

DEPARTMENT OF MOLECULAR MEDICINE AND SURGERY,  
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Karolinska Institutet  
Stockholm, Sweden

**DETECTION AND STAGING OF COLONIC  
LESIONS USING COMPUTED  
TOMOGRAPHY AND MAGNETIC  
RESONANCE IMAGING**

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**Karolinska  
Institutet**

Stockholm 2017

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Published by Karolinska Institutet.

Printed by Eprint AB 2017

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ISBN 978-91-7676-818-1

# Detection and staging of colonic lesions using computed tomography and magnetic resonance imaging

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

Publicly defended in Rehasalen, Norrbacka S2:01, Karolinska University Hospital, Solna

Friday December 15<sup>th</sup>, 2017, 9:00 am

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*Success is not measured by what a man accomplishes, but by the opposition he has encountered and the courage with which he has maintained the struggle against overwhelming odds.*

*Charles Lindbergh*



## ABSTRACT

In Sweden, more than 6000 new patients were diagnosed with colorectal cancer in 2015 of which over 4000 patients had colon cancer and 1800 died from the disease. It is the second most common cancer after breast- and prostate cancer. In the last decade, significant improvement in the treatment of both rectal and colon cancer have been achieved.

Diagnostic imaging, using CT, MRI and PET/CT, has become essential in the preoperative work-up. New neoadjuvant treatment strategies are under study in colon cancer. In the selection of patients for these treatments, pre- and post-treatment imaging has also become of interest. The overall aim of this thesis is to evaluate cross sectional imaging modalities for detection of colonic polyps and staging of patients with colon cancer using CT and MRI.

The aim of paper 1 was to investigate the impact of radiation dose and spatial resolution in detecting colonic polyps in a phantom study simulating computed tomographic colonography (CTC). By using different scanning protocols with different slice -thickness, pitch and tube current we showed that the dose level could be substantially reduced by lowering the tube current without compromising the detection rate for polyps larger than 5 mm.

The aim of paper 2 was to evaluate if high resolution MRI of colon cancer contributed to the standard staging procedure with CT with respect to assessment of local tumour extent, nodal staging and extramural venous invasion (EMVI). An advantage of MRI over CT due to its soft tissue discrimination to identify prognostic factors such as tumour stage and extramural venous invasion was found. The result of nodal staging for both modalities were equally moderate.

The aim of paper 3 was to evaluate commonly used imaging CT criteria for lymph node metastases in predicting stage III disease. Of the different imaging criteria, morphological features performed best specifically internal heterogeneity and irregular outer border. None of the size criteria were predictive.

The aim of paper 4 was to validate morphological CT criteria from paper 3 in a prospectively collected patient cohort using two observers. By using the criteria internal heterogeneity and a combination including irregular outer border, a moderate sensitivity and high specificity was achieved predicting stage III disease.

CT and high resolution MRI can be used to classify colonic tumours into not locally advanced or locally advanced. The prediction of lymph node metastases with the most commonly used image modalities is however unsettled and challenged. In the setting of selecting patients to neoadjuvant chemotherapy, the ongoing trials so far have used inclusion criteria based on tumour T-stage only (T3cd-T4 as locally advanced). Patients with lower tumour T-stage but still have other adverse prognostic feature such as regional metastases will therefore potentially be undertreated and patients with no metastases will potentially be overtreated. Search for other prognostic factors identified on cross sectional imaging has to be performed.



## LIST OF SCIENTIFIC PAPERS

I. **Polyp detection with MDCT: a phantom-based evaluation of the impact of dose and spatial resolution**

Ozgül A, **Rollvén E**, Blomqvist L, Bremmer S, Odh R, Fransson A

AJR Am J Roentgenol. 2005 Apr;184(4):1181-8. PubMed PMID: 15788591.

II. **Potentials of high resolution magnetic resonance imaging versus computed tomography for preoperative local staging of colon cancer**

**Rollvén E**, Holm T, Glimelius B, Lörinc E, Blomqvist L

Acta Radiol. 2013 Sep;54(7):722-30. PubMed PMID: 23550186.

III. **Assessment and diagnostic accuracy of lymph node status to predict stage III colon cancer using computed tomography**

**Rollvén E**, Abraham-Nordling M, Holm T, Blomqvist L

Cancer Imaging. 2017 Jan 19;17(1):3. PubMed PMID: 28103922.

IV. **Morphological predictors for lymph node metastases on computed tomography in colon cancer**

**Rollvén E**, Blomqvist L, Öistämö E, Hjern F, Csanaky G, Abraham-Nordling M

Submitted manuscript.



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## LIST OF ABBREVIATIONS

APC	Adenoma Polyposis Coli
CEA	Carcinoembryonic Antigen
CECT	Contrast Enhanced Computed Tomography
CME	Complete Mesocolic Excision
CRC	Colorectal Cancer
CRM	Circumferential Resection Margin
CRS	Colorectal Surgery
CT	Computed Tomography
CTC	Computed Tomographic Colonography
DWI	Diffusion Weighted Imaging
EMVI	Extramural Vascular Invasion
ENE	Extra Nodal Growth
FAP	Familial Adenomatous Polyposis
FDG	Fluorodeoxyglucose
FIT	Faecal Immunohistochemical Test
FOBT	Faecal Occult Blood Test
HU	Hounsfield Units
ICA	Ileocolic Artery
IVC	Intra Venous Contrast
LS	Lynch Syndrome
MCA	Middle Colic Artery
MDCT	Multidetector Computed Tomography
MDT	Multidisciplinary Team Conferences
MRC	Magnetic Resonance Colonography
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
OS	Optical Colonoscopy
PC	Peritoneal Carcinomatosis
PCI	Peritoneal Cancer Index
PET	Positron Emission Tomography

SCRCR	Swedish ColoRectal Cancer Registry
SE	Spin Echo
SMA	Superior Mesenteric Artery
TNM	Tumour Node Metastasis System
UICC	Union International Contre le Cancer stage classification
WHO	World Health Organisation

# 1 BACKGROUND

## 1.1 EPIDEMIOLOGY

Colorectal cancer is one of the most common cancer in the world with 1.3 million new cases in 2012 (1). According to Sweden, 6759 new patients were diagnosed with colorectal cancer in 2015 of which 4490 patients with colon cancer and 1869 patients died from the disease (2). The incidence is increasing with age and 75% of the patients are over 65 years and only 5% are under 50 years of age. The mortality of colon cancer is slowly decreasing (3) (Figure 1).

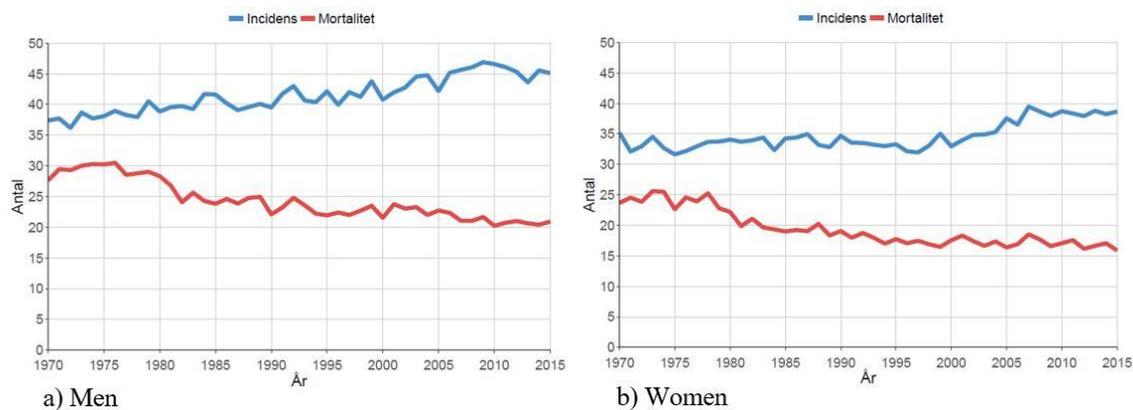


Figure 1. According to age-standardized of incidence and mortality from colon cancer for a) men and b) women per 100 000 individuals in Sweden 1970-2015 (3).

The survival decreases with increasing stage. Of all poor prognostic factors, T-stage is the most important and recent publications show as high as >90% in relative 5-year survival rate in early stage colon cancer (stage I). There are differences and overlap in the 5-year survival between the sub stages of stage II (stage IIA 87%, IIB 63%) and stage III (stage IIIA 89%, IIIB 69%, stage IIIC 53%) (4). Metastatic disease (stage IV) have poor prognosis and as low as <20% in 5-year survival has been reported.

## 1.2 AETIOLOGY OF COLON CANCER

The development of cancer starts in a single cell and through several steps of changing it eventually turns to a cancer cell with capability to invade nearby tissues and metastasize. Those changes are based on the person's genetic and epigenetic factors and control the cells signalling system, cell function and angiogenesis.

Colorectal cancer results mostly from the progressive accumulation of genetic and epigenetic alterations which transforms the normal colonic epithelium to colon adenocarcinoma (5). Other less common cancer forms in colon are carcinoid, leiomyosarcoma and lymphoma.

### **1.2.1 Cancer genetics and epigenetics**

The general description of cancer development from a single cell is genetic and epigenetic modifications that will alter the signal transmission between cells, cell cycle function, genome stability and induce angiogenesis causing uncontrolled cell growth and the ability to disrespect natural borders and metastasize. Adenocarcinomas develops from a normal epithelial gland cell into a cancer cell in several steps and the most well-known pathogenesis is the chromosomal instability pathway also called adenoma - carcinoma sequence (6, 7).

Genetic events along the adenoma-carcinoma sequence lead to the development of sequential transformation from normal to dysplastic epithelium and finally to colorectal cancer by specific genetic changes. Accumulated both genetic and epigenetic alterations of the cellular genome transforms lead to changes from normal glandular epithelium into adenocarcinoma. The genetic mechanisms for cancer development are mainly caused by alterations in oncogenes, tumour suppressor genes and DNA repair genes (8).

The most common genetic cause of CRC development is mutations in the oncogene. KRAS mutations leading to cell growth, proliferation and metastasis (9, 10).

Mutation in tumour suppressor genes causes effects on cell regulation, growth factors and lack of control of apoptosis. The adenoma polyposis coli (APC) gene are mutated in up to 70% of all sporadic adenocarcinomas in colon cancer (11, 12). Other tumour suppressor genes in this family are DCC and TP53 (6, 13).

DNA repair genes (mismatch repair genes, MMR genes) participates in the maintaining the stability of the genome during the DNA replication. There are several mismatch genes known (hMLH1, hMSH2, hPMS2 etc.) and one event of mutation causes non-coding sequences of DNA accumulates called microsatellite instability (MSI) or replication errors (14). If mutations of repair genes occur it will accelerate mutations in oncogenes and tumour suppressor genes. MSI is frequently observed in LS patients and up to 15% of sporadic colorectal cancer (15).

Carcinoembryonic antigen (CEA) is an important standard biomarker in CRC. CEA is a family of glycoproteins predominately on the cell membrane and is overexpressed in CRC and is thought to be involved in the ability to metastasize (16). Because of its poor sensitivity and specificity as a screening tool or in diagnosis in early stage CRC the biomarker is used for predicting prognosis, monitoring recurrence and treatment response (17).

### **1.2.2 Heredity - Family history - Predisposition**

Age is the most important risk factor for colorectal cancer and the incidence is increasing over the age of 50 (3). Based on genetic background most of the acquired colorectal cancer (>80%) are sporadic cancers (18). There are inherited forms of polyposis syndromes such as familial adenomatous polyposis (FAP), Lynch syndrome (LS), (former called hereditary non polyposis coli (HNPCC)) with increased risk of developing CRC.

FAP is a rare syndrome and accounts for ~1% of CRC, where the patients in early adolescence starts to develop small polyps which could be hundreds to thousands of adenomatous polyps in the colon and rectum later in life. Some of the benign adenomas will grow into adenocarcinomas. Annual colonoscopy is recommended from the age of 12 for removal of polyps until total colectomy is performed (19). Nearly 95% of the patients have mutations in the tumour suppressor gene adenomatous polyposis coli (APC) (20). There are variants of FAP depending of mutated genes such as Peutz-Jeghers disease and MUTYH-associated polyposis (MAP).

LS accounts for up to 5 % of CRC and the most common form of hereditary CRC (14). These patients have a mutation in one of the DNA mismatch repair (MMR) genes (MLH-1, MSH-2, MSH-6 and PMS-2). Compared to FAP, patients with LS do not develop the same amount of polyps but the polyps can develop into cancer in 1-2 years. Colonoscopy, at least biannually, is recommended in this group of patients. Patients with LS also have an increased risk of developing cancer in other organs such as endometrium, ovary, stomach, hepatobiliary tract upper urinary tract, skin and the brain.

Environmental and life style factors play a role in the incidence of colon cancer that may induce genetic and epigenetic changes in the cells. Dietary factors as red meat, low intake of vegetables, fruit and fibers have been proposed having an effect on developing colorectal cancer. Obesity and obesity related insulin resistance and associated hyper-insulinemia are assumed to be associated with colon cancer pathogenesis (21, 22). High alcohol intake and smoking also contributes in developing cancer (23). By altering dietary factors as red meat reduction, increase fruit and vegetables intake and lifestyle factors as weight control, increase exercise and reduced alcohol consumption, a reduction of 15-30% of developing colorectal cancer have been estimated (24). Dietary micronutrients such as vitamin A, C, E, beta-carotene and selenium have anti-oxidant or anti-inflammatory effects and are considered to have anti-carcinogenic effect (25, 26). The use of aspirin and related non-steroidal anti-inflammatory drugs has in epidemiological studies and clinical trials have indicated an effect against colorectal cancer but the mechanisms are not fully understood (27-29).

Inflammatory bowel disease, ulcerative colitis, is associated with a cumulative risk of colon cancer and is increasing over the years with the disease (30).

### **1.3 EMBRYOLOGY AND ANATOMY**

Colon can be divided in subparts; the caecum, ascending-, transverse-, descending- and sigmoid colon. The rectum and anal canal are the distal parts of gastro intestinal tract. The anatomical definition of the rectum is at the level of the third sacral segment, where there is no posterior peritoneum, and the surgical definition is at the sacral promontory. The rectum is usually defined as the distal part 12-15 cm from anal verge.

The gastro intestinal tract originates from a primitive tube forming the foregut, midgut and hindgut. The foregut is forming the GI tract to the end of the duodenal ampulla. The midgut is extending from duodenal ampulla to the distal part of the transverse colon and is supplied by

the ileocolic artery (ICA) and the middle colic artery (MCA), both originating from superior mesenteric artery (SMA). The distal third of the transverse colon, descending colon and rectum develops from the hindgut and are supplied by the inferior mesenteric artery (IMA). Between branches of these vessels, the colon segments are supplied by marginal arcades. In the mesentery, in which the bowel is attached, runs the supplying arteries, veins, nerves, lymphatic drainage, local- and regional lymph nodes (Figure 2).

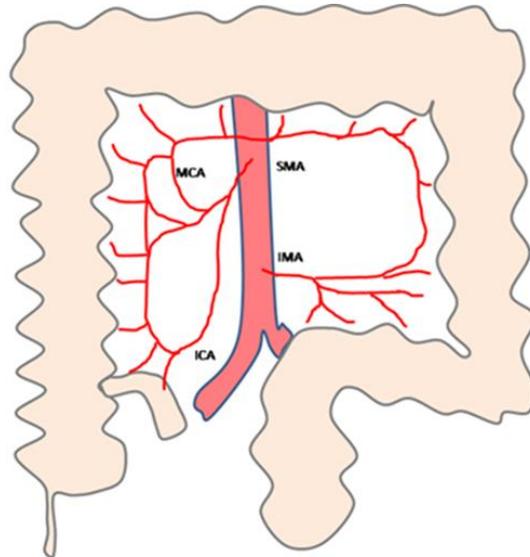


Figure 2. Schematic anatomical figure of the vessel supply of the colon. Note: SMA=superior mesenteric artery, IMA=inferior mesenteric artery, ICA=ileocolic artery, MCA=medial colic artery.

The posterior surface of ascending and descending colon are fused and fixed to the retroperitoneum and the anterior and lateral aspects are covered with serosa, and are to be regarded as intraperitoneal structures. The transverse colon and the sigmoid colon are almost covered with serosa and are regarded as intraperitoneal (Figure 3). Rectum is covered with surrounding fat, mesorectum, and below the peritoneal reflection fixed within this mesorectum.

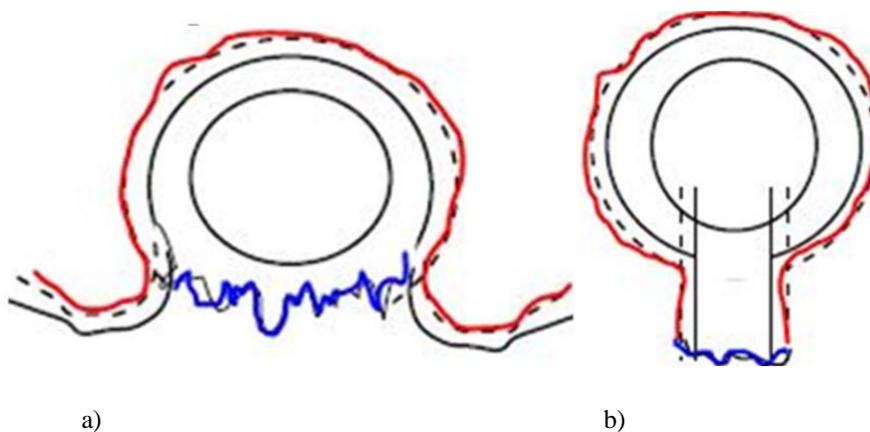


Figure 3. Schematic anatomical figure of peritoneal coverage (red line) and the site of sharp dissection (blue line) in different parts of the colon where a) represents ascending and descending colon and b) represents the transverse colon and the sigmoid colon. Modified schematic figure from SCRCR (31).

The large bowel wall consists of several layers. The epithelium or mucosa, towards the lumen of the bowel, harbours the glands. The muscularis mucosae, the submucosa, the muscularis propria regulates the autonomous bowel movements. The outer layer, serosa, is the fascia towards the peritoneal cavity (Figure 4).

