published papers by University of Copenhagen 1st of October 2009 and defended on 22nd of January 2010.

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Dan Med Bull 2010;57:(10) B4195.

THE 3 ORIGINAL PAPERS ARE

I. Achiam MP, Burgdorf SK, Wilhelmsen M, Alamili M, Rosenberg J. Inadequate preoperative colonic evaluation for synchronous colorectal cancer. Scand J Surg 2009;98:62-7.

II. Achiam MP, Chabanova E, Løgager V, Thomsen HS, Rosenberg J. Implementation of MR colonography. Abdom imaging 2007;32:457-62.

III. Achiam MP, Chabanova E, Løgager V, Thomsen HS, Rosenberg J. Preoperative evaluation of synchronous colorectal cancer using MR colonography. Acad Radiol 2009 Jul;16:790-7.

INTRODUCTION

Colorectal Cancer and Current Diagnostic Modalities

Colorectal cancer (CRC) is one of the leading cancers in the Western World with an incidence of approximately 4300 new incidences every year in Denmark alone [1]. Furthermore, in patients with CRC it is well known that synchronous cancers (SC) and synchronous polyps occur with an incidence of 2-11% and 12-58%, respectively [2-7]. SC may not occur often, but they may lead to increased morbidity and mortality for the patients involved.

As stated by the adenoma-carcinoma sequence theory [8], CRC and SC are, for the most part, believed to evolve from benign adenomas through slow malignant transformation. Thus, it has been speculated that detection and removal of adenomas will decrease the incidence and mortality of CRC. Indeed some studies have shown reduced CRC mortality by 15 to 33% by detecting and removing polyps in asymptomatic individuals [9-11].

At present time, several diagnostic modalities are used for colonic evaluation including: rectoscopy, sigmoideoscopy, colonoscopy (CC), fecal occult blood testing, double contrast barium enema (DBCE) and MR-/CT colonography. However, CC is considered to be gold standard due to high sensitivity/specificity and the option of therapeutic intervention. Although CC is an excellent examination, it still has several disadvantages in form of serious complications, incomplete procedures and the need for sedation and post procedural monitoring. Therefore, there is a considerable interest in finding safer, more sensitive and more patient friendly methods for colonic evaluation.

Introduction to MR Colonography

Virtual colonoscopy was first described in 1994 by Vining et al.[12] involving helical CT scans and 2 D- and 3D reconstructions to create a non-invasive colon imaging method. In 1997, virtual colonoscopy using magnetic resonance (MR) [13] was introduced, and since then the two modalities have continuously developed and have evolved into numerous different non-invasive diagnostic sub methods (e.g. 3D double contrast, fecal tagging, fecal cracking, colon dissection display, digital subtraction, computer assisted detection, translucency rendering [14-21]) centered mainly around the two key modalities, CT and MR colonography. The potential gain in early detection of colorectal cancer has been a powerful motivator in the continuing development and research into CT and MR colonography. Thus, in the last decade colonography has gone from an innovative technique to daily routine.

CT colonography (CTC) has rapidly developed since the beginning due to good diagnostic outcome, widespread accessibility and low cost. It is already a part of the standard daily diagnostic methods in most larger hospitals and medical centers. MR colonography (MRC) on the other hand, has for the most part been developed in a few specialized centers around the world, is less readily used in everyday routines and still needs larger randomized trials in low risk populations. Despite the fact that MRC [22,23] has shown equal or better results than CTC approaching 100% for larger polyps and does not involve the risks from radiation. CTC radiation yields around 9.7 mSv per examination, a dose that has not significantly decreased since 2004 [24], which for a 25-year-old is a risk of cancer induction of about 1 in 900 persons [25].

Indications of MR Colonography

The main indication for MRC is for diagnosing colorectal lesions (polyps and cancers, figure a). Studies have shown high sensitivities (86-100%) for lesions > 5 mm [26,27]. However, in the literature only around 40 studies with original data have been published so far, mostly smaller, single center, non-randomized studies with a highly selected patient population. The larger

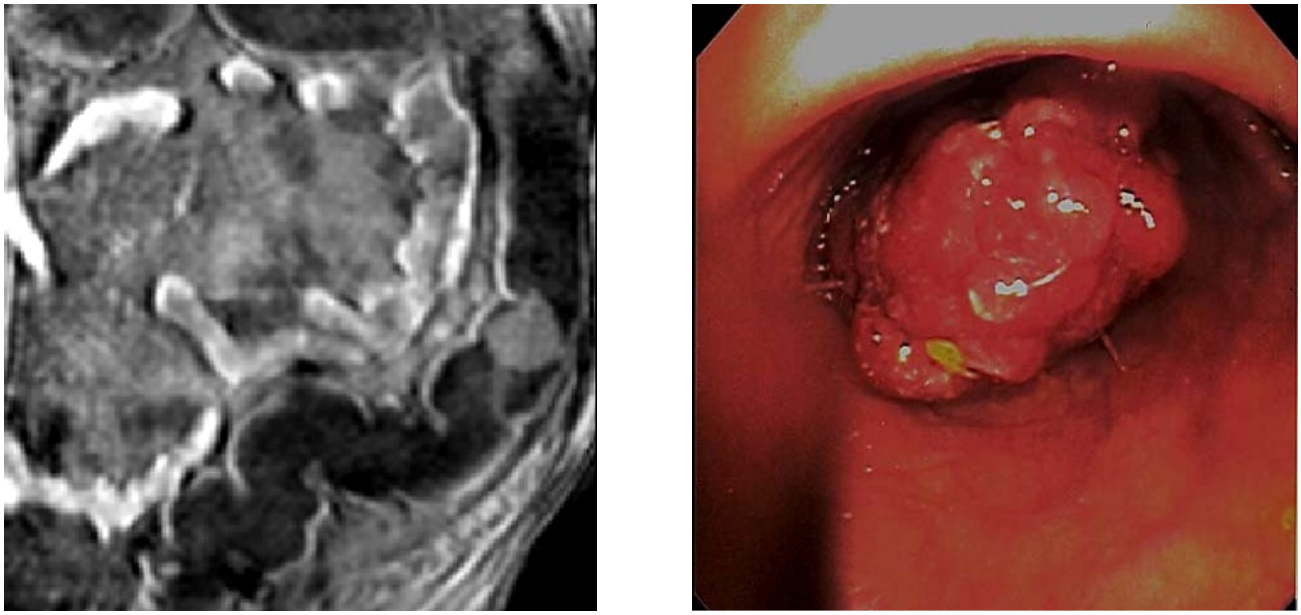

Figure a
T1-weighted MRI image of a 40 mm polyp in the sigmoid colon.
Left picture: Dark lumen MR colonography White arrow: 20 mm polyp.
Right picture: Conventional colonoscopy. Captured image of the same polyp.

studies (> 50 patients) are shown in table 1. Especially in the cases of difficult conventional colonoscopy (CC) due to colons with reoccurring loops, insufficient bowel purgation, patients who refuse CC due to previous traumatic experiences, and patients judged to be too frail for CC, MRC seems to be a realistic alternative to CTC and double contrast barium enema.

