Advances in MRI of the colon and pelvic floor
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Chapter 1

General Introduction and Outline of the Thesis
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Part I: MRI of the colon

First part of this thesis focuses on magnetic resonance (MR) colonography as a method for the detection of colorectal lesions in patients suspected for colorectal cancer. An overview of the results of MR colonography in the present literature is presented and diagnostic accuracy in colorectal polyp detection is estimated. Furthermore, performance characteristics of observers with a different educational background in polyp detection were assessed. Finally, we focused on the gaseous distension of the colon using 3.0T MR colonography. Below, a concise description of colorectal cancer screening, computed tomographic (CT) colonography and MR colonography is provided.

Colorectal cancer

Colorectal cancer (CRC) is one of the most prevalent causes of cancer related death in the Western world. Each year, approximately one million people are diagnosed with CRC worldwide and this cancer accounts for around 500,000 deaths [1]. The adenoma-carcinoma sequence is considered to be crucial for development of CRC, in which an adenomatous polyp advances to a carcinoma in an estimated time-scale of approximately ten years [2].

There is strong evidence that strategies aiming to detect and remove these benign precursors of CRC result in reduced cancer-related mortality and incidence [3,4]. Furthermore the detection of CRC in a confined stage, consequently preventing advanced disease, reduces both cancer-related mortality and morbidity [5]. Thus, early detection of CRC and its precursor is the main objective in population screening programs for CRC [6].

Screening test for CRC either concerns faecal tests or luminal tests. The principal advantage of faecal tests over luminal screening tests, include low-costs and the lack of a pre-procedural bowel preparation. These stool-based tests concern guaiac faecal occult blood test (gFOBT), faecal immunochemical test (FIT) and faecal DNA tests. For gFOBT has been demonstrated that it significantly decreases colon cancer mortality [7], although the test characteristics are rather mediocre. FIT has superior yield (exclusively detects human haemoglobin) and participation rate as compared to gFOBT and is for several countries (including the Netherlands) the preferred screening test [8]. Finally, faecal DNA testing encompasses a fairly novel stool-based test which requires further research [9].

Luminal screening tests seek to detect (precursors of) CRC directly, and include conventional colonoscopy, sigmoidoscopy, barium double contrast examination (barium enema) and computed tomographic (CT) colonography. To
date, conventional colonoscopy is the most accurate technique for adenoma and CRC screening. It combines both the detection of lesions with subsequent polypectomy and histopathology, and is generally recommended in subjects at increased risk for CRC and symptomatic patients [10]. Even though sigmoidoscopy as screening tool has been demonstrated to lead to a reduction in CRC incidence and mortality larger than in gFOBT screening [11], the tendency to develop proximal colon neoplasia with advancing age and therefore polyp-undetectability during distal colon screening, is a recognized limitation [12]. Further, the use of a barium enema is obsolete if other luminal screening tests are available, whereas its accuracies in polyp-detecting are fairly poor [9]. The use of CT colonography in polyp detection is briefly summarized in the next paragraph.

**Computed tomographic (CT) colonography**

Although endoscopy is frequently applied, it entails a rather invasive procedure. Conventional colonoscopy is characterized by a high procedural discomfort, which eventually result in confined participation rates in CRC screening programs [13].

Therefore less invasive luminal techniques have emerged, of which computed tomographic (CT) colonography has gained most interest in the literature in the last decade [14,15]. Overall, based on recent research CT colonography demonstrates an excellent accuracy for detecting clinically significant colorectal lesions.

In CT colonography the patient is scanned in the supine and prone position using a multislice CT scanner, enabling a cross-sectional assessment of the colon and extra colonic structures. For optimal evaluation of the colon, it is either cleansed, using cathartic bowel preparation, or prepared with a faecal tagging agent for mimicking stool rests [15]. High-osmolar iodine contrast tagging is a frequently applied tagging regimen in CT colonography, demonstrating high-image quality already at low tagging doses consequently resulting in lesser patient burden [16]. During CT colonography, the colorectum is distended by the insufflation of carbon dioxide (CO₂) which is mostly achieved by the use of an automated insufflator. CO₂ is quickly absorbed through the colon wall and excreted, therefore resulting in lesser patient discomfort. Furthermore, bowel relaxing agents are used to improve colonic distension and diminishing per procedural discomfort.

Following acquisition, image interpretation includes an two-dimensional (2D) axial read with three-dimensional (3D) comparison for problem solving or primary 3D read with 2D comparison for problem solving. Yet, the accuracy of CT
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Colonography in polyp detecting is significantly determined by reader performance which is inherently correlated with reader experience [17]. Proposed double interpretation strategies to improve CT colonography accuracies include the use of computer-aided diagnosis (CAD) and the use of non-radiologists as second readers.