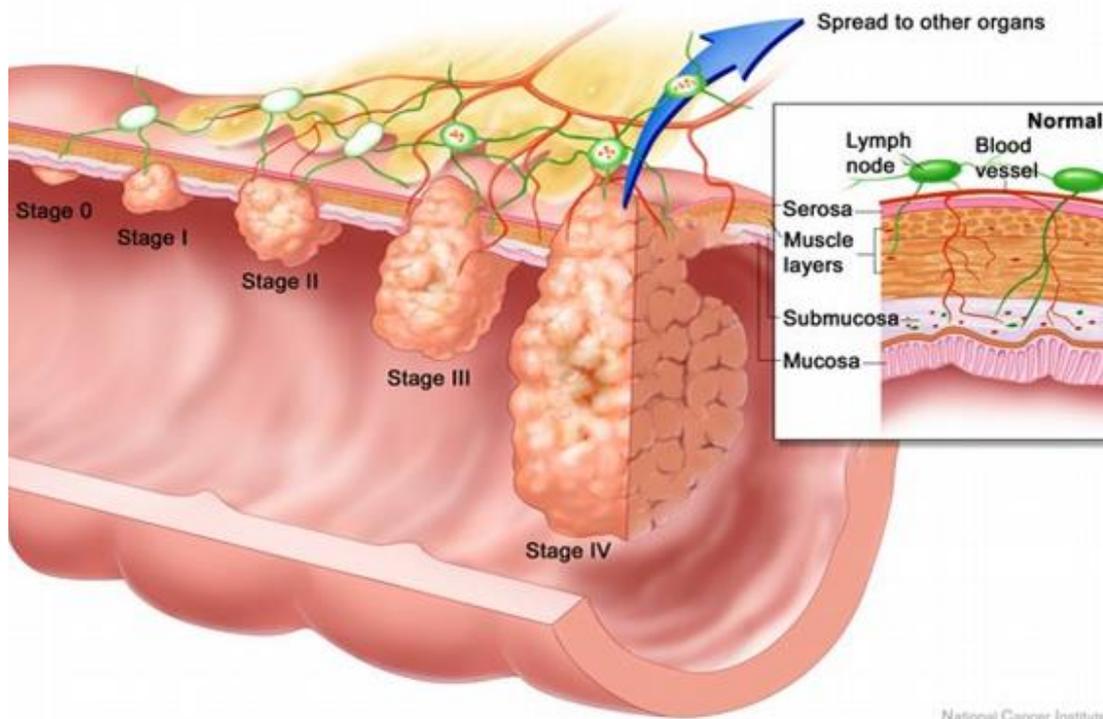


Figure 4. Illustration of colonic wall and different stages of colon cancer (stage 0-IV). For the National Cancer Institute © 2005 Terese Winslow LLC, U.S. Govt. has certain rights.

## 1.4 HISTOPATHOLOGY

### 1.4.1 General

The grading and staging system of CRC is based according to WHO Classification of tumours of the digestive system 2010 and the 7th edition of UICC/TNM Classification of Malignant tumours (32, 33). The adenocarcinomas infiltrates into and eventually outside the bowel wall and tend to bulge into the bowel lumen (Figure 4). Microscopically, the tumour cells are atypical glandular cells and based on the glandular appearance in the microscope the tumour cells are divided into low or high differentiated. Other subtypes of CRC are mucinous adenocarcinomas. These are composed of large pools of extracellular mucin (>50%). Signet-ring carcinomas are tumours with intracytoplasmic mucin. Both these subtypes have poorer outcome with higher rate of recurrence and decreased survival (34-36). Other tumour entities in the colon are carcinoids, lymphomas or leiomyosarcomas. The projects included in this thesis will focus on adenocarcinomas.

After a biopsy of the polyp/lesion or surgical resection, biopsies and specimen are carefully taken care of by a pathologist performing gross sectional examination either on a fresh or paraffin embedded specimen. This is followed by a microscopic examination after staining

using haematoxylin and eosin to visually separate the cell nuclei from other tissue structures for further morphological assessment.

### **1.4.2 Staging TNM**

Colorectal cancer is classified according to the tumour invasion depth of the bowel wall (T-stage), tumour invasion in lymph nodes (N-stage) and presence of distant metastases (M-stage) in the TNM classification system of malignant tumours (TNM) (33) (Table 1). For therapeutic guidance and for prognostic information the TNM stages are combined into an overall stage definition; Union International Contre le Cancer (UICC) (Table 2).

#### *Tumour stage*

The size of the tumour has limited prognostic significance (37). The tumour arises from the glands in the epithelium/mucosa and can grow through the layers of the bowel wall. If the tumour is confined within the bowel wall it is classified as T2. If the tumour is growing outside the layer of muscularis propria and out in the surrounding mesenteric fat it is defined as T3. Depending on the depth of extra mural tumour extent, T3 tumour stage can be further subdivided in T3a (1mm tumour extent outside the MP), T3b (<5mm), T3c (5-15mm) and T3d (>15mm). If the tumour is growing directly into the peritoneal cavity through the serosa layer or to an adjacent organ or structure the tumour is classified as T4.

#### *Nodal stage*

The lymphatic drainage and lymph nodes runs along the vessels (arteries) within the mesentery. The lymph nodes adjacent to the tumour are called local lymph nodes and the lymph nodes more central in the mesentery are called regional lymph nodes. Lymph nodes around the aorta are categorised as distant lymph nodes and is not part of N-stage classification. Lymph nodes maybe be gradually infiltrated by tumour and normal lymph node cells will be replaced by tumour cells. If further invasion the tumour cells occur tumour will grow outside the lymph node, so called periglandular growth.

#### *Metastases*

The mechanisms for tumour spread are vascular (haematogenous), lymphogenic, perineural or direct spread into the peritoneal cavity and other organs (38, 39). In haematogenous spread, tumour cells spread through the blood stream to distant organs. The lymphatic spread originates from local lymph nodes and follow the lymph vessels to regional and distant lymph nodes and then enter the systemic circulation and thereafter distant organ metastases (39). Distant metastases are mainly located in the liver, lungs and central lymph nodes around the aorta and in the peritoneal cavity (peritoneum), but other locations could also be present such as the brain and bone (40). Presence of liver metastases has been reported as high as 15-23% in patients with CRC at the time of diagnosis and up to 50 - 70% will develop liver metastases at follow up (41, 42). The second most common metastatic organ is the lungs but pulmonary metastases are more common in rectal cancer than in colon cancer. This is thought to be due to the venous circulation and the rectal veins are connected with the systemic

circulation whilst the veins colon drains via the portal veins to the liver (43). The main importance of this is that rectal cancer may spread into the lungs before metastasizing to the liver. Presence of small (<10 mm) nodules in the lungs on CT is sometimes difficult to interpret regarding their significance. These intermediate nodules are therefore re-examined in follow up program (31). In absence of liver metastases, there is a small risk of having lung metastases alone (44, 45). In absence of metastases in the liver or the lungs, other organ sites are uncommon (46).

T-Tumour stage	T1	Tumour growing in the inner surface, mucosa/submucosa
	T2	Tumour growing into the muscularis propria layer
	T3	Tumour growing outside the wall - T3a, T3b, T3c, T3d
	T4	T4a - Peritoneal spread    T4b - Adjacent organ or structure
N-Nodal stage	N0	No lymph node metastases
	N1	1-3 lymph node metastases - N1a, N1b, N1c (td)
	N2	4+ lymph node metastases - N2a, N2b
M-Metastases	M0	No metastases
	M1	Distant metastases - M1a, M1b

Table 1. TNM classification 7<sup>th</sup> edition.

AJCC/UICC staging system		T-stage	N-stage	M-stage
Stage 0		Tis	N0	M0
Stage I		T1, T2	N0	M0
Stage II		T3, T4	N0	M0
	Stage IIA	T3	N0	M0
	Stage IIB	T4a	N0	M0
	Stage IIC	T4b	N0	M0
Stage III		Any T	N1, N2	M0
	Stage IIIA	T1, T2	N1	M0
		T1	N2a	M0
	Stage IIIB	T3, T4a	N1	M0
		T2, T3	N2a	M0
		T1, T2	N2b	M0
	Stage IIIC	T4a	N2a	M0
		T3, T4a	N2b	M0
		T4b	N1, N2	M0
Stage IV		Any T	Any N	M1
	Stage IVA	Any T	Any N	M1a
	Stage IVB	Any T	Any N	M1b

Table 2. Classification for colorectal cancer according to AJCC/UICC staging system.

### *Residual Tumour Classification and circumferential resections margins.*

The residual tumour classification reflects tumour status after surgery and demonstrates absence or presence of tumour at the resection margin (33) (Table 3). Tumour near or reaching the circumferential resection margin is referred as circumferential resection margin (CRM) positive. When performing surgery it is important to know if the standard surgical procedure has to be modified to achieve R0 resection. If the surgical margin is involved or if the distance is short (<1mm) the risk of recurrent tumour is high and the prognosis worse than if there is a R0 resection or involvement of the CRM (47, 48).

---

R0	No residual tumour, minimal distance between tumour and resection margin >1 mm
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

---

Table 3. Residual Tumour Classification.

### *Histopathological prognostic factors*

Poor prognostic factors beyond high stage are factors that worsen the prognosis and outcome for the patient. Examples of those recorded in the pathologists report are; tumour invasion in veins (EMVI), lymph vessel or perineural spaces. If a tumour extent beyond the bowel wall the tumour can infiltrate the nearby small veins (EMVI) and lymph vessels. Regarding venous invasion additional immunohistochemical tests with the endothelial marker CD31 and CD34 and for lymphatic marker D2-40 can be used. Extra nodal extension growth (ENE) is associated with poorer outcome as overall survival and risk of recurrence (49).

### *Biomarkers*

Many biomarkers are described in literature but not in standard use. To get additional information from the tissue, biomarkers as microsatellite instability (MSI) and chromosomal instability (CIN) can be tested, potentially useful for deciding further treatment (50). For patients suitable for adjuvant treatment biomarkers for mutation of KRAS and BRAF can be used (51).

## **1.5 COLON CANCER DIAGNOSIS**

### **1.5.1 Clinical and laboratory**

Since 2016 new care flows for management of cancer have been introduced in Sweden. These are called SVF (standardiserat vårdförlopp) or standardized care flows. Patients with symptoms indicating colorectal cancer are categorised into degrees of suspicion of having a colorectal tumour. Examples of symptoms are altered bowel habits, blood in stool, anaemia and weight loss. The new management aims at shortening the investigation time for colonoscopy, histopathology and imaging to diagnose and start treatment within certain time limits (31).

Patients with suspected colorectal disease are first clinically examined including rectal palpation and procto-rectoscopy. Laboratory test as faecal occult blood test (FOBT) or faecal immunochemical test (FIT) and serum carcinoembryonic antigen (CEA) are performed (31).

In Stockholm-Gotland a screening program is ongoing (age 60-69) since 2008 using FOBT biannually. The Screening for Swedish Colons (SCREESCO) study started in 2014 to compare screening strategies such as colonoscopy or FIT. Screening for colorectal cancer has been found to be cost effective compared with no screening with favour for repeated colonoscopy (52).

### **1.5.2 Optical Colonoscopy (OS)**

Flexible sigmoidoscopy or OS is the first line examination after clinical examination. The examination is performed after a fully cleansed bowel. If suspicion of a polyp or a tumour, multiple biopsies are taken and analysed by a GI pathologist. A complete OS of the whole colon requires caecal intubation and the procedure is highly dependent on the individual expertise of the endoscopist (53). As a quality level for a successful OS >90% is recommended (54). When the whole colon can not be visualised by OS the examination is reported as incomplete. The reported rate of incomplete OS is approximately 10-15% (55, 56).

### **1.5.3 Computed Tomography (CT)**

A computed tomography (CT) scanner consists of a X-ray generator and a detector, placed in diametrically opposite side, that rotates around an object (i.e. the body of a patient) and measures the density of tissues. The technique was rewarded the Nobel Prize in 1979 (57). The first scanners in the late 1970's consisted of one X-ray source and one opposite detector. After one rotation of the x-ray source and detector the patient moved and the next rotation was initiated. Only axial images were obtained with this technique. Later, developments resulted in faster acquisitions, continuously moving table and newer detector configurations than single-slice CT allowing volumetric examinations to create images in various planes. Today the modern CT scanner has developed to have sub millimetre multidetector configuration called multidetector-CT (MDCT) and offers fast scanning time, multiplanare image reconstructions in 2D and 3D and offers different optimization techniques for radiation

dose reduction. A further development is Dual Energy Computed Tomography (DECT). It is a technique that have been available since the late 2000s. The technique combines two different spectra of energy based on their tube voltage (often 80 and 140 kV) to separate and characterize the body tissue. DECT has been used for subtraction of high density material such as bones, osteosynthesis material and kidney stones but could also be used for iodine quantification in tumour volume assessment. Some studies have also shown the potential to reduce radiation dose using DECT compared to commonly used (single energy) CT (SECT) (58).

In colorectal cancer, a full examination of the thorax and abdomen is performed to stage the tumour and presence of distant metastases. The examination is performed with intra venous contrast (ivc) material which is administered via a peripheral venous catheter. The CT scan protocol is generally performed using a multi detector CT with 64 slices or more detectors that generate sections which are typically in order of 0.625 mm thick. The original sections can be reconstructed to thicker image slices, normally 2-5 mm, in three orthogonal planes; axial, sagittal and coronal. The scans are normally acquired in the portal-venous phase when the contrast medium has reached the solid vascularized organs of the body. When tumour staging is addressed, scanning is typically performed in three different phases; native (before ivc), arterial phase and portal-venous phase mainly in order to assess the liver. If suspicion of focal lever lesions (not benign) dedicated ultrasound (including intravenous contrast agent – micro bubbles) or MRI examination of the liver is performed.

#### *Computed Tomographic Colonography (CTC)*

CTC is an alternative to OS and was mainly introduced when CT went from single slice to multi slice thus enabling thin slices and more volumetric applications. The technique was described in the 90's (59, 60). CTC has out concurred the former colon examination method of double-contrast barium enema (DCBE) (55). In CTC, not only cross sectional imaging of the bowel and adjacent organs can be performed but also allowing assessment of the bowel wall by distending the bowel with air or carbon dioxide. The examination is evaluated using 2D and 3D-reconstructions (fly-through) in a manner that makes some of the visual interpretation similar to OS. Even though OS is the golden standard for polyp detection, the false negative rate using this technique has been reported as high as over 25 % (61-63). For detecting CRC, CTC is comparable to OS (64, 65). In order to locate the tumour site CTC performed better than OS especially in the left colon (66). In cases of incomplete preoperative OS when there is no possibility to evaluate the colon proximal to the tumour, CTC can therefore be useful to assess the whole colon. This examination is also useful when the patient cannot tolerate OS. CTC is less invasive than OS and the detection accuracy in both high-risk population and low prevalence group are similar. There are guidelines regarding clinical indications for CTC from European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and also a consensus statement how to perform, interpret and report CTC (55, 67).

When performing CTC, the patient is examined in both prone and supine position after bowel cleansing and gas (CO<sup>2</sup> or air) administered via a catheter in the rectum to distend the colon. CTC can also be performed without intra venous contrast and with lower radiation dose compared with the dose used for tumour staging. The low dose technique is used when detection of polyps is the primary issue, such as for screening purposes and as an alternative to OS. The radiation dose depends on the tube voltage, tube current setting, the pitch factor and the collimated beam size. To adapt CT to a low-dose configuration there will always be a trade-off between the radiation dose and spatial resolution. A typical low-dose protocol consists of high tube voltage and low tube current and high pitch. This will create images suitable for detection of intra luminal findings in the colon but no assessment of bowel wall or parenchymal findings. There are different approaches to colon cancer screening in the world. In Sweden there is an ongoing study and screening program (SCREESCO) for patients between 59-62 years of age comparing colonoscopy and a modified F-Hb test so called FIT. CTC has a high sensitivity for polyps/tumours  $\geq 6\text{mm}$  (68).

#### **1.5.4 Magnetic Resonance Imaging (MRI)**

Nuclear magnetic resonance (NMR) technique has originated from the early 1930-40. The technique has developed massively during the following years and many research groups and researchers have contributed to its success which have been rewarded with the Nobel prize in 2003 (69). MRI uses the electromagnetic activity of atomic nuclei (the protons). The protons are positively charged and have spins around its own axis. In MRI, the technique is based on odd numbered nuclei and the spins of the protons and neutrons do not cancel each other out and induces a magnetic field. In clinical MRI hydrogen protons is used because of the vast amount of in the body in forms of water and fat. When the hydrogen protons are into a MRI scanner, which consists of a great outer magnetic field ( $B_0$ ), the hydrogen protons spin interacts with the external field causes the nuclei to wobble or precess. Some protons are parallel to the magnetic axis and some are in the opposite direction. The sum of all magnetic moments is a net magnetization vector ( $M$ ).

To generate images in MRI, radio frequency pulses (gradients) in the magnetic fields are generated. These gradients will form differences in the magnetic field in defined directions in the body. When the gradients are turned on the  $M$ -vector will flip and when the gradients are turned off the protons will return to the relax state and emit radio frequency waves and an antenna coil will receive the signal to be used for further image creation. There are two main types of pulse sequences to generate images; spin-echo (SE) and gradient echo (GRE) sequences. The SE sequences are designed to reduce the artefacts due to inhomogeneities in the magnetic field and take a relatively longer time to accomplish than GRE sequences. The GRE sequences on the other hand are more sensitive for those artefacts but are much faster. There are numerous variants of these pulse sequences.

By varying the different parameters of the pulse sequences, image contrast can be produced between different tissues depending of the relaxation characteristics in the body.

To create contrast in the morphological images, the different tissues T1 and T2 effects are used. The T1 effect represent the time after a RF pulse to restore magnetization in the longitudinal plane and T2 effect represent the dephasing of protons after a RF pulse in the transverse plane.

In T1w imaging the goal is to present the difference in T1-relaxation between different tissues depending on their proton/fat content. Fat relax relatively fast and water relatively slow. In these images fat will appear with a high image signal intensity and water with a low image signal intensity.

T2w imaging is mostly based on SE sequences (usually turbo or fast SE, TSE or FSE). In T2 imaging water will appear with high and fat with moderate signal intensity. Depending on the degree of T2-weighted imaging used, images can either display different tissues or water only content as in magnetic resonance cholangiopancreaticography (MRCP).

Modern clinical MRI scanners typically use a static magnetic field of 1.5 or 3.0 Tesla (T). For some purposes even higher field strengths are used as high as 7.0 T or more, in particular in the research setting. To receive the signal (radio waves) from the body parts, coils (or antennas) are used. There are different types of coils, in build coil in the scanner or surface body coils, to be attached on the body part examined. Several surface coils can be connected together to cover a larger examination area – so called phased array coils.

In rectal cancer, MRI has for more than a decade been the modality of choice for local staging of the tumour. Dedicated protocols based on T2w imaging in three orthogonal planes; axial, sagittal and coronal, and an additional plane perpendicular to the tumour to assess the extension and tumour penetrating the bowel wall can be performed. For colon cancer there is a broad range of anatomy to consider when performing MRI. MRI of the colon is generally more time consuming and sensitive for motion artefacts (breathing or bowel movements) depending on which part of the colon. To reduce motions artefacts breath-hold sequences are usually preferable. To reduce bowel motion artefacts spasmolytic drugs are also recommended.

#### *Applications for MRI examinations of the colon*

MR colonography (MRC) is a technique to detect colonic lesions with MRI. MRC requires the same bowel preparations as CTC and oral contrast tagging material is preferable (70). Even if prolonging the scanning time, dual positioning is the most recommended use (71). As in CTC, an antispasmodic drug is used to minimize bowel peristalsis. Intravenous contrast agent could also be used to differentiate between polyps and residual stool, fluid and air. To cover the entire colon it is preferable to use surface coils in conjunction with the body coil. MRC can be performed in two ways; with bright-lumen or dark-lumen technique. In

detecting colonic lesions MRC have similar reported sensitivities and specificities compared to CTC but the major drawback is the low detection rate for polyps <5mm (72, 73).

The term bright-lumen MRC is referred to installation of water and diluted gadolinium (Gd) chelate solution in the bowel. Pockets of air will be black and interfere with the interpretation of intra luminal lesions. The dual positioning is mandatory with this technique.

The term dark-lumen MRC is referred to the bowel lumen is dark by insufflation of air or carbon dioxide for the distention of the colon as in CTC and this technique is more used in the clinical practice compared to bright lumen MRI (74). Some interference of residual water tend to occur when using this technique.