Another indication for MRC is colonic stenosis. In two studies with patients who had an incomplete CC (due to stenosis, pain or elongated colon), MRC has proved to be feasible with 100% sensitivity for polyps > 5 mm. Furthermore, 80-96% of the colonic segments were successfully evaluated compared to 40-41% evaluated with the incomplete CCs [28,29]. Especially in patients with incomplete CC, where colonic evaluation past the stenosis (malignant or benign) may be impossible, MRC can prove to be a vital diagnostic tool. By distending the colon using water or air, which can pass a malignant or benign stenotic segment, MRC can evaluate the proximal colon and diagnose lesions with high sensitivities (figure b). This is highly relevant in patients planned for

Table 1
Larger MR colonography studies
1) Value not given or unable to calculate from given information.
2) The results of two observers combined

Study	Year	Patients	Group	Preparation	Method	Colon distention	Per polyp/cancer sensitivity		Per patient			
							6-10 mm	≥ 10 mm	Sensitivity 6-10 mm	Specificity 6-10 mm	Sensitivity ≥ 10 mm	Specificity ≥ 10 mm
Pappalardo et al. [83]	2000	70	High risk	Bowel purgation	Bright lumen	Water	93%	100%	100 %	98%	100%	100%
Luboldt et al. [84]	2000	122	High risk	Bowel purgation	Bright lumen	Water	[1]	[1]	[1]	[1]	93%	99%
Ajaj et al. [44]	2003	120	High risk	Bowel purgation	Dark lumen	Water	88%	100%	[1]	[1]	[1]	[1]
Ajaj et al. [79]	2004	55	High risk/volunteers	Bowel purgation	Dark lumen	Water/air	100%	100%	100%	100%	100%	100%
Hartmann et al. [22]	2006	100	High risk	Bowel purgation	Dark lumen	Water	78%	100%	84%	99%	100%	100%
Ajaj et al. [32]	2006	72	High risk	Bowel purgation	Dark lumen	Water	88% (≥ 6 mm)	[1]	[1]	[1]	[1]	[1]
Florie et al. [91]	2007	200	High risk	Bowel purgation	Bright lumen	Water	73% [2] (≥ 6 mm)	77% [2]	65% [2] (≥ 6 mm)	67% [2] (≥ 6 mm)	75% [2]	93% [2]
Saar et al. [26]	2007	120	High risk	Bowel purgation	Bright lumen	Water	86% (5-10 mm)	94%	84% (all lesions)	97% (all lesions)	[1]	[1]
Wong et al. [27]	2007	50	High risk/ incomplete CC	Bowel purgation	Dark lumen	Air	100%	96%	100%	100%	[1]	[1]
Kuehle et al. [36]	2007	315	Screening	Fecal tagging	Dark lumen	Water	58%	74%	60%	98%	70%	100%
Achiam et al. [33]	2008	56	High risk	Fecal tagging	Dark lumen	Water	86 % [2]	81% [2]	100% [2]	80% [2]	100% [2]	91% [2]
Kerker et al. [92]	2008	88	High risk	Bowel purgation	Dark lumen	Water	38%	89%	32% (all lesions)	[1]	[1]	[1]
Rodriguez et al. [93]	2008	71	High risk	Fecal tagging	Dark lumen	Water/air	43%	100%	[1]	[1]	[1]	[1]

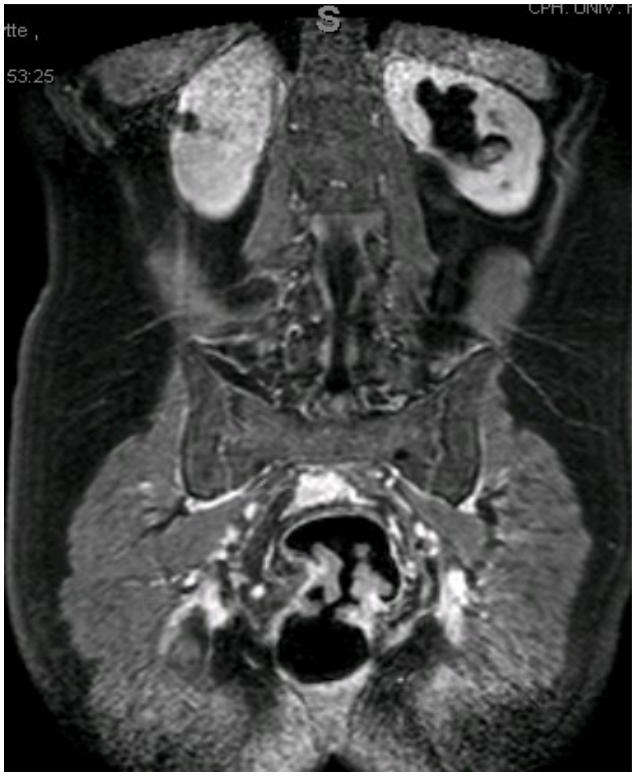

Figure b
MR colonography T1-weighted image of rectal high grade stenosis.
White arrow: High grade stenosis due to rectal cancer impassable to conventional colonoscopy.
Broken arrow: Left-sided hydronephrosis due to tumor obstruction of the ureter.

surgery due to colorectal cancer, where high grade stenosis may be present. In these patients, the incidences of synchronous cancers and polyps are 2-11% and 12-58%, respectively [3-7]. In a recent study, we found that in 47 patients with colorectal cancer with no preoperative colon evaluation performed or incomplete CC because of cancer stenosis, preoperative MRC found 12 synchronous lesions (1 cancer, 2 plaques of carcinosis, and 9 adenomas) which were confirmed during surgery or postoperative CC [30]. Full colonic evaluation with MRC was possible in 98% of the patients. Similarly, in preoperative CTC Neri et al [31] found 3 synchronous cancers and 10 colorectal cancers in 34 patients overlooked by an incomplete CC.

In colorectal cancer screening, the indication for MRC has not been established yet. The central idea behind colorectal cancer screening states that detection and removal of polyps reduce colorectal cancer as the majority of all cancers evolve slowly from adenomas [8]. While MRC possesses the quality of a good screening tool (non-invasive, high patient acceptance, no sedation, no radiation, high sensitivity), the low sensitivity (0-9%) for polyps < 5 mm is concerning [22,32,33]. The clinical relevance for pedunculated smaller polyps has been questioned with good reason, since a study concluded that only 4% of polyps < 5 mm showed signs of dysplasia [32]. However, low detection-rates for flat adenomas are worrying because they have an increased malignant potential, as shown in two large studies [34,35]. In respect to this, the results of the only study that has evaluated MRC in a larger asymptomatic screening population are troubling, finding only 10% for polyps < 5 mm and 62% of all lesions > 5mm [36]. However, looking exclusively at adenomatous lesions, which are the most clinically relevant since only adenomatous lesions have a malignant potential [8], the results are more encouraging with a sensitivity of 83% for lesions > 5 mm.