Magnetic resonance (MR) colonography

An important issue of CT colonography as a mass screening tool applied in average-risk population, is the benefit-risk ratio of the examination related to the cancer risk associated with the radiation exposure [18]. Therefore efforts have been made to obtain a per-examination radiation exposure which is as low as reasonable achievable with maintenance of adequate image quality [19]. Still, the risk is not negligible and consequently a comparable imaging technique with similar accuracy estimates but without radiation exposure would be preferable. Magnetic resonance imaging (MRI) could fulfill this role. The clinical role of MRI in colorectal imaging is increasing and this technique is currently commonly applied in the areas of inflammatory bowel disease (IBD) [20] and rectal cancer staging [21]. Similar to CT colonography for the detection of (precursors of) CRC, in magnetic resonance (MR) colonography the colon is cross-sectional evaluated following colonic distension with the use of a luminal contrast medium [22].

Major impetus for the use of MR colonography in the detection and screening for precursors of CRC, would be the lack of ionizing radiation exposure and the high soft tissue contrast. However, the limited availability, relatively high costs and rather complexity of MR colonography as compared to CT colonography has limited the use of MRI in this area [23]. Nonetheless, several research groups have studied MR colonography [24-26], with however a substantial diversity in proposed bowel preparation methods, luminal distending agents and technical parameters, which makes it rather difficult to interpret and compare the available study data.

Procedural discomfort is dependent of applied study elements, which among others includes the type of bowel preparation and type of luminal distending agent. Traditionally, in MR colonography the administration of a water-based enema has been preferred over gaseous distension due to technical issues related to the presence of artefacts on the air/soft-tissue interfaces, which has negatively influenced patient acceptance of MR colonography [27]. Utilizing gaseous agents as luminal distending agent, as applied in CT-colonography, will
most likely positively influence procedural discomfort but attained only limited interest in MR colonography literature.

**Part II: MRI of the pelvic floor**

Second part of this thesis concerns the evaluation of the female pelvic floor using both conventional static and dynamic MRI techniques which enables to describe the functional pelvic floor support on a macro structural level. Also a more extended MRI technique is introduced to describe micro structural characteristics of the pelvic floor support.

The pelvic floor is multifunctional unit of muscles, fasciae and ligaments that have numerous interconnections and connections to bony structures, organs and the fibro elastic network within fat-containing spaces. Below, a brief description is presented of the basic female pelvic floor anatomy, pelvic floor disorders and the available imaging techniques.

**Anatomy of the female pelvic floor**

*Pelvic diaphragm*

The endopelvic fascia comprises the most superior supporting layer of the pelvic floor. It consists of connective tissue surrounding and supporting the pelvic viscera [28]. The pelvic floor is principally formed by the *pelvic diaphragm* which is generally considered to consist of paired striated muscles, combined recognized as the levator ani muscle and coccygeus muscle, and associated fascia. The levator ani muscle consists of several subdivisions that are defined by their origin and point of insertion (*Figure 1*). The pubovisceral muscle, originating from the dorsal aspect of the pubic bone, supports and elevates the abdominopelvic viscera and is composed of the pubovaginal -, the puboperineal - and the puboanal muscle, respectively (*Figure 2*) [29].

The interior margin of the pubovisceral muscle forms the urogenital hiatus’ border, through which passes the urethra, vagina and anal sphincter. Whereas the key function of these muscles is to support the pelvic viscera, damage of this muscular support will ultimately result in a loss of support and compromised function of pelvic organs [30]. The second subdivision of the levator ani musculature is located at the inferior border of the pelvic diaphragm, this is the puborectal muscle which forms a sling just below the anorectal junction which subsequently forms the anorectal angle (*Figure 2*). During defecation, the puborectal muscle relaxes and the anorectal angle becomes obtuse, facilitating
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defecation. The most posterior subdivision of the levator ani muscle is the iliococcygeus muscle, originating laterally from the *tendinous arch of the levator ani*, (which is formed by the internal obturator fascia) and inserting medially to the anococcygeal ligament and inferior part of the coccygeal bone. The iliococcygeus muscle is frequently poorly developed [31]. Separately from the levator ani muscle, the coccygeus muscle is the posterior constituent of the pelvic diaphragm, arising from the ischial spine and inserting at the lateral side of the coccyx and the lowest part of the sacrum [28].