Both bright and dark lumen colonic MRI have not gained clinical acceptance as an alternative to OS such as CTC. Reasons for this are the technical challenges and cost.

#### *High resolution MRI*

When performing tumour staging it is important to have adequate pulse sequences and receiver coils (usually phased array surface coils) with high spatial resolution and acceptable signal to noise ratio (SNR).

#### *Diffusion weighted imaging, DWI*

Diffusion weighted imaging was not used in this thesis but today the technique is used in most oncological MR protocols to distinguish normal healthy tissue from pathological and for evaluating treatment response. The technique refers to the assessment of the random motion of water molecules in tissues is hampered in high cellularity tissues and areas such as tumours by using diffusion weighted gradients to create contrast in MR images. Areas with hampered or restricted diffusion will appear with high signal intensity as bright areas on DWI images. The condition could also appear in tissue inflammation or in abscesses. The DWI sequence used is a fast T2 weighted sequence combined with diffusion gradients (b-value). When using at least two diffusions gradients (two b-values), the diffusion can also be quantified measuring the apparent diffusion coefficient (ADC) (75). Some tissues, such as lymph nodes, will appear with relative impeded diffusion compared to surrounding tissues. This will facilitate detection of these tissues. For characterization, such as distinguishing between lymph node involved by malignant tissue or not, it is hazardous because of minor difference and overlap between diffusion in benign and malignant lymph nodes due to high cellularity in a normal lymph node (76).

### **1.5.5 Positron Emission Tomography (<sup>18</sup>F-FDG) PET/CT**

Positron emission tomography (PET) is a nuclear medicine technique often referred as functional imaging, obtaining the metabolic and biochemical activity in the body. PET is based on the decay of unstable radioactive positron emitting isotopes and measures the two annihilation gamma photons. The most commonly radiotracer used in oncology is (fluorine 18)fluoro-deoxy-glucose (<sup>18</sup>F-FDG) and is produced in cyclotron and have a half-time decay

of ~100 minutes and therefore suitable for medical imaging. The FDG molecule is a glucose analogue where oxygen is replaced with 18-fluorine. One of the mechanisms to absorb glucose into the cell is via the system of active transportation proteins (GLUTs) (77). Both glucose and FDG are phosphorylated within the cell and glucose is used for energy production. FDG on the other hand is trapped and cannot move further on. Cancer cells tend to have elevated expression of transport proteins and higher metabolic activity and also use other pathways for glucose uptake than normal tissues (78). Therefore, FDG tend to accumulate in cancer cells. Inflammation and hyperactivity of muscles will also accumulate FDG due to normal increased metabolism.

The combination of FDG-PET/CT combines anatomical information from CT and functional information in forms of uptake of radiolabelled substances from FDG-PET. In colorectal cancer imaging this examination is not part of the routine work up in primary colon cancer staging and mainly used before major surgery, detection of distant metastases when conventional imaging is unequivocal or for work up of recurrent disease (79).

## **1.6 DIAGNOSIS IMAGING FOR STAGING OF COLON CANCER**

Accurate preoperative staging in colorectal cancer is essential for evaluating local tumour extent and presence of metastases for treatment planning and evaluation of prognosis. After local or systemic pre-operative treatment re-staging may result in altered management.

### **1.6.1 CT**

The standardized work up for patients with colorectal cancer is contrast enhanced CT of the thorax and abdomen for evaluation of local tumour spread and presence of distant metastases. The main purpose of the examination is to exclude metastatic disease but it is also important to evaluate the local tumour extent, in particular presence of locally advanced disease to be able to adequately prepare and perform the surgical procedure. There are parts of the colon that are more challenging to evaluate due on one hand close presence to nearby organs and on the other hand circumferential serosal coverage. Bowel preparation prior to the examination is often not used and has probably little importance.

#### *ctT-stage*

For tumour staging with CT, the muscularis propria is not visible in the same extent as with MRI. For the lower T-stage is not possible to discriminate T1 and T2 tumours. To evaluate if the tumour is growing outside the bowel wall (T3) it is important to have perpendicular images over the tumour area. If the bowel wall in that area is indistinct or bulging there is a risk of tumour extension in the surrounding fat. If the tumour extension is limited to the mesocolon it is measured and classified into T3a-d. There could be other reasons for indistinct bowel wall than tumour due to inflammation or oedema. For anatomical reasons

there are parts of the colon with little amount of surrounding fat and a short distance to the serosa.

#### *ctN-stage*

No imaging modality has yet proven to accurately identify lymph nodes metastases in colorectal cancer. Regarding cross sectional imaging, and particular for CT, widely accepted criteria for assessing lymph nodes metastases have not yet been established. Various criteria have been used. Short axis of more than 10 mm, short-long axis diameter ratio, internal heterogeneity, irregular outer border, attenuation values > 100 HU, cluster of at least three “normal” sized lymph nodes or a various combination of those have all been used in the literature (80-86) (Figure 5). The diagnostic accuracy for detection of lymph node metastases on CT has also been analysed in a meta-analysis of eleven studies and 753 patients with a sample weighted sensitivity/specificity of 76/55 % respectively (87). Normal lymph nodes appear as homogenous oval structures with well-defined borders.



Figure 5. Tumour in the ascending colon, pT4a+b (tumour invades directly the ileum and having serosal components). pN2b, lymph node with irregular outer border (white arrow) and lymph node with internal heterogeneity (white and black arrow).

#### *ctM-stage*

Distant metastases are defined as metastases localized beyond the lymph node metastases in the large bowel mesentery; in the paraaortic lymph nodes, peritoneum, liver, lungs, skeleton and brain, the latter less common. The most common metastatic sites are the liver and the lungs (46). If high suspicion of distant metastases on CT further investigation is needed according to the care flow to tailor treatment (31). On CT, liver metastases usually appears as focal more or less indistinct defined low attenuating lesions separated from benign well defined benign cyst, which are common finding (Figure 7). For further assessment and for treatment planning dedicated MRI examination of the liver is offered. For indeterminate pulmonary nodules, a follow up is often recommended by the MDT (31).

## 1.6.2 MRI

The main benefit of using MRI in colorectal oncological imaging is the high soft tissue contrast resolution and the functional capabilities. In rectal cancer MRI has been routinely used since the past two decades for local tumour staging (88-91). The pelvis and in particular the rectum is nearly ideal for MRI examination due to its fixed location. In the colon, the anatomy and the course of the bowel is more complex. As in rectal cancer, an MRI of a colonic tumour is performed with fasting but without intra venous contrast and no other bowel preparations (no cleansing). The major and most important sequences are T2w sequences in three orthogonal planes and one high resolution sequence perpendicular to the bowel over the tumour. Visualization and location of the tumour can be challenging when using MRI specially when planning the perpendicular imaging over the tumour to assess the extent of the tumour within or through the bowel wall into the neighbouring tissues. Motion artefacts related to bowel movements or breathing are also more frequent occurring and challenging in the colon compared to the rectum. To reduce motion artefacts, careful patient instructions, surface coil positioning and spasmolytic drugs are all used. The MR procedure is generally more time consuming than a CT examination and often requires a radiologist on site to plan and monitor the examination, in particular position of slices perpendicular to the bowel wall at the level of the tumour.

### *mriT-stage*

The bowel wall is consisted of several layers (Figure 4). The inner layer, towards the bowel lumen, is the mucosae and muscularis mucosae which will appear as a thin dark band on T2w imaging, and not always visible. The submucosa will appear as a bright band between the muscularis mucosae and the propria muscle. The next layer is the muscularis propria (MP) which appear dark on T2w imaging. This muscle is a landmark for distinguishing T2 from T3 tumours. If this muscle layer is partially disrupted by a tumour this is a sign of a T2 tumour. If the layer is fully disrupted it is a sign of full thickness T2 or limited extra mural extension. If the tumour extends beyond the MP and extends in the surrounding fat, the tumour will be staged as T3 or T4a depending on whether the tumour is present on a peritonealised or non-peritonealised surface (Figure 6).

### *mriN-stage*

For nodal staging in rectal cancer, morphological criteria are used when performing MRI. If the lymph node (>3mm) showed internal heterogeneity and/or irregular outer border or low signal on T2w images it is regarded as metastasis with a reported sensitivity and specificity of 85% and 97% respectively compared to histopathology (92). In colon cancer, there are so far no such adopted criteria for mriN-staging.

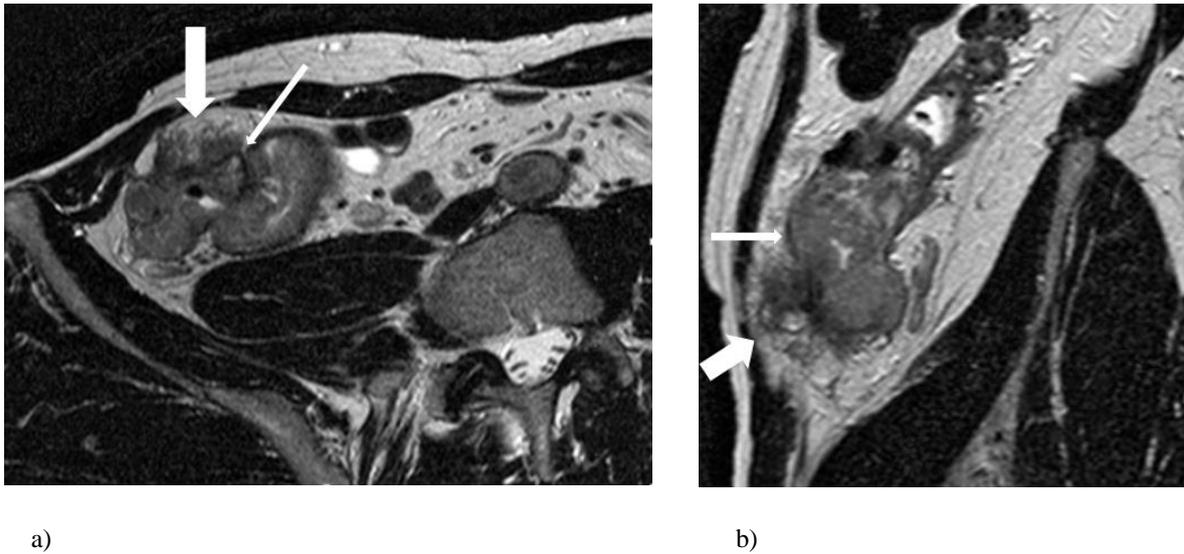


Figure 6. T2-weighted MR images of tumour in the caecum and ascending colon. a) Axial perpendicular plane b) Sagittal plane. Narrow white arrows show muscularis propria as a dark band. Bold white arrows show extramural tumour extensions in the fat involving the anterior abdominal wall.

#### *mriM-stage*

MRI is particular used when focal liver lesions cannot be characterised by multiphasic CT. The standard protocol for liver lesions such as metastases includes morphological T1 and T2 axial sequences, in and out of phase sequences, dynamic T1 sequences after intra venous contrast and DWI sequences.

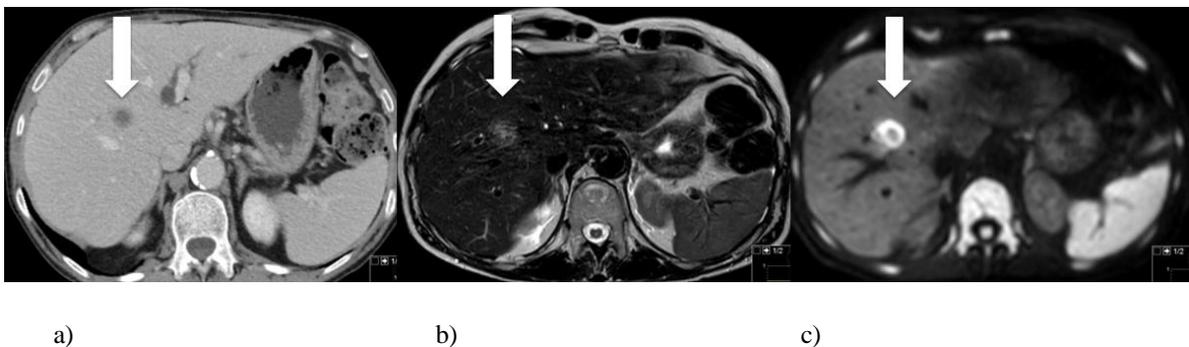


Figure 7. Focal metastasis in the right liver lobe (white arrow). a) On CECT ill-defined low attenuated. b) Moderate high signal intensity on T2-weighted MRI image. c) High signal intensity on DWI image (b-value: 800 s/mm<sup>2</sup>).

Ultrasound (US) can be used for characterization of solitary liver lesions. MRI offer better sensitivity regarding evaluation of the number of metastases compared both CT and US. MRI is the standard modality for treatment planning when liver surgery is an option for curative treatment in CRC (93-95).

### *Further prognostic feature on MRI*

Extramural vascular invasion (EMVI) is associated with poor prognosis in rectal cancer (91, 96). On MRI, the normal small vascular structures present with a serpiginous or tortuous appearance with tumour signal on T2-weighted images. A recent study reported that MRI could accurately predict EMVI compared to histopathology in rectal cancer (97).

### *Potential circumferential resection margin*

When the potential circumferential resection margin (CRM) is involved at imaging this means that the tumour extends within one mm from the original embryological plane or affecting nearby structures or organ(s). In the colon, the CRM is the retroperitoneal fascia. When involved this requires modified surgical resection to achieve macroscopically tumour free resection (R0 resection).

### **1.6.3 <sup>18</sup>FDG-PET/CT**

<sup>18</sup>FDG-PET/CT is well established as a diagnostic tool in the evaluation of patients with rising carcinoembryonic antigen (CEA) and suspected local recurrence or metastases of colorectal cancer, as shown in a recent review (79). There is not sufficient evidence to use <sup>18</sup>FDG-PET/CT in the primary staging unless conventional staging indicates need for additional information. When major surgery of locally advanced or recurrent disease is considered <sup>18</sup>FDG-PET/CT can be suggested at the MDT conference (98) (Figure 8).

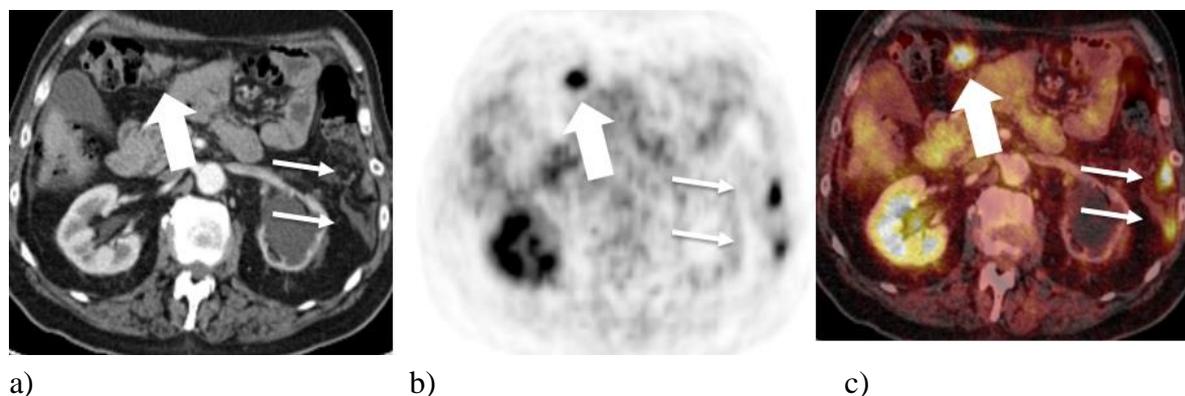


Fig 8. Recurrent disease. Metachronous tumour in the transverse colon (white bold arrow) and peritoneal carcinomatosis in the left side of the peritoneal cavity (white narrow arrow) on a) contrast enhanced CT (CECT), b) FDG-PET and c) fusion image.

## **1.7 MULTIDISCIPLINARY TEAM CONFERENCES**

To optimize the management of oncological patients, multi-disciplinary team (MDT) management is gaining acceptance to individualize the treatment and has been shown to improve the oncological outcome (99). The team members represent different medical specialties; surgeons, oncologists, radiologists, pathologists and coordinators. CRC patients are individually discussed both pre- and post-operatively.

## **1.8 PRE-TREATMENT**

In colon cancer, no routine pre-treatment is performed. For some patients with metastatic disease or locally advanced colon cancer, preoperative chemotherapy can be given. The neo-adjuvant treatment is discussed in section 1.10.1.

## **1.9 SURGICAL MANAGEMENT**

### **1.9.1 Polypectomy**

Small tumours, limited to a polyp without any signs of spread through the bowel wall, to lymph nodes or vessels can in some patients be locally excised through a colonoscope.

### **1.9.2 Conventional open surgery**

Colon cancer surgery is divided into right sided hemicolectomy, left sided hemicolectomy, sigmoid resection and total colectomy depending on the site of the tumour. Surgical treatment for colon cancer surgery should be performed in an elective setting, if possible, to obtain best curative and oncological outcome (100). In the emergency setting, due to bowel obstruction, perforation or bleeding acute interventions are sometimes inevitable. In such instances, limited procedures not jeopardizing the oncological outcome such as temporarily ileostomy is performed and leave cancer surgery to a well-planned elective setting. The general contemporary treatment of colon cancer is the complete mesocolic excision (CME) concept by surgical removal of the tumour containing segment together with local and regional lymph nodes within the mesocolon en bloc tying of the supplying vessels as central as possible (i.e. “high tigh”) (101). Surgery is performed by sharp dissection within the holy plane between the visceral and peritoneal fascia layers that are fused together. For colon cancer this CME method was introduced by Prof Hohenberger and has proven to reduce the recurrent rate and improve survival (102). According to the location of the tumour the surgical approach can either be from the medial or the lateral side. Tumours located in the flexures and transvers colon often requires extended dissection of the vessels and lymph node beneath the pancreas and gastroepiploic arcade to require a R0 dissection (103). After the tumour bearing segment is removed the remaining bowel ends are reconnected by sewing or staples in an anastomosis. In some cases, a temporary colostomy is considered if the bowel ends cannot be fused together or to unload the anastomosis until the bowel can be reconnected.

### **1.9.3 Laparoscopic surgery**

This procedure is less invasive than open surgery. Percutaneous incisions into the peritoneal cavity are performed to administer camera and instruments. A laparoscopic procedure is often the method of choice in non-locally advanced cancers without any complicating factors.

### **1.9.4 Treatment of distant metastases**

At diagnosis, approximately up to 20% of patients with colorectal cancer present with metastatic disease (3, 42). The most common distant metastatic site is the liver and up to 50 - 70% of the CRC patients will develop liver metastases (41, 42). The mortality in metastatic

CRC when the liver is the metastatic site is primarily determined by the burden of liver metastases (41). If metastases, especially in the liver, are present this does not exclude the patient from curative treatment or to achieve hepatic tumour control. At the MDT conference, the most appropriate sequential treatment to surgically remove both primary tumour and distant metastases either at the same time or different occasions is discussed. If a two-stage procedure is preferred, it is also discussed whether to remove the primary tumour or the metastasis/metastases first. Surgical treatment (removal) of liver metastases is the only curative treatment and increases the chances for prolonged survival (104, 105). The possibility of surgically removal of liver metastases is dependent on the size of the future liver remnant is adequate (104). If the liver metastases are not primarily resectable, local treatment of liver metastases can also be performed by minimally invasive procedures as local radiofrequency ablation (RFA), microwave ablation, cryoablation or chemoembolization or local chemotherapy (106, 107). For some patients or in controlled trials systemic chemotherapy can downsize the metastasis for later removal (108). For metastases in the lungs, treatment with chemotherapy and/or surgical resection is feasible according to national guidelines (31).