Another issue which is relevant from a screening point of view is whether the results reported in MRC studies are given as per-polyp or per-patient. From a technical view-point, it is relevant and interesting to know the per-polyp sensitivity, but from a screening view-point, per-patient sensitivity and specificity is more essential, because at least one positive finding > 5 mm automatically results in a subsequent therapeutic CC. On the other hand, having a 98% per-polyp sensitivity for e.g. lesions > 10 mm is inadequate, if one patient has 49 lesions and another patient has one lesion which is missed. This would result in a per-patient sensitivity of 50%, and could result in overlooked cancers or polyps with high grade dysplasia. Naturally, this is a simplified, hypothetical situation and the two sensitivities (per-patient and per-polyp) are of course, to some degree, inter-linked. Nevertheless, it is an aspect that must be considered for everyday clinicians, as MRC draws closer to being a daily routine examination and is mentioned as a possible future screening tool.

MRC has also been evaluated in inflammatory bowel disease with CC and histopathology as gold standards. In 23 patients known with inflammatory bowel disease and with severe inflammation (leucocytosis > 13,000/nl or C reactive protein >1.5 mg/dl), Ajaj et al. found [37] a sensitivity and specificity of 87% and 100%, respectively, considering all colonic segments, not differentiating between Crohn's disease and ulcerative colitis. In another study, Schreyer et al. found a sensitivity and specificity of 32% and 100%, respectively, for Crohn's disease and 59% and 91%, respectively, for ulcerative colitis using a score of 1-3 (1 = no inflammation, 2 = mild inflammation, 3 = inflammation) on a segmental basis [38]. While the low sensitivity for diagnosing Crohn's disease was mainly due to overlooked mild inflammation and in only one segment severe inflammation was overlooked, ulcerative colitis was incorrectly judged to have severe inflammation or no inflammation in 24 % of the segments and incorrectly judged regarding inflammation grading in 14%. The conclusion of the article was that MRC may detect severe (clinically relevant) inflammation, but still had trouble detecting mild inflammation.

Other indications for MRC include detection and assessment of diverticulitis. From colonic wall thickening, segmental narrowing of the colon, presence of diverticula, pericolic fatty infiltration, ascites, and abscesses the studies have shown a sensitivity of 86-94% when assessing diverticulitis with MRC [39,40]. Furthermore, our group has been able to differentiate between benign and malignant stenoses using fast dynamic gadolinium-enhanced MR colonography [41]. Another study from Ajaj et al. [42] evaluated the findings in extra-colonic organs, where 260 of the 375 patients had extra-colonic findings, hereof 12% that were therapeutically relevant. MRC has also been used in assessing colonic anastomosis after surgical treatment. In a study by Ajaj et al. [43] promising results that showed an overall sensitivity/specificity of 84%/100% for the assessment of the anastomosis, were obtained with MRC. Furthermore, recurrent tumors were diagnosed in two patients.

Patient Preparation

MRC can be performed with or without bowel purgation [26,44]. Most MRC studies have used bowel purgation, since stool can both hide and mimic pathology by making differentiation from bowel wall and lesions difficult as shown in figure c [45-47].

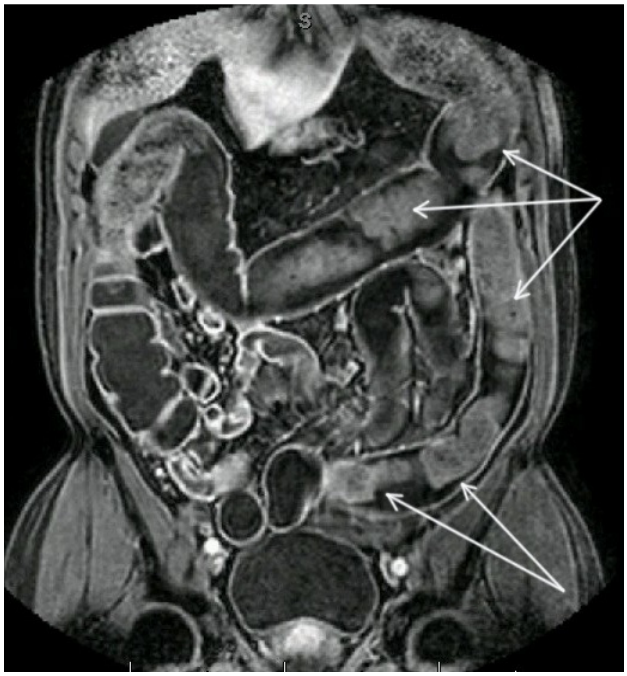

Figure c
Stool in the colon which can hide lesions or make it difficult todetect polyps and cancers.
White arrows: Stool in the transverse colon, the descending colon and the sigmoid colon.

Different bowel preparations have been used to obtain a clean colon, usually sodium phosphates (e.g. Phosphoral® (De Witt, E.C. De Witt & Co. Limited, Cheshire, England)) or polyethylene glycol (electrolyte solution, e.g. Golytely® (Braintree Laboratories, Braintree, Massachusetts, USA)).

MRC can also be performed without bowel purgation by decreasing the signal intensity of the stool and thus rendering it "invisible". Several studies have been published with orally ingested barium-based contrast agents which renders stool dark (figure d). MRC "dark lumen" has the advantage that lesions enhance after intravenous administration of gadolinium, while signal intensity of stool is not enhanced. By comparing pre- and post-contrast T1- weighted sequences this allows differentiation between stool and bowel wall lesions. The results of MRC "dark lumen" have been very promising with sensitivities between 83-89% for larger polyps > 5 mm [33,36,39,48,49]. For gadolinium-based oral contrast agents, the stool is rendered bright and with no intravenous gadolinium administered, the bowel wall and lesions remains dark in a bright lumen [17,23]. Other methods to avoid bowel purgation have been published using "fecal cracking", which uses a combination of lactulose and a 0.5%-docusate sodium enema to soften up the stool and decrease the signal intensity [14] or a partially hepatobiliary excreted gadolinium-based MR contrast agent to achieve intraluminal enhancement [50].

Patient Acceptance

Patient acceptance is one of the major factors that influence patient participation in screening programs. At present time, CC is the gold standard in colonic evaluation and the procedure has many advantages e.g. the ability to visualize and to evaluate the mucosa directly and the therapeutic option of polypectomy, biopsy, coagulating and stenting. However, due to invasive nature of the procedure, serious complications, procedure related pain and sedatives non-invasive examinations such as MRC are speculated to be more accepted by patients. Another issue is the bowel purgation, which often presents a serious challenge for especially elderly patients, but also for younger patients who spends up to two days at home with the colon preparation. Furthermore, since bowel purgation is rated as one of the most uncomfortable parts of the CC procedure [51,52] MRC without bowel preparation is thought to be even more acceptable to patients. Indeed, four studies (three with fecal tagging) have shown higher patient preference for MRC (46-71%) than for CC [23,53-55]. Another study found that a majority (75%) of the patients would still prefer MRC over CC, if MRC was done with bowel purgation instead of fecal tagging [55]. However, one smaller study found that 67% preferred CC, but only patients with inflammatory bowel disease who had previously experienced CC were included in this study [56].