![Diagram of pelvic anatomy](image)

**Figure 1.** The levator ani muscle seen from above looking over the sacral promontory (SAC) showing the pubovaginal muscle (PVM). The urethra, vagina, and rectum have been transected just above the pelvic floor. PAM = puboanal muscle; ATLA = arcus tendineus levator ani; and ICM = iliococcygeus muscle. (The internal obturator muscles have been removed to clarify levator muscle origins.) (Copyright © Delancey 2003. Kearney R, Sawhney R, Delancey J0. Levator ani muscle anatomy evaluated by origin-insertion pairs. Obstet Gynecol. 2004;104(1):168-73. With permission.)

**Perineum**
The area inferior to the pelvic diaphragm is the perineum which is anatomically demarcated from anterior to posterior by the pubic symphysis, inferior pubic ramus, ischial tuberosity, sacrotuberous ligament and the coccyx. The *urogenital*
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diaphragm comprises a small layer of striated muscle, which covers the anterior aspect of the perineum and encloses the urethra and vagina and is considered as the most inferior layer of the pelvic floor. Although its precise composition is still under debate, among others it comprises both fibromuscular components of the compressor urethra and the external urethral sphincter muscle [28]. Centrally at the posterior border of the urogenital diaphragm, directly anterior of the anal sphincter, the central perineal tendon is located which is organized of several fibromuscular structures converging at this location (\textit{Figure 2}). In women this structure is more distinct if compared to men, and often is defined as the perineal body. Anatomical structures interweaving in this complex area include the superficial transverse perineal muscle, the puboperineal muscle, the bulbospongiosus muscle and fibers of the external anal sphincter [28]. The most superficial layer of the perineum is formed by the bulbospongiosus - , ischiocavernosus - and superficial transverse perineal muscle.

\textit{The anal and urethral sphincter complex}
The anal canal is surrounded by two muscular cylindrical layers which include both the inner layer of the internal sphincter and outer layer comprising the striated external anal sphincter and puborectal muscle. The internal anal sphincter is composed of smooth muscle cells and its function is exclusively involuntary. The lower half of the outer layer is the external anal sphincter. The external sphincter has a voluntary function and is bounded superiorly by the puborectal muscle, which forms the upper outer part of the anal sphincter complex and is also characterized by a voluntary muscle contraction and - relaxation.

Similar to the anal canal, the female urethra is enclosed by two predominantly circular orientated muscular layers. The inner layer consists of a smooth muscle sphincter (lissospincter), the outer layer is formed by a striated muscle sphincter, the rhabdosphincter.

\textit{Pelvic floor disorders}
The pelvic floor provides support to the abdominopelvic viscera, i.e. bladder, vagina, uterus and lower part of the gastrointestinal tract. Also it plays a prominent role in the maintenance of urinary and faecal continence. Therefore, weakening or damage to the pelvic floor support will result in a decrease of support and ultimately in functional pelvic floor disorders such as pelvic organ prolapse and urinary / faecal incontinence. These functional disorders result in a
wide range of symptoms (e.g. incontinence, prolaps) and have a considerable effect on the quality of life [32,33].

Pelvic organ prolapse entails the descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix), or the apex of the vagina in correlation with associated symptoms (e.g. vaginal bulging, increased pelvic pressure) [34]. These associated symptoms are believed to occur if the prolapse reaches the hymen level [34, 35]. It represents an important health care concern, affecting women in particular at higher age. The aetiology of pelvic organ
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Prolapse is complex and multifactorial and is currently only partly understood. It is believed to result from a combination of different causal factors which among others include advancing age, obesity, connective tissue abnormalities, complicated vaginal delivery, denervation and/or weakness of the pelvic floor [36].

An increased weakening and misbalance of the passive and active components of the pelvic support can consequently result in prolapse of unsupported pelvic viscera of at least one of the three anatomical pelvic floor compartments (i.e. anterior, middle and posterior compartment). It can thus involve a pathologic protrusion of the urethra (urethrocele) or bladder (cystocele); vaginal apex or uterus descent (vaginal vault or uterine prolapse); small bowel (enterocele), peritoneum (peritonocele), sigmoid or rectum (sigmoidocele or rectocele, respectively). The severity of both symptoms and the maximum grade of protrusion will ultimately determine treatment of the organ prolapse [37]. If surgical prolapse repair is considered, an adequate preoperative triage is essential to prevent surgical failure. Pelvic floor imaging, to complement frequently used clinical assessment systems [38], currently plays a limited role in the assessment of pelvic floor disorders. However, given the high recurrence rates after initial surgical treatment [39], there is an increasing interest in using additional pelvic floor imaging [40-42].

Imaging of the female pelvic floor

Initially, defecography was the principal diagnostic imaging tool to assess pelvic floor dysfunction and still is frequently applied. Especially in case of a suspected posterior wall prolapse, defecography has been demonstrated to be valuable in the standard diagnostic work-up [43].