### **1.9.5 Treatment of peritoneal carcinomatosis (PC)**

Beyond the mechanisms of haematogenous and lymphatic tumour spread, colon cancer frequently cause transcoelomic spread from serosa involvement into the visceral peritoneum at the site of the tumour and may cause PC and have been shown in up to 3-28% in CRC patients (109). PC can be either limited outside the serosa of the bowel or extensive with tumour spread at different sites in the peritoneal cavity. Peritoneal tumour spread can potentially be surgically removed by parietal and visceral peritonectomy so called cytoreductive surgery (110). The treatment today combines meticulous surgical resections of peritoneal surfaces and intraperitoneal chemotherapy (HIPEC) (111-113). Pre-operative CT for staging is generally performed for quantifying the peritoneal cancer index (PCI) and exclude presence of distant metastases. Difficult areas for staging and treatment are the small bowel mesentery, retroperitoneum, the ligaments around the liver. The accuracy of pre-treatment PCI staging with CT as compared to surgical PCI staging is moderate (112, 114). Often diagnostic laparoscopic procedures are performed before to avoid unnecessary laparotomy.

## **1.10 ONCOLOGICAL TREATMENT**

The main effect of the chemotherapy is to attack cells with rapid cell growth (i.e. cancer cells) and there are different types of chemotherapy with different ways of interfere with or end the cell cycle forming new cancer cells. The side-effects of chemotherapy depend on the type of drug used, administration (intra venous or oral) and treatment duration. Other cells in the body with rapid cell growth and divides quickly are bone marrow, the epithelium in mouth and GI tract and hair follicles could also be affected during chemotherapy. Usual side-effects symptoms are fatigue, increased risk of infection, mouth sores, nausea and vomiting,

diarrhoea and hair loss. For some patients, the side effects are too severe to continue the treatment.

### **1.10.1 Neoadjuvant treatment**

Neoadjuvant chemotherapy has demonstrated effect and are well established in other malignant tumours such as in rectal, oesophagus, gastric and breast cancer (115-118). The theoretical benefits of neoadjuvant treatment are better oxygen and blood supply prior curative surgery and post-operative conditions compared to the adjuvant treatment setting. In high risk rectal cancer, chemotherapy or chemo radio therapy and TME surgery has been shown to improve the disease free survival and mortality (119).

In colon cancer, there is not yet established consensus regarding the role of neo adjuvant therapy. In patients with metastatic disease (stage IV) colon cancer, the current treatment is chemotherapy for down staging prior eventual surgery (31).

Neoadjuvant treatment in this setting is at question and is evaluated in several ongoing trials. The FOxTROT (Fluoropyrimidine Oxaliplatin and Targeted Receptor Pre-Operative Therapy) trial includes patients with tumour stage T3cd and T4 into different regimes of chemotherapy (OxMdG, Oxaliplatin, I-folonic acid, fluorouracil) in a randomized controlled trial results. One of the hypotheses as well as preliminary experience is that a lower portion of patients require adjuvant treatment if neoadjuvant treatment has been administered (120). A similar study including patients with colon cancer with tumour stage T4 and T3cd tumours and no metastases or PC could after neoadjuvant chemotherapy demonstrate a significant reduction in tumour size, EMVI, number and size of enlarged lymph nodes using CT in re-staging (121). Additionally a recently published study showed some benefit of neoadjuvant chemotherapy in T4b patients but not in T3 and T4a (122).

### **1.10.2 Adjuvant treatment**

Adjuvant treatment is chemotherapy after curative colon cancer surgery. The intention with treatment is to kill micro metastases and reduce the risk of cancer recurrence. The adjuvant treatment is based on the histopathological findings such as the pTNM staging and assessment of the other prognostic adverse features.

For stage I colon cancer there have been so far no shown benefit of additional post-surgical chemotherapy treatment. The adjuvant treatment today is offered to stage III patients which reduces the risk of death by 10-15% compared with no adjuvant treatment after curative surgery (123). For some stage II patients with other risk or prognostic adverse features (risk factors) adjuvant treatment can be offered. Those risk factors may consist of tumour stage T4, few lymph nodes examined by pathologist, CRM involvement, low differentiated tumour, tumour growth in veins or nerves or emergent surgery. Stage II is a heterogeneous group and is often divided in low and high risk group depending on number of risk factors. The risk of recurrence and death in the stage II low risk group is 20% and for the high risk group 30-40% and for stage III the risk is 40-60% (31). In a recent systematic review and meta-analysis the

five-year disease free survival (DFS) for stage II not treated with adjuvant therapy was around 80% and for stage III, treated with adjuvant therapy 64% (124).

5-Flourouracil (5-FU) has been used for decades in colon cancer and is used for adjuvant and palliative setting and has rather moderate side effects. Modern recommendations regarding chemotherapy includes a combination of 5-FU with oxaliplatin for high risk patients.

In locally advanced colon cancer, chemotherapy can be used to downsize the tumour and to relieve patient's symptom and facilitate the surgical procedure.

#### *1.10.2.1 Treatment of metastatic colon cancer*

Treatment of metastatic colon cancer has developed and is customized for the individual treatment purpose. About 20% of the patients with colorectal cancer will present with metastatic disease at the time of diagnosis. Surgical resection of liver and lung metastases can be performed more than one time and improve 5-year survival for this patient group (125, 126).

Chemotherapy is not only based on 5-FU but also irinotecan and oxaliplatin are used in metastatic disease. New treatments with targeted antibodies effecting the endothelial growth factor and epidermal growth factors and tyrosinkinase inhibitors have also been introduced (31).

Often a combination of chemotherapy and targeted therapy is given to enhance the treatment. Targeted therapy can also be given alone when conventional chemotherapy does not have any effect. Targeted therapy attacks the cancer cells by for an example affecting growth factors to inhibit angiogenesis. Patients with mutation in the KRAS-gene are likely to be non-responders to some targeted adjuvant chemotherapy such as cetuximab and panitumumab (98, 99). Treatment of metastatic disease is complex and delicate and must involve a specialised oncologist.

## **2 AIMS OF THESIS**

### **General Aim**

To investigate new cross sectional imaging technology for detection and staging of colonic tumours.

### **2.1 PAPER I**

*“Polyp detection with MDCT: a phantom-based evaluation of the impact of dose and spatial resolution.”*

The aim of study was to evaluate the impact of radiation dose and axial spatial resolution on detection of colonic polyps using 4-MDCT in vitro.

### **2.2 PAPER II**

*“Potentials of high resolution magnetic resonance imaging versus computed tomography for preoperative local staging of colon cancer.”*

The aim of study was to compare high resolution MRI with standard preoperative CT protocol in distinguishing locally advanced from not locally advanced colon cancer.

### **2.3 PAPER III**

*“Assessment and diagnostic accuracy of lymph node status to predict stage III colon cancer using computed tomography.”*

The aim of the study was to assess whether the number of lymph nodes, their anatomical location and distribution, size, size ratio, internal heterogeneity, irregular outer border and attenuation values on preoperative CT, either alone or in combination, were predictive for stage III disease in colon cancer.

### **2.4 PAPER IV**

*“Morphological predictors for lymph node metastases on computed tomography in colon cancer.”*

The aim of the study was to assess the accuracy and interobserver variation for morphological criteria for lymph node characterization on preoperative CT, either alone or in combination for prediction of stage III disease in colon cancer



### 3 PATIENTS AND METHODS

#### 3.1 PAPER I

*“Polyp detection with MDCT: a phantom-based evaluation of the impact of dose and spatial resolution.”*

This phantom study was performed during the early era of computed tomographic colonography (CTC) when numerous studies proposed different CT protocols for patients with symptoms or in the screening situation (127-131). To reduce the radiation dose, to the patients several attempts were performed to create low-dose protocols (130, 132). For CT procedures in general and in screening settings in particular, the radiation dose to the patient has to be taken into account. The radiation dose on CT depends on the tube voltage, tube current, pitch factor and the collimated beam size. Despite technological advances, there will always a trade-off between the radiation dose, spatial resolution and image noise.

To simulate the large bowel, twenty-four latex phantoms at a length of 50 cm contain artificial polyps of different sizes and shapes were constructed. At every 3-5 cm, a fold (artificial haustrae) yielding various degrees of distention was simulated to create inner diameters varying from 1 to 7 cm (Figure 11).

A total of 240 synthetic polyps were made from the latex material. The polyps were divided into three size groups; x, y and z (diameter; (x) 0-2, (y) 2-5 and (z) 5-10 mm) and were categorised into four shape groups: pedunculated, broad-based, ulcerated or depressed and sessile or flat. The polyps were evenly distributed among the size groups, resulting in 80 polyps of each size interval. There was also an even distribution of polyps among the different shapes, resulting in 20 polyps of each shape in each size interval.

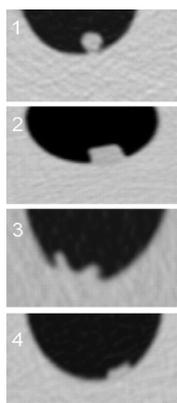


Fig 9.

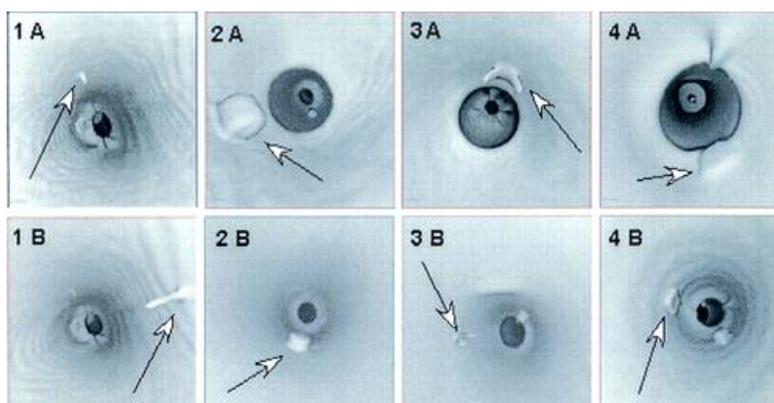


Fig 10.

Figure 9. Axial CT scans (2D) show polyps of different shapes. 1, pedunculated; 2, broad-based; 3, ulcerated or depressed with elevated margins; and 4, sessile or flat.

Figure 10. Endoluminal views from CT scans (3D) of colon polyps of different shapes. 1A and 1B, pedunculated; 2A and 2B, broad-based; 3A and 3B, ulcerated or depressed with elevated margins; and 4A and 4B, sessile or flat.

The colon phantoms were submerged in a water tank and scanned on a 4-channel multi slice CT scanner using 12 protocols with various settings of slice thickness, pitch and X-ray tube current (Table 3). The images were independently evaluated by three radiologists using axial 2D multiplanare reconstruction images and a 3D surface-rendering technique (so called “fly-through”).

The experimental and evaluation protocols were designed to study the effects of the tube current setting, pitch factor and nominal slice thickness on the detection of colonic polyps of different size and shape hence these parameters are likely to have a significant impact on polyp detection. Although the kilo voltage (kV) setting could also influence detection and will impact the dose delivered to the patient, it was excluded from this study because all clinical experience with abdominal CT at our clinic is based on 120 kV data.

### Experimental CT scanning protocol

The experimental protocol included a series of 12 CT scanning sequences. An outline of the protocol is given in Table 3. The tube potential was kept constant at 120 kV in all sequences. Estimates of the dose-length product (DLP) were calculated from measured normalized CT dose index-weighted ( $nCTDI_w$ ) values for the different beam collimations used - that is, 5 (or  $4 \times 1.25$ ), 10 ( $4 \times 2.5$ ), and 15 ( $4 \times 3.75$ ) mm, respectively. The standard CT sequence used for colonography in the clinic was based on the following settings: 100 mA, 1.5 pitch, 2.5-mm slice thickness (CT8 in Table 3).

CT <sub>i</sub>	Slice Thickness (mm)	Beam Collimation (mm)	Table Feed (mm/sec)	Pitch Factor	$nCTDI_w$ (mGy/mAs)	Total Scanning Time <sup>a</sup>	Tube Current <sup>b</sup> (mA)	Relative DLP (%)	Effective Dose <sup>c</sup> (mSv)
1	1.25	5	3.75	0.75	0.121	80	40 (41)	100	3.0
2	1.25	5	7.5	1.5	0.121	40	80 (82)	100	3.0
3	1.25	5	7.5	1.5	0.121	40	115 (115)	140	4.2
4	1.25	5	3.75	0.75	0.121	80	200	486	14.5
5	2.5	10	15	1.5	9.95	20	40 (40)	40	1.2
6	2.5	10	15	1.5	9.95	20	60 (60)	60	1.8
7	2.5	10	15	1.5	9.95	20	80 (80)	80	2.4
8	2.5	10	15	1.5	9.95	20	100 (100)	100	3.0
9	3.75	15	11.25	0.75	9.5	26.7	20 (21)	40	1.2
10	3.75	15	11.25	0.75	9.5	26.7	30 (31)	60	1.8
11	3.75	15	11.25	0.75	9.5	26.7	40 (42)	80	2.4
12	3.75	15	11.25	0.75	9.5	26.7	50 (52)	100	3.0

Note.—CT<sub>i</sub> = CT protocol number,  $nCTDI_w$  = normalized CT dose index weighted, DLP = dose-length product.

<sup>a</sup>Total scanning time is the time required to complete a 30-cm scan. The gantry rotation time equals 0.8 sec.

<sup>b</sup>The number in parentheses is the tube current setting calculated from the DLP value that was defined for the sequence. Because of restrictions in the scanner software, those values could not always be implemented. The first value is the tube current actually used during scanning.

<sup>c</sup>For the calculation of effective dose, a  $w_R$  value (conversion factor from DLP) of 0.015 mSv/mGycm was used. The effective dose corresponds to a 30-cm abdominal scan.

Table 3. Twelve CT protocols with different slice thickness, beam collimation, table feed, pitch factor, scanning time and tube current resulting in different radiation dose (DLP).

The DLP of the standard sequence was defined as the 100% dose level. The ratio of DLP for any given experimental sequence and DLP of the standard sequence was calculated and was referred to as the “relative DLP” in Table 3. The relative DLP values were in the range of 40-486% of the standard sequence, and the corresponding tube current values were calculated. Because of restrictions in the scanner software, small deviations in the tube current settings

from those calculated had to be accepted for some sequences. The corresponding effective dose values were calculated (Table 3).

A total of 24 colon phantoms (12 CT scanning sequences  $\times$  2 colon phantoms per radiologist and sequence) were constructed. The colon phantoms were submerged in a tank constructed from polymethylmethacrylate and filled with water (Figure 11). The dimensions of the tank are representative of the object size for adult bowel CT examinations (length 40 cm, width 25 cm, height 19.5 cm). The scanning procedure included two colon phantoms in each acquisition.

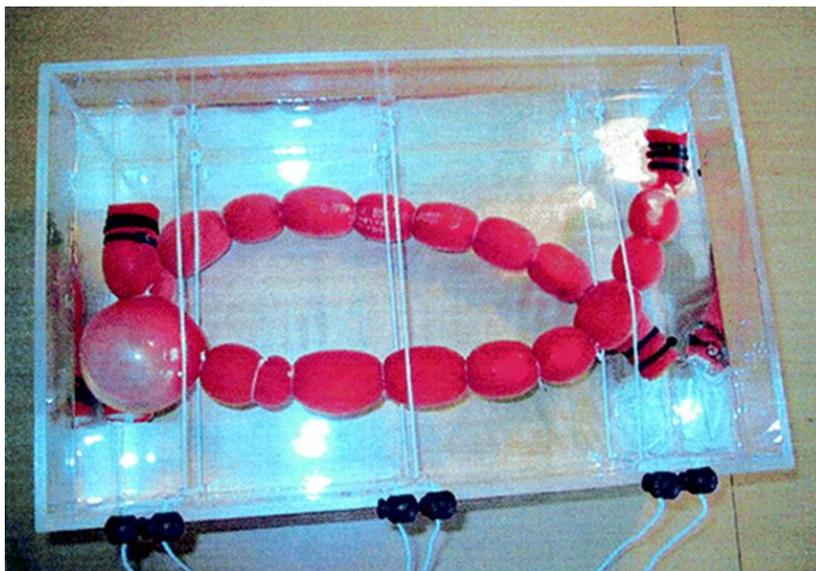


Figure 11. A typical setup with two colon phantoms, inflated with air and submerged in the water tank.

To simulate the clinical CTC examination setting, the observers were blinded to the number and shape of the polyps in the colon phantoms. In addition, the same observer evaluated a specific phantom only one time. Finally, the total number and size of the polyps to be evaluated for each CT sequence were kept constant. On the basis of these requirements, three criteria were defined and applied to each of the 12 different CT sequences. The first criterion was that evaluations should be performed independently by three observers with similar CTC experience. The second criterion was that six different colon phantoms should be included (two for each radiologist). The third criterion was that a total of 60 polyps (20 in each size group) should be distributed among the six phantoms.

Three radiologists with at least 2 years of experience in CTC were chosen to participate as observers in the study and were informed of the different polyp shapes and size intervals prior to data evaluation. The 24 phantoms were distributed in four groups, each with six phantoms. Each phantom group was then used to acquire data for three CT scanning sequences. The rotational scheme of the phantoms in each group is shown in figure 12. After completion of the study, each radiologist had examined all 24 phantoms.

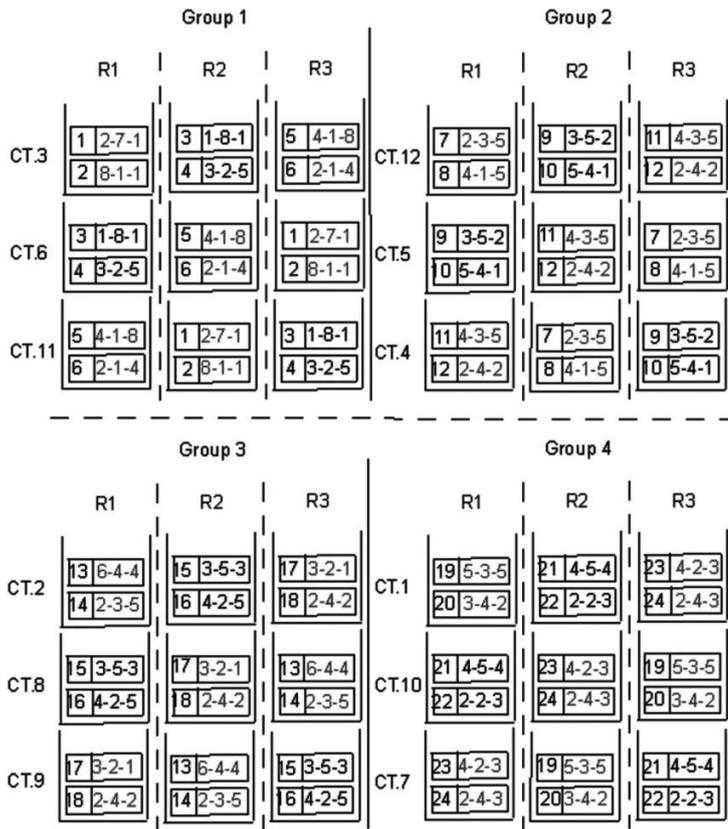


Figure. 12. Diagram shows rotational scheme of 24 phantoms used during data acquisition. R1, R2, and R3 refer to radiologists 1, 2, and 3, respectively. Colon phantoms are displayed as rectangular boxes. The reference number of phantom used to acquire data for a given sequence is indicated in the left subsection of each box. The numbers in the right subsection refer to the number of polyps in size groups X, Y, and Z, respectively. For each scan sequence, the number of polyps in each size group was kept constant and equal to 20.