Aim

The purpose of this PhD thesis was to evaluate the present preoperative colonic evaluation and to describe the consequences of this. The goal was to introduce MRC in Denmark and to evaluate the benefits of MRC in preoperative colonic evaluation in patients with CRC. Furthermore, the aim of this thesis was to create a background for further randomized clinical trials and to lead the way for the implementation of MRC in Denmark and the use of MRC in the everyday clinical situation.

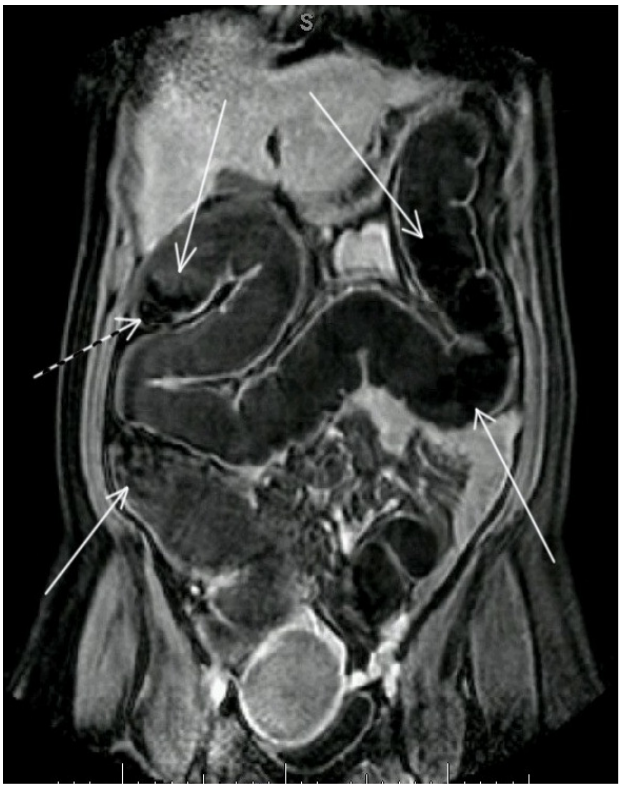

Figure d
Orally ingested barium-based contrast agents which renders stool dark on dark lumen MR colonography.
White arrows: Stool in the transverse colon and the coecum.
Broken arrows: Ferumoxsil artefact.

MATERIAL AND METHODS

Study I

The study design of Study I was a retrospective evaluation of the records of all patients operated for CRC in Copenhagen University Hospital Gentofte from January 2001 to December 2007. A search in our database found the records for all patients having undergone colonic or rectal operations, and only patients with colorectal carcinomas were included. During the review of the patient records, we focused on: a) preoperative evaluation – b) peroperative evaluation – c) postoperative evaluation. Regarding the preoperative evaluation, the main focus was whether or not the patient had a complete preoperative colonic evaluation, which evaluation had been used and whether there had been an impassable obstructive cancer or not. The main focus for the peroperative part was the findings by intraoperative palpation and pathology in the resected specimen. In the postoperative evaluation, the main focus was which postoperative evaluation had been performed, when it had occurred, and findings of the evaluation. In Study I, the definition of SCs was according to Berson's definition [57], which stated that a cancer is considered synchronous if it is detected within a year from the first cancer finding, and considered metachronous if it is detected after one year.

Study II

Study II was a prospective study from May 2005 to November 2005. Patients referred to CC at the Department of Surgical Gastroenterology, Copenhagen University Hospital Gentofte was offered MRC. As a part of the optimization of the MRC-method, different concentrations of barium sulphate (from 20 mg/ml to 1 gram/ml) (Mixobar, Astra Tech, Mölndal, Sweden or Micropaque, Guerbet, Paris, France) and an iron-containing T2 contrast agent ferumoxsil (Lumirem, Guerbet, Paris, France) were tested in different groups. Before and after MRC and CC, the patients were asked a series of questions concerning the comfort/discomfort of the oral contrast agent or bowel purgation agent (yes/no?), the comfort/discomfort of MRC or CC (rating 1 to 5 (1 = no discomfort, 2 = minor discomfort, 3 = discomfort, 4 = very unpleasant, 5 = worst imaginable)) and the future preference of examination (MRC/CC?). In addition, the patients were asked to name a future preference (MRC/CC?), if MRC was to be done with bowel purgation instead of fecal tagging with oral contrast agent. The tagging quality of the oral contrast agent was evaluated by a blind observer on a scale from 1 to 3 (1 = bright stool, poor differentiation from bowel, 2 = dark stool, sufficient differentiation from bowel, 3 = darker stool, good differentiation from bowel).

Study III

Study III was a prospective study between March 2007 and April 2008, where patients with rectal- or sigmoid colon cancer and no preoperative or incomplete colonic evaluation were asked to participate. The patients were recruited from the Department of Surgical Gastroenterology in four hospitals in the greater Copenhagen area (University Hospitals in Herlev, Gentofte, Hvidovre and Hillerød). Findings on MRC were compared to intraoperative findings and the result of the postoperative CC. MRC was performed either ambulant or the night before surgery and one observer (MA), who had evaluated more than a hundred MRC examinations prior to the study, evaluated all MRCs. Only in case of positive findings the performing surgeon was informed preoperatively.

Patient Preparation for MR Colonography

In Study II, the patients received oral contrast agent of different doses (figure 1, second paper), and in Study III the patients received bowel purgation as described above.

Before the imaging acquisition began, patients were administered butylscopolamine intravenously or glucagon to minimize bowel peristalsis and colonic spasm, which can mimic bowel wall thickening and prevent optimal evaluation of the colonic segment.

A water distended colon lumen is obligatory to obtain quality images. The distension of the colon is continued until all of the water is given or the patient halts the filling process because of increasing abdominal pressure.

MRC was performed as "dark lumen" where the colon lumen is dark and the contrast enhanced (intravenously administered gadolinium) bowel wall and lesions become bright.

When the colon was distended different sequences, of which most were breath-hold sequences, were applied. The scanning time was approximately 20 s. per sequence adding up to a total scanning time of approximately 10-15 minutes. During the MRC a Gadolinium based contrast agent was injected during a sequence to induce enhancement of the bowel wall and lesions.

Conventional Colonoscopy

In Study II CC was performed with a standard endoscope (Olympus CFQ160DL) by the attending senior surgeon in the endoscopy suite. Prior to CC, all patients had a standard preparation for bowel purgation (oral ingestion of Phosphoral, De Witt, Runcorn, England). Before colonoscopy all patients were administered 2-4 mg midazolam (Dormicum, Roche, Basel, Schweiz) and 50-100 µg fentanyl (Fentanyl, Hameln Pharmaceuticals, Hameln, Germany). The examination time, including possible polypectomy, was noted. In Study III, similar setups were used for CC, but due to the multicenter design of the study, no standardized CC setup could be implemented.

Exclusions Criteria

In Study I, the exclusion criteria were emergency laparotomy due to acute ileus or perforation. In Study I and III, the exclusion criteria were contraindications to MR (pregnancy, claustrophobia, electronic implant etc.) or known allergy to the contrast agent.