In anal incontinence, endoanal ultrasound and to a limited extent MRI are used for the evaluation of anal sphincter anatomy and injury. Translabial or transperineal two -, three - or four dimensional (2D / 3D/ 4D) ultrasound is a clinical easy accessible real-time diagnostic imaging tool in the investigation of pelvic floor disorders which has been increasingly recommended in pelvic floor disorders [44]. The levator ani muscle integrity and the degree of hiatal distension can be easily determined using this dynamic technique, which has also shown high accuracies in the identification of anal sphincter defects [45]. Principal limitations of pelvic floor ultrasound include the operator dependency and the restricted visualization of the complete pelvic floor.
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In the past two decades, both static and dynamic magnetic resonance imaging (MRI) have substantially developed [40,46,47]. The lack of ionizing radiation and the high-contrast evaluation of the complete pelvic floor muscles and pelvic viscera, advantages MRI over conventional X-ray defecography. Limitation is that the MRI examination is performed in the supine position. Dynamic MR imaging permits the evaluation of all three anatomical pelvic floor compartments at rest and during straining, with or without the use of vaginal and/or rectal contrast opacification. By the use of standardized pelvic anatomical landmarks and reference lines, pelvic floor prolapse can be graded [40,48]. Still, the exact correlation of MRI findings with respect to subjective pelvic floor symptoms and prolapse stage is largely unknown and therefore the additional value of dynamic MRI in pelvic floor disorders remains unclear.

Continuing MRI developments currently allow static data acquisition of the pelvic floor with high spatial resolution, enabling the identification of structural levator ani muscle defects [49] and reliable categorization of these structural supportive muscle defects [50]. Towards an advanced understanding of the supportive defects associated with pelvic floor dysfunction, three-dimensional (3D) rendering techniques of high resolution two-dimensional (2D) static pelvic floor MRI images have recently been reported [51]. Evidently, MRI might have the potential to give new insights in the precise pathophysiology which contributes to pelvic organ prolapse, yet current conventional MRI techniques seem to have reached their technical optimisation limits.
Outline of the thesis

This thesis focuses on magnetic resonance imaging (MRI) of the colon and female pelvic floor. *Part I* of this thesis studies MR colonography as a possible imaging technique for the evaluation of the colon.

*Chapter 2* presents an overview of the results of MR colonography in detecting (precursors of) colorectal cancer (CRC) as presented in the literature. Both diagnostic values and patient acceptance of different acquisition methods are discussed. In *chapter 3* the literature on the accuracy of MR-colonography is summarized in a systematic review.

Observer performance plays an important role in measures of accuracy of MR-colonography for detection of (precursors of) CRC. Double read strategies have been effective in limiting inter-observer variability, and the use of trained non-radiologists as potential second readers in MR colonography might be feasible. The aim of *chapter 4* was to assess and compare performance of trained radiographers to the performance of trained radiologists in the detection of colorectal polyps using bright lumen MR colonography examinations.

Prerequisite for an adequate assessment of the colonic wall using MR colonography is an optimal distended colon. The feasibility of automated insufflated carbon dioxide (CO₂) as distending agent in MR colonography, particularly regarding the presence of susceptibility artefacts is evaluated in *chapter 5*. We studied CO₂ insufflation with different applied bowel preparation regimes in terms of image quality and burden.

*Part II* of this thesis focuses on the ability of MRI to study the normal female pelvic floor and to evaluate potential clinical applications, using both frequently used and advanced MRI examination methods.

Static and dynamic MRI is increasingly proposed to supplement clinical data and physical examination in diagnosing and grading pelvic organ prolapse. In *chapter 6* we investigated the reliability of prolapse staging using dynamic MRI, as assessed in women with and without pelvic organ prolapse. In addition, we compared prolapse stages as assessed on dynamic MRI with a standardized method of clinical prolapse staging.

In *chapter 7* we assessed the feasibility of visualizing the normal pelvic floor support in nulliparous women using diffusion tensor imaging (DTI) at 3.0T MRI. In addition we established a range of anisotropic measures for clinically relevant anatomical structures in the pelvic floor. In the study described in *chapter 8*, we prospectively investigated the potential clinical application of DTI...
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and fiber tractography by comparing microstructure tissue parameters of the pelvic floor support of women with pelvic organ prolapse to women without pelvic organ prolapse and to asymptomatic nulliparous women. Also the inter-rater agreement was assessed.  

Chapter 9 contains the summary, conclusions and implications of this thesis. Chapter 10 includes the Dutch translation of the summary, conclusions and implications.
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