The impact of residual fluid on polyp detection in the colon lumen was evaluated by rescanning phantoms in group 4 (i.e., sequences CT1, 7, and 10) after the addition of some water. The water filled approximately 20-30% of the lumen volume. The submerged polyps were not visible with the viewing settings used in the evaluations. To complete the experimental protocol, a total of 45 data acquisitions were performed: 36 ( $12 \times 3$ ) with phantoms having no water inside and nine ( $3 \times 3$ ) with phantoms partially filled with water. The study design included a total of 720 polyps ( $12 \times 60$ ) to be evaluated in air filled colon phantoms without water and an additional 180 polyps ( $3 \times 60$ ) in phantoms partially filled with water.

### Evaluation Protocol

The CT scans were evaluated on a dedicated workstation (Advantage Windows 3.1, GE Healthcare) using a software tool (Navigator [version 2], GE Healthcare) using the same viewing settings of the workstation monitor as those used during clinical CTC examinations (window width, 1600 HU; window level, 400 HU). Two different evaluation methods were used: axial images were displayed in three orthogonal directions (referred to as “2D multiplanare reconstruction (MPR) technique”) and virtual colonoscopy images, yielded by a

3D surface-rendering technique (referred to as “fly-through” 3D technique”), were shown. Using the 2D MPR technique, the number of polyps in each size group (x, y, z) was defined for each colon phantom. Using the 3D technique, the total number of polyps of each of the four defined shapes, independent of size, was detected using forward and backward “fly-through” of the phantom. No polyp matching was done. If the number of polyps registered for a given shape exceeded the correct number, those in excess were regarded as misclassified and all others were regarded as correctly classified.

### **3.2 PAPER II**

*“Potentials of high resolution magnetic resonance imaging versus computed tomography for preoperative local staging of colon cancer.”*

Patients with a biopsy proven colon cancer were admitted from the surgical department for CT of the abdomen and chest X-ray as well as MRI during the years 2005-2009. Forty-nine patients were prospectively enrolled in the study after approval of the regional ethical review board. After exclusion criteria, the final cohort consisted of twenty-eight patients with 29 tumours.

The pre-operative MRI examination were performed on a 1.5 T MRI scanner in supine position using a cardiac five-channel surface receiver coil. After a coronal localizer with a Half-Fourier T2-weighted single-shot sequence for tumour localization, high-resolution, respiratory triggered T2-weighted turbo spin-echo sequences (TR 1800, TE 120 ms) were performed covering the tumour area in at least three different orthogonal planes; axial, sagittal, and coronal as well as a perpendicular sequence to the lumen of the bowel (true axial imaging). The voxel size in the high resolution sequence was (0.5–0.6 x 0.5–0.8 x 3.0 mm) with a field of view of 375 x 262 mm and 255 x 217 mm.

The preoperative CT examinations were from different radiological units and were performed with a range of different CT-scanners from single slice technology up to 64-slice helical CT scanners with intravenous contrast media in the portal venous phase. The saved imaging data from these scans included images with a reconstructed section thickness that varied between 5 and 8 mm.

The imaging examinations were retrospectively and independently evaluated by two experienced GI radiologists in reading abdominal MR and CT examinations and evaluated at different occasions making sure that MR and CT examination from the same patient could not be recognized and were blinded to one another and to the histopathological reports. The examinations were assessed according to the Tumour Node Metastasis classification (TNM) 6 edition according to UICC (133).

Tumour stage was classified as not locally advanced, with maximum extramural tumour extent was less than 5 mm (T0-T3ab) and locally advanced, with extra mural tumour extent

>5mm or tumour stage T4 (T3cd-T4). Nodal stage and presence of extra mural vascular invasion (EMVI) were also evaluated.

The surgical procedure was performed by total mesenteric excision including central ligation of the supplying arteries and draining veins together with a maximum of harvested mesenteric lymph nodes according to established techniques of complete mesocolic excision (CME) (102, 134). The surgical specimens were processed according to local work-up routines for colon cancer where tumour sections were selected for histopathological analysis and dissection of the pericolic fat in the search for lymph nodes was performed. The histopathological slides were retrospectively reviewed by a consultant GI pathologist.

Descriptive statistics using sensitivity and specificity and observed agreement (accuracy) was used to assess T-stage (not locally advanced vs local advanced), N-stage, and EMVI for both MRI and CT compared to histopathology. To compare the inter-observer agreement between the both observers and both modalities Kappa statistics according to Cohen was calculated and was categorised as poor agreement, fair, moderate, good and very good according to Kappa (k) values, 0-0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80 and 0.81-1.00, respectively.

### **3.3 PAPER III**

*“Assessment and diagnostic accuracy of lymph node status to predict stage III colon cancer using computed tomography.”*

From the Swedish colorectal cancer registry (SCRCR), 483 consecutive patients having a histology proven colon cancer and operated between the years 2008 and 2011 and examined with abdominal CT (64 detector CT-scanner) with intravenous contrast before surgery at our institution were identified.

After exclusion, a cohort of 119 patients with histologically proven colon cancer without metastases and stage IV were included. There were 63 women and 56 men with a median age of 69 (range 32-91 years). All patients had preoperative investigations with CT of the abdomen with intravenous contrast on one of four different 64 slice CT scanners. After the examination, reformatted images in axial, coronal and sagittal planes with 5 mm thickness (increment 2.5 mm) were routinely generated together with the original (thin slices) 0.625 mm images.

#### **CT evaluation**

All CT examinations were retrospectively reviewed by one radiologist and blinded for the histology and surgical reports. Examinations were assessed according to a dedicated evaluation protocol. All measurements and assessments were performed on a SECTRA Workstation IDS7 (version 15.1.14.41) using the 5 mm reformatted images with 2.5 mm increment. The original thin slices (0.625 mm) were used for detection of small lymph nodes ( $\leq 4$  mm).

## Anatomical distribution

The colonic mesentery, 5 cm oral and aboral from the tumour site, was divided in three anatomical regions (region 1–3), as a modified variant of the guidelines from the Japanese Society for Cancer in the Colon and Rectum (135). Region 1 was defined as the region most adjacent to the tumour (+/-5 cm) and 3 cm proximal along the vessels to the branch artery divides covering the pericolonc and marginal lymph nodes. Region 3 was defined as the most proximal part of the mesentery including the undivided mesenteric artery from the aorta (proximal lymph nodes). Region 2 was defined as the region between region 1 and 3 (Figure 13).

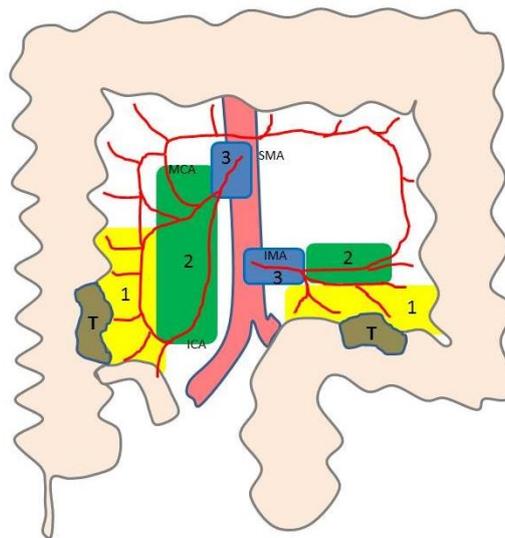


Figure 13 Anatomical location of lymph nodes regions 1-3. T=Tumour in the ascending colon and sigmoid colon respectively. SMA=Superior mesenteric artery. IMA=Inferior mesenteric artery.

## Number, size and size-ratio of lymph nodes

All lymph nodes  $\geq 2$  mm in size were separately registered in total and in each anatomical region. For lymph nodes  $\geq 4$  mm in shortest diameter, the short axis and the long axis were also separately measured and the ratio between the short and long axis diameter was calculated. The size ratio (ratio between two orthogonal (short/long) axis diameters) was used to test whether a more rounded shape was predictive for metastasis. A  $>0.8$  ratio between diameter was used as cut off point according to a previous study (136). The presence of a cluster (within a range of the lymph node diameter) of three or more lymph nodes was also separately noted in every region.

## Internal heterogeneity and irregular outer borders of lymph nodes

As possible morphological predictors of lymph node metastases, internal heterogeneity (IH, mixed attenuation within the lymph node) as well as the irregular outer border (IOB, indistinct demarcation of the lymph node) were evaluated both on reformatted and thin sections (Figure 14 and 15).



Figure 14.

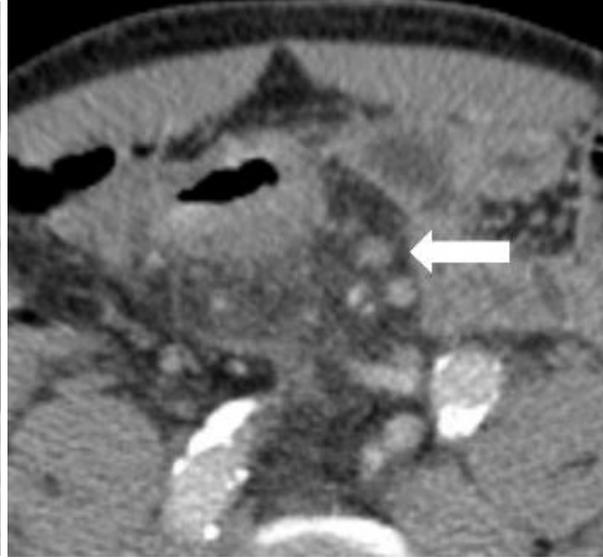


Figure 15.

Figure 14. Coronal reformatted (5 mm section post iv contrast portal phase) CT image illustrating the appearance of 10 × 15 mm lymph node (white arrow) in region 1 with internal heterogeneity and well defined borders in a patient with pT3 tumour in the ascending colon. At histopathology, 4 metastatic lymph nodes out of 43 were harvested.

Figure 15. Transaxial reformatted (5 mm section post iv contrast portal phase) CT image illustrating the appearance of a 7 × 7 mm mesocolic lymph node (white arrow) in region 2 with irregular outer border and internal heterogeneity in a patient with a pT3 tumour in the sigmoid colon with 1 metastatic lymph nodes out of 16 harvested at histopathology.

### Attenuation values

Attenuation measurement of each lymph node in the portal venous phase and, when available, in the arterial phase was also performed. All density measurements (using HU) were performed by placing as large a region of interest (ROI) as possible (>2 mm<sup>2</sup>) on the lymph node in the portal venous phase and in the arterial phase when available. Attenuation values of ≥50 and ≥100 HU in the portal venous phase were separately noted as well as ratio portal venous/arterial phase. Inhomogeneous contrast enhancement as indicative for tumour involvement was distinguished from either presence of a fatty lymph node hilum or a contrast filled vessel in the vicinity of a lymph node.

### Surgery

All patients in the study were operated in an elective setting and according to colorectal surgery praxis (TME). The resection of colon cancer was made by clear lateral margins, resection of the loco-regional lymph node bearing mesentery.

## Histopathology

Histopathology was performed according to standard procedures at the university hospital pathology department by a specialised GI pathologist (initially using TNM version 6 and later TNM version 7) (33, 133). From the pathologists' report the T- and N-stage, the total number of harvested and metastatic lymph nodes served as reference standard.

## Statistics

Descriptive statistics were applied to the different lymph node characteristics calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Odds ratio for the prediction of stage III disease. Significance level was set to  $p \leq 0.05$  when using Mann-Whitney U test. Univariate and multiple logistic regression analyses were used for categorical data. Receiver operating characteristics (ROC) and area under the curve (AUC) were used to compare different lymph node size cut off values as predictor for malignancy.

### 3.4 PAPER IV

*“Morphological predictors for lymph node metastases on computed tomography in colon cancer.”*

From the results from paper III a validating study using the morphological criteria internal heterogeneity and irregular outer border as predictors for lymph node metastases with CT was performed.

The patients were included and examined at Danderyd University Hospital, Stockholm, Sweden. Prior to initiation of the study a fixed examination protocol for CT and for reporting surgical and histopathological findings had been established.

All patients scheduled for surgery for histopathology proven colon cancer (adenocarcinoma) from February 2012 to December 2014 were included in the study. Informed consent was obtained from each patient before entering the study.

Patients were routinely scheduled for CT for screening of metastatic disease and for assessment of the primary tumour. Demographic data, pre-and-postoperative variables, carcinoembryonic antigen assay (CEA) (ref <5 µg/l), tumour location were recorded. In total 112 consecutive patients were enrolled. Eighteen patients were excluded due to CT examination not fulfilling study protocol or presence of distant metastases.

The remaining cohort of patients (n=94) comprised of 45 women and 49 men with a median age of 72 (range 45-90) years.

## Computed tomography

All CT examinations included abdomen/pelvis and thorax with intravenous contrast in portal-venous phase using a 64 channel multislice CT scanner (GE Light Speed-VCT). Original

images were reconstructed to 5 mm slice thickness with 1 mm overlap (interval 4) and axial, coronal and sagittal MPRs were routinely generated together with the original (thin slices) 0.625 mm images.

### CT evaluation

All CT examinations were retrospectively, independently reviewed by two GI-radiologists with more than 20 years of experience in cross sectional imaging of colorectal cancer and blinded to all clinical information including tumour location but except the inclusion criteria. Examinations were assessed according to a dedicated evaluation protocol. In case of no visible tumour in the colon, the tumour T-stage was assessed as T0. Both observers assessed tumour location (caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon and sigmoid colon), tumour stage into not locally advanced (T0-T3ab) and locally advanced (T3cd and T4). The tumour stage T0 was referred into the tumour stage (T0-T3ab) group for further analyses. The assessment of lymph node status (N0/N+) was limited to three morphological criteria in line with paper III (137); a, internal heterogeneity within at least one lymph node (IH) b, irregular outer border (IOB) and c, combination of the two criteria, so called combined criteria (Figure 16).

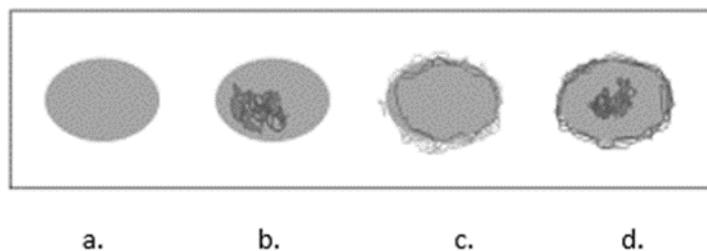


Figure 16. Schematic description of the four different morphological lymph node features on CT. a) Normal lymph node, b) Lymph node with internal heterogeneity, c) Lymph node with irregular outer border, d) Lymph node with both internal heterogeneity and irregular outer border.

All measurements and assessments were performed both using the 5 mm reformatted images and the original thin slices (0.625 mm), the latter primary for detection of small lymph nodes ( $\leq 5$  mm) but were also in some cases additionally merged into 2 and 3 mm slice thickness.

All patients in the study were operated in a curative elective setting and according to colorectal surgical praxis. Histopathology was performed according to standard procedures at the university hospital pathology department by a specialised GI pathologist according to TNM version 7 and served as reference standard.

### Statistical analysis

Descriptive statistics were applied to the different tumour stage and lymph node characteristics calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the prediction of stage III disease. Statistical significance level was set to  $p \leq 0.05$ . Inter observer variation was classified using Cohens Kappa statistics. Data were evaluated using statistical analysis software, IBM SPSS Statistics (Version 24).

## 4 RESULTS

### 4.1 PAPER I

*“Polyp detection with MDCT: a phantom-based evaluation of the impact of dose and spatial resolution.”*

#### Effect of Radiation Dose on Polyp Detection Rate

The dependence on radiation dose was similar for both evaluation techniques (2D and 3D), with improved detection rate at a higher dose. For the standard sequence (CT5-8; 2.50-mm slice thickness, 1.5 pitch), the efficiency in detecting polyps of all sizes decreased from approximately 70% at 100% DLP (100 mA) to 55% at 40% DLP (40 mA) (Figure 17).

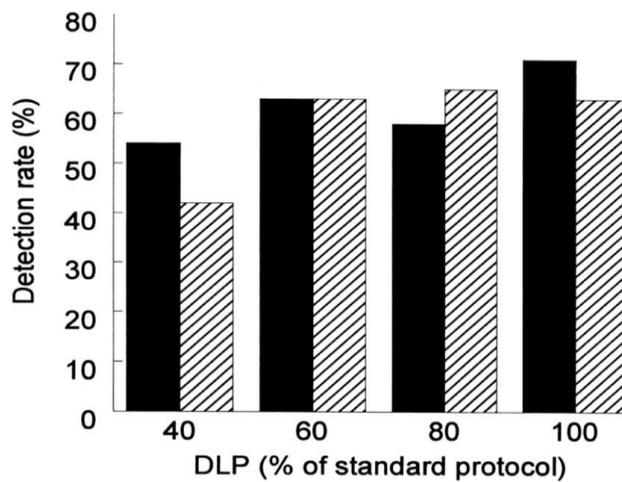


Figure 17. Bar graph showing percentage of detected polyps as function of dose-length product (DLP) using the spatial resolution of the standard protocol. Black bars = 2D multiplanar reconstruction technique, striped bars = 3D fly-through technique.

The results of splitting the 2D evaluations of figure 17 into the different polyp size groups are displayed in figure 18. At all DLP levels, the detection rate increased for larger polyps. For instance, at 60% DLP (relative to the standard protocol), approximately 20% of the smallest polyps were detected, with the detection rate increasing to almost 80% for medium-sized polyps and reaching 90% for the largest polyps.

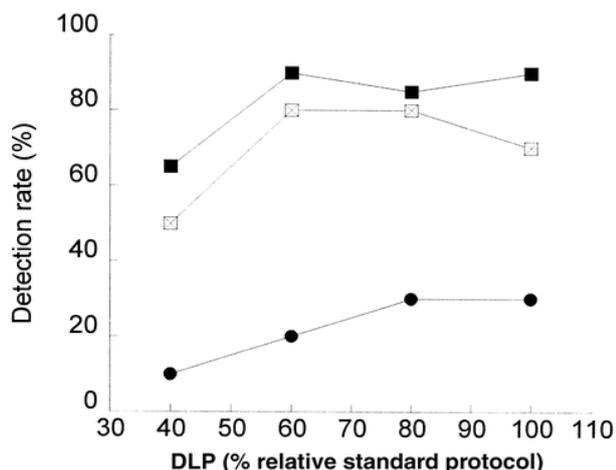


Figure 18 Graph shows percentage of detected polyps of different sizes as a function of dose-length product (DLP), which was obtained from data with the same spatial resolution as standard protocol. ■ = polyps > 5 mm; □ = 2- to 5-mm polyps; • = 0- to 2-mm polyps.