ETHICAL CONSIDERATIONS

In Study II and III, all patients only participated after oral and written informed consent and in accordance with the Helsinki-II declaration. The local ethics committee approved the studies under the following ID-numbers: Study II = KA 05029, Study III = KA 05030. Furthermore, the studiea were registered at clinicaltrials.gov under the following ID-numbers: Study II = NCT 00114842, Study-III = NCT 00300547. In accordance with the act of processing of personal data, Studies II and III were also registered and approved by the Danish Data Protection Agency.

STATISTICAL CONSIDERATIONS

In Study I and III, the statistics are purely descriptive, while non-parametric statistics (Wilcoxon's signed rank test) have been applied in Study II.

RESULTS

Study I

From January 2001 to December 2007, 562 patients underwent surgery for CRC of whom 534 patients were included in the study.

An impassable obstructing cancer was diagnosed in 23% of the patients, and full preoperative colonic evaluation was not performed in 78% of all the patients. The methods of preoperative evaluation are shown in figure 2 (first paper). In the group with an obstructing cancer, 10% had a full preoperative colonic evaluation, while the group without an obstructing cancer 26% had a full preoperative colonic evaluation (figure 3, first paper). In the group without an obstructing cancer, 74% did not have a full preoperative colonic evaluation. Their type of colonic examination is shown in figure 4 (first paper).

A total of 39 SC were found in 36 patients, of which seven SC were diagnosed postoperatively in seven patients. Two of the seven patients had a preoperative colonic evaluation with DCBE, which missed the SC. The remaining five patients did not have full preoperative colonic evaluation, and of these two patients were inoperable due to metastases. One patient was inoperable because of local tumor spread, one patient died of a anastomosis leakage and one patient had a pulmonary embolism. These numbers are different from the article that is published. When the data analysis of the PhD thesis was done, we found a typing error in the published article. It should have been "two patients were inoperable". The article reported three patients inoperable due to metastasis. This small error, however, did not change the conclusion of the study. Out of the 36 patients with SC, ten patients had a full preoperative colonic evaluation, and in spite of this nine patients had a SC. Five patients had a preoperative CC and four patients had a preoperative DCBE. Of the 78% of patients, who did not have a full preoperative colonic evaluation only 62% had a complete postoperative colonic evaluation.

Study II

A total of 30 patients participated in the study and of those 57% reported no discomfort with the contrast agent. When asked to rate MRC on a scale from 1 to 5 (1 = 0 discomfort, 2 = minor discomfort, 3 = discomfort, 4 = very unpleasant, 5 = worst imaginable), 17% of the patients rated MRC to 1, 70% rated 2, 13% rated 3. No patients rated MRC to 4 or 5.

Concerning bowel purgation for CC, 67% of the patients reported some discomfort. When asked to rate CC on the scale from 1 to 5, 4% of the patients rated CC to 1, 55% rated 2, 28% rated 3, 10% rated 4 and 3% rated 5. The difference in rating between MRC and CC was statistically significant in favour of MRC ($p = 0.005$, Wilcoxon's signed rang test) on the final data analysis. Furthermore, when asked for the preferable future examination 63% chose MRC, 10% chose CC, 23% had no preference and 3% had dropped out of the study, the difference being statistically significant ($p = 0.002$, Wilcoxon's signed rank test). Future preferences of the patients, if MRC was to be done with bowel purgation instead of fecal tagging, was shown to be 40% in favor of MRC, 23% in favor of CC, 33% had no preference and 3% had dropped out of the study.

The median time in the MR suite was 44 minutes with 23 minutes to MRC examination alone. The median evaluation time of MRC was nine minutes. For CC the median examination time was 32 minutes and patients routinely spent 60 minutes in post-procedure monitoring.

Study III

In Study III, 47 patients participated and full preoperative colonic evaluation with MRC was possible in 98%. MRC in one patient was incomplete due to tumor stenosis, which prevented insertion of the rectal tube in the rectum. Preoperative MRC found 12 synchronous lesions in four patients. One patient had an eight cm SC in the coecum (figure 1, third paper), one patient had two SC (3x2 cm in the sigmoid colon, 3x3 cm in the coecum), one patient had a 20 mm synchronous polyp in the sigmoid colon (figure 3, third paper) and one patient had eight synchronous polyps (5 mm, 22 mm, 15 mm , 11 mm, 12 mm, 15 mm and 5 mm polyps in the sigmoid colon and a flat 32 mm polyp in the coecum). The performing surgeon was informed prior to surgery, which led to a change in operative strategy in three patients (one colectomy, one extended resection and one patient was abstained from surgery). Preoperative CC was incomplete in 20 patients (43%) due to an impassable obstructing cancer, of whom three patients (15%) had a synchronous lesion. Postoperative CC found one 8 mm polyp and one 4 x 10 mm flat polyp which were missed on preoperative endoscopy, MRC and intraoperative palpation. Postoperatively, CC also found two 7 mm polyps, one 5 mm polyp and one 4 mm polyp missed on MRC and intraoperative palpation. The last two polyps were missed by the first two postoperative therapeutic CC's in the patient with the eight other synchronous polyps.

DISCUSSION

In the three studies (I+II+III), we have shown that there are some problems with the present gold standard of colonic evaluation; that there is an increased morbidity and mortality in the group of patients with missed SC; that patients have a preference for MRC and for fecal tagging compared with CC and bowel purgation, and that there is a potential gain in doing preoperative colonic evaluation with MRC in all patients with rectal- or sigmoid colon cancer. In Study I, we found that full preoperative colonic evaluation was not performed in 78% of all the patients who underwent surgery for CRC, despite that only 23% of all the patients had an impassable obstructive cancer that prevented full colonic evaluation with CC. Furthermore, seven patients had a SC that was diagnosed postoperatively, two of whom had a SC that was missed on preoperative DCBE and five patients who never had a full preoperative colonic evaluation. In Study II, 57% of the patients reported no discomfort with the contrast agent for fecal tagging compared with 67% who reported some discomfort with the bowel purgation agent. The patients rated MRC significantly less uncomfortable compared with CC and patients would prefer MRC as the future colonic evaluation compared to CC. Study II also showed that the examination time of MRC and the actual evaluation time were shorter than the time spent on CC. The potential gain of full preoperative colonic evaluation by MRC was shown in Study III, where we found three SC and nine synchronous polyps. All synchronous lesions were confirmed either during surgery or postoperative CC, and there was a 100% sensitivity for SC and larger penduculated polyps.

Conventional Colonoscopy

The adenoma – carcinoma sequence states that the majority of CRCs evolve from benign adenomas [8], but more evidence is emerging as to the complexity of CRC. Some studies have shown increased malignant potential and increased transformation speed of flat adenomas [34,35] while other studies have shown that hyperplastic polyps may not all be benign and may have a malignant potential as well [58,59]. However, the adenoma-carcinoma sequence is still widely accepted and is the cornerstone of the attempts to localize and remove colonic polyps at an early stage to reduce CRC. At present time, CC is considered gold standard due to the high sensitivity and specificity of the examination, the availability and the therapeutic options of the exami-

nation. Still, CC does have some disadvantages, some of which can be minimized and others which are unavoidable by the nature of the examination.