### Effect of Axial Spatial Resolution on Polyp Detection Rate

The axial spatial resolution - i.e. the slice thickness and the pitch factor - significantly affected the detection rate of polyps. When the radiation dose (DLP) was kept constant and equal to that of the standard sequence (2.5 mm slice thickness, 100 mA, 1.5 pitch), the highest detection rate of polyps larger than 2 mm was obtained using the sequence with 1.25 mm section thickness and 0.75 pitch, followed by the sequence with 1.25 mm slice thickness and 1.5 pitch (2D MPR technique). This is despite the significantly reduced tube current settings used with the narrower slice sequences to balance DLP (40 and 80 mA, respectively). The results are shown in figure 19.

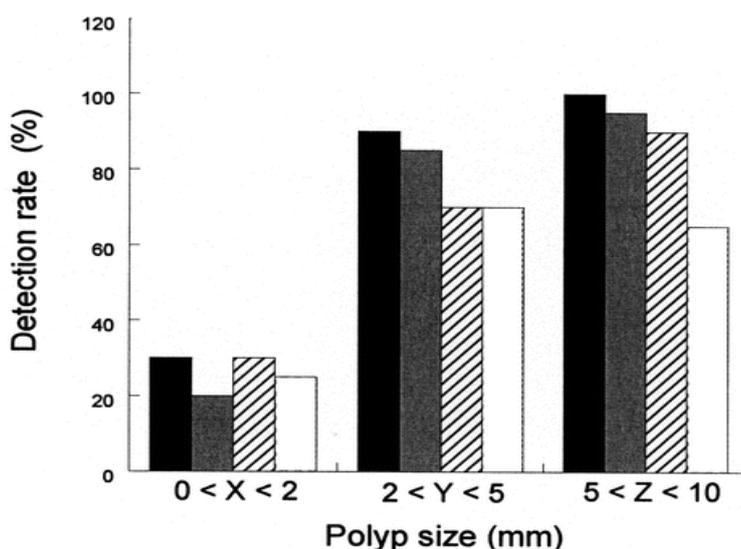


Figure 19. Graph shows percentage of detected polyps as a function of polyp size for different settings of slice width and pitch factor. Radiation dose (i.e., dose-length product) was kept constant and equal to standard sequence. Black bars = slice width of 1.25 mm and pitch of 0.75, gray bars = slice width of 1.25 mm and pitch of 1.5, striped bars = slice width of 2.5 mm and pitch of 1.5 (standard protocol), white bars = slice width of 3.75 mm and pitch of 0.75.

## Effect of Residual Fluid on Polyp Detection

A common challenge during CT examination of the colon is the presence of residual liquid and stool. As we previously mentioned, the effect of residual content on polyp detection was simulated by the addition of water in phantom group 4 (Figure 20).

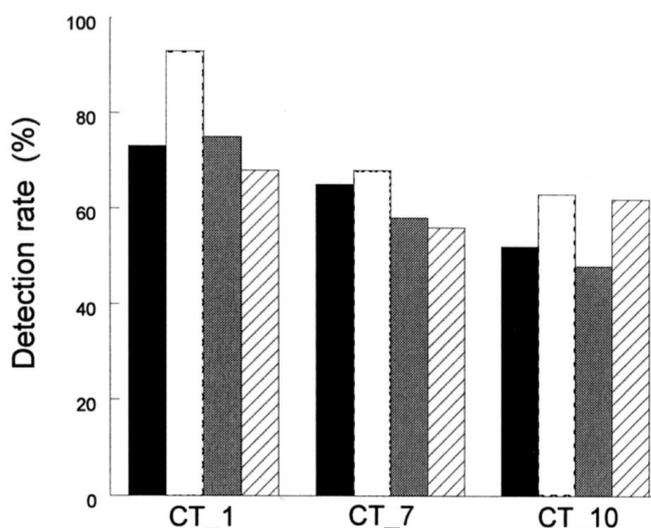


Figure 20. Graph shows detection rate of polyps in phantoms with and without water for three CT sequences. CT\_1 used slice width of 1.25 mm and pitch of 0.75 (dose-length product [DLP], 100%). CT\_7 used slice width of 2.5 mm and pitch of 1.5 (DLP, 80%); CT\_10 used slice width of 3.75 mm and pitch of 0.75 (DLP, 60%). Black bars = 2D multiplanare reconstruction (MPR) technique, white bars = 2D MPR technique with water, gray bars = fly-through technique, striped bars = fly-through technique with water.

## Shape Analysis

The evaluation of polyp shape yielded small differences between the CT sequences with regard to misclassified polyps, and the number of such polyps was always three or fewer per CT sequence ( $\leq 5\%$  of all polyps) for sequences with no added water. For sequences with water added to the phantom, the number of misclassified polyps increased substantially and resulted in between seven and 11 misclassified polyps (up to 18%). The misclassified polyps in phantoms containing water were always registered in polyp shape group 2 (Figures 9 and 10), indicating that those were most likely water drops attached to the phantom wall.

## 4.2 PAPER II

*“Potentials of high resolution magnetic resonance imaging versus computed tomography for preoperative local staging of colon cancer.”*

Six out of 29 tumours were located in the cecum, ten in the ascending colon, five in the transverse colon, and eight in the sigmoid colon.

In 6 out of 28 patients involvement of neighbouring organs or potential resection margin was indicated by prospective evaluation of MR images and the surgical procedure in these cases was extended. In four of these patients, tumour infiltration of (a) neighbouring organ(s) or structure(s) was also suspected at surgery but could not be confirmed by histopathology (Figure 21).

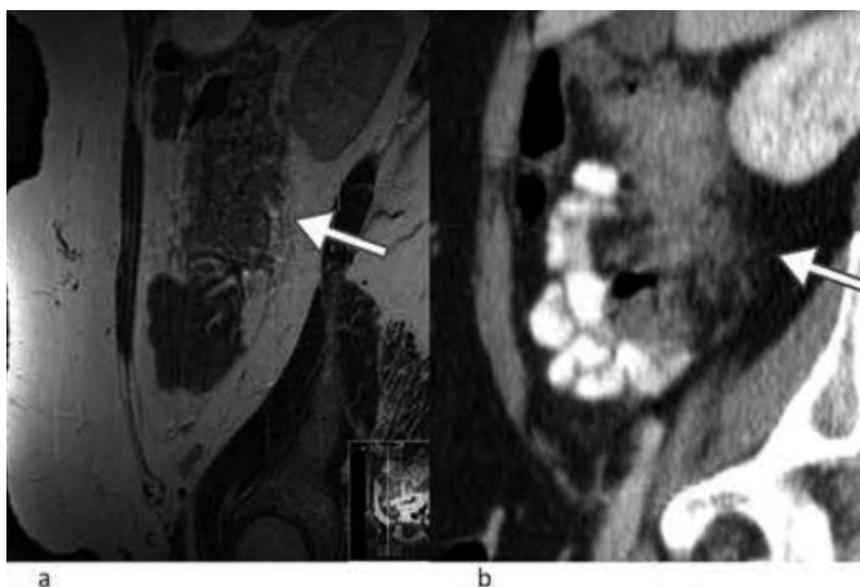


Figure 21. Sagittal a) MRI and b) CT images of a right-sided locally advanced tumour showing involved retroperitoneal dorsal surgical margin (Gerotas fascia). In this case surgery was extended due to imaging findings

In three of these six patients, resected structures such as the abdominal wall, perinephric fat, or Gerotas fascia were not mentioned in the histopathological report and could not retrospectively be confirmed. In two other patients, the MRI examination postulated a high grade of suspicion regarding serosa involvement, which also was noted at surgery but could not be verified at histopathology.

### ***Retrospective image analysis***

#### T-stage

Surgical and histopathological findings revealed that six out of 29 patients had T4 tumours seven patients T3 cd, eight T3 ab, and eight T2 tumours.

The correlation between T-stage assessed by MRI and CT by observers 1 and 2 and histopathology is shown in table 4. For MRI, observer 1 was able to identify 10/13 patients with locally advanced tumours and understaged 3/13. Observer 2 was able to identify 12/13 pathologically proven locally advanced tumours by MRI, only understaging one tumour. For CT, observers 1 and 2 were both able to predict 9/13 locally advanced tumours, understaging four tumours. Observed agreement (accuracy) for MRI and CT was 0.90 and 0.82, respectively. Inter-observer agreement (Kappa statistics) for MRI was 0.79 (95% confidence interval (CI), 0.56-1.00;  $p < 0.001$ ) and for CT 0.64 (95% CI, 0.36-0.92;  $p < 0.001$ ).

Histopathology	MRI					
	Observer 1			Observer 2		
	T0-T3ab	T3cd-T4	Total	T0-T3ab	T3cd-T4	Total
pT0-T3ab	16	0	16	15	1	16
pT3cd-T4	3	10	13	1	12	13
Total	19	10	29	16	13	29

Observer 1: Kappa (95% CI) = 0.786 (0.563–1.000);  $P < 0.001$ , Accuracy (observed agreement) = 0.897 (0.736–0.964), Sensitivity (95% CI) = 0.769 (0.497–0.918), Specificity (95% CI) = 1.000 (0.806–1.000). Observer 2: Kappa (95% CI) = 0.861 (0.674–1.000);  $P < 0.001$ , Accuracy (observed agreement) = 0.931 (0.780–0.981), Sensitivity (95% CI) = 0.923 (0.667–0.986), Specificity (95% CI) = 0.938 (0.717–0.989)

Histopathology	CT					
	Observer 1			Observer 2		
	T0-T3ab	T3cd-T4	Total	T0-T3ab	T3cd-T4	Total
pT0-T3ab	14	2	16	13	3	16
pT3cd-T4	4	9	13	4	9	13
Total	18	11	29	17	12	29

Observer 1: Kappa (95% CI) = 0.576 (0.277–0.874);  $P < 0.001$ , Accuracy (observed agreement) = 0.793 (0.616–0.902), Sensitivity (95% CI) = 0.692 (0.424–0.873), Specificity (95% CI) = 0.875 (0.640–0.965). Observer 2: Kappa (95% CI) = 0.508 (0.193–0.824);  $P = 0.003$ , Accuracy (observed agreement) = 0.759 (0.579–0.878), Sensitivity (95% CI) = 0.692 (0.424–0.873), Specificity (95% CI) = 0.813 (0.570–0.934)

Table 4. Summary statistics of tumour staging with MRI and CT by observer.

## N-stage

Seven patients had local lymph node metastases according to histopathology. Of those, four had N1 disease and three had N2 disease. The correlation between the N-stage as assessed by MRI and CT by observers 1 and 2 and histopathology is shown in table 5.

The presence of local metastatic lymph nodes was correctly predicted in 6/7 cases by both observers with MRI and in 4/7 cases (observer 1) and 3/7 cases (observer 2) with CT. The presence or non-presence of metastatic lymph nodes was predicted in 21/29 and 20/29 with MRI by observer 1 and observer 2, respectively, and 21/29 and 21/29 with CT. Observed agreement (accuracy) for MRI and CT was 0.55 and 0.86, respectively. Inter-observer agreement for MRI kappa was 0.10 (95% CI, -0.26-0.46;  $p = 0.92$ ) and for CT 0.66 (95% CI, 0.35-0.96;  $p < 0.001$ ).

Histopathology	MRI					
	Observer 1			Observer 2		
	Negative	Positive	Total	Negative	Positive	Total
Negative	15	7	22	14	8	22
Positive	1	6	7	1	6	7
Total	16	13	29	15	14	29

Observer 1: Kappa (95% CI) = 0.417 (0.110–0.724);  $P = 0.006$ , Accuracy (observed agreement) = 0.724 (0.543–0.853), Sensitivity (95% CI) = 0.857 (0.487–0.974), Specificity (95% CI) = 0.682 (0.473–0.836). Observer 2: Kappa (95% CI) = 0.368 (0.070–0.666);  $P = 0.011$ , Accuracy (observed agreement) = 0.690 (0.508–0.827), Sensitivity (95% CI) = 0.857 (0.487–0.974), Specificity (95% CI) = 0.636 (0.430–0.803)

Histopathology	CT					
	Observer 1			Observer 2		
	Negative	Positive	Total	Negative	Positive	Total
Negative	17	5	22	18	4	22
Positive	3	4	7	4	3	7
Total	20	9	29	22	7	29

Observer 1: Kappa (95% CI) = 0.314 (–0.060–0.687);  $P = 0.043$ , Accuracy (observed agreement) = 0.724 (0.543–0.853), Sensitivity (95% CI) = 0.571 (0.250–0.842), Specificity (95% CI) = 0.773 (0.566–0.899). Observer 2: Kappa (95% CI) = 0.247 (–0.148–0.642);  $P = 0.092$ , Accuracy (observed agreement) = 0.724 (0.543–0.853), Sensitivity (95% CI) = 0.429 (0.158–0.750), Specificity (95% CI) = 0.818 (0.615–0.927)

Table 5. Summary statistics of nodal staging with MRI and CT by observer.

## EMVI

Out of 27 evaluable cases, eight cases (30%) had local vascular invasion according to histopathology.

Six of eight cases were predicted by MRI by both observers and 3/8 by CT by both observers. The correlation between histopathology and extramural venous invasion as assessed by MRI and CT (by observers 1 and 2) is shown in table 6.

Observed agreement (accuracy) for MRI was 0.89 and for CT was 0.74. Inter-observer agreement Kappa statistics for MRI and CT was 0.76 (95% CI, 0.50-1.00;  $p < 0.001$ ) and for CT 0.22 (95% CI, -0.19-0.62;  $p = 0.117$ ).

Histopathology	MRI					
	Observer 1			Observer 2		
	Negative	Positive	Total	Negative	Positive	Total
Negative	16	3	19	15	4	19
Positive	2	6	8	2	6	8
Total	18	9	27	17	10	27

Observer 1: Kappa (95% CI) = 0.571 (0.239–0.904);  $P = 0.001$ , Accuracy (observed agreement) = 0.815 (0.633–0.918), Sensitivity (95% CI) = 0.750 (0.409–0.929), Specificity (95% CI) = 0.842 (0.624–0.945). Observer 2: Kappa (95% CI) = 0.503 (0.163–0.844);  $P = 0.004$ , Accuracy (observed agreement) = 0.778 (0.592–0.894), Sensitivity (95% CI) = 0.750 (0.409–0.929), Specificity (95% CI) = 0.789 (0.567–0.915)

Histopathology	CT					
	Observer 1			Observer 2		
	Negative	Positive	Total	Negative	Positive	Total
Negative	18	1	19	15	4	19
Positive	5	3	8	5	3	8
Total	23	4	27	20	7	27

Observer 1: Kappa (95% CI) = 0.377 (–0.003–0.757);  $P = 0.016$ , Accuracy (observed agreement) = 0.778 (0.592–0.894), Sensitivity (95% CI) = 0.375 (0.137–0.694), Specificity (95% CI) = 0.947 (0.754–0.991). Observer 2: Kappa (95% CI) = 0.171 (–0.223–0.564);  $P = 0.187$ , Accuracy (observed agreement) = 0.667 (0.478–0.814), Sensitivity (95% CI) = 0.375 (0.137–0.694), Specificity (95% CI) = 0.789 (0.567–0.915)

Table 6. Summary statistics of extramural venous invasion with MRI and CT by observer.

### 4.3 PAPER III

*“Assessment and diagnostic accuracy of lymph node status to predict stage III colon cancer using computed tomography.”*

#### Histopathology

Thirty-nine out of 119 patients had lymph node positive (stage III) disease (28 patients N1 and 11 patients N2). According to histopathology 80 patients were stage I-II and 39 were stage III (Table 7).

<b>Characteristics</b>	<b>Number (%)</b>
Sex (female/male)	63/56
Age (median)	69 (32-91)
<b><u>Histopathological evaluation</u></b>	
<b>Tumour localization</b>	
Caecum	23 (19%)
Ascending colon	22 (18%)
Hepatic flexure	8 (7%)
Transverse colon	11 (9%)
Splenic flexure	4 (3%)
Descending colon	6 (5%)
Sigmoid colon	45 (38%)
<b>Tumour Stage</b>	
T1	10 (8%)
T2	16 (13%)
T3	93 (78%)
<b>Positive lymph node status</b>	
T1 tumours	2/10 (20%)
T2 tumours	2/16 (12%)
T3 tumours	35/93 (38%)
<b>Stage</b>	
Stage I	22 (18%)
Stage II	58 (49%)
Stage III	39 (33%)
<b>Lymph nodes, total number</b>	
Harvested lymph nodes PAD	2542
Positive lymph nodes PAD	123
<b><u>CT evaluation</u></b>	
Detected lymph nodes $\geq 4$ mm/tot	442/1312(34%)
Region 1	261/835 (31%)
Region 2	161/389 (41%)
Region 3	20/88 (23%)

Table 7. Demographics table of 119 patients/tumours.

The median time interval between pre-operative CT examination and surgery was 28 days (range 4-59 days), mean 29 days (standard deviation 13 days). A total of 2542 lymph nodes were harvested (median 19 lymph nodes/patient, range 4-69) and of those 123 were assessed as metastases (median, 2 lymph nodes/patient, range 1-10). Whether TNM 6 or TNM 7 was used did not affect these figures.

## CT evaluation

### *Number, anatomical distribution, size and size-ratio of lymph nodes*

At CT, most of the lymph nodes were located in region 1. Region 2 had higher proportion of lymph nodes  $\geq 4$  mm (41%) compared to the other regions (Table 7). The mean number of lymph nodes found was 7.2 for pT1 tumours, 8.6 for pT2 tumours and 11.8 for pT3 tumours (not shown in Table).

### *Evaluation of lymph nodes*

Using size thresholds of  $\geq 4, 5, 6, 7, 8$  and  $10$  mm as criteria for lymph node metastases, the results are presented as a ROC-curve in figure 22. Regarding lymph node size ratio, a cut-off point of  $0.8$  resulted in an overall sensitivity and specificity of  $85\%$  and  $30\%$  respectively (Table 7). If the results for size ratio is split by the three anatomical regions, the sensitivity/specificity were as follows: region 1,  $80/35\%$ ; region 2,  $54/74\%$  and region 3,  $5/94\%$ , respectively.

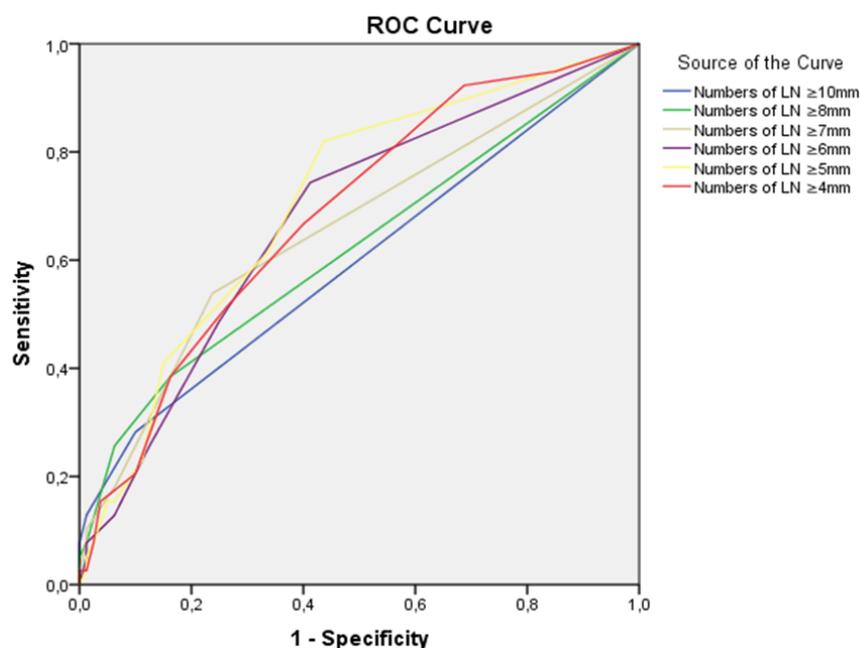


Figure 22. Size criteria ( $\geq 4, 5, 6, 7, 8$  and  $10$  mm) in shortest diameter according to CT presented as receiver operating characteristics (ROC), and area under the curve (AUC).