In the former category, the serious complications are associated with the examination. While colonic bleeding, primarily, occurs in therapeutic colonoscopies, perforations, which are reported with incidences of 0.63 – 0.03% [60-62], are also associated with pure diagnostic CC. However, the predominant part of the perforations is caused by therapeutic CC. In the study by Brynitz et al. [60], the perforation rates of therapeutic and diagnostic CC were 0.7% and 0.6%, respectively, while others [63] have found perforation rates of 0.3% and 0.2%, respectively. Some studies have, furthermore, reported mortality from perforation related operations between 9% and 43% [60,63-65]. In the first categories, there are also incomplete examinations as high as 17-23% [62,65] in routine CC and up to 54% [66] preoperatively in patients with CRC, and procedure related discomfort (pain) caused by loops in the colon or excessive use of force. While all these factors can be minimized by using experienced endoscopists, the factors cannot be completely eliminated, and the way the Danish healthcare system is organized, it is not possible to have very experienced endoscopists performing all the procedures. Another factor that should be considered is the fact that a lot of colonic evaluations, which ideally should have been done by CC, will not be done or will be done by other methods for colonic evaluation due to the long waiting time for an ambulant CC. This is clearly evident in Study I, where the majority of all examinations are sigmoidoscopies. This will certainly just be worsened by the increasing demand for a quicker diagnosis, staging and treatment for CRC. A disadvantage of CC that can be minimized, but is routine in many hospitals at present time, is the use of sedatives. The use of sedation requires trained personnel both during and after CC, room for post procedural monitoring and monitoring equipment. Moreover, the need for sedatives will exclude some patients due to co-morbidity.

The disadvantages that are unavoidable are the incomplete colonic evaluations due to stenosis (of either malignant or benign ethiology), elongated colon or pain. Furthermore, some colonic evaluations are not suited for CC due to either past traumatic patient experience or elderly patients being too weak and frail for sedation.

Current Preoperative Colonic Evaluation

As shown in Study I, the preoperative colonic evaluation at present time is not optimal. Although the Danish Colorectal Cancer Group and The Danish Surgical Society in 2005 recommended that colonic evaluation in patients with CRC should be performed either by preoperative CC or at least by a three months postoperative clean colon CC [67], other international studies have recommended a full preoperative colonic evaluation [6,68,69]. As mentioned above, the majority of the patients with CRC, as reported in Study II, do not undergo full preoperative colonic evaluation, because they either have rectoscopy or sigmoidoscopy performed. Nevertheless, even if CC was fully implemented in all patients with CRC, the colonic evaluation would not be optimal since up to 23% (Study I) of all CRC include an impassable obstructing cancer. In the group of patients with an obstructing cancer, 12% (15 of 124 patients) had a SC in Study I, which would not have been detected with CC. Moreover, earlier studies have shown that up to 5% of carcinomas [70], 37% of all polyps and up to 11% of advanced adenomas can be missed by CC [71-73]. This is in line with our results in Study I, where five SC were missed during preoperative colonic evaluation.

The suboptimal preoperative colonic evaluation combined with the risk of missing SC by intraoperative palpation, in one study up to 69% of the incidences [74], is worrying. Considering also the study by Howard et al. [75], which showed fewer local recurrences, fewer distant metastasis and longer disease free survival times in patients who had undergone preoperative CC, combined with the increased morbidity and mortality of patients with missed SC, the strive for optimizing preoperative colonic evaluation seems warranted.

Clinical Implications of MR Colonography

For the past decade MRC along with CTC have been promising non-invasive diagnostic modalities. They not only lack the therapeutic option, but also many of the disadvantages of CC. MRC has so far not reported any incidences of perforation. One can speculate if this is due to the lower pressure applied by water distention of the colon compared to the pressure applied by CC or air insufflation/distention. Air distention is generally used by CTC, which has reported perforation incidences up to 0.06% [76]. However, this theory has not been proven right and so far the number of CTC examinations exceeds MRC examinations by far, so the difference could be statistically non-significant.

MRC is also considerably better tolerated by patients compared to CC [23,54]. One study found that the main reason for MRC as a future preference was that MRC had no or less discomfort and no or less pain compared to CC [55], while Study II showed that 63% of the patients preferred MRC as a future examination. This was not only due to patient acceptance of fecal tagging, since a majority of the patients in Study II (40%) and the majority (75%) in another Study [55] would prefer MRC as a future examination even if MRC was performed with bowel purgation. The option of fecal tagging is another advantage of MRC, which has been speculated to increase patient acceptance of a colonic evaluation. Bowel purgation, which is used and necessary for CC, is a physiological strain on the body, especially among elderly and frail patients. Due to the nature of bowel purgation, the patients often become dehydrated, fatigue and dizzy. Furthermore, the procedure is time consuming, and patients need to stay home for days to complete the purgation properly. Moreover, studies have shown [51,52] that bowel purgation is considered one of the worst, if not the worst, part of the examination, and as illustrated in Study II and by Achiam et al. [55] patients had significantly less discomfort in ingesting an oral contrast agent used for fecal tagging in MRC. This, however, is not true for all types of oral contrast agents. Goethe et al. [77] found that barium sulphate alone as contrast agent was the single most disturbing factor in MRC and also an poor overall patient acceptance for MRC. We had similar experience with patient discomfort of barium sulphate alone as a contrast agent, since barium sulphate has a very thick and rich texture. We therefore added ferumoxsil, a paramagnetic MRI contrast agent, which is much more liquid and the result was that we had a better fecal tagging ability of the new contrast agent as shown in Study II. We also found a higher percentage of patients who would prefer MRC as a future examination as shown in a later study of patient acceptance [55].

Another advantage of MRC is that it is a faster examination than CC for both the patients and the doctors. In Study II, we had a median examination time of 23 minutes for MRC, but as illustrated in figure 2 (second paper) we had some high evaluation times in the beginning due to implementation of MRC. In the last ten patients, the median evaluation time was 20 minutes. Moreover, in unpublished data we have reduced the median MRC examination time to 15 minutes. The shorter examination time

may also increase patient acceptance compared to CC just as the lack of sedation in MRC will mean no routine post-procedural observation time as seen in CC. A fact that has also been speculated to increase patient acceptance of MRC is the lack of sedation, since patients are able to leave the hospital right away and drive a car immediately after the examination.

As mentioned above, MRC offers the possibility of full colonic evaluation in patients with an obstructing cancer, which is an advantage compared to CC. In Study III, 98% of the preoperative colonic evaluations were complete even though 43% of the patients had an impassable obstructing cancer. In this study, MRC showed its value in the preoperative colonic evaluation by finding three SC and seven synchronous polyps larger than 11 mm, which led to a changed operative strategy in three patients. Since none of the patients in Study III had a full preoperative colonic evaluation, at least one re-operation due to SC potentially could have been avoided if intraoperative palpation had missed the SC. The other two cancers later turned out to be plaques of carcinosis, which were impossible to miss during surgery. Furthermore, despite the fact that none of the patients had a complete preoperative colonic evaluation, CC still missed a flat adenoma (4 x 10 mm) and an 8 mm polyp, and both polyps were in the segments visualized by CC. This illustrates that even though MRC missed some smaller polyps and one flat polyp, CC also misses larger polyps in the everyday clinical situation. Taking the disadvantages of CC into consideration, MRC seems very promising and as shown in Study III, there is a potential gain of preoperative colonic evaluation in patients with rectal- or sigmoid colon cancer of which many patients have an obstructing cancer.

As mentioned above, an important aspect of both MRC and CTC is the lack of therapeutic option. At present time, a polyp detected on either examination must be referred to a therapeutic procedure which predominantly would be CC or operation. It has been debated whether MRC would be cost-efficient if a therapeutic procedure (CC or operation) has to be added to the total cost. So far no studies have been published on the cost effectiveness of MRC, and the answer of cost effectiveness is complicated by the different clinical choices that have to be considered, e.g. cut-off size and patient population. Naturally, the higher the cut-off size is for therapeutic intervention (fewer relevant polyps to remove), just as evaluating an asymptomatic vs. a symptomatic patient group, the more cost-effective the MRC becomes. One study have been published on the cost-effectiveness of CTC compared to CC [78]. The total cost of time consumption, salaries, medication, minor equipment and major equipment used by CTC or CC with a cut-off value > 6 mm was calculated. The study found that in one center CTC was more cost-effective than CC, even when the therapeutic CC prompted by a positive CTC was included in the total cost for CTC. Whether this is applicable to MRC is uncertain since the modality is different from CTC, both economically and practically, and further studies are warrented.

MR- and CT Colonography

The benefits of MRC as a non-invasive fast examination, which can diagnose extra-colonic pathology, are the same as CTC. CTC is basically the same examination and has advantages of being more widespread and implemented just as CT-scanners are more abundant. In addition to this, there is a conception that CTC is an easier examination to implement and to read. At present time, the resolution and software for CTC also appear to be better and the examination may be slightly faster. However, with an effective scan time per sequence of around 20 seconds and optimally five sequences per MRC and a total of approximately 15 minutes in effective scanner room time, MRC is close to CTC and in all regards a very fast examination. Moreover, as we have shown in Study II and in another study of diagnostic accuracy [33], it is not difficult to implement MRC or to obtain high sensitivity/specificities.

Another issue that has been raised against MRC compared to CTC is the notion that air for colonic distension is more patient acceptable and easier to work with. However, this viewpoint is not substantiated. In a study by Ajaj et al., the discomfort levels for MRC were similar with air compared to water [79], and Lam et al. found that only 38% preferred MRC using air for distention compared to 62 % that preferred CC [80]. This number is substantially lower than the percentages of preference for MRC shown in Study II and in other studies [23,54,55] and raises doubts of the superiority of air for colon distention. Patient acceptance in our studies shows that we have found little discomfort in distending colon with water. Furthermore, the problem with residual water in CTC and false-negatives caused by this is not a problem in MRC, where water is routinely used for colonic distension especially with dark lumen methods.

A major drawback of CTC is the issue of ionizing radiation, which is absent in MRC. A recent study [24] showed that although CTC had lowered the dose, the average dose in everyday clinical CTC situations has not significantly decreased since 2004 and the effective dose is, at present time, around 9.7 mSv per examination. According to the linear non-threshold model, this dose constitutes a risk of a cancer in one out of 100 individuals for a 25 year-old, and a risk of 1 in 1800 for a fatal cancer [25,81]. The issue of radiation may not be important when talking about a single examination in an elderly person, but since the perspective of colonography may include repeated polyps controls, screening in an asymptomatic population etc., which is where the trend and direction of the future is heading, radiation might be a very important factor. Even if the risk of radiation induced cancers should be questioned as extrapolated numbers, the public has an increased awareness of radiation exposure, which may lead to a reduction of patient acceptance for CTC. All in all, the risk of a radiation induced fatal cancer is comparable to the risk of colon perforation by CC, but the mortality is considerably lower for CC. MRC, however, has not yet been shown to have a similar risk, which is a significant advantage.

Limitations of the Studies

There are several limitations of the studies in this PhD thesis. In Study I, the disadvantages of a retrospective study are clear from imprecise, heterogeneous information and descriptions throughout the patient records to the different methods applied and the potentially imprecise information. In addition to this, there is a risk of SC being missed in the retrospective evaluation of the records in spite of best efforts to be as methodological as possible. Furthermore, in the study the precise location of the SC and the primary cancer are not given, which would have shown a more detailed picture of the nature of SC. However, due to the retrospective design information of this kind was inconsistent at best. It would also have been helpful to have information concerning synchronous polyps, but this was also very difficult in the retrospective analysis due to inconsistent reporting on CC. Nevertheless, we have tried to make up for the lack of information on location of SC by giving information of whether the SC was in the resected specimen or not.

In Study II, one of the weaknesses is the small number of patients and the heterogeneous distribution of the patients. While the number is too small for any final recommendations, the dif-

ferences found between the groups of contrast are statistically significant, and the small number reflects the study, which was a description of the implementation process and the development of the MRC modality and the contrast agent. Another weakness of the study is that all the patients from the three different groups of contrast agents are pooled together in the evaluation of patient acceptance. The result is a high patient preference (40%) for MRC versus CC, but the patient preference is somewhat lower than later studies of patient acceptance [23,55]. This could be explained by the patient discomfort for barium sulphate as tagging agent alone as mentioned above. The questionnaire, which is very simplified in this study, is also a weakness. The design of the questionnaire is based on free patient response and not a formal constructed interview, which limits the information obtained in the interview and only relays on the information given freely by the patient. In addition to this, the free form design does not allow for a standardized evaluation of discomfort in ingesting the contrast agent or the bowel purgation agent. The last question in the questionnaire, in which the patients were asked to name a preferable future examination, is also biased. In the questionnaire, it is assumed that modalities of MRC and CC are equally sensitive. The patient preference might therefore have been higher for CC if the patient would have had knowledge of a lower overall sensitivity for polyps of all sizes on the MRC modality. There is no analysis of preference related to neither gender, age nor indication for referral to CC. Another weakness of the questionnaire is that it may be difficult to interpret or determine what "discomfort" is to patients. Is it pain and if so, to what degree, or is it just a little discomfort? Still, the questionnaires do offer a sense of direction concerning patient acceptance of MRC versus CC, a notion which, as mentioned above, also has been found in other similar studies of patient acceptance. Furthermore, the free forms of questionnaire do have some advantages compared to the more standardized formal response. It gives the patient the opportunity to describe the experience of the examination without being restricted to predetermined answers.