### *Internal heterogeneity and irregular outer border*

Forty-four out of 119 patients had at least one (range 1-6) lymph node with internal heterogeneity according to CT and a total number of 94 lymph nodes with this morphological feature were detected. Compared to histopathology, the sensitivity and specificity for predicting stage III disease with this criterion was 79 and 84%, respectively,  $p \leq 0.001$ , Odds ratio (OR) = 20 (Table 8). If divided by anatomical region, the sensitivity/specificity were as follows: region 1, 64/91%; region 2, 51/92% and region 3, 3/97%, respectively.

Thirty-eight patients had at least one (range 1-8) lymph node with an irregular outer border. Compared to histopathology, lymph nodes with an irregular outer border showed sensitivity and specificity for prediction of stage III disease of 59 and 81%, respectively,  $p \leq 0.001$ , OR = 6.3 (Table 8). If divided by anatomical region, the sensitivity/specificity were as follows: region 1, 49/89%; region 2, 33/91%, and region 3, 0/99%, respectively.

In patients with at least one lymph node with internal heterogeneity and a lymph node with an irregular outer border, regardless of location, the sensitivity and specificity for stage III disease was 54 and 90%, respectively. Patients with any lymph node showing internal heterogeneity and/or irregular outer borders, meaning that either one of the criteria were present or both in combination, showed an overall sensitivity and specificity for stage III disease of 85 and 75%, respectively,  $p \leq 0.001$ , OR = 16.5 (Table 8).

### *Contrast enhancement*

The overall sensitivity and specificity prediction of stage III disease for lymph nodes having a HU value  $\geq 50$  or  $\geq 100$  post contrast in portal venous phase were, 95 and 20%, and 44 and 68%, respectively (Table 8).

### *Cluster of three or more normal shaped and sized lymph nodes*

This criterion resulted in an overall sensitivity of 13% and a specificity of 89% (Table 8).

Variables	Number	Sensitivity	Specificity	PPV	NPV	OR	p-value
Size $\geq 5$ mm	287	90	31	39	86	1.33	0.002
Size $\geq 10$ mm	29	28	90	58	72	2.67	0.009
Ratio cut off 0.8	244	85	30	37	80	2.36	0.090
Internal heterogeneity (IH)	94	79	84	70	89	20.0	<0.001
Irregular outer border (IOB)	73	59	81	61	82	6.23	<0.001
IH and/or IOB	67	85	75	62	91	16.5	<0.001
HU $\geq 50$	396	95	20	37	89	4.63	0.049
HU $\geq 100$	81	44	68	40	71	1.60	0.239
Cluster of three	14	13	89	36	68	1.16	0.803

Table 8. Sensitivity, specificity, PPV and NPV (%) for the different CT characteristics of lymph nodes  $>4$ mm in shortest diameter compared to histopathology.

*Combination of different variables using multivariate logistic regression analyses*

The strongest predictor for stage III disease in our study was internal heterogeneity. No other variable contributed significantly when the variable internal heterogeneity was included in the multivariate regression model (Figure 23).

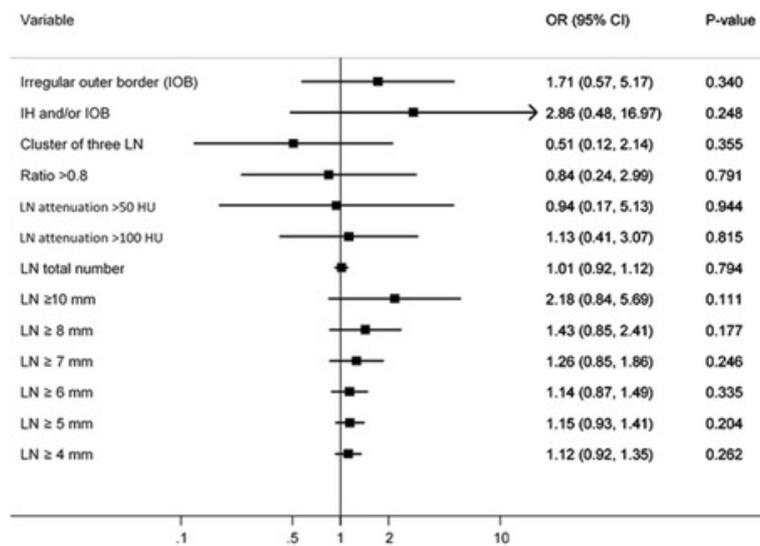


Figure 23. Multivariate logistic regression analyses for odds ratio of different lymph node characteristics when internal heterogeneity is included in the model.

## 4.4 PAPER IV

*“Morphological predictors for lymph node metastases on computed tomography in colon cancer.”*

### Histopathology

The majority of the tumours, 56 out of 94 (60%), were right sided located in the caecum and ascending colon. The histopathological distribution of T and N stages in the cohort is presented in table 1. Thirty-five (37%) of the patients were lymph node positive (Table 9).

A total of 2086 lymph nodes were harvested (median 20 lymph nodes per patient, range 3-69) and of those 173 lymph nodes were assessed as metastases (median 3 lymph nodes per patient, range 1-21 (Table 9).

<b>Characteristics</b>	<b>Number (%)</b>
Sex (female/male)	45/49
Age (median, range)	72 (45-90)
<b><u>Histopathological evaluation</u></b>	
<b>Tumour localization</b>	
Caecum	25 (27%)
Ascending colon	31 (33%)
Hepatic flexure	1 (1%)
Transverse colon	7 (7%)
Splenic flexure	1 (1%)
Descending colon	2 (2%)
Sigmoid colon	27 (29%)
<b>Tumour Stage</b>	
T1	7 (7%)
T2	19 (20%)
T3	58 (62%)
T4	10 (11%)
<b>Lymph node status</b>	
N0	59 (63%)
N1	19 (20%)
N2	16 (17%)
<b>Positive lymph node status</b>	
T1 tumours	0/7 (0%)
T2 tumours	4/19 (21%)
T3 tumours	25/58 (43%)
T4 tumours	7/10 (70%)
<b>Stage</b>	
Stage I	22 (23%)
Stage II	37 (39%)
Stage III	35 (37%)
<b>Lymph nodes, total number</b>	
Harvested lymph nodes PAD	2086
Positive lymph nodes PAD total	173
Positive lymph nodes PAD <5mm	56
Positive lymph nodes PAD 5-10mm	62
Positive lymph nodes PAD >10mm	18

Table 9. Demographics table of 94 patients/tumours

## CT evaluation

### T-stage

In 16 and 21 patients respectively, the observers were not able to detect any tumour (ctT0). Twelve (75%) and fourteen (67%), respectively, of those patients had a pT1-T2 tumour according to histopathology. Others reached tumour stage pT3a and pT3b. When stratifying ctT-stage in not locally advanced (ctT1-T3ab) and locally advanced (ctT3cd-T4) the sensitivity and specificity for observer 1 compared to the pT-stage were 79% and 96% , for observer 2 61% and 97% and consensus 75% and 97% respectively. Interobserver agreement for ctT-stage (Cohens Kappa) was 0.76 (good agreement).

### N-stage

The assessment of lymph node status (ctN0/N+) was limited to three morphological criteria in line with a previous study; a, internal heterogeneity within at least one lymph node (IH) b, irregular outer border (IOB) and c, combination of the two criteria, so called combined criteria (Figure 24).

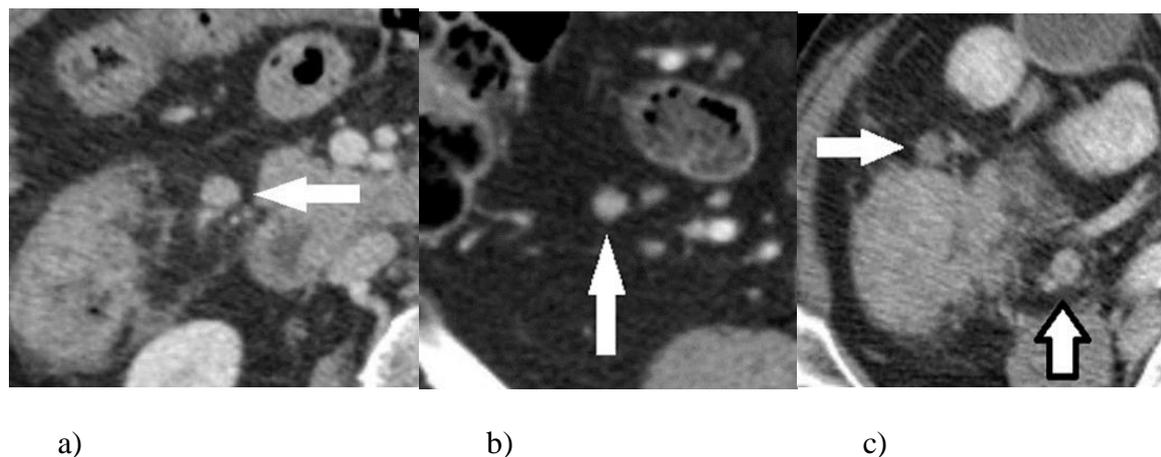


Figure 24. CT images of lymph nodes. a) Lymph node without morphological features of malignancy (7x6 mm) (white arrow), b) Lymph node (7x6mm) assessed by the criteria IOB (white arrow), c) Lymph node (6x6mm) with IH (black/white arrow) and lymph node (7x6mm) with IH and IOB within the same lymph node (white arrow).

The number of lymph nodes and patients with each morphological feature assessed by CT is displayed in table 10 as well as sensitivity, specificity, PPV and NPV for each feature.

### *Internal heterogeneity*

IH was detected in at least one lymph node in 28 (30%) and 26 (28%) out of 94 patients by observer 1 and 2 respectively. A total number of 93 and 64 lymph nodes respectively with this morphologic feature were detected for each observer. Sensitivity/specificity for ctN-stage compared to pN-stage for both observers were 77/95% and 66/95% respectively. Interobserver agreement (Cohens Kappa) for ctN-stage was 0.74 (good agreement).

### *Irregular outer border*

Lymph nodes assessed as presenting IOB were detected at least in one lymph node in 20 and 19 out of 94 patients respectively by observer 1 and 2. Sensitivity/specificity for ctN-stage compared to pN-stage for both observers were 54/97% and 49/97% respectively.

### *Both internal heterogeneity and irregular outer border in one lymph node*

The combination of IH and IOB in the same lymph node were assessed in 18 out of 94 patients by both observers. Sensitivity/specificity for ctN-stage compared to pN-stage for both observers were 49/97% and 46/97% respectively.

### *Nodal stage – IH, IOB and IH/IOB - combined criteria*

When combining the three possible criteria; IH, IOB or IH/IOB, for lymph nodes and if at least one event occurred in one patient, this was assessed in 28 and 27 out of 94 patients respectively by both observers. Sensitivity/specificity for ctN-stage compared to pN-stage for both observers were 77/95% and 67/95% respectively (Table 10). Interobserver agreement (Cohens Kappa) for ctN-stage was 0.72 (good agreement). Consensus ctN-stage compared to pN-stage for metastases resulted in a sensitivity and specificity of 69% and 100%.

	IH		IOB		IH/IOB		IH / IOB / (IH/IOB)	
	Obs 1	Obs 2	Obs 1	Obs 2	Obs 1	Obs 2	Obs 1	Obs 2
No of pat	28	26	20	19	18	18	28	27
No of ln	93	64	28	24	35	30	93	66
TN	58	56	57	57	57	57	58	56
FN	8	12	16	18	18	19	8	11
FP	1	3	2	2	2	2	1	3
TP	27	23	19	17	17	16	27	24
Sensitivity	77	66	54	49	49	46	77	67
Specificity	95	95	97	97	97	97	95	95
PPV	96	88	91	90	90	89	96	89
NPV	88	82	78	76	76	75	88	84

Table 10. Sensitivity, specificity, positive and negative predictive value for the different CT-criteria for lymph node metastases. Note: TN = True negative, FN = False negative, FP = False positive, TP = True positive, PPV = Positive Predictive Value, NPV = Negative Predictive Value, IH = Internal Heterogeneity, IOB = Irregular Outer Border, IH / IOB / (IH/IOB) = N+

In the present study the major discrepancy was understaging (false negatives, FN) (table 10). For observer 1 there were 8 FN cases. In these patients, there were a total of sixteen metastatic lymph nodes according to histopathology and none of the metastatic nodes were >10 mm in size. Eleven (69%) metastatic lymph nodes were <5 mm. For observer 2 there were 11 FN cases with a total of 24 metastatic lymph nodes according to histopathology and none of the metastatic nodes >10 mm in size. Fifteen (62%) metastatic lymph nodes were <5 mm according to histopathology.

In consensus reading the observers had 11 FN cases according to histopathology. Of the total number of 25 lymph node metastases, none were >10 mm, 8 lymph nodes were between 5-10 mm and 17 (68%) were <5 mm in size.

## 5 DISCUSSION AND CONCLUSIONS

The papers in this thesis has been an attempt to improve detecting colonic lesion in vitro with lowering the radiation dose and improve staging colon cancer using CT and MRI.

**In paper I** we systematically evaluated CT parameters in a phantom study for detection of polyps in the colon.

This study illustrates the importance of a high axial spatial resolution (i.e., thin slices and low pitch) for the detection of polyps in the colon. If no adjustments are done such scanning settings result in an increase in the radiation dose to the patient. With adjustment of the tube current, polyps can be detected using high-spatial-resolution settings without increasing the radiation dose.

The results of this study indicate that imaging for polyps larger than approximately 5 mm can be performed at significantly reduced dose levels without compromising the detection rate. In clinical practice polyps smaller than 5 mm are usually of less importance (138, 139).

CTC involves the definition of objects (polyps) having a high contrast to the surroundings (air in the colon). The detection of objects in such high-contrast images is, in general, less susceptible to an increased level of stochastic noise and therefore also to a decrease in the tube current (and dose) of the CT sequences.

Other groups have also reported the use of special low-dose protocols in CTC (128, 130, 132, 140). Although there is evidence that polyps of clinically relevant sizes (5-10 mm) can be detected with reduced milliamperes-second (mAs) settings in CTC (132), little comparative clinical data that prove the relative benefit of using such high-resolution protocols in combination with reduced mAs settings is available.

Because of the obvious differences between artificial phantoms and patients, the three observers in study I regarded them as relevant descriptors of the clinical situation. Important characteristics of the phantoms in our study that contribute to their relevance in the clinical setting are that they were flexible, inflatable, and contained simulated haustral folds. The use of artificial removal of residual water and debris has been tested by others but was not used in this study nor in the clinical setting at the time (141).

The presence of water in the phantom increased the detection rate using a 2D MPR evaluation, whereas the results of the flythrough technique tended toward the opposite. We conclude that misclassification of water drops attached to the wall in the water-filled phantoms is always a risk and that such false polyps will influence the detection rate. We do not have an obvious explanation of the discrepancies between the results of the two evaluation techniques. However, our experience gained from this study indicates that the capacity to distinguish different polyp shapes is improved with the fly-through technique compared with the 2D MPR technique. This is believed to have influenced the results

presented in Figure 8, reducing the number of water drops classified as polyps with the fly-through compared with the 2D MPR technique.

At dose levels used in diagnostic X-ray procedures, the associated risk to the patient relates to the stochastic induction of cell damage that could cause long-term effects, such as cancer. The current belief is that stochastic effects can be induced regardless of the radiation dose, with a higher incidence at higher dose levels. The radiation burden to the public from CT examinations is significant. A relatively recent study from the United Kingdom showed that although CT accounted for only about 4% of all X-ray examinations, it contributed 40% of the dose to the population (142). Similar results have been presented by groups in other countries (143). The question of screening patients using techniques based on ionizing radiation is controversial, and it has not been the intention of this work to cover the topic. If the CTC technique could perform significantly better than currently used screening techniques in detecting colon cancer and if diagnosis of the disease using screening could clearly influence clinical outcome, there might be arguments for introducing CTC as a screening for parts of the population. CTC indeed offers a number of advantages over current screening techniques for colorectal cancer.

Today CTC is used both in clinical setting and in screening situations. Modern protocols offer different dose options depending on the probability of positive finding. Modern CT scanners have multiple x-ray detectors, today at a minimum of 64. Also the rotation time of the generator and detectors are reduced and the combination of table speed enabling full coverage of the abdomen during breath hold scans. To overcome the issue of residual content in the colon faecal tagging is now often used. The use of computer-aided detection (CAD) has been implemented and used as a second reader by some investigators (144, 145).

In a screening or other clinical settings it is amendable to avoid unnecessary radiation exposure and to keep as “As Low As Reasonable Achievable” (ALARA-principle) (146). Some patients are difficult to examine with colonoscopy due to long or tortuous colon or adhesions after periods of inflammatory events such as diverticulitis. In those patients CTC is an alternative. In screening situations, low radiation dose is desirable. The goal is to detect polyps >5 mm or tumours and the sensitivity and specificity for CTC in those situations is equal to OS. The major limitation with CTC is that there is no possibility to obtain biopsies.

The major limitation with an increased axial spatial resolution is the prolonged examination time, restricting the use of breath-hold techniques depending on the scanner used. The results also show that a substantial increase in image noise by the reduced tube current setting can be adequate when the analysis is restricted to polyps >5 mm.

In conclusion, the results of this study indicate that axial spatial resolution plays a dominant role for the detection of polyps in the colon using CTC. CTC conducted at a given dose level and spatial resolution could therefore possibly perform better at an increased spatial resolution (low pitch, thin slices), keeping the dose constant by reducing the tube current setting.

**In paper II** we compared high resolution MRI and standard CT for colon cancer staging. Both of the modalities can be used to distinguish locally advanced cancers from those that are not locally advanced with relatively high accuracy. In a previous systematic review of radiological local staging in colon cancer with CT, the weighted accuracy for T-staging was 67% and for N-staging 69% (87). In this study, we were able to show a higher observed agreement (accuracy) by the two observers with MRI 90% (observer 1) and 93% (observer 2) than with CT 79% (observer 1) and 76% (observer 2) compared to histopathology in categorizing T-stage into locally advanced or not locally advanced. The inter-observer agreement (Kappa) between the two observers was also in favour of MRI (0.79) versus CT (0.64) for T-stage. Compared to the rectum, the large bowel is a greater challenge for cross-sectional imaging due to anatomical considerations such as peritoneal coverage, the retroperitoneal fascia, bowel motility and tortuosity. One reason for understaging was detecting tumour penetrating the serosa, which occurred in 3 out of 4 misclassified tumours and one tumour by observer 1 and 2 with MRI, respectively. The corresponding figures for CT were 3 out of 4 tumours for both observers.

Regarding nodal staging we demonstrated equal moderate performance between the both modalities MRI (accuracy 0.72 and 0.69) and CT (accuracy 0.72 and 0.72) and higher sensitivity with MR than with CT, but lower specificity. The accuracies were in line with previous CT studies (87, 147). The inter-observer agreement overall was surprisingly low with MRI (0.10) but slightly better with CT (0.66). The reason for this was mainly due to overstaging of different patients with MRI by the two observers and the criteria for lymph node involvement were applied differently by the two observers and/or the criteria were not optimal.

In assessment of EMVI, MRI performed better with accurate staging in 6 out of 8 cases than with CT (3 out of 8). MRI showed a higher inter-observer agreement to detect EMVI (k 0.75) than CT (k 0.22). In rectal cancer, EMVI has been reported to be identified with a sensitivity and specificity of 62% and 88%, respectively (91), but has to our knowledge not been evaluated with MRI for colon cancer staging. In colon cancer, Burton et al. showed accuracies between 54.5% and 61% in predicting EMVI with CT with poor interobserver agreement of 0.178 (82). In our study, the number of patients was too small to draw any firm conclusions but it is potentially interesting and worth further studies.

In this study we identified a number of limitations. A substantial proportion of patients were excluded during the study period either due to extensive disease and also periods with limited access to MRI scanner. The CT examinations were assessed retrospectively and there were variations in scanners configurations and scanning parameters. There were also differences in the time between MRI and CT examinations and surgery in different patients which limits the conclusions that can be made comparing MRI with CT. There was no matching of individual lymph nodes compared to histopathology. Furthermore, diffusion-weighted MR sequences (DWI) were not part of the imaging protocol in the study period but would have been interesting to apply due to their potential for tumour detection. Regarding stage distribution,

only seven patients (25%) in this study proved to have stage III disease, which is rather low (148).

In conclusion, distinguishing locally advanced colon cancer (defined as tumour stage T3cd-T4) from not locally advanced (T1-T3ab) can be performed with high resolution MRI and CT, even when CT is performed with a standard metastasis staging imaging protocol. High resolution MRI does have an advantage due to its high soft tissue discrimination to identify certain prognostic factors such as T-stage and extramural venous invasion. The down side with MRI compared to CT is that the examination often requires a radiologist on site during the examination for tumour detection and planning imaging planes and coverage depending on tumour localisation the examination. Regarding MRI, the motion artefacts can also be of a challenge to work around.

**In paper III** we focused on lymph nodes and previously reported criteria for lymph node metastases on CT as a predictor for stage III disease in colon cancer. Of all the studied imaging criteria in this study, morphological predictors were superior to size and attenuation criteria, with reasonable sensitivity and specificity.

The combination of internal heterogeneity and/or irregular outer borders showed a moderate sensitivity of 85% and specificity of 75%. Using logistic regression the strongest predictor for stage III disease in our study was internal heterogeneity both alone or combined with other variables. Our results, using CT for morphological assessment, are comparable in sensitivity but lower in specificity, with a previous work by Brown et al., using morphological predictors as mixed signal intensity or irregular border for mesorectal lymph node with MRI of rectal cancer with a sensitivity of 85% and specificity of 97% (92).

Using up to date CT technique, a study with 106 patients using  $>1$  cm and/or cluster of  $\geq 3$  “normal” lymph nodes as criteria for nodal metastases resulted in a sensitivity of 71% and specificity of 41% (149). In our study, only 19 patients had lymph nodes  $\geq 10$  mm and only 14 patients had lymph nodes in a cluster of three, which reduces the impact of these criteria for prediction of stage III. Another CT study used size criteria  $>5$  mm and/ or irregular outer border were considered to be positive for nodal disease with sensitivity 64% and specificity of 53% (150). If we used this criterion in our study this would have shown a similar sensitivity of 56% but a higher specificity of 84%. We have no explanation for this difference.

Our study don not support size criteria alone as predictive for stage III disease. In a previous study it has been reported that up to 70% of histopathologically found lymph nodes with metastases in colorectal cancer are as small as  $\leq 5$  mm in diameter (151). The majority of the detected lymph nodes ( $n = 870$ , 66%) in our study were  $<4$  mm and thus could not be further assessed because of their small size using CT. When using the size threshold of  $\geq 10$  mm of the lymph node and a combination of criteria including a cluster of more than three nodes along the locoregional vascular pedicle, spiculated and indistinct node borders, and a mottled

heterogeneous pattern with CT, Kwak et al. reported sensitivity of 87% and specificity of 29% (152). The surprisingly low specificity was maybe due to the large threshold.

Studies using FDG-PET have reported low sensitivities (29–37%) but higher specificity (87%) for nodal staging, suggesting that the additional value of PET/CT is limited in detecting metastatic regional lymph nodes near the primary tumour area due to high false negative rate (153, 154). There are some controversies about the use of PET/CT in primary staging in colon cancer. Some authors claim that PET/CT can alter or change the management in stage III patients (6.5%) and stage IV patients (12.7%) while other authors claim that it does not (155, 156).

Kanamoto et al. used the criteria of cut-off point of 0.8 or greater in short/long axis diameter ratio measured in the axial plane on CT and reported both high sensitivity of 87% and specificity of 80%. (136). In study III we measured the true short and long axis and found similar sensitivity (85%) for this criterion but much lower specificity (30%) due to a high rate of false positive findings (70%). Benign lymph nodes, regardless of size, can be either oval or rounded, which is a limitation using this criterion.

The use of CT for assessment of lymph node status alone as predictor of prognosis is still premature at this stage. If the selection for neoadjuvant chemotherapy was based on presence of stage III disease using the best combination of criteria (heterogeneity and/or irregular border) from study III, 20 patients out of 80 (25%) would be potentially be overtreated and 6 patients out of 39 (15%) would be undertreated. This emphasizes the need to decide on such treatment based on other prognostic factors or use them in combination with the assessed lymph node status.

A strength of study III was that all patients were examined with a 64- multidetector CT and all having primary surgery allowing histopathology of the resected specimen as reference.

The retrospective setting in study III is a limitation. Using only one observer in assessment could reduce the evaluation robustness and reproducibility of the imaging criteria. There were also some of the criteria that was present in a limited number of patients which limits their applicability. There was also no possibility to match individual lymph nodes between imaging and histopathology. A possible further limitation was that we excluded T4 tumours in the study. The reasons for this was to reduce the possible bias because if relatively high rate (37%) of lymph node metastases in this group. At the time of the study, no software solution for quantitative analysis for lymph nodes such as texture analysis was available. Texture analysis is being evaluated in oncologic CT (157). We believe that texture analysis may have a role in the context of characterizing regional lymph nodes on CT in colon cancer although the approach is rather unexplored in small lymph nodes and may be subjected to a separate study.

In conclusion, various imaging criteria for lymph node metastases on CT have previously been used. Results from study III do not support use of the commonly used size criteria. From

study III it can be concluded that imaging criteria that allow the best prediction of nodal involvement are either the presence of at least one lymph node with internal heterogeneity or the presence of at least one lymph node with internal heterogeneity and/or irregular outer border.

**In paper IV** the aim of the study was to validate, by two observers, the diagnostic performance of morphological lymph node features on CT on a per-patient basis as predictive for stage III disease in colon cancer, based on the results in paper III.

Our results show that that IH and the combined combination assessment of the chosen criteria, internal heterogeneity and irregular outer border and a combination of those results in a high specificity but moderate sensitivity which are in line with other comparable studies, yet inferior to the work using morphological criteria in MRI of rectal cancer (92). The present results are better regarding specificity than reports in a recent meta-analysis, including 16 CT studies were sensitivity of 71% and specificity of 67% was reported (158).

Regarding the size of the lymph nodes at histopathology in the pN+ population there were only 18 out of 173 (10%) metastatic lymph nodes in 9 out of 35 patients that exceeded 10 mm. It has been reported in previous studies that nearly 50-70% of the lymph nodes found at histopathology are below 5mm in size (151, 159). In our study 56 out of 136 by pathologist size measured metastatic lymph nodes (41%) were below 5 mm in size. The large proportion of small relative large lymph nodes illustrates the challenge for imaging in assessment of metastatic lymph nodes.

The classification of tumour stage into not locally advanced (T1-T3ab) or locally advanced (T3cd-T4) resulted in moderate sensitivity (61-79%) and high specificity (97-97%) in study IV. The sensitivity is in line with a recent meta-analysis including four studies with a pooled sensitivity of 77% and specificity of 70%, but our study resulted in higher specificity (158). Other reports using MRI for detection and staging of colon cancer has shown similar results (160-162). In line with study II we understaged the extramural tumour component in T3cd tumours and were not able to assess small serosal tumour involvement.

The selection for neoadjuvant treatment in rectal cancer is based on the clinical stage where magnetic resonance imaging plays the most important role. Well-known important prognostic factors in colorectal cancer are tumour stage, extramural vascular invasion and lymph node involvement (163). Hence, neoadjuvant treatment has resulted in reduction in tumour size and recurrence rates (164).

For colon cancer, there is yet no established neoadjuvant treatment regimen in clinical practice. The ongoing FOxTROT trial uses T-stage and extramural tumour depth >5mm as an inclusion criteria based on CT. In another study using both CT and MRI for detection of lymph node metastases in early colorectal cancer (with submucosal invasion), a sensitivity of 79% and specificity of 75% was achieved when using size criteria of 4.1 mm in short diameter of the lymph node. These authors points out to pay more attention to small nodes in

early cancer, because they are more likely to be malignant than reactive as in more advanced cancers (165).

The present study does not support the use of morphological CT criteria alone for prediction of stage III disease. The evaluation of the low sensitivity is limited by the limited presence of visible morphological features for metastases on CT. The high specificity is caused by false negatives and reflects absence of morphological CT criteria in positive lymph node patients according to histopathology. The reason for this is that small lymph nodes (<5mm) and microscopic tumour growth in normal lymph nodes are not assessable with CT.

In the scenario of selecting patients for neoadjuvant treatment based on preoperatively assessed stage III disease from the morphological criteria in study IV, eleven out of 35 patients would potentially have been undertreated and none overtreated. On the other hand, if a certain neoadjuvant treatment has potential significant side effect to the extent that overtreatment is not justified, the high specificity of the morphological criteria on CT may play an important role which have to be further investigated.

The strength of this study is the homogenous consecutive patient cohort. The data was prospective collected. All patients were examined with the same CT. The evaluation was independent and all patients having primary curative surgery without neoadjuvant treatment allowing protocol proforma based detailed histopathology of the resected specimen as a reference. This assessment even included not only the number but also size of the lymph nodes.

There are some limitations of the study. The assessment of the morphological imaging criteria was performed by two highly experienced radiologists and may not simulate the clinical everyday setting. The study was on a per-patient basis and no matching of individual lymph nodes between imaging and histopathology was performed.

The visual assessment was to simulate the clinical setting. No software using quantitative analysis of morphology such as texture analysis was used. Texture analysis and other similar quantitative tools may potentially have a role in the context of characterizing regional lymph nodes on CT in colon cancer although the approaches in this setting are rather unexplored. Small size of lymph nodes and presence of microscopic foci of cancer cells within these lymph nodes will be challenges when performing such analysis.

To conclude, morphological criteria for lymph node metastases on CT in colon cancer results in high specificity and moderate sensitivity in predicting stage III in colon cancer.

**Overall conclusion in staging of colon cancer:**

In the routine work up in staging colon cancer patients, CT has relatively high prediction rate to classify tumour stage into either not locally advanced or locally advanced. The prediction of lymph node metastases with the most commonly used image modalities is unsettled and challenged. In the era of selecting patients to neoadjuvant chemotherapy, the ongoing trials have used the inclusion criteria based on tumour stage only (T3cd-T4). Patients with lower tumour T-stage but presence of regional metastases will therefore potentially be undertreated and patients with no metastases will potentially be overtreated. In order to reduce the risk of recurrence and prolong survival after curative surgery, other mechanisms may have to be taken to account including tumour biology and other prognostic biomarkers at early stage.

## 6 FUTURE ASPECTS

The detection of colonic lesion using state of the art CT has improved over the years. New CT scanners have much larger number of detectors and the standard pixel size is now as thin as 0.625 mm or less. The original thin slices from the CT scanner can be reconstructed into preferable thickness to overcome to low signal to noise ratio. Modern CT scanners today also provide different dose reduction features and the different CT manufacturers use different dose reduction techniques. In order to improve the imaging modalities in CRC staging there is ongoing continuous work. Regarding CT, the major advantage is the high spatial resolution and reproducibility of the technique. In comparison with MRI, there are limitations with CT regarding soft tissue discrimination to separate one tissue from another. The DECT technique is emerging and may contribute to improve soft tissue contrast resolution on CT (166).

The use of CTC in colon cancer screening is debated especially in countries with low availability for colonoscopy. Several suggestions of low and ultra-low dose protocols have now been presented since the time we published study I (167, 168). The use of computer-aided detection (CAD) in CTC is likely to increase and CTC has been adopted for screening in some countries (169).

In this thesis we used the clinical setting when evaluating the tumour, nodal and metastasis stage on CT and MRI with no additional quantitative analysis software tools. Texture analysis is one of several upcoming techniques using various different algorithms to quantify the image characteristics, even those not clearly visible for the radiological eye. In texture analysis, CT images are processed by analysing the pixel value distribution histogram by different range of parameters such as entropy, uniformity, kurtosis, skewness and standard deviation (157, 170). The technique has been used to differentiate tumours like gastro intestinal stroma cells tumour (GIST) into low and high grade, oesophageal cancer and for treatment response in breast cancer, characterization of lung nodules, lung cancer and in CTC examinations (171). It is a promising technique and prove to have additional value as in patients with lung cancer in differentiating between malignant and benign lymph nodes larger than 1 cm in the mediastinum (172). It is not yet explored but should be considered to use for analysis of lymph nodes in CRC.

MRI on the other hand has high intrinsic soft tissue discrimination and in specific dedicated protocols also high spatial resolution. The evolving hybrid combination of PET/MRI provides potential advantage compared to PET/CT allowing for simultaneous assessment of functional parameters provided both by PET and MRI. The technique has been used for colorectal staging and has proved to have higher accuracy in predicting T-stage and liver metastases than PET/CT (173, 174). Although PET/MRI could be used for CRC staging, as well as for surgical planning, assessment of treatment response to neoadjuvant therapies and monitoring stable and recurrent disease the role is presently unexplored (175).

In the era of computer science, artificial intelligence (AI) is growing in many fields of development. AI will affect clinical health care and modern imaging of all kinds in the future. The AI technique mainly comprises different techniques including machine learning (ML) and convolutional neural networks (CNN). The techniques of mathematical algorithms have been around for 30 years and have often been designed to precise tasks to discover, classify and characterize data. There have been several attempts to implement ML and CNN in medicine, both in radiology and histopathology, in evaluating diagnostic imaging with encouraging results. AI have been used in mammography, histopathology, automatic segmentation of target volume and organ at risk in RT planning in rectal cancer (176-178) and has also been used in identification in predictive biomarkers for gene expression (179). All this new technology could be of help for radiologist to reduce variability in description and quantification and act as clinical decision support.

The workhorse in today's functional oncologic imaging, FDG-PET/CT, is associated with limitations when dealing with distinction between inflammatory lesions, cancers and mucinous tumours. Newer PET agents need to be more tumour specific, such as the targeted radiotracers of <sup>68</sup>Ga-PSMA for prostate cancers, which is a radionuclide that binds to a prostate specific antigen useful to detect tumours and metastases. There are ongoing studies concerning a promising PET tracer (<sup>124</sup>I-CLR1404) which is alkyl phosphocholine (APC) analog designed to enter the cancer cells via lipid rafts in the plasma membranes and has been proven to be highly selective for malignant tumours and is not retained in inflammatory or benign lesions (180).

Further studies are needed to evaluate the proper criteria in selection patients for neoadjuvant treatment. There are several ongoing studies on this matter and they will hopefully soon publish their results in a near future (120, 121).

CRC is a heterogeneous disease. Different tumours have different tumour biology. There are small CRC that can metastasize even if the tumour has not penetrated the muscularis mucosae (165). The tumour biology may also change over time such as the ability to metastasize and the effect from chemotherapy will alter the genetic expression. Great effort is being made in searching for predictive biomarkers for predicting the risk of developing metastases, recurrence and to assess prognosis. If a representative preoperative biopsy is taken at an early stage some prognostic features may alter treatment. Which prognostic factors are the most important? Should focus be to further evaluate the varying molecular mechanisms for initiating the carcinogenesis? Is it possible to predict the risk of early metastases, prognosis and outcome as early as at the stage of the first biopsy? If these questions can be answered, the use of diagnostic imaging will change and when performed also focused differently. We have to be prepared for this future.

## 7 ACKNOWLEDGEMENTS

I want to express my sincere gratitude to all of you who, in different ways, have contributed for making this thesis possible.

First of all, to my main supervisor, Lennart Blomqvist, who from the very beginning has inspired me in the field of clinical radiology and research. You have always been enthusiastic, a dear colleague, a true friend and has always encouraged and supported me in my endeavour and in decisions during all these years.

My co-supervisor and head of the colorectal surgical team, Torbjörn Holm, for your knowledge, financial support, discussions and helping in writing in paper II and III.

My co-supervisor, Mirna Abraham-Nordling, for your enthusiastic and valuable support in paper III and IV.

My co-supervisor, Annette Fransson-Andreo, for your valuable contribution in paper I and knowledge in CT and interesting discussions.

To Johan Lindholm, pathologist, for interesting discussions concerning the serosa margins in the beginning of this project and in paper II.

To Esther Lörinc, pathologist, and Bengt Glimelius, senior oncologist, for your valuable knowledge and contribution as co-authors work in paper II.

To Vahit Özgün, physicist, for our work and your magnificent contribution as first author in paper I.

To my co-authors in paper I and IV, Staffan Bremner, Richard Odh, Fredrik Hjern, Emma Östämö and György Csanaky for your contribution in evaluation, CT knowledge, manuscript editing, data collection and histopathological analysis.

To Christina Stjernholm, department of radiology, Danderyd University Hospital, for your help in paper IV.

To Roberto Vargas, MR technician and friend, for your knowledge MRI, both in the field of the abdomen and the knee.

To my friend, Patrik Simonsson, always helpful and a master of Excel.

To my research colleagues and friends, Mikael Skorpil, Fredrik Jäderling and Jacob Farnebo, Susanne Fridsten, Chikako Suzuki, Fredrik Strand and Patricia Sandqvist for scientific struggle and entertaining discussions.

To my head of lower abdominal group and friend, Jan Bohlin, for research support and encouraging

To actual head of the department Anders Wennerberg and the former head, Henry Lindholm, for giving me the resources to start and fulfil this thesis.

To all my colleagues at the radiology and nuclear medicine department in any “subgroup” they may belong into and especially my hard working colleagues at lower abdominal group, Magnus T, Michael Ö, Rezgar M, Barwar O, Karin v S, Ulrika S, Louise J, Nikolaos V, Badri R, Vitali G and Anastasios M.

Colleagues at the surgical department for professional discussions at the MDT meetings.

To my beloved son, Jacob, who always has been supportive, understanding and caring, giving me strengths.

To my parents, Göran and Saini, and my brother Henrik and family, for understanding and support in any ways.

To my love, Ulrika, and her daughters Ingrid and Carmen for your support and care.

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