In Study III, one of the weaknesses of the study is the selection bias of the patient group, hereunder the inclusion criteria; no preoperative colonic evaluation or incomplete CC. In addition to this, the majority of the patients had a rectal cancer. These biases may influence the numbers of the synchronous lesions and the location as well as the stage of the primary cancer. Another weakness of Study III is that it is a multi-center study, which means that there is no standardized treatment, and that the retrospective evaluation of the postoperative CC might be slightly different from each center. Besides the well-known fact that CC may miss polyps and carcinomas, it is also known that the evaluation of polyp size and location with CC is very inconsistent [82]. Since no formalized guidelines for the postoperative CC was set out in the study design, this will have to be considered in the final results. Although these weaknesses may influence the results of Study III, the study also has the advantage of showing the potential and feasibility of MRC as a preoperative evaluation in a clinical everyday situation without introducing standardized guidelines to all the centers involved in the study. Thus, one of the weaknesses of the study becomes one of the strengths of the PhD thesis, since it describes the clinical impact of the implementation of MRC and the advantages of the examination.

PERSPECTIVES AND CONCLUSION

At this time, the clinical application of MRC is not established in the international literature. However, it only seems reasonable, given the high sensitivity obtained in many studies [22,23,27,33,79,83,84], to recommend MRC on selected indications. As shown in this PhD thesis, one of these indications may be preoperative colonic evaluation of all patients with known CRC. Possibly only patients with cancers in the left side of the colon, since a substantial percentage of these patients have an obstructing cancer, which will, as shown Studies I & III, result in incomplete preoperative evaluation. Furthermore, indications for MRC could be the same as the indications for CTC, which are supplement to CC after an incomplete or a very difficult examination. Nevertheless, before MRC is implemented it is important to attempt to keep MRC in a few specialized MR centers, which then would have the task of educating and certifying radiologists and departments interested in implementing MRC. This should be done to avoid devaluation of the examination by having low sensitivity and specificity at local MRC centers without the essential experience or with radiologists not committed to MRC. This is often the case of the every-day-clinical examinations of DCBE and to some extend CC and should be sought to be avoided while MRC is yet to be implemented. This point is also backed up by a study from our group where we showed that the sensitivity of the busy everyday-clinical MR radiologist, although very experienced, was slightly lower than the committed reader, who had more time and dedication to perform the MRC evaluation [33].

Before widespread use of MRC can be expected, further multicenter studies concerning diagnostic accuracy and patient acceptance in the clinical application are warranted. Future indications may also very well include MRC for screening purposes or follow-up after polypectomy or cancer surgery, just as MRC might be needed to outplace most, if not all, of the diagnostic CC performed at present time. Although no studies have been performed on the consequences of MRC for all diagnostic colonic evaluations that CC otherwise would have done, one study has made a calculation on the impact of CTC on the number of CC [85]. This study shows that if CTC was to comprise all the diagnostic colonic evaluations and a threshold of 6 or 10 mm was supplied, the numbers of CC would be reduced by 9% and 22%, respectively. This is of course a mathematical model and does not consider the increased public interest in colonic evaluation and the presumably lower threshold for referral to colonic evaluation. This could lead to an increased number of pure diagnostic evaluations as seen with MRCP versus ERCP and could also result in a higher number of therapeutic CC as well. In addition to this, a study found that the follow-up CC after a false positive CTC requires more time than a screening CC and that the endoscopic productivity, as a consequence, most likely would decrease as a result of screening with CTC [86]. This illustrates the uncertainties and discussions concerning future screening models. Since CTC is already implemented in every clinical practice, and MRC is ready for implementation, discussion of polyp size and cut-off value is therefore an essential discussion that must be addressed in the nearest future. At this time, a generalized cut-out value of > 5mm has been suggested for CTC [87,88]. For polyps between 6-9 mm the authors suggested a 3-year CTC surveillance period and for polyps > 9mm polypectomy was recommended. This seems reasonable since it has been shown that primarily polyps larger than 10 mm have a malignant potential [89] and moreover, another study has shown that a majority of the polyps between 5 and 9 mm will remain unchanged or will diminish over a 3-year period [90]. Larger studies are needed to determine whether a cut-off size of 10 mm can be accepted or a 6 mm cut-out value should be accepted with the option of surveillance colonographies to evaluate the development of the polyp. The cut-off value recommen-

dations may also very well influence the total cost-effectiveness of MRC just as studies on MRC cost-effectiveness may influence the final recommendation on cut-off value.

In conclusion, we have shown that everyday-clinical preoperative evaluation of patients with CRC has some serious problems and can be improved. The low percentage (22%) of the patients who had a full colonic evaluation and the fact that only 63% of the remaining 78% of patients underwent a postoperative colonic evaluation are reasons to concern. This, of course, reflects a local problem, but may also represent a logistical problem in the Danish health care system. Furthermore, once you put the responsibility of booking the essential postoperative colonic evaluation in the hands of doctors or secretaries, there is a risk of human error. This could be eliminated by doing a preoperative colonic evaluation in all patients with CRC. In this PhD-thesis we have also shown that MRC can be implemented and improved, and that patient acceptance seems to be higher for MRC compared to CC. The examination time in MRC is also shorter for both patients and doctors. In the Study III, we have shown that implementing MRC as a part of the clinical preoperative evaluation in patients with CRC is feasible and may lead to reduced morbidity and mortality from missed SC. The clinical significance of full implementation of MRC in the preoperative colonic evaluation and in the everyday difficult or incomplete colonic evaluations by CC remains to be settled and larger studies are warranted to determine this.

LIST OF ABBREVIATIONS

CC = **Conventional colonoscopy**
CRC = Colorectal cancer
CT = Computed tomography
CTC = CT colonography
DCBE = Double contrast barium enema
MR = **Magnetic resonance**
MRC = MR colonography
SC = Synchronous cancer

SUMMARY IN ENGLISH

Since first described in 1997, MR colonography (MRC) has since been labelled as a promising new, non-invasive technique for examining the colon. At present time, the examination is ready to be implemented as a supplement to incomplete colonoscopy or preoperative colonic evaluation. Furthermore, MRC seems to have a great potential in the screening for colorectal cancer, since detection of polyps and polypectomy might reduce on the incidence of colorectal cancer. This is speculated in the adenoma-carcinoma sequence theory, which states that most cancers evolve from polyps over a long period and that polypectomy might be curative.

Colonoscopy remains the gold standard for full colon evaluation. However, the result of our studies can justify clinical use of MRC on selected indications, e.g. in the cases where colonoscopy is incomplete or technically difficult. Since up to 54 % of all preoperative colon evaluations in patients with colorectal cancer and up to 17 - 23% of regular colonoscopies are incomplete, the clinical potential of MRC is evident. Furthermore, in our studies (I+III) we have shown the insufficiency of preoperative colonic evaluation by CC. In addition, considering the invasiveness, the serious complications (perforation, bleeding, death) and the lack of patient acceptance in colonoscopy, the need for a safe, patient friendly alternative examination with high sensitivity, is clear.

In conclusion, in the three studies (I+II+III) that made up this PhD thesis, we have shown; that there are some flaws to the present gold standard of colonic evaluation; that there is an increased morbidity and mortality in the group of patients with missed SC; that patients have a preference for MRC and for fecal tagging compared to CC and bowel purgation and that there is a potential gain in doing preoperative colonic evaluation with MRC on all patients with rectal- or sigmoid colon cancer.